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ORIGINAL RESEARCH

Oral Zeolite Therapy for Management of Mild to Moderate Lead Poisoning: A Randomized Clinical Trial

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Abstract: **Introduction:** Lead poisoning can present with a spectrum of symptoms, from fatigue to severe multiorgan complication; and Zeolite is known for its ability to remove heavy metals. This study aimed to assess the impact of zeolite on serum lead levels and blood parameters of patients with mild to moderate lead poisoning. **Methods:** This double-blind randomized clinical trial evaluated the effects of zeolite on serum lead levels of patients with mild to moderate lead poisoning, conducted between August 2022 and December 2022. The intervention group received oral zeolite tablets in addition to standard treatment, while the control group received only standard treatment. The impact of zeolite administration on serum lead levels and blood parameters was investigated using an appropriate statistical test. **Results:** 80 patients with a mean age of 39.84 ± 11.94 (range: 23-75) years were randomized (78.75% male). The two groups were similar regarding age (p = 0.329), sex (p = 0.785), baseline serum lead levels (p = 0.596), and liver enzymes (p = 0.648).The Zeolit group had lower serum lead levels (25.22 ± 13.26 vs. 37.68 ± 15.34; p < 0.001, ES: 0.869) and hematocrit (36.21 ± 7.83 vs. 39.53 ± 5.60; ES: 0.488; p = 0.032) after 2 weeks of treatment. **Conclusion:** Zeolite tablets show considerable promise as an adjunct therapy for mild to moderate lead poisoning. They effectively lower serum lead levels without adverse effects. This intervention could reduce the metal burden in the bloodstream and mitigate lead-induced multiorgan damage, offering a more effective and less invasive treatment option.

Keywords: Zeolites; Lead poisoning; Chelating agents

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1. Introduction

Acute or chronic lead poisoning can arise from various sources, including car exhaust, industrial pollution, and contaminated substances in everyday food through ingestion, inhalation, and skin contact (1). Most individuals exposed to lead are industrial workers who handle lead-containing materials (2). Additionally, rare causes of lead intoxication have been documented, including clinical manifestations in drug abusers, particularly those abusing opium. In Iran, lead exposure is widespread and uncontrolled, with opium use being a significant factor in lead toxicity due to the high prevalence of opium addiction in the country (3). Excess lead exposure can lead to complications primarily affecting the hematologic, renal, and liver systems (since most lead initially accumulates in the kidneys and liver) (4) while also impacting multiple organ systems, resulting in vague symptoms such as fatigue, apathy, irritability, and gastrointestinal issues (5, 6). Chronic lead exposure can also cause significant damage to the nervous system and impact cellular activities and enzyme systems (7, 8). According to the World Health Organization (WHO) guidelines for the clinical management of exposure to lead, for individuals with serum lead levels 5 µg/dL, the source(s) of lead exposure should be identified, and proper action must be taken (9). When addressing lead poisoning, the first crucial step involves relocating patients from the exposure site and removing potential lead sources. In the case of a blood lead level above 40 g/dL or

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the presence of significant symptoms, pharmacologic treatment is necessary (10). In this regard, chelation agents play an essential role in managing lead poisoning; however, this type of treatment needs to be carefully administered under strict medical care due to the risks associated with the chelating agents, which may result in more severe adverse effects than the toxicity induced by metals (11). Hence, suitable and cost-effective alternatives that pose no inherent risks or side effects and do not require medical supervision in hospitals could be superior choices for treating patients with mild to moderate lead poisoning who are not in critical condition. Zeolites are natural aluminosilicates with distinctive physicochemical properties, such as high crystallinity, regular subnanometric cavities, and highly selective ion-exchange capacity (12, 13).

Studies focusing on the detoxification properties of Zeolites have predominantly been conducted on animals or in the decontamination of natural sources, providing compelling evidence of their alleviating effects during exposure to different toxicants. Adding zeolite to tomato plants grown in soil with accumulated lead effectively reduced the lead content of the plants (14). Additionally, Li et al. showed that synthetic clinoptilolite, a type of zeolite, could remove Zn2+, Pb2+, Cd2+, and Cu2+ ions from water-based solutions (15). In an animal study on Nile tilapia (Oreochromis niloticus), including zeolite in the fish diet before and during lead exposure reduced lead levels and reversed the pathological changes caused by lead toxicity. This reversal included restoring protein and albumin levels, as well as decreasing the levels of glucose, cholesterol, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) (16). However, human studies focusing on the detoxification properties of zeolites in the case of lead poisoning are scarce; thus, this study aimed to evaluate the effect of zeolite on the serum lead levels and blood parameters of individuals with mild to moderate lead poisoning.

2. Methods

2.1. Study design and setting

This randomized clinical trial was conducted on patients with high serum lead levels who were referred to the outpatient clinic of the Medical Toxicology Department of the Poisoning Center of Loghman Hakim Hospital in Tehran, Iran, from August 2022 to December 2022.

The principal investigator, outcome assessors, and data analysts were blinded to group assignments to minimize bias. In contrast, randomization and dispensing personnel remained unblinded to ensure accurate administration of zeolite or standard care. The study protocol was prepared following the Recommendations for Interventional Trials (SPIRIT) reporting guidelines (17).

The study was conducted adhering to the Declaration of Helsinki (18). Ethical approval for this study (IR.SBMU.RETECH.REC.1401.217, 65168, July 24, 2022) was granted by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences. This study was registered in the Iranian Registery of Clinical Trials (IRCT) on August 31, 2022 (registration number: IRCT20211213053375N2). All participants were informed of the proposal and voluntarily provided written informed consent before enrollment.

2.2. Participants

The study included patients of both sexes, aged above 18 years, with lead poisoning who met the following criteria: serum lead levels between 20 and 60 µg/dL, and no signs of severe lead poisoning. Patients with pre-existing underlying conditions such as liver disease, diabetes, heart failure, and renal failure were excluded. Additionally, individuals who had previously been treated with chelating agents, which are commonly used for lead poisoning, were excluded. Furthermore, patients with severe lead poisoning or known allergic reactions to zeolite compositions were also not considered for inclusion.

2.3. Randomization and allocation concealment

Patients were randomly allocated to the zeolite or control group using a computer-generated random number table. An independent statistician performed the randomization, and group assignments were concealed in sealed envelopes. Patients were enrolled consecutively based on their presentation to the outpatient clinic, ensuring a representative sample of eligible participants. Group allocations (A or B) were revealed only to randomization and dispensing personnel to facilitate treatment administration. At the same time, all other study staff, including those involved in patient care and outcome assessment, remained blinded to minimize bias. In this study, only the researchers responsible for randomizing the samples and the medical staff involved in prescribing medication (since the patients in the control group did not receive a placebo) were not blinded to the study, which meant that they knew whether A or B belonged to the control or treatment group. Unblinded staff were excluded from patient follow-up, data collection, and analysis, with standardized protocols enforced for treatment delivery to further reduce potential bias. In addition, the patients and the principal investigator responsible for assessing toxicity results and reviewing laboratory results, as well as the person responsible for data collection and statistical analysis, were blinded to the study. The toxicity and laboratory results ratings were standardized and included predefined criteria, minimizing subjectivity in these assessments. All outcome data were reviewed and analyzed independently by a biostatistician not involved in patient care or the randomization process.

2.4. Interventions

Zeolite was prepared as oral tablets at the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences. After providing in-

formed consent, eighty patients were enrolled and randomly allocated to the zeolite or control group (40 patients each). The Zeolite group received daily oral zeolite (1000 mg) for two weeks in addition to standard treatments for patients with lead intoxication. The control group received only standard treatments for lead poisoning. Standard treatments included removing the person from the source of contamination in the first stage and symptomatic therapy in the later stages. For example, if the patient suffered from abdominal pain or neurological symptoms such as insomnia, the patient was given medication for constipation or abdominal colic, or was prescribed hypnotics to relieve the symptoms.

2.5. Data gathering

Before Zeolite administration and 14 days after the start of the administration, serum levels of lead, complete blood count (CBC), hemoglobin (HB), and hematocrit (Hct), liver enzymes, creatinine, blood urea nitrogen levels, and serum electrolytes were measured using Cobas Integra 400 Plus, Mindray BS-800, or Sysmex-KX-212 and Medica EasyLyte electrolytes. Adverse events were monitored throughout the study, including gastrointestinal symptoms (such as nausea, vomiting, diarrhea, and abdominal pain), allergic reactions (such as skin rash or itching), and other reported complications, such as headache or fatigue. Data was collected using a predesigned checklist prepared by the first author.

2.6. Statistical Analysis

Before this study, no research had evaluated zeolite's therapeutic effect on patients' blood lead levels. Therefore, we conducted a pilot study with 10 participants per group (unpublished data) at the outset of this research to estimate the effect size for sample size calculation. This pilot study assessed the therapeutic reduction in serum lead levels, indicating a potential effect that informed our sample size estimation. However, it should be noted that our pilot study may have included the preventive effects of zeolite, which could influence the applicability of its effect size to this therapeutic study. This limitation was considered in the interpretation of the results. The pilot study aimed to test our methodologies and gather preliminary data, which informed our sample size estimation. A power analysis showed that a minimum sample size of 35 people per group was needed, along with a reduction rate of 15 percent at =0.05 and a dropout rate of 10 percent within a power value of 90 percent. A total of 80 samples were considered for this study, 40 in each group. The recruitment process for the study participants is illustrated in the Consolidated Standards of Reporting Trials (CONSORT) (19) flowchart in Figure 1.

Baseline measurements and demographic profiles were compared using the chi-square and independent t-test. Additionally, univariate analysis was performed to evaluate the impact of zeolite administration on achieving a clinically significant reduction in serum lead levels, adjusting for blood urea nitrogen (BUN) and Cr. We used the Shapiro-Wilk test to test normality and visually inspected histograms and Q-Q plots for all continuous variables. Appropriate nonparametric tests were considered if the data did not meet the normality assumption.

All analyses were conducted on an intention-to-treat (ITT) basis. SPSS for Windows version 22 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Significance level was set at $P < 0.05$. The effect size of zeolite on the dependent variables examined in the present study was calculated based on Cohen's index.

3. Results

3.1. Baseline characteristics of studied patients

A total of 83 participants were initially enrolled in the study, and three were excluded (Figure 1). Finally, a total of 80 patients with a mean age of 39.84 ± 11.94 (range: 23-75) years were randomized (78.75% male). Table 1 compares the baseline characteristics of the studied patients between groups. The mean age of patients was 41.15 ± 13.65 years in the zeolite group and 38.53 ± 9.94 years in the control group ($p = 0.329$). The female population accounted for 20.0% of the Zeolite group and 22.5% of the control group ($p = 0.785$). Comparing baseline serum lead levels ($p = 0.596$) and liver enzymes ($p = 0.648$) revealed no significant differences between the two groups. However, patients assigned to the zeolite group exhibited significantly lower serum BUN ($p = 0.023$) and Cr ($p = 0.032$) levels than those in the control group.

3.2. Outcomes

The findings revealed a statistically significant reduction in post-intervention serum lead levels in the intervention group (25.22 ± 13.26 vs. 37.68 ± 15.34; $p < 0.001$, ES: 0.869; $F = 9.785$). BUN was identified as a significant confounder ($p = 0.032$, Partial Eta Squared = 0.059), whereas Cr showed no significant confounding effect ($p = 0.856$, Partial Eta Squared = 0.000). Adjusting for BUN improved the precision of the effect size estimate, confirming the intervention's effectiveness in lowering serum lead levels and highlighting the necessity of controlling for confounders, particularly BUN, to ensure accurate statistical analysis. Finally, the analytical model accounted for 25.2 percent of the variance in serum lead levels, indicating a modest accuracy.

For hematocrit, the zeolite group had a lower mean (36.21 ± 7.83) compared to the control group (39.53 ± 5.60), with an effect size of 0.488 ($p= 0.032$). In contrast, for liver enzymes such as alanine transaminase (ES = 0.246) and aspartate transaminase (ES = 0.179), as well as hemoglobin (ES = 0.049), the effect sizes were small, and the differences were not statistically significant ($p > 0.05$). Regarding BUN (ES = 0.400) and Cr (ES = 0.526), the model showed medium effect sizes, but the differences were not significant ($p = 0.997$ and $p = 0.406$, respectively).

4. Discussion

Our findings demonstrate that a 2-week daily treatment with Zeolite reduces serum lead levels in patients with mild to moderate lead toxicity, and the age and sex of the recipients may influence the effect on blood parameters. Chelation therapy plays a significant role in managing acute lead poisoning, as it involves using chelating agents to form lead chelation complexes in the bloodstream and transport them through the urine. However, due to the need for frequent hospital visits and the risk of side effects, chelation therapy is primarily recommended for patients with severe lead poisoning (20, 21).

Therefore, when facing mild to moderate lead poisoning, it is preferable to choose safer treatment options that patients can better tolerate. Zeolites are natural aluminosilicates with microscopically porous structures that efficiently remove heavy metals and cations such as lead by utilizing ion exchange and adsorption properties. These compounds have been extensively researched in animal studies for their ability to eradicate environmental pollution (22). For instance, in lead-exposed mice, modified natural clinoptilolite significantly decreased lead buildup in the intestines by more than 70%, showing a protective impact on brain tissue (23). Furthermore, the combined intake of clinoptilolite and EDTA provided added protection to the brains of lead-intoxicated mice by triggering antioxidant mechanisms and enhancing the activity of enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and glutathione (24). A small number of human studies have explored their potential in the treatment of metal poisoning. The purification of clinoptilolite, a natural zeolite, reduced the enteral absorption of lead by up to 90% in healthy individuals, as evidenced by reduced lead levels in serum and urine (25). In another study on healthy participants, oral intake of activated clinoptilolite suspended in water for seven or 30 days effectively reduced the body's burden of heavy metals, including lead, through increased urine exertion without the undesirable depletion of physiologically essential electrolytes (26). As expected, we also found that serum lead levels were significantly reduced following zeolite treatment, independent of the age or sex of individuals. Zeolites are generally considered safe; however, concerns have been raised about potential lead leakage from natural zeolite materials into the intestine since these materials can be preloaded with metals in nature (27). However, as Petrakakis et al. (28) reported, metal release from clinoptilolite loaded with lead primarily occurs at pH below 1, which is insignificant in the human body. Nevertheless, recent clinical trials involving human subjects using natural clinoptilolite material (PMA zeolite) have revealed that preloaded metals do not transit from the intestine into the blood circulation (27). The inconsistency in lead levels observed in the blood, which was only evident in a study involving individuals with osteoporosis, is attributed to the initiation of detoxification processes resulting from bone remodeling. Even in this case, as the treatment duration progressed, the lead levels remained consistently low (29). Our study not only revealed no signs of organ toxicity associated with zeolite but also indicated its potential to restore normal function in cases of lead poisoning-related liver, kidney, and hematopoietic issues. Although the blood parameters of our participants remained within the reference range throughout the study in both the zeolite and control groups, the decrease in liver enzymes and increase in hemoglobin levels were significant after zeolite treatment depending on the patient's sex. The exposed and supplemented mice exhibited a noteworthy decrease of 84% in the carcass, 89% in the liver, 91% in the kidneys, 77% in the bones, and 88% in the feces. These findings may suggest an overall protective role for zeolites that lowers circulating serum lead and potentially eliminates toxins stored in organs (23).

Preclinical evidence showed that zeolite performs well in vitro and in vivo. Montinaro et al. conducted a study involving pre-treating cells with micronized zeolite for 24 hours in mice. The results suggest that micronized zeolite may be a novel potential adjuvant for alleviating oxidative stress and plaque accumulation in neurodegenerative diseases (30). The study by Zarkovic et al. (31) focused on treating cancer in mice and dogs with micronized zeolite clinoptilolite. The results showed that micronized zeolite reduced the metabolic rate of cancer cells and increased the binding of 4-hydroxynonenal to albumin in vitro. Pavelić et al. (32) conducted a study to evaluate the detoxification properties of clinoptilolite materials in vitro and in rats intoxicated with AlCl3 in vivo. Their results represent the first documented evidence of the effectiveness of clinoptilolite (zeolite) in detoxifying aluminum in vivo. The study also provides scientific data on safety aspects and recommends using clinoptilolite for detoxification. Furthermore, the research highlights differences in the physicochemical properties of each clinoptilolite (zeolite) material tested and their connection to the production method (32).

The rationale behind the enhanced tissue-protective effect of zeolite when comparing sexes in our study has not been fully clarified. However, existing evidence indicates that men and women exhibit disparities in their susceptibility to oxidative stress, a fundamental mechanism underlying tissue damage induced by metal toxins. Women are inherently more resilient owing to the protective influence of estrogen and lower levels of NADPH oxidase activity, resulting in reduced production of reactive oxygen species (33).

Although further long-term clinical trials focused on the safety profile and role of zeolite in reversing multiorgan complications of lead poisoning are necessary, our study results suggest the potential of zeolite as a favorable treatment for lead poisoning and its associated complications.

5. Limitations

Several limitations need to be taken into account. A limitation of this study is the absence of a placebo in the control group, which prevented full double-blinding. Patients

were blinded to their treatment allocation, and medications were dispensed by staff who were uninvolved in outcome assessment, and outcome assessors were also blinded, but this approach may not eliminate performance bias. The lack of a placebo may have introduced performance bias, although measures to blind participants and outcome assessors were implemented to mitigate this issue. Future studies should incorporate a placebo-controlled, double-blind design to enhance blinding integrity and further validate these findings. Another limitation is that the effect size derived from the pilot study may not be entirely applicable to the therapeutic context, as it likely included the preventive effects of zeolite. Also, due to the critical condition of patients with severe lead poisoning and ethical reasons regarding the necessity of intensive treatments, we excluded these patients to minimize the confounding effects of chelation therapy, and our findings may not apply to this population. Additionally, our study protocol involved administering a specific dose of zeolite (1000 mg/day) and measuring its effects only at two time-points, limited to baseline and two weeks after treatment. Longer-term supplementation or observations at intervals may have yielded more comprehensive results.

No adverse events associated with zeolite administration were observed.

6. Conclusions

It seems that, zeolite tablets could be considered as a potential adjunct therapy for mild to moderate lead poisoning. This intervention shows promise for reducing the metal burden in the bloodstream and mitigating the multiorgan injury induced by lead exposure. Furthermore, our findings indicate that the patient's sex may play a role in this process.

7. Declarations

7.1. Acknowledgments

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7.2. Conflict of interest

The authors declare no conflict of interest.

7.3. Funding

No funding

7.4. Availability of data

The datasets used and analyzed during the current study are available upon request from the corresponding author.

7.5. Ethical considerations

The study was conducted adhering to the Declaration of Helsinki (18). Ethical approval for this study (IR.SBMU.RETECH.REC.1401.217, 65168, July 24, 2022) was granted by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences. On August 31, 2022, this study was registered in the Iranian Registry of Clinical Trials (IRCT registration number: IRCT20211213053375N2). All participants were informed of the proposal and voluntarily provided written informed consent before enrollment.

7.6. Authors' contributions

ST obtained ethical approval and prepared the manuscript. ND, AKh, MR, PETE, MT, BM, MB, and ShSh collaborated on the study results' design, analysis, and interpretation. The authors have also contributed to the writing of this manuscript. MT specifically helped to analyze and interpret the data. All authors thoroughly reviewed and edited the manuscript and endorsed the final version.

7.7. Using artificial intelligence chatbots

We employed AI-powered tools to check grammar and enhance the academic quality of the text, primarily authored by the writers.

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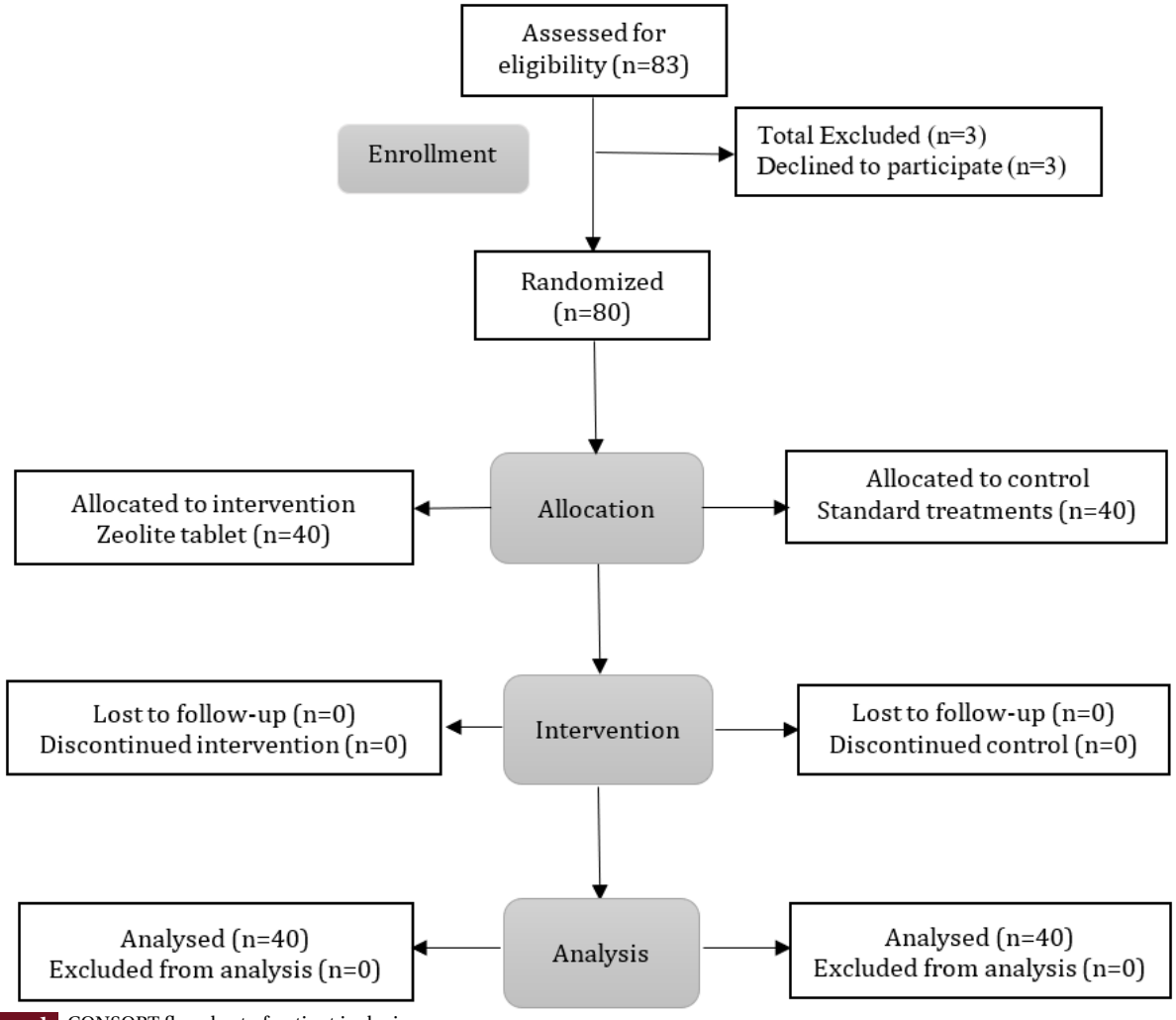

Figure 1: CONSORT flowchart of patient inclusion.

Table 1: Comparing the baseline characteristics of cases between the two groups

Variables	Groups		P value
	Zeolite (n = 40)	Control (n = 40)	
Age (year)			
Mean ± SD	38.53 ± 9.94	41.15 ± 13.65	0.329
Sex			
Male	38 (95.0)	31 (77.5)	0.778
Female	2 (5.0)	9 (22.5)	
Cause of poisoning			
Organic	4 (10.0)	2 (5.0)	0.671
Inorganic (metallic)	36 (90.0)	38 (95.0)	0.731
Vital signs			
SBP (mmHg)	120.1 ± 15.2	125.2 ± 18.1	0.234
DBP (mmHg)	80.2 ± 10.3	82.2 ± 12.1	0.456
Pulse rate (/minute)	75.2 ± 10.1	78.5 ± 12.2	0.321
Respiratory rate (/minute)	16.3 ± 3.5	17.4 ± 4.1	0.189
Habitual history			
Smoking	15 (37.5)	18 (45.0)	0.489
Alcohol Consumption	10 (25)	12 (30.0)	0.617
Confounding factor			
Hypertension	8 (20.0)	10 (25.0)	0.592
Diabetes mellitus	5 (12.5)	7 (17.5)	0.533
Hyperlipidemia	6 (15.0)	8 (20.0)	0.556
Laboratory at baseline			
Serum lead level (mcg/dL)	45.06 ± 12.94	43.43 ±14.34	0.596
ALT (U/L)	34.91 ± 27.79	34.91 ± 26.41	0.221
AST (U/L)	32.68 ± 20.30	31.93 ± 23.31	0.583
BUN (mg/dL)	15.76 ± 5.70	18.56 ± 5.07	0.008
Creatinine (mg/dL)	0.952 ± 0.278	1.096 ± 0. 307	0.032
Hemoglobin (g/dl)	12.15 ± 2.34	13.00 ± 2.07	0.089
Hematocrit (%)	36.63 ± 6.72	38.72 ± 5.87	0.143

Data are presented as mean ± standard deviation (SD) or frequency (%). ALT: alanine transaminase;
AST: aspartate transaminase; BUN: blood urea nitrogen; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 2: The effect of 14 days of oral zeolite therapy on serum lead level and laboratory parameters

Parameter	Group	Mean ± S.D	± S.E	P	ES
Serum lead level (mcg/dL)	Zeolite	25.22±13.25	-12.463±3.205	<0.001	0.869
	Control	37.68±15.33			
Alanine transaminase (U/L)	Zeolite	25.25±16.33	-3.950±3.594	0.275	0.246
	Control	29.20±15.80			
Aspartate transaminase (U/L)	Zeolite	23.43±11.05	-2.225±2.783	0.426	0.179
	Control	25.65±13.70			
Blood urea nitrogen (mg/dL)	Zeolite	14.42±5.35	0.003±0.810	0.997	0.400
	Control	16.61±5.57			
Creatinine (mg/dL)	Zeolite	0.880±0.208	-0.018±0.021	0.406	0.526
	Control	1.010±0.279			
Hemoglobine (g/dl)	Zeolite	13.05±3.94	-0.153±0.694	0.827	0.049
	Control	13.20±1.92			
Hematocrit (%)	Zeolite	36.21±7.83	-3.323±1.524	0.032	0.488
	Control	39.53±5.60			

ES: effect size; SD: standard deviation; S.E: standard error.