Lead And Kidney Disease

Farzaneh Najafi ,MD

Nephrologist

Associate Professor Of Shahid Sadoughi University Of Medical Sciences-Yazd

Lead poisoning

Lead (Pb) intoxication has been recognized as a public health risk, mostly in developing countries.

It is known as a potent occupational and environmental toxin through various sources such as gasoline, paints, containing pipes, ceramic glazes, industrial processes like lead smelting and coal combustion, battery recycling, grids and bearings, food contaminated during processing, Pb-adulterated alcohol.

At present, exposure to high concentrations of Pb is less common, due to better industrial management and the fact that Pb is no longer added to paint and petrol.

However, Pb contamination is still a public health problem in many countries in Africa, Asia and Latin America due to domestic exposure through contaminated water and soil.

Nowadays, unusual causes of chronic lead poisoning have been reported such as adulterated opium and marijuana. Journal of Renal Endocrinology 2018;4:e03.

An important route of exposure that should not be neglected is the inhalation of tobacco smoke . Clinical Kidney Journal, 2017, vol. 10, no. 6, 747–758

LEAD NEPHROTOXICITY

The toxic effects of Pb have been known for more than2000 years, since lead intake was a common problem among the Romans.

The first reported case of nephrotoxicity associated with Pb was described in the 19th century.

Pb is the most common environmental nephrotoxicant

At present, exposure to high concentrations of Pb is less common, due to better industrial management and the fact that Pb is no longer added to paint and petrol. However, Pb contamination is still a public health problem in many countries in Africa,Asia and Latin America due to domestic exposure through contaminated water and soil.

Nefrologia 2012;32(3):279-86

Two cross-sectional studies analyzed the US NHANES from 1999 to 2002 and 1999 to 2006 and found that even low blood Pb levels may be associated with CKD.

In the US NHANES 1999 to 2002, the prevalence of CKD among adults was found to be higher in those with higher blood Pb levels.The adjusted ORs of prevalent CKD increased with increasing quartiles of blood Pb level (Q1 < 1.06

mg/dL, Q2 = 1.06-1.63 mg/dL, Q3 = 1.63-2.7 mg/dL, Q4 ≥ 2.47 mg/dL) (OR = 1.49, 95% CI = 0.75-2.98; OR = 1.89, 95% CI = 1.09-3.30; and OR = 2.72, 95% CI = 1.47-5.04, respectively, for the second, third, and fourth quartiles) .

Another analysis of the US NHANES 1999 to 2006 reported that among adults with a blood Pb level > 2.4 mg/dL, the OR for prevalent CKD was 1.56 (95% CI = 1.17-2.08) compared to adults with a blood Pb level ≤ 1.1 mg/dL

In addition, a NHANES from 2007 to 2012 demonstrated that a positive association between urine Pb level and an inverse association between blood Pb level and eGFR .

Similarly, a cross-sectional study of Korean adults reported a positive association between blood Pb levels and renal dysfunction.

An increasing number of longitudinal studies have supported that Pb exposure contributes to an increased risk of kidney disease. Yu et al. explored the association between low-level environmental Pb exposure and renal function among 121 patients with non-diabetic CKD in Taiwan .After 4 years, every increase of 1 mg/dL in blood Pb level at baseline was associated with a decrease in GFR of 4.0 mL/min/1.73 m2.

International Journal of Medical Sciences 2021; 18(5): 1121-1129. doi: 10.7150/ijms.51594

Absorption and distribution

Pb is mainly absorbed by the intestine and the respiratory system and, to a lesser extent, through the skin.

Intestinal absorption is mediated by DMT-1 and increases with deficient intake of Fe and Zn.

The respiratory system is a highly efficient route of absorption, with an uptake rate of more than 40% of inhaled Pb; however, the molecular mechanism by which Pb is absorbed is unknown.

Corporeal handling of Pb is much less under stood. Following absorption, Pb is transported to the blood plasma and within minutes is transferred to the erythrocytes where it is primarily bound to haemoglobin. Only 6% circulates in the plasma from where it is distributed to the soft tissues (e.g. kidney), teeth and the skeleton, which contains up to 95% of the total Pb burden. Bone is the main reservoir for lead in the body and Pb transport to the bloodstream increases during times with the highest bone turnover, such as adolescence and pregnancy.

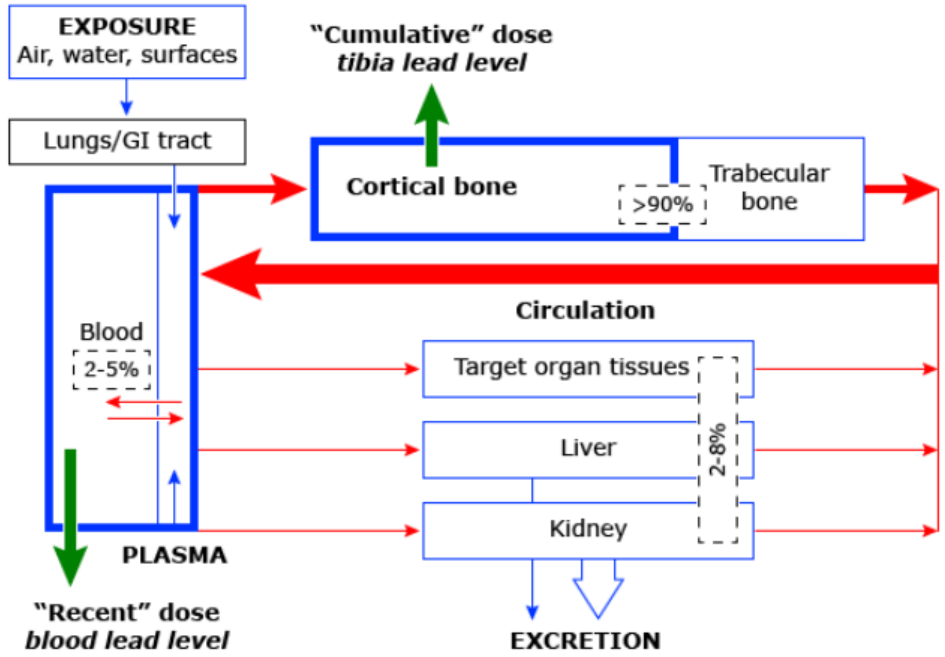
Pb circulates in the blood, and it is either excreted by the kidneys or accumulates in bone.

Urinary excretion is the main route of Pb elimination from the body. Circulating Pb bound to low molecular weight proteins (<1% of the total) is filtered freely through the glomerulus and partially reabsorbed by the proximal tubule.

The half-life of Pb in the blood is around 35 days, compared to 10-30 years in bone.

Compartmental model for lead

Compartmental model for lead



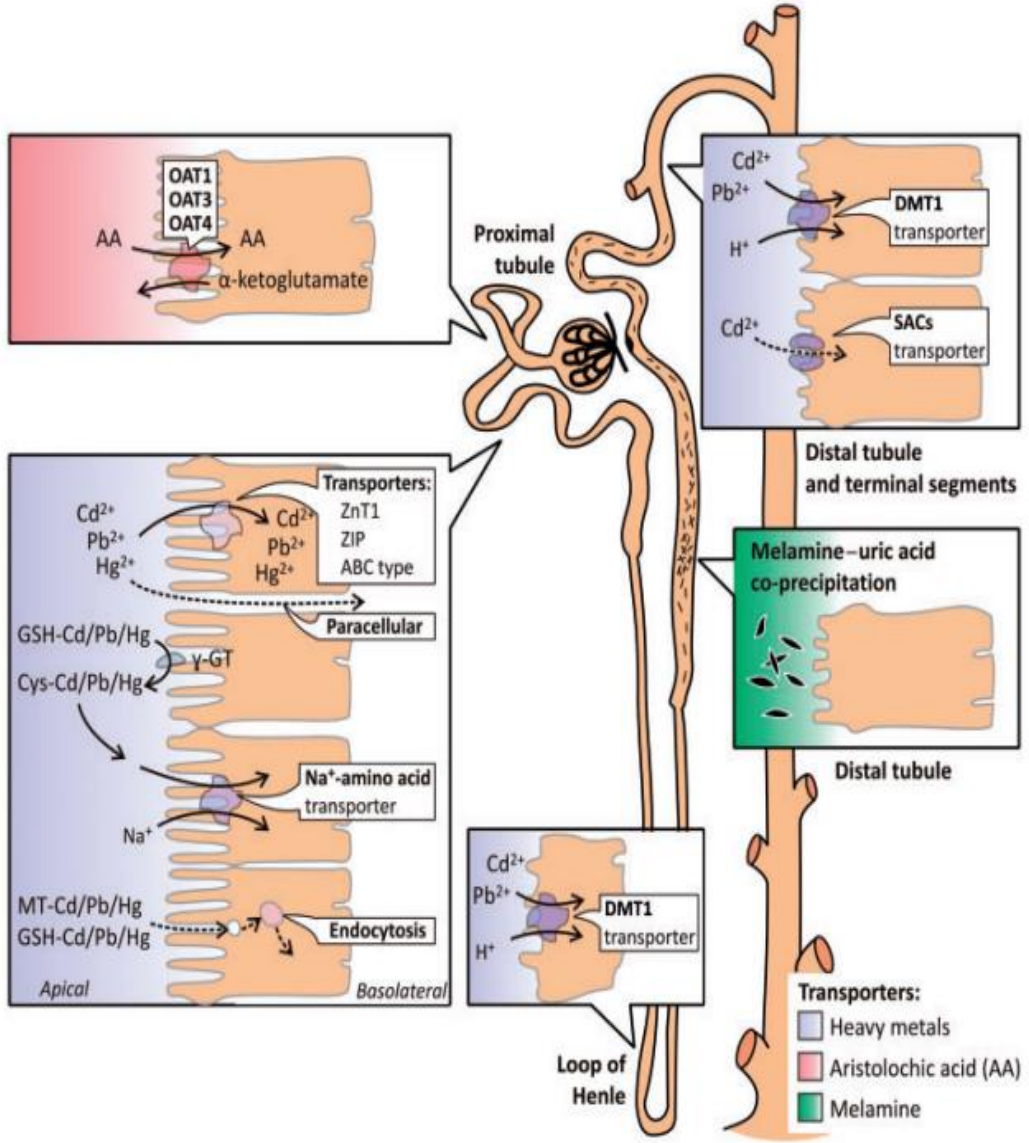


Fig. 4. Mechanisms involved in the uptake and action of aristolochic acid, melamine and the heavy metals Cd, Pb and Hg along the nephron. Adapted from Barbier *et al.* [111] with permission.

Clinical Kidney Journal, 2017, vol. 10, no. 6, 747–758

doi: 10.1093/ckj/sfx062
Advance Access Publication Date: 28 July 2017
CKJ Review

CKJ REVIEW

Environmental toxin-induced acute kidney injury

Benjamin A. Vervaet, Patrick C. D'Haese and Anja Verhulst

Department of Biomedical Sciences, Laboratory of Pathophysiology, University Antwerp, Antwerp, Belgiun

Correspondence and offprint requests to: Patrick C. D'Haese; E-mail: benjamin.vervaet@uantwerpen.be

The proximal tubule is a central player in metal toxicity for the vast majority of metals. This is particularly due to its bulk reabsorbing activity.The mechanisms involved in the uptake of Cd, Pb and Hg along the nephron have been elegantly described by Barbieret al.

In the proximal tubule, several transporters of essential metals are involved in the uptake of free forms of Cd, Pb and Hg [e.g. zinc transporter 1 (ZnT1), ZRT/IRTlike protein (ZIP) and ATP-binding cassette (ABC) protein] . Furthermore, after conjugation with metallothionein and glutathione (GSH), these metals can also be reabsorbed by endocytosis or by transport of Cys conjugates through the Na+ amino acid co-transporter after degradation of GSH by the brush border enzyme ɣ-glutamyltransferase.

In the distal tubule or connecting ducts, divalent metal transporter 1 (DMT1) and stretch-activated channels (SACs) could play an important role in the uptake of ionized forms of Cd, Pb and Hg.

DMT1 is probably a major transporter of metals in the loop of Henle.

Paracellular pathways may also participate in metal transport along the proximal tubule and the loop of Henle.

Cellular toxicity of Pb & Physiopathology

Cellular toxicity of Pb is complex and may develop via different pathways.

First, exposure to Pb may induce oxidative stress, thereby initiating a cascade of events that may lead to vascular resistance and high blood pressure.

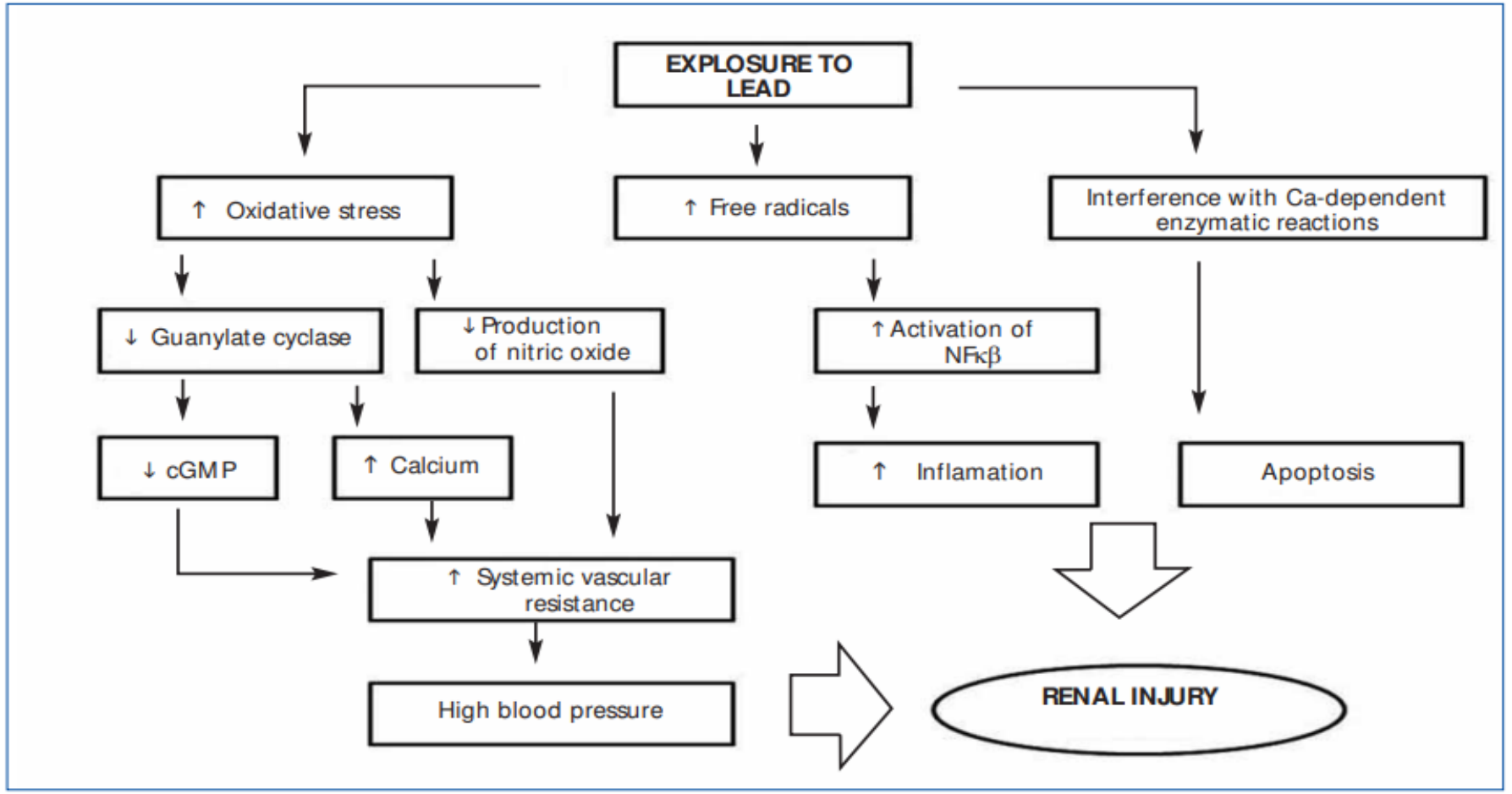
Second, free radicals may be generated that activate nuclear factor Ķß and inflammation.

Third, Pb may interfere with Ca dependent enzymatic reactions and the induction of apoptosis.

Fourth, depletion of intracellular antioxidant glutathione.

These various pathways can ultimately lead to the development of renal injury

Nefrologia 2012;32(3):279-86



Clinical manifestations

Acute Pb toxicity (blood Pb level > 80–100 µg/dL) has been reported to cause proximal tubular injury, possibly due to cytoplasmic, mitochondrial and intranuclear inclusion bodies composed of Pb–protein complexes , and the clinical manifestations include glucosuria, aminoaciduria, phosphaturia, and Fanconi syndrome. (Int. J. Med. Sci. 2021, Vol. 18)

Other clinical manifestations include haemolytic anaemia, acute attacks of gout, intense abdominal pain (“painter’s colic”) and encephalopathy.

Chronic Pb poisoning (blood Pb level > 60 µg/dL) has been reported to cause Pb nephropathy, which is characterized by glomerular sclerosis, tubular atrophy, tubulointerstitial nephritis and fibrosis, and finally reduced GFR . Urinary excretion of urates decreases due to the effect of Pb on the PCT and renal blood flow decreases as well, resulting in increased urate levels in the bloodstream.

Diagnosing chronic nephritis due to Pb is difficult, since urinary symptoms and findings are variable and lack specificity.

Diagnosis is therefore based largely on a clinical history of exposure.

In addition, chronic low Pb exposure (blood Pb level < 5-10 µg/dL) has been reported to potentially contribute to the development of CKD and the progression of established CKD . The association between body Pb level and CKD has also been reported to be affected by age, sex, diabetes, hypertension, and uric acid level.

LEAD-RELATED NEPHROTOXICITY

Prolonged lead exposure at the lower levels encountered in developed countries may contribute to renal toxicity, which refers to as lead-related nephrotoxicity . This is most likely to occur in patients at increased risk for kidney disease, including those with diabetes mellitus or hypertension, and in patients with underlying chronic kidney disease (CKD) from non-lead causes. These patients typically do not have extrarenal manifestations of lead poisoning.

The data reviewed indicate that lead contributes to nephrotoxicity, even at blood lead levels below 5 μg/dl. This is particularly true in susceptible populations, such as those with hypertension (HTN), diabetes, and/or CKD. Low socioeconomic status is a risk factor for both lead exposure and diseases that increase susceptibility. Future public health risk for lead-related nephrotoxicity may be most significant in those rapidly developing countries where risk factors for CKD, including obesity and secondary HTN and diabetes mellitus, are increasing more rapidly than lead exposure is declining. Global efforts to reduce lead exposure remain important

review

http://www.kidney-international.org

Lead-related nephrotoxicity: A review of the epidemiologic evidence

EB Ekong[1], BG Jaar[2,3] and VM Weaver[1,3]

[1]Division of Occupational and Environmental Health, Department of Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA and [3]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

LEAD-RELATED NEPHROTOXICITY

Plasma Lead Concentration and Risk of Late Kidney Allograft Failure: Findings From the TransplantLines Biobank and Cohort Studies

Camilo G. Sotomayor, Flavia Giubergia,* Dion Groothof, Catterina Ferreccio, Ilja M. Nolte, Gerjan J. Navis, Antonio W. Gomes-Neto, Daan Kremer, Tim J. Knobbe, Michele F. Eisenga, Ramón Rodrigo, Daan J. Touw, and Stephan J.L. Bakker, on behalf of the TransplantLines Investigators*

Rationale & Objective: Heavy metals are known to induce kidney damage, and recent studies have linked minor exposures to cadmium and arsenic with increased risk of kidney allograft failure, yet the potential association of lead with late graft failure in kidney transplant recipients (KTRs) remains unknown.

Study Design: Prospective cohort study in The Netherlands.

Setting & Participants: We studied outpatient KTRs (n = 670) with a functioning graft for ≥1 year recruited at a university setting (2008-2011) and followed for a median of 4.9 (interquartile range, 3.4-5.5) years. Additionally, patients with chronic kidney disease (n = 46) enrolled in the ongoing TransplantLines Cohort and Biobank Study (2016-2017, ClinicalTrials.gov identifier NCT03272841) were studied at admission for transplant and at 3, 6, 12, and 24 months after transplant.

Exposure: Plasma lead concentration was $\log_2$-transformed to estimate the association with outcomes per doubling of plasma lead concentration and also considered categorically as tertiles of lead distribution.

Outcome: Kidney graft failure (restart of dialysis or repeat transplant) with the competing event of death with a functioning graft.

Analytical Approach: Multivariable-adjusted cause-specific hazards models in which follow-up of KTRs who died with a functioning graft was censored.

Results: Median baseline plasma lead concentration was 0.31 (interquartile range, 0.22-0.45) μg/L among all KTRs. During follow-up, 78 (12%) KTRs experienced graft failure. Higher plasma lead concentration was associated with increased risk of graft failure (hazard ratio, 1.59 [95% CI, 1.14-2.21] per doubling; P = 0.006) independent of age, sex, transplant characteristics, estimated glomerular filtration rate, proteinuria, smoking status, alcohol intake, and plasma concentrations of cadmium and arsenic. These findings remained materially unchanged after additional adjustment for dietary intake and were consistent with those of analyses examining lead categorically. In serial measurements, plasma lead concentration was significantly higher at admission for transplant than at 3 months after transplant (P = 0.001), after which it remained stable over 2 years of follow-up (P = 0.2).

Limitations: Observational study design.

Conclusions: Pretransplant plasma lead concentrations, which decrease after transplant, are associated with increased risk of late kidney allograft failure. These findings warrant further studies to evaluate whether preventive or therapeutic interventions to decrease plasma lead concentration may represent novel risk-management strategies to decrease the rate of kidney allograft failure.

Visual Abstract online

Complete author and article information (including a list of the TransplantLines Investigators) provided before references.

Correspondence to C.G. Sotomayor (c.g.sotomayor.campos@umcg.nl)

**C.G.S. and F.G. contributed equally to this work.*

Am J Kidney Dis. 80(1): 87-97. Published online December 4, 2021.

doi: 10.1053/j.ajkd.2021.10.009

Lead and kidney stones

A study of participants from five consecutive US NHANES 2-year cycles (2007–2016) showed that blood Pb level was associated with the risk of kidney stones in adults. (may be other mechanisms for lead nephrotoxicity)

Mechanisms:

Firstly, Pb induce hypercalciuria, a leading pathophysiological factor for calcium nephrolithiasis . Defects in renal Ca2+handling can lead to hypercalciuria, kidney stone formation, and obstructive nephropathy .

As B Pb concentration doubled, urine calcium increased by 0.21 mmol/24-h in a model adjusted with sex and age .

The extracellular calcium-sensing receptor (CaSR) is a plasma-membrane G protein-coupled receptor activated by extracellular calcium and expressed in kidney tubular cells. It inhibits calcium reabsorption in the ascending limb and distal convoluted tubule when stimulated by high serum calcium.

Secondly, Pb induces tubular dysfunction, another pathological process involved in the formation of kidney stones.

Journal of Trace Elements in Medicine and Biology 68 (2021) 126852

Hyperuricemia

Hyperuricemia resulting from impaired tubular function and altered purine metabolism through the inhibition of guanine aminohydrolase dependent hydrolytic deamination of guanine to xanthine.

Hyperuricemia can mediate both hypertension and kidney injury as elevated uric acid levels have been shown to worsen endothelial dysfunction and through the stimulation of vascular smooth muscle proliferation resulting in thickening of the afferent arteriole of the glomerulus.

Hyperuricemia is also shown to inhibit the release of nitric oxide within the vasculature of the kidneys which worsens renal blood flow and impairs glomerular filtration.

All these mechanisms explain the role of hyperuricemia in the pathogenesis of lead nephropathy and the frequent association of chronic lead nephropathy with gout.

Evaluation and Diagnosis

- **High index of suspicion is required**
- **The assessment of lead exposure can be made using a lead exposure risk assessment questionnaire**
- **Assesing the lead burden:**

Blood lead level in lead nephropathy is expected to be above 40 ug/dL with the risk of renal failure at blood lead levels above 60 ug/dL. The blood lead levels in acute lead nephropathy are usually above 100 ug/dL and

Heme enzymes such as zinc-protoporphyrin and free erythrocyte protoporphyrin are altered by lead and can be used as indirect means of assessing lead exposure. The levels of these enzymes are elevated in lead toxicity with erythrocyte protoporphyrin levels above 35 ug/dL and 50 ug/dL correlating with blood lead level above 25 ug/dL and 40ug/dL, respectively.

The best measure for assessing the total accumulation of lead in the body is CaNa2 EDTA lead mobilization test. The test is performed by administering CaNa2EDTA 2 gr intramuscularly in 2 divided doses 12 hours apart or 1 gr intravenously, and by collecting urine for 24 hours. Patients with renal insufficiency should collect urine over 3-6 days. EDTA chelates lead sequestered in the body storage sites and mobilizes it for renal excretion in the form of lead-EDTA chelate. Individuals without any unusual prior exposure to lead would excrete less than 650 ug of lead over the collection period, a cumulative excretion greater than this level is indicative of excessive lead burden.

DMSA chelation test

The other methods of measuring body lead burden are methods which assess bone lead. These methods include X-ray fluorescence (XRF) which has been shown to be a safe, non-invasive, and reliable technique to measure lead in the skeleton. It measures subperiosteal and full thickness of bone lead as well as direct measurement of dense bone lead content.

Lead line in the gums of a patient with occupational lead poisoning

Lead line in the gums of a patient with occupational lead poisoning

- **Assessing renal function: evaluation of global renal function and assessment of tubular and glomerular parameters. (Bun,creatinine,eGFR,proteinuria, both urine NAGand urine a-1-microglobulin useful indicators in early lead nephropathy) .**

- **A full blood count (FBC) test, with anemia → peripheral blood smear → hypochromic microcytic anemia and basophilic stippling.**

- **Given the possibility of lead-related nephrotoxicity in those with CKD, suggest to screen patients who have stage 3 or greater CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m2) for lead exposure using a self-administered questionnaire.If the screening questionnaire indicates current exposure to lead, all sources of exposure should be eliminated and a blood lead level measured.**

Treatment

- ✓ Minimizing further exogenous lead exposure is essential in the treatment of lead nephropathy. If exposure is occupational, referral to an occupational medicine clinician with expertise in lead exposure, workplace accommodations, and workers' compensation are important. Follow-up blood lead measurements, if elevated initially, are also recommended.
- ✓ Chelation therapy; In adults, chelation should be considered for patients with blood lead levels greater than or equal to 70 ug/dL; however, symptomatic adults with blood lead levels exceeding 50ug/dL may also be candidates for chelation therapy. The preferable chelation agents for adults are CaNa2EDTA or DMSA.
- ✓ Post treatment care; It is advised that the diet should provide sufficient calories and be rich in calcium, zinc, and iron.
- ✓ Lead-related nephropathy; In developed countries, blood lead levels >5 mcg/dL (0.24 micromol/L) should be rechecked approximately four weeks after the identified source of lead exposure is eliminated. In developed countries, such values are more likely to be due to exogenous exposure that can be identified and reduced.Patients who have repeated blood lead levels >5 mcg/dL (0.24 micromol/L) should be referred to a clinician with expertise in occupational and environmental medicine.

A higher blood lead referral level may be necessary in countries in which there is a greater degree of lead exposure (eg, leaded gasoline has not been banned) and occupational and environmental medicine specialists are rare.

- ✓ **Interpretation of the blood lead level requires an understanding of data from the general population. NHANES data from 2015 to 2016, well after the removal of lead from gasoline in the United States, revealed a geometric mean blood lead level of 0.92 mcg/dL (0.04 micromol/L) in adults aged ≥20 years .**

Sources of lead exposure

Sources of lead exposure

Occupational
Plumbers, pipe fitters
Lead miners
Lead smelters and refiners
Painters
Auto repairers
Glass manufacturers
Shipbuilders
Printers
Plastic manufacturers
Police officers
Steel welders or cutters
Construction workers (especially renovation and rehabilitation)
Rubber product manufacturers
Gas station attendants (past exposure)
Battery manufacturers
Battery recyclers
Bridge reconstruction workers
Firing range instructors

Homes/Buildings
Lead-containing paint/pigment
Soil/dust near lead industries, roadways, lead-painted homes
Plumbing leachate
Ceramic ware (especially imported)
Leaded gasoline
Vinyl miniblinds*
Hobbies and related activities
Glazed pottery making
Target shooting at firing ranges
Lead soldering (eg, electronics)
Painting
Preparing lead shot, fishing sinkers
Stained-glass making
Car or boat repair
Home remodeling
Other sources
Folk remedies (Mexican: azarcon, greta; Asian: ba-baw-san, bali goli)
Tobacco smoking
Cosmetics
Moonshine whiskey
Gasoline "huffing"
Ayurvedic medications

Adult lead exposure questionnaire

Adult lead exposure questionnaire

Are you currently exposed to lead [See list of lead exposure sources]?

☐ YES ☐ NO ☐ DO NOT KNOW

If no, have you ever been exposed to lead?

☐ YES ☐ NO ☐ DO NOT KNOW

If yes, describe below:

Have you ever had a blood test for lead?

☐ YES ☐ NO ☐ DO NOT KNOW

If yes, what was the result?

If you answered yes to any of these questions:

Have you ever had medical treatment for lead exposure?

☐ YES ☐ NO ☐ DO NOT KNOW

If yes, describe below:

Have you ever been removed from work due to excess lead exposure?

☐ YES ☐ NO ☐ DO NOT KNOW

Lead exposure sources list

Lead exposure sources list

Lead mining
Primary or secondary lead smelting or refining
Scrap metal processing or recycling
Radiator manufacturing or repair
Lead glaze or frit manufacture or use, such as in pottery making
Battery manufacture, recycling, or repair
Construction work on pre-1978 structures or on exterior structures such as bridges, ships, or water towers regardless of age
Welding on painted steel
Power operations, such as cutting or sanding, on painted structures
Abrasive blasting
Demolition work
Bridge maintenance and repair
Shipbuilding
Paint removal on pre-1978 structures or on exterior structures of any age
Lead abatement
Rubber products and plastics industries using lead stabilizers
Cable making, splicing, or stripping
Burning lead-painted wood
Auto body repair shops
Automotive repair shop or junkyard work involving welding or other operations, such as power sanding or cutting, on lead painted surfaces or lead batteries
Furniture refinishing if paint removal creates inhalable lead (eg, power sanding)
Making lead fishing weights (sinkers), soldiers or bullets
Indoor firing range instructors, custodial staff, inspectors in firearms manufacturing
Lead bullet manufacturing
Leaded solder use (welding, stained glass production, plumbing, valve and pipe fittings, jewelry making, electronics)
Retained lead bullet
Metal casting or other foundry work
Lead grinding, polishing or buffing

Potential for lead exposure from eating, drinking, or using any of the following:
Imported or glazed pottery such as a Mexican bean pot
Foods canned outside the US
Imported candy (eg, tamarind or chili-based Mexican candies)
Home-distilled alcoholic beverages (moonshine; liquor from homemade still)
Imported lead-containing cosmetics, such as kohl eye make-up
Pica (ingestion of lead-containing nonfood items, eg, ceramic, plaster or paint chips; soil; primarily considered in children, but sometimes occurs in pregnant women)
Imported folk remedies
Ayurvedic herbal medicine products
Mexican folk remedies such as those used to treat the colic-like illness "empacho"
Alarcon
Coral
Liga
Maria Luisa
Rueda
Azarcon
Greta
Alkohl
Nutritional pills other than vitamins
Hazard
Pay-loo-ah
Lead-containing remedies used in Asian communities including
Ba-baw-san
Bali goli
Chuifong
Ghasard
Kandu
Tokuwan
Middle Eastern remedies and cosmetics include
Alkohl
Cebagin
Saoott
Immigrants from low- and middle-income countries


Thank
You