Toxic Metals, Cardiovascular Disease, and EDTA Chelation Therapy

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Financial Conflict Statement

- I have no relevant financial relationships with any commercial interests to disclose.

- The content of this presentation has been peer reviewed for fair balance and evidence based medicine.
Learning Objectives:

1. Relevance of TACT trial
2. Connection between toxic metals, CVD and EDTA
3. Tests for Toxic metals
4. Treatment strategies for Toxic metals and CVD
5. EDTA chelation protocol
6. Case studies
Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction
The TACT Randomized Trial

Gervasio A. Lamas, MD
Christine Goertz, DC, PhD
Robin Boineau, MD, MA
Daniel B. Mark, MD, MPH
Theodore Rozema, MD
Richard L. Nahin, PhD, MPH
Lauren Lindblad, MS
Eldrin F. Lewis, MD, MPH

Importance Chelation therapy with disodium EDTA has been used for more than 50 years to treat atherosclerosis without proof of efficacy.

Objective To determine if an EDTA-based chelation regimen reduces cardiovascular events.

Design, Setting, and Participants Double-blind, placebo-controlled, 2 × 2 factorial randomized trial enrolling 1708 patients aged 50 years or older who had experienced a myocardial infarction (MI) at least 6 weeks prior and had serum creatinine levels of 2.0 mg/dL or less. Participants were recruited at 134 US and Canadian sites. Enrollment began in September 2003 and follow-up took place until October 2011 (median, 55 months). Two hundred eighty-nine patients (17% of total; n=115 in the EDTA group and n=174 in the placebo group) withdrew consent during the trial.

Conclusions and Relevance Among stable patients with a history of MI, use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI.

Trial Registration clinicaltrials.gov Identifier: NCT00044213

JAMA. 2013;309(12):1241-1250

www.jama.com

Mean age was 63 years, 48% were female, 8% were nonwhite, and 31% were diabetic. The primary end point occurred in 222 (26%) of the chelation group and 261 (30%) of the placebo group (hazard ratio [HR], 0.82 [95% CI, 0.69-0.99]; P=0.035).
TACT Trial (Trial to Assess Chelation Therapy)

**Purpose** – To determine the safety and effectiveness of EDTA chelation therapy in individuals with CAD

**Study Design** – Double Blind, Placebo Control

**Sponsor** – NIH and NCCAM

**Study lead investigator** – Tony Lamas, M.D.

**Enrollment** – 1708 patients

**Total infusions** – 55,222

**Start date** – September 2003

**End date** – October 2012
Results of the Trial to Assess Chelation Therapy (TACT)

Background: According to reports from the CDC, the use of chelation therapy with disodium ethylene diamine tetra acetic acid (EDTA) therapy to treat atherosclerosis is increasing in the United States. Whether or not it is safe or effective cannot be determined based on current clinical data.

Purpose: To evaluate the safety and effectiveness of an EDTA chelation solution v. placebo in post myocardial infarction (MI) patients.

Methods: N= 1708; post-MI patients (≥ 6 weeks post-MI) who also received standard care; age ≥ 50 years; f/u average=4 years. Randomized, 2x2 factorial, multi-center, double blind, NIH-sponsored, placebo-controlled. 40 infusions of an EDTA-chelation solution vs. placebo, and of an oral, high-dose multivitamin and mineral supplement vs. placebo.

Primary endpoints: Composite: mortality (all cause), MI, stroke, coronary revascularization, or angina hospitalization.
Secondary endpoints: composite CV death, non-fatal MI, non-fatal stroke

- % Reduction in Clinical Events with Chelation

<table>
<thead>
<tr>
<th>Events</th>
<th>Composite</th>
<th>Diabetes</th>
<th>Non-diabetes</th>
<th>Anterior MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction</td>
<td>18%</td>
<td>39%</td>
<td>0.04%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Results: Composite endpoints: 18% reduction EDTA vs. placebo (p=0.035); SUBGROUPS: Diabetes: 39% reduction in composite endpoints vs. placebo (p=0.002); Non-diabetics: 0.04% reduction vs. placebo (p=0.725); Anterior MI: 37% reduction vs. placebo.

Conclusions: Post-MI patients who received chelation therapy had fewer clinical events vs. placebo. Two groups benefited most: diabetics and those who had experienced an anterior MI. Additional research is needed to confirm these findings and to understand the mechanisms of action for the benefits seen in this trial. This is not ready for implementation into clinical practice.

Presented by: Lamas GA, AHA Scientific Sessions, Los Angeles

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TACT Trial – Trial to Assess Chelation Therapy

Outcome:

NIH Trial Gives Surprising Boost To Chelation Therapy
What’s the connection?

- CVD
- Heavy metals
- EDTA chelation
Heavy (Toxic) Metals

- Heavy metals are generally considered to be those that negatively impact patients health.

<table>
<thead>
<tr>
<th>Aluminum (Al)</th>
<th>Lead (Pb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic (As)</td>
<td>Mercury (Hg)</td>
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<tr>
<td>Cadmium (Cd)</td>
<td>Nickel (Ni)</td>
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<tr>
<td>Chromium (Cr)</td>
<td>Tin (Sn)</td>
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<tr>
<td>Cobalt (Co)</td>
<td>Vanadium (V)</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>Zinc (Zn)</td>
</tr>
</tbody>
</table>
Lead education focused on Kids

- If your home was built before 1978, your child could be at risk for lead poisoning from lead paint.
- Lead can harm your child’s brain, causing lifelong learning and behavior problems.
- Almost one million children under age six in the U.S. suffer from lead poisoning.
- Children under age six are most at risk. When a pregnant woman is exposed to lead, it can harm her unborn baby.

Put a Lid on Lead

National Lead Poisoning Prevention Week
October 23-29, 2005

For information about childhood lead poisoning, contact your local health department or the National Lead Information Center at 1-800-424-LEAD (5323)
Lead – Toxicity in Children

- Death
- Nephropathy
- Colic
- Encephalopathy
- Frank Anemia
- Hemoglobin Synthesis
- Vitamin D Metabolism
- Erythrocyte Protoporphyrin
- Vitamin D Metabolism (?)
- Nerve Conduction Velocity
- Developmental Toxicity
- IQ Hearing Growth
- Transplacental Transfer

↓ = Decreased function
↑ = Increased function
Lead – Our focus

LEAD
Exposure in Adults

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Lead – Typical Sources of Exposure

- Lead pipe in domestic water systems until 1970
- **Glazed jugs – red / yellow**
- **lead crystal – 12-28%**
- Embedded bullet
- Sniffing petrol fumes
- **Herbal medicine**
- Paints, varnish, polishes
- Dirt in your garden
- Paint chips

- **Industrial exposure:**
  - metal smelter
  - car/ship wrecking
  - Construction
  - petroleum refining
  - **Lead – acid battery**
  - paint manufacturing

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The FDA is worried about some earthenware from Mexico.
Lead – Unlikely sources of Exposure

Toxics in Jewelry
Department of Toxic Substances Control

Cadmium and Lead in Jewelry... Don’t Risk It!

Exposure to lead and/or cadmium can cause negative health effects ranging from behavioral problems, kidney damage and even death. Cadmium is a known carcinogen. Young children are more susceptible to adverse health effects because their bodies are growing quickly and their brains are still developing.

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Lead – In Jewelry

Non-Compliant Jewelry Examples

NECKLACE CONTAINING 972,000 PPM LEAD;
DISCOVERED FOR SALE AT JOIA TRADING INC; LOS ANGELES, CA
LABELED “IN COMPLIANCE” WITH STANDARDS FOR LEAD LEVELS

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Lead – In Lipstick

Lead In Lipstick

Lead in lipstick? Turns out, the urban legend is true. In October 2007, the Campaign for Safe Cosmetics tested 33 popular brands of lipsticks at an independent lab for lead content.

The results: 61 percent of lipsticks contained lead, with levels ranging up to 0.65 parts per million. Lead-contaminated brands included L’Oreal, Cover Girl and even a $24 tube of Dior Addict. The U.S. Food and Drug Administration promised it would conduct an investigation, but dragged its feet in doing so.

It took nearly two years, pressure from consumers and a letter from three U.S. Senators, but in 2009 the FDA released a follow-up study that found lead in all samples of lipstick it tested, at levels ranging from 0.09 to 3.06 ppm – levels four times higher than the levels found in the Campaign study. FDA found the highest lead levels in lipsticks made
Lead – In Purses

High Levels of Lead in Purses
Two major retailers agree to test their purses for lead.

02:26 | 01/22/2010

RELATED LINKS:
- Too Much Lead Found in Women’s Handbags

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Vinyl Blinds and Candles

Most vinyl mini-blinds imported to the United States are a source of lead, which is used as a vinyl stabilizing additive for rigidity and color retention. Tests by the Consumer Product Safety Commission have determined that these mini-blinds deteriorate and their dust contains high levels of lead that can end up on children's hands and in their mouths.

Burning candles with lead in their wicks can raise the concentration of lead in the air - as much as 36 times that allowed by the EPA - for many hours after the candle is no longer burning.
Lead – In Water

• Acidic chemicals added to water magnify the uptake of lead into the body
• 98% of homes have lead in their plumbing from lead and copper pipes connected by lead solder
• Chrome-plated faucets are made of brass containing up to 8% lead
Lead – Adverse Health Affects

- Symptoms of Lead Poisoning / Accumulation
  - Fatigue / irritability
  - Hearing loss
  - Reduced IQ
  - Infertility
  - Hypertension
  - Heart disease
  - Chronic Kidney Disease
  - Peripheral Neuropathy
  - Arthralgia, Myalgias and Gout
  - Nausea / constipation
  - Antisocial (criminal) behavior
  - Seizures, coma, death, at very high levels

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Lead – Blood Levels Considered Elevated

- **ELEVATED**
- **SERIOUSLY ELEVATED**
- **EXTREMELY DANGEROUS**

<table>
<thead>
<tr>
<th>Exposure Occurring</th>
<th>Background</th>
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<tr>
<td></td>
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<table>
<thead>
<tr>
<th>micrograms per deciliter (µg/dL)</th>
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<tr>
<td>0</td>
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**DR.MORRISON**
Lead – Adverse health effects

- HTN
- Associated with MI and Stroke
- Chronic Kidney Disease (CKD)

- What’s the evidence?
The relationship of bone and blood lead to hypertension. The Normative Aging Study.
Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A.
Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.

Erratum in

Abstract
OBJECTIVE: To test the hypothesis that long-term lead accumulation, as reflected by levels of lead in bone (as opposed to blood which reflects recent lead exposure), is associated with an increased odds of developing hypertension.

DESIGN: Case-control study of participants in the Veterans Administration (now Department of Veterans Affairs) Normative Aging Study, a 30-year longitudinal study of men.

PARTICIPANTS: Of 1171 active subjects who were seen between August 1991 and December 1994, 590 (50%) participated in this investigation and had data on all variables of interest.

MAIN OUTCOME MEASURES: Hypertension was defined as taking daily medication for the treatment of hypertension or systolic blood pressure higher than 160 mm Hg or diastolic blood pressure of 96 mm Hg or higher during the time of examination. Levels of lead in the tibia (representing cortical bone) and the patella (representing trabecular bone) were measured in vivo with a K x-ray fluorescence (KXRF) instrument. Levels of lead in blood were measured by graphite furnace atomic absorption spectroscopy.

RESULTS: Blood lead levels were low, ranging from less than 0.05 to 1.35 micromol/L (<1 to 28 microgram/dL), with a mean (SD) of 0.30 (0.20) micromol/L.

Conclusion. —Our findings suggest that long-term lead accumulation, as reflected by levels of lead in bone, may be an independent risk factor for developing hypertension in men in the general population. (JAMA. 1996;275:1171-1176)

CONCLUSION: Our findings suggest that long-term lead accumulation, as reflected by levels of lead in bone, may be an independent risk factor for developing hypertension in men in the general population.
Blood Lead, Blood Pressure, and Hypertension in Perimenopausal and Postmenopausal Women

Denis Nash, PhD, MPH
Laurence Magder, PhD, MPH
Mark Lustberg, PhD
Roger W. Sherwin, MD
Robert J. Rubin, PhD
Rachel B. Kaufmann, PhD
Ellen K. Silbergeld, PhD

Since the 1970s, considerable attention has been paid to the possibility that low levels of lead exposure among adults in the United States, as well as the current US occupational exposure limit guidelines (40 μg/dL), blood lead level is positively associated with both systolic and diastolic blood pressure and risks of both systolic and diastolic hypertension among women aged 40 to 59 years. The relationship between blood lead level and systolic and diastolic hypertension is most pronounced in postmenopausal women. These results provide support for continued efforts to reduce lead levels in the general population, especially women.

JAMA. 2003;289:1523-1532
Lead – Associated with MI and Stroke

Blood Lead Below 0.48 \( \mu \text{mol/L (10 } \mu \text{g/dL) and Mortality Among US Adults}

Andy Menke, MPH; Paul Muntner, PhD; Vecihi Batuman, MD;
Ellen K. Silbergeld, PhD; Eliseo Guallar, MD, DrPH

**Background**—Blood lead levels above 0.48 \( \mu \text{mol/L (10 } \mu \text{g/dL) in adults have been associated with increased risk of cardiovascular, cancer, and all-cause mortality. The objective of the present study was to determine the association between blood lead levels below 0.48 \( \mu \text{mol/L and mortality in the general US population.}

**Methods and Results**—Blood lead levels were measured in a nationally representative sample of 13,946 adult participants of the Third National Health and Nutrition Examination Survey recruited in 1988 to 1994 and followed up for up to 12 years for all-cause and cause-specific mortality. The geometric mean blood lead level in study participants was 0.12 \( \mu \text{mol/L (2.58 } \mu \text{g/dL). After multivariate adjustment, the hazard ratios (95% CI) for comparisons of participants in the highest tertile of blood lead \((>0.17 \mu \text{mol/L [} \geqslant 3.62 \mu \text{g/dL]) with those in the lowest tertile (<0.09 } \mu \text{mol/L [<1.94 g/dL]) were 1.25 (1.04 to 1.51; } P_{\text{trend}} \text{ across tertiles=0.002) for all-cause mortality and 1.55 (1.08 to 2.24; } P_{\text{trend}} \text{ across tertiles=0.003) for cardiovascular mortality. Blood lead level was significantly associated with both myocardial infarction and stroke mortality, and the association was evident at levels >0.10 \mu \text{mol/L (} \geqslant 2 \mu \text{g/dL). There was no association between blood lead and cancer mortality in this range of exposure.}}

Blood lead level was significantly associated with both myocardial infarction and stroke mortality, and the association was evident at levels >0.10 \( \mu \text{mol/L (} \geqslant 2 \mu \text{g/dL). There was no association between blood lead and cancer mortality in this range of exposure.}

(Circulation. 2006;114:1388-1394.)

**Key Words:** risk factors ▪ mortality ▪ cardiovascular diseases ▪ myocardial infarction ▪ stroke
Lead Levels and Ischemic Heart Disease in a Prospective Study of Middle-Aged and Elderly Men: the VA Normative Aging Study

Nitin B. Jain, Vijayalakshmi Potula, Joel Schwartz, Pantel S. Vokonas, David Sparrow, Robert O. Wright, Huing Nie, and Howard Hu

1Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA; 2Health Investigations Branch, Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia, USA; 3Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA; 4Normative Aging Study, VA Boston Healthcare System and Department of Medicine at Boston University School of Medicine, Boston, Massachusetts, USA

BACKGROUND: Lead exposure has been associated with higher blood pressure, hypertension, electrocardiogram abnormalities, and increased mortality from circulatory causes.

OBJECTIVE: We assessed the association between bone lead—a more accurate biomarker of chronic lead exposure than blood lead—and risk for future ischemic heart disease (IHD).

METHODS: In a prospective cohort study (VA Normative Aging Study), 837 men who underwent blood or bone lead measurements at baseline were followed-up for an ischemic heart disease event between 1 September 1991 and 31 December 2001. IHD was defined as either a diagnosis of myocardial infarction or angina pectoris that was confirmed by a cardiologist. Events of fatal myocardial infarction were assessed from death certificates.

RESULTS: An IHD event occurred in 83 cases (70 nonfatal and 13 fatal). The mean blood, tibia, and patella lead levels were higher in IHD cases than in noncases. In multivariate Cox-proportional hazards models, one standard deviation increase in blood lead level was associated with a 1.27 (95% confidence interval, 1.01–1.59) fold greater risk for ischemic heart disease. Similarly, a one standard deviation increase in bone lead level was associated with a 1.39 (95% confidence interval, 1.12–1.72) fold greater risk for ischemic heart disease.

CONCLUSIONS: Men with increased blood and bone lead levels were at increased risk for future IHD. Although the pathogenesis of IHD is multifactorial, lead exposure may be one of the risk factors.

A Prospective Study of Bone Lead Concentration and Death From All Causes, Cardiovascular Diseases, and Cancer in the Department of Veterans Affairs Normative Aging Study

Marc G. Weisskopf, PhD; Nitin Jain, MD; Huiling Nie, PhD; David Sparrow, DSc; Pantel Vokonas, MD; Joel Schwartz, PhD; Howard Hu, MD

Background—Blood lead concentration has been associated with mortality from different causes in several studies. Many effects of lead exposure that might increase risk of death are likely to result from cumulative exposure, for which bone lead is a better biomarker than blood lead. The association between bone lead levels and mortality has not been explored.

Methods and Results—We prospectively assessed the association between both blood lead and bone lead, analyzed with the use of K-shell x-ray fluorescence, and mortality among 868 men in the Normative Aging Study. We identified 241 deaths over an average of 8.9 (SD=3.9) years of follow-up. We calculated adjusted hazard ratios and 95% confidence intervals using Cox proportional hazards. Compared with the lowest tertile of patella bone lead, the fully adjusted hazard ratios in the highest tertile for all-cause and cardiovascular mortality (n=137 deaths) were 2.52 (95% confidence interval, 1.17 to 5.41) and 5.63 (95% confidence interval, 1.73 to 18.3), respectively. The age-, smoking-, and race-adjusted hazard ratio for ischemic heart disease mortality (n=62 deaths) in the highest tertile was 8.37 (95% confidence interval, 1.29 to 54.4). Results were similar for tibia lead. Bone lead was not associated with cancer, and blood lead was not associated with any mortality category.

Conclusions—We found bone lead to be associated with all-cause and cardiovascular mortality in an environmentally exposed population with low blood lead levels. This study suggests that cumulative lead exposure from prior decades of high environmental exposures continues to significantly affect risk of death despite recent declines in environmental lead exposure. *Circulation. 2009;120:1056-1064.*
Lead – Causes Cardiovascular Disease

Lead Contributes to Arterial Intimal Hyperplasia Through Nuclear Factor Erythroid 2–Related Factor–Mediated Endothelial Interleukin 8 Synthesis and Subsequent Invasion of Smooth Muscle Cells

Iris Zeller, Michael Knoflach, Andreas Seubert, Simone B. Kreutmayer, Marlies E. Stelzmüller, Evelyn Wallnoefer, Stefan Blunder, Sandra Frotschnig, Barbara Messner, Johann Willeit, Paul Debbage, Georg Wick, Stefan Kiechl, Günther Lauffer, David Bernhard

Objective—To validate the hypothesis that the toxic heavy metal lead (Pb) may be linked to cardiovascular diseases via the initiation of atherosclerosis, in vivo and in vitro studies were conducted.

Methods and Results—During the human study part of this project, serum Pb levels of healthy young women were correlated to carotid intima-media thickness. Multivariate logistic regression analyses showed that increased serum Pb levels were significantly associated with an increased intima-media thickness ($P=0.01$; odds ratio per SD unit, 1.6 [95% CI, 1.1 to 2.4]). In vitro, Pb induced an increase in interleukin 8 production and secretion by vascular endothelial cells.

Conclusion—Our data support the hypothesis that Pb is a novel, independent, and significant risk factor for intimal hyperplasia. (Arterioscler Thromb Vasc Biol. 2010;30:1733-1740.)

Key Words: Pb □ heavy metal □ endothelial □ Nrf2 □ interleukin □ smooth muscle cell □ invasion □ migration □ vascular □ pathophysiology □ risk factor □ intima media thickness □ atherosclerosis
CLINICAL RESEARCH STUDY

Low-level Environmental Exposure to Lead and Progressive Chronic Kidney Diseases

Ja-Liang Lin, MD, Dan-Tzu Lin-Tan, RN, Yi-Jung Li, MD, Kuan-Hsing Chen, MD, Yen-Lin Huang
Department of Nephrology and Division of Clinical Toxicology, Chang Gung Memorial Hospital, Lin-Kou Medical Center, School of Medicine, Chang Gung University, Taipei, Taiwan, ROC.

ABSTRACT

PURPOSE: To determine whether low-normal body lead burden (BLB) accelerates progressive renal insufficiency in nondiabetic patients with chronic kidney disease (CKD).

METHODS: One hundred eighty CKD patients (serum creatinine between 1.5 and 2.9 mg/dL) with low-normal BLB (<80 μg) and no lead exposure history were observed for 24 months. Following the observation, 32 patients with low-normal BLB (≥20 μg and <80 μg) were randomly assigned to chelation and control groups. The chelation group patients were given edetate calcium disodium (EDTA) chelation therapy for 3 months and repeated chelation therapy during the following 24 months to maintain their BLB below 20 μg, while the control group patients underwent placebo therapy. The primary endpoint was an increased serum creatinine level to 1.25 times the baseline value. The secondary endpoint was temporal changes in renal function.

RESULTS: The primary endpoint occurred in 14 patients in the observation period. Baseline BLB was

CONCLUSION: Environmental exposure to lead, even at low level, may accelerate progressive renal insufficiency of nondiabetic patients with CKD. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Progressive renal insufficiency; Repeated lead chelation therapy; Low-level environmental lead exposure; Nondiabetic chronic kidney diseases
Lead, at low levels, accelerates arteriolopathy and tubulointerstitial injury in chronic kidney disease

Carlos Roncal, Wei Mu, Sirirat Reungjui, Kyung Mee Kim, George N. Henderson, Xiaosen Ouyang, Takahiko Nakagawa, and Richard J. Johnson

Division of Nephrology, Hypertension, and Transplantation, University of Florida, Gainesville, Florida
Submitted 10 May 2007; accepted in final form 20 July 2007

Sprague-Dawley rats were administered lead (L; 150 ppm in drinking water, \(n = 16\)) for 4 wk, followed by remnant kidney (RK) surgery with continuation of lead for an additional 12 wk; control rats (\(n = 9\)) were treated similarly but did not receive lead. Systolic blood pressure was associated with higher systolic blood pressure \((P < 0.05)\) and worse renal function (creatinine clearance \(1.4 \pm 0.4\) vs. \(1.8 \pm 0.5\) ml/min, RK+L vs. RK, \(P < 0.05)\), and with a tendency for greater proteinuria \((6.6 \pm 6.1\) vs. \(3.6 \pm 1.5\) mg protein/mg creatinine, RK+L vs. RK, \(P = 0.08)\). While glomerulonephropathy tended to be worse in lead-treated rats \((37.6 \pm 11\) vs. \(28.8 \pm 6\) glomeruli per section), the effect on renal histology was variable. Our primary finding is that lead can induce microvascular, inflammatory, and tubulointerstitial injury that accelerates renal disease.

12 wk after surgery, body weight was measured and pressure (SBP) was assessed as the mean value of three consecutive measurements obtained in the morning by using a tail-cuff sphygmomanometer (Visitech BP2000, Visitech Systems, Apex, NC). All animals were preconditioned for blood pressure measure-
Lead – How does it cause CVD?

Clinical evidence for lead-induced inhibition of nitric oxide formation

Abstract Lead exposure has been associated with increased cardiovascular risk, possibly from lead-induced increases in oxidative stress and depressed nitric oxide (NO) availability. However, no previous clinical study has examined whether lead exposure is associated with significant effects on biomarkers of NO activity (plasma nitrites, nitrates, and cyclic guanosine 3′,5′-monophosphate; cGMP). We investigated whether there is an association between the circulating concentrations of nitrites, nitrates, and

Keywords Cyclic GMP · Lead toxicology · Nitric oxide · Nitrates · Nitrites · Plasma lead · Whole blood lead
NO – Nitric Oxide and CVD

- Dilates blood vessels
- Reduces platelet stickiness
- Reduces oxidation of LDL cholesterol (major component of plaque)
- Reduces release of superoxide radicals
- Reduces multiplication of smooth muscle cells of the artery wall
- Reduces monocyte stickiness (prevents formation of plaque)
NO – Nitric Oxide and CVD

- Signaling molecule
- Powerful vasodilator
- Vascular endothelium involved in release of NO
- aka – endothelium-derived relaxing factor (EDRF)
- Drugs that enhance NO production:
  - NTG
  - Viagra
- “Endothelial dysfunction is the initial step in pathogenesis of atherosclerosis”
Endothelial Function and Oxidative Stress in Cardiovascular Diseases

Yukihito Higashi, MD; Kensuke Noma, MD; Masao Yoshizumi, MD; Yasuki Kihara, MD*

The vascular endothelium is involved in the release of various vasodilators, including nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor, as well as vasoconstrictors. NO plays an important role in the regulation of vascular tone, inhibition of platelet aggregation, and suppression of smooth muscle cell proliferation. Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis. Atherosclerotic diseases are associated with endothelial dysfunction. It is well known that the grade of endothelial function is a predictor of cardiovascular outcomes. Oxidative stress plays an important role in the pathogenesis and development of cardiovascular diseases. Several mechanisms contribute to impairment of endothelial function. An imbalance of reduced production of NO or increased production of reactive oxygen species, mainly superoxide, may promote endothelial dysfunction. One mechanism by which endothelium-dependent vasodilation is impaired may promote endothelial dysfunction. One mechanism by which endothelium-dependent vasodilation is impaired is an increase in oxidative stress that inactivates NO. This review focuses on recent findings and interaction between endothelial function and oxidative stress in cardiovascular diseases. (Circ J 2009; 73: 411–418)
Lead - adverse health affects

- **Mechanism of disease progression**
  - Causes - oxidative stress
  - Produces - reactive oxygen species (ROS)
  - Lowers - production of NO

- **Leads to development of diseases:**
  - HTN
  - CAD
  - IDCM
  - MI and Stroke
  - Chronic Kidney Disease (CKD)
Tests for Toxic Metals

- **Blood** – gold standard for acute exposure
- **Urine** – accepted for assessing body burden
- **Hair** – rarely recommend
Heavy Metal Testing – Blood Lead

At levels above 80 µg/dL, serious, permanent health damage may occur (extremely dangerous).

Between 40 and 80 µg/dL, serious health damage may be occurring, even if there are no symptoms (seriously elevated).

Between 25 and 40 µg/dL, regular exposure is occurring. There is some evidence of potential physiologic problems (elevated).

Between 10 and 25 µg/dL, lead is building up in the body and some exposure is occurring.

The typical level for U.S. adults is less than 10 µg/dL (mean = 3 µg/dL).
# Heavy Metal Testing - Urine

## Toxic Metals; Urine

<table>
<thead>
<tr>
<th>TOXIC METALS</th>
<th>RESULT µg/g creat</th>
<th>REFERENCE INTERVAL</th>
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<th>OUTSIDE REFERENCE</th>
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<td>&lt; 0.4</td>
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<td>&lt; 117</td>
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<td>&lt; 7</td>
<td></td>
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<td>&lt; 10</td>
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<td>Gadolinium (Gd)</td>
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<td>&lt; 0.4</td>
<td></td>
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<tr>
<td>Lead (Pb)</td>
<td>7.3</td>
<td>&lt; 2</td>
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<tr>
<td>Mercury (Hg)</td>
<td>21</td>
<td>&lt; 4</td>
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<td>Nickel (Ni)</td>
<td>12</td>
<td>&lt; 12</td>
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<tr>
<td>Palladium (Pd)</td>
<td>&lt; dl</td>
<td>&lt; 0.3</td>
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<td>Platinum (Pt)</td>
<td>&lt; dl</td>
<td>&lt; 1</td>
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<td>Tellurium (Te)</td>
<td>&lt; dl</td>
<td>&lt; 0.8</td>
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<tr>
<td>Thallium (Tl)</td>
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<tr>
<td>Thorium (Th)</td>
<td>&lt; dl</td>
<td>&lt; 0.03</td>
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<tr>
<td>Tin (Sn)</td>
<td>0.4</td>
<td>&lt; 10</td>
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<tr>
<td>Tungsten (W)</td>
<td>&lt; dl</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uranium (U)</td>
<td>0.1</td>
<td>&lt; 0.04</td>
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## Urine Creatinine

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<thead>
<tr>
<th>RESULT mg/dL</th>
<th>REFERENCE INTERVAL</th>
<th>-2SD</th>
<th>-1SD</th>
<th>MEAN</th>
<th>+1SD</th>
<th>+2SD</th>
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<tr>
<td>Creatinine</td>
<td>84.3</td>
<td>35</td>
<td>225</td>
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The most reliable methods of measuring body lead burden are bone x-ray fluorescence studies and calcium disodium EDTA mobilization tests. A per-
### Toxic Element Exposure Profile: Hair

<table>
<thead>
<tr>
<th>TOXIC METALS</th>
<th>RESULT µg/g</th>
<th>REFERENCE INTERVAL</th>
<th>68th PERCENTILE</th>
<th>95th PERCENTILE</th>
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<td>Arsenic (As)</td>
<td>0.021</td>
<td>&lt; 0.14</td>
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<tr>
<td>Lead (Pb)</td>
<td>0.38</td>
<td>&lt; 3.0</td>
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<td></td>
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<tr>
<td>Mercury (Hg)</td>
<td>0.21</td>
<td>&lt; 3.0</td>
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<tr>
<td>Cadmium (Cd)</td>
<td>0.032</td>
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<tr>
<td>Chromium (Cr)</td>
<td>0.52</td>
<td>&lt; 0.85</td>
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<tr>
<td>Beryllium (Be)</td>
<td>&lt; 0.01</td>
<td>&lt; 0.050</td>
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<td>Cobalt (Co)</td>
<td>0.010</td>
<td>&lt; 0.15</td>
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<td>Nickel (Ni)</td>
<td>0.54</td>
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<tr>
<td>Zinc (Zn)</td>
<td>170</td>
<td>&lt; 300</td>
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<tr>
<td>Copper (Cu)</td>
<td>160</td>
<td>&lt; 70</td>
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<tr>
<td>Thorium (Th)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
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<tr>
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<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
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<tr>
<td>Barium (Ba)</td>
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<td>Manganese (Mn)</td>
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<td>Selenium (Se)</td>
<td>0.70</td>
<td>&lt; 2.1</td>
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<tr>
<td>Bismuth (Bi)</td>
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<td>Vanadium (V)</td>
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<td>Silver (Ag)</td>
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<td>&lt; 1.6</td>
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<tr>
<td>Antimony (Sb)</td>
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<td>&lt; 0.12</td>
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<tr>
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<td>0.011</td>
<td>&lt; 0.015</td>
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<td>Aluminum (Al)</td>
<td>24</td>
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<td>&lt; 0.003</td>
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<td>&lt; 0.015</td>
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<td>Tin (Sn)</td>
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<td>Gold (Au)</td>
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<td>Germanium (Ge)</td>
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<td>Titanium (Ti)</td>
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<tr>
<td>Gadolinium (Gd)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.008</td>
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Treatment Strategies

- Avoid Exposure
- Sweating
- Chelation therapy
Treatment Strategies – Avoid Exposure

- **Lead**
  - Remove lead paint from your home
  - Use lead test strips
  - Drink filtered water
  - Choose herbal products tested for heavy metals
Treatment Strategies – Avoid Exposure

Lead, Mercury, and Arsenic in US- and Indian-Manufactured Ayurvedic Medicines Sold via the Internet

Robert B. Saper, MD, MPH
Russell S. Phillips, MD
Anusha Sehgal, MD(Ayurveda)
Nadia Khouri, MPH
Roger B. Davis, ScD
Janet Paquin, PhD
Venkatesh Thuppi, PhD
Stefanos N. Kales, MD, MPH

A YURVEDA IS A TRADITIONAL medical system used by a majority of India’s 1.1 billion population.\(^1\) Ayurveda is also used worldwide by the South Asian diaspora and others.\(^1\) However, since 1978 more than 80 cases of lead poisoning associated with Ayurvedic medicine use have been reported worldwide.\(^2,3\) Ayurveda divided into only and \textit{rasa} an ancient practice involving herbs (curry, lead, iron), and gynandra experts claim that these medicines, if properly prepared and administered, are safe and therapeutic.\(^4,5\) Of 70 Ayurvedic medicines manufactured in South Asia and sold in Boston, Massa-

Context Lead, mercury, and arsenic have been detected in a substantial proportion of Indian-manufactured traditional Ayurvedic medicines. Metals may be present due to the practice of \textit{rasa shastra} (combining herbs with metals, minerals, and gems). Whether toxic metals are present in both US- and Indian-manufactured Ayurvedic medicines is unknown.

Objectives To determine the prevalence of Ayurvedic medicines available via the Internet containing detectable lead, mercury, or arsenic and to compare the prevalence of toxic metals in US- vs Indian-manufactured medicines and between \textit{rasa shastra} and non-\textit{rasa shastra} medicines.

Design A search using 5 Internet search engines and the search terms \textit{Ayurveda} and \textit{Ayurvedic medicine} identified 25 Web sites offering traditional Ayurvedic herbs, formulas, or ingredients commonly used in Ayurveda, indicated for oral use, and available for sale. From 673 identified products, 230 Ayurvedic medicines were randomly selected for purchase in August-October 2005. Country of manufacturer/Web site supplier, \textit{rasa shastra} status, and claims of Good Manufacturing Practices were recorded. Metal concentrations were measured using x-ray fluorescence spectroscopy.

Main Outcome Measures Prevalence of medicines with detectable toxic metals in the entire sample and stratified by country of manufacture and \textit{rasa shastra} status.

Results One hundred ninety-three of the 230 requested medicines were received and analyzed. The prevalence of metal-containing products was 20.7\% (95\% confidence interval, 11.3\%–30.1\%) and higher mercury (20.800 \%) were sold. All metals take of toxic metals.

Conclusion One-fifth of both US-manufactured and Indian-manufactured Ayurvedic medicines purchased via the Internet contain detectable lead, mercury, or arsenic.

\textit{JAMA.} 2008;300(8):915-923

www.jama.com
Treatment Strategies – Sweating

- Sauna and Exercise remove heavy metals
Treatment Strategies – Sweating

Review Article
Arsenic, Cadmium, Lead, and Mercury in Sweat: A Systematic Review

Margaret E. Sears,1,2 Kathleen J. Kerr,3,4 and Riina I. Bray3,4

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2Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, ON, Canada K1Y 4E9
3Environmental Health Clinic, Women’s College Hospital, Toronto, ON, Canada M5S 1B2
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Received 16 July 2011; Accepted 23 October 2011

Undoubtedly further research in this area would improve understanding, but the available evidence suggests that physicians could consider recommending sweating as tolerated via exercise (preferred) and/or use of a sauna as a low-risk, potentially beneficial treatment for individuals who may be experiencing effects of toxic elements, or for individuals with regular exposure to or accretion of toxicants.

with endurance compared with intensive exercise. Mercury levels normalized with repeated saunas in a case report. Sweating deserves consideration for toxic element detoxification. Research including appropriately sized trials is needed to establish safe, effective therapeutic protocols.
Repeated sauna therapy improves myocardial perfusion in patients with chronically occluded coronary artery-related ischemia.

The Second Department of Internal Medicine, Graduate School of Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan.

Abstract

BACKGROUND: Repeated low-temperature sauna (Waon) therapy relieves ischemic symptoms in patients with peripheral arterial disease. We investigated whether Waon therapy could improve myocardial perfusion in patients with ischemia related to chronic total occlusion (CTO) of coronary arteries.

METHODS: Twenty-four patients who had ischemia in the CTO-related area were examined. The severity of ischemia was quantified by thallium-201 myocardial perfusion scintigraphy with adenosine. The Waon group (n=16) was treated daily for three weeks with a 60°C far infrared-ray dry sauna bath for 15min and then kept in a bed covered with blankets for 30min. The control group (n=8) underwent myocardial perfusion scintigraphy twice with a three-week interval.

RESULTS: In the control group, neither summed stress score (SSS) nor summed difference score (SDS) of myocardial scintigraphy changed. However, Waon therapy improved both SSS (16±7 to 9±6, p<0.01) and SDS (7±4 to 3±2, p<0.01), and the improvement was greater in patients with higher SSS and SDS scores at the baseline. Waon therapy extended treadmill exercise time (430±185 to 511±192s, p<0.01) and improved flow-mediated dilation of the brachial artery (4.1±1.3 to 5.9±1.8%, p<0.05), but tended to decrease the number of circulating CD34-positive bone marrow-derived cells.

CONCLUSIONS: Waon therapy improves CTO-related myocardial ischemia in association with improvement of vascular endothelial function. This therapy could be a complementary and alternative tool in patients with severe coronary lesions not suitable for coronary intervention.
Treatment Strategy – Chelation therapy

- Removal of toxic metals
- May improve CVD and renal insufficiency
# Table of chelating agents

<table>
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<tr>
<th>Chelating Agent</th>
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<th>Route</th>
<th>Drug</th>
</tr>
</thead>
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<tr>
<td>Dimercaprol (BAL)</td>
<td>Arsenic Lead</td>
<td>i.m.</td>
<td>Dimercaptol Injection B.P. BAL in Oil</td>
</tr>
<tr>
<td></td>
<td>Mercury (inorganic)</td>
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</tr>
<tr>
<td>Dimercaptosiccinic acid</td>
<td>Arsenic Lead</td>
<td>p.o.</td>
<td>Chemet</td>
</tr>
<tr>
<td>(DMSA, Succimer)</td>
<td>Mercury</td>
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<tr>
<td>Dimercaptopropanesulfonate (DMPS)</td>
<td>Arsenic Mercury</td>
<td>p.o.</td>
<td>Bulk form (for compounding by pharmacists)</td>
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<tr>
<td></td>
<td></td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td>D-pencillamine</td>
<td>Arsenic Mercury</td>
<td>p.o.</td>
<td>Metalcaptase</td>
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<tr>
<td></td>
<td>Lead</td>
<td></td>
<td>Pencillamine</td>
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<td></td>
<td></td>
<td></td>
<td>Cuprimine</td>
</tr>
<tr>
<td></td>
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<td>Depen</td>
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<tr>
<td>Ethylenediaminetetraacetic acid</td>
<td>Iron</td>
<td>IV</td>
<td>Chealamide Versenate</td>
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<tr>
<td>(EDTA) (Edetate disodium)</td>
<td>Lead</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Cadmium Aluminum</td>
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</table>
Definition of Chelation Therapy

- The word *chelate* is derived from the Greek word *chele* (claw of a crab) implying the firm binding action of a chemical to a metal ion.

- **Morgan** and **Drew** defined the term *chelation* in 1920 as - the incorporation of a *metal ion* into a **Heterocyclic Ring Structure**
Heterocyclic Ring Structure in Nature

Chlorophyll is a chelate of Magnesium

PORPHYRIN RING (light-absorbing “head” of molecule)
Hemoglobin is a chelate of Iron
(EthyleneDiamineTetraacetic Acid)

Octahedral structure:
- The EDTA molecule binds to a mineral or metal cation by donating up to 6 electron groups.
- By binding at these positions, a cation is surrounded by the EDTA molecule to form an 8 sided (octahedral) structure.

Calcium DiSodium EDTA

Hemoglobin
EDTA: Improves Renal Insufficiency

Chelation Therapy for Patients with Elevated Body Lead Burden and Progressive Renal Insufficiency
A Randomized, Controlled Trial
Ja-Liang Lin, MD; Huei-Huang Ho, MD; and Chun-Chen Yu, MD

Background: Nephropathy is known to occur in persons exposed to high levels of lead, but the question of whether long-term exposure to low levels of environmental lead is associated with impaired renal function remains controversial.

Objective: To examine whether chelation therapy slows the progression of renal insufficiency in patients with mildly elevated body lead burden.

Setting: Academic medical center in Taiwan.

Patients: 32 patients with chronic renal insufficiency (serum creatinine level > 132.6 μmol/L [1.5 mg/dL] and < 353.8 μmol/L [4.0 mg/dL]), mildly elevated body lead burden (>0.72 μmol [150 μg] of lead per 72-hour urine collection and < 2.90 μmol [600 μg] of lead per 72-hour urine collection [EDTA mobilization tests]), and no history of heavy lead exposure.

Intervention: The treatment group received 2 months of chelation therapy; the control group received no therapy.

Measurements: The reciprocal of serum creatinine (1/Cr) was used as an index of progressive renal insufficiency.

Results: Rates of progression of renal insufficiency were similar in the treatment group and the control group during a 12-month baseline observation period (1/Cr, 0.000054 U/μmol per month compared with 0.000046 U/μmol per month; P > 0.2). After the 2-month treatment

Conclusion: Chelation therapy seems to slow the progression of renal insufficiency in patients with mildly elevated body lead burden. This implies that long-term exposure to low levels of environmental lead may be associated with impaired renal function in patients with chronic renal disease.

Nephropathy related to exposure to high levels of lead has been well investigated (1-4), but it is still not clear whether exposure to low levels of environmental lead can impair renal function. Several recent epidemiologic studies (5-7) showed that serum creatinine level or creatinine clearance is inversely associated with levels of lead in the blood. However, these studies did not elucidate the causal relation between exposures to lead and outcomes. In addition, although EDTA chelation therapy has been used to treat chronic lead-related nephropathy in a few persons with occupational exposure to lead (2, 3), the efficacy of this therapy in patients exposed to low levels of lead is unknown.

We studied patients with chronic renal insufficiency, mildly elevated body lead burden, and no previous known heavy lead exposure to examine the association between chronic exposure to low levels of environmental lead and progression of renal insufficiency.

Methods

Participants

One hundred two patients with abnormal renal function (serum creatinine level > 132.6 μmol/L [1.5 mg/dL] and < 353.8 μmol/L [4.0 mg/dL]) who had been followed for at least 1 year in the outpatient department of our institution were examined for possible inclusion in our study. To avoid the possibility that changes in the rate of progression of renal insufficiency are due to other factors, patients with malignant hypertension, urinary tract infection, hypercalcemia, or drug-induced nephrotoxicity were
Environmental Lead Exposure and Progressive Renal Insufficiency

Ja-Liang Lin, MD; Dan-Tzu Tan, RN; Kuan-Huang Hsu, PhD; Chun-Chen Yu, MD

**Background:** Several recent studies show that serum creatinine level or creatinine clearance is inversely associated with blood lead levels. However, the studies do not allow direct inferences about causality.

**Objective:** To evaluate the relation between blood lead burden (BLB) and progressive renal insufficiency in patients without previous heavy lead exposure.

**Design:** A prospective, longitudinal study with a controlled clinical trial.

**Patients:** One hundred ten patients with chronic renal insufficiency (serum creatinine level, 133-354 μmol/L [1.5-4.0 mg/dL]) and normal BLB (EDTA mobilization tests, <600 μg per 72-hour urine collection) and a history of previous heavy lead exposure were divided into 2 groups according to BLB: the high-normal BLB group (BLB ≥80 μg and <600 μg) and the low-normal BLB group (BLB <80 μg). Patients were prospectively followed up for 2 years.

**Main Outcome Measures:** The primary outcome was a 1.5 times increase in the initial creatinine level. The secondary outcome was a change over time in the serum creatinine clearance. At the end of follow-up, a 3-month clinical trial with chelation therapy for patients with high-normal BLB was performed to clarify the role of environmental lead exposure in progressive renal insufficiency. After chelation therapy, significant improvement in renal function was noted. In addition, the effect of improving renal function lasted for more than 12 months in these patients.

**Conclusions:** Long-term low-level environmental lead exposure may subtly affect progressive renal insufficiency in the general population. Progressive renal insufficiency may be improved for at least 1 year after lead-chelating therapy. Further investigations are needed to clarify this observation.

*Arch Intern Med. 2001;161:264-271*
EDTA: Improves Renal Insufficiency – 24mo

Environmental Lead Exposure and Progression of Chronic Renal Diseases in Patients without Diabetes

Ja-Liang Lin, M.D., Dan-Tzu Lin-Tan, R.N., Kuang-Hung Hsu, Ph.D., and Chun-Chen Yu, M.D.

ABSTRACT

BACKGROUND

Previous research suggests that environmental lead exposure correlates with age-related decreases in renal function.

METHODS

Two hundred two patients with chronic renal insufficiency (indicated by a serum creatinine level of at least 1.5 mg/dl) were divided into an experimental lead-chelation and a control group. The experimental chelation group received lead-chelation therapy with calcium disodium EDTA, and the control group received placebo. During the ensuing 24 months, repeated chelation therapy was administered weekly to 32 patients with high-normal body lead burdens (at least 80 μg but less than 600 μg) unless on repeated testing the body lead burden fell below 60 μg; the other 32 patients served as controls and received weekly placebo infusions for 5 weeks every 6 months. The primary end point was an increase in the serum creatinine level to 1.5 times the baseline value during the observation period. A secondary end point was the change in renal function during the intervention period.

RESULTS

The primary end point occurred in 24 patients during the observation period; the serum creatinine levels and body lead burden at baseline were the most important risk factors. The glomerular filtration rate improved significantly by the end of the 27-month intervention period in patients receiving chelation therapy: the mean (±SD) change in the glomerular filtration rate in the patients in the chelation group was 2.1±5.7 ml per minute per 1.73 m² of body-surface area, as compared with -6.0±5.8 ml per minute per 1.73 m² of body-surface area in the controls (P<0.001). The rate of decline in the glomerular filtration rate in the chelation group was also lower than that in the controls.

CONCLUSIONS

Low-level environmental lead exposure may accelerate progressive renal insufficiency in patients without diabetes who have chronic renal disease. Repeated chelation therapy may improve renal function and slow the progression of renal insufficiency.
EDTA: Improves Renal Insufficiency – 48mo

Long-term outcome of repeated lead chelation therapy in progressive non-diabetic chronic kidney diseases

Dan-Tzu Lin-Tan, Ja-Liang Lin, Tzung-Hai Yen, Kuan-Hsing Chen and Yen-Lin Huang

Divisions of Nephrology, Chang Gung Memorial Hospital, Lin-Kou Medical Center, Medical College of Chang Gung University/Taipei, Taiwan, ROC

Abstract

Background. Previous research suggest that repeated lead-chelation therapy decelerates progression of renal insufficiency in non-diabetic (non-DM) patients with high-normal body lead burden (BLB). Study findings are limited by relatively short-term follow-up and small sample size.

Methods. A total of 116 non-DM patients with chronic kidney diseases (serum creatinine level of 1.5–3.9 mg/dl), high-normal BLB (>60 μg and <600 μg) and no lead exposure history were randomly assigned to a chelation or control group in this 4-year clinical trial. For 3 months, the 58 chelation group patients received initial lead-chelation therapy with calcium disodium EDTA, and the 58 control group patients received placebo. During the ensuing 48 months, repeated chelation therapy was administered weekly to chelation group patients unless, on repeated testing, BLB was <60 μg; the control group patients received weekly placebo infusions for 5 weeks at 6-month intervals.

Results. Mean change in the glomerular filtration rate (GFR) in the chelation group was $-1.8 \pm 8.8 \text{mL/min/1.73m}^2$, as compared with $-12.7 \pm 8.4 \text{mL/min/1.73m}^2$ in the control group ($p < 0.0001$) at study end. Chelation group rates of decline in the GFR was lower than that in the control group, although they had similar decline rates before chelation. At study end, 18 patients, including 15 control group patients, had elevated serum creatinine levels. In the control group, 18 patients had elevated serum creatinine levels. In the control group, 18 patients had elevated serum creatinine levels.

Conclusions. Repeated chelation therapies can, over a four-year period, slow progression of renal insufficiency in non-DM patients with high-normal BLB.

Keywords: body lead burden; glomerular filtration rate; long-term outcome; progression of renal insufficiency; repeated chelation therapy

Introduction

The renal toxic effects of lead are well established [1]. The most accurate technique for measuring body lead burden (BLB) are bone X-ray fluorescence and calcium disodium EDTA (ethylene-diamine-tetraacetate) mobilizations because blood lead levels (BLL) only reflect recent exposure to lead [2]. A person who has a BLB of <600 μg, as assessed by EDTA mobilization, is considered to have a normal BLB [2]. Clinical studies [3–8] utilizing EDTA-mobilization tests to determine BLB of chronic kidney disease (CKD) patients without known lead exposure indicate that long-term low-level environmental lead exposure is associated with renal insufficiency progression. A placebo-controlled, randomized, 2-year clinical trial [9] that repeated lead chelation therapy decreased progressive renal insufficiency in patients with CKD and high-normal BLB, even when related factors that influence levels were well controlled [10–15]. Additionally, none (0/32) of the chelation group patients had elevated serum creatinine concentrations ≥50% during treatment with repeated chelation therapy to maintain BLB <60 μg, compared with 21.9% (7/32) of patients in the placebo group. Since a relatively small sample size and short duration of follow-up were noted limitations in the previous study, this 51-month placebo-controlled clinical trial assessed the long-term effect of repeated chelation in progression of renal insufficiency of 116 patients with high-normal BLB.
EDTA: How does it Improve CVD?

Background: Chelation therapy with sodium edetate (EDTA) improved renal function and slowed the progression of renal insufficiency in patients subjected to lead intoxication. This study was performed to identify the underlying mechanism of the ability of EDTA treatment to protect kidneys from damage.

Induced by 90 minutes ischemia followed by 90 minutes reperfusion, renal ischemic damage was evaluated by histological studies and by functional studies, namely serum creatinine and blood urea nitrogen levels. Treatment with EDTA was performed 30 minutes before the induction of ischemia. Polymorphonuclear cell (PMN) adhesion capability, plasmatic nitric oxide (NO) levels and endothelial NO synthase (eNOS) renal expression were studied as well as the EDTA protection from the TNFα-induced vascular leakage in the kidneys. Data was compared by two-way analysis of variance followed by a post hoc test.

Results: EDTA administration resulted in the preservation of both functional and histological parameters of rat kidneys. PMN obtained from peripheral blood of EDTA-treated ischemized rats, displayed a significant reduction in the expression of the adhesion molecule Mac-1 with respect to

Conclusion: This data provides evidence that EDTA treatment is able to protect rat kidneys from ischemic damage possibly through the stimulation of NO production.
EDTA Chelation Therapy

An Intravenous treatment used for:

- **FDA approved uses:**
  - Removing heavy metals (lead) - CaEDTA
  - Treating hypercalcemia - NaEDTA
  - Controlling ventricular arrhythmias secondary to digitalis toxicity - NaEDTA

- **Non-FDA approved uses:**
  - Treating chronic heavy metal accumulation
  - Treating Renal Insufficiency
  - Management of atherosclerosis
EDTA – Biochemistry of Chelation

- **In Vitro Factors:**
  - **pH** - In low pH (more acidic), EDTA chelates become less stable and will release its ion more easily.
  - **Binding Constant** - The higher the binding constant, the stronger a cation is bound to EDTA.
  - **Concentration** - The higher the concentration of a cation, the more likely it is to bind to EDTA.
### EDTA - In Vitro Binding Constants

<table>
<thead>
<tr>
<th>Metal Cation</th>
<th>Log K</th>
<th>Metal Cation</th>
<th>Log K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr²⁺ (Chromium)</td>
<td>????</td>
<td>Cd²⁺ (Cadmium)</td>
<td>16.5</td>
</tr>
<tr>
<td>Fe³⁺ (Iron)</td>
<td>25.1</td>
<td>Co²⁺ (Cobalt)</td>
<td>16.3</td>
</tr>
<tr>
<td>Hg²⁺ (Mercury)</td>
<td>21.8</td>
<td>Al³⁺⁺ (Aluminum)</td>
<td>16.1</td>
</tr>
<tr>
<td>Cu²⁺ (Copper)</td>
<td>18.8</td>
<td>Fe²⁺ (Iron)</td>
<td>14.3</td>
</tr>
<tr>
<td>Pb²⁺ (Lead)</td>
<td>18.5</td>
<td>Mn²⁺ (Manganese)</td>
<td>13.7</td>
</tr>
<tr>
<td>Ni²⁺ (Nickle)</td>
<td>18.0</td>
<td>Ca²⁺ (Calcium)</td>
<td>10.7</td>
</tr>
<tr>
<td>Zn²⁺ (Zinc)</td>
<td>16.5</td>
<td>Mg²⁺ (Magnesium)</td>
<td>8.7</td>
</tr>
</tbody>
</table>
In Vivo binding constants Special considerations

- **pH** - is not as much a factor in clinical practice due to the tight regulation of physiologic buffers.
  - High pH (basic pH) *in vitro* is associated with greater binding stability.
  - It is still important to encourage an alkaline diet as part of the chelation protocol to optimize outcomes.
In Vivo binding constants **Special considerations**

- **Concentration of Metals**
  - Through mass action – a high concentration of lower binding constant metals can displace metals of greater stability when they are present in low concentrations.
  - For example, **Calcium** is low in the stability constant table, however, a great deal of it is chelated by NaEDTA, because of its relative high concentration in the plasma.
  - This is why a patient may become hypocalcemic and it is unsafe to infuse NaEDTA quickly.
In Vivo binding constants **Special considerations**

- **Concentration of Metals**
  - Although the binding constant for **zinc** is in the moderate range, great quantities of **Zinc** are removed with EDTA because of the relatively high concentration of **Zinc** in the body.

  **Important**
  
  - This is why **Zinc** must be replenished when a patient undergoes a course of EDTA chelation therapy.
In Vivo binding constants Special considerations

- **Binding constants** help direct treatment plan
  - **Fe+++** (ferric iron) has a high binding constant and is **easily removed with EDTA**.
  - This is good for patients with iron overload (hemochromatosis)
  - This may be bad for patients with iron deficiency anemia
In Vivo binding constants  

**Special considerations**

- The binding of **Mercury (Hg)** to EDTA **In Vivo** is not consistent with it’s binding constant
  - Although **mercury** has a relatively high binding constant **In Vitro**, EDTA does not extract much **mercury** out of the tissues **In Vivo**.
  - This is because **mercury** is extremely tightly bound to organic Sulfhydryal groups in tissues.
Commercial preparations of EDTA

IMPORTANT

- **DiSodium EDTA (NaEDTA)** – approved by the FDA for use in:
  - Hypercalcemia
  - Ventricular Arrhythmias associated with Digitalis Toxicity
- **Calcium DiSodium EDTA (CaEDTA)** – approved by the FDA for:
  - Removal of lead and other heavy metals
    - It is excreted primarily by the kidney with about 50% excreted in one hour and over 95% excreted within 24 hours.
    - Almost none of the compound is metabolized
    - Only about 5% is absorbed from oral administration
**WARNING**

**NaEDTA** must only be given by the intravenous (IV) route. If it is administered intramuscularly (IM), the patient will experience severe pain associated with tissue sloughing at the injection site.

**NaEDTA** must only be given by slow IV infusion at 1gm / hour (16mg/min) or less.
Precautions for using EDTA:

- **Drug Interactions:** None Known
- **Pregnancy:** Category B (however, EDTA should **NOT** be used during pregnancy!)
- **Nursing Mothers:** It is unknown whether CaEDTA is excreted in mother’s milk. Caution should be exercised if it is used.
- **Pediatric Use:** Since lead poisoning occurs in children and adults, but is more severe in children, CaEDTA is used in all ages.
Precautions for using EDTA:

- **Contraindications:** Severe allergy to EDTA, pregnancy, anuria or acute lead encephalopathy.
- **Relative Contraindications:** Renal dialysis
- **Possible Side Effects:**
  - Nephrotoxicity – very rare if infused at proper rate, dose and frequency
  - Minimize this risk by re-checking kidney function tests every 5 to 10 treatments and adjust EDTA dose based on creatinine clearance
Precautions for using EDTA:

- **Possible Side Effects:**
  - **Hypocalcemia** – Occurs if infused too rapidly or in excessive doses
    - Watch for muscle cramps, numbness and tingling
    - May be reversed with IV Calcium gluconate
  - **Allergy** – True allergy to EDTA is rare
    - Allergic symptoms more likely from an admixture ingredient or preservative
    - Typically allergy to lidocaine or B-vitamin
    - Try to get preservative free ingredients
Precautions for using EDTA:

- **Possible Side Effects:**
  - **Thrombophlebitis** – From local irritation at the infusion site

- **Prevention** of thrombophlebitis:
  - Use Heparin 1000iu to 5000iu in infusion mixture
  - Buffer to physiologic pH with Bicarbonate
  - Use a larger vein
  - Reduce the rate of infusion

- **Treatment** – topical moist heat, NSAIDS, arnica, bromelain
Precautions for using EDTA:

**Possible Side Effects:**

- **Congestive Heart Failure** – In patients with cardiovascular disease, the increased fluid load of the chelation may aggravate CHF.
  - Weigh cardiac patients each visit
  - Continue diuretic use and increase dose if needed
  - Decrease sodium content of infusion (IV Vit C contains 11% sodium by weight)
  - Slow the infusion rate
  - Decrease the calculated therapeutic dose of EDTA in proportionally less fluid
Precautions for using EDTA:

- Possible Side Effects:
  - **Hypoglycemia** – Blood glucose may fall during an EDTA IV
    - Ensure adequate protein intake before and during IV
    - Patients should bring a fruit snack
    - A 50% dextrose solution for IV use should be readily available.
  - **Fatigue** – patients may complain of feeling “washed out” for 24-48hrs after a single treatment
    - Use IV nutritional infusions without EDTA in between chelation treatments
    - Increase interval between treatments
Before initiating chelation therapy always:

- Perform an H&P on your patient.
- Check
  - Liver function tests
  - BUN / Cr, UA and Creatinine clearance
  - CBC with Dif, electrolytes, EKG
  - Whole blood lead and provoked urine lead levels
  - condition specific work-up.
- Inform patient of risks and benefits of NaEDTA:
  - Pain / bleeding at infusion site
  - Hypoglycemia
  - Renal toxicity
  - Zinc deficiency
Minimize Pain

Use Magnesium

- Reduce the discomfort of the infusion by releasing the heat in the bottle instead of the patient.
- The combination of NaEDTA with Magnesium in the infusion bottle prior to administration releases eight (8) kcal of heat in an Exothermic reaction.
Minimize Pain

Alkinalize the solution

- Pain at the infusion site can be due to **acidity** of the solution. The EDTA solution becomes acidic due to the release of Hydrogen ions when Mg\(^{++}\) is added to the EDTA. (As the Mg\(^{++}\) is chelated by EDTA in the bottle, H\(^+\) (hydrogen ions) are released).
- The carrier solution can be made more alkaline by adding **Sodium Bicarbonate**
Minimize Pain

Create an Isotonic solution

- Care must be taken to choose the ingredients for the carrier solution to balance the osmolarity. Pain will occur if the solution is Hypertonic (too concentrated) or Hypotonic (too dilute) in relation to the normal osmolarity of blood.
- An isotonic solution has a similar concentration to blood.
# IV Na EDTA Chelation Protocol – 50mg/kg/day at 1gm/hour

<table>
<thead>
<tr>
<th>Volume</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>250cc – 500cc</td>
<td>Sterile Water</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Pyridoxine (Vitamin B6) (100mg/cc)</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Thiamine (Vitamin B1) (100mg/cc)</td>
</tr>
<tr>
<td>10cc</td>
<td>Sodium Bicarbonate (1mEq/ml)</td>
</tr>
<tr>
<td>5cc</td>
<td>Procaine 1% or Lidocaine 1%</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Vitamin B5 (250mg/cc)</td>
</tr>
<tr>
<td>10.0cc</td>
<td>Vitamin C (500mg/cc)</td>
</tr>
<tr>
<td>2.0cc</td>
<td>Magnesium Chloride</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Potassium Chloride (2mEq/cc)</td>
</tr>
<tr>
<td>10 - 20cc</td>
<td>DiSodium EDTA (150mg/cc) adjust per Cackcroft Gault Formula</td>
</tr>
<tr>
<td>0.25cc</td>
<td>Heparin (1000U/cc)</td>
</tr>
<tr>
<td>Volume</td>
<td>Medication</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>100cc</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Vitamin B6 (100mg/cc)</td>
</tr>
<tr>
<td>0.25cc</td>
<td>Vitamin B1 (100mg/cc)</td>
</tr>
<tr>
<td>0.25cc</td>
<td>B complex 100</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Vitamin B12 (1000mcg/cc)</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Vitamin B5 (250mg/cc)</td>
</tr>
<tr>
<td>3.0cc</td>
<td>Vitamin C (500mg/cc)</td>
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<tr>
<td>2.0cc</td>
<td>Magnesium Chloride (200mg/cc)</td>
</tr>
<tr>
<td>1.0cc</td>
<td>Potassium Chloride (2Meq/cc)</td>
</tr>
<tr>
<td>5 – 10cc</td>
<td>Calcium DiSodium EDTA (300mg/cc) adjust per Cackcroft Gault Formula</td>
</tr>
<tr>
<td>0.1cc</td>
<td>Heparin (1000U/cc)</td>
</tr>
</tbody>
</table>
Summary

1. Relevance of TACT trial
   - EDTA may reduce recurrence of ischemia
2. Connection between toxic metals, CVD and EDTA
   - Nitric oxide
3. Tests for Toxic metals
   - Pre and post provoked heavy metal test
4. Treatment strategies for CVD and Toxic metals
   - Avoid exposure
   - You can safely administer EDTA chelation therapy
Case Study CaEDTA: Mr D.

- 81 year old male in good state of health presents with concerns about fatigue and memory changes. (He has trouble remembering names.)
- Pmhx – CAD, MI, hypercholesterolemia
- Pshx – CABG x3 - Dec. 1984
- Meds – ASA, Atenolol, Plavix
- Occupation – Supervisor at Bear Sterns
- Requests chelation therapy
Mr D cont’d…

- Ht: 5’ 3”
- Wt: 162lbs
- Cr: 1.2
- Blood lead: 4 mcg/dl (ref range <10)
- EDTA dose calculated to be >3.0gm
- Provoked tests done with 1.5gm CaEDTA
- Treatment done with 2.0gm CaEDTA
### URINE TOXIC METALS

#### POTENTIALLY TOXIC METALS

<table>
<thead>
<tr>
<th>METALS</th>
<th>RESULT µg/g CREAT</th>
<th>REFERENCE RANGE</th>
<th>WITHIN REFERENCE RANGE</th>
<th>ELEVATED</th>
<th>VERY ELEVATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>62</td>
<td>&lt; 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony</td>
<td>&lt; dl</td>
<td>&lt; 0.6</td>
<td></td>
<td></td>
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<tr>
<td>Arsenic</td>
<td>61</td>
<td>&lt; 120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beryllium</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>&lt; 0.7</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Thorium</td>
<td>&lt; dl</td>
<td>&lt; 0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tin</td>
<td>1.3</td>
<td>&lt; 9</td>
<td></td>
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</tr>
<tr>
<td>Tungsten</td>
<td>&lt; dl</td>
<td>&lt; 0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>2.6</td>
<td>&lt; 2</td>
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<tr>
<td>Lead</td>
<td>44</td>
<td>&lt; 5</td>
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<tr>
<td>Mercury</td>
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<td>&lt; 3</td>
<td></td>
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</tr>
<tr>
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<td>7.4</td>
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<tr>
<td>Platinum</td>
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<td>&lt; 1</td>
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</table>

#### CREATININE

<table>
<thead>
<tr>
<th>RESULT mg/dL</th>
<th>REFERENCE RANGE</th>
<th>2SD LOW</th>
<th>1SD LOW</th>
<th>MEAN</th>
<th>1SD HIGH</th>
<th>2SD HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>24</td>
<td>45 - 225</td>
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#### SPECIMEN DATA

- **Comments:**
  - Date Collected: 8/21/2007
  - Method: ICP-MS
  - Collection Period: timed: 6 hours
  - Date Received: 8/23/2007
  - <dl: less than detection limit
  - Volume: 1,850 mL
  - Provoking Agent: CA EDTA
  - Provocation: POST PROVOCATIVE

Toxic metals are reported as µg/g creatinine to account for urine dilution variations. Reference ranges are representative of a healthy population under non-challenge or non-provoked conditions. No safe reference levels for toxic metals have been established.

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After 10 CaEDTA tx

- Improved
- Memory
- Energy

### URINE TOXIC METALS

#### POTENTIALLY TOXIC METALS

<table>
<thead>
<tr>
<th>METALS</th>
<th>RESULT µg CREAT</th>
<th>REFERENCE RANGE</th>
<th>WITHIN REFERENCE RANGE</th>
<th>ELEVATED</th>
<th>VERY ELEVATED</th>
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<td>Nickel</td>
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</tr>
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<tr>
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<tr>
<td>Tin</td>
<td>1.8</td>
<td>&lt; 9</td>
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</tr>
<tr>
<td>Tungsten</td>
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<td></td>
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<tr>
<td>Uranium</td>
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<td>&lt; 0.1</td>
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#### CREATININE

<table>
<thead>
<tr>
<th>RESULT mg/dL</th>
<th>REFERENCE RANGE</th>
<th>2SD LOW</th>
<th>1SD LOW</th>
<th>MEAN</th>
<th>1SD HIGH</th>
<th>2SD HIGH</th>
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<tbody>
<tr>
<td>Creatinine</td>
<td>38</td>
<td>45-225</td>
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</table>

#### SPECIMEN DATA

- Comments: Method: ICP-MS  
- Collection Period: timed: 6 hours  
- Volume: 800 ml  
- Provocation: POST PROVOCATIVE

Toxic metals are reported as µg/g creatinine to account for urine dilution variations. Reference ranges are representative of a healthy population under non-challenge or non-provoked conditions. No safe reference levels for toxic metals have been established.
Case Study NaEDTA: Mrs B

- 78 y.o. Female patient present for second opinion on Carotid Endarterectomy, s/p R retinal artery branch occlusion and Carotid Doppler showing B/L Internal carotid artery 50-59% stenosis.
- Patient complained of fatigue, change in vision right eye
- EKG, Holter monitor and Echo showed no source for embolisation.
- Refused TEE
- Refused Carotid Endarterectomy
• Evaluation from Cardiologist #1 4/28/2005
  • Recommendations:
    • TEE
    • Urgent consultation with vascular surgeon for carotid endarterectomy
  • Medical treatment:
    ▪ ACE inhibitor, statin medication, ASA
  • Patient refused all treatment
Thank you for referring Ms. Burns for cardiologic evaluation. As you know, she is a 78 year old woman who recently suffered sudden right visual loss, due to a retinal artery branch occlusion supplying the right upper retinal field; this was, as you know, evaluated expertly by Dr. Levitsky. She was started on aspirin by you, and I suggested increasing it to 325 mg/d pending completion of evaluation.

She denies any cardiac symptoms, including chest pain, dyspnea, palpitations, syncope, edema, other neurologic symptoms, or claudication.

As her past medical history is well known to you, I will not recite it here. Her father had an MI at age 73.

Physical examination reveals blood pressure of 132/70 and pulse of 88 and regular. The remainder of the cardiopulmonary examination reveals only a pectus excavatum; the remainder is normal.

ECG reveals sinus rhythm at 60-70 bpm, with frequent APC’s, and minimal (1/4 mm) upsloping ST depressions in V5 and V6.

Recent cardiac testing has been forwarded to you; carotid Doppler revealed 50-60% bilateral internal carotid stenosis; echocardiography was a technically difficult study, but did not reveal an obvious source of embolism and had no major abnormalities; Holter monitor did not reveal atrial fibrillation or flutter. Limited additional echo today, performed due to technically difficult echo imaging due to closely spaced ribs and pectus deformity, revealed significant aortic arch and abdominal aortic atherosclerotic plaque, with possible small emboli in transit apparently visualized.

After lengthy discussions today and on 4/24/06 regarding the evaluation of stroke and all diagnostic and therapeutic implications, she has declined to undergo recommended transesophageal echocardiography. She is also reluctant to add a statin and ACEI as I have strongly advised.

The exact cause of Ms. Burns' retinal stroke (permanent / persistent visual defect at this point) is not fully certain, but it could clearly be explained by embolization from her moderate stenosis of the right internal carotid artery. Likewise, it could be explained by the patient's refusal of TEE.
Recommended therapy for symptomatic carotid stenosis of > 50% narrowing would be carotid endarterectomy, aspirin, statin, and ACE inhibitor. Urgent consultation with a vascular surgeon of your choice was advised, but she declines both surgery and even a vascular surgery consultation at present. Based on the presence of a cardiac antibody, I doubt it would affect therapy, given the probable source of embolism from the carotid artery and/or aortic arch.

The full differential diagnosis of stroke and embolism, as well as all diagnostic and therapeutic implications of findings to date, were discussed in great detail with Ms. Burns. She declines TEE, agrees to continue aspirin at 325 mg/d with food, and is non-committal about my recommendation to add a statin (regardless of LDL level) and atorvastatin. She also declines to see a vascular surgeon as I advised her to do. She understands the serious risk of stroke, embolism, disability, blindness, and death. She is non-committal about whether she wants me to just perform cardiovascular testing only for her, or whether she wishes for me to join in her care. It appears for now that she wishes that I perform the tests only, and that she will follow up with you and with Dr. Levitsky. Follow up carotid Doppler in 1 year, and echocardiography in about 2 years, was advised. Given her frequent APC's, TSH should be checked, if not already done. BP should be well controlled; she states her BP is always normal, and lower than it was here today.

Given diffuse atherosclerotic disease and minimal non-specific repolarization changes on ECG, an exercise myoview stress test was recommended, which she declined. Ms. Burns requested that I would only see her as needed, and for future cardiovascular testing.

Thank you again for referring Ms. Burns; as always, you have my warmest personal regards.

Best wishes,

Richard L. Mueller, MD, FACC, FACP, FASE
RM/fm
cc: Dr. Levitsky

1/27/06
Evaluation by me on 6/2006

- 78 yo Female patient c/o fatigue and recent change in R visual field s/p R Retinal artery branch occlusion.
- PE – WNL except noticeable pale skin color and malaise
- Lab work WNL
- NaEDTA 3.0 gm qwk x 40 treatments
- After chelation, refer to new cardiologist for second opinion and retesting when complete course of treatment
30 March 2007

Jeffrey Morrison, M.D.
103 5\textsuperscript{th} Ave.—6\textsuperscript{th} Fl.
N.Y. N.Y. 10003

Dear Jeff,

Thank you for referring Ms. Burns for cardiac evaluation. She has suffered a right retinal embolic event in 2005, although a definite cardiac source was not identified. There was no evidence of serious arrhythmia, atrial fibrillation, or intra-cardiac embolic sources. She has had several trans-thoracic echocardiograms, but has steadfastly refused trans-esophageal echo exams. There was no evidence of an atrial septal defect nor patent foramen ovale on one of her trans-thoracic studies. Of note is the presence of 50-60% bilateral carotid disease, and some aortic arch and abdominal aortic atherosclerotic disease. The proximal aortic plaques may have shown evidence of embolization during one of her echo tests. She is currently undergoing chelation therapy under your guidance, and is taking an organic “platelet inhibitor” instead of aspirin; she has refused COUMADIN therapy. Her physical examination in my office showed no evidence of active vascular disease, and her BP was 130/70, with a regular pulse. Office ECG showed only APC’S.

After extensive discussion with the patient, she has agreed to undergo a trans-esophageal echocardiogram, which will be done at the Cardiology Division at Roosevelt Hosp, (her main concern was gagging during the procedure). Although the results of the TEE will not alter treatment, it may localize a probable source of the emboli. As far as treatment is concerned, she continues to refuse COUMADIN, but will re-consider ASA treatment, and high dose STATIN therapy. I discussed the importance of PLAQUE STABILIZATION with the patient, as well as possible plaque reversal with STATIN treatment. In addition, it is important to repeat her CAROTID DOPPLER examination, (the last being 4/06), especially after completing a course of chelation therapy.

I will send you the results of the TEE as they become available; thank you again for your kind referral. Best regards for a happy Spring!

Very truly yours,

Anthony J. Pepe, M.D., F.A.C.C.
Evaluation from Cardiologist #2

- Recommendation for:
  - TEE
  - Medical treatment:
    - ACE inhibitor, statin medication, ASA
  - Repeat B/L carotid artery doppler
Columbus Cardiology Associates  
425W 59th Street  
Suite 8B  
New York, NY 10019  
Tel. (212) 376-3180

Date: 4/10/2007  
DOB: 8/24/1927  
Referring Physician: Dr. Anthony Pepe, MD

Duplex Ultrasound Evaluation of the Carotid Arteries

Evaluation of both carotid arteries was performed using a HP 5000 HDI ultrasound machine. All vessels were evaluated using color Doppler as well as gray scale imaging. Transverse and sagittal views were obtained and Doppler flow measurements performed in the proximal, mid and distal common carotid artery and proximal mid and distal internal carotid artery. Direction of flow was determined for the vertebral arteries and evaluation of the external carotid arteries including assessment of stenosis in these vessels was performed. Color Doppler images were recorded where appropriate.

Findings:

**Carotid Arteries**

**Right side:** The velocity measurement and ultrasound images are consistent with a 20-39% stenosis. Moderate calcified plaque was seen in the right internal carotid artery. Mild plaque was seen in the right common carotid artery.

**Left side:** The velocity measurement and ultrasound images are consistent with a 20-39% stenosis. Moderate calcified plaque was seen in the left internal carotid artery. Mild plaque was seen in the left common carotid artery.

**Impression:**

20-39% stenosis of the Right ICA  
20-39% stenosis of the Left ICA

Olivier Frankenberger, MD
Last Evaluation of Mrs B by Dr Morrison

- After completion of 40 IV NaEDTA chelation treatments patient reported increased energy and had a visible improvement in color of skin.
- Patient is on maintenance IV NaEDTA 3.0gm once a month and still doing well.
Toxic Metals, Cardiovascular Disease, and EDTA Chelation Therapy

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