Metal pollutants and cardiovascular disease: Mechanisms and consequences of exposure

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Introduction There is epidemiological evidence that metal contaminants may play a role in the development of atherosclerosis and its complications. Moreover, a recent clinical trial of a metal chelator had a surprisingly positive result in reducing cardiovascular events in a secondary prevention population, strengthening the link between metal exposure and cardiovascular disease (CVD). This is, therefore, an opportune moment to review evidence that exposure to metal pollutants, such as arsenic, lead, cadmium, and mercury, is a significant risk factor for CVD.

Methods We reviewed the English-speaking medical literature to assess and present the epidemiological evidence that 4 metals having no role in the human body (xenobiotic), mercury, lead, cadmium, and arsenic, have epidemiologic and mechanistic links to atherosclerosis and CVD. Moreover, we briefly review how the results of the Trial to Assess Chelation Therapy (TACT) strengthen the link between atherosclerosis and xenobiotic metal contamination in humans.

Conclusions There is strong evidence that xenobiotic metal contamination is linked to atherosclerotic disease and is a modifiable risk factor. (Am Heart J 2014;168:812-22.)

The result of a recent clinical trial of a metal chelator showing reduced cardiovascular events in a secondary prevention population highlights the potential connection between metal pollutants and cardiovascular disease (CVD). This is, therefore, an opportune moment to review the causal link between metal exposure and CVD. The most commonly used terms for metal pollutants, *heavy metals* or *toxic heavy metals*, refer to specific density, atomic weight, atomic number, or other chemical properties. We have chosen to use the term *xenobiotic*, to denote a foreign chemical substance found within an organism, thus, xenobiotic metal.

Definitions

Xenobiotic metals have no biological role at any dose. These include lead, arsenic, mercury, cadmium, and many others. We will focus on these 4 toxic, xenobiotic metals that are ranked among the top 10 on the current Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances.[1] Arsenic, lead, and mercury are ranked as the top 3 hazardous substances.

Lead

Distribution. Lead is the most common toxic element. Volcanic activity and geochemical weathering are the greatest natural sources. Lead-based paints, gasoline additives, food-can soldering, battery making, and soldered joints of drinking water pipe systems represent anthropogenic sources of lead in the environment.[2,3] Recommendations to limit lead paints since 1978 have led to substantial reductions in childhood lead toxicity.[4] Many children, however, continue to live in houses with either nonintact lead-based paint or high levels of lead in dust. Exposure to lead also occurs through airborne emissions and occupational exposures, water, and foods or occasionally through the use of alternative health care products, such as herbal remedies[5] (Table). Tetraethyl lead as a gasoline additive for land-based vehicles has now been largely banned worldwide. However, it is still present in aviation fuel for piston engine aircraft. Particles of lead suspended in the atmosphere, along with fuel-based and other sources of lead,[3,6] can represent a source of continued exposure.

Absorption, body distribution, and excretion. Approximately 30% to 40% of inhaled and 5% to 10% of

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Table. Metal exposure, half-life, ingestion, excretion, and ways to measure

Metal	Exposure	Half-life	Ingestion	Excretion	Measure
Lead	Food, water, air, gasoline additives, food-can soldering, lead-based paints, ceramic glazes, drinking water pipe systems, folk remedies	In blood 36 d; in bones 20-30 y	Inhalation with 30%-40% absorbed; ingestion with 5% absorbed in adults and up to 50% in children	Urine, sweat, hair, nails	Blood level x-ray fluorescence of bone, urine level
Cadmium	Contaminated food (leafy vegetables, grains, organ meats, and crustaceans), drinking water, inhalation of polluted air, occupational exposure in industries, tobacco smoke	In liver 4-19 y; in kidneys, 6-38 y	Inhalation with 40%-50% absorbed; ingestion with 3%-7% absorbed	No efficient excretory mechanism, small amounts excreted via urine	Blood level, urine level, biopsy of the liver, kidneys, hair
Mercury	Contaminated fish, meat and organ tissue of marine mammals or feral wildlife, dental amalgams, skin-lightening creams, antiseptic facial products, mercury-containing laxatives or diuretics, teething powders, latex paint	Elemental: in blood, 1-3 d; in the whole body, 1-3 wk Inorganic: in blood, 1-3 wk Organic: in blood and the whole body, 50 d	Elemental: inhalation with 80% absorbed, ingestion with 0.01% absorbed Inorganic: inhalation or inhalation with 10% absorbed, skin with 2%-3% absorbed Organic: inhalation or inhalation with 95%-100% absorbed	Metabolized in the liver and excreted through the bile duct 10% excreted via urine	Blood level, urine level, toenail level
Arsenic	Contaminated fish, tobacco smoke, arsenic treated wood, ingestion of high-arsenic drinking water	Inorganic: in blood, 4-6 h Methylated: in blood 20-30 h	Inhalation with 40%-60% absorbed, ingestion with 95% absorbed	Urine, nails, hair	Blood level, urine level, hair and nail levels

ingested lead is absorbed into the bloodstream. Gastrointestinal (GI) absorption, however, can reach as high as 30% to 50% in children[3] (Table). Once absorbed, 99% of lead binds to red blood cells, and 1% remains in serum.[3] The half-life of lead in the bloodstream is relatively short (36 days), whereas in bones, it is 20 to 30 years.[3] Absorbed lead is excreted from the body via urine, sweat, hair, and nails.[2,3]

Exposure evaluation. Blood lead assesses acute exposure to lead.[3] Blood lead levels, however, represent only recent short-term exposures and account for approximately 1% to 5% of total body lead burden; the rest is stored in bone and other tissues.[3] Bone acts as an endogenous source of lead by continuous release of the metal to the plasma, long after exposure has ended, when the rate of bone turnover increases. Indeed, noninvasive x-ray fluorescence of bone is the most accurate technique to assess body lead burden.[7,8] Urine lead may be used to assess lead exposure and for monitoring of therapy for lead toxicity.

Blood lead levels have exhibited a steady decline over the last decades, concurrent with the mandated discontinuation of leaded gasoline for ground vehicles. The mean blood lead level in the US population 30 years ago was 12.8 μg/dL, which decreased to 1.45 μg/dL more recently, with 99% of US adults having blood lead levels <10 μg/dL.[9] Epidemiological data strongly suggest that there may be no safe threshold level for lead, however.[10]

Cardiovascular effects. Increased cardiovascular mortality has been attributed to both elevated blood and bone lead levels with stronger association shown for bone levels.[11,12] (Figure 1A). Weisskopf et al[13] analyzed the association between tertiles of patella and tibia lead and mortality in 868 male participants of the Veterans Affairs Normative Aging Study. After multivariable adjustments, when compared to the first tertile, participants in the third tertile were more likely to die of all causes (hazard ratio [HR] 2.52, 95% CI 1.17-5.41, P = .02) and cardiovascular causes (HR 5.63, 95% CI 1.73-18.3, P = .003) and nearly 10 times more likely to die of ischemic heart disease (HR 8.37, 95% CI 1.29-54.4, P = .01). In the second National Health and Nutrition Examination Survey (NHANES), Lustberg and Silbergeld[14] reported that subjects with blood lead levels of 20 to 29 μg/dL had increased all-cause mortality (relative risk [RR] 1.46, 95% CI 1.14-1.86) and circulatory mortality (RR 1.39, 95% CI 1.01-1.91) compared with those having blood lead levels <10 μg/dL.

Menke et al[10] studied 13,946 adult participants of the NHANES III with blood lead levels <0.48 μmol/L (10 μg/dL) followed up for up to 12 years. After multivariate adjustment, the risk of cardiovascular events was significantly greater in participants with the highest tertile of lead exposure (≥0.17 μmol/L or 3.62 μg/dL), compared with those in the lowest tertile (<0.09 μmol/L or 1.94 μg/dL). All-cause mortality was higher by 25% (HR 1.25, 95% CI 1.04-1.51) in the third tertile versus the first tertile, whereas cardiovascular mortality was higher (HR 1.55, 95% CI 1.08-2.24), mortality from myocardial infarction was higher (HR 1.89, 95% CI 1.04-3.43), and mortality from stroke was higher by more than 2-fold (HR 2.51, 95% CI 1.20-5.26).[10]

The NHANES survey (1999-2000) showed that blood lead was associated with an increased prevalence of peripheral arterial disease (PAD), even at levels below current safety standards.[11]

The association of lead exposure with hypertension is one of the best established cardiovascular effects of this metal.[15,16] Meta-analyses of 61 original studies, including approximately 60,000 participants,[17] showed that a doubling of blood lead was associated with an increase in systolic blood pressure (SBP) of 1.0 to 1.25 mm Hg and diastolic blood pressure (DBP) of 0.6 mm Hg.[15] Although small in magnitude, these increases in SBP and DBP could have clinical relevance in large populations.

Lead exposure has also been linked to dyslipidemia and atherosclerosis.[14,18,19] Experimental and human autopsy studies showed an association between lead exposure and aortic atherosclerotic plaque burden.[14,19-21] There are some interesting findings that support the association of lead with atherosclerosis. For example, the cardioprotective antioxidant activity of high-density lipoprotein is partially mediated by paraoxonase activity, an enzyme that is closely bound to the high-density lipoprotein particle and involved in inhibition of low-density lipoprotein (LDL) oxidation. Lead as well as other metals can inactivate paraoxonase and, therefore, promote LDL oxidation and atherosclerosis development.[22-24]

Cadmium

Distribution

Cadmium is considered one of the most toxic environmental substances due to its ubiquity, toxicity, and long half-life. Exposure to cadmium occurs through inhalation (particularly in active cigarette smokers), water consumption, industrial exposure, and contaminated food (Table). Tobacco plants are highly efficient in absorbing cadmium from soil and accumulating it in the leaf.[25] Therefore, any exposure to tobacco smoke leads to high exposure to cadmium,[26] and smokers have cadmium levels that are at least twice as high as those of nonsmokers.[25,27] High levels of cadmium can be found in vegetables, fruits, and grains, with the highest levels in greens and potatoes. Shellfish and organ meats contain elevated cadmium concentrations as well, and agricultural fertilizer has also been reported to contain cadmium.[25,28,29]

Absorption, body distribution, and excretion. Approximately 40% to 50% of inhaled and 3% to 7% of ingested cadmium is absorbed. Similar to lead, GI absorption of cadmium is greater in the young[25,30] (Table). Intestinal cadmium absorption occurs through a transporter shared with iron, and when accompanied by iron deficiency, GI cadmium absorption may increase.[31] Once absorbed, cadmium is protein bound via erythrocytes or albumin and undergoes hepatic conjugation to metallothionein, a cysteine-rich protein.[25] This cadmium-metallothionein-cadmium complex then accumulates in the kidneys and may cause renal impairment.[25] Cadmium is also stored in bones, pancreas, adrenals, testes, and placenta.[25]

Cadmium has no efficient excretory mechanism. It is excreted in the urine, but it remains bound to metallothionein, which is almost completely reabsorbed in the renal tubules.[25] Cadmium half-life in the liver is between 4 and 19 years and, in the kidneys, is between 6 and 38 years.[25,27]

Exposure evaluation

Cadmium levels can be measured in blood, urine, liver, kidney, hair, and other tissues.[25] Blood cadmium level is indicative of recent exposure.[25] The geometric mean level in occupationally nonexposed adults in the United States is 0.315 μg/L. In heavy smokers, this level may be as high as 1.58 μg/L (Table).

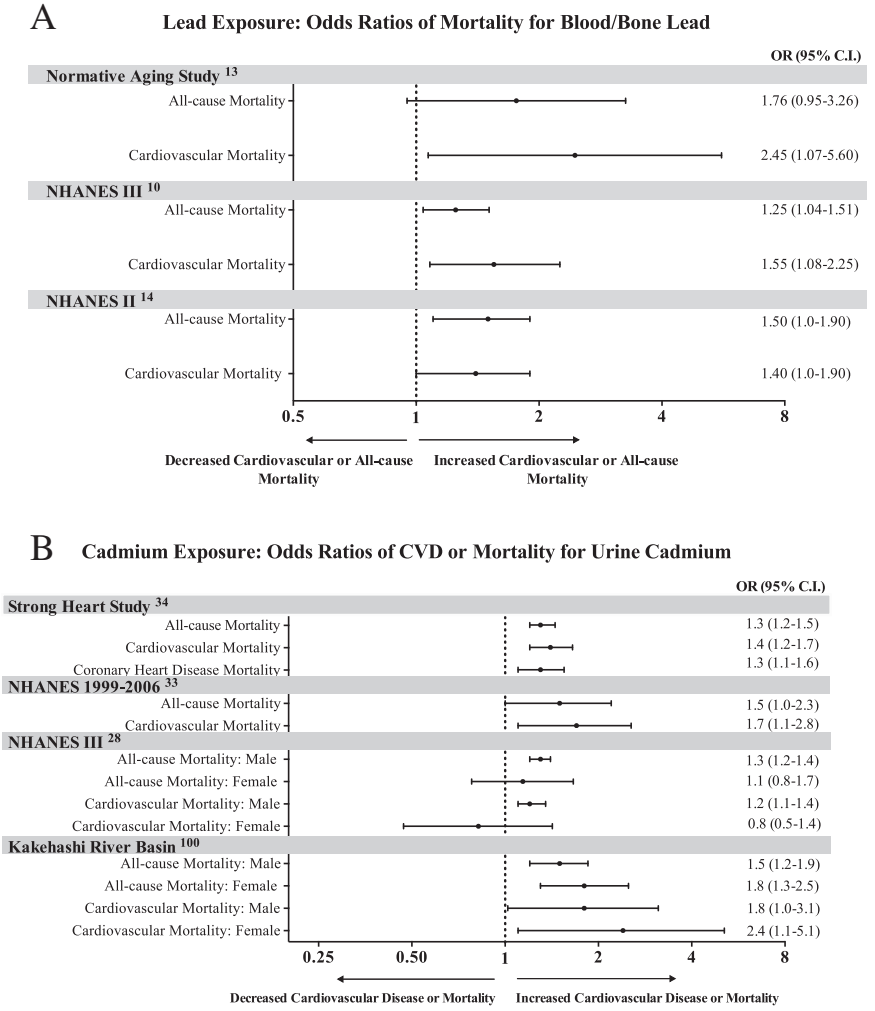
Urine cadmium reflects mainly total body burden, although urine levels change with recent exposure as well. In the US general population, the geometric mean urinary cadmium level in adults is 0.232 μg/L (or 0.247 μg/g creatinine)[32] (Table).

Cardiovascular effects. Cadmium is associated with cardiovascular and all-cause mortality (Figure 1B). Menke et al[28] reported that every 2-fold increase in creatinine adjusted urinary cadmium levels in men is associated with an increase in risk of all-cause (HR 1.28, 95% CI 1.15-1.23) and cardiovascular mortality (HR 1.21, 95% CI 1.07-1.36). The risk of coronary artery disease (CAD)–associated mortality was also increased (HR 1.36, 95% CI 1.11-1.66). Although these associations were not observed in women, other studies showed cardiovascular mortality to be associated with urinary cadmium levels in both genders.[33,34] In a review published recently by Tellez-Plaza et al,[35] based on 12 studies the pooled RRs for CVD, CAD, stroke, and PAD were 1.36 (95% CI 1.11-1.66), 1.30 (95% CI 1.12-1.52), 1.18 (95% CI 0.86-1.59), and 1.49 (95% CI 1.15-1.92), respectively.[35] The pooled RRs for CAD in men, women and never smokers were 1.29 (1.12, 1.48), 1.20 (0.92, 1.56), and 1.27 (0.97, 1.67), respectively.[35] These are modest in magnitude but quite consistent.

Cadmium has also been associated with PAD in both men and women.[11,35-37] Blood and urine cadmium levels were 16% (95% CI 4.7-28.7) and 36% (95% CI 1-83) higher,[11,37] respectively, in patients with PAD. After adjustment for age, sex, race, smoking status, and urinary creatinine, the odds ratio for PAD comparing the highest versus lowest quartile of urine cadmium distribution was 3.05 (95% CI 0.97-9.58).[37]

The largest epidemiologic examination of the association between cadmium exposure and blood pressure change was based on the 1999-2004 NHANES survey.[38] Among 15,332 participants older than 20 years, Tellez-Plaza et al[38] reported an association of blood, but not urine, cadmium levels with a modest elevation of blood pressure. The geometric mean of blood cadmium was

Figure 1



A, Lead exposure: odds ratios for mortality for blood/bone lead. **B**, Cadmium exposure: odds ratios for CVD or mortality for urine cadmium. **C**, Mercury exposure: odds ratios for CVD or death. **D**, Arsenic exposure: odds ratios for CVD and death for urine arsenic. References cited in this figure: 98, 99, 100. KIHD 2005[98], HPFS[99], Kakehashi River Basin[100].

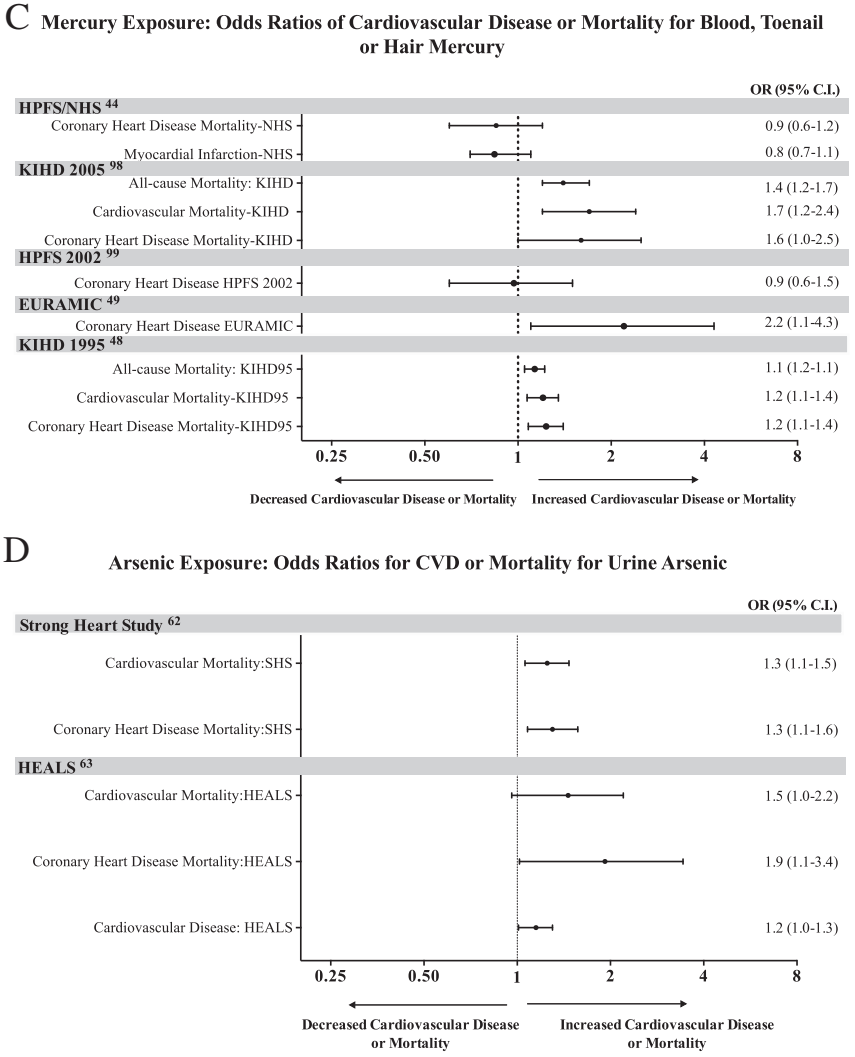
3.77 nmol/L (0.42 μg/L). Participants in the 90th percentile of blood cadmium distribution had 1.36 mm Hg (95% CI 0.24-3.24) higher SBP and 1.68 mm Hg (95% CI 0.57-2.78) higher DBP levels when compared to participants in the 10th percentile of blood cadmium distribution.

Mercury

Distribution. Mercury has been ranked as the third most toxic environmental hazard after arsenic and lead.[1] Common sources of mercury exposure include proximity to mercury mining sites, recycling facilities, medical or municipal incinerators, coal-fired power plants, or mercury-containing latex paint.[39] Dietary sources include fresh water fish or seafood[40] with high mercury content, high-fructose corn syrup, rice, and other dietary products. In addition, dental amalgam is a historic source of mercury exposure.[38] There have also been reports of mercury contamination in beauty products, laxatives, and infant products.[39,41] Another potential source of mercury is thimerosal-containing vaccines. Thimerosal, a controversial ethylmercury compound that has been used as a preservative in vaccines, has been completely removed from pediatric vaccines and mostly removed from adult products.

Absorption, body distribution, and excretion. Approximately 80% of inhaled and 0.01% of ingested elemental mercury is absorbed.[38] For inorganic mercury, absorption of inhaled versus ingested mercury is equal (10%), whereas 2% to 3% of inorganic mercury is absorbed through the skin.[38] Organic mercury (most

Figure 1



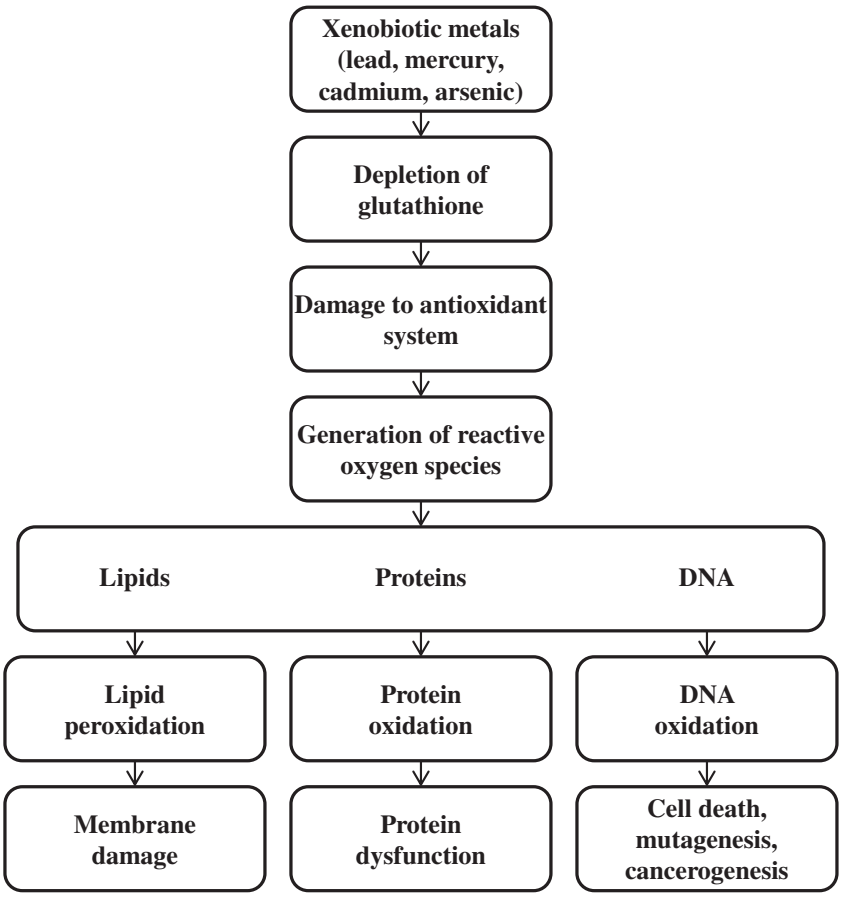
(*Continued*).

commonly found in fish), if ingested or inhaled, is almost completely (95%-100%) absorbed and is the most toxic form of mercury that is distributed to all organs and tissues including brain and placenta[38] (Table). Elimination of organic mercury from the body occurs through either demethylation to inorganic mercury or degradation to L-cystein complex in bile. Approximately 10% of organic mercury is excreted through the urine. Selenium, vitamin C, and vitamin E can decrease toxic effects of mercury by multiple mechanisms.[42-44]

Exposure evaluation. Blood, urine, and toenail levels of mercury have been used to estimate mercury exposure[38] (Table). Blood mercury levels peak sharply during exposure and then decrease rapidly.[45] The mean total mercury levels in whole blood and urine of the general population are approximately 1 to 8 μg/L and 4 to 5 μg/L, respectively.[46] Mercury levels as high as 200 μg/L have been reported in individuals with high fish intake,[46] which is striking in the context of US occupational exposures being limited to <15 μg/L.[38,47] Urine mercury may be used for assessment of inorganic mercury exposure, as organic mercury represents only a small fraction of urinary mercury. Urine mercury levels may vary greatly during the day and from day to day in the same individual, as well as show inter-individual variability, even in a setting of constant exposure.[38] Current Occupational Safety and Health Administration recommendations require urinary mercury levels not to exceed 35 μg mercury per gram of creatinine.[47]

Cardiovascular effects. When evaluating the association of mercury levels and CVD, it is important to note that this relationship may be confounded by fish

Figure 2



Hypothetical Mechanisms of Metal Toxicity.

consumption, which raises mercury levels but lowers cardiovascular risk (Figure 1C).

In 1995, Salonen et al[48] reported an association between high levels of mercury exposure via freshwater fish consumption and risk of acute myocardial infarction (AMI), all-cause, and cardiovascular mortality. Men in the highest tertile of hair mercury content when compared to the lowest tertile had RR of fatal or nonfatal AMI of 1.69 (95% CI 1.03-2.76, $P = .038$), RR of CVD of 2.9 (95% CI 1.2-6.6, $P = .014$), and RR of death from any cause of 2.3 (95% CI 1.4-3.6, $P < .001$). The RR of coronary death in this study was not associated with hair mercury content. In a case-control study, Guallar et al[49] showed an association between higher levels of toenail mercury and risk of nonfatal AMI. More recently, Mozaffarian et al[44] found no association between toenail mercury and CAD, stroke, or total CVD in participants with either normal or low levels of selenium, which may protect against mercury toxicity.

Data regarding a relationship between mercury exposure and blood pressure changes are inconsistent.[50-53] Studies of chronic occupational mercury exposure in miners revealed a 46% increase in incidence of hypertension when compared to age-matched controls.[54] Correlations have been reported between hair or blood mercury and elevated blood pressure.[50,51]

Arsenic

Distribution. Arsenic is highly toxic to human health.[1] Inorganic and most toxic forms of arsenic (arsenate and arsenite) are found in soils, crops, and water, particularly in groundwater from deep wells, often used as drinking water. These compounds are also found in environmental tobacco smoke and arsenic-treated wood, used in most outdoor wooden structures in the United States.[55] High levels of arsenic are present in agricultural fertilizer that is used for soil treatment; therefore, vegetables and fruits, if grown in this soil, contain high levels of arsenic[55] (Table). Arsenic has also been used as an additive to poultry feed to inhibit parasites. Arsenic is emitted by coal-burning power plants. As for organic forms of arsenic, large amounts of arsenobetaine or arsenocholine are found in

contaminated fish; however, these forms are considered to be essentially nontoxic.[55-57]

Absorption, body distribution, and excretion. The primary routes of arsenic absorption are gastrointestinal and respiratory[55] (Table). Approximately 40% to 60% of inhaled and 95% of ingested arsenic is absorbed.[55] Arsenic metabolism includes 2 main reactions: conversion of arsenate to arsenite by oxidation/reduction reactions forming glutathione-arsenic complexes and methylation that occurs mainly in the liver producing water soluble monomethylarsinic acid and dimethylarsinic acid that are eliminated through the urine. Arsenic metabolism is an area of active investigation, as differences in methylation of arsenic have been associated with differences in health outcomes, including CVD.[55,58,59]

Exposure evaluation. Because arsenic is cleared from the blood within a few hours of exposure, measurement of blood arsenic can only be used to assess a very recent exposure[55] (Table). Typical values in nonexposed individuals should be <1 μg/L.[60]

Urine is considered to be the most reliable body sample to detect arsenic exposure. The American Conference of Governmental Industrial Hygienists considers urine arsenic <35 μg/L to be acceptable for nontoxic exposed individuals. Yet, other reports[61] suggest that there may be no safe threshold of arsenic exposure. Arsenic can be detected in urine of people with no known exposure.[55] This could be due to high consumption of certain seafood that contain a nontoxic organic form of arsenic, arsenobetaine.[55] Therefore, the measurement of speciated urinary arsenic, rather than total urinary arsenic, is preferred for assessments of cardiovascular toxicity. Finally, arsenic tends to accumulate in nails and hair, wherein acceptable levels of arsenic are <1 ppm.[60]

Cardiovascular effects. There is only limited evidence on the relationship between arsenic and cardiovascular morbidity and mortality (Figure 1D). The only prospective cohort study, published recently by Moon et al,[62] reported that long-term exposure to low to moderate arsenic levels is associated with CVD incidence and cardiovascular mortality. Participants of this study had a median urinary arsenic level of 9.7 μg/g creatinine, with a range from 1 to 183.4 μg/g creatinine and interquartile range between 5.8 and 15.7 μg/g creatinine. The hazard ratios for CVD mortality, CAD mortality, and stroke mortality per interquartile range were 1.65 (95% CI 1.20-2.27; $P < .001$ for trend), 1.71 (95% CI 1.19-2.44, $P < .001$ for trend), and 3.03 (95% CI 1.08-8.50, $P < .001$ for trend), respectively. The association of arsenic with CVD mortality was stronger in participants with diabetes. Evidence is also accumulating on the association between higher levels of arsenic exposure and cardiovascular morbidity and mortality in Bangladesh.[63]

High levels of well-water arsenic exposure are recognized as being causative in the development of PAD,[37,64,65] such as blackfoot disease. This is a severe form of PAD endemic to Taiwan characterized by thromboangiitis obliterans, severe arteriosclerosis, and high levels of vessel wall arsenic.[37,64,65] However, the generalizability of these findings is limited, due to the nature of the exposure (deep well water) and the extremely high estimated levels of arsenic exposure.

Finally, although the literature is limited, there is evidence to suggest a positive relationship between arsenic exposure and hypertension.[66]

Hypothetical mechanisms of metal toxicity

There are general mechanisms that apply to all toxic metals and specific mechanisms that are idiosyncratic to the individual metal in question. These mechanisms center on oxidative stress. Although the science underlying these mechanisms is accurately quoted, attribution of benefit to metal chelation because of these mechanisms has to be considered speculative. Moreover, the oxidative-stress = oxidative-damage hypothesis has been challenged as well.

Oxidative stress results from an imbalance between the production and detoxification of reactive oxygen species (ROS). The toxicity of ROS is based on their ability to oxidize intracellular and extracellular structures such as proteins, lipids, and nucleic acids (Figure 2). Several enzyme systems are known to protect the body against ROS. These enzymes include superoxide dismutase, catalase, glutathione peroxidase, paraoxonase, thioredoxin, heme oxygenase, and others. Glutathione peroxidase is of particular interest.

Many metals have electron-sharing properties and, therefore, are capable of forming covalent bonds with sulfhydryl groups of proteins (eg, glutathione, cystein, homocysteine, metallothionein, and albumin).[67] By binding to glutathione, these metals deplete its levels and, therefore, increase the intracellular concentration of ROS. The consequences include promotion of lipid peroxidation; cell membrane damage; DNA damage; oxidation of aminoacids in proteins and, therefore, changes in their conformation and function; and inactivation of enzymes. According to current concepts of atherogenesis, oxidative modification of LDL, a free radical-driven lipid peroxidation process, is an early event in atherosclerosis development.[68]

Many metals have been shown to increase lipid peroxidation.[69,70] In addition, metal-related, ROS-mediated changes include microtubule destruction, mitochondrial damage by disruption of the membrane potential, inhibition of adenosine triphosphate production, followed by dysfunction of ion transporters such as Ca–adenosine triphosphatase and Na–K–adenosine triphosphatase causing changes in calcium homeostasis.[71]

By binding to sulfhydryl groups of proteins not involved in the detoxification of ROS, metals may cause other biological impairments. Lead causes endothelial dysfunction by

binding and inhibiting endothelial nitric oxide synthase and decreasing nitric oxide production.[72,73] Mercury has also been reported to impair nitric oxide metabolism by binding to sulfhydryl (SH) groups of NF-kB and changing its effects on gene expression and, thus, resulting in decreased expression of inducible nitric oxide synthase.[74] Cadmium has been shown to inhibit endothelial and calcium-calmodulin constitutive nitric oxide synthase as well.[75] Arsenic exposure was linked to impairment of nitric oxide production and increased generation of ROS, perhaps by uncoupling of endothelial nitric oxide synthase production.[76]

There are additional, idiosyncratic mechanisms of toxicity. Thus, lead, competing with zinc, binds to sulfhydryl groups of delta-aminolevulinic acid dehydratase (the enzyme involved in heme metabolism), preventing binding of delta-aminolevulinic acid dehydratase to aminolevulinic acid,[77] generating ROS.[78] Lead has also been shown to promote endothelial release of endothelin, to elevate serum levels of norepinephrine, angiotensin-converting enzyme, and thromboxane and to decrease production of prostacyclin.[79,80] All these changes may mediate vascular constriction. In addition, lead, being one of the calcium-like elements, competes with calcium for transport by channels and pumps in endoplasmic reticulum. Lead may also substitute for calcium in calcium-dependent processes and can interact with calmodulin.

Arsenic inhibits pyruvate and α-ketoglutarate dehydrogenases, important enzymes of gluconeogenesis and glycolysis.[81] It can also replace phosphate in glycolysis, generating arseno-3-phosphoglycerate instead of 1,3-bisphosphoglycerate, which leads to uncoupling of oxidative phosphorylation.[81] Moreover, arsenic has been linked to increased intravascular inflammation by upregulating interleukin 6; tumor necrosis factor α; and monocyte chemotactic protein, vascular cell adhesion molecule and intercellular adhesion molecule.[82] Furthermore, arsenic inhibits expression of peroxisome proliferator–activated receptor γ causing hyperglycemia and dyslipidemia.[83]

Macrophages and endothelial cells take up cadmium by endocytosis causing foam cell production followed by foam cell necrosis and endothelial cell disruption followed by endothelial cell necrosis. Once the endothelial layer is disrupted, cadmium reaches smooth muscle cells and accumulates there, activating smooth muscle cell proliferation and apoptosis. Cadmium may also substitute for iron and copper in proteins that contain these biologically necessary metals. As a result, iron and copper, after being released from its usual binding proteins, may produce ROS, as both elements can be more easily involved in reduction-oxidation reactions.[84] Cadmium is also associated with perturbations in inflammation and coagulation, including elevated blood C-reactive protein and fibrinogen in a general US population, even after adjustment for other CVD risk factors such as smoking.[82,85,86] Moreover, cadmium exposure has been associated with elevations of mediators or markers of systemic inflammation, including interleukin 6, tumor necrosis factor α, and vascular cell adhesion molecule 1.[87]

Oxidative stress, metals, and diabetes

Patients with diabetes are thought to be especially susceptible to oxidative stress. The formation of advanced glycation end-products, advanced lipoxygenation products, and protein oxidation products require nonenzymatically, metal catalyzed oxygen chemistry. These oxidized and cross-linked complexes are long lived and form the basis of diabetes complications, activating the receptor for advanced glycation end-products[88] and multiple other downstream inflammatory cascades,[89-91] and although the transition elements most closely associated with these reactions are iron and copper, xenobiotic transition elements, such as cadmium and others (cobalt and tungsten),[92] might be also involved.

Potential interventions

Chelation therapy with EDTA (edetate disodium) has been used to treat atherosclerotic disease since 1956,[93] without a solid scientific base. In 2002, the Cochrane Collaborative[94] reported that there was insufficient evidence to make a recommendation for or against chelation therapy. Yet patients continued to seek, and practitioners to use, EDTA to prevent or treat atherosclerotic disease of the coronaries, carotids, and peripheral arteries. In 2002, TACT, a 2 × 2 factorial trial testing 40 disodium EDTA infusions versus placebo and oral high-dose multivitamins and minerals versus oral placebo was designed[95] and funded. TACT enrolled 1,708 patients[96] who had sustained a prior myocardial infarction, were at least 50 years old, and had a creatinine of ≤2.0 mg/dL. TACT administered 55,222 infusions of EDTA-based chelation or placebo. EDTA chelation significantly reduced, by 18% ($p = 0.035$), a combined cardiovascular endpoint, with a 5-year number needed to treat of 18. In 633 patients who had diabetes,[97] a diagnosis associated with a strong prooxidant state, the reduction in events was greater, with a 41% reduction in events and a number needed to treat of 6.5 patients over 5 years (unadjusted $P = .0002$). Thus TACT provides a strong inferential support for the conclusion that environmental metal pollution may be a potent and modifiable risk factor for atherosclerotic disease.

Conclusions

Prudent public health measures should be taken to fully assess, then minimize, the public's exposure to xenobiotic metals. In addition, given the present state of the science, it appears reasonable to consider the results of the recently published chelation trial (TACT) as biologically plausible and, in selected patients, especially those with

diabetes and coronary disease, actionable. This will be the topic of the next trial, TACT2, now in its planning phase.

Disclosures

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The authors are solely responsible for the design and conduct of the TACT study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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