

REVIEW TOPIC OF THE WEEK

Heavy Metals, Cardiovascular Disease, and the Unexpected Benefits of Chelation Therapy



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ABSTRACT

This review summarizes evidence from 2 lines of research previously thought to be unrelated: the unexpectedly positive results of TACT (Trial to Assess Chelation Therapy), and a body of epidemiological data showing that accumulation of biologically active metals, such as lead and cadmium, is an important risk factor for cardiovascular disease. Considering these 2 areas of work together may lead to the identification of new, modifiable risk factors for atherosclerotic cardiovascular disease. We examine the history of chelation up through the report of TACT. We then describe work connecting higher metal levels in the body with the future risk of cardiovascular disease. We conclude by presenting a brief overview of a newly planned National Institutes of Health trial, TACT2, in which we will attempt to replicate the findings of TACT and to establish that removal of toxic metal stores from the body is a plausible mechanistic explanation for the benefits of edetate disodium treatment. (J Am Coll Cardiol 2016;67:2411-8) © 2016 by the American College of Cardiology Foundation.

On November 4, 2012, the TACT (Trial to Assess Chelation Therapy) investigators reported publicly the first large, randomized, placebo-controlled trial evidence that edetate disodium (disodium ethylenediaminetetraacetic acid) chelation therapy significantly reduced cardiac events in stable post-myocardial infarction (MI) patients. These results were so unexpected that many in the cardiology community greeted the report initially with either skepticism (it is probably wrong) or outright disbelief (it is definitely wrong) (1). The TACT trial had been controversial since the announcement of its funding in 2002. The primary justification used by the National Center for Complementary and Alternative Medicine and the National Heart, Lung, and Blood Institute for the study was that it was being conducted to prove that chelation did not work, so that the many patients who sought out this therapy every year would be armed against

the unjustified assertions of those in the alternative medicine community who promoted its use. The skeptical reactions to the positive TACT results were mostly focused in 2 areas: 1) technical issues regarding blinding, high dropout rates, differential follow-up, and other trial conduct issues; and 2) the lack of a plausible mechanism by which ethylenediaminetetraacetic acid chelation could cause the observed benefit. The former issues were addressed at length in the primary TACT publication in 2013 and in its online appendix (2). The most important issue centered on a 17% consent withdrawal rate. Consent withdrawal, however, was more likely in the placebo patients, thus preventing attribution of more events in the placebo group than in the chelation group. This introduced a conservative bias, likely reducing the observed effect size of the active treatment. The latter criticism, lack of mechanism, reflected a prevalent confusion in medicine about the



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ABBREVIATIONS AND ACRONYMS

MI = myocardial infarction

NHANES = National Health and
Nutrition Examination Survey

NNT = number needed to treat

OMVM = active oral
multivitamins and minerals

roles of pathophysiological models and related theories in our understanding of therapeutic effectiveness. For any set of experimental observations (including clinical trial results), many “explanatory” pathophysiological models can be proposed to fit the known facts. Thus, mature pathophysiological models defining therapeutic mechanisms are not necessary to demonstrate that a therapy is effective.

Furthermore, the history of medicine is replete with examples where unexpected findings led to both novel therapeutic discoveries and previously unsuspected mechanisms (3). Thalidomide and sildenafil are 2 well-known examples where current clinical utility was discovered essentially by accident. We believe that edetate disodium chelation therapy for atherosclerotic disease may provide another example of this phenomenon.

We briefly summarize evidence from 2 previously unrelated lines of research: the unexpectedly positive results of the TACT trial, and a body of epidemiological data showing that accumulation of biologically active metals, such as lead and cadmium, is an important risk factor for cardiovascular disease. We believe that considering these 2 areas of work together may lead to the identification of a major new modifiable risk factor for atherosclerotic cardiovascular disease. We start by reviewing the history of chelation up through the report of TACT. We then describe work connecting higher metal levels in the body with the future risk of cardiovascular disease. We conclude by presenting a brief overview of a newly funded National Institutes of Health trial, TACT2, in which we will attempt to replicate the findings of TACT and establish that removal of toxic metal stores from the body is a plausible mechanistic explanation for the benefits of edetate disodium treatment.

BRIEF HISTORY OF CHELATION

Metal ions that enter the body from the environment can bind to many of the molecules in body tissues, including proteins and polysaccharides. Furthermore, many of these metals are biologically active, participating in a variety of different physiological and pathophysiological reactions. Chelation, in the context of medical therapeutics, is a process in which the organic chelator molecules are introduced into the blood, where they bind the target metal ions with high affinity. The complex of chelator and metal ion remains in the blood compartment until filtered by the kidneys or excreted by the liver, thus removing the metal ions from the body. Edetate disodium, a

synthetic chelating agent first synthesized in Germany in the 1930s, has up to 6 binding sites with which to hold and envelop metal ions (4).

The medical utility of edetate disodium was only discovered after some trial and error. After World War II, the U.S. Navy discovered that edetate disodium was effective in treating lead poisoning in naval shipyard workers using lead-based paint (5). The first paper on the use of intravenous infusions of edetate disodium to treat atherosclerotic heart disease, published in 1956 by Clarke et al. (6), reported improvement in 19 of 20 patients with angina. The authors noted the delayed onset of therapeutic effect, requiring about 20 infusions before clinical effects became evident. At that time, there were no effective treatments for coronary disease. Physicians did not uniformly view cigarette smoking as atherogenic (7). Aspirin, statins, and revascularization had not been developed as cardiovascular therapies. Autopsied hearts from that era demonstrated coronary arteries that were often profoundly calcified. This had given Clarke et al. (6) the idea that perhaps edetate disodium was acting to decalcify coronary obstructions and thereby relieve angina. Subsequent investigations in the 1960s by a different group in another small cohort found more mixed results (8). Some patients still showed the delayed symptomatic improvement reported earlier, but the durability of the effect seemed quite variable (in the context of no risk factor control), and the investigators felt that the prognosis of the patients in this small case series had not been affected. The therapy was ultimately considered “not useful” and conventional medicine lost interest (9). Yet, edetate chelation for atherosclerosis did not vanish.

Over the subsequent years, chelation and alternative medicine physicians implemented clinical protocols for safer use of edetate disodium, principally restricting the dose and infusion rates (10). In the 1980s and 1990s, alternative medicine journals published case reports and case series, mostly reporting spectacular results in treating cardiovascular disease (11). Patients continued to seek and physicians continued to administer edetate disodium for various indications, including atherosclerotic heart disease (12). Within traditional cardiology, there were 3 small trials performed to assess whether edetate disodium treatments led to relief of angina or claudication (13-15). Although nominally negative, these trials were too small to exclude a small or even moderate-sized benefit in clinical endpoints for patients with atherosclerotic cardiovascular disease (16).

In 2001, the National Center for Complementary and Alternative Medicine, with cofunding from the National Heart, Lung, and Blood Institute, released a

request for applications for a clinical trial of edetate disodium chelation in cardiovascular disease. The resulting trial, TACT, was funded in August 2002. Because of the expectation that TACT would be a debunking study, it was designed as a clinical trial without a mechanistic component.

DESIGN AND RESULTS OF TACT

The request for applications called for testing the most prevalent chelation solution and treatment strategy. In 2002, clinical chelation practice most commonly involved multiple administrations of an edetate disodium-based infusion that contained other components, including vitamin C, B vitamins, heparin, electrolytes, and procaine. In addition, chelating physicians also recommended high doses of oral antioxidant vitamins and minerals to be taken concurrently with the intravenous chelation treatments. Therefore, a factorial design was selected for TACT, in which eligible patients were randomly assigned to 1 of 4 groups (17).

1. Active intravenous (IV) chelation infusions + active oral multivitamins and minerals (OMVM)
2. Active IV chelation infusions + placebo OMVM
3. Placebo IV chelation infusions + active OMVM
4. Placebo IV chelation infusions + placebo OMVM

Eligible patients were at least 50 years of age, had sustained an acute MI >6 weeks before the enrollment date, and had a serum creatinine level ≤2.0 mg/dl.

The treatment regimen consisted of 40 chelation or placebo-based infusions administered as 30 weekly infusions, followed by 10 additional maintenance infusions, 2 to 8 weeks apart. OMVM were to be taken daily throughout the duration of the trial. The primary endpoint for the study was a composite of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for angina. The major secondary endpoint was cardiovascular mortality, stroke, or recurrent MI.

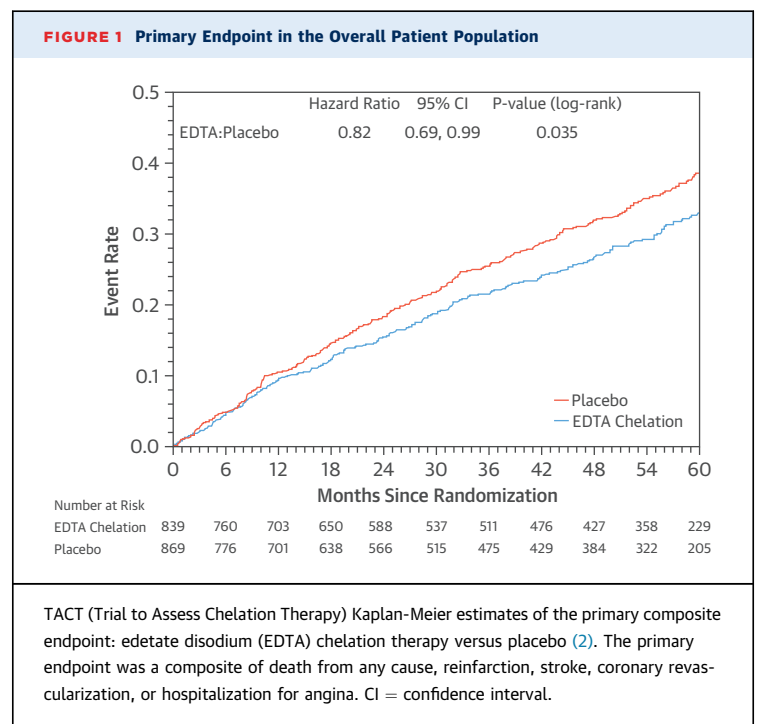
TACT enrolled 1,708 participants (839 in the chelation treatment group and 869 in the chelation placebo group) at 134 sites in the United States and Canada. Study patients had a median age of 65 years, 18% were female, 9% were nonwhite, 37% were diabetic, and 83% had either a prior coronary bypass or percutaneous coronary intervention. The trial strongly encouraged concomitant use of conventional, evidence-based post-MI cardiac therapies. At baseline, 92% were taking aspirin, clopidogrel, or warfarin, and 73% were taking statins. The median low-density lipoprotein was 89 mg/dl. A total of

55,222 placebo or active infusions were administered. At least 30 infusions were completed by 76% of patients, and 65% completed all 40 infusions. Subjects were followed for a median of 55 months.

Edetate chelation reduced the primary composite endpoint by 18% (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.69 to 0.99; $p = 0.035$); the number needed to treat (NNT) to prevent 1 event over 5 years of follow-up was 18 (Figure 1). One intriguing finding was that the event curves for edetate and placebo continued to diverge even after the infusions were completed, suggesting that edetate was altering the risk for future cardiovascular events in structural ways that did not depend on continued exposure to the therapeutic agent. The comparison of 2 factorial groups, chelation + OMVM versus placebo + placebo demonstrated an even larger difference between groups (HR: 0.74; 95% CI: 0.57 to 0.95; $p = 0.016$), with an NNT to prevent 1 event over 5 years of follow-up of 12 (HR: 0.74; 95% CI: 0.57 to 0.95; $p = 0.016$). With regard to safety, the masked medical monitor attributed 2 deaths to study therapy: 1 was in the chelation group, and 1 in placebo.

RESULTS IN PATIENTS WITH DIABETES

A total of 633 TACT participants (37%) had diabetes, a pre-specified subgroup. Diabetes was pre-specified because it confers increased risk for cardiovascular events, and not due to any information available to



the study team suggesting a unique benefit from edetate disodium (2,18). Edetate disodium treatment reduced the relative risk of the primary endpoint by 41% (HR: 0.59; 95% CI: 0.44 to 0.79; $p = 0.0002$) over 5 years (Figure 2). The NNT to prevent 1 event over 5 years of follow-up was 6.5. The principal secondary endpoint, cardiovascular death or recurrent MI or stroke, occurred in 17% of placebo patients and 11% of edetate disodium-treated patients, a 40% relative reduction in risk (HR: 0.60; 95% CI: 0.39 to 0.91; $p = 0.017$). There was a 52% relative reduction in the risk of recurrent MI among patients with diabetes (HR: 0.48; 95% CI: 0.26 to 0.88; $p = 0.015$), and a 43% relative reduction in the risk of death from any cause in patients with diabetes (HR: 0.57; 95% CI: 0.36 to 0.88; $p = 0.011$). There was no difference between groups in control of glucose, as defined by fasting glycemia, during the course of the initial 30 infusions.

WHAT DOES EDETATE DISODIUM CHELATE?

Although the treatment regimens tested in TACT were complex, the most reasonable presumption is that edetate disodium was the primary active therapeutic agent responsible for the results. To investigate the chelating effect of edetate disodium, Waters et al. (19) collected 24-h urines for 2 days before and 2 days after an edetate disodium-based infusion similar to that used in TACT and analyzed the samples for

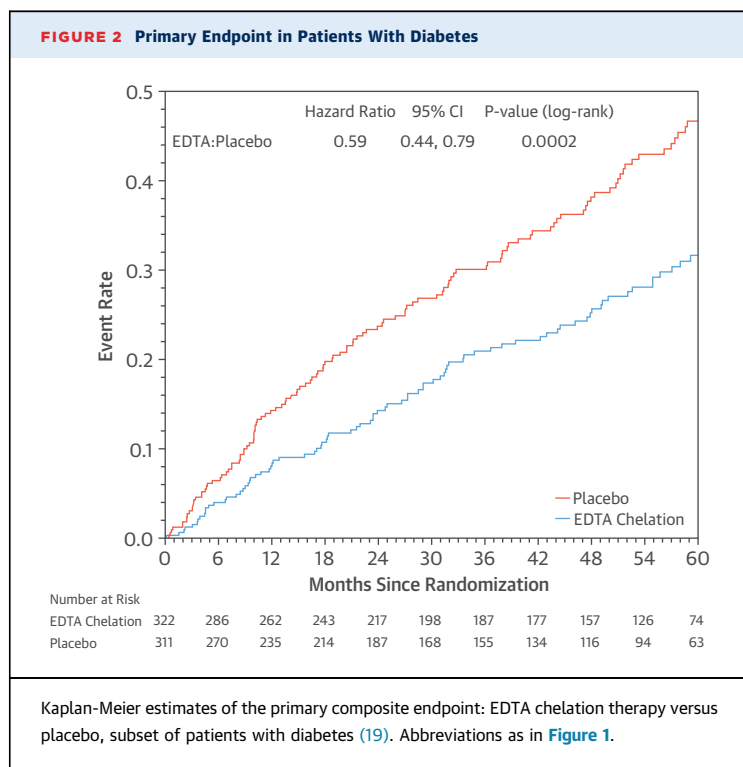
various toxic and essential metals. Following the infusion, the excretion of lead over 2 days increased by 3,830%, and of cadmium by 514%. A similar experiment performed by Arenas et al. (20) demonstrated similar results, but in this case with the identical TACT solution in TACT-eligible patients. Compared with baseline, a single infusion increased lead excretion by 3,887%, and cadmium by 670%. These findings raise the possibility that edetate disodium mobilizes lead and cadmium from their chronic tissue storage compartments and facilitates their excretion. In our review, we focus on cadmium and lead because those are the metals with the strongest epidemiological and experimental evidence in support of a role in cardiovascular disease development.

EVIDENCE SUPPORTING TOXIC METALS AS AN EMERGING CARDIOVASCULAR RISK FACTOR

The association of environmental pollutants, including metals, with cardiovascular disease has been reviewed elsewhere (21,22). In this review, we will summarize the evidence for the 2 metals that are chelated most effectively by edetate disodium and that have convincing published reports documenting their cardiovascular toxicity: lead and cadmium, ranked second and seventh, respectively, as environmental chemicals of concern by the Agency for Toxic Substances and Disease Registry (23).

LEAD SOURCES AND BIOLOGICAL STORAGE. Lead exposure in the United States markedly increased from the end of World War II through the mid-1970s, largely the result of use of tetraethyl lead in gasoline as an octane booster combined with the increased number of automobiles in use (24). At the peak of lead production, the atmospheric release of lead reached 600,000 tons annually (25). Lead exposure then began to decrease following the elimination of lead in gasoline for road-driven vehicles by 1980. The half-life of lead in the body, however, is extremely long, as lead is not excreted efficiently, and it accumulates in bone. As a result, anyone living in the United States during the period from 1945 to 1980 accumulated much more lead in his or her body than has happened at any other time in history. Lead exposure, moreover, remains ubiquitous through soil, batteries, toys, house paint, plumbing, and industrial sources, as well as smoking and secondhand smoke exposure (26).

Lead measured in whole blood is the major biomarker of lead exposure, and has a half-life of 35 days. Blood lead accounts for only 1% to 5% of total body lead burden, however, as most lead in the body



is contained in bone and other calcified tissues (27). The half-life for lead in bone approaches 30 years for cortical bone and years to decades for trabecular bone (27). Once in the chronic storage compartment, bone lead leaches out over time, serving as an endogenous source of blood lead and resulting in ongoing, years-long low-level lead exposure to the cardiovascular system, neural tissues, and kidneys. Lead can be mobilized from the internal body stores and excreted through the urine following chelation. Chelation with edetate disodium, the chelating agent used in TACT and proposed for TACT2, mobilizes lead from bone, whereas other chelating agents, for instance 2,3-dimercaptosuccinic acid, mobilize lead mostly from soft tissues (28).

LEAD AND CARDIOVASCULAR DISEASE. The possible association between lead and cardiovascular disease has been recognized for many years (21,22,29). The most robust studies evaluating the association of blood lead with cardiovascular outcomes have been conducted using data from the National Health and Nutrition Examination Surveys (NHANES). NHANES studies reported that despite the remarkable drop in blood lead following the elimination of leaded gasoline, blood lead levels remain associated with cardiovascular outcomes of atherosclerotic origin, including coronary heart disease, hypertension, stroke, and peripheral arterial disease (30,31).

Cumulative lead exposure, as reflected by bone lead, and cardiovascular events have been studied in the Veterans' Normative Aging Study, a longitudinal study among community-based male veterans in the greater Boston area enrolled in 1963. Patients had a single measurement of tibial and patellar bone lead between 1991 and 1999 (32). The HR for ischemic heart disease mortality comparing patellar lead >35 to <22 $\mu\text{g/g}$ was 8.37 (95% CI: 1.29 to 54.4).

Lead is an established risk factor for hypertension on the basis of consistent epidemiological evidence in populations around the world, as well as experimental evidence showing increases in blood pressure levels in animal models (29,33). Substantial in vivo and in vitro evidence supports that lead reduces nitric oxide bioavailability (34), as well as promotes oxidative stress and inflammation. These mechanisms are believed to play a major role in lead-related vascular disease (Central Illustration). In experimental models, lead-induced hypertension was reversible, either with a chelating agent or with antioxidant treatment (34). Recent studies suggest that there may be epigenetic modifications due to lead exposure, for instance, with hypomethylation in a promoter of the *COL1A2* gene (35).

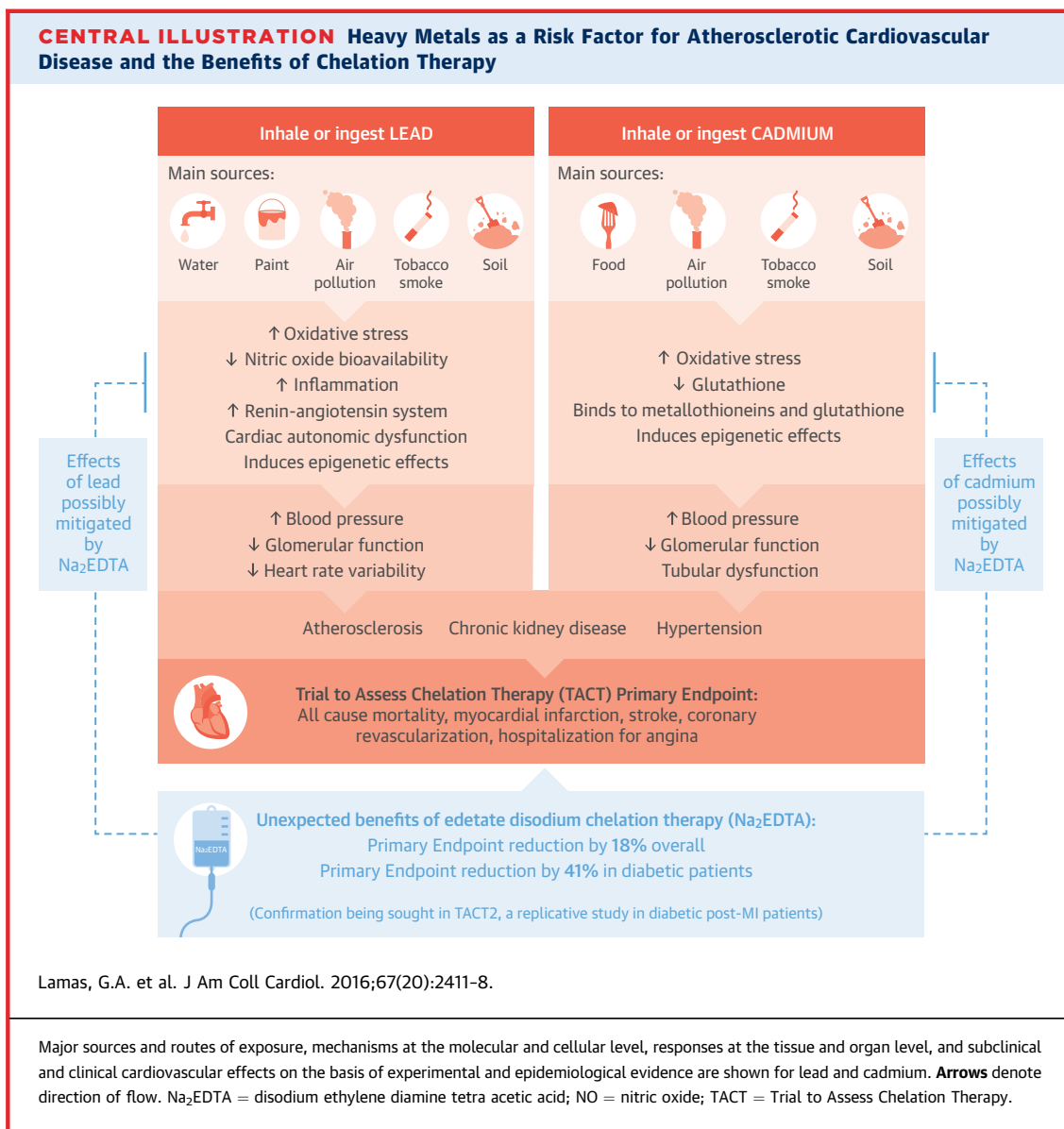
CADMIUM SOURCES AND BIOLOGICAL STORAGE.

Cadmium production markedly increased during the 20th century, especially between 1945 and the 1980s (36), as a result of cadmium use in the production of nickel-cadmium batteries, metal coatings, and plastic stabilizers. Food and smoking are the major sources of cadmium for the general population (37). The potential toxicity of cadmium is amplified by its extremely slow excretion rate. Once ingested, cadmium is stored predominantly in the kidneys, liver, lungs, pancreas, and central nervous system, with a half-life for excretion of over 15 to 45 years (38,39). In blood, cadmium has 2 compartments, 1 that represents recent exposure and has a half-life of ~ 35 days and another that is in equilibrium with internal cadmium stores and has a half-life of decades.

CADMIUM AND CARDIOVASCULAR DISEASE. Several studies have evaluated the association between cadmium and cardiovascular disease in the general U.S. population using NHANES data (39-41). In NHANES 1988 to 1994, for every doubling of urine cadmium, there was a 36% increase in coronary heart disease mortality in men, but no increase was observed in women. In NHANES 1999 to 2004, however, blood and urine cadmium were associated with increased cardiovascular disease mortality, including coronary heart disease, in both men and women. In the Strong Heart Study, participants with diabetes showed stronger associations between cadmium and CVD outcomes than did those without diabetes, and the difference was statistically significant (42).

Cadmium exposure has also been related to peripheral arterial disease. In NHANES analyses, it was proposed that cadmium could potentially mediate at least part of the effect of smoking on peripheral arterial disease (41). A recent systematic review concluded that the evidence supports the role of cadmium as a cardiovascular disease risk factor, especially for coronary heart disease (43).

Cadmium is thought to promote atherosclerosis through oxidative mechanisms (44). Cadmium can indirectly deplete antioxidants, such as glutathione, increasing reactive oxygen species (Central Illustration) (45). Subclinically, cadmium has been related to early atherosclerosis, including higher carotid intima-media thickness and carotid plaque in women from Europe (44). In experimental studies, low-level cadmium exposure can increase endothelial permeability, inhibit proliferation of endothelial cells, and induce cell death. Cadmium has also been related to gene expression and differential methylation in genes encoding proteins involved in



longevity, cardiovascular disease severity, and vascular calcification (RASAL1 and Klotho) (46,47).

DIABETES AND METALS. Specific adverse effects of metals in patients with diabetes mellitus have been discussed for over 20 years. Complications of diabetes mellitus may be partially mediated through the accumulation of advanced glycation end-products and activation of the receptor of advanced glycation end-products (48), with downstream inflammatory cascades (49,50). Glycation end-products are created by the nonenzymatic interaction of glucose with proteins, lipids, and nucleic acids (51). Most advanced glycation end-products require metal-catalyzed oxygen chemistry for their formation. Metals bind to

glycation end-products and promote the formation of reactive oxygen species in an autocatalytic reaction. The resultant oxidized end-products accumulate in tissues, where they promote inflammation and oxidative stress, hallmarks of atherosclerosis. These processes may provide a plausible explanation for the amplified benefit seen with edetate chelation in the diabetic subgroup of TACT (18,52,53). This is a hypothesis that merits testing. A direct connection to lead and cadmium has yet to be demonstrated.

REPLICATION OF TACT: THE TACT2 STUDY

The hallmark of science is replication, and so it needs to be with the use of edetate disodium chelation as a

treatment to reduce cardiovascular risk. We recently received funding through the National Center for Complementary and Integrative Health for a planning year for TACT2, a replicative study in post-MI diabetic patients comparing the TACT regimen with placebo. Although the final protocol is still under development, there is agreement that TACT2 should replicate the most encouraging findings from TACT as closely as possible. We have proposed a similar 2 × 2 factorial design for TACT2, randomly assigning patients to 40 infusions of the TACT chelation solution versus placebo infusions and high doses of OMVM versus oral placebo. TACT2 will also begin to explore the most likely mechanistic hypotheses. We have proposed blood and urine collections throughout the infusion period and will attempt to relate baseline lead and cadmium levels to risk of future events. In addition, we will perform analyses to determine whether

reduction in lead and cadmium levels is causally associated with reduced cardiovascular risk. In recognition that these are hypotheses that may be disproven, a biorepository of specimens, including deoxyribonucleic acid (DNA), has also been proposed. If fully funded, the final protocol will crystallize over the coming months. At present, TACT2 is still seeking enrollment sites.

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