Is There a Role for Edetate Disodium Chelation in PAD and Specifically CLTI?

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There are approximately 8.5 million Americans diagnosed with peripheral arterial disease (PAD).[1] In spite of management with guideline-directed medical therapy, many progress to the most severe form of PAD, critical limb-threatening ischemia (CLTI). The most severe disease course is seen in patients with diabetes, with over 150,000 individuals having the end-stage of the disease, resulting in a lower-extremity amputation.[2] A systematic review reported a 1-year cumulative incidence for mortality and amputation of approximately 20% in individuals with CLTI.[3] Although many new therapies have been made available to improve the disease course and avoid lower-extremity amputations, the rates of amputations are stagnant. Some data suggest rates in patients with diabetes are increasing, so we need to cast a wider net for "alternative" therapies to change the course of PAD, specifically CLTI, and avoid the life-changing and irreversible outcome of lower-extremity amputation.

Substantial evidence supports traditional/conventional risk factors for PAD. Modern medicine and our arsenal of available treatment options have focused on decreasing, modifying, or stabilizing these conventional risk factors to alter the disease course of PAD. Diabetes, smoking, dyslipidemia, and hypertension are known to increase the risk of developing PAD. Patients with diabetes have a 2- to 3-times greater risk of developing lower-extremity claudication compared with patients without diabetes.[4,5] In addition, diabetes has an increased risk of disease progression to CLTI, with 70% of nontraumatic lower-extremity amputations in the United States occurring in patients with diabetes.[6] Much like diabetes, cigarette smoking also increases the risk for PAD.[7] Previous studies have shown the risk is cumulative, and individuals who started smoking prior to age 16 have the greater risk.[8,9] Tobacco, and now electronic cigarettes, are known to have numerous toxic components that are hazardous to our health. Although we counsel smokers on the importance of smoking cessation to decrease the risk of vascular disease, epidemiologic studies have demonstrated that it takes about 30 years of smoking cessation for the risk for PAD to drop to that of nonsmokers (curiously, the half-life of cardmium and lead in the human body).

Current therapy for PAD focuses on altering the conventional risk factors through lifestyle modifications such as smoking cessation. Therapies such as antihypertensives, statins, antiplatelets, and most recently, dual-pathway inhibition with rivaroxaban, have been our mainstays in medical therapy. Endovascular therapy has demonstrated an improvement in quality of life and, at times, wound healing with revascularization. Yet CLTI still presents as a healthcare and human burden in the United States.

Is It Time to Look at Nonconventional Risk Factors?

The 2021 Scientific Statement from the American Heart Association (AHA) identified several nonconventional risk factors for PAD. These include an increase in inflammatory markers, human immunodeficiency virus, depression, and environmental factors such as air pollution and metal contaminants.[10] Over the last decade, epidemiologic evidence has demonstrated an association between metal contaminants, such as lead and cadmium, with PAD.[11] We may ask ourselves why, in the 21st century, we should be concerned with metal contaminants, as we have eliminated the use of leaded gasoline and lead paint, and replaced some lead-based pipes with polyvinyl chloride. Today, an individual has a more than 100-fold lead burden than a preindustrial human being. Thus, with evidence of an association between environmental pollutants and PAD, how do we modify our risk with potential therapies?

In 2003, the Trial to Assess Chelation Therapy (TACT) began enrolling patients at least 50 years of age with a history of myocardial infarction (MI) in a double-blind, placebo-controlled trial of 40 edetate disodium-based infusions or placebo.[12] Edetate disodium is an artificial amino acid with a high affinity to divalent cations such as lead, cadmium, and calcium. The first clinical series was published in 1956 by Clarke and colleagues, who hypothesized that by treating patients with edetate disodium to decalcify, arteries might improve. Although initial small case series were promising, the therapy lost supporters during the advent of beta-blocker therapy and coronary bypass. The edetates, calcium and disodium, "jumped" into alternative medicine and were eschewed by conventional, or mainstream, cardiology. Chelation received a Class III recommendation by the AHA/American College of Cardiology for treatment of stable ischemic heart disease or PAD. And there matters stood for a potentially useful medical strategy until 2002, when the National Center for Complimentary and Integrative Health funded the TACT.

Over a 10-year period, TACT enrolled and followed 1708 patients who received 55,222 infusions of active chelation or placebo. The results were unexpected and, understating the reaction of cardiologists, controversial. TACT demonstrated a statistically significant modest improvement in the primary endpoint (first occurrence of death, recurrent MI, stroke, coronary revascularization, or

hospitalization for angina) by 18% (P=.035).[13] In particular, edetate disodium-based chelation demonstrated the most benefit in patients with diabetes, with an even greater reduction by 41% (P=.0002) in the primary endpoint.[14] In patients with self-identified PAD, there was a reduction of 48% (P=.0069) in the primary endpoint.[15] In addition, there were no differences when compared with placebo in serious adverse events; the drug was safe. With these surprising results, speculation on the possible mechanisms of benefits arose.

Metal Hypothesis

Due to a high affinity to cadmium and lead, infusions of edetate disodium may decrease the body burden of these vasculotoxic metals. Arenas et al administered a single TACT infusion to patients with a history of MI. The study demonstrated an increase of urinary lead excretion of about 4000% and urine cadmium excretion of nearly 700% when compared with preinfusion urine metals.[16] Alam et al, in a case series of patients treated with several infusions of edetate disodium-based therapy, reported a decrease in the body burden of urinary lead over time.[17] Why is this important? Lead and cadmium have been shown in bench studies to increase inflammatory markers, cause endothelial dysfunction, and increase reactive oxygen species, all proatherosclerotic; and in epidemiologic studies, to be associated with cardiovascular events and death.

Metal Oxidation Hypothesis

Why was the benefit greater in diabetes? Patients with diabetes are at an increased risk when it comes to cardiovascular endpoints; their risk of PAD is 2- to-3-times greater.[4,5] In addition, as stated previously, their rate of amputation is vastly increased compared with nondiabetic patients. One hypothesis as to why elevated blood sugars are toxic is the formation of advanced glycation end products (AGEs), protein, and lipid oxidation products. All these, in particular AGEs, need metal-catalyzed oxygen chemistry for their formation.[18,19] AGEs provoke the release of toxic cytokines through the AGE receptor and may have a central role in the vasculotoxic nature of diabetes. Thus, chelation and removal of toxic metals may interrupt or reduce this cascade.

Decalcification Hypothesis

Edetate disodium does not only have a high affinity to cadmium and lead but also to calcium.[20] In fact, infusions of edetate disodium should be administered at a slow rate to avoid hypocalcemia. This is the earliest hypothesis and what initially set Clarke and colleagues in their proposal of edetate disodium as a potential therapy for atherosclerotic disease. Unfortunately, data are lacking and no published case reports have demonstrated a convincing improvement in arterial calcium burden.

Conclusion

With current evidence, should edetate disodium therapy be offered to patients with CLTI? Scant modern evidence exists. We can, however, state with confidence that when used like TACT, in patients at least 50 years old with a creatinine of 2.0 mg/dL or less, and on the schedule and dosing we reported, the infusions are safe. Our evidence is based on 10 patients with CLTI who received open-label chelation as a last option for limb salvage in patients with diabetes with no other option for revascularization. In the 7 patients completing at least 20 infusions, there was pain relief, and patients avoided all amputations. This leads to our opinion, which is still based on developing science. We cautiously recommend that in the absence of a clinical trial at your institution, prior to scheduling a patient to undergo minor or major amputation, if no underlying active infection such as osteomyelitis is present, attempt limb salvage with edetate disodium chelation.

Two important trials will further add to the ongoing knowledge to disprove or accept edetate disodium as a treatment for atherosclerosis. TACT2 in patients with diabetes and a history of MI is nearing completion and currently in the follow-up phase of the trial (NCT02733185). In addition, TACT3a in patients with diabetes and CLTI is currently enrolling at Mount Sinai in Miami Beach (NCT03982693). We are also trying to develop a proposal for a definitive NIH study in CLTI. We invite potentially interested centers to contact us. We are on the threshold of a new therapy for a particularly serious disease. ■

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