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Potential Role of Edetate Disodium-Based Therapy in the Treatment of Atherosclerosis in Patients with Diabetes

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Abbreviation: CAD: Coronary Artery Disease; MI: Myocardial Infarction; PAD: Peripheral Artery Disease; ATSDR: Agency for Toxic Substances and Disease Registry; CLI: Critical Limb Ischemia; TACT: Trial to Assess Chelation Therapy

Introduction

In 2017, 30.3 million patients had diabetes in the United States (9.4% of the US population.) An additional 7.2 million have undiagnosed diabetes [1]. Diabetes is the seventh leading cause of death in the United States [2], and increases the risk of coronary artery disease (CAD). As such, diabetes contributes to the complications of CAD, including myocardial infarction (MI), revascularization, and death. Diabetes also contributes to the risk of lower extremity vascular disease and associated procedures, including amputation [3,4]. Although revascularization techniques and medical therapy have improved the management of atherosclerosis, there remains ample residual risk and opportunity for novel therapies, such as the one discussed here. This mini-review will explore the effect of toxic metals on vascular health and emerging benefit of therapies targeting reduction of body burden of toxic metals, particularly lead and cadmium, in patients with diabetes.

Toxic Metals and Vascular Disease

Lead

Epidemiologic studies suggest that toxic metal exposure, especially to lead, is associated with atherosclerosis, hypertension, CAD, and peripheral artery disease (PAD) [5,6]. Lead is listed as #2 in the Agency for Toxic Substances and Disease Registry (ATSDR) Substance Priority list determined to pose the largest threat to health via toxicity and exposure potential, only second to arsenic since 1997 [7]. Lead exposure continues to be a widespread issue due to chronic contamination from soldered joints in water pipes, lead-based paints, soil contaminated with prior leaded gasoline, and airborne emissions [8,9]. Once absorbed, lead has an intravascular half-life of about a month [10,11]. It then moves to bone, with a half-life of about 30 years [11]. Lead substitutes for calcium in various intracellular reactions and, as such, inhibits endothelial nitric oxide synthase leading to endothelial dysfunction, oxidative stress, and increased inflammation [12]. Lead concentrations as low as 5µg/dL are associated with an increased risk of cardiovascular disease mortality, suggesting that there may be no "safe" lead level [5]. Urine lead after a chelation challenge with edetate disodium infusion may inform on total body metal burden.

Cadmium

Cadmium is a toxic heavy metal widely distributed in the environment and ranked as #7 in the ATSDR Substance Priority list. Cadmium use has increased since the 1940s in conjunction with industrialization. Sources of environmental cadmium include construction, plastics processing, rechargeable batteries, and others. Cadmium makes its way into the food supply via contaminated water and fertilizer [13]. The biological half-life of cadmium varies between 17-30 years with limited excretion from the body[8]. Urine cadmium may inform on total body cadmium burden. Cadmium inhibits nitric oxide synthesis in endothelial cells and increases oxidative stress by catalyzing reactive oxidative species [14].

Furthermore, cadmium decreases the function of serum paraoxonase, which diminishes the antioxidant effect of high-density lipoprotein particles [15]. Cadmium-induced adipose tissue dysfunction promotes insulin resistance, even in patients without obesity [16]. In the Strong Heart Study, elevated levels of urinary cadmium were associated with increased cardiovascular and all-cause mortality, especially in patients with diabetes [13]. Our own studies in a different, far smaller population suggested an association between cadmium level and severity of PAD in both spontaneous and post-edetate disodium infusion urine. The highest urine cadmium levels were present in patients with critical limb ischemia (CLI) [17].

Chelation of lead and cadmium: Edetate disodium has a high affinity to bind metal cations, such as cadmium and lead. Thus, a treatment regimen might have the potential to decrease total body burden of these toxic metals. Arenas et al. demonstrated that a single infusion of edetate disodium-based infusion can increase total urinary metal by 71% compared to baseline (P<0.0001) with the highest effects in lead (3835%) and cadmium (633%) [18].

Clinical benefit of edetate disodium chelation: The NIH-funded Trial to Assess Chelation Therapy (TACT) was the first well-powered randomized, double-blinded, placebo-controlled trial to assess the benefit of edetate disodium-based therapy in post-MI patients [19,20]. The overall study was positive[19]. In the pre-specified subgroup of patients with diabetes, however, edetate disodium-based chelation demonstrated a marked reduction in the primary endpoint (death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina: HR=0.59; 95% CI, 0.44-0.79; P<0.001, Figure 1) [20]. There was a strong effect size on both recurrent myocardial infarction and death from any cause- which were significantly reduced by 52% and 43%, respectively[20]. Supporting the potent biological activity of this treatment, there is emerging evidence of clinical benefit in patients with CLI and risk of amputation (Figure 2) [21,22].

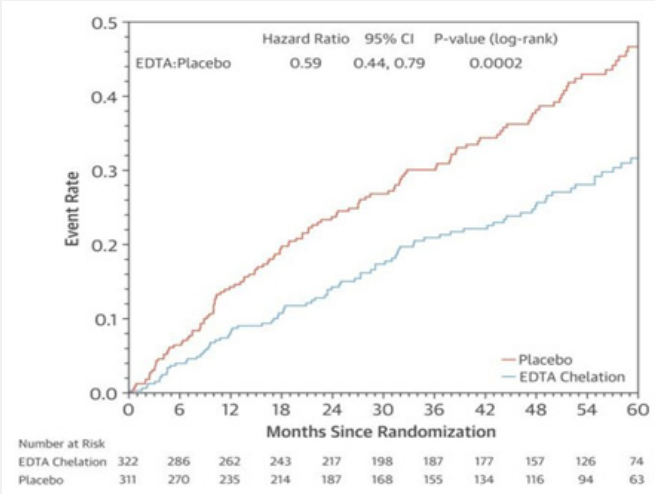

Figure 1: Primary endpoint in patients with diabetes. The primary endpoint was a composite of death of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. Kaplan- Meier Estimates of the Primary Composite Endpoint EDTA Chelation Therapy vs. Placebo: Subset of Patients with Diabetes: Hx, Med Use or Baseline Glucose>=126; CI: Confidence Interval [20].

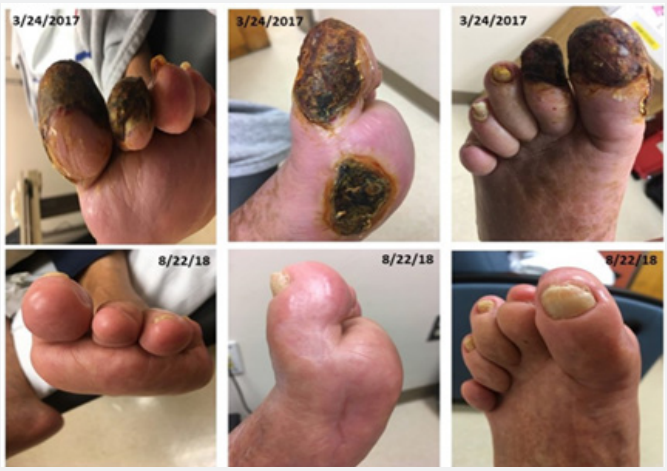

Figure 2: Patient with CLI and diabetes at baseline and after 40 infusions with edetate disodium-based chelation [21].

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Vascular decalcification by edetate disodium – an alternative hypothesis: Edetate disodium may have the ability to directly bind and remove calcium complexes within the medial vasculature along the elastic lamellae (Mönckeberg's sclerosis), thus improving vascular compliance. Mönckeberg's sclerosis is found in patients with diabetes and renal dysfunction. As this is correlated with increased cardiovascular events and leg amputation in patients with diabetes, preliminary data based on localized nanoparticle periadventitial delivery of chelation suggest that edetate disodium could be used to reverse elastin-specific medial vascular calcification without sacrificing bone integrity or blood calcium levels [23]. Similarly, Maniscalco et al. demonstrated in a study totaling 100 patients with high coronary artery calcium scores that treatment with edetate disodium and tetracycline demonstrated a 57% significant decrease in total coronary arterial calcium (P=0.001) in the 77 patients completing the study [24]. Thus, as with all new therapies, there are competing hypotheses for mechanisms, all of which may be right.

Conclusion

Edetate disodium-based infusions enhance urinary excretion of toxic metals, notably lead and cadmium. We hypothesize that offloading vasculotoxic metals decreases cardiovascular events, particularly in patients with diabetes. Decalcification of small arteries and arterioles may also have a mechanistic role. Regardless of mechanism, we believe that there is a role for edetate disodium treatment of patients with a prior MI or CLI, particularly if they have diabetes. TACT2 (post-MI patients with diabetes) and TACT3a (patients with diabetes and CLI) will further explore the potential benefits of edetate disodium-based therapy in patients with diabetes and atherosclerotic disease.

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