

## Should chelation therapy be abandoned?



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The year 2013 marks a new era in understanding the clinical importance of low-level xenobiotic heavy metal intoxication on human disease, and the efficacy and safety of ethylene diamine tetraacetic acid (EDTA) chelation for atherosclerotic disease. It is, therefore, the singular worst moment in over 50 years to consider abandoning this therapy.

At present, in the face of emerging data, the use of chelation therapy still remains controversial. The US FDA approves chelation therapy only for the treatment of heavy metal poisoning and toxicity – such toxicity is defined by levels higher than those associated with clinical illness in epidemiological studies. Complementary and alternative medicine practitioners, however, utilize chelation therapy for a wide spectrum of clinical conditions, including cardiovascular diseases. According to the 2009 National Health Statistic Report, approximately 111,000 adult Americans received chelation therapy annually [1]. If an average of ten infusions per patient were received, the out-of-pocket costs might be

as high as US\$200 million. Yet these are likely bare minimum estimates. The American College of Advancement in Medicine, the leading organization of chelating physicians, estimated that over 500,000 US adults underwent chelation treatments each year, with 800,000 patient visits and significantly higher total out-of-pocket costs [2]. US surveys convincingly demonstrate that, in spite of the controversy over chelation therapy, or perhaps because of it, the use of chelation therapy has increased over the years. There are no clear data that identify which diagnoses – vascular or nonvascular – are being treated.

EDTA remains the most commonly utilized and certainly most controversial chelation agent. This compound was synthesized in 1935 and extensively used for lead poisoning after the second world war. The first report that suggested new potential uses of EDTA chelation was published in 1955 by Clarke *et al.* [3]. While studying medical therapies for lead intoxication, the authors observed that EDTA chelation improved circulation in patients with known

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peripheral artery disease (PAD). A year later the same group of authors reported a positive effect of EDTA chelation therapy in patients with angina pectoris [4]. Since then multiple studies demonstrated positive effects of chelation therapy on coronary artery disease (CAD) [5] and PAD [6]. These reports included relief of angina and increased exercise capacity in patients with CAD, and improvement of claudication, healing of ulcerations and avoidance of amputations in patients with PAD.

Every single one of these reports of benefit, however, was fatally flawed by being a case report, case series or other nonrandomized observation. Thus, while suggestive, these studies ultimately led to a null, not negative, estimate of benefit. Several small, randomized studies of EDTA chelation were carried out in the 1990s and early 2000s, but, again, they were flawed. They were too small to exclude a modest benefit or harm of chelation therapy. They used surrogate end points, and again ultimately led to null results regarding harm or benefit of EDTA chelation in cardiovascular disease. The Cochrane collaborative [7] and others [8] reviewed the evidence on chelation therapy and came to similar conclusions – data were simply not interpretable to determine whether there was benefit or harm from EDTA chelation.

Nonetheless, plausible mechanisms of benefit for chelation therapy have been proposed, and epidemiological evidence is supportive. The best recognized and least controversial effect of chelation therapy is the removal of toxic heavy metals from the body. Therefore, if chelation has efficacy against cardiovascular disease, then logic would dictate that there be a connection between xenobiotic heavy metal intoxication and cardiovascular disease. Such a connection has been amply demonstrated. Multiple studies link total body burden or blood levels of different metals with all-cause and cardiovascular mortality [9–11]. Heavy metals are associated with hypertension, atherosclerosis and related conditions such as CAD and PAD. Heavy metals have also been linked to development of idiopathic dilated cardiomyopathy [12] and different cardiac conduction abnormalities. Experimental studies demonstrate that heavy metal-induced injury on the cellular level occurs mainly due to increased oxidative stress because metals deplete cellular antioxidant mechanisms [13]. As a result highly toxic reactive oxygen species accumulate and

oxidize intra- and extra-cellular structures such as proteins, lipids and nucleic acids, resulting in cell membrane damage, DNA damage and protein dysfunction. Oxidized lipids promote atherosclerosis via foam cell formation, endothelial proinflammatory, and proapoptotic and prothrombotic effects.

In addition to the controversy regarding clinical outcomes of chelation therapy, several deaths over the last decades were traced to EDTA infusions. It is important to mention that there are two forms of EDTA that can be utilized in a medical practice – calcium-EDTA and disodium-EDTA. Only calcium-EDTA has an FDA indication – for lead toxicity. Deaths reported in children resulted from improper use of disodium-EDTA [14]. In the adult population, most of the beneficial effects of chelation therapy have been associated with the use of disodium-EDTA. However, other side effects and even deaths have been reported with the misuse of this compound. This controversy – leading to clinical equipoise – was the state of the science in 2002, when the US National Center for Complementary and Alternative Medicine and the National Heart, Lung and Blood Institute released a Request for Applications for a definitive clinical trial of chelation therapy for coronary disease; the Trial to Assess Chelation Therapy (TACT) was born [15].

Interestingly, during the beginning of this 10-year trial heralding the start of a new era of chelation therapy research, Lin *et al.* demonstrated that EDTA chelation prevented a time-dependent fall in glomerular filtration rate, in patients with chelatable lead. This provided evidence that low-level lead intoxication was a reversible cause of chronic kidney disease [16,17].

Our team led the first randomized double-blind placebo-controlled multicenter clinical trial, TACT, to investigate the safety and effectiveness of EDTA chelation therapy in individuals with coronary artery disease [18]. This trial enrolled 1708 participants in 134 sites in the USA and Canada who were at least 50 years of age, had sustained a prior myocardial infarction, and had a blood creatinine level of  $\leq 2.0$  mg/dl ( $176.8 \mu\text{mol/l}$ ). Participants were randomly assigned to chelation (839) or placebo (869), and received a total of 55,222 infusions. They were followed for a median of 55 months. The primary end point was time to the first occurrence of death from any cause, myocardial infarction,

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stroke, coronary revascularization, or hospitalization for angina. The trial met the prespecified significance boundary (hazard ratio: 0.82; 95% CI: 0.69–0.99;  $p = 0.035$ ). Each of the components of the primary end point demonstrated a point estimate of  $<1.0$  with chelation therapy. Although not individually significant, in aggregate, as described above, they were. Analyses of predefined subgroups demonstrated that diabetics and patients with anterior myocardial infarctions had a significant interaction with study treatment and much greater therapeutic benefit. We are currently analyzing these findings in detail. Careful safety analyses were performed. Within the safety net of the clinical trial, EDTA chelation was absolutely safe.

Thus, the first large-scale trial of chelation therapy for atherosclerotic coronary disease was positive for efficacy, and demonstrated safety. Additional analyses and publications of

subgroups, interaction with oral vitamins, and effect on renal function are in progress and advanced. Extending these findings to peripheral artery disease and developing a deeper understanding of mechanisms is critical. The evidence base, therefore, supports our contention that it would be deeply misguided to abandon chelation therapy in 2013.

#### Financial & competing interests disclosure

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