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Editorial

Does Calcium Disodium EDTA Slow CKD Progression?

Related Article, p. 530

Given the increasing incidence and prevalence of chronic kidney disease (CKD),[1,2] approaches to slow disease progression are essential. For more than a decade, Ja-Liang Lin and colleagues have published randomized placebo-controlled clinical trials reporting that treatment with calcium disodium EDTA slows CKD progression. Lead chelation has been implicated as the mechanism, and benefits in diabetic and nondiabetic patients with CKD with mean blood lead levels as low as 2.6 μg/dL have been reported (Table 1). Similar study designs have been used across publications. Initially, patients are observed to compare CKD progression prior to chelation. Then, patients whose chelatable lead levels are within certain ranges (generally 60-600 μg excreted in a 72-hour urine collection after intravenous administration of 1 g of calcium disodium EDTA and thus lower than the level commonly considered for chelation in lead poisoning) are randomly assigned. The treatment group receives weekly calcium disodium EDTA until lead levels decrease to a defined target. The control group receives placebo infusions. In the follow-up period, chelation is repeated for defined indications, such as increased serum creatinine level or chelatable lead levels higher than specified cutoffs. The results of their latest trial,[3] which is focused on patients with type 2 diabetes with nephropathy, are reported in this issue of the *American Journal of Kidney Diseases* and are consistent with earlier trials in observing a benefit of calcium disodium EDTA in slowing CKD progression. The present study builds on a 2006 study[4] of patients with diabetes by including a larger sample size and doubling the follow-up time. The chelation data reported by these authors to date are summarized in Table 1.

Strengths of this body of research include prospective study design with longitudinal statistical analyses, randomization, assessment of bioavailable lead dose, and controlling for multiple risk factors for CKD progression. However, a number of limitations also have been raised. First, the results are at best single blinded. The researchers are not blinded and the treatment protocol, which includes additional calcium disodium EDTA infusions as needed based on lead levels during follow-up, may differ from the placebo protocol; therefore, patients may be able to discern their treatment group. Second, the generalizability of these findings to other populations is commonly questioned, in particular, whether lead exposure in Taiwanese patients is higher compared with other countries, such as the United States. However, the mean blood lead level in participants in the lowest lead-exposed study[5] was lower than that observed in a recent large general population study of 50- to 70-year-olds in Baltimore, MD.[6] Last, sample sizes are small, raising concerns that despite randomization, differences between groups, such as the cause of CKD (in studies of nondiabetic CKD) or socioeconomic status, may be explanatory factors.

Despite these limitations, the body of research raises an important question: should practitioners consider the use of chelation therapy in their patients with CKD with lead levels that are not typical of "lead poisoning"? As we have stated previously,[7] such therapy cannot be recommended without additional double-blind randomized studies in larger and diverse populations at other centers. However, such research is clearly indicated based on the Taiwanese work to date. If a benefit of therapy with calcium disodium EDTA (or preferably with an oral chelating agent such as dimercaptosuccinic acid [DMSA]) is proved without an adverse impact on other organs (eg, the central nervous system, through lead mobilization or from chelation itself), the potential public health impact would be very significant.

Whether such research will ever be conducted is uncertain. An editorial that accompanied the 2003 chelation publication of Lin et al[8] referred to an earlier study,[9] noting:

> Inexplicably, even though that study was a well-designed prospective trial, it has had a limited effect on the nephrology community. Very few clinics that treat progressive renal failure assess the body lead burden, even in patients with possible 'saturnine gout.' Critics argued that this small study was neither blinded nor placebo-controlled. Clinicians may not have identified with the unique nature of the population under study (in Taiwan) or may have been dissuaded by historical caveats about EDTA toxicity.[10(p346)]

Despite continued publications by Lin and colleagues in high-impact journals, these statements remain as true in 2012 as they were in 2003. This may be because this body of research deals with 2 controversial areas: (1) whether low-level lead exposure

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Table 1. Chelation Data Reported by Lin and Colleagues

Study[a]	CKD Cause	Treatment/ Follow-up (mo)	Group	No.	Lead		Kidney Function[b]	
					Blood Level (μg/dL)[c]	Chelatable (μg/72 h)[c]	Pretreatment[c]	Annual Change
Lin et al[9] (1999)	Non-DM	14	CaEDTA	15	NR	254.9 ± 118.1	0.0043 ± 0.0016[d]	+0.00034[d]
			Control	16	NR	279.7 ± 149.2	0.0042 ± 0.0013[d]	−0.00051[d]
Lin et al[11] (2001)	Non-DM	14	CaEDTA	24	5.2 ± 2.5	198.0 ± 83.9	37.8 ± 15.6[e]	+2.6[e]
			Control	12	5.4 ± 2.7	212.0 ± 132.0	34.8 ± 12.0[e]	−5.1[e]
Lin et al[8] (2003)	Non-DM	27	CaEDTA	32	6.1 ± 2.5	150.9 ± 62.4	32.0 ± 12.1	+1.1
			Control	32	5.9 ± 3.0	144.5 ± 87.9	31.5 ± 9.0	−2.7
Lin et al[4] (2006)	T2DM	15	CaEDTA	15	7.5 ± 4.6	148.0 ± 88.6	22.4 ± 4.4	−3.5
			Control	15	5.9 ± 2.2	131.4 ± 77.4	26.3 ± 6.2	−10.6
Lin et al[5] (2006)	Non-DM[f]	27	CaEDTA	16	2.6 ± 1.0	43.1 ± 13.7	41.2 ± 11.2	+3.0
			Control	16	3.0 ± 1.1	47.1 ± 15.8	42.6 ± 9.7	−2.0
Lin-Tan et al[12] (2007)	Non-DM	51	CaEDTA	58	5.0 ± 2.2	164.1 ± 111.1	36.8 ± 12.7	−0.3
			Control	58	5.1 ± 2.6	151.5 ± 92.6	36.0 ± 11.2	−2.9
Chen et al[3] (2012)	T2DM	27	CaEDTA	25	7.1 ± 4.1	142.1 ± 39.2	27.6 ± 4.7	−4.6
			Control	25	6.3 ± 2.4	151.3 ± 93.6	29.5 ± 6.2	−8.8

Abbreviations: CaEDTA, calcium disodium EDTA; CKD, chronic kidney disease; DM, diabetes mellitus; NR, not reported; T2DM, type 2 diabetes mellitus.

[a]Reference number and year published.

[b]Kidney function is estimated glomerular filtration rate (in mL/min/1.73 m^2) except where indicated.

[c]Lead dose and kidney function data are those just prior to onset of chelation unless only baseline data at the beginning of observation period are provided.

[d]1/serum creatinine (L/μmol).

[e]Creatinine clearance (mL/min).

[f]Group with lowest lead exposure.

causes nephrotoxicity, and (2) the settings in which lead chelation is beneficial.

The vast majority of nephrologists have never received formal training for heavy metal toxicity. High-level lead exposure is known to cause lead nephropathy; however, fortunately, this is increasingly rare. Lead-related nephrotoxicity at lower exposure levels, as a cofactor with diabetes, hypertension, or other traditional CKD risk factors, is not commonly considered. Thus, Lin's research may have limited resonance in the nephrology community. However, the impact of chelation therapy on CKD progression is not necessarily related to the nephrotoxicity of environmental lead exposure. If such therapy is beneficial, the mechanism may be due to removing lead from the body, but chelation also might directly benefit kidney function regardless of lead exposure. Antioxidant effects of calcium disodium EDTA have been reported.[13,14] Calcium disodium EDTA administration has been shown to reduce kidney damage in a rat model of acute kidney injury induced by ischemia.[15] Similarly, in a non–lead-exposed rat model, giving DMSA during nephrosclerosis induction is reported to prevent kidney damage.[16] In rodent models of lead-related nephrotoxicity,[17-19] the benefits of chelation do not appear to accrue as a result of undoing structural damage,[19] again suggesting that the underlying mechanism may involve improving hemodynamics by reducing reactive oxidant species through lower lead levels and/or by direct action of the chelating agent.[16]

In regard to the second controversy, indications for chelation in lead poisoning continue to be debated in the occupational medicine and clinical toxicology communities. Chelation with DMSA did not improve cognitive function in lead-poisoned children,[20,21] although the dose used may not have achieved adequate reduction of brain lead levels.[22] Side effects of chelation also are considerations. At much higher equivalent doses than the calcium disodium EDTA protocol used by Lin and colleagues, DMSA is known to impair cognitive function in rats without lead exposure.[23] Acute kidney injury has been reported with early use of calcium disodium EDTA at high doses.[24] Alternative medicine practitioners have used EDTA without calcium for autism and coronary artery disease, a practice that has caused deaths from hypocalcemia.[25] The ongoing National Institutes of Health–sponsored Trial to Assess Chelation Therapy (TACT) for cardiac disease (http://nccam.nih.gov/health/chelation/), which, importantly, used EDTA without calcium, has proved controversial due in part to concerns regarding safety.[26] Thus, chelation may be viewed cautiously or with frank skepticism by many in the medical community. How-

ever, although it is important to monitor chelation side effects, it is important to note that the Taiwanese group uses EDTA at a dose that is much lower than those associated with side effects in the literature described above and in a form that contains calcium.

In order to circumvent these controversies in an effort to move this research line forward, the question can be reframed to ask: Does treatment with calcium disodium EDTA (or an oral agent such as DMSA) slow progression of CKD? The study of agents that may modulate inflammation and oxidative stress in order to slow CKD progression is not novel. Recently, bardoxolone methyl, an oral antioxidant inflammation modulator, has shown promise in the treatment of advanced diabetic nephropathy.[27] Pentoxifylline, with diverse anti-inflammatory, antiproliferative, and antifibrotic properties, has been examined in multiple studies of animals and humans and currently is being examined in the PREDIAN (Pentoxifylline for Renoprotection in Diabetic Nephropathy) trial to determine its efficacy in slowing CKD progression in patients with diabetic nephropathy.[28] Statins, which are known to have "lipid-independent actions" involving oxidative stress modulation, have been examined repeatedly for benefit in slowing CKD progression and decreasing cardiovascular morbidity and mortality in patients with CKD.[29] Multiple other agents, such as uric acid–lowering drugs, angiotensin-converting enzyme inhibitors, vitamin D, omega-3 fatty acids, and *N*-acetylcysteine, have been examined in acute and chronic kidney injury, with direct or indirect effects on oxidative stress and inflammation implicated in the mechanism of potential benefit. In the context of therapy to slow CKD progression, potentially through an antioxidant mechanism, calcium disodium EDTA may be more relevant to the broader nephrology community and considered worthy of further study.

In the interim, how should the existing research by Lin and colleagues affect the clinical care of patients with CKD? An occupational and environmental history is essential; a patient-administered questionnaire that can be used for this purpose is available online.[7] If work or hobbies involving nephrotoxicants are identified, patients can be counseled to reduce or stop exposure. Occupational physicians can be consulted to assist with workplace accommodations as needed.

Given the global public health burden of CKD, strategies to prevent CKD and delay its progression remain a priority. Skepticism concerning the nephrotoxicity of low-level lead exposure may persist after reading the most recent study[3] by Lin's group, and as with any research study, there is a risk that future trials to replicate the results, if attempted by others, may not show the same benefits. However, the slowing of CKD progression with calcium disodium EDTA has been consistent across multiple studies from this group and remains intriguing. Because a minority of the strategies studied to date to slow CKD progression have consistently been successful, this body of research makes a compelling case for further well-designed, preferably multicenter, studies.

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