0163–4984/99/7003–0265 $12.00

EDTA Chelation Therapy Does Not Selectively Increase Chromium Losses

RICHARD A. ANDERSON,* NOELLA A. BRYDEN, AND ROBERT WATERS

Nutrient Requirements and Functions Laboratory Beltsville Human Nutrition Research Center U.S. Department of Agriculture, Agricultural Research Service, Beltsville, MD 20705-2350; and Waters Preventive Medicine Center, Wisconsin Dells, WI

Received October 24, 1998; Accepted March 1, 1999

ABSTRACT

Chelation therapy and supplemental Cr have both been shown to lead to improved blood glucose, lipids, and insulin activity. Chelation therapy leads to the removal of toxic as well as essential metals. To determine if chelation therapy leads to increased urinary Cr losses and altered Cr homeostasis, 2 groups of subjects (1 group that had undergone only 1 or no chelation therapy and 1 group in which all subjects had undergone at least 19 chelation sessions) were evaluated for differences in possible Cr homeostasis based on urinary Cr losses. There were no significant differences in urinary Cr losses between the two groups of subjects and there were no significant increases in urinary Cr losses resulting from chelation therapy. Increases in urinary Cr losses were strongly influenced by supplementation but not chelation therapy.

Index Entries: Chromium; Trace elements; Diabetes; Chelation therapy; EDTA.

INTRODUCTION

Chelation therapy is a medical treatment employed to chelate or remove undesirable metals such as lead, mercury, and cadmium from the body. By removing toxic metals and undesirable levels of iron and other

*Author to whom all correspondence and reprint requests should be addressed.

Table 1
Characteristics of Subjects

Subject #	Sex	Age	Ht	Wt	EDTA prior (g)	EDTA (g) study day
1	F	63	172	92	1	3
2	M	76	183	77	1	3
3	M	60	185	98	0	3
4	F	77	163	72	1	3
5	F	70	157	68	0	3
6	M	63	183	108	0	1.2
7	F	68	165	88	0	3
8	M	75	173	77	0	1.5
9	M	75	183	89	0	3.0
10	M	51	185	86	133	3
11	M	56	188	89	159	3
12	M	73	183	89	132	3
13	M	67	173	69	163	3
14	M	52	188	95	102	3
15	M	74	166	65	237	3
16	F	73	168	76	48	3

free-radical catalysts with ethylenediamine tetraacetic acid (EDTA), lipid peroxidation can be reduced several-fold *(1)*. Other postulated benefits include uncoupling of disulfide and metallic crosslinkages, normalization of calcium metabolism, reactivation of enzymes inhibited by toxic metals, and restoration of normal prostacyclin production in blood vessel walls *(1)*. However, EDTA is a relatively nonspecific chelator that also chelates beneficial metals other than calcium and iron such as zinc, manganese, magnesium, and possibly chromium.

Chromium has beneficial effects on fasting blood glucose, glucose tolerance, and insulin activity *(2)*. Chelation therapy has also been shown to improve these parameters *(3)*. Cranton et al. *(4)* reported a 27% increase in Cr in a single fasting morning urine sample following chelation therapy. Nonspecific stresses, including high-sugar diets, exercise, and physical trauma, also increase Cr losses *(5)*. Beneficial effects of EDTA chelation therapy on chromium homeostasis would not be anticipated if EDTA depleted Cr stores, because Cr intake is suboptimal *(6,7)*.

This study was undertaken to determine if EDTA chelation therapy chelates Cr and to determine if several sessions of chelation therapy would alter Cr homeostasis. The latter could be therapeutically important because Cr is an essential nutrient and its depletion by EDTA chelation therapy would necessitate increased replacement therapy.

MATERIALS AND METHODS

Subjects

The subject population included those with 0 or 1 EDTA treatment (subjects 1–9) and those with 19 or more EDTA chelation treatments (subjects 10–16) (Table 1). Chelation therapy of the subjects was part of their normal medical treatment and subjects were not reimbursed for their participation. Subjects were free to withdraw from the study at anytime. Following a thorough explanation of the study and purposes of the collection of the urine and serum samples, subjects signed an informed consent agreement. Study was approved by the Clinic Human Studies Review Board, Wisconsin Dells, WI.

Urine Collection

Twenty-four-hour urine samples were collected in 4-L sample containers (Fisher Scientific Co., Pittsburgh, PA) 2 d prior to chelation therapy, the day of chelation therapy, and the following day. Control urine samples were collected on Monday and Tuesday and the chelation urine samples on Wednesday and Thursday.

Chelation Therapy

Because 95% of a dose of EDTA is cleared by the kidneys and renal toxicity of EDTA is a well-known phenomenon, it is important to maintain the dose of EDTA at no more than 50 mg/kg body weight with normal kidney function and a correspondingly lower dose based on an estimate of kidney function in patients with renal impairment. The dosage of EDTA was predicated on measurement of kidney function in each patient based on an estimation of creatinine clearance using serum creatinine, an estimate of lean body mass *(8)*. On Wednesday morning of the study week, an intravenous infusion of EDTA mixed in sterile water with 5 g of sodium ascorbate, 2500 units of heparin, 3 mL of 2% procaine, 100 mg of pyridoxine HC1, 4 meq of KCl, 1 mL of sodium bicarbonate (8.4%), 1000 µg hydroxycobalamin, 1 mL vitamin B complex, and 7 mL of magnesium sulfate equivalent to 686 mg of elemental magnesium was given in an arm vein over a 2.5–3-h period.

Chromium Analyses

Urinary Cr concentrations were determined by a method of additions on nonashed urine samples (30 µL) with a model 5000 Zeeman atomic absorption spectrophotometer and a model HGA-500 graphite furnace (Perkin Elmer Corp., Norwalk, CT) by use of pyrolytically coated tubes *(9)*. Two pooled urine samples whose chromium concentration had been verified by two independent methods were assayed at least twice

Table 2
Characteristics of Subjects

Subject #	Supplemental Cr intake (μg/d)	Urinary Cr (μg/d) EDTA Chelation[2] Basal[1]	Day 1	Day 2
1	0	0.13	0.60	0.09
2	133	0.43	0.97	1.14
3	25	0.30	8.9	6.42
4	100	0.50	0.95	1.03
5	200	1.95	5.1	7.7
6	0	0.07	0.34	0.20
7	2000	13.3	14.9	13.5
8	120	0.84	0.80	0.89
9	0	0.5	0.71	0.76
10	1200	19.0	6.24	32.4
11	1100	0.3	0.52	0.19
12	7	0.75	0.69	0.52
13	200	0.88	1.31	1.36
14	200	1.32	1.55	2.35
15	50	0.37	0.51	0.41
16	200	0.82	0.95	1.44
Mean ± SEM	346 ± 143	2.60 ± 1.35	2.82 ± 1.02	5.65 ± 2.49

[1] Basal Cr excretion is the average 24-h Cr excretion on the 2 d prior to chelation therapy.
[2] EDTA chelation day 1 is the urinary Cr excretion on the day of the chelation therapy. Day 2 is the ensuing 24-h period.

daily as internal checks on the analytical reliability of the Cr determinations *(10)*.

RESULTS

Two groups of adult subjects ranging in age from 51 to 77 yr were recruited to ascertain the effects of chelation therapy on urinary Cr losses (Table 1). Subjects 1–9 had undergone chelation therapy once or less and subjects 10–16 had undergone more than 18 sessions. There were no apparent differences in the basal Cr excretion of the two groups of subjects (Table 2). There was a correlation ($p<0.01$) between urinary Cr excretion and supplemental Cr intake (Fig. 1). The linear regression equation for the line was urinary Cr excretion = 0.27 + (0.004) × supplemental Cr Intake). Values plotted in Fig. 1 are for supplemental Cr intakes below 250 μg/d.

There were no significant effects of chelation therapy on urinary Cr losses (Table 2). The urinary Cr losses on the day of chelation were

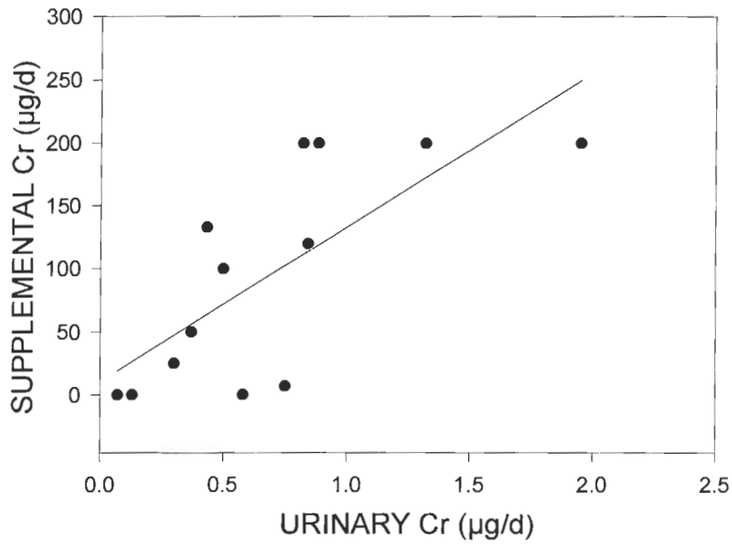

Fig. 1. Correlation of supplemental chromium with urinary Cr losses. Basal daily Cr intake of the female subjects would be approximately 28 µg and 33 µg for the males. The solid line is a computer-generated first-order linear regression line. Data are for subjects with supplemental Cr intake of 250 µg/d or less. Values are an average of the 2 d prior to chelation therapy. The linear regression equation for the line is chromium excretion = 0.27 + (0.004 × supplemental Cr intake). (From ref. *6*.)

usually higher and d 2 of chelation was also usually higher than d 1. Because the effects of EDTA occur in the first few hours following therapy, the effects observed on d 2 following chelation therapy are likely nonspecific and not the result of the specific chelation of Cr with EDTA. Apparent increases on d 1 appear to also be nonspecific and may relate to the nonspecific stresses associated with chelation therapy *(5)*.

The effects of supplemental Cr on urinary Cr losses appear to be much larger than any specific effects due to EDTA–Cr chelation. There were only three subjects that did not report taking supplements containing Cr (subjects 1, 6, and 9, Table 2). Basal urinary Cr excretion of two of these subjects was in the region of 0.2 µg/d, which is consistent with values we normally see for nonsupplemented subjects *(9)*. There was an increase in urinary Cr losses in these three subjects that appears to be the result of specific EDTA chelation. However, during chelation therapy, 250 mL of the EDTA solution was administered. Triplicate analyses of two batches of EDTA solutions contained 1.76 and 1.54 ng Cr/mL. Therefore, approximately 0.4 µg of Cr would be injected into each patient during therapy, which is greater than the apparent increases in urinary Cr losses.

DISCUSSION

Ethylenediamine tetraacetic acid chelation therapy has been used for decades for the treatment of vascular disease, alone or in combination with other treatments *(3)*. EDTA therapy was used initially in the clinical treatment of lead toxicity before 1950 and in the treatment of hypercalcemia beginning in 1950 *(11)*. Following chelation therapy for lead-toxicity patients reported improvements in angina pectoris, which led to the use of EDTA chelation therapy in the treatment of atherosclerotic diseases *(12)*.

Ethylenediamine tetraacetic acid therapy has multiple mechanisms that may positively affect plaque formation and cell-membrane function *(3)*. Improvements in platelet aggregation and free-radical scavengers, reduced iron overload, improved blood lipids, and restoration of electromagnetic potential across cell membranes have been proposed to explain the improvements attributed to chelation therapy. The benefits, mechanisms, indications, contraindications, and side effects of EDTA chelation therapy have been reviewed *(3)*.

Ethylenediamine tetraacetic acid chelation therapy is a safe medical procedure, and when administered properly, side effects are rare. However, EDTA chelation is nonspecific and the essential metals are likely to be chelated and removed along with toxic metals and toxic levels of the essential metals. Part of the chelation therapy treatments are the replenishment of metals and other nutrients removed during therapy, such as zinc, manganese, copper, chromium, and selenium along with synergistic antioxidants and B-complex vitamins *(3)*.

Although Cr is routinely added back following chelation therapy, there is no strong evidence to show that Cr is chelated and removed during EDTA chelation therapy. Tandon and Gaur *(13)* reported that EDTA and diethylenetriamine pentacetic acid (DTPA) were effective in vivo in the removal of Cr from animals poisoned with Cr $(NO_3)_3 \cdot 9H_2O$. However, ascorbic acid and 3,4-dihydroxy-L-phenyl alanine (L-DOPA) were more effective in vitro than EDTA and DTPA. No relationship was observed between the structure or the molecular weight of the various chelating agents and their ability to remove Cr from tissues or in vitro from subcellular fractions *(13)*.

N-Acetylcysteine (NAC) was shown to be effective in the removal of Cr from rats poisoned with potassium dichromate. Calcium EDTA treatment led to small increases in Cr lost in the urine that was several-fold less than that of NAC *(14)*.

Cranton et al. *(4)* reported a 27% increase in urinary Cr excretion in humans following chelation therapy, but increases were not significant. Sata et al. *(15)* reported an increase in urinary Cr excretion 1 h after Ca EDTA injection in 18 male foundry workers. They concluded that "chromium absorbed in human tissues might be mobilized by Ca EDTA."

Our results also suggest that increases in urinary Cr losses from EDTA chelation therapy are small and may be the result of the contaminating Cr present in the chelating solutions. Although the concentration of the Cr in the EDTA chelating solution is low, approximately 1.6 ng Cr/mL, it still would amount to approximately 0.4 µg of Cr injected into the blood that would subsequently be excreted in the urine. Because the total amount of Cr lost in the urine of nonsupplemented people is approximately 0.2 µg/d, an increase of 0.4 µg becomes significant and could account for the apparent increases in urinary Cr excretion due to chelation therapy.

Stress also leads to increased urinary Cr losses *(5)* and the stresses associated with the chelation therapy could lead to nonspecific increases in urinary Cr losses. Urinary Cr losses are correlated with the degree of stress and are correlated with the stress hormone cortisol *(16)*. Therefore, the nonspecific increases in Cr losses would differ among individuals as a result of the perceived duration and intensity of the stress.

If there was an increase in urinary Cr losses resulting from chelation therapy, the day of the chelation should be higher than the following stress days because the chelating action of EDTA would be essentially complete in the first 4 h or less following therapy. The effective half-life of EDTA in humans is 60 min *(17)*. In our work, there were no significant differences in urinary Cr losses on the 2 d prior to chelation or on the day of chelation and the following day.

Chromium supplementation was common in our group of patients undergoing chelation therapy. This would be expected because Cr is routinely one of the nutrients replenished following chelation therapy. The increases in urinary Cr losses as a result of supplementation were much greater than those associated with chelation therapy. The urinary Cr losses of the patients could be predicted by the equation urinary Cr excretion = 0.27 + (0.004 × supplemental Cr intake). This is consistent with our earlier work that showed that Cr absorption from supplemental Cr was approximately 0.4% *(9)*.

Although our results do not show significant losses of Cr resulting from EDTA chelation therapy, they also do not support changes in replenishment of Cr following chelation therapy. Because dietary Cr intake is suboptimal and stress increases Cr losses, replenishment of Cr stores following chelation therapy is still recommended.

REFERENCES

1. E. M. Cranton and J. P. Frackelton, Free radical pathology in age-associated diseases: treatment with EDTA chelation, nutrition, and antioxidants, *J. Adv. Med.* **2,** 17–54 (1989).
2. R. A. Anderson, Recent advances in the clinical and biochemical manifestation of chromium deficiency in human and animal nutrition, *J. Trace Element Exp. Med.* **11,** 241–250 (1998).

3. L. T. Chappell and M. Janson, EDTA chelation therapy in the treatment of vascular disease, *J. Cardiovasc. Nutr.* **10,** 78–86 (1996).
4. E. M. Cranton, Z. X. Liu, and I. M. Smith, Urinary trace and toxic elements and minerals in untimed urine specimens relative to urine creatinine, Part I: concentrations of elements in fasting urine, *J. Adv. Med.* **2,** 331–348 (1989).
5. R. A. Anderson, Stress effects on chromium nutrition of humans and farm animals, in *Proc. Alltech's Tenth Symposium Biotechnology in the Feed Industry*, Nottingham University Press, Loughbrough, England, pp. 267–274 (1994).
6. R. A. Anderson and A. S. Kozlovsky, Chromium intake, absorption and excretion of subjects consuming self-selected diets, *Am. J. Clin. Nutr.* **41,** 1177–1183 (1985).
7. R. A. Anderson, N. A. Bryden, and M. M. Polansky, Dietary chromium intake–freely chosen diets, institutional diets and individual foods, *Biol. Trace Element Res.* **32,** 117–121 (1992).
8. D. W. Cockcroft and M. H. Gault, Prediction of creatinine clearance from serum creatinine, *Nephron* **16,** 31–41 (1976).
9. R. A. Anderson, M. M. Polansky, N. A. Bryden, K. Y. Patterson, C. Veillon, and W. Glinsmann, Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters, *J. Nutr.* **113,** 276–281 (1983).
10. C. Veillon, W. R. Wolf, and B. E. Guthrie, Determination of chromium in biological materials by stable isotope dilution, *Anal. Chem.* **51,** 1022–1024 (1979).
11. A. Popovici, C. F. Geschichter, A. Reinovsky, and M. Rubin, Experimental control of serum calcium levels in vivo, *Proc. Soc. Exp. Biol. Med.* **74,** 415–422 (1950).
12. N. E. Clarke, C. N. Clarke, and R. E. Moscher, Treatment of angina pectoris with disodium ethylene diamine tetraacetic acid, *Am. J. Med. Sci.* **4,** 654–666 (1956).
13. S. K. Tandon and J. S. Gaur, Chelation in metal intoxication. IV. Removal of chromium from organs of experimentally poisoned animals, *Clin. Toxicol.* **11,** 257–264 (1977).
14. W. Banner, Jr., M. Koch, D. M. Capin, S. B. Hopf, S. Chang, and T. G. Tong, Experimental chelation therapy in chromium, lead and boron intoxication with *N*-acetylcysteine and other compounds, *Toxicol. Appl. Pharmacol.* **83,** 142–147 (1986).
15. F. Sata, S. Araki, K. Murata, and H. Aono, Behavior of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: observations in metal workers, *J. Toxicol. Environ. Health* **54,** 167–178 (1988).
16. R. A. Anderson, N. A. Bryden, M. M. Polansky, and J. W. Thorp, Effect of carbohydrate loading and underwater exercise on circulating cortisol, insulin and urinary losses of chromium and zinc, *Eur. J. Appl. Physiol.* **63,** 146–150 (1991).
17. L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 3rd ed., MacMillian Co., New York, p. 950 (1985).