

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 23, 2003

VOL. 348 NO. 4

Environmental Lead Exposure and Progression of Chronic Renal Diseases in Patients without Diabetes

Ja-Liang Lin, M.D., Dan-Tzu Lin-Tan, R.N., Kuang-Hung Hsu, Ph.D., and Chun-Chen Yu, M.D.

ABSTRACT

BACKGROUND

Previous research suggests that environmental lead exposure correlates with age-related decreases in renal function.

METHODS

Two hundred two patients with chronic renal insufficiency (indicated by a serum creatinine level between 1.5 mg per deciliter and 3.9 mg per deciliter) who had a normal total-body lead burden and no history of exposure to lead were observed for 24 months. After the observation period, 64 subjects with an elevated body lead burden were randomly assigned to the chelation control groups. For three months, the patients in the chelation group received lead-chelation therapy with calcium disodium EDTA, and the control group received placebo. During the ensuing 24 months, repeated chelation therapy was administered weekly to 32 patients with high-normal body lead burdens (at least 80 μg but less than 600 μg) unless on repeated testing the body lead burden fell below 60 μg ; the other 32 patients served as controls and received weekly placebo infusions for 5 weeks every 6 months. The primary end point was an increase in the serum creatinine level to 1.5 times the base-line value during the observation period. A secondary end point was the change in renal function during the intervention period.

RESULTS

The primary end point occurred in 24 patients during the observation period; the serum creatinine levels and body lead burden at base line were the most important risk factors. The glomerular filtration rate improved significantly by the end of the 27-month intervention period in patients receiving chelation therapy: the mean (\pm SD) change in the glomerular filtration rate in the patients in the chelation group was 2.1 ± 5.7 ml per minute per 1.73 m^2 of body-surface area, as compared with -6.0 ± 5.8 ml per minute per 1.73 m^2 of body-surface area in the controls ($P < 0.001$). The rate of decline in the glomerular filtration rate in the chelation group was also lower than that in the controls during the 24-month period of repeated chelation therapy or placebo.

CONCLUSIONS

Low-level environmental lead exposure may accelerate progressive renal insufficiency in patients without diabetes who have chronic renal disease. Repeated chelation therapy may improve renal function and slow the progression of renal insufficiency.

From the Divisions of Nephrology and Clinical Toxicology, Chang Gung Memorial Hospital, Lin-Kou Medical Center, Medical College of Chang Gung University (J.-L.L., D.-T.L.-T., C.-C.Y.); and the Laboratory for Epidemiology, Department of Health Care Management, Chang Gung University (K.-H.H.), Taipei, Taiwan. Address reprint requests to Dr. Lin at the Poison Center and Division of Nephrology, Chang Gung Memorial Hospital, 199 Tung Hwa North Rd., Taipei, Taiwan, or at jllin99@hotmail.com.

N Engl J Med 2003;348:277-86.

Copyright © 2003 Massachusetts Medical Society.

LEAD-INDUCED NEPHROPATHY IS WELL recognized in persons with a high level of exposure to lead.¹⁻⁴ Several epidemiologic studies⁵⁻⁷ have demonstrated a positive association between blood lead levels and the rate of the usual decrease in renal function that occurs with age in the general population. However, those studies did not control for factors that influence progression, such as blood pressure, the presence or absence of hyperlipidemia, and urinary protein excretion.⁸⁻¹³ The blood lead level reflects only recent lead exposure and not the lead burden of the body. Thus, whether low-level environmental lead exposure influences the progression of renal insufficiency remains unknown.

The most reliable methods of measuring body lead burden are bone x-ray fluorescence studies and calcium disodium EDTA mobilization tests.¹⁴ A person with a body lead burden of more than 600 μg (2.90 μmol), as assessed by calcium disodium EDTA mobilization, is considered to have lead poisoning. We previously conducted EDTA-mobilization tests to assess the body lead burden of patients without known lead exposure who had renal insufficiency¹⁵⁻²⁰; the results suggest that long-term low-level environmental lead exposure may be associated with the progression of renal insufficiency,^{15,16} as well as with renal tubular and glomerular damage in the general population.^{19,20} Although short-term lead-chelation therapy has been used to improve renal function and slow the progression of renal insufficiency in lead workers,⁹ in patients with chronic renal insufficiency,¹⁵ and in rats with long-term low-level lead exposure,²¹ the efficacy of long-term, repeated lead-chelation therapy in slowing progressive renal insufficiency remains undetermined.

We conducted a 24-month prospective observational study, followed by a 27-month placebo-controlled clinical trial of chelation therapy, to determine whether chronic, low-level environmental lead exposure influences the progression of renal insufficiency and whether chelation can retard its course.

METHODS

SUBJECTS

The Medical Ethics Committee of Chang Gung Memorial Hospital in Taipei, Taiwan, approved the protocol, and all patients provided written informed consent.

Patients from 18 through 80 years of age who had chronic renal insufficiency were eligible if they had a serum creatinine concentration between 1.5

mg per deciliter (132.6 μmol per liter) and 3.9 mg per deciliter (344.8 μmol per liter), with a decrease in the glomerular filtration rate of less than 5 ml per minute over a period of at least six months; blood pressure less than 140/90 mm Hg; a cholesterol level below 240 mg per deciliter (6.21 mmol per liter); daily protein intake under 1 g per kilogram of body weight; and no known history of exposure to lead or other heavy metals (body lead burden, less than 600 μg [2.90 μmol], as measured by EDTA mobilization testing and 72-hour urine collection). Specific renal diagnoses were based on the patient's history and the results of laboratory evaluations, renal imaging, and renal histologic examination.²²

The exclusion criteria were renal insufficiency with a potentially reversible cause, such as malignant hypertension, urinary tract infection, hypercalcemia, or drug-induced nephrotoxic effects; systemic diseases, such as connective-tissue diseases or diabetes mellitus; use of drugs that might alter the course of renal disease, such as nonsteroidal anti-inflammatory agents, steroids, or immunosuppressive drugs; rapidly progressive glomerulonephritis or a high level of 24-hour urinary protein excretion (more than 8 g per day); previous marked exposure to lead (lead poisoning or occupational exposure); drug allergies; and absence of informed consent.

Blood pressure was controlled with diuretics and angiotensin-converting-enzyme inhibitors, with or without nondihydropyridine calcium-blocking agents. No angiotensin-receptor-antagonist agents were used. Patients with normal blood pressure were not prescribed angiotensin-converting-enzyme inhibitors, in accordance with practice in Taiwan at the time of the study. Blood pressure, cholesterol, and protein intake were well controlled in all patients. Calcium carbonate was prescribed to control phosphate levels. No patients received vitamin D₃ supplements or erythropoietin treatment. The patients received dietary consultation, with recommendation of a normal-protein diet (0.8 to 1.0 g of protein per kilogram of body weight per day, provided by foods such as meat, fish, chicken, and eggs). A nutritionist reviewed the dietary intake of each patient every three to six months, and 24-hour urea excretion was measured every three months to determine nitrogen balance and dietary compliance.²³

MEASUREMENTS OF BLOOD LEAD LEVELS AND BODY LEAD BURDEN

Blood lead levels and body lead burden were measured as described previously.^{15,16,22} Body lead burden was measured by EDTA-mobilization tests de-

veloped by Emmerson and modified by Behringer et al.²⁴ Blood lead levels and body lead burden assessed by 72-hour urinary lead excretion after the intravenous infusion of 1 g of calcium disodium EDTA (edetate calcium disodium [Calcium Disodium Versenate], Abbott Laboratories) were measured by electrothermal atomic-absorption spectrometry (model 5100 PC, Perkin-Elmer) with Zeeman background correction and a L'vov platform. Internal and external quality-control procedures yielded consistently satisfactory results.²²

STUDY PROTOCOL

Base-Line Data-Collection Period

Base-line blood lead levels, hemoglobin levels, and body lead burden were assessed for nine months before the study in 250 patients. Serum creatinine, blood urea nitrogen, and cholesterol, as well as urinary protein, creatinine, and urea excretion, were measured every three months with use of an autoanalyzer system (Hitachi) to ensure that the entry criteria were met.

Longitudinal Observation Period

Serum creatinine, blood urea nitrogen, and cholesterol, as well as urinary protein, creatinine, and urea excretion, were determined every three months from month 0 to month 24 in 202 patients who completed the observation period. Urinary excretion measurements were the average of values from two consecutive 24-hour urine collections. Renal function was assessed by measurement of creatinine clearance and estimation of the glomerular filtration rate (both in milliliters per minute per 1.73 m² of body-surface area).²⁵

Intervention Period

The 24-month observational study was followed by a single-blind, randomized, placebo-controlled study, lasting a total of 27 months, in which all patients were randomly assigned to receive placebo or chelation therapy during the first 3 months and then received either placebo or repeated chelation therapy, if necessary, over the next 24 months.

On the basis of previous work,¹⁶ a high-normal body lead burden was defined as at least 80 µg (0.39 µmol) and less than 600 µg (2.90 µmol) of lead. Among the 202 patients who completed the observation period, 64 with high-normal body lead burden and serum creatinine levels of less than 4.2 mg per deciliter (371.3 µmol per liter) were randomly assigned to the control or chelation group in

a 1:1 ratio. During the first three months, the patients in the chelation group received intravenous infusions of one vial (1 g) of calcium disodium EDTA mixed with 200 ml of normal saline over a period of two hours weekly unless the body lead burden fell below 60 µg (0.29 µmol). Control patients received weekly infusions of one vial (20 ml) of 50 percent glucose mixed with 200 ml of normal saline over a period of two hours for five weeks.¹⁶

Laboratory measurements were performed every 3 months for an additional 24 months after the initial placebo or chelation therapy to document possible changes in renal function. The patients in the chelation group received repeated lead-chelation therapy with weekly infusions of 1 g of calcium disodium EDTA, as in the first three months, if their body lead burden, assessed every six months during this period, exceeded 60 µg. Control patients received placebo weekly for five weeks every six months during this period.

ADHERENCE

Patients were withdrawn from the study if they dropped out or if there was nonadherence to therapy, development of poorly controlled hypertension (blood pressure above 160/95 mm Hg), hyperlipidemia (cholesterol above 260 mg per deciliter [6.72 mmol per liter]), a protein intake exceeding 1.5 g per kilogram per day for more than six months, or acute deterioration of renal function.

OUTCOME MEASURES

The primary end point was an increase in serum creatinine to 1.5 times the base-line value, measured on two occasions one month apart, or the need for hemodialysis during the longitudinal observation period. A secondary end point was a change in the creatinine clearance or glomerular filtration rate during the intervention period.

STATISTICAL ANALYSIS

The sample size was calculated with PASS software (power analysis and sample-size package, NCSS statistical software). For a two-sided test at the 0.05 significance level, a sample size of 64 patients (32 in each group) would be sufficient to permit the study to detect a difference between treatment groups in the rate of change in the glomerular filtration rate of 0.31 ml per minute per three-month interval, with a power of 0.95. The Cox proportional-hazards model was used to determine the significance of the variables in predicting the primary

end point during the observation period. This model considered all variables related to the progression of renal insufficiency in the literature.⁴⁻⁶ To examine further whether a predictor was associated with the progression of renal insufficiency in the study subjects during the observation period, generalized estimating equations were used in longitudinal multivariate analyses with SAS statistical software (version 6.12). The differences in the rates of progressive renal failure between the two groups were analyzed with a chi-square test, a paired t-test, and Student's t-test. The Mann-Whitney U test was used for data that were not normally distributed. All P values were two-tailed, and all results are presented as means \pm SD. An intention-to-treat analysis was performed, but a sensitivity analysis was not performed, because only three patients were lost to follow-up during the intervention period. Randomization was performed by the random-digit method, on the basis of computer-generated numbers.

RESULTS

LONGITUDINAL OBSERVATION PERIOD

Two hundred two of the 250 patients initially enrolled completed the 24-month observation period (167 men and 35 women) (Fig. 1). At base line, the patients' mean age was 56.6 ± 12.6 years (range, 25 to 80); their body-mass index (the weight in kilograms divided by the square of the height in meters), 25.4 ± 3.5 (range, 17.7 to 35.0); serum creatinine level, 2.1 ± 0.6 mg per deciliter (185.6 ± 53.0 μ mol per liter; range, 1.5 to 3.9 mg per deciliter [132.6 to 344.8 μ mol per liter]); creatinine clearance rate, 40.0 ± 13.1 ml per minute per 1.73 m² of body-surface area (range, 12.7 to 72.7); estimated glomerular filtration rate, 41.6 ± 14.4 ml per minute per 1.73 m² of body-surface area (range, 16.0 to 81.3); daily protein excretion, 0.82 ± 1.01 g (range, 0.03 to 6.5 g); daily protein intake, 0.87 ± 0.23 g per kilogram (range, 0.29 to 1.82); blood lead level, 5.3 ± 2.9 μ g per deciliter (0.26 ± 0.14 μ mol per liter; range, 0.6 to 16.1 μ g per deciliter [0.03 to 0.78 μ mol per liter]); and body lead burden, 104.5 ± 106.3 μ g (0.50 ± 0.51 μ mol; range, 80 to 596 μ g [0.39 to 2.88 μ mol]). Forty-six patients (22.8 percent) had hyperlipidemia. One hundred thirty-nine patients (68.8 percent) had hypertension, which was treated with angiotensin-converting-enzyme inhibitors in 125 (61.9 percent). Nineteen patients (9.4 percent) smoked.

Underlying renal diseases included chronic glo-

merulonephritis in 102 patients (50.5 percent), hypertensive nephropathy in 23 (11.4 percent), analgesic nephropathy in 25 (12.4 percent), polycystic kidney disease in 14 (6.9 percent), obstructive uropathy in 9 (4.5 percent), and unknown diseases in 29 (14.4 percent). At the end of the 24-month observation period, the serum creatinine level was 2.6 ± 1.2 mg per deciliter (229.8 ± 106.1 μ mol per liter; range, 1.5 to 8.6 mg per deciliter [132.6 to 760.2 μ mol per liter]), the creatinine clearance rate was 36.1 ± 14.6 ml per minute per 1.73 m² of body-surface area (range, 8.3 to 72.1), and the estimated glomerular filtration rate was 36.5 ± 14.6 ml per minute per 1.73 m² of body-surface area (range, 7.9 to 70.6).

Twenty-four patients reached the primary end point during the observation period, but none needed hemodialysis. Cox regression analysis showed that the base-line creatinine level and body lead burden were the most significant risk factors for the progression of renal insufficiency, even after adjustment for other factors (Table 1). Longitudinal multivariate analysis with a generalized estimating equation of the data from all patients revealed that higher base-line serum creatinine level, higher body lead burden, higher daily urinary protein excretion, and the presence of polycystic kidney disease were significant predictors of progressive decline in the glomerular filtration rate but that male sex and higher daily protein intake were significant predictors of a progressive increase in the glomerular filtration rate. Specifically, each increase of 100 μ g (0.5 μ mol) in the body lead burden led to a decrease in the glomerular filtration rate of 0.3 ml per minute per 1.73 m² of body-surface area during the observation period, after adjustment for other factors ($P < 0.001$) (Table 2).

INTERVENTION PERIOD

Initial Chelation Therapy

A total of 64 patients with a high-normal body lead burden participated in the intervention trial. They were randomly divided into two groups, consisting of 32 patients each. One group received chelation therapy for three months, and the other (the controls) received placebo. The groups had similar base-line characteristics (Table 3). After three months of lead-chelation therapy, the body lead burden of the patients in the chelation group decreased to 43.2 ± 22.3 μ g (0.21 ± 0.11 μ mol; range, 2.5 to 59.8 μ g [0.01 to 0.29 μ mol]), and their blood lead levels decreased to 3.9 ± 1.3 μ g per deciliter (0.19 ± 0.06 μ mol per liter; range, 1.9 to 7.1 μ g per decili-

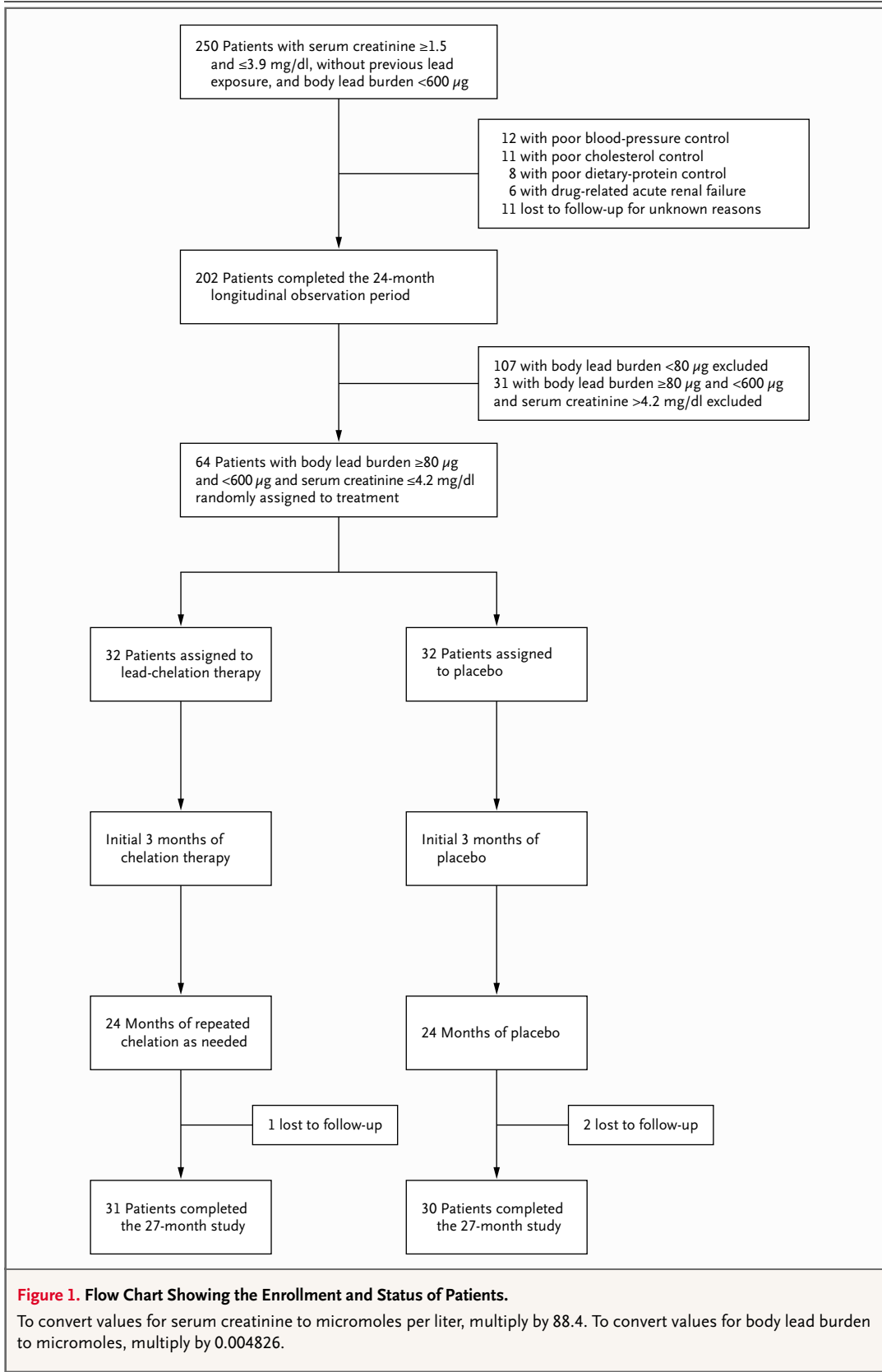


Table 1. Cox Regression Analysis of the Overall Risk of the Primary Outcome of Progressive Renal Insufficiency in 202 Patients, According to Base-Line Prognostic Factors.*

Variable	Relative Risk (95% CI)	P Value
Age (each increment of 1 yr)	1.02 (0.98–1.05)	0.43
Female sex	1.88 (0.67–5.29)	0.23
Base-line body-mass index (each increment of 1)	0.92 (0.80–1.07)	0.28
Smoking	2.61 (0.85–8.00)	0.09
Base-line serum creatinine (each increment of 1 mg/dl [88 μmol/liter])	2.75 (1.46–5.18)	0.002
Body lead burden (each increment of 1 μg)	1.00 (1.00–1.01)	0.03
Base-line daily protein excretion (each increment of 1 g)	1.32 (0.97–1.81)	0.07
Base-line daily protein intake (each increment of 1 g/kg)	0.47 (0.05–3.91)	0.47
Hypertension	1.50 (0.52–4.31)	0.46
Hyperlipidemia	1.42 (0.53–3.80)	0.49
Chronic glomerulonephritis	0.75 (0.26–2.13)	0.59

* CI denotes confidence interval. The body-mass index is the weight in kilograms divided by the square of the height in meters. The primary end point was defined as an increase in the serum creatinine level to 1.5 times the base-line value during the observation period.

Table 2. Longitudinal Analysis of Predictors of Progressive Change in the Glomerular Filtration Rate, with Use of Generalized Estimating Equations, in 202 Patients during the 24-Month Longitudinal Observational Period.

Variable	Estimate (Interactive Effect)*	P Value
Age (each increment of 1 yr)	-0.0017	0.70
Sex (male vs. female)	0.3475	0.01
Body-mass index (each increment of 1)	-0.0041	0.80
Hyperlipidemia (yes vs. no)	-0.0011	0.99
Hypertension (yes vs. no)	0.0689	0.59
Smoking (yes vs. no)	0.0178	0.94
Base-line serum creatinine (each increment of 1 mg/dl [88 μmol/liter])	-0.2142	0.004
Body lead burden (each increment of 1 μg)	-0.0030	<0.001
Daily protein excretion (each increment of 1 g)	-0.2799	<0.001
Daily protein intake (each increment of 1 g/kg)	0.5765	0.007
Underlying disease		
Chronic glomerulonephritis	-0.1855	0.25
Hypertensive nephropathy	-0.1704	0.40
Analgesic nephropathy	0.0348	0.87
Polycystic kidney disease	-0.8159	0.02
Obstructive uropathy	0.3918	0.20
Unknown†	—	—

* The interactive effect of variables was calculated by generalized estimating equations. Negative values for the interactive effect indicate a decline in the glomerular filtration rate, and positive values indicate an increase.

† The unknown group was the reference group.

ter [0.09 to 0.34 μmol per liter]). The therapeutic dose of calcium disodium EDTA averaged 5.2±2.0 g (range, 4 to 13). The change in the glomerular filtration rate in the chelation group was 3.4±4.4 ml per minute per 1.73 m² of body-surface area, as compared with -1.0±3.7 ml per minute per 1.73 m² of body-surface area in the control group (P<0.001 by the Mann-Whitney U test) after initial chelation therapy (Table 4).

There were no significant differences between the two groups in body-mass index, mean arterial pressure, serum cholesterol level, daily urinary protein excretion, or daily protein intake throughout the intervention period. The improvement in renal function and the slower progression of renal insufficiency after initial chelation therapy in the chelation group persisted for at least 24 months (Table 4). In contrast, the rate of decline in the glomerular filtration rate in both groups was similar during the observation period (Fig. 2).

Repeated Chelation Therapy

Nineteen patients in the chelation group (59 percent) required repeated chelation therapy because they had serum creatinine levels that increased above their pre-chelation levels (the base-line levels at the beginning of the intervention period). None required more than one repeated chelation treatment during the 24 months after the initial 3 months of therapy. The mean body lead burden of these pa-

tients increased to $111.2 \pm 49.3 \mu\text{g}$ ($0.54 \pm 0.24 \mu\text{mol}$; range, 63 to $246 \mu\text{g}$ [0.30 to $1.19 \mu\text{mol}$]), and the mean dose of calcium disodium EDTA for repeated chelation therapy was $4.1 \pm 0.9 \text{ g}$ (range, 3 to 5). The average time between initial and subsequent chelation therapy was 13.7 ± 4.4 months (range, 6 to 18), and the mean body lead burden after repeated chelation therapy was $33.8 \pm 22.0 \mu\text{g}$ ($0.16 \pm 0.11 \mu\text{mol}$; range, 0 to $59.2 \mu\text{g}$ [0 to $0.29 \mu\text{mol}$]) in these patients. The glomerular filtration rate improved from $29.5 \pm 9.7 \text{ ml per minute per } 1.73 \text{ m}^2$ of body-surface area before repeated chelation to $34.5 \pm 11.6 \text{ ml per minute per } 1.73 \text{ m}^2$ of body-surface area after repeated chelation ($P < 0.001$ by the paired t-test). No adverse effects of chelating agents were noted.

One of the 32 patients in the chelation group and 2 control patients were not followed during the final 24 months of the intervention period, for unknown reasons.

DISCUSSION

The results of the present study indicate that body lead burden and initial serum creatinine levels may be important in determining the progression of renal insufficiency. Each increase of $100 \mu\text{g}$ ($0.5 \mu\text{mol}$) in the body lead burden was associated with a decrease in the glomerular filtration rate of $0.3 \text{ ml per minute per } 1.73 \text{ m}^2$ of body-surface area, after adjustment for other factors ($P < 0.001$). The mean blood lead level of the study participants was only $5.3 \mu\text{g per deciliter}$, whereas the mean body lead burden was $104.5 \mu\text{g}$ —far less than the upper limit of the normal range (blood lead level, $20 \mu\text{g per deciliter}$ [$0.97 \mu\text{mol per liter}$]; body lead burden, $600 \mu\text{g}$ [$2.90 \mu\text{mol}$]).¹³ The mean blood lead level in our patients was similar to that reported in a nationwide survey of lead levels in Taiwan ($7.7 \mu\text{g per deciliter}$ [$0.37 \mu\text{mol per liter}$])²⁶ and lies within the range reported for the general population in Europe ($11.4 \mu\text{g per deciliter}$ [$0.55 \mu\text{mol per liter}$])¹¹ and the United States ($2.8 \mu\text{g per deciliter}$ [$0.14 \mu\text{mol per liter}$]).²⁷ These findings suggest that chronic low-level environmental lead exposure may subtly influence the progression of renal insufficiency in patients without diabetes who have chronic renal disease.

After initial lead-chelation therapy, the body lead burden in the chelation group decreased from $150.9 \mu\text{g}$ ($0.73 \mu\text{mol}$) to $43.2 \mu\text{g}$ ($0.21 \mu\text{mol}$), and the glomerular filtration rate increased by 11.9 percent. Simultaneously, the glomerular filtration rate in the control group decreased by 3.6 percent, a result consistent with our earlier report.¹⁵

Table 3. Base-Line Characteristics of Patients in the Chelation and Control Groups with a High-Normal Body Lead Burden at Entry into the Trial.*

Variable	Chelation Group (N=32)	Control Group (N=32)	P Value†
Age (yr)			0.92
Mean \pm SD	57.9 ± 10.7	57.6 ± 12.8	
Range	39–79	27–80	
Sex (no. of patients)			1.0
Male	26	25	
Female	6	7	
Body-mass index			0.74
Mean \pm SD	24.9 ± 2.6	25.1 ± 3.5	
Range	20.4–30.5	19.4–31.9	
Serum creatinine (mg/dl)‡			0.58
Mean \pm SD	2.7 ± 0.9	2.6 ± 0.5	
Range	1.6–4.1	1.5–3.8	
Creatinine clearance rate (ml/min/1.73 m ²)			0.81
Mean \pm SD	32.3 ± 12.9	31.6 ± 9.9	
Range	14.8–58	17.5–55.1	
Glomerular filtration rate (ml/min/1.73 m ²)			0.87
Mean \pm SD	32.0 ± 12.1	31.5 ± 9.0	
Range	18.0–55.8	17.8–56.6	
Blood lead ($\mu\text{g/dl}$)§			0.81
Mean \pm SD	6.1 ± 2.5	5.9 ± 3.0	
Range	2.4–12.3	1.3–14.8	
Body lead burden (μg)§			0.74
Mean \pm SD	150.9 ± 62.4	144.5 ± 87.9	
Range	81.0–349.8	80.0–530	
Hyperlipidemia (no. of patients)¶	18	20	0.76
Hypertension (no. of patients)¶	22	24	0.78
Use of angiotensin-converting-enzyme inhibitors for hypertension (no. of patients)	20	24	0.42
Use of nondihydropyridine calcium-channel blockers (no. of patients)	16	18	0.63
Use of dihydropyridine calcium-channel blockers (no. of patients)	8	6	0.56
Smoking (no. of patients)	3	2	1.0
Underlying renal disease (no. of patients)			
Chronic glomerulonephritis	16	14	0.80
Hypertensive nephropathy	3	4	1.0
Analgesic nephropathy	1	2	1.0
Polycystic kidney disease	2	3	1.0
Obstructive uropathy	2	3	1.0
Unknown	8	6	0.56

* A high-normal body lead burden was defined as a lead value of at least $80 \mu\text{g}$ ($0.39 \mu\text{mol}$) but less than $600 \mu\text{g}$ ($2.9 \mu\text{mol}$).

† P values were calculated by Fisher's chi-square test, except in the comparisons of age, body-mass index, serum creatinine, creatinine clearance, glomerular filtration rate, blood lead level, and body lead level, which were calculated by Student's t-test.

‡ To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

§ To convert values for lead to micromoles per liter, multiply by 0.04286.

¶ Hyperlipidemia was defined as a serum cholesterol level above $240 \text{ mg per deciliter}$ ($6.2 \text{ mmol per liter}$) after diet control.

|| Hypertension was defined by the presence of at least two blood-pressure measurements above $140/90 \text{ mm Hg}$ in a patient receiving antihypertensive drugs.

Table 4. Intention-to-Treat Analysis of Renal Function during the Observation and Intervention Periods.*

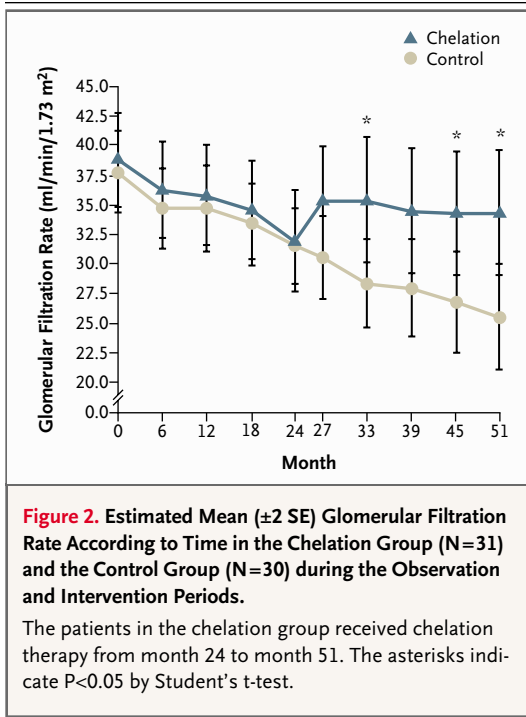
Measurement	Chelation Group (N=32)	Control Group (N=32)	P Value†	95% CI for the Difference between Groups
<i>ml/min/1.73 m²</i>				
Observation period (months 0–24)				
Month 0				
Creatinine clearance rate	38.6±13.3	37.2±10.1	0.65	–7.2 to 4.6
Glomerular filtration rate	38.8±11.3	37.7±9.7	0.67	–6.4 to 4.1
Month 6				
Creatinine clearance rate	36.4±12.8	34.7±10.7	0.58	–7.5 to 4.3
Glomerular filtration rate	36.3±11.3	34.7±9.6	0.55	–6.8 to 3.7
Month 12				
Creatinine clearance rate	36.1±13.6	34.6±12.0	0.66	–7.8 to 5.0
Glomerular filtration rate	35.8±11.9	34.7±10.3	0.69	–6.7 to 4.4
Month 18				
Creatinine clearance rate	34.4±12.8	33.4±10.7	0.74	–6.9 to 4.9
Glomerular filtration rate	34.6±11.8	33.4±9.7	0.67	–6.6 to 4.2
Month 24				
Creatinine clearance rate	32.3±12.9	31.6±9.9	0.81	–6.4 to 5.0
Glomerular filtration rate	32.0±12.1	31.5±9.0	0.87	–5.8 to 4.9
Yearly rate of change in renal function during the observation period				
Creatinine clearance rate	–3.2±2.3	–2.8±2.5	0.58	–1.5 to 0.9
Glomerular filtration rate	–3.4±2.6	–3.0±2.9	0.42	–1.9 to 0.9
Intervention period (months 24–51)				
Initial chelation therapy (months 24–27)				
Change in renal function after initial chelation therapy				
Creatinine clearance rate	2.6±3.0	–0.9±3.4	<0.001	–9.7 to 0.4
Glomerular filtration rate	3.4±4.4	–1.0±3.7	<0.001	–5.5 to 4.1
Repeated chelation therapy (months 27–51)				
Month 27				
Creatinine clearance rate	35.0±13.3	30.7±9.7	0.15	–10.1 to 1.6
Glomerular filtration rate	35.3±12.8	30.5±9.9	0.10	–10.5 to 0.9
Month 33‡				
Creatinine clearance rate	35.5±15.5	29.0±10.8	0.06	–13.3 to 0.3
Glomerular filtration rate	35.4±14.6	28.4±10.3	0.03	–13.4 to –0.6
Month 39§				
Creatinine clearance rate	34.4±15.8	28.3±11.1	0.09	–13.1 to 0.9
Glomerular filtration rate	34.5±14.7	28.0±11.2	0.06	–13.2 to 0.2
Month 45§				
Creatinine clearance rate	34.7±15.2	27.3±11.7	0.04	–14.3 to –0.3
Glomerular filtration rate	34.3±14.5	26.8±11.8	0.03	–14.3 to –0.7
Month 51§				
Creatinine clearance rate	34.8±15.7	26.1±11.6	0.02	–15.7 to –1.7
Glomerular filtration rate	34.4±14.7	25.5±12.3	0.01	–15.8 to –1.9
Yearly rate of decrease in renal function during repeated chelation therapy				
Creatinine clearance rate	0.3±2.1	2.4±2.1	<0.001	1.0 to 3.2
Glomerular filtration rate	0.7±2.5	2.6±2.7	0.001	0.6 to 3.2
Change in renal function at the end of the clinical trial				
Creatinine clearance rate	2.1±4.9	–5.6±4.9	<0.001	–10.3 to –5.3
Glomerular filtration rate	2.1±5.7	–6.0±5.8	<0.001	–11.0 to –5.1

* Plus–minus values are means ±SD. CI denotes confidence interval. The study lasted a total of 51 months, consisting of a 24-month observation period, an initial 3-month period of chelation therapy or placebo, and a further 24-month period of repeated chelation therapy, as needed, or placebo.

† P values for yearly rates of decrease and changes were calculated by the Mann–Whitney test; other P values were calculated by Student’s t-test. P<0.05 was considered to indicate a significant difference.

‡ The chelation and the control group each had 31 remaining patients.

§ The chelation and the control group had 31 and 30 remaining patients, respectively.



Despite the success of initial chelation therapy, both serum creatinine levels and values for the body lead burden gradually increased in patients treated with chelating agents in the months after therapy. This increase in body lead burden may originate from either bone lead stores⁹ or renewed low-level exposure to lead in diet or water.¹⁰ However, the serum creatinine levels decreased after the increased body lead burden had again been reduced by repeated chelation therapy, suggesting that chronic low-level environmental lead exposure is important in accelerating the progression of renal insufficiency. The role of calcium disodium EDTA itself is unclear, but use of this agent was associated with lowering of the total body lead burden. Chelation with a smaller dose of calcium disodium EDTA at longer intervals appears safe for treating patients with chronic renal insufficiency.^{7-10,15-20,22,28} Some authors, such as Wedeen et al.,²⁹ have used calcium disodium EDTA extensively and have never noted toxic effects. Hence, it seems reasonable to consider repeated chelation therapy with calcium disodium EDTA as a method of treating patients who have progressive renal insufficiency and high-normal body lead burdens.

The mechanism by which lead-chelation therapy improves renal function and retards the progression of renal insufficiency is unknown. Chelation ap-

pears to be effective in treating nephropathy²¹ and hypertension³⁰ induced in animals by long-term, low-level lead exposure. Chronic low-level lead exposure, but not high-level exposure, may increase the level of reactive oxygen species, including nitrotyrosine and malondialdehyde, and increase nitric oxide inactivation.^{31,32} Furthermore, lead-chelation therapy may reduce the levels of reactive oxygen species associated with nitric oxide inactivation and thus enhance the availability of nitric oxide to the vascular smooth muscle, potentially improving renal function and ameliorating hypertension after the removal of body lead.^{21,31} The improvement in renal function in our patients after chelation therapy may have resulted in part from a reduction in the level of reactive oxygen species.

We used creatinine clearance and the estimated glomerular filtration rate as indicators of renal function, given constraints on resources that prevented the use of inulin or isotopic clearances.³² The use of creatinine clearance to assess changes in renal function may limit the results of this study. However, an estimation of the glomerular filtration rate by Levey et al.²⁵ indicated a strong association with isotopic glomerular filtration rate ($r^2=0.91$). Other limitations include the relatively small number of patients receiving chelation therapy and the unknown effects of calcium disodium EDTA. It is uncertain whether the present findings can be generalized to patients with multifactorial causes of renal insufficiency.

Our findings suggest that repeated chelation therapy can improve renal function and retard the progression of renal insufficiency for at least 24 months. At the end of the study, the difference in the glomerular filtration rate between the chelation and control groups was approximately 8.1 ml per minute per 1.73 m² of body-surface area. This finding implies that treated patients might delay dialysis therapy by about three years, given the rate of decline in the glomerular filtration rate of approximately 3.0 ml per minute per year. The cost of this treatment for all 32 patients in the chelation group, including chelating agents, measurements of lead, frequent hospital visits, and staff salaries, was approximately \$120,000 (or \$3,750 per patient). However, the cost of three years of hemodialysis for this number of patients would be approximately \$1,950,000 (\$61,000 per patient). Thus, the treatment is likely to be cost effective.

Supported in part by a grant (NSC90-2314-B-182A-081) from the National Science Council Foundation of the Republic of China.

REFERENCES

1. Henderson DA. The aetiology of chronic nephritis in Queensland. *Med J Aust* 1958;1:377-86.
2. Wedeen RP, Maesaka JK, Weiner B, et al. Occupational lead nephropathy. *Am J Med* 1975;59:630-41.
3. Wedeen RP, Mallick DK, Batuman V. Detection and treatment of occupational lead nephropathy. *Arch Intern Med* 1979;139:53-7.
4. Nuyts GD, Daelemans RA, Jorens PG, Elseviers MM, Van de Vyver FL, De Broe ME. Does lead play a role in the development of chronic renal disease? *Nephrol Dial Transplant* 1991;6:307-15.
5. Staessen JA, Lauwerys RR, Buchet J-P, et al. Impairment of renal function with increasing blood lead concentrations in the general population. *N Engl J Med* 1992;327:151-6.
6. Payton M, Hu H, Sparrow D, Weiss ST. Low-level lead exposure and renal function in the Normative Aging Study. *Am J Epidemiol* 1994;140:821-9.
7. Kim R, Rotnitsky A, Sparrow D, Weiss S, Wager C, Hu H. A longitudinal study of low-level lead exposure and impairment of renal function: the Normative Aging Study. *JAMA* 1996;275:1177-81.
8. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981;241:F85-F93.
9. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 1982;307:652-9.
10. Obrador GT, Arora P, Kausz AT, Pereira BJ. Pre-end-stage renal disease care in the United States: a state of disrepair. *J Am Soc Nephrol* 1998;9:Suppl:S44-S54.
11. Henrich WL. Approach to volume control, cardiac preservation, and blood pressure control in the pre-end-stage renal disease patient. *J Am Soc Nephrol* 1998;9:Suppl:S63-S65.
12. Mitch WE. Dietary therapy in uremia: the impact on nutrition and progressive renal failure. *Kidney Int Suppl* 2000;75:S38-S43.
13. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 1997;51:1908-19.
14. Pollock CA, Ibels LS. Lead nephropathy — a preventable cause of renal failure. *Int J Artif Organs* 1988;11:75-8.
15. Lin JL, Ho HH, Yu CC. Chelation therapy for patients with elevated body lead burden and progressive renal insufficiency: a randomized, controlled trial. *Ann Intern Med* 1999;130:7-13.
16. Lin JL, Tan DT, Hsu KH, Yu CC. Environmental lead exposure and progressive renal insufficiency. *Arch Intern Med* 2001;161:264-71.
17. Lin JL, Lim PS. Does lead play a role in the development of renal insufficiency in some patients with essential hypertension? *J Hum Hypertens* 1994;8:495-500.
18. Lin JL, Huang PT. Body lead stores and urate excretion in men with chronic renal disease. *J Rheumatol* 1994;21:705-9.
19. Lin JL, Lim PS. Disappearance of immune deposits with EDTA chelation therapy in a case of IgA nephropathy. *Am J Nephrol* 1992;12:457-60.
20. Lin JL, Yeh KH, Tseng HC, Chen WY, Lai HH, Lin YC. Urinary N-acetyl-glucosaminidase excretion and environmental lead exposure. *Am J Nephrol* 1993;13:442-7.
21. Khalil-Manesh F, Gonick HC, Cohen A, Bergamaschi E, Mutti A. Experimental model of lead nephropathy. II. Effect of removal from lead exposure and chelation treatment with dimercaptosuccinic acid (DMSA). *Environ Res* 1992;58:35-54.
22. Lin JL, Yu CC, Lin-Tan DT, Ho HH. Lead chelation therapy and urate excretion in patients with chronic renal diseases and gout. *Kidney Int* 2001;60:266-71.
23. Isaksson B. Urinary nitrogen output as a validity test in dietary surveys. *Am J Clin Nutr* 1980;33:4-5.
24. Behringer D, Craswell P, Mohl C, Stoeppler M, Ritz E. Urinary lead excretion in uremic patients. *Nephron* 1986;42:323-9.
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-70.
26. Liou SH, Wu TN, Chiang HC, et al. Three-year survey of blood lead levels in 8828 Taiwanese adults. *Int Arch Occup Environ Health* 1996;68:80-7.
27. Pirkle JL, Brody DJ, Gunter EW, et al. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). *JAMA* 1994;272:284-91.
28. Batuman V. Lead nephropathy, gout, and hypertension. *Am J Med Sci* 1993;305:241-7.
29. Wedeen RP, Batuman V, Landy E. Safety of the EDTA lead-mobilization test. *Environ Res* 1983;30:58-62.
30. Vaziri ND, Liang K, Ding Y. Increased nitric oxide inactivation by reactive oxygen species in lead-induced hypertension. *Kidney Int* 1999;56:1492-8.
31. Ding Y, Vaziri ND, Gonick HC. Lead-induced hypertension. II. Response to sequential infusions of L-arginine, superoxide dismutase, and nitroprusside. *Environ Res* 1998;76:107-13.
32. Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. *Annu Rev Med* 1988;39:465-90.

Copyright © 2003 Massachusetts Medical Society.