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# Lead chelation therapy and urate excretion in patients with chronic renal diseases and gout

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*Background.* It is known that chronic renal insufficiency (CRI) patients with gout may have subtle lead poisoning. In addition, gout episodes frequently aggravate progressive renal insufficiency because of the use of nephrotoxic drugs and urate deposition. Our study was arranged to evaluate the causal effect of environmental lead exposure on urate excretion in CRI patients.

*Methods.* A cross-section study and a randomized, controlled trial were performed. Initially, 101 patients with CRI and without a history of previous lead exposure received ethylenediaminetetraacetic acid mobilization tests to assess body lead stores (BLS). Then, a clinical trial was performed; 30 CRI patients with gout and high-normal BLS and the changes of urate excretion in these patients were compared before and after lead chelating therapy. The treated group received four-week chelating therapy, and the control group received a placebo therapy.

*Results.* The BLS of patients with CRI and gout was higher than that of patients with CRI only, and none had subtle lead poisoning. The BLS, not the blood lead level (BLL), significantly correlated to indices of urate excretion in all CRI patients after related factors were adjusted. In addition, after lead chelating therapy, urate clearance markedly improved after a reduction of the BLS of patients with CRI and gout (study group 67.9 ± 80.0% vs. control group 1.2 ± 34.0%, $P = 0.0056$).

*Conclusion.* Our findings suggest that the chronic low-level environmental lead exposure may interfere with urate excretion of CRI patients. Importantly, the inhibition of urate excretion can be markedly improved by lead chelating therapies. These data shed light on additional treatment of CRI patients with gout; however, more studies are needed to confirm our findings.

Lead is one of the main environmental pollutants, despite its well-established toxic properties and precautions taken during its use [1–5]. Although gout and impaired renal function have been observed in the workers with chronic high-level lead exposures [1, 2], it is unclear whether chronic low-level environmental lead exposures have the same effects on the general population with chronic renal diseases. In the past, only a few articles have described a correlation between serum urate and blood lead levels (BLL) [6–8]. However, the BLL is only an index of recent lead exposure and not an index of total body lead stores (BLS). In addition, related factors, for example, creatinine clearance ($C_{Cr}$), were not adjusted in those studies. Although previous reports suggested that chronic renal insufficiency (CRI) patients with gout had subtle lead poisoning [6–8] or higher BLS [9, 10], the causal effect of lead on urate excretion is still unclear. In clinical practice, gout episodes frequently aggravate the progression of renal insufficiency in these patients because of the use of nephrotoxic anti-inflammatory drugs and urate deposition on the kidneys. Hence, it is important to clarify the causal effect of lead on inhibition of urate excretion in CRI patients.

This prospective study was designed to determine whether chronic low-level environmental lead exposure affects urate excretion in patients with CRI and whether the removal of body lead increases urate excretion.

## METHODS

This prospective study was conducted during a one-year period. The study was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, and all of the patients gave their informed consent.

### Patients

One hundred fifty adults with CRI [serum creatinine ($S_{Cr}$) ≥1.5 mg/dL and <3.0 mg/dL] followed at our nephrologic outpatient department for at least six months were included in our study. Renal diseases were diagnosed from the results of the patient's history, laboratory evaluations, renal echogram, radiological and renal histologic examinations. Chronic glomerulonephritis (CGN) was diagnosed, after other possible causes were excluded, based on

**Key words:** environmental lead exposure, chronic renal insufficiency, nephrotoxicity, pollutant, serum urate.

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initial renal biopsy reports, persistent severe proteinuria (>2 g/day) prerenal function impairment and postrenal function impairment or persistent nephritic syndrome (microhematuria with red blood cell casts and proteinuria >1 g/day). Essential hypertension-related nephropathy was diagnosed by a renal biopsy or as determined in our previous work [11]. The criteria of essential hypertension-related nephropathy for inclusion required that the clinical diagnosis of essential hypertension precede the onset of CRI. In addition, every patient had been followed up at our hospital and had complete medical records for at least eight years that demonstrated a history of hypertension preceding the clinical identification of renal function impairment by 8 to 21 years. Patients without diabetes mellitus who could not be classified to any definite etiology of CRI, including CGN, essential hypertension-related nephropathy, polycystic kidney disease, obstructive uropathy, lupus nephritis, or analgesia nephropathy, were classified as "unknown causes."

Gouty arthritis was diagnosed by our rheumatologist based on monosodium urate crystal in the synovial fluid or a history of podogra, abrupt onset and remission within two weeks, and at least two or more attacks [12]. The patients with a definite history of a gout episode after CRI recorded in the medical chart were included in this study, even those with inactive gout for several years. All patients with diabetes mellitus, alcoholism, nephrotic syndrome, primary gout prior to CRI [1], pregnancy, family histories of gout, or known histories of lead exposure were excluded. Medication affecting urate metabolism or renal function, including alcohol, cimetidine, diuretics, and nonsteroid anti-inflammatory drugs had been discontinued in all patients for at least four weeks prior to and during the study period [6–8]. All patients received a dietary consultation and avoided a high purine diet for at least three days before uric acid was checked. The 24-hour urine urea excretion was measured to assess daily protein intake [13].

### Laboratory evaluations

Blood chemistries were analyzed using routine laboratory methods using an autoanalyzer (Model 736; Hitachi, Tokyo, Japan). Three consecutive 24-hour urine collections were obtained from each patient and analyzed for creatinine and urate. The method for the determination of creatinine in blood and urine samples was based on the Jaffe reaction [14]. Urate in both serum and urine was measured by automated colorimetric procedures using an uricase peroxidase system [15]. Creatinine clearance ($C_{Cr}$), daily excretion of urate ($U_{urate}E$), urate clearance ($C_{urate}$), and fractional excretion of urate ($FE_{urate}$; calculated as $C_{urate}/C_{Cr} \times 100$) were calculated using standard formulae [16]. The results of $C_{Cr}$, $U_{urate}E$, $C_{urate}$, and $FE_{urate}$ were expressed as the arithmetic means of the three collections.

### Randomly controlled clinical trial

A randomly controlled chelating trial was performed to clarify the role of lead in urate excretion after the cross-sectional survey. Thirty CRI patients with gout and high-normal BLS were randomly divided into two groups on the proportion 2:1. The study group ($N = 20$) and the control group ($N = 10$) were divided according to a randomly digitized method in which the random numbers came directly from the computer software program. The high-normal BLS was defined as greater than the mean (64.2 μg) BLS of the CRI group patients. Informed consent forms were obtained from all patients. The study group patients received a weekly intravenous infusion of 1 amp (1 g) of calcium disodium ethylenediaminetetraacetic acid (EDTA) mixed with 200 mL normal saline for over two hours for four weeks. BLS was measured again at the end of chelating therapy. The control group patients received a weekly intravenous infusion of 1 amp (20 mL) 50% glucose as a placebo, in 200 mL normal saline for over two hours for four weeks. The injected drugs were mixed in the pharmacy room. None of the patients knew which drugs they received. The treatment course was set four weeks according to the experience of our previous studies [17, 18]. In addition, the $C_{Cr}$ and indices of urate excretion of both groups were measured at the end of chelating therapy. Three consecutive 24-hour urine collections were obtained from each patient and were analyzed for creatinine and urate. The results of $C_{Cr}$, $U_{urate}E$, $C_{urate}$, and $FE_{urate}$ were expressed as the arithmetic means of the three collections.

### Assessment of body lead store

Body lead stores were determined using the protocol developed by Emmerson and modified by Behringer et al [19]. On the first day of the study, each patient emptied his bladder and then received an intravenous infusion of 1 g of calcium disodium EDTA mixed with 200 mL 5% dextrose in water over two hours. The patients were requested to collect a 24-hour urine in 2 L lead-free bottles over three consecutive days on an outpatient basis. The total amount of urine lead collected over three days (72 hours) was considered the BLS. Daily urine amount was collected by spontaneous voiding. The patients were hydrated orally with water in amounts sufficient to provide a steady rate of urine flow of at least 1 mL/min. Any patients without an accurate urine collection (more than 1 lost urine collection) or inadequate urine flow (less than 4500 mL during the 3-day collection) were excluded.

### Measurement of lead

The samples were assessed at the Chang Gung Memorial Hospital by using electrothermal atomic absorption spectrometry (Perkin-Elmer 5100 PC, Norwalk, CT, USA) with a Zeeman background correction and L'vov plat-

**Table 1.** Characteristics of patients ($N = 101$) in the two study groups: Chronic renal insufficiency only (CRI) and CRI plus gout

| | CRI only ($N = 34$) | CRI and gout ($N = 67$) | $P$ |
|---|---|---|---|
| Age *years* | 56.1 ± 11.6 (36–79) | 55.1 ± 11.2 (34–71) | 0.6666 |
| Sex | 25M 9F | 52M 15F | 0.6317[a] |
| Body mass index $kg/m^2$ | 24.7 ± 2.9 (20.2–32.5) | 25.1 ± 2.7 (17.1–30.5) | 0.5044 |
| Daily protein intake *g/kg/day* | 1.00 ± 0.15 (0.69–1.40) | 1.03 ± 0.24 (0.58–1.89) | 0.4329 |
| Creatinine clearance *mL/min* | 50.8 ± 18.2 (24.0–100) | 50.4 ± 16.3 (16.2–86.3) | 0.9123 |
| Blood lead levels *μg/dL* | 4.39 ± 1.87 (1.2–7.6) | 5.36 ± 3.12 (1.2–12.5) | 0.0988 |
| Body lead store *μg* | 64.2 ± 45.6 (5.2–216.4) | 138.1 ± 116.6 (3.6–545) | 0.0006 |
| Serum urate *mg/dL* | 8.6 ± 1.6 (5.4–14.3) | 9.9 ± 2.1 (5.1–15.5) | 0.0018 |
| Daily urate excretion *mg/day* | 536.7 ± 182.5 (207–975) | 452.7 ± 200.9 (95–1056) | 0.0439 |
| Urate clearance *mL/min* | 4.40 ± 1.62 (1.92–8.10) | 3.39 ± 1.85 (0.73–8.80) | 0.0079 |
| Fractional urate excretion % | 9.4 ± 4.4 (4.0–23.0) | 7.4 ± 3.9 (1.0–25.9) | 0.0199 |
| Underlying renal disease | | | |
| CGN | 16 | 24 | 0.5170[a] |
| HT | 5 | 10 | 0.9999[a] |
| Analgesia | 4 | 6 | 0.5179[a] |
| PKD | 2 | 4 | 0.9999[a] |
| Lupus | 1 | 2 | 0.9999[a] |
| Unknown | 9 | 21 | 0.6457[a] |

Abbreviations are: CRI, chronic renal insufficiency with serum creatinine ≥1.5 and <3.0 mg/dL; CGN, chronic glomerulonephritis; HT, essential hypertension-related nephropathy; Lupus, lupus nephropathy; PKD, polycystic kidney disease; Analgesia, analgesic nephropathy; Unknown, renal disease with unknown origins.
[a] As measured by the Chi-square with Fisher's test

form [19]. All lead determinations were performed at least in duplicate. Throughout this study, both internal and external quality control procedures were used, with consistently satisfactory results. A certified, commercially prepared product (Seronorm Trace Elements, Sero AS, Billingstads, Norway) was used to monitor intrabatch accuracy and ensure interbatch standardization. The coefficient of variation for lead measurement was 5.3% or less. External quality control was maintained by participation in two major programs: the National Quality-Control Program conducted by the government and the international program run by the College of American Pathologists. Since anemia influences the measurement of blood lead, BLLs of study patients were calculated from the formula: BLL = initial BLL × 15 (g/dL)/patient's hemoglobin (g/dL). Hemoglobin was evaluated by using a computerized Sysmex counter (Sysmex, Kobe, Japan).

### Statistical analysis

Comparisons between groups were made with the Student $t$ test, Mann–Whitney $U$ test, and $\chi^2$ with Fisher tests. Comparisons within each group were made with a paired Student $t$ test before and after lead chelation therapy. A $P$ value <0.05 was considered to be statistically significant. Stepwise and multiple linear regression analyses were used to measure correlations between variables. A $P$ value <0.05 was considered statistically significant for a correlation. Data in this study are presented as mean ± SD.

## RESULTS

Twenty-one patients who took drugs affecting urate metabolism or renal function four weeks prior to and during the study period, 14 patients with inaccurate urine collection or inadequate urine flow, 11 patients with primary gout prior to CRI, and 3 patients with loss follow-up were excluded. A total of 101 patients with CRI was surveyed in this study. Table 1 lists the characteristics of the CRI patients and the CRI patients with gout. No patient had a BLS of more than 600 μg. There were no significant differences of age, sex, body mass index, daily protein intake, BLL, $C_{Cr}$, and underlying diseases between the two study groups. Serum urate levels and BLS of CRI patients with gout were significantly higher than those of the CRI group. Daily urate excretion, urate clearance, and fractional excretion of urate values of the CRI patients with gout were significantly lower than those of the CRI patient group. In a simple linear regression analysis, BLL positively correlated with the BLS ($r = 0.532$, $P < 0.0001$) and $S_{urate}$ ($r = 0.222$, $P = 0.0258$) in all patients; however, BLL did not correlate with daily $U_{urate}E$ ($r = -0.166$, $P = 0.0980$), $C_{urate}$ ($r = -0.154$, $P = 0.1240$), and $FE_{urate}$ ($r = -0.106$, $P = 0.2928$). However, BLS positively correlated with $S_{urate}$ ($r = 0.457$, $P < 0.0001$) but negatively with daily $U_{urate}E$ ($r = -0.375$, $P = 0.0001$), $C_{urate}$ ($r = -0.436$, $P < 0.0001$), and $FE_{urate}$ ($r = -0.365$, $P = 0.0002$) in all CRI patients ($N = 101$). In a stepwise regression analysis to assess age, sex, body mass index, daily protein intake, $C_{Cr}$, and BLS, the BLS value was the most significant factor in determining urate clearance.

Table 2 reveals the correlations between indices of lead and urate excretion in all CRI patients ($N = 101$) after age, sex, body mass index, daily protein intake, and $C_{Cr}$ were adjusted using multiple linear regression. BLL did not correlate with $S_{urate}$, daily $U_{urate}E$, $FE_{urate}$, and $C_{urate}$

**Table 2.** Relationships between indices of lead and urate excretion in the patients with chronic renal insufficiency after age, sex, body mass index, daily protein intake and creatinine clearance were adjusted ($N = 101$)

| Variable | β coefficients ± SE | *P* |
|---|---|---|
| Correlation with blood lead levels | | |
| Serum urate *mg/dL* | 0.131 ± 0.076 | 0.0858 |
| Daily urate excretion *mg* | −8.25 ± 6.73 | 0.2235 |
| Urate clearance *mL/min* | −0.052 ± 0.063 | 0.4200 |
| Fractional urate excretion % | −0.002 ± 0.001 | 0.1155 |
| Correlation with body lead stores | | |
| Serum urate *mg/dL* | 0.009 ± 0.002 | <0.0001 |
| Daily urate excretion *mg* | −0.636 ± 0.189 | 0.0011 |
| Urate clearance *mL/min* | −0.007 ± 0.002 | <0.0001 |
| Fractional urate excretion % | −0.0002 ± 0.00004 | <0.0001 |

A *P* value <0.05 shows significant correlation in multiple linear regression analysis.

after adjusting related variables. However, BLS significantly correlated with $S_{urate}$, daily $U_{urate}E$, $C_{urate}$, and $FE_{urate}$.

Table 3 shows the basal data of the study and control groups who had a high-normal BLS level. There were no significant differences in age, sex, body mass index, daily protein intake, BLL, BLS, $C_{Cr}$, and underlying renal disease between the two study group patients.

Table 4 shows $C_{Cr}$, daily protein intakes, and the indices of urate excretion of the study and control group patients before and after lead chelating therapy. The BLS of the study patients significantly decreased to 41.0 ± 31.6 μg after the EDTA chelating treatment. Between the two groups, there was less serum urate and there was a greater fractional urate excretion in the study group patients than the control group after chelating therapy. Similarly, within the study group, there was less $S_{urate}$ ($P = 0.0047$) and greater daily $U_{urate}E$ ($P = 0.0049$), $C_{urate}$ ($P = 0.0018$), and $FE_{urate}$ ($P = 0.0057$) after the chelating therapy, and marginally greater $C_{Cr}$ ($P = 0.0623$) was noted.

The changes (%) of $C_{Cr}$, daily protein intakes, and indices of urate excretion after the chelating therapies are noted on Table 5. There were significant decreases of $S_{urate}$ and increases of daily $U_{urate}E$, $C_{urate}$, and $FE_{urate}$ in the study group versus those of the control group patients after the chelating therapy, even though borderline significant changes of $C_{Cr}$ were noted.

## DISCUSSION

Our study demonstrates that BLS, not BLL, is associated with indices of urate excretion after related factors were adjusted, although BLL initially correlated with serum urate. In addition, BLS, not $C_{Cr}$, was the most important factor in determining urate clearance in all of the CRI patients. The mean BLL and BLS of our patients were only 4.62 μg/dL and 113.2 μg, which were far less than the "safe" values (<20 μg/dL of BLL and <600 μg of BLS) found in studies of other general populations [19–21]. The mean BLL level in our study was similar to that of recent studies in European and American populations [3, 4]. CRI patients with gout had a higher BLS and a lower urate clearance than those of patients with CRI only, although none of them had subtle lead poisoning. These findings suggest that chronic environmental lead exposures, even at low levels, influence the urate excretion of patients with chronic renal diseases. In addition, the markedly increasing urate excretion after lead chelating therapies suggests that the lead chelating therapy may be an effective alternative treatment for CRI patients with gout.

To our knowledge, Campbell et al were the first to suggest an association between hyperuricemia and BLL in patients without a history of overt lead exposure [7]. In contrast, Baker et al failed to find a relationship [8]. The controversy may be due to the small sample size in their studies. In the British Regional Heart Study, after allowing for the influence of alcohol consumption, there was a weakly positive correlation between serum urate and low BLL (<37 μg/dL) in 7364 middle-aged men from 24 British towns [6]. While the finding of a relationship between BLL and serum urate is in agreement with the results of our current work, neither study assessed BLS nor were the related factors adjusted statistically.

Batuman et al [20] and Sanchez-Fructuoso et al [22] reported that there was greater excretion of chelatable urinary lead levels in the patients with renal failure and gout. The mean BLS values of their study patients (444 μg [20], 671.5 μg [22]) were approximately 3.4 and 5.0 times greater than that of our patients (138.1 μg) because they did not completely exclude the patients with alcohol (moonshine) ingestion or lead poisoning in their analyses. In addition, in those studies no attempt to assess relationship between indices of urate excretion and BLS is mentioned. In another study, Reynolds et al failed to find a relationship between BLS and hyperuricemia in gout patients with chronic renal disease, since their patient cohort included those with diabetes mellitus, alcoholism, and moonshine ingestion [23]. Based on these reasons, our current work may provide a more definite conclusion about the relationship between urate and chronic low-level environmental lead exposure in patients with CRI.

Our randomly controlled clinical trial first demonstrated that there was an increase of urate clearance (67.9%) and fractional excretion of urate (55.6%) in the CRI patients with high-normal BLS, although a borderline significant increase of their $C_{Cr}$ (8.0%, $P = 0.0646$) was found after the lead chelating therapies. In contrast, no significant changes of renal function and indices of urate excretion were noted in the control group patients. The results clarify the causal effect of environmental lead exposure on urate excretion, and importantly, show that the impairment of urate excretion can be treated

**Table 3.** Characteristics of patients with lead chelating therapy ($N = 30$)

| Variable | Study group ($N = 20$) | Control group ($N = 10$) | $P$ |
|---|---|---|---|
| Age *years* | 53.4 ± 11.9 (34–72) | 54.3 ± 10.4 (37–68) | 0.8324 |
| Sex | 16M 4F | 7M 3F | 0.8787 |
| Body mass index $kg/m^2$ | 24.5 ± 3.0 (20.4–31.2) | 23.6 ± 4.0 (16.4–31.2) | 0.5113 |
| Creatinine clearance *mL/min* | 50.8 ± 14.6 (23–81.2) | 47.7 ± 17.9 (17.4–70.0) | 0.6100 |
| Daily protein intake *g/kg/day* | 0.95 ± 0.18 (0.63–1.38) | 0.96 ± 0.21 (0.60–1.25) | 0.8644 |
| Blood lead levels *μg/dL* | 5.96 ± 2.46 (2.1–10.8) | 6.70 ± 4.23 (2.8–15.7) | 0.3342 |
| Body lead store *μg* | 159.2 ± 71.4 (80.2–361) | 133.7 ± 67.0 (80.6–262) | 0.3536 |
| Underlying renal disease | | | |
| CGN | 8 | 5 | 0.7055 |
| HT | 2 | 1 | 0.9999 |
| Analgesia | 3 | 1 | 0.9999 |
| Unknown | 7 | 3 | 0.9999 |

Abbreviations are: CGN, chronic glomerulonephritis (including IgA nephropathy); HT, essential hypertension-related nephropathy; Analgesia, analgesic nephropathy; Unknown, renal disease with unknown origin. A $P$ value <0.05 means significant differences.

**Table 4.** Means creatinine clearance and serum urate values, and indices of urate excretion between the control and study group patients before and after four weeks of lead chelating therapy

| Variable | Study ($N = 20$) | Control ($N = 10$) | $P$ | 95% CI interval |
|---|---|---|---|---|
| Daily protein intake *g/kg/day* | | | | |
| Pre-chelation | 0.95 ± 0.18 | 0.96 ± 0.21 | 0.8644 | −0.16–0.14 |
| Post-chelation | 0.97 ± 0.15 | 1.01 ± 0.15 | 0.4426 | −0.16–0.07 |
| Creatinine clearance *mL/min* | | | | |
| Pre-chelation | 50.8 ± 14.6 | 47.7 ± 17.9 | 0.6100 | −9.3–15.6 |
| Post-chelation | 54.2 ± 15.0 | 46.5 ± 17.4 | 0.2173 | −4.8–20.3 |
| Serum urate *mg/dL* | | | | |
| Pre-chelation | 10.2 ± 1.7 | 10.3 ± 1.8 | 0.8896 | −1.5–1.3 |
| Post-chelation | 8.6 ± 1.9[b] | 10.5 ± 1.5 | 0.0091 | −3.3–5.1 |
| Daily urate excretion *mg* | | | | |
| Pre-chelation | 385.3 ± 130.3 | 385.0 ± 178.7 | 0.9958 | −116.8–117.4 |
| Post-chelation | 508.6 ± 207.6[b] | 359.0 ± 170.9 | 0.0594 | −6.3–305.5 |
| Urate clearance *mL/min* | | | | |
| Pre-chelation | 2.66 ± 0.97 | 2.70 ± 1.40 | 0.9374 | −0.93–0.86 |
| Post-chelation | 4.22 ± 1.92[b] | 2.45 ± 0.93 | 0.0841 | 0.45–3.09 |
| Fractional urate excretion % | | | | |
| Pre-chelation | 5.5 ± 2.5 | 5.5 ± 1.2 | 0.9754 | −1.7–1.7 |
| Post-chelation | 8.0 ± 3.7[a] | 5.5 ± 1.4 | 0.0485 | 0.07–5.0 |

A $P$ value <0.05 means significant differences by the Student $t$ test between the study and control group patients. CI is confidence interval.
[a] $P < 0.05$ and [b] $P < 0.005$ by the paired $t$ test within the study group patients before and after chelation therapy

**Table 5.** Changes (%) of serum urate and indices of urate excretion between the control and study group patients after four weeks of lead chelating therapies

| Changes of variable | Study ($N = 20$) | Control ($N = 10$) | $P$ | 95% CI interval |
|---|---|---|---|---|
| Daily protein intake % | 2.4 ± 9.5 | 5.6 ± 13.4 | 0.3116 | −11.9–5.5 |
| Creatinine clearance % | 8.0 ± 15.0 | −1.8 ± 6.3 | 0.0646 | −0.4–20.1 |
| Serum urate % | −22.4 ± 32 | 1.4 ± 16.7 | 0.0197 | −46.0–1.5 |
| Daily urate excretion % | 40.6 ± 58.5 | 3.4 ± 50.0 | 0.0155 | −7.2–81.5 |
| Urate clearance % | 67.9 ± 80.0 | 1.2 ± 34.0 | 0.0056 | 12.2–121.2 |
| Fractional urate excretion % | 55.6 ± 71.7 | 2.4 ± 29.7 | 0.0197 | 4.4–102.0 |

A $P$ value <0.05 means significant differences by the Mann–Whitney U test between the study and control group patients. CI is confidence interval.

by lead chelating therapy. In contrast, a recent study suggested that the lead chelating therapy did not improve the urate excretion of CRI patients [24]. However, their patients had lead poisoning rather than low-level environmental lead exposure, because the BLS of these patients was up to 1568 μg. The BLS value after chelation therapy was up to 425 μg, which was four times higher than the basal BLS value and ten times higher than the post-therapy BLS value of our patients. It is not strange that the urate excretion did not improve in their patients after the chelating therapy [24]. In addition, that study had a small sample size ($N = 6$) and no control group; hence, it is not sufficiently rigorous in assessing environmental lead exposure.

The mechanism of improvement of urate excretion after the removal of BLS is still unknown. Although EDTA also removes some divalent cations such as calcium and copper from the body, to our knowledge there is no study of the relationship between urate excretion and these divalent cations. The most plausible explanation is that, even at a low level, lead may affect urate excretion. There is a large body of evidence suggesting that heavy lead exposure or lead poisoning may cause proximal tubular dysfunction. The decreased urinary urate excretion may be partially explained by a lead-induced inhibition of urate excretion [23, 25]. However, the hypotheses may not explain our observation in a general population of low-level environmental lead exposure. Low-level chronic lead exposure may influence the renin-angiotensin system or endothelium-derived relaxing factor [26, 27] and cause a reduction of renal blood flow. In addition, some investigators have shown that patients with chronic low-level lead exposure are likely to have a reduced renal blood flow that may predispose to an acquired defect of urate excretion [28]. Hence, lead may directly or indirectly affect urate excretion, and the removal of body lead may improve urate excretion and decrease serum urate levels in patients with CRI. However, further study is needed to clarify a definite pathogenesis.

In conclusion, we postulate that the small amount of lead absorbed from the environment plays a role in urate excretion in patients with CRI. Importantly, the lead-induced inhibition of urate excretion can be treated by chelating therapies. If urate excretion can be improved, the episodes of gout should be reduced, and the progressive renal insufficiency in CRI patients be delayed or alleviated. This observation sheds more light on the treatment CRI patients with gout. Clearly, further study is needed to clarify the hypotheses.

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