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ORIGINAL RESEARCH

Positive correlation between environmental $PM_{2.5}$ and blood lead levels in patients undergoing maintenance hemodialysis

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Abstract: Patients undergoing hemodialysis (HD) have significantly higher mean blood lead levels (BLLs) than those in healthy individuals. Because elementary lead can be found in particulate matter with a diameter of <2.5 µm ($PM_{2.5}$), this cross-sectional study was conducted to assess the effect of environmental $PM_{2.5}$ exposure and other clinical variables on BLLs in patients receiving HD. We recruited 921 patients on maintenance HD (MHD) who had undergone HD for at least 6 months and who had previously participated in a BLL study. Mean $PM_{2.5}$ concentrations in living environments in the previous 12 and 24 months were analyzed using a blood lead test. From a multivariate analysis, after adjustment for related factors, the mean $PM_{2.5}$ concentrations in the previous 12 and 24 months were positively associated with log BLLs. In addition, days with $PM_{2.5}$ levels exceeding the standard level during the previous 12 and 24 months were positively associated with log BLLs. Patients exposed to higher $PM_{2.5}$ concentrations and more days with $PM_{2.5}$ levels exceeding the standard level exhibited a higher prevalence of high and high-normal BLLs and a lower prevalence of low-normal BLLs. After adjustment for related variables, the BLLs exhibited a significantly positive association with environmental $PM_{2.5}$ in patients undergoing MHD.

Keywords: air pollution, particulate matter, $PM_{2.5}$, lead, hemodialysis

Introduction

Patients undergoing hemodialysis (HD) have significantly higher mean blood lead levels (BLLs) than those in healthy individuals.[1–3] In such patients, BLLs were associated with mortality.[4,5] The sources of lead absorption are categorized as food, beverages, drinking water, paint, factory emissions, and automobile exhausts.[6] Therefore, patients undergoing HD are advised to avoid ingesting foods containing lead, such as deep-sea fish, deep-sea food, lead-related Chinese herbs, and soup boiled with the pig or cattle bones, as well as to avoid contact with lead-related factories or painting. However, inspiration of elemental lead from air tends to be neglected. Recently, air pollution, especially particulate matter with a diameter of <2.5 µm ($PM_{2.5}$), has become a crucial problem because of its chronic effect on human health. Zereini et al[7] measured heavy metal concentrations in airborne dust and revealed that the main fraction of lead was found in fine particles with a diameter of <2.1 µm. According to our review of the relevant literature, studies on the relationship between environmental $PM_{2.5}$ and BLL in patients undergoing HD are limited, and this relationship remains obscure. Therefore, the aim of the current cross-sectional study was to assess the effect of environmental $PM_{2.5}$ exposure and other clinical variables on BLLs in patients undergoing HD.

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Methods

The study protocol was approved by the institutional review board of Chang Gung Memorial Hospital. Because this was a retrospective cross-sectional study, no informed consent was required. All patient information was protected and was available only to the investigators, and all medical records, including medical history, laboratory data, and inclusion and exclusion criteria, were reviewed by senior nephrologists during the study period. All primary data were collected according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Patients

Patients were recruited from the HD centers of the Chang Gung Memorial Hospital branches in Linkou, Taipei, and Taoyuan. Only patients on maintenance HD (MHD) who had undergone HD for at least 6 months, were aged ≥18 years, and had previous blood lead studies[4,8] were enrolled (Figure 1). A questionnaire was arranged to survey patients to identify and exclude those who had a history of occupational exposure to lead or previous lead intoxication or those who lived in lead-contaminated areas. In addition, patients with malignancies or infectious diseases or those who had been hospitalized or had undergone surgery within the previous 3 months were excluded. Diabetes mellitus (DM) was identified according to either a physician's diagnosis, antidiabetic drug treatment, or 2 consecutive analyses demonstrating fasting blood glucose levels of >126 mg/dL. Most patients underwent 4 h of HD 3 times a week. HD was performed using single-use hollow-fiber dialyzers equipped with modified cellulose, polyamide, or polysulfone membranes. The dialysate used in all cases had a standard ionic composition with a bicarbonate-based buffer. Patients who had undergone hemodiafiltration (HDF) 3 times a week for ≥3 months were enrolled. We evaluated the prevalence of cardiovascular diseases (CVDs), including cerebrovascular disease, coronary artery disease, congestive heart failure, and peripheral vascular disease, in the patients. Hypertension was defined as the regular use of antihypertensive drugs for controlling blood pressure or at least 2 blood pressure measurements of >140/90 mmHg. In addition, smoking behavior (with smokers being defined as those who smoked in the past 30 days) was analyzed.

Laboratory, nutritional, and inflammatory parameters

All blood samples were obtained from the arterial end of the vascular access immediately after the initial 2-day interval for HD and were then centrifuged and stored at −80°C until use. Serum creatinine levels, normalized protein catabolic rates (nPCRs), and serum albumin levels were assayed and recorded as nutritional markers. High-sensitivity C-reactive protein (hsCRP) levels were measured as the indices of inflammation. Serum hsCRP levels were measured

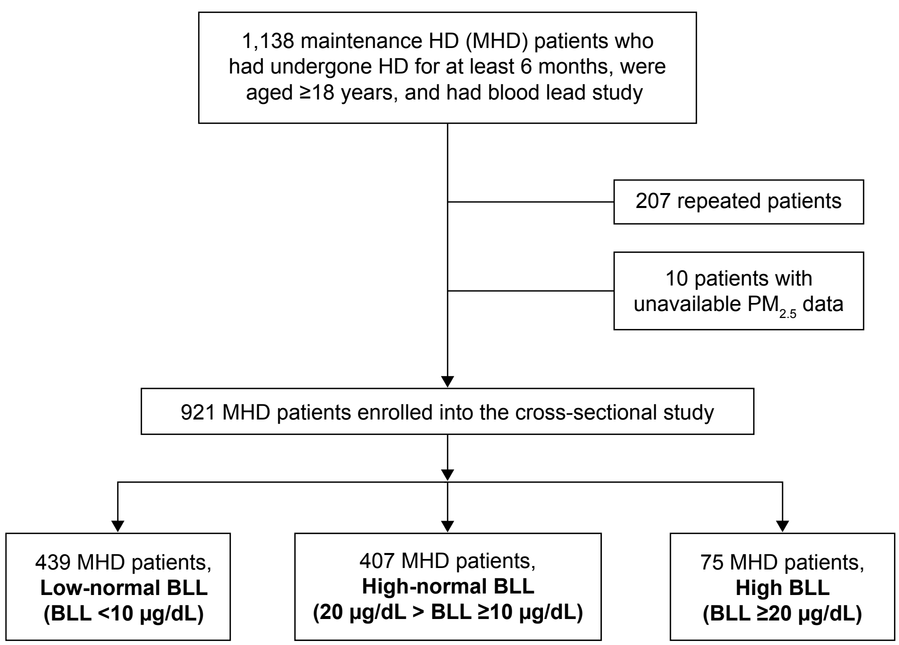

Figure 1 Flowchart of patient enrollment.
Abbreviations: BLL, blood lead level; HD, hemodialysis; $PM_{2.5}$, particulate matter with diameter <2.5 μm.

using immunonephelometry (Nanopia CRP; Daiichi Inc, Tokyo, Japan). The lowest detection limit was <0.15 mg/L. All other biochemical parameters were measured using the standard laboratory approach with an automatic analyzer. In patients on HD, the dialyzer clearance of urea was measured using the method described by Daugirdas[9] and was expressed as Kt/V_{urea}. The nPCR of the patients on HD was calculated using validated equations and was normalized to their body weight.[10] The serum calcium level was corrected using the serum albumin level with the following formula: corrected calcium level (mg/dL) = serum calcium level +0.8× (4.0 − serum albumin level). Nonanuria was defined as a daily urine output of ≥100 mL.

Measurement of blood lead levels

BLLs were measured using a previously described method.[4,8,11] To exclude the possibility that patients on MHD were exposed to lead through the contamination of water or dialysate during HD, we collected at least 2 samples of water and dialysate from outlets of reverse osmosis systems and inlets of dialysate of dialyzers in lead-free plastic bottles from each HD center.[4] Lead levels were measured using an electrothermal atomic absorption spectrometer (SpectrAA-200Z; Varian, Lexington, MA, USA) with Zeeman background correction and an L'vov platform. A certified commercially prepared product (Seronorm Trace Elements; Sero AS, Billingstad, Norway) was used to determine intrabatch accuracy and confirm interbatch standardization. The coefficient of variation for lead measurement was ≤5.0%. External quality control was maintained through patient participation in the National Quality Control Program conducted by the government. BLLs of each patient were measured 2 times with a 3-month interval. The BLL grade was defined as follows: low-normal BLL, BLL <10 µg/dL; high-normal BLL, 20 µg/dL > BLL ≥10 µg/dL; high BLL, and BLL ≥20 µg/dL.[2,8]

Environmental particulate matter – $PM_{2.5}$

Data from the Taiwan Air Quality Monitoring Network, including the database on the air quality status in Taiwan, were analyzed.[12] Individual exposure to air pollution was estimated using a geographic information system with the mean concentrations of air pollutants in the previous 12 and 24 months.[13–17] Because no previous studies have focused on this issue, the mean concentrations of $PM_{2.5}$ in the previous 12 and 24 months were considered for each participant. A mean 24 h $PM_{2.5}$ concentration level of <35 µg/m^3 is defined as normal.[12]

Statistical analysis

Data were analyzed using SPSS version 12.0 for Windows 95 (SPSS Inc, Chicago, IL, USA). The normal distribution of variables was analyzed using the Kolmogorov–Smirnov test. A *P*-value of >0.05 was considered to indicate normal distribution. Data are expressed in terms of median and interquartile range in nonnormal distribution variables and as mean ± standard deviation in normal distribution variables, and categorical variables are expressed as numbers or percentages. Chi-squared test or Fisher's exact test was used for analyzing the correlation between categorical variables. One-way analysis of variance was performed to compare the clinical variables among the 3 groups. Linear trends were used to analyze the correlation between ordinal variables. The data on hsCRP, intact parathyroid hormone (iPTH), BLL, and ferritin levels were log transformed for analysis. To evaluate the variables related to BLL, univariate and multivariate (stepwise method) linear regression analyses were performed to assess the standardized coefficients (β) and 95% confidence intervals (CIs) for the baseline variables, including age, male sex, body mass index (BMI), smoking status, DM, hypertension, previous CVD, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, HD duration, use of erythropoietin (EPO), KT/V_{urea}, nPCR, nonanuria status, hemoglobin levels, serum albumin levels, serum creatinine levels, corrected-calcium (C-Ca) levels, inorganic phosphate levels, log ferritin levels, log iPTH levels, log hsCRP levels, cholesterol levels, triglyceride levels, and environmental $PM_{2.5}$ levels/the number of days with $PM_{2.5}$ exceeding the standard level (variables with $P<0.1$ in the univariate linear regression were selected for multivariate linear regression). All the nominal variables in the logistic regression were transformed into dummy codes. Missing data were removed using listwise deletion. The level of significance was set at $P<0.05$.

Results

This study comprised a total of 921 patients on MHD (469 men and 452 women), with a mean MHD duration of 6.68±5.33 years. Moreover, $PM_{2.5}$ data of 36 monitoring stations from the Taiwan Air Quality Monitoring Network, which is operated by the Environmental Protection Administration, including the database and report on the air quality status in the previous 12 and 24 months, were analyzed. Table 1 lists the patient characteristics including age, sex, and BMI, in addition to biological, hematological, and HD data. Of all the patients on HD, 50.9% were men, 22% had a medical history of DM, 4.6% had CVDs, 2.7% had lupus, 17.8% were habitual tobacco users, 80.2% had an arteriovenous

Table 1 Characteristics of 921 study patients on MHD

Characteristics	Total (N=921)
Demographics	
Age (years)	55.98±13.53
Male sex (yes), pt no	469 (50.9%)
Body mass index (kg/m²)	22.21±3.19
Smoking (yes), pt no	164 (17.8%)
Comorbidity	
Diabetes mellitus (yes), pt no	203 (22%)
Hypertension (yes), pt no	358 (38.9%)
Previous CVD (yes), pt no	42 (4.6%)
HBV (yes), pt no	104 (11.3%)
HCV (yes), pt no	166 (18%)
Dialysis-related data	
Hemodialysis duration (years)	6.68±5.33
Erythropoietin (U/kg/week)	73.91±46.80
Fistula as blood access (yes), pt no	739 (80.2%)
Hemodiafiltration (yes), pt no	193 (21%)
Kt/V_{urea} [9]	1.79±0.32
nPCR (g/kg/day)	1.18±0.26
Residual daily urine of >100 mL, pt no	194 (21.1%)
Biochemical data	
Hemoglobin (g/dL)	10.51±1.34
Albumin (g/dL)	4.07±0.34
Creatinine (mg/dL)	10.88±2.38
Ferritin (μg/L)*	305.7 (129.5, 506.9)
Corrected-calcium (mg/dL)	9.92±0.93
Phosphate (mg/dL)	4.81±1.36
Intact parathyroid hormone (pg/mL)*	127 (51.85, 303.7)
hsCRP (mg/L)*	2.85 (1.36, 6.89)
Cardiovascular risks	
Cholesterol (mg/dL)	171.69±37.36
Triglyceride (mg/dL)	164.29±117.84
LDL (mg/dL)	95.06±30.24
Environmental factors	
Mean environmental $PM_{2.5}$ (μg/m³), previous 12 months	28.51±3.55
Blood lead (Pb) (μg/dL)*	10.32 (7.27, 13.95)

Notes: Data presented as mean ± SD or n (%). *Nonnormal distribution data are presented as median (interquartile range); Kt/V_{urea}, dialyzer clearance of urea.
Abbreviations: CVD, cardiovascular disease; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MHD, maintenance hemodialysis; nPCR, normalized protein catabolic rate; $PM_{2.5}$, particulate matter with diameter <2.5 μm; pt no, patient number; SD, standard deviation.

fistula, 11.3% had HBV infection, 18% had HCV infection, 8.1% had high blood lead concentrations, 44.2% had high-normal blood lead concentrations, and 47.7% had low-normal blood lead concentrations. Patients who were exposed to higher $PM_{2.5}$ concentration levels and more days with $PM_{2.5}$ exceeding the standard level had a higher prevalence of high and high-normal BLL and lower prevalence of low-normal BLLs (Figures 2 and 3).

To further clarify the factors associated with log lead levels in our study patients, we used univariate and multivariate linear regression "stepwise" methods for analyses.

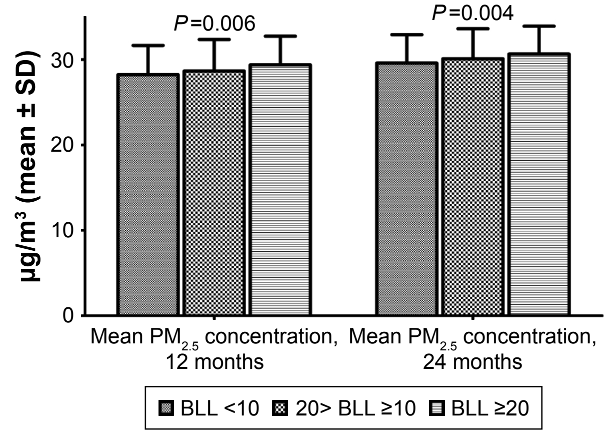

Figure 2 Comparison of patients with low-normal, high-normal, and high BLLs in terms of mean $PM_{2.5}$ concentrations in the previous 12 and 24 months.
Notes: In the previous 12-month group, the mean $PM_{2.5}$ concentration for low-normal BLL was 28.23±3.42 μg/m³, high-normal BLL was 28.66±3.69 μg/m³, and high BLL was 29.37±3.37 μg/m³. In the previous 24-month group, the mean $PM_{2.5}$ concentration for low-normal BLL was 29.59±3.32 μg/m³, high-normal BLL was 30.09±3.52 μg/m³, and high BLL was 30.65±3.26 μg/m³. $P<0.005$ between low-normal BLL, high-normal BLL, and high BLL in a linear trend test. Low-normal BLL, BLL <10 μg/dL; high-normal BLL, 20 μg/dL > BLL ≥10 μg/dL; and high BLL, BLL ≥20 μg/dL.
Abbreviations: BLL, blood lead level; $PM_{2.5}$, particulate matter with diameter <2.5 μm; SD, standard deviation.

Table 2 presents the univariate linear regression analysis of the clinical variables on BLL. HCV (standardized coefficients [β]: 0.114, 95% CI [0.025, 0.089]), HD duration (β: 0.295, 95% CI [0.008, 0.013]), fistula as blood access (β: 0.069, 95% CI [0.002, 0.065]), HDF (β: 0.166, 95% CI

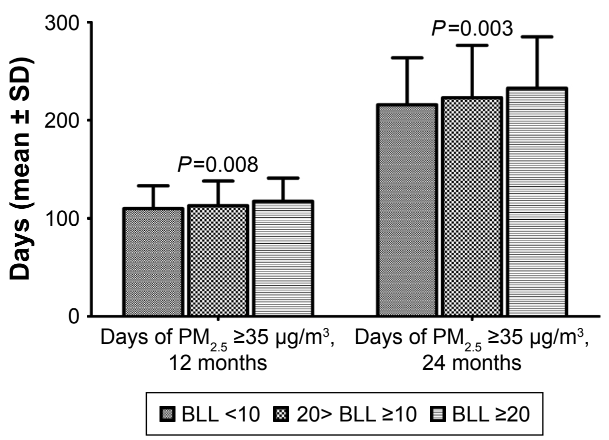

Figure 3 Comparison of patients with low-normal, high-normal, and high BLLs in terms of the number of days with a daily mean $PM_{2.5}$ concentration of >35 μg/m³ in the previous 12 and 24 months.
Notes: In the previous 12-month group, the number of days with a daily mean $PM_{2.5}$ concentration of >35 μg/m³ in low-normal BLL was 109.95±23.16 days, high-normal BLL was 112.77±25.22 days, and high BLL was 117.40±23.61 days. In the previous 24-month group, the number of days with a daily mean $PM_{2.5}$ concentration of >35 μg/m³ in low-normal BLL was 215.79±47.88 days, high-normal BLL was 222.94±53.41 days, and high BLL was 232.60±52.41 days. $P<0.005$ between low-normal BLL, high-normal BLL, and high BLL in a linear trend test. Low-normal BLL, BLL <10 μg/dL; high-normal BLL, 20 μg/dL > BLL ≥10 μg/dL; and high BLL, BLL ≥20 μg/dL.
Abbreviations: BLL, blood lead level; $PM_{2.5}$, particulate matter with diameter <2.5 μm; SD, standard deviation.

Table 2 Univariate linear regression analysis between log Pb and clinical variables in patients on MHD

Characteristics	Univariate logistic regression	*P*-value
Variables	**Odds ratio (95% confidence interval)**	
Age (years)	–0.028 (–0.001, 0.001)	0.39
Male sex	0.034 (–0.012, 0.038)	0.30
Body mass index (kg/m²)	–0.116 (–0.011, –0.003)	<0.001
Smoking (yes)	0.003 (–0.031, 0.034)	0.93
Diabetes mellitus (yes)	–0.236 (–0.139, –0.081)	<0.001
Hypertension (yes)	–0.047 (–0.044, 0.007)	0.15
Previous CVD (yes)	–0.007 (–0.066, 0.054)	0.84
HBV (yes)	0.05 (–0.009, 0.07)	0.12
HCV (yes)	0.114 (0.025, 0.089)	0.001
Hemodialysis duration (years)	0.295 (0.008, 0.013)	<0.001
Use of EPO (yes)	–0.143 (–0.148, –0.057)	<0.001
Fistula as blood access (yes)	0.069 (0.002, 0.065)	0.035
Hemodiafiltration (yes)	0.166 (0.048, 0.109)	<0.001
Kt/V_{urea}[9]	0.176 (0.068, 0.145)	<0.001
nPCR (g/kg/day)	0.002 (–0.046, 0.049)	0.94
Non-anuria	–0.04 (–0.05, 0.012)	0.22
Hemoglobin (g/dL)	0.111 (0.007, 0.025)	0.001
Albumin (g/dL)	–0.032 (–0.054, 0.018)	0.32
Creatinine (mg/dL)	0.022 (–0.003, 0.007)	0.51
C-Ca (mg/dL)	0.073 (0.002, 0.029)	0.026
Phosphate (mg/dL)	0.004 (–0.009, 0.01)	0.91
Log ferritin	–0.09 (–0.062, –0.01)	0.006
Log iPTH	0.161 (0.031, 0.072)	<0.001
Log hsCRP	–0.067 (–0.05, –0.001)	0.045
Cholesterol (mg/dL)	0.044 (–0.001, 0.001)	0.18
Triglyceride (mg/dL)	–0.051 (–0.0001, 0.0001)	0.12
Environmental $PM_{2.5}$ (μg/m³), previous 12 months	0.107 (0.002, 0.009)	0.001
Environmental $PM_{2.5}$ (μg/m³), previous 24 months	0.118 (0.003, 0.01)	<0.001
Days of $PM_{2.5}$ exceeding the daily standard level during previous 12 months	0.104 (0.0001, 0.001)	0.002
Days of $PM_{2.5}$ exceeding the daily standard level during previous 24 months	0.121 (0.0001, 0.001)	<0.001

Note: Kt/V_{urea}, dialyzer clearance of urea.
Abbreviations: BMI, body mass index; C-Ca, corrected calcium; CVD, cardiovascular disease; DM, diabetes mellitus; EPO, erythropoietin; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; MHD, maintenance hemodialysis; nPCR, normalized protein catabolic rate; Pb, lead; $PM_{2.5}$, particulate matter with diameter <2.5 μm.

[0.048, 0.109]), Kt/V_{urea} (β: 0.176, 95% CI [0.068, 0.145]), Hb level (β: 0.111, 95% CI [0.007, 0.025]), C-Ca level (β: 0.073, 95% CI [0.002, 0.029]), log iPTH (β: 0.161, 95% CI [0.031, 0.072]), and environmental $PM_{2.5}$ concentration (β: 0.107, 95% CI [0.002, 0.009]) were positively associated with log BLLs. In contrast, BMI (β: 0.116, 95% CI [–0.011, –0.003]), DM (β: 0.236, 95% CI [–0.139, –0.081]), EPO use (β: 0.143, 95% CI [–0.148, –0.057]), log ferritin (β: 0.09, 95% CI [–0.062, –0.01]), and log hsCRP (β: 0.067, 95% CI [–0.05, –0.001]) were negatively associated with log BLLs.

An advanced multivariate linear regression analysis (Table 3) indicated that after adjustment for the studied variables, the mean $PM_{2.5}$ concentration in the previous 12 months (β: 0.158, 95% CI [0.004, 0.013]) was significantly positively correlated with log BLLs. After adjustment for the studied variables, the number of days with $PM_{2.5}$ exceeding the standard level in the previous 12 months (β: 0.087, 95% CI [0.0001, 0.001]) was positively associated with log BLLs (Table 4). We also observed that after adjustment for related factors, the mean environmental $PM_{2.5}$ concentration (β: 0.191, 95% CI [0.006, 0.016]; Table 5) and the number of days with $PM_{2.5}$ exceeding the standard level (β: 0.098, 95% CI [0.0001, 0.001]; Table 6) during the 24 months were positively associated with log BLLs.

Discussion

The results of this study demonstrate that after adjustment for related variables, BLLs exhibited a significantly positive association with environmental $PM_{2.5}$ in patients on MHD.

Table 3 Multivariate linear regression analysis (stepwise method) between log Pb and clinical variables (including $PM_{2.5}$ concentration)

Characteristics	Multivariate linear regression	*P*-value
Variables	**Standardized coefficients, *β* (95% confidence interval)**	
Body mass index (kg/m^2)		
Diabetes mellitus (yes)	–0.177 (–0.112, –0.053)	<0.001
HCV (yes)		
Hemodialysis duration (years)	0.182 (0.004, 0.009)	<0.001
KT/V_{urea}	0.118 (0.032, 0.11)	<0.001
HDF		
Use of EPO	–0.126 (–0.137, –0.046)	<0.001
Hemoglobin (g/dL)		
Corrected-calcium (mg/dL)		
Log ferritin		
Log iPTH		
Log hsCRP		
Mean environmental $PM_{2.5}$ (μg/m^3), previous 12 months	0.158 (0.004, 0.013)	<0.001

Note: Kt/V_{urea}, dialyzer clearance of urea.
Abbreviations: HCV, hepatitis C virus infection; HDF, hemodiafiltration; hsCRP, high-sensitivity C-reactive protein; EPO, erythropoietin; iPTH, intact-parathyroid hormone; Pb, lead; $PM_{2.5}$, particulate matter with diameter <2.5 μm.

In general, the sources of body lead include ingestion and inhalation.[18] Educating individuals on the ingestion of lead and avoiding contact with lead-containing appliances should help reduce the BLLs in adults and children. In an analysis of the effect of air lead on BLLs, Hammond et al[19] observed a curvilinear relationship between the level of lead in air and that of lead in blood. During 1976–1980, in the US, when the lead level in gasoline was reduced by >50%, the observed blood lead decreased, on average, by 37%.[20] Coincidentally, Elinder et al[21] reported that in Sweden, from 1980 to 1948, an average decrease in blood lead of ~34% was observed due to the decreased use of lead in gasoline. In addition, factors such as age, sex, and change in residence during the observation period did not influence the result.[21] In Taiwan, the use of gasoline without lead had been implemented gradually since 1986 until 2000, when the use of lead-containing gasoline was completely banned. In a 2012 cross-sectional study of 934 children, Lin et al[22] demonstrated that the average BLL in children was 1.86±1.55 μg/dL, which is lower than the upper limit value of 5 μg/dL recommended by the Centers for Disease Control, with only 16 children (1.8%) having BLLs exceeding 5 μg/dL and 2 children (0.21%) having BLLs exceeding 10 μg/dL. In addition, a study of 230 cord blood samples[23] demonstrated that the average lead level was 1.14 μg/dL (range: 0.016–4.32 μg/dL). These results evidence that exposure to lead in Taiwan's environment has improved.

Whether the effect of airborne lead on BLLs ceased after the use of unleaded gasoline warrants discussion. Recently, air pollution, particularly the $PM_{2.5}$ type, has become the focus of considerable attention. Although the disadvantages of airborne $PM_{2.5}$ are well known, this is the first study to investigate the effect of airborne $PM_{2.5}$ on BLLs in patients on MHD. The composition of airborne $PM_{2.5}$ is complex, and lead was found to be its main component.[7] Of the sources of $PM_{2.5}$ in Taiwan, 23% were vehicles and exposed dust,

Table 4 Multivariate linear regression analysis (stepwise method) between log Pb and clinical variables (including days with high $PM_{2.5}$)

Characteristics	Multivariate linear regression	*P*-value
Variables	**Standardized coefficients, *β* (95% confidence interval)**	
Body mass index (kg/m^2)		
Diabetes mellitus (yes)	–0.175 (–0.111, –0.052)	<0.001
HCV (yes)		
Hemodialysis duration (years)	0.184 (0.004, 0.009)	<0.001
KT/V_{urea}	0.119 (0.033, 0.11)	<0.001
HDF		
Use of EPO	–0.129 (–0.139, –0.048)	<0.001
Hemoglobin (g/dL)		
Corrected-calcium (mg/dL)		
Log ferritin		
Log iPTH		
Log hsCRP		
Days of $PM_{2.5}$ exceeding the standard level during the previous 12 months	0.087 (0.000, 0.001)	0.005

Note: Kt/V_{urea}, dialyzer clearance of urea.
Abbreviations: HCV, hepatitis C virus infection; HDF, hemodiafiltration; EPO, erythropoietin; hsCRP, high-sensitivity C-reactive protein; iPTH, intact-parathyroid hormone; Pb, lead; $PM_{2.5}$, particulate matter with diameter <2.5 μm.

Table 5 Multivariate linear regression analysis (stepwise method) between log Pb and clinical variables (including $PM_{2.5}$ concentration)

Characteristics	Multivariate linear regression	*P*-value
Variables	**Standardized coefficients, *β* (95% confidence interval)**	
Body mass index (kg/m²)		
Diabetes mellitus (yes)	–0.175 (–0.111, –0.053)	<0.001
HCV (yes)		
Hemodialysis duration (years)	0.180 (0.004, 0.009)	<0.001
KT/V_{urea}	0.117 (0.032, 0.109)	<0.001
HDF		
Use of EPO	–0.123 (–0.135, –0.044)	<0.001
Hemoglobin (g/dL)		
Corrected-calcium (mg/dL)		
Log ferritin		
Log iPTH		
Log hsCRP		
Mean environmental $PM_{2.5}$ (μg/m³), previous 24 months	0.191 (0.006, 0.016)	<0.001

Note: Kt/V_{urea}, dialyzer clearance of urea.
Abbreviations: HCV, hepatitis C virus infection; HDF, hemodiafiltration; EPO, erythropoietin; iPTH, intact-parathyroid hormone; hsCRP, high-sensitivity C-reactive protein; Pb, lead; $PM_{2.5}$, particulate matter with diameter <2.5 μm.

22.7% were road transport, 13.5% were agriculture, 8.5% were catering, 7.2% were construction industry and mines, 4.5% were basic steel industries, 4% were electric power industries, 2.8% were chemical materials manufacturing, 2.3% were cement and ready-mixed concrete, and 11.4% were others.[24] In Taiwan, secondary aerosols (NH_4^+, NO_3^-, and SO_4^{2-}) constituted ~50%–60% of the chemical composition of $PM_{2.5}$ mass.[25] The mass percentage of lead in $PM_{2.5}$ was different in different sources (~15% in industrial emissions, 0% in secondary aerosols, 7.5% in soil dust, 5% in sea salt, and 85% in vehicle emissions).[26] Chen et al[27] found that the lead component in $PM_{2.5}$ mainly existed in an insoluble form, accounting for 78.9% of the total amount of lead, whereas water-soluble and liposoluble lead constituted 20.6% and 0.3% of the total amount of lead, respectively. In addition, the authors indicated that water-soluble lead, rather than insoluble lead, in $PM_{2.5}$ may be a potential source of blood lead in adults. The results of these studies are consistent

Table 6 Multivariate linear regression analysis (stepwise method) between log Pb and clinical variables (including days with high $PM_{2.5}$)

Characteristics	Multivariate linear regression	*P*-value
Variables	**Standardized coefficients, *β* (95% confidence interval)**	
Body mass index (kg/m²)		
Diabetes mellitus (yes)	–0.174 (–0.111, –0.052)	<0.001
HCV (yes)		
Hemodialysis duration (years)	0.182 (0.004, 0.009)	<0.001
KT/V_{urea}	0.119 (0.033, 0.11)	<0.001
HDF		
Use of EPO	–0.128 (–0.139, –0.048)	<0.001
Hemoglobin (g/dL)		
Corrected-calcium (mg/dL)		
Log ferritin		
Log iPTH		
Log hsCRP		
Days of $PM_{2.5}$ exceeding the standard level during the previous 24 months	0.098 (0.0001, 0.001)	0.002

Note: Kt/V_{urea}, dialyzer clearance of urea.
Abbreviations: HCV, hepatitis C virus infection; EPO, erythropoietin; HDF, hemodiafiltration; hsCRP, high-sensitivity C-reactive protein; iPTH, intact-parathyroid hormone; Pb, lead; $PM_{2.5}$, particulate matter with diameter <2.5 μm.

with our findings of the positive correlation between BLLs and $PM_{2.5}$ concentrations or the duration of $PM_{2.5}$ exceeding normal values. Several studies have clearly demonstrated the cardiovascular, pulmonary, carcinogenic, and mortality risks of airborne $PM_{2.5}$.[28–33] Moreover, BLLs have been related to iPTH levels, hemoglobin levels, blood pressure, and mortality in patients on MHD.[1,4,34,35] Whether BLL is an intermediate medium between airborne $PM_{2.5}$ and cardiovascular events or mortality in patients on MHD requires clarification in future studies.

The pharmacokinetics of lead in humans is complex. Most of the lead absorbed in the body is excreted through either renal clearance or biliary clearance in feces. Generally, in healthy people, significant drops in BLLs may occur over several months, or sometimes years, even after complete elimination of exposure to the lead sources.[36] Blood lead is excreted in both the urine and feces in healthy individuals, and the dose of exposure could affect the excretion volume.[37,38] However, in patients with renal failure, blood lead excretion is aggravated because of the loss of renal clearance. Therefore, patients on HD have significantly higher mean BLLs than healthy individuals.[1–3] According to our review of the relevant literature, studies on particulate matter in terms of BLLs are limited. Enkhbat et al[39] and Batterman et al[40] have revealed no significant correlation between particulate matter concentrations and BLLs in children and middle-aged women. However, in a study involving nonhuman primates, O'Flaherty et al[41] indicated that the urinary clearance of absorbed lead in these animals was 14%–24% of the estimated glomerular filtration rate and that fecal clearance was 78%–85% of the urinary clearance; however, fecal clearance was anomalous and appeared to be an artifact of a very high dose. Two studies[37,41] have demonstrated the importance of blood lead excretion in urine. However, the participants in the studies of Enkhbat et al[39] and Batterman et al[40] were healthy without renal insufficiency or dialysis receipt, which suggests that both normal urinary and fecal excretion of blood lead can maintain stable BLLs during chronic exposure to environmental $PM_{2.5}$. The loss of renal function in our study patients was possibly the reason for obtaining accumulative BLLs during the chronic exposure to environmental $PM_{2.5}$ in our patients on HD.

A linear regression analysis revealed that within the previous 12 and 24 months, both the mean $PM_{2.5}$ concentrations and the number of days with $PM_{2.5}$ exceeding the standard level were positively correlated with BLLs in our study patients; this finding indicates the probability of chronic accumulation of blood lead from inspired $PM_{2.5}$. In Figure 2, the mean concentration difference between the 3 groups did not exceed 35 μg/m^3. However, Figure 3 illustrates that the higher the number of days exceeding the standard $PM_{2.5}$ exposure level, the higher the BLLs. The odds ratio of the number of days with $PM_{2.5}$ exceeding the standard level during 24 months (0.098) was higher than that during 12 months (0.087; Tables 4 and 6). Exposure is characterized by the magnitude, frequency, and duration of contact with an agent. Therefore, the number of days exceeding the standard value (≥35 μg/m^3) is an important factor in our chronic $PM_{2.5}$ exposure assessment.

This study has some limitations. First, data on whether there was a daily intake of lead through food were unavailable. However, in our dialysis centers, diet/nutrition education (including the importance of avoiding heavy metals) is routinely provided to patients. In addition, in our unpublished study, we found that deep-sea fish ingestion is not a factor for elevated BLLs in patients on HD. Second, the present study applied a cross-sectional design, and we determined only the correlation between environmental $PM_{2.5}$ and BLLs and not the cause–effect relationship. However, we used the mean $PM_{2.5}$ levels in the previous 12 and 24 months for our analysis of BLLs, which appears to be similar to a semicohort-designed study. Our study suggests that chronic environmental $PM_{2.5}$ exposure might be associated with the accumulation of blood lead in patients on MHD who have lost the normal ability of urinary excretion of lead. Third, exposure misclassification could not be avoided, which indicates that we may have underestimated or overestimated the correlation between environmental $PM_{2.5}$ and BLLs by using short-term air pollutant levels. To reduce the study error, we used the mean $PM_{2.5}$ levels in the previous 12 and 24 months for analysis.

Conclusion

After adjustment for related factors, we found that chronic exposure to $PM_{2.5}$ in living environments was positively associated with BLLs in patients on MHD. Therefore, the study findings suggest the existence of a possible correlation between environmental air quality and heavy metal levels in the blood of patients on MHD.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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