Original Paper

Association Between Environmental Particulate Matter and Carpal Tunnel Syndrome in Patients Undergoing Hemodialysis

Cheng-Hao Weng^{a,b} Ching-Chih Hu^{b,c} Tzung-Hai Yen^{a,b} Wen-Hung Huang^{a,b}

^aDepartment of Nephrology and Division of Clinical Toxicology, Chang Gung Memorial Hospital, Linkou Medical Center, ^bChang Gung University College of Medicine, Taoyuan, ^cDepartment of Hepatogastroenterology and Liver Research Unit, Chang Gung Memorial Hospital, Keelung, Taiwan

Key Words

PM_{2.5} • Carpal tunnel syndrome

Abstract

Background/Aims: The deposition of β 2-microglobulin induced by reactive inflammation causing carpal tunnel syndrome (CTS) is one of the complications of dialysis-related amyloidosis in maintenance hemodialysis (MHD) patients. Air pollution levels, especially particulate matter with an aerodynamic diameter of <2.5 mm (PM_{2.5}) have significantly been associated with the elevation of systemic inflammatory markers. There is no previous research on possible associations between CTS and PM_{2.5}. **Methods:** This study enrolled 866 MHD patients treated at the outpatient HD centers. Senior neurologists diagnosed the presence of CTS. Air pollution levels were recorded by a network of 27 monitoring stations near or in the patients' living areas throughout Taiwan. The 12- and 24-month average concentrations of PM with an aerodynamic diameter of <10 and <2.5 mm (PM₁₀ and PM_{2.5}, respectively), sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone were included. **Results:** Multivariate logistic regression analyses showed that HD duration, the normalized protein catabolic rate (nPCR), hypoalbuminemia (albumin < 4 g/dl), and the mean previous 12-month environmental PM_{2.5} were positively associated with CTS; HD duration, nPCR, hypoalbuminemia (albumin < 4 g/dl), and the mean previous 24-month environmental PM_{2.5} were positively associated with CTS; HD duration, hypoalbuminemia (albumin < 4 g/dl), and previous 12-month PM_{2.5} excess days were positively associated with CTS; and HD duration, nPCR, hypoalbuminemia (albumin < 4 g/dl), and previous 24-month PM_{2.5} excess days were positively associated with CTS. **Conclusion:** PM_{2.5} levels and PM_{2.5} excessing days were positively correlated with CTS.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Wen-Hung Huang

Department of Nephrology and Division of Clinical Toxicology, Chang Gung Memorial Hospital, Linkou Medical Center, 5, Fu-Shing St, Gueishan, Taoyuan 333 (Taiwan)
E-Mail williammedia@gmail.com

Introduction

The deposition of β 2-microglobulin in the carpal tunnel causing carpal tunnel syndrome is one of the complications of dialysis-related amyloidosis in maintenance hemodialysis (MHD) patients [1]. Accumulation of β 2-microglobulin may be due to decreased removal and intra-dialytic production by the reactive inflammation by bio-incompatible artificial kidney membranes [2]. Air pollution levels, especially particulate matter with an aerodynamic diameter of <2.5 mm (PM_{2.5}), are significantly associated with elevation of systemic inflammatory markers [3-5]. We have previously showed that air pollution was significantly associated with arterial stiffness, systemic inflammation, infection, secondary hyperparathyroidism, and even mortality in MHD patients [6-10]. In the current study, we hypothesize that there might be a correlation between environment particulate matter and carpal tunnel syndrome (CTS) in MHD which has not been surveyed previously.

Materials and Methods

Patients

The study patients were recruited from the 3 HD centers of Chang Gung Memorial Hospital, Lin-Kou Medical Center at both the Taipei and Taoyuan branches. Only MHD patients who were 18 years of age or older and had undergone HD for at least 6 months were enrolled in this study. Patients with malignancies or obvious infectious diseases, as well as those who had been hospitalized or had undergone surgery within 3 months of the investigation, were excluded. Diabetes mellitus (DM) was defined by either a physician's diagnosis and antidiabetic drug treatment or 2 subsequent analyses demonstrating fasting blood glucose levels of >126 mg/dL. Most patients underwent 4 hours of HD, 3 times a week, which 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. We noted the incidence of cardiovascular diseases (CVDs) including cerebrovascular disease, coronary artery disease, congestive heart failure, and peripheral vascular disease in these patients. Hypertension was defined as the regular use of antihypertensive drugs to control blood pressure or at least 2 blood pressure measurements of more than 140/90 mmHg. Senior neurologists diagnosed the presence of CTS.

Air quality status and analysis

Levels of air pollution were recorded by a network of 26 monitoring stations near the patients' living areas in Taiwan, as described in our previous study. Data from the database on the air quality status of the Taiwan Air Quality Monitoring Network were analyzed. The previous average exposure of 365 and 730 days concentration of PMs was used for each subject. Previous 12 and 24 -month average concentrations of PMs with an aerodynamic diameter of <10 and <2.5 mm (PM₁₀ and PM_{2.5}, respectively), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon monoxide (CO), and ozone (O₃) were included as reference items. Air pollution levels were recorded by a network of 27 monitoring stations near or in the patients' living areas throughout Taiwan. Therefore, the average of approximately 8760 and 17520 ($24 \times 365 = 8760$ and $24 \times 365 \times 2 = 17520$) pieces of data for every monitoring station were calculated. The reference items were generally obtained from monitoring stations in the same area. If a patient lived between 2 monitoring stations, we selected the air pollutant data from the nearest station for analysis. If there was no monitoring station in a patient's living district, we selected the reference from the nearest station (<15 km).

Laboratory, Nutritional, and Inflammatory Parameters

All blood samples were drawn 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 (Cr) levels, normalized protein catabolism rate (nPCR), and serum albumin levels were assayed and recorded as nutritional markers. High-sensitivity C-reactive protein (hsCRP) levels were measured as indices of inflammation. All other biochemical indices were measured using a standard laboratory approach with an automatic analyzer. In the HD patients, dialyzer clearance of urea was measured using a method described by Daugirdas and was expressed as Kt/V urea. The nPCR of the HD patients was calculated using validated

Table 1. Baseline characteristics of 866 MHD patients. Abbreviations: MHD: maintenance haemodialysis CVD: cardiovascular disease HBV: hepatitis B virus infection HCV: hepatitis C virus infection nPCR, normalized protein catabolic rate hsCRP= high-sensitivity C-reactive protein, LDL= low density lipoprotein Kt/V urea= dialysis clearance of urea PM_{2.5}= particulate matter with an aerodynamic diameter of <2.5mm *Non-normal distribution data are presented as median (interquartile range)

Characteristics	Total(n=866) Mean ± SD/Median(interquartile range)
Demographics	
Age (y)	56.18±13.59
Male gender	440 (50.8%)
Body mass index (kg/m ²)	22.19±3.18
Smoking (Yes)	150(17.3%)
Co-Morbidity	
Diabetes mellitus (Yes)	192(22.2%)
Hypertension (Yes)	339 (39.1%)
Previous CVD (Yes)	41(4.7%)
HBV (Yes)	98 (11.3%)
HCV (Yes)	168(19.4%)
Carpal tunnel syndrome	76 (8.8%)
Dialysis Related Data	
Hemodialysis duration (y)	6.96±5.35
Erythropoietin (U/kg/week)	73.62±47.37
Fistula as blood access (Yes)	689(79.6%)
Hemodiafiltration (Yes)	187(21.6%)
Kt/V urea	1.79±0.32
nPCR (g/kg/day)	1.18±0.26
Residual daily urine of >100 ml	178(20.6%)
Biochemical Data	
Hemoglobin (g/dl)	10.51±1.36
Albumin (g/dl)	4.06±0.34
Creatinine (mg/dl)	10.88±2.39
Ferritin (µg/l)*	305.0(129.57, 504.45)
Corrected-calcium (mg/dl)	9.94±0.93
Phosphate (mg/dl)	4.84±1.35
Intact parathyroid hormone (pg/ml)*	130.1 (52.52, 319.2)
hsCRP (mg/l)*	2.95(1.4, 7.01)
hsCRP>3 mg/l, Pt. No.	420 (48.5%)
Cardiovascular Risks	
Cholesterol (mg/dl)	171.3±37.66
Triglyceride (mg/dl)	164.33±115.8
LDL(mg/dl)	94.83±30.59
Mean previous 12-month Environmental PM _{2.5} (ug/m ³)	29.95±3.53
Mean previous 24-month Environmental PM _{2.5} (ug/m ³)	28.57±3.66
Previous 12-month PM2.5 excess days	112.23±25.17
Previous 24-month PM2.5 excess days	221.39±53.04

equations and was normalized to the patients' body weight. Anuria was defined as a daily urine amount less than 100 mL. The serum calcium level was adjusted using the serum albumin level with the following formula: corrected calcium level (mg/dL) = serum calcium level + 0.8 × (4.0 – serum albumin level). Non-anuria was defined as a daily urine amount of ≥100 mL.

Definition of PM_{2.5} excess days

A mean 24 hour PM_{2.5} concentration level of 35 µg/m³ was defined as normal. The number of days with a mean 24 hour PM_{2.5} concentration level higher than 35 µg/m³ was defined as PM_{2.5} excess days.

Statistical Analysis

The Kolmogorov–Smirnov test was used to test if variables were normally distributed. A P value of >0.05 was required to assume a normal distribution. Continuous variables are expressed as the mean ± standard deviation/median (interquartile range), and categorical variables are expressed as numbers or

Table 2. Comparison between MHD patients with CTS and without CTS Abbreviations: MHD: maintenance haemodialysis CVD: cardiovascular disease HBV: hepatitis B virus infection HCV: hepatitis C virus infection nPCR, normalized protein catabolic rate hsCRP= high-sensitivity C-reactive protein, LDL= low density lipoprotein Kt/V urea= dialysis clearance of urea PM_{2.5} = particulate matter with an aerodynamic diameter of <2.5mm Note: A P of <0.05 represents significant variance between the groups. *Non-normal distribution data are presented as median (interquartile range)

Characteristics	CTS (76, 8.8%)	Without CTS (790, 91.2%)	P
Age (y)	57.36±12.46	56.07±13.69	0.43
Male sex	35 (46.1%)	405 (51.3%)	0.4
Body mass index (kg/m ²)	21.85±3.15	22.22±3.18	0.33
Smoking (Yes)	10	140	0.27
Diabetes mellitus (Yes)	7 (9.2%)	185(23.4%)	0.003
Hypertension (Yes)	29 (38.2%)	310 (39.2%)	0.9
Previous CVD (Yes)	2(2.6%)	39(4.9%)	0.57
HBV (Yes)	6 (7.9%)	92 (11.6%)	0.44
HCV (Yes)	24(31.6%)	144 (18.2%)	0.009
Hemodialysis duration (year)	12.3±5.79	6.45±5.02	<0.001
Erythropoietin (U/kg/week)	60.84±46.65	74.85±47.28	0.014
Fistula as blood access (Yes)	66 (86.8%)	623 (78.9%)	0.1
Hemodiafiltration (Yes)	22 (28.9%)	165 (20.9%)	0.1
Kt/V urea	1.92±0.36	1.78±0.32	<0.001
nPCR (g/kg/day)	1.26±0.27	1.18±0.26	0.007
Non-Anuria (>100 cc/day)	6 (7.9%)	172 (21.8%)	0.003
Hemoglobin (g/dl)	10.84±1.55	10.48±1.34	0.02
Albumin (g/dl)	3.98±0.34	4.07±0.34	0.033
Creatinine (mg/dl)	10.61±2.22	10.91±2.4	0.3
Ferritin (µg/l)*	272.4(147.6,488.4)	306.2(126.5, 506.35)	0.8
Corrected-calcium (mg/dl)	10.08±1.03	9.93±0.92	0.18
Phosphate (mg/dl)	4.76±1.16	4.85±1.37	0.57
Intact parathyroid hormone (pg/ml)*	254.35(106.27, 509.75)	122.25(48.6, 290.95)	<0.001
hsCRP (mg/l)*	3.23(1.75, 5.85)	2.89(1.37,7.28)	0.8
Cholesterol (mg/dl)	173.26±36.33	171.11±37.8	0.63
Triglyceride (mg/dl)	160.05±115.69	164.74±115.88	0.73
LDL(mg/dl)	97.04±29.41	94.62±30.72	0.51
Mean previous 12-month Environmental PM _{2.5} (ug/m ³)	29.71±3.87	28.46±3.63	0.005
Mean previous 24-month Environmental PM _{2.5} (ug/m ³)	31.03±3.69	29.85±3.5	0.005
Previous 12-month PM2.5 excess days	119.26±27.23	111.55±24.88	0.011
Previous 24-month PM2.5 excess days	238.59±59.67	219.74±52.10	0.003

percentages. Chi- square or Fisher's exact test was used to analyze the correlation between categorical variables. Comparisons between 2 groups were performed using the Mann-Whitney U test or Student's t-test. Data involving hsCRP, intact parathyroid hormone (iPTH), and ferritin levels were log-transformed for analysis. Univariate and multivariate logistic regression analyses were performed to evaluate the variables related to UP. Missing data were handled using list-wise deletion. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test to compare the number of observed and predicted uremic pruritus in risk groups for the entire range of uremic pruritus probabilities. Discrimination was assessed by the area under the receiver operating characteristic (AUROC) analysis. The AUROCs were compared using a non-parametric approach, and AUROC analyses were also used to calculate cutoff values, sensitivity, specificity, and overall correctness. Finally, the cutoff points were calculated by acquiring the best Youden index (sensitivity + specificity - 1). Data were analyzed using SPSS, version 12.0 for Windows 95 (SPSS Inc., Chicago, IL, USA). The level of significance was set at a P <0.05.

Table 3. Univariate Logistic Regression Analysis of CTS in MHD Patients Abbreviations: MHD= maintenance haemodialysis CVD= cardiovascular disease HBV= hepatitis B virus infection HCV= hepatitis C virus infection nPCR= normalized protein catabolic rate hsCRP= high-sensitivity C-reactive protein, LDL= low density lipoprotein Kt/V urea=dialysis clearance of urea PM_{2.5}= particulate matter with an aerodynamic diameter of <2.5mm C-Ca= corrected calcium

Characteristics Variables	Univariate logistic regression	
	Odds ratio (OR), 95% confidence intervals (CI)	P
Age (years)	1.007(0.99,1.025)	0.432
Male sex	0.812(0.5,1.30)	0.386
Body mass index (kg/m ²)	0.96(0.89,1.03)	0.33
Smoking (Yes)	0.7(0.35,1.4)	0.31
Diabetes mellitus (Yes)	0.33(0.15,0.73)	0.007
Hypertension (Yes)	0.95(0.58,1.55)	0.85
Previous CVD (Yes)	0.52(0.12, 2.19)	0.37
HBV (Yes)	0.65(0.27, 1.53)	0.32
HCV (Yes)	2.07(1.23, 3.47)	0.006
Haemodialysis duration (years)	1.17(1.13, 1.22)	<0.001
Fistula as blood access (Yes)	1.76(0.89, 3.51)	0.1
Hemodiafiltration (Yes)	1.54 (0.91, 2.6)	0.11
Kt/V urea	3.39 (1.71, 6.7)	<0.001
nPCR (g/kg/day)	3.17(1.35, 7.4)	0.008
Non-Anuria	0.3(0.13, 0.72)	0.007
Hemoglobin (g/dl)	1.21(1.02, 1.43)	0.027
Albumin<4 g/dl	2.038(1.26, 3.27)	0.003
Albumin	0.489(0.253,0.946)	0.034
Creatinine (mg/dl)	0.94(0.85, 1.04)	0.3
C-Ca	1.18(0.92, 1.51)	0.18
Phosphate (mg/dl)	0.95(0.79, 1.13)	0.57
Log ferritin	1.07(0.65, 1.78)	0.76
Log iPTH	2.62(1.63,4.22)	<0.001
hsCRP >3.0 mg/l	1.18(0.73, 1.90)	0.48
Cholesterol (mg/dl)	1.002(0.99, 1.008)	0.63
Triglyceride (mg/dl)	1.00(0.99, 1.002)	0.73
Mean previous 12-month Environmental PM _{2.5} (ug/m ³)	1.092(1.027,1.162)	0.005
Mean previous 24-month Environmental PM _{2.5} (ug/m ³)	1.099(1.028, 1.174)	0.005
Previous 12-month PM _{2.5} excess days	1.011(1.003, 1.02)	0.011
Previous 24-month PM _{2.5} excess days	1.006(1.002, 1.01)	0.003

Table 4. Multivariate Logistic Regression Analysis of CTS in MHD Patients Abbreviations: MHD= maintenance haemodialysis CTS= carpal tunnel syndrome nPCR= normalized protein catabolic rate PM_{2.5}= particulate matter with an aerodynamic diameter of <2.5mm

Variables	Odds ratio, 95% confidence intervals	P
Analysis A		
Hemodialysis duration (years)	1.218(1.155,1.284)	<0.001
nPCR (g/kg/day)	3.108(1.276,7.568)	0.013
Albumin < 4 g/dl	1.969(1.165,3.328)	0.011
Mean previous 12-month Environmental PM _{2.5} (ug/m ³)	1.078(1.008,1.153)	0.027
Analysis B		
Hemodialysis duration (years)	1.217(1.154,1.283)	<0.001
nPCR (g/kg/day)	3.089(1.268,7.527)	0.013
Albumin < 4 g/dl	2.000(1.184,3.379)	0.010
Mean previous 24-month Environmental PM _{2.5} (ug/m ³)	1.082(1.007, 1.163)	0.032

Results

Study Population Characteristics

Eight hundred and sixty-six MHD patients were included. The patients were 56.18 ± 13.59 years old and 440 patients were male (50.8%). The average HD duration was 6.96 ± 5.35 years. Seventy-six patients (8.8%) had carpal tunnel syndrome. The mean previous 12-month environmental PM_{2.5} was $29.95 \pm 3.53 \mu\text{g}/\text{m}^3$ and the mean previous 24-month environmental PM_{2.5} was $28.57 \pm 3.66 \mu\text{g}/\text{m}^3$. The mean previous 12-month environmental PM_{2.5} excess days was 112.23 ± 25.17 days and the mean previous 24-month environmental PM_{2.5} excess days was 221.39 ± 53.04 days (Table 1). Patients with CTS had a higher incidence of hepatitis C infection (HCV) and anuria, and higher HD durations, and higher Kt/V_{urea} (Daugirdes), nPCR, hemoglobin (Hb), iPTH, mean previous 12-month environmental PM_{2.5}, mean previous 24-month environmental PM_{2.5}, mean previous 12-month environmental PM_{2.5} excess days, and mean previous 24-month environmental PM_{2.5} excess days levels, compared to the patients without CTS. A lower incidence of DM, lower dosages of erythropoietin, and lower levels of albumin were noted in CTS patients (Table 2).

Predictors of carpal tunnel syndrome by univariate logistic regression (Table 3)

Univariate logistic regression analyses showed that HCV, HD duration, Kt/V urea (Daugirdes), nPCR, anuria, Hb, hypoalbuminemia (albumin < 4 g/dl), log iPTH, mean previous 12-month environmental PM_{2.5}, mean previous 24-month environmental PM_{2.5}, mean previous 12-month environmental PM_{2.5} excess days, and mean previous 24-month environmental PM_{2.5} excess days were positively associated with CTS. Diabetes mellitus and albumin were negatively associated with CTS.

Predictors of carpal tunnel syndrome by multivariate logistic regression

Univariate logistic regression demonstrated that 4 kinds of PM_{2.5} variables were all predictors of CTS. We analyzed multivariate logistic regression to include 4 PM_{2.5} variables independently and those with $P < 0.05$ in univariate logistic regression. Analysis A showed that HD duration [odds ratio (OR): 1.218, 95% confidence interval (CI): 1.155 – 1.284, $P < 0.001$], nPCR (OR: 3.108, 95% CI: 1.276 – 7.568, $P = 0.013$), hypoalbuminemia (albumin < 4 g/dl) (OR: 1.969, 95% CI: 1.125 – 3.328, $P = 0.011$), and mean previous 12-month environmental PM_{2.5} (OR: 1.078, 95% CI: 1.008 – 1.153, $P = 0.027$) were positively associated

Table 5. Multivariate Logistic Regression Analysis of relationship between CTS and previous 12- and 24-month PM_{2.5} exceeding days in MHD Patients Abbreviations: MHD= maintenance haemodialysis CTS= carpal tunnel syndrome nPCR= normalized protein catabolic rate PM_{2.5}= particulate matter with an aerodynamic diameter of <2.5mm

Variables	Odds ratio, 95% confidence intervals	P
Analysis C		
Hemodialysis duration (years)	1.219(1.156,1.285)	<0.001
nPCR (g/kg/day)	3.137(1.289,7.635)	0.012
Albumin<4.0 g/dl	1.977(1.170,3.339)	0.011
Previous 12-month PM _{2.5} excess days	1.010(1.001,1.020)	0.034
Analysis D		
Hemodialysis duration (years)	1.217(1.155,1.283)	<0.001
nPCR (g/kg/day)	3.131(1.285,7.628)	0.012
Albumin<4 g/dl	1.987(1.175,3.360)	0.010
Previous 24-month PM _{2.5} excess days	1.005(1.001,1.010)	0.019

Table 6. Multivariate Logistic Regression Analysis of relationship between CTS and PM_{2.5} exceeding days longer than 227 days and 116 days in MHD Patients Abbreviations: MHD= maintenance haemodialysis CTS= carpal tunnel syndrome nPCR= normalized protein catabolic rate PM_{2.5}= particulate matter with an aerodynamic diameter of <2.5mm

Variables	Odds ratio, 95% confidence intervals	P
Analysis E		
Hemodialysis duration (years)	1.216(1.152,1.283)	<0.001
nPCR (g/kg/day)	2.803(1.121,7.009)	0.028
Albumin<4 g/dl	1.928(1.129,3.295)	0.016
Previous 24-month PM _{2.5} excess days≥227 days (yes)	3.626(2.153,6.107)	<0.001
Analysis F		
Haemodialysis duration (years)	1.213(1.149,1.280)	<0.001
nPCR (g/kg/day)	2.650(1.053,6.668)	0.038
Albumin<4 g/dl	1.955(1.141,3.352)	0.015
Previous 12-month PM _{2.5} excess days≥116 days (yes)	4.366(2.573,7.408)	<0.001

with CTS. Analysis B showed that HD duration (OR: 1.217, 95% CI: 1.154 – 1.283, P < 0.001), nPCR (OR: 3.089, 95% CI: 1.278 – 7.527, P = 0.013), hypoalbuminemia (albumin < 4 g/dl) (OR: 2.000, 95% CI: 1.184 – 3.379, P = 0.010), and mean previous 24-month environmental PM_{2.5} (OR: 1.082, 95% CI: 1.007 – 1.163, P = 0.032) were positively associated with CTS (Table 4). Analysis C showed that HD duration (OR: 1.219, 95% CI: 1.156 – 1.285, P < 0.001), nPCR (OR: 3.137, 95% CI: 1.289 – 7.635, P = 0.012), hypoalbuminemia (albumin < 4 g/dl) (OR: 1.977, 95% CI: 1.170 – 3.339, P = 0.011), and previous 12-month PM_{2.5} excess days (OR: 1.010, 95% CI: 1.001 – 1.020, P = 0.034) were positively associated with CTS. Analysis

D showed that HD duration (OR: 1.217, 95% CI: 1.155 – 1.283, $P < 0.001$), nPCR (OR: 3.131, 95% CI: 1.285 – 7.628, $P = 0.012$), hypoalbuminemia (albumin < 4 g/dl) (OR: 1.987, 95% CI: 1.175 – 3.360, $P = 0.010$), and previous 24-month PM_{2.5} excess days (OR: 1.005, 95% CI: 1.001 – 1.010, $P = 0.019$) were positively associated with CTS (Table 5).

Discrimination, and correlation for previous PM_{2.5} excess days and carpal tunnel syndrome

The discrimination power of previous 12-month PM_{2.5} excess days was AUROC $\pm$ SE: 0.633 ± 0.036 with $P < 0.001$. The cutoff point of previous 12-month PM_{2.5} excess days to predict CTS was 116 days. The discrimination power of previous 24-month PM_{2.5} excess days was AUROC $\pm$ SE: 0.647 ± 0.034 with $P < 0.001$. The cutoff point of previous 24-month PM_{2.5} excess days to predict CTS was 227 days. Analysis E showed that previous 24-month PM_{2.5} excess days (> 227 days) was a significant predictor of CTS (OR: 3.626, 95% CI: 2.153 – 6.107, $P < 0.001$) by multivariate logistic regression. Analysis F showed that previous 12-month PM_{2.5} excess days (> 116 days) was a significant predictor of CTS (OR: 4.366, 95% CI: 2.573 – 7.408, $P < 0.001$) by multivariate logistic regression (Table 6).

Discussion

Carpal tunnel syndrome in patients on MHD was caused by dialysis-related $\beta 2$ -microglobulin amyloid deposition in the carpal tunnel [11]. PM_{2.5} was associated with airway inflammation and hyper responsiveness [12]. Systemic oxidative stress and inflammation were also associated with PM_{2.5} [13]. Reactive inflammation in lesions in which $\beta 2$ -microglobulin amyloid was deposited was associated with a marked infiltration of activated macrophages expressing cytokines, such as interleukin-1, tumor necrosis factor- α , and transforming growth factor- β [14]. Only animal study also showed that after oropharyngeal aspiration of PM_{2.5}, robust production of IL-1 by leukocytes in the lung tissue was noted [15, 16]. Brucker et al. showed that PM_{2.5} was also associated with higher inflammatory markers, including IL-1 β in taxi drivers with occupational exposure to air pollution [17]. Therefore, by inducing IL-1, PM_{2.5} may cause $\beta 2$ -microglobulin amyloid deposition in the carpal tunnel.

Different kinds of cell cultures studies have demonstrated that PM_{2.5} could significantly increase TNF- α expression [18-20]. Adults exposed to diesel exhaust including 300 μg PM_{2.5}/m³ for 120 min also had an increased serum concentration of TNF- α [21]. Ambient air pollution evaluated by the level of PM_{2.5} in Beijing also induced higher levels of TNF- α expression in participants' bronchial epithelial cells [22]. PM_{2.5} might be associated with CTS in HD patients by inducing TNF- α based on these *in vivo* and *in vitro* studies.

Mice with inhalation exposure to ambient PM_{2.5} demonstrated hepatic fibrosis by activation of the transforming growth factor β -SMAD3 signaling [23]. PM_{2.5} also accentuated virus-induced myocarditis through the increase of TGF- β in myocardium through the Treg responses [24]. PM_{2.5} exacerbated stiffness-induced alveolar epithelial cell mechanoactivation of TGF- β [25]. TGF- β might also be a mediator of PM_{2.5} to induce CTS in our MHD patients.

Our study also showed that PM_{2.5} excess days were also a significant predictor of CTS in MHD patients. In patients with chronic obstructive pulmonary disease, the number of days with high levels of PM_{2.5} per month was significantly associated with the total number of COPD exacerbation [26]. Luong et al. showed that an increase in 10 $\mu\text{g}/\text{m}^3$ of PM_{2.5} was associated with an increase in the risk of respiratory admission of 2.2% on the same day of exposure [27]. Therefore, not only a yearly average level of PM_{2.5} was associated with CTS, but also the number of PM_{2.5} excess days was also a significant predictor of CTS. In days with PM_{2.5} > 35 $\mu\text{g}/\text{m}^3$, we suggested MHD patients stay indoors to prevent respiratory diseases and CTS.

Conclusion

PM_{2.5}, an air pollution level, and PM_{2.5} excess days were associated with CTS in MHD patients. Patients on MHD should avoid going outside in the days when air quality is poor to prevent CTS.

Disclosure Statement

The authors have declared that no competing interests exist.

Acknowledgements

Wen-Hung Huang was funded by research grants from the Chang Gung Memorial Hospital, Linkou (CORPG5G0061, CMRPG3G0511).

References

- 1 Dember LM, Jaber BL: Dialysis-related amyloidosis: late finding or hidden epidemic? *Semin Dial* 2006;19:105-109.
- 2 Floege J, Koch KM: Beta 2-microglobulin associated amyloidosis and therapy with high flux hemodialysis membranes. *Clin Nephrol* 1994;42:S52-56.
- 3 Dabass A, Talbott EO, Venkat A, Rager J, Marsh GM, Sharma RK, Holguin F: Association of exposure to particulate matter (PM_{2.5}) air pollution and biomarkers of cardiovascular disease risk in adult NHANES participants (2001-2008). *Int J Hyg Environ Health* 2016;219:301-310.
- 4 Mirowsky JE, Peltier RE, Lippmann M, Thurston G, Chen LC, Neas L, Diaz-Sanchez D, Laumbach R, Carter JD, Gordon T: Repeated measures of inflammation, blood pressure, and heart rate variability associated with traffic exposures in healthy adults. *Environ Health* 2015;14:66.
- 5 Viehmann A, Hertel S, Fuks K, Eisele L, Moebus S, Mohlenkamp S, Nonnemacher M, Jakobs H, Erbel R, Jockel KH, Hoffmann B, Heinz Nixdorf Recall Investigator G: Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. *Occup Environ Med* 2015;72:656-663.
- 6 Weng CH, Hu CC, Yen TH, Huang WH: Association between environmental particulate matter and arterial stiffness in patients undergoing hemodialysis. *BMC Cardiovasc Disord* 2015;15:115.
- 7 Weng CH, Hu CC, Yen TH, Huang WH: Association between ambient carbon monoxide and secondary hyperparathyroidism in nondiabetic patients undergoing peritoneal dialysis. *Ther Clin Risk Manag* 2015;11:1401-1408.
- 8 Lin JH, Yen TH, Weng CH, Huang WH: Environmental NO₂ level is associated with 2-year mortality in patients undergoing peritoneal dialysis. *Medicine (Baltimore)* 2015;94:e368.
- 9 Huang WH, Lin JL, Lin-Tan DT, Chen KH, Hsu CW, Yen TH: Impact of living environment on 2-year mortality in elderly maintenance hemodialysis patients. *PLoS One* 2013;8:e74358.
- 10 Huang WH, Yen TH, Chan MJ, Su YJ: Impact of environmental particulate matter and peritoneal dialysis-related infection in patients undergoing peritoneal dialysis. *Medicine (Baltimore)* 2014;93:e149.
- 11 Gilbert MS, Robinson A, Baez A, Gupta S, Glabman S, Haimov M: Carpal tunnel syndrome in patients who are receiving long-term renal hemodialysis. *J Bone Joint Surg Am* 1988;70:1145-1153.
- 12 Ogino K, Nagaoka K, Okuda T, Oka A, Kubo M, Eguchi E, Fujikura Y: PM_{2.5}-induced airway inflammation and hyperresponsiveness in NC/Nga mice. *Environ Toxicol* 2017;32:1047-1054.
- 13 Zhang X, Staimer N, Gillen DL, Tjoa T, Schauer JJ, Shafer MM, Hasheminassab S, Pakbin P, Vaziri ND, Sioutas C, Delfino RJ: Associations of oxidative stress and inflammatory biomarkers with chemically-characterized air pollutant exposures in an elderly cohort. *Environ Res* 2016;150:306-319.

- 14 Matsuo K, Ikizler TA, Hoover RL, Nakamoto M, Yasunaga C, Pupim LB, Hakim RM: Transforming growth factor-beta is involved in the pathogenesis of dialysis-related amyloidosis. *Kidney Int* 2000;57:697-708.
- 15 Ogino K, Zhang R, Takahashi H, Takemoto K, Kubo M, Murakami I, Wang DH, Fujikura Y: Allergic airway inflammation by nasal inoculation of particulate matter (PM2.5) in NC/Nga mice. *PLoS One* 2014;9:e92710.
- 16 Van Winkle LS, Bein K, Anderson D, Pinkerton KE, Tablin F, Wilson D, Wexler AS: Biological dose response to PM2.5: effect of particle extraction method on platelet and lung responses. *Toxicol Sci* 2015;143:349-359.
- 17 Brucker N, Moro AM, Charao MF, Durgante J, Freitas F, Baierle M, Nascimento S, Gauer B, Bulcao RP, Bubols GB, Ferrari PD, Thiesen FV, Gioda A, Duarte MM, de Castro I, Saldiva PH, Garcia SC: Biomarkers of occupational exposure to air pollution, inflammation and oxidative damage in taxi drivers. *Sci Total Environ* 2013;463-464:884-893.
- 18 Chen H, Chen X, Hong X, Liu C, Huang H, Wang Q, Chen S, Chen H, Yang K, Sun Q: Maternal exposure to ambient PM2.5 exaggerates fetal cardiovascular maldevelopment induced by homocysteine in rats. *Environ Toxicol* 2017;32:877-889.
- 19 Zhao Q, Chen H, Yang T, Rui W, Liu F, Zhang F, Zhao Y, Ding W: Direct effects of airborne PM2.5 exposure on macrophage polarizations. *Biochim Biophys Acta* 2016;1860:2835-2843.
- 20 Bo L, Jiang S, Xie Y, Kan H, Song W, Zhao J: Effect of Vitamin E and Omega-3 Fatty Acids on Protecting Ambient PM2.5-Induced Inflammatory Response and Oxidative Stress in Vascular Endothelial Cells. *PLoS One* 2016;11:e0152216.
- 21 Cliff R, Curran J, Hirota JA, Brauer M, Feldman H, Carlsten C: Effect of diesel exhaust inhalation on blood markers of inflammation and neurotoxicity: a controlled, blinded crossover study. *Inhal Toxicol* 2016;28:145-153.
- 22 Liu Q, Baumgartner J, Zhang Y, Liu Y, Sun Y, Zhang M: Oxidative potential and inflammatory impacts of source apportioned ambient air pollution in Beijing. *Environ Sci Technol* 2014;48:12920-12929.
- 23 Zheng Z, Zhang X, Wang J, Dandekar A, Kim H, Qiu Y, Xu X, Cui Y, Wang A, Chen LC, Rajagopalan S, Sun Q, Zhang K: Exposure to fine airborne particulate matters induces hepatic fibrosis in murine models. *J Hepatol* 2015;63:1397-1404.
- 24 Xie Y, Gong C, Bo L, Jiang S, Kan H, Song W, Zhao J, Li Y: Treg responses are associated with PM2.5-induced exacerbation of viral myocarditis. *Inhal Toxicol* 2015;27:281-286.
- 25 Dysart MM, Galvis BR, Russell AG, Barker TH: Environmental particulate (PM2.5) augments stiffness-induced alveolar epithelial cell mechanoactivation of transforming growth factor beta. *PLoS One* 2014;9:e106821.
- 26 Stevanovic I, Jovasevic-Stojanovic M, Stosic JJ: Association between ambient air pollution, meteorological conditions and exacerbations of asthma and chronic obstructive pulmonary disease in adult citizens of the town of Smederevo. *Vojnosanit Pregl* 2016;73:152-158.
- 27 Luong LM, Phung D, Sly PD, Morawska L, Thai PK: The association between particulate air pollution and respiratory admissions among young children in Hanoi, Vietnam. *Sci Total Environ* 2017;578:249-255.