ORIGINAL ARTICLE

Expressions of macrophage migration inhibitory factor in patients with chronic kidney disease

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Abstract

Context: Uremic cardiomyopathy is a risk factor of end-stage renal disease (ESRD) and is responsible for high mortality rates and increased left ventricular mass index (LVMI). Macrophage migration inhibitory factor (MIF) promotes inflammation and is an important factor in uremic cardiomyopathy.

Aims: The aim of this study is to investigate the effects of serum macrophage MIF on myocardial hypertrophy in ESRD patients and to examine the relation of this factor to clinical characteristics.

Settings and Design: One hundred forty-four patients with chronic kidney disease (CKD) were divided into three groups: (1) CKD, (2) peritoneal dialysis (PD), and (3) hemodialysis (HD) groups. A control group included subjects without kidney disease. Serum macrophage migratory inflammatory factor was measured using the Bio-Plex cytokine assay and LVMI was measured.

Subjects and Methods: MIF was determined using the Bio-Plex cytokine assay. LVMI was calculated by color Doppler ultrasound measurements.

Statistical Analysis Used: Statistical analyses to compare data among groups included: The Kruskal–Wallis test to measure skewness of data and Spearman's rank correlation test to measure associations among continuous and ordinal variables. Logistic regression analysis was performed to determine relative risk.

Results: Serum macrophage migratory inflammatory factor levels were higher in HD patients (982.74 pg/mL) than that of PD patients (762.20 pg/mL), CKD patients (755.66 pg/mL), or healthy controls (336.81 pg/mL) (P = 0.009). Levels were also significantly increased in patients with left ventricular hypertrophy, and they correlated with the levels of other inflammatory factors.

Conclusions: This study suggests that macrophage migratory inflammatory factor promoted the occurrence and development of uremic cardiomyopathy in patients with ESRD.

Key words: End-stage renal disease, inflammation, macrophage migration inhibitory factor, uremic cardiomyopathy, ventricular hypertrophy

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Introduction

The incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) has increased by over 10%

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annually and is due to the increased number of older individuals in the population;[1] in China, it is estimated that the prevalence of patients with ESRD will reach 1200/million people by 2020, and uremic cardiomyopathy is responsible for the high mortality rates in these patients.[2]

Uremic cardiomyopathy in CKD patients results in myocardial damage caused by hypertension, blood volume overload, and a complicated internal environment that leads to malignant arrhythmia and heart failure.[3] Current diagnosis for uremic cardiomyopathy is echocardiogram, which is manifested by dilated left ventricle and left ventricular hypertrophy (LVH).

Seventy-four percent of dialysis patients have LVH, which is considered an independent risk factor of decreased survival in ESRD and dialysis patients.[4]

Hypertension and blood volume overload are considered to be the main mechanisms behind uremic cardiomyopathy. However, correcting hypertension or relieving blood volume overload does not alleviate LVH, which indicates mechanistic causes, such as microinflammation.[5,6] Microinflammation is a chronic systemic inflammatory state associated with increased inflammatory factors that cause cardiac damage such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-1.[7,8] Recently, macrophage migration inhibitory factor (MIF) was shown to be involved in several diseases such as cancer, atherosclerosis, and autoimmune diseases and was regarded as a bridge between the human endocrine and immune systems.[9-11] MIF functions as a proinflammatory cytokine that inhibits macrophage migration while enhancing its adhesion, aggregation, and phagocytic ability. It also induces macrophage release of proinflammatory cytokines including TNF-α, IL-1, IL-2, IL-6, IL-8, and interferon-γ (IFN-γ).[12,13] Expression of MIF-173 CC gene is upregulated in patients with ESRD and this expression is associated with the expression of CRP.[14,15] However, the effect of MIF and high-sensitivity CRP (hsCRP) on myocardial hypertrophy in ESRD patients remains unknown. Our study investigates the effect of serum MIF on myocardial hypertrophy in ESRD patients and examines its relationship to other clinical and biochemical characteristics such as hsCRP.

Subjects and Methods

Ethical statement

Informed consent was obtained from all participants included in the study. All procedures involving human participants were in accordance with the Ethical Standards of the Institutional and/or the National Research Committee and with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards. No animals were used in this study.

Patient recruitment took place at the Blood Purification Center of Taian City Central Hospital and Qingdao City Central Hospital, Shandong Province in China. The study was approved by the Ethics Committee of Taian City Central Hospital and Qingdao City Central Hospital.

Patients

Patients were on dialysis for >3 months or not on dialysis and were ≥18 years of age. CKD patients were selected according to the 2002 K/DOQI guideline: Glomerular filtration rate (GFR) <60 mL/(min·1.73 m^2) or kidney injury for any reason that was present for >3 months.[16] Patients were excluded if any of the following situations occurred within 1 month of the study start: Infection, trauma, surgery, acute cardiovascular, cerebrovascular events, active hepatitis, malignant neoplasms, systemic lupus erythematosus, glucocorticosteroids, or immunosuppressive therapy and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker.

Sample collection and analysis

Blood was collected from fasted patients. For dialyzed patients, blood samples were collected before dialysis. Blood samples were centrifuged at 4500 rpm for 10 min. Serum was stored at −80°C until analyses. Serum concentrations of albumin, blood urea nitrogen (BUN), creatinine, lipids, and hsCRP were measured using the Roche Cobas 8000 modular analyzer series C701(Roche, Inc., Mannheim, Germany). Hemoglobin (Hb) was detected using the SYSMEX 2100 hematology analyzer (Sysmex, Kobe, Japan). Serum MIF was determined using the Bio-Plex cytokine assay (Bio-Rad Laboratories Inc., Hercules, CA, USA) according to manufacturer's instructions.

Left ventricular mass index

Left ventricular end diastolic dimension (LVDD), interventricular septum thickness (IVST), left ventricular ejection fraction (%), and left ventricular posterior wall thickness (LVPWT) were measured using the iU22 ultrasound system (Philips Medical Systems, Bothell, WA, USA). Left ventricular mass (LVM) was calculated using the ASE-recommended formula, LVM = 0.8 (1.04× [(LVDD + IVST + LVPWT)^3 − LVDD^3]) + 0.6, and was indexed for the body surface area (LVM index [LVMI]). LVH was defined by LVMI >134 g/m^2 in male subjects and >110 g/m^2 in female subjects.[17,18] Subjects were divided into hypertrophy group and nonhypertrophy group. Uremic cardiomyopathy was defined according to previously published standards.[19]

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as mean and standard deviation (normally distributed variables) or median and range (nonnormal distribution) unless otherwise indicated. As the MIF and hsCRP data were not normally distributed, Kruskal–Wallis

Test was used to analyze potential statistical significance across different groups and between healthy subject groups and patient groups. Spearman's rank correlation test was used to measure associations among continuous and ordinal variables. In addition, logistic regression analysis was performed to determine relative risk (RR). $P < 0.05$ was considered statistically significant.

Results

Subject data

A total of 144 CKDs patients (80 male and 64 female) were recruited to the study. Sixty-three CKD patients in K/DOQI stages 4–5 (creatinine clearance 20.5 ± 2.7 mL/min) received conservative therapy. Patients were divided into CKD group (CKD), peritoneal dialysis (PD) group (n = 30), and hemodialysis (HD) group (n = 51). Healthy subjects (n = 30; 17 male and 13 female) were used as controls. CKD group had 63 subjects (36 male and 27 female) between 21 and 86 years old. Causes of CKD (CKD stage 4-5) in this study population were chronic glomerulonephritis (n = 14), hypertensive renal damage (n = 17), diabetic nephropathy (n = 11), polycystic kidney disease (n = 7), chronic interstitial nephritis (n = 5), obstructive nephropathy (n = 4), and unknown cause (n = 5). There was no statistically significant difference between gender and age in the three groups. PD group had thirty subjects (17 male and 13 female) between 19 and 79 years old. All patients received an adequate amount of standard lactate continuous ambulatory PD. The causes of ESRD in this study population were chronic glomerulonephritis (n = 12), hypertensive renal damage (n = 8), diabetic nephropathy (n = 3), polycystic kidney disease (n = 3), and chronic interstitial nephritis (n = 4). HD group had 51 subjects (27 male and 24 female) between 20 and 81 years old. All patients were dialyzed using a bicarbonate dialysate and disposable Baxter BM-25 dialyzer with 500 mL/min flow and blood flow of 200–250 mL/min, and HD was adequate. The causes of ESRD in this study population were chronic glomerulonephritis (n = 13), hypertensive renal damage (n = 11), diabetic nephropathy (n = 10), polycystic kidney disease (n = 5), chronic interstitial nephritis (n = 4), obstructive nephropathy (n = 2), IgA nephropathy (n = 3), and unknown causes (n = 3). General characteristics of patients are summarized in Table 1.

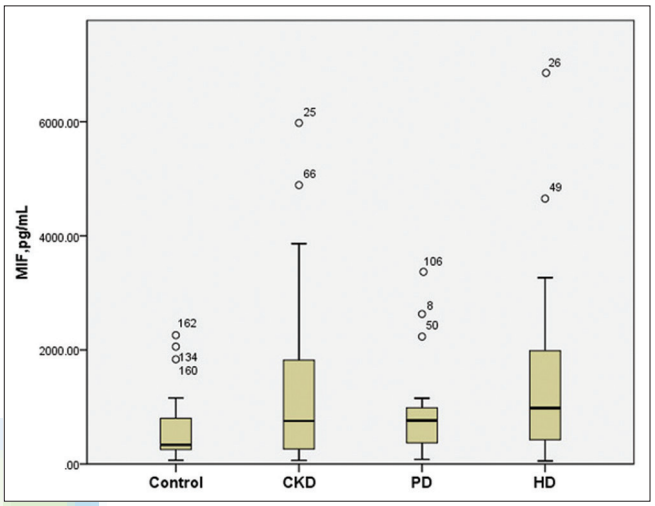

Figure 1: Serum migration inhibitory factor levels in control, chronic kidney disease, peritoneal dialysis, and hemodialysis groups. Data are shown as the median and range of values. The circles indicate outliers in each group. The number next to the circle is a serial number. Serum migration inhibitory factor levels in the hemodialysis group were highest, followed by peritoneal dialysis group and chronic kidney disease group. Finally, the control group migration inhibitory factor values were lowest based on Kruskal–Wallis test ($P < 0.05$ means significant difference). CKD=Chronic kidney disease; PD=Peritoneal dialysis; HD=Hemodialysis

Table 1: General patient characteristics

Parameters	Control group (n=30)	CKD group (n=63)	PD group (n=30)	HD group (n=51)	P
Age, years	54.7±16.1	57.4±14.4	53.0±15.6	53.8±17.7	>0.05
Sex, male/female	17/13	36/27	17/13	27/24	>0.05
Course of disease (months)	0	26.3±27.0	26.0±22.4	27.2±27.8	>0.05
Systolic pressure	129.3±10.6	150.2±22.9	148.7±19.3	151.8±18.5	<0.05
Diastolic pressure	71.2±8.2	82.3±14.3	81.5±10.4	86.3±14.8	<0.05
Primary diseases					
Chronic glomerulonephritis	-	14 (22.2)	12 (40.0)	13 (25.5)	>0.05
Hypertensive nephropathy	-	17 (27.1)	8 (26.7)	11 (21.6)	>0.05
Diabetic nephropathy	-	11 (17.5)	3 (10.0)	10 (19.6)	>0.05
Polycystic kidney disease	-	7 (11.1)	3 (10.0)	5 (9.8)	>0.05
Chronic interstitial nephritis	-	5 (7.9)	4 (13.3)	4 (7.8)	>0.05
Obstructive nephropathy	-	4 (6.3)	-	2 (3.9)	>0.05
IgA nephropathy	-	-	-	3 (5.9)	-
Unknown	-	5 (7.9)	-	3 (5.9)	>0.05

Values are means±SD; unless specified otherwise. P<0.05 indicating a statistical difference. Except the control group; comparisons among the other three groups have no statistical difference (P>0.05). HD=Hemodialysis; PD=Peritoneal dialysis; CKD=Chronic kidney disease; SD=Standard deviation

Migration inhibitory factor levels in chronic kidney disease patients versus healthy controls

Serum MIF levels in patient were assayed using a magnetic bead method. Serum MIF levels were 755.66 pg/mL (62.85–5979.54 pg/mL) in CKD patients, 762.20 pg/mL (82.31–3348.99 pg/mL) in PD patients, 982.74 pg/mL (54.79–6857 pg/mL) in HD patients, and 336.81 pg/mL (65.02–2258.65 pg/mL) in healthy subjects [Figure 1]. The Kruskal–Wallis test was used to analyze potential statistical differences among different groups since data were not normally distributed. Serum MIF levels were statistically greater in the three patient groups compared to healthy control group ($P < 0.05$).

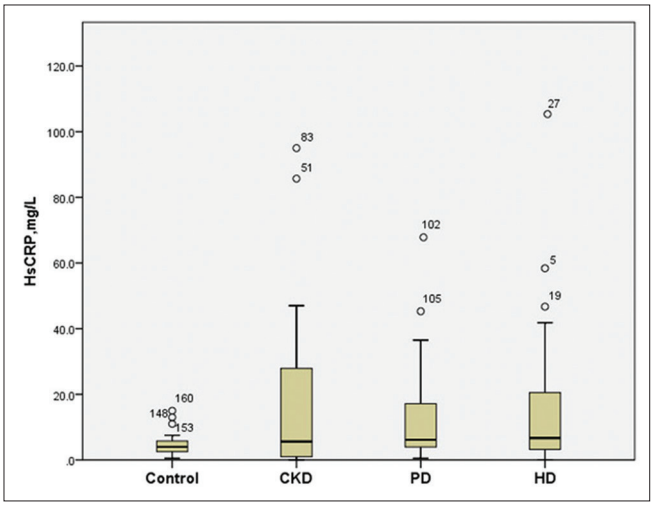

Figure 2: Serum high-sensitivity C-reactive protein levels in control, chronic kidney disease, peritoneal dialysis, and hemodialysis groups. Data are shown as the median and range of values. Circles indicate outlier values in each group. The number next to circles is a serial number. Serum high-sensitivity C-reactive protein increased most in hemodialysis group, followed by peritoneal dialysis group and chronic kidney disease group. Finally, the control group high-sensitivity C-reactive protein values were lowest based on Kruskal–Wallis test ($P < 0.05$ means significant difference). CKD=Chronic kidney disease; PD=Peritoneal dialysis; HD=Hemodialysis

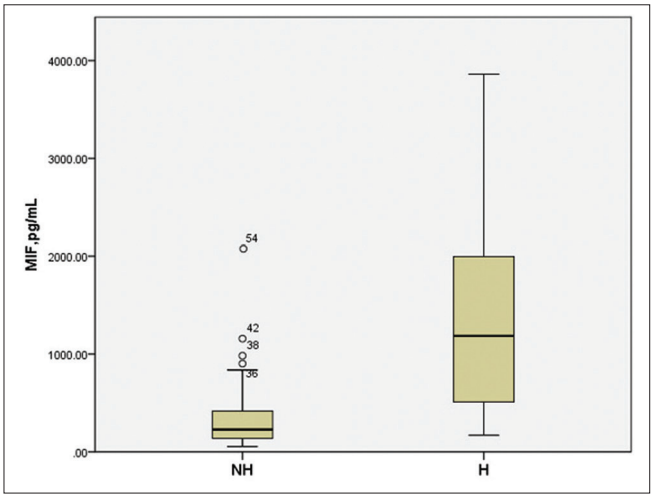

Figure 3: Serum migration inhibitory factor levels in nonhypertrophy and hypertrophy groups. Data are shown as the median and range of values. Circles indicate outlier values in each group. Serum migration inhibitory factor in patients with left ventricular hypertrophy was significantly higher than that of patients with left nonventricular hypertrophy based on Kruskal–Wallis test ($P < 0.05$ means significant difference). NH=Nonhypertrophy group; H=Hypertrophy group

High-sensitivity C-reactive protein levels in chronic kidney disease patients versus healthy controls

Serum hsCRP levels in CKD, PD, HD patients, and healthy people were 5.6 (0.04–195) mg/L, 6.2 (0.5–68.2) mg/L, 6.7 (0.1–105.5) mg/L, and 4.0 (0.5–15) mg/L, respectively [Figure 2]. The Kruskal–Wallis test indicated that there were no differences across the four groups ($P > 0.05$).

Correlation of migration inhibitory factor and clinical characteristics in chronic kidney disease patients

Serum MIF levels were correlated with inflammatory factors, hsCRP, Hb, albumin, and BUN [Table 2].

Association among relevant factors and left ventricular mass index

Associations among relevant factors, including MIF, Hb, red blood cell, albumin, Cr, and LVH, were analyzed.

Table 2: Spearman rank correlations for macrophage migration inhibitory factor in chronic kidney disease patients

	Spearman correlation	*P*
Systolic pressure	−0.03	0.7
Diastolic pressure	0.06	0.5
hsCRP	−0.30*	0.01
Hemoglobin	0.21*	0.02
Albumin	0.21*	0.02
Cholesterol	−0.10	0.2
Triglycerides	0.01	0.9
Apo A	−0.00	1.0
Apo B	−0.09	0.3
BUN	0.25*	0.004
Creatinine	0.06	0.5
LVEF%	−0.05	0.7

*$P<0.05$ statistical difference. hsCRP=High C-reactive protein; Apo=Apolipoprotein; BUN=Blood urea nitrogen; LVEF%=Left ventricular ejection fraction

Table 3: Logistic regression model of left ventricular mass index

Variable	*B*	SE	Wald	*P*	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
MIF	2.542	0.810	9.850	0.002	12.706	2.598	62.151
Constant	−0.345	0.317	1.183	0.277	-	-	-

MIF=Migration inhibitory factor; SE=Standard error; CI=Confidence interval

LVH was defined as the dependent variable, and patients were divided into hypertrophy group (H) and nonhypertrophy group (NH) according to an LVMI >134 g/m^2 in male subjects and >110 g/m^2 in female subjects. MIF was associated with LVMI with a concentration of 1186.0 pg/mL (170.0–3862.0 pg/mL) for hypertrophy group and 228.5 pg/mL (55.0–2079.0 pg/mL) for nonhypertrophy group [Figure 3]. Logistical correlation analysis was carried out to examine the RR of MIF to LVH. An MIF >1100 pg/mL was defined as abnormal while an MIF ≤1100 pg/mL was defined as normal.[20] When considering OR, LVH is 12.706 times more likely to occur in patients with increased serum MIF than a low serum MIF [Table 3].

Discussion

Recent studies demonstrated that several cytokines and inflammatory mediators are elevated in ESRD patients, leading to microinflammation, indicating a reliable index for prognosis of ESRD.[21] MIF is a pluripotent cytokine that attracts aggregation of macrophages and T lymphocytes in localized inflammation and enhances macrophage phagocytosis. MIF can also stimulate macrophage secretion of IL-1β, IL-6, IL-8, TNF-α, and IFN-γ, which then activates the mitogen-activated protein kinase (MAPK) signaling pathway and the downstream transcription factor family, nuclear factor-kappa B (NF-κB). This induces myocardial hypertrophy and collagen synthesis, eventually leading to cardiac remodeling and heart failure.[8] Through this complicated pathway, MIF could be the underlying cause of myocardial damage in CKD. Besides, MIF was significantly elevated in CKD patients in our study and MIF was elevated in patients with several different glomerular and tubular kidney diseases as demonstrated by Honda *et al.*[22] MIF was also closely related to creatinine clearance in this study.

Renal anemia due to CKD results from absolute or relative lack of erythropoietin (EPO) reduction of glomerular filtration rate (GFR) and damage to the renal cortex and medulla. However, microinflammation may also play a role in anemia since MIF induces proinflammatory cytokine release that then suppresses erythroid colony forming unit and causes EPO resistance leading to anemia.

In this study, increased serum MIF in HD patients and PD patients may be due to the inflammatory cytokine release as a result of incompatible dialysis membranes and solutions or endotoxin contamination of dialysate.[23] The PD solution could induce peritoneal immune responses resulting in unexpected cytokine release.[24]

Diagnosis of uremic cardiomyopathy relies on echocardiogram after a definitive diagnosis of chronic renal failure. LVMI is an effective measure of LVH. Our study shows that elevated serum MIF is correlated with LVMI, independent of age, sex, and blood pressure, and is different from previous studies.[25] Garner *et al.* demonstrated that increased MIF expression in the heart promotes cardiac inflammation, apoptosis, and cardiac insufficiency by phosphorylation of p38MAPK, JNK, and caspase-3 (caspase-3).[26,27] Neutralizing MIF effects have been shown to increase expression of survival factors, increase myocardial cell activity, and improve heart function, which suggests that MIF is an important factor in cardiac insufficiency.[27] In addition, MIF release during ischemia activated ERK1/2 MAPK, JAB1/AP-1, and NF-κB pathways cause a cascade reaction of myocardial injury, injured myocardial cells, macrophage recruitment of additional macrophages, neutrophils, and T cells into an inflammatory focus. This inflammatory process results in a positive feedback and a vicious circle, causing that causes myocardial infarction and heart failure. Our study found that incidence rate of myocardial hypertrophy in patients with MIF >1100 pg/mL was 12.7 times of those with MIF ≤1100 pg/mL.

Leng *et al.* found that MIF may have a transmembrane protein receptor, CD74, that causes cell proliferation and inflammatory mediator release, and that blocking CD74 can significantly inhibit its function, indicating a possible target to treat uremic cardiomyopathy.[28] Another study found both high MIF mRNA expression in peripheral blood leukocytes and elevated serum MIF.[29] Increased MIF expression by smooth muscle cells promoted aggregation, activation of monocyte and macrophage, and inhibited their migration in location of the plaques. Thus, promoting proliferation of inflammatory cell, activating inflammatory factors such as IL-1β and TNF-α, and inducing expression of intercellular adhesion molecule-1 by vascular endothelial cells, which accelerates macrophage to foam cell conversion, increases extracellular matrix metalloproteinase degradation, increases instability, and ruptures coronary plaques, result in acute coronary syndrome.[30,31]

Conclusion

In summary, our study demonstrated that serum MIF was increased in patients with ESRD, especially in HD patients. Serum MIF levels were associated with myocardial hypertrophy, and not nonmyocardial hypertrophy. Most importantly, we have shown evidence that in ESRD patients with myocardial damage, MIF promoted occurrence and development of uremic cardiomyopathy.

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Conflicts of interest

There are no conflicts of interest.

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