

Elevated Serum Macrophage Migration Inhibitory Factor (MIF) Concentrations in Chronic Kidney Disease (CKD) Are Associated with Markers of Oxidative Stress and Endothelial Activation

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Chronic kidney disease (CKD) carries an increased risk of cardiovascular disease (CVD). Macrophage migration inhibiting factor (MIF) is a proinflammatory cytokine implicated in the pathogenesis of sepsis, autoimmune disease, atherogenesis, and plaque instability, and is a known cardiac depressant. This *post-hoc*, cross-sectional study examined whether MIF serum concentrations are elevated in CKD patients. Our study included CKD 3–5 patients with moderate to severe renal dysfunction ($n = 257$) (mean age \pm SD; 55 ± 12 years) and 53 controls (60 ± 12 years). Serum MIF concentrations, measured by enzyme-linked immunosorbent assay (ELISA), were studied in relation to glomerular filtration rate (GFR), presence of CVD, outcome and inflammatory and oxidative stress markers. MIF was significantly elevated in CKD patients compared with controls (CKD: median 676 [range 118–8275 pg/mL] controls: 433 [142–4707] pg/mL; $P = 0.008$). MIF was also associated with 8-hydroxy-2-deoxyguanosine (8-OH-dG) levels ($\rho = 0.26$; $P = 0.001$), a marker of oxidative stress, and ICAM-1 levels ($\rho = 0.14$; $P = 0.02$), a marker of endothelial activation. However, the elevated MIF concentrations were neither correlated with glomerular filtration rate (GFR) nor inflammatory markers such as CRP, IL-6, and TNF. When combining MIF and IL-6 as a marker of inflammation, a significant increase in risk for CVD was found, but when analyzing all-cause mortality, this did not differ significantly with regard to mortality from inflamed patients with low MIF levels. The data suggest that increased serum MIF levels found in CKD is not caused primarily by poor renal function, but is associated with markers of oxidative stress and endothelial activation and may play a role in vascular disease associated with CKD.

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INTRODUCTION

Chronic inflammation, measured with biomarkers such as interleukin-6 (IL-6), neutrophils, and C-reactive protein (CRP), has been the focus of numerous studies in chronic kidney disease (CKD). These inflammatory markers have been found to be predictors of all-cause and cardiovas-

cular mortality independent of traditional risk factors for cardiovascular disease (CVD) and are thus associated with atherosclerotic cardiovascular disease (1–4). Age-controlled CVD mortality rates are about 10 to 20 times higher in dialysis patients than those in the general population (5). It has been suggested that inflamma-

tory mediators might be causal in the accelerated atherosclerotic process observed in this patient population (5,6).

Macrophage migration inhibitory factor (MIF), a cytokine discovered in 1966, is recognized as a pleiotropic proinflammatory molecule (7,8). The actions of MIF in inflammation are numerous, including in monocytes and macrophages, T and B lymphocytes, endothelial cells, and eosinophilic neutrophils. MIF has been identified as a proinflammatory cytokine in sepsis as well as in autoimmune diseases such as rheumatoid arthritis, and systemic lupus erythematosus (9). MIF has been implicated in atherogenesis and atheroma formation as

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well as instability of human arteriosclerotic plaques (10,11). In recent spontaneous atherosclerosis animal models, aortic inflammation was reduced and neointimal plaques were stabilized after administration of anti-MIF antibody (12,13). The concept of anti-MIF therapy in arteriosclerotic and inflammatory disease in CKD is therefore of considerable interest. The available literature on the role of MIF in renal patients is, however, quite limited. One study reported increased circulating MIF levels in vasculitis patients and another study examined MIF in the urine of transplanted patients (14,15). However, these studies were small and did not control for the influence of renal function. The aim of this current study was, therefore, to determine whether circulating MIF levels were elevated in CKD 3–5 patients with a wide range of GFR.

MATERIALS AND METHODS

A total of 257 CKD patients were investigated as part of an ongoing prospective study in part described previously (16). The CKD 3–5 group ($n = 257$) consisted of 190 CKD 5 patients prior to the start of dialysis therapy ($\text{GFR} < 15 \text{ mL/min}$) and 67 CKD 3–4 patients ($\text{GFR} 15\text{--}60 \text{ mL/min}$) and these were compared with 53 controls. These controls were recruited from a population-based group in the Stockholm region and were used for comparative analyses of biochemical and metabolic parameters. The control group was comprised of individuals who agreed to participate, as volunteers, in response to an invitation sent to 1,000 randomly selected individuals in the Stockholm region by Statistics Sweden. No additional exclusion criteria other than unwillingness to participate in the study were applied in the selection of the control group. The CKD exclusion criteria were clinical signs of acute infection, acute vasculitis, or liver disease at the time of evaluation, or unwillingness to participate in the study.

The causes of kidney failure in the CKD 3–5 group were diabetes mellitus, $n = 76$ (30%); chronic glomerulonephritis,

$n = 59$ (23%); polycystic kidney disease, $n = 26$ (10%); nephrosclerosis, $n = 27$ (10%); vasculitis, $n = 4$ (2%); and 65 patients (25%) could not be classified.

After an overnight fast, venous blood samples were drawn and the sera stored at -70°C for future biochemical analyses. High-sensitivity CRP (hs-CRP), serum albumin, HbA_{1c} , and hemoglobin (Hb) were analyzed subsequently. The hs-CRP was analyzed using an immunonephelometric procedure (Behring AG, Marburg, Germany), whereas the remaining biochemical analyses were carried out using routine methods at the Department of Clinical Chemistry at Karolinska University Hospital at Huddinge. GFR was estimated by the mean of creatinine and urea clearances from a 24 h collection of urine, or iothexol-clearance. Routine laboratory tests including CRP were analyzed by standard methods. TNF and IL-6 were analyzed in serum by immunometric assays on an Immulite Analyzer (DPC, Los Angeles, CA, USA) according to the instructions of the manufacturers. Measurements of soluble vascular cell adhesion molecule-1 (sVCAM-1) and intracellular vascular cell adhesion molecule (sICAM-1) were performed using commercial kits (R&D Systems Europe Ltd, Abington, UK); 8-OH-dG concentration was determined by a competitive ELISA kit (Japanese Institute for the Control of Aging, Fukuroi, Shizuoka, Japan). MIF concentrations were measured by commercial ELISA (R&D Systems, MN, USA) and studied in relation to inflammatory and oxidative stress markers as well as GFR.

STATISTICAL ANALYSIS

Results are expressed as mean and standard deviation (SD; normally distributed variables) or median and range (non-normal distribution) unless otherwise indicated, with $P < 0.05$ indicating significance. Comparisons between groups for nominal variables were made using the chi-square test. Spearman's rank correlation test was used for continuous and ordinal variables. Determinants of CVD and odd ratios (ORs) with 95% confidence intervals (CI) were stud-

ied with a multinomial logistic regression model. Kaplan–Meier survival analysis was performed and adjusted relative risk of all-cause mortality was calculated from a Cox proportional hazards model. The statistical analysis was performed using statistical software SAS version 9.1.4 (SAS Institute Inc., Cary, NC, USA).

The study protocol was approved by the Ethics Committee of Karolinska University Hospital Huddinge, Stockholm, Sweden, and informed consent was obtained from each subject.

RESULTS

MIF Plasma Levels in CKD Patients

General characteristics of the patients versus controls are summarized in Table 1. Median (and range) serum MIF levels in CKD 3–5 patients were significantly higher than in the controls (676 [118–8275] versus 433 [414–4707] pg/mL , respectively) shown in Figure 1A. Median MIF levels did not differ significantly between CKD 3–4 and CKD 5 patients. The sensitivity of the assay was 31.25 pg/mL .

There were no differences in MIF levels among patients with or without clinical cardiovascular disease, diabetes mellitus, gender, or protein-energy wasting as assessed by SGA (Subjective Global Assessment)—data not shown.

Univariate and Multivariate Correlates for MIF Levels

MIF levels showed no significant correlation with GFR, CRP, IL-6, or TNF and primary kidney disease. When analyzing the largest subgroup of diabetic patients separately, we found no further association between MIF and clinical and laboratory parameters including BMI and HbA_{1c} . However, there were significant correlations in the CKD 3–5 cohort between serum MIF concentrations and both serum 8-OH-dG concentrations, a marker of oxidative stress and ICAM-1 concentrations, a marker of endothelial activation (Figures 1B,1C). Apolipoprotein B (apo B), which reflects the concentration of potentially

Table 1. General characteristics.

	Controls (n = 53)	CKD 3–5 patients (n = 257)	P value
Age, years	60.12	55.12	<0.05
Gender, male %	68	64	ns ^a
Diabetes, %	4	34	<0.001
CVD, %	9	35	<0.001
GFR mL/min/1.73 m ²	85 (58–118)	7.3 (0.8–52.0)	<0.001
CRP ^b mg/L	1.2 (0.2–32.0)	4.2 (0.2–218.0)	<0.05
IL-6, ^b pg/mL	2.2 (0.4–10.0)	4.3 (0.7–48.4)	<0.05
Cholesterol, ^c mmol/L	5.2 ± 0.8	5.2 ± 1.3	ns ^a
Triglycerides, ^c mmol/L	1.4 ± 0.7	2.1 ± 1.3	<0.001
BMI, ^c kg/m ²	26.1 ± 4.2	24.9 ± 4.6	<0.05
Albumin, ^c g/L	39 ± 3	33 ± 6	<0.05
Apo A-I, ^c g/L	1.5 ± 0.3	1.4 ± 0.3	0.006
Apo B, ^c g/L	0.97 ± 0.21	1.02 ± 0.32	ns ^a
Apo B/apo A-I ratio ^c	0.68 ± 0.20	0.81 ± 0.34	0.02

^aNot significant.^bMedian and range.^cMean ± SD.

atherogenic lipoprotein particles, and apolipoprotein A-I (apo A-I), which reflects the corresponding concentration of the anti-atherogenic HDL also were investigated. Apo A-I was correlated negatively with MIF; apo B/apo A-I ratio was correlated positively with MIF, although apo B alone was not correlated significantly (Table 2).

We tested the hypothesis that there might be a different risk pattern for MIF in the presence or absence of inflammation. In this study, inflammation was defined according to the median levels of IL-6 (4.3 pg/mL). In this context, the contribution of low or high MIF (defined by the median of 676 pg/mL) was studied to predict CVD, which was recorded from patient charts and included coronary artery disease, such as myocardial infarction and angina pectoris, stroke, and significant peripheral vascular disease. IL-6 was used as an inflammatory marker because IL-6 is possibly the most reliable predictor of cardiovascular disease and mortality in patients with end stage renal disease (4). Thus, in a logistic regression model, which included factors known to affect CVD such as gender, diabetes, and age (Table 3), the group with inflammation and high MIF was the only one that significantly predicted CVD whereas the absence of inflammation

and high MIF was associated negatively with CVD.

Finally, we assessed all-cause mortality risk of median 35 (range 1–72) months. In the presence of inflammation, groups with high or low MIF exhibited a similar probability of dying, both crude and after adjustment for age, sex, CVD, and diabetes mellitus (DM) (Table 4).

DISCUSSION

The main finding of the current study indicated serum MIF concentrations were elevated significantly in CKD 3–5 compared with controls. MIF levels were also associated positively with 8-hydroxy-2-deoxyguanosine (8-OH-dG) levels and ICAM-1 levels. However, we observed no correlation between MIF and GFR or inflammatory markers such as CRP, IL-6, or TNF.

CKD is characterized as a state of chronic inflammation and accelerated atherosclerosis with important repercussions for morbidity and mortality independent of traditional risk factors (1–4). MIF, a proinflammatory cytokine of the innate immune system, has been implicated in atherogenesis and atheroma formation as well as plaque instability in human arteriosclerotic disease (8–14). To the best of our knowledge this is the first study that addresses circulating MIF

and the role of renal function, and possible associations to CVD in CKD.

Since CKD is associated with inflammation, it was somewhat surprising that MIF in this population was not associated with common inflammatory markers. This differs from previous CKD studies that have identified GFR as an important predictor of elevated circulating pro-inflammatory cytokines such as IL-10, IL-6, TNF, and HMGB-1 (17–19). We found this to be untrue for MIF, suggesting the primary cause of increased serum MIF may not be due to poor renal function in this population.

The association between MIF and 8-OH-dG levels as a marker of oxidative stress, and ICAM-1 levels as a marker of endothelial activation raises the question of a possible role for MIF in vascular disease and associated myocardial damage in CKD. However, in the stepwise regression analysis, elevated levels of MIF alone did not predict the risk of CVD, although increased MIF in the presence of elevated concentrations of IL-6 was linked to an increased likelihood of CVD.

No previous study has examined circulating MIF in CKD with a wide range of GFR. A recent paper by Zaza *et al.* studied specific genomic patterns associated with systemic microinflammation in dialysis patients. By microarray analysis the gene for MIF was upregulated and directly associated with CRP levels (20). This was a genomic association and no further data with regard to circulating levels or cardiovascular events were available. In the current study, some weak but significant associations with MIF were also found in the lipoprotein variables apo A-I and the ratio apo B/apo A-I, which may further indicate vascular involvement (21). Data from the global INTERHEART study suggests that apo B/apo A-I is superior to any of the cholesterol ratios for estimation of the risk of cardiovascular events in the general population (22). Recently, a clinical study of anti-TNF therapy in rheumatoid arthritis (RA) suggested a link between clinical improvement, CRP, and MIF reduction, and an improved apo B/apo A-I

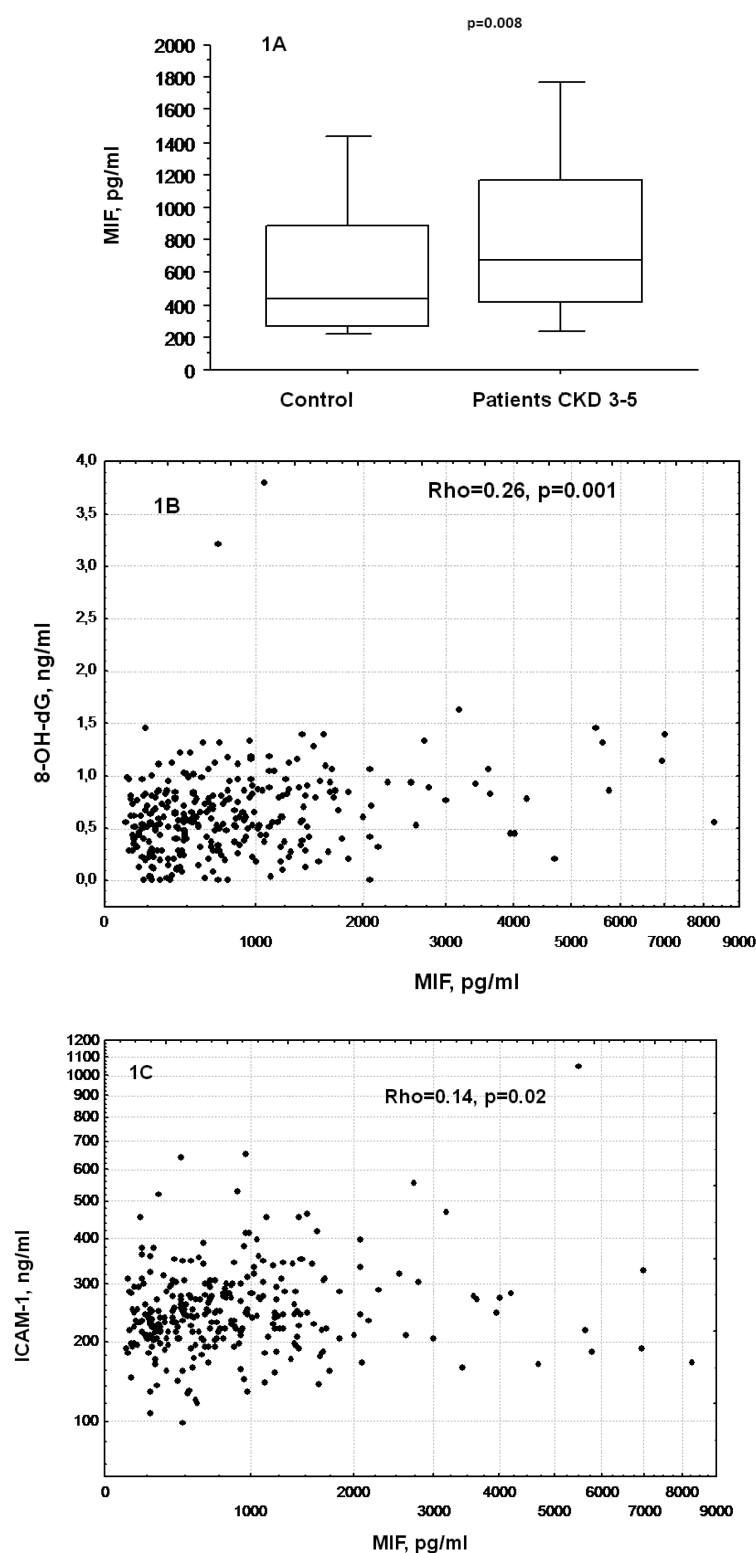


Figure 1. (A) MIF is elevated in CKD 3–5 patients as compared with healthy individuals. (B) Spearman Rank correlations between MIF levels and 8-hydroxy-2'-deoxyguanosine (8-OH-dG) in the CKD 3–5 patients. (C) Spearman Rank correlations between MIF levels and ICAM-1 in the CKD 3–5 patients.

Table 2. Spearman rank correlations for MIF in CKD 3–5 patients.

	Spearman rho	P value
Age	0.04	0.5
GFR	0.01	0.8
CRP	0.04	0.4
IL-6	-0.01	0.9
TNF	-0.06	0.3
VCAM-1	0.02	0.8
BMI	0.05	0.4
Albumin	-0.01	0.9
Cholesterol	-0.09	0.1
Triglycerides	0.01	0.8
Apo B	0.04	0.4
Apo A-I	-0.16	0.01
Apo B/apo A-I ratio	0.14	0.05

ratio (23). This potential cardiovascular benefit in RA, which is recognized as an inflammatory disease with accelerated atherogenesis, could be of interest in other conditions with a similar cardiovascular risk profile such as CKD and lupus. In the current study, the combination of elevated IL-6 and MIF was significantly associated with an increased risk of CVD. A reasonable speculation is that the systemic chronic inflammation found in CKD may amplify atherosclerosis in the presence of atherogenic and inflammatory factors, such as MIF, eliciting oxidative stress and endothelial activation. MIF, on the other hand, is known to induce proinflammatory mediators in both acute and chronic inflammatory conditions (8,9). Understanding of shared inflammatory mechanisms may lead to earlier detection of cardiovascular risk and conceivably prevention of complications.

The current study has several limitations. The number of patients and controls was limited, and MIF values were measured *post hoc* by single determinations. Moreover, as atherosclerosis is accelerated in CKD, serial measurements of MIF, over time, paired with clinical data and dialysis vintage would, perhaps, have been more useful to evaluate any predictive value in this patient population. Data on therapy were not included,

Table 3. Significant predictors of CVD in a multinomial logistic regression CKD 3–5 patients.

Parameter	Odds ratio	95% CI		P value
		Lower	Upper	
Intercept of CVD				<0.0001
Diabetes mellitus, presence	2.35	1.26	4.39	0.007
Sex, men	2.21	1.16	4.22	0.01
Age, 50–65 years	4.61	1.97	10.79	0.0004
Age, > 65 years	10.60	4.41	25.48	<0.0001
Non inflamed and high MIF	0.83	0.33	2.06	0.7
Inflamed and low MIF	2.11	0.89	4.99	0.09
Inflamed and high MIF	2.39	1.02	5.63	0.04

The model included CVD as the dependent variable and all factors significantly associated with the dependent variable in univariate analysis. Inflamed patients were defined as those with IL-6 >4.3 pg/mL (median), and high MIF was defined as those with >676 pg/mL (median); Pseudo $r^2 = 0.22$; $P < 0.001$; ages 20–49. Non-inflamed patients with low MIF were considered reference groups.

which is another weakness of the study as medication might influence MIF values. Information regarding MIF gene polymorphism is not yet available in CKD. However, in one study of RA patients, a correlation between disease severity, genetic functional variants, and circulating levels of MIF has been shown (24). Recent data also suggest that CD74, the MIF-receptor, is upregulated by high concentrations of glucose and TNF- α in glomerular podocytes, and may play a role in the pathogenesis of diabetic nephropathy (25). In the diabetic patients, we did, however, not find any clear association between MIF and clinical and laboratory parameters.

We could not find an effect on survival stratified by MIF levels alone. Again, the patient sample was possibly too small, but as CVD, which dominates mortality in CKD, is multifactorial, other risk factors may be stronger predictors of outcome in this population. Moreover, patient diagnosis relies on patient charts. As clinical CVD is not always recognized and confirmed by appropriate clinical investigations, we may have underestimated the true prevalence of CVD in our patient population (26). Finally, even though high MIF combined with elevated IL-6 was a significant predictor of CVD in a logistic regression model, elevated IL-6 with low MIF levels predicted

all-cause mortality equally, which raises the question of disparities regarding the influence of MIF in this setting.

In conclusion, although circulating serum levels of MIF are elevated significantly in CKD patients compared with controls, no association with GFR or common inflammatory markers was found. Instead, our data suggest an association with markers of oxidative stress and endothelial activation with possible implications for a role in vascular processes in this population. Undoubtedly, further studies are needed to shed light on the involvement of MIF as a possible active regulator in CVD associated with CKD.

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DISCLOSURE

We declare that the authors have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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Table 4. Crude and adjusted relative risk of all-cause mortality in CKD3–5 patients.

	All-cause (crude)	Hazard Ratio	(95% CI)	P value
Non-inflamed, high MIF	1.02	0.47	2.20	0.9
Inflamed, low MIF	3.38	1.76	6.47	0.0002
Inflamed, high MIF	3.23	1.69	6.15	0.0004
	All-cause (adjusted)	Hazard Ratio	(95% CI)	P value
Non-inflamed, high MIF	0.92	0.42	2.01	0.8
Inflamed, low MIF	2.94	1.49	5.77	0.001
Inflamed, high MIF	2.87	1.48	5.58	0.001

Data are presented as hazard ratios (95% CIs) and P values. Inflamed patients were defined as those with IL-6 >4.3 pg/mL (median), and high MIF was defined as those with >676 pg/mL (median). Multivariate Cox proportional hazard model was adjusted for age, sex, CVD, and DM; non-inflamed patients with low MIF were considered reference groups.

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