Elevated plasma migration inhibitory factor in hypertension–hyperlipidemia patients correlates with impaired endothelial function

Boda Zhou, MDa, Chuan Ren, MDa, Lingyun Zu, MDa,b, Lemin Zheng, PhDb, Lijun Guo, MDa, Wei Gao, MDa

Abstract

Migration inhibitory factor (MIF) has been shown to be critical in the pathology of early atherosclerosis; this article aims to investigate the plasma levels of MIF in hypertension plus hyperlipidemia patients.

A total of 39 hypertension plus hyperlipidemia patients without any previous treatment were enrolled (HTN-HLP). Twenty-five healthy subjects were enrolled as the healthy control group (HEALTHY). Plasma MIF was measured by ELISA; laboratory and clinical characteristics were analyzed. HUVECs were treated with pooled plasma from HTN-HLP and HEALTHY groups, and the protein levels of adhesion molecules VCAM-1 and ICAM-1 were determined by ELISA. We found that plasma MIF was significantly elevated in the HTN-HLP group. Serum NO and eNOS levels were significantly lower; serum ET-1 (endothelin) levels were significantly higher in the HTN-HLP group. Furthermore, blood pressure, baPWV (brachial-ankle pulse wave velocity), and serum ET-1 level were significantly positively; serum NO and eNOS levels were negatively correlated with plasma MIF levels. Plasma from HTN-HLP significantly stimulated VCAM-1 and ICAM-1 protein expression on the surface of HUVECs.

Plasma MIF was elevated in HTN–HLP patients and correlates with impaired endothelial function.

Abbreviations: ABI = ankle brachial index, ALT = alanine aminotransferase, ApoA1 = apolipoprotein A-1, ApoB = apolipoprotein B, AST = aspartate aminotransferase, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, BUN = blood urea nitrogen, CHD = coronary heart disease, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, ECM = endothelial cell medium, eNOS = endothelial nitric oxide synthase, ET-1 = endothelin, FBS = fasting blood glucose, FBSG = fast blood glucose, HDL-C = high density lipoprotein-cholesterol, HEALTHY = healthy adults, Hs-CRP = high sensitivity-C reactive protein, HTN–HLP = hypertension–hyperlipidemia, HUVEC = human umbilical vein endothelial cells, ICAM-1 = intercellular adhesion molecule-1, LDL-C = low density lipoprotein-cholesterol, Lp-a = lipoprotein-a, MIF = migration inhibitory factor, NO = nitric oxide, PLT = platelet, SBP = systolic blood pressure, Scr = serum creatinine, SD = standard deviation, TCHO = total cholesterol, TG = triglyceride, UA = uric acid, VCAM-1 = vascular cell adhesion molecule-1, WBC = white blood cell.

Keywords: adhesion molecule, endothelial function, hyperlipidemia, hypertension, MIF

1. Introduction

Hypertension–hyperlipidemia (HTN–HLP) is the most common combination of chronic conditions among Medicare beneficiaries in USA,[1] counting for 56% men and 53.5% women in patients >65 years old. In China, there were about 180 million people with hypertension and 70 million people with hyperlipidemia in 2008.[2] Although the number of patients suffered from both hypertension and hyperlipidemia is not yet clear, we could see that the burden of HTN–HLP is significant. Moreover, hypertension and hyperlipidemia as independent risk factors for coronary heart disease (CHD) could accelerate the progression of atherosclerosis and CHD. HTN caused endothelial dysfunction in patient,[3–7] probably by upregulating adhesion molecules ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1),[8] which may promote endothelium-leukocyte adhesion and inflammation.[9,10] HLP contributes to endothelial dysfunction accompanied by the expression of adhesion molecules and chemokines and thereby leads to early subintimal infiltration with mononuclear cells.[11,12] However, the exact impacts of HTN–HLP on endothelial function and underlying mechanism has not been fully elucidated.

The migration inhibitory factor (MIF) is a highly conserved cytokine with proven impacts in acute myocardial infarction.[13]
The expression of MIF has also been shown to correlate with increased intima-media thickening and lipid deposition in human carotid artery plaques, indicating critical roles in early atherosclerosis. Hypertension and hyperlipidemia are both important risk factors of atherosclerosis; it is possible that MIF played indispensable roles in the pathogenesis of HTN-HLP. Unfortunately, such involvement has not been shown. MIF was elevated in the aorta of patients with hypertension as well as coronary atherosclerosis with serum MIF levels higher in women with metabolic syndrome than in healthy subjects. MIF was also found to promote endothelial expressions of ICAM-1 and VCAM-1. However, to our best knowledge, there is no report on the serum level of MIF in patients with hyperlipidemia or hypertension. Here in this article, we will compare plasma MIF levels between HTN-HLP patients and healthy adults (HEALTHY) and discuss its correlation with clinical characteristics, atherosclerosis parameters, and endothelial function markers.

2. Materials and methods

2.1. Study subjects
This is a mono-center retrospective case-control study. The study subjects were selected in the out-patient department in Peking University Third Hospital from 1st January 2014 to 31st December 2014. There were 39 patients enrolled as the HTN-HLP group. The inclusion criteria were age 50 to 60 years; newly diagnosed grade 1 to 2 hypertension without previous treatment. Exclusion criteria were diabetes mellitus, aspirin in the past 2 weeks, cardiac or cerebral ischemic vascular diseases, impaired hepatic and renal function, and other major or acute pathologies. Secondary hypertension was excluded by routine diagnostic procedures. Twenty-five gender- and age-matched healthy subjects without any previous medical history were enrolled as healthy control group (HEALTHY). Each participant was assigned a randomized research number, and authors had no access to personal information that could identify individual participants during or after data collection. The protocol was approved by institutional guidelines of the Ethics Committee of Peking University Third hospital (IRB00006761-2011096(2)). All subjects were aware of the investigational nature of the study and gave their written consents.

2.2. Laboratory and bioanalytical procedures
Routine laboratory tests including blood HCT (red blood cell specific volume), WBC (white blood cell), PLT (platelet), SrC (serum creatinine), BUN (blood urea nitrogen), UA (uric acid), FBG (fasting blood glucose), Hba1C (glycosylated hemoglobin), HDL-C (high-density lipoprotein-cholesterol), ApoA1 (apolipoprotein A-1), Lp-a (lipoprotein-a), TCHO (total cholesterol), LDL-C (low density lipoprotein-cholesterol), TG (triglyceride), ApoB (apolipoprotein B), Hs-CRP (high sensitivity-C reactive protein), serum ALT (alanine aminotransferase), and AST (aspartate aminotransferase) were determined by the standard method. Hematic minerals, and a low concentration of fetal bovine serum (FBS) (5%) at 37°C in humidified air containing 5% CO2. The cells were expanded and frozen to provide enough cells. The cells were used from 3 to 5 passages in this experiment.

2.3. Assessment of baPWV and ABI
Brachial–ankle pulse wave velocity (baPWV) and ankle brachial index (ABI) were measured using a volume-plethymographic apparatus (BP203RPE-III; Omron-Colin, Japan). Participants were rested in the supine position for at least 15 minutes. Pneumatic pressure cuffs were placed snugly around both arms and both ankles.

2.4. Assessment of CIMT
The carotid intima-media thickness (CIMT) was measured using B-mode ultrasound and a 7.5 MHz transducer. Intimal-medial thickness was defined as the distance between the leading edge of the first echogenic line (lumen-intima interface) and the second echogenic line (media-adventitia interface) of the far wall. Measurements were taken from 0.5 to 2 cm below the carotid bifurcation of the common carotid artery on each side, and their means were calculated as the intimal-medial thickness. All the CIMT measurements were performed by a single radiologist.

2.5. Measurement of MIF
Blood samples were drawn by venipuncture into vacutainer tubes containing heparin lithium. Plasma was isolated from whole blood by centrifugation and kept in −80°C until experiment in March 2015. Plasma MIF was measured in duplicates using Quantikine MIF ELISA kits (DMF00B, R&D Systems) according to manufacturer’s specifications.

2.6. Measurement of NO, eNOS, and ET-1
Serum was isolated from whole blood by centrifugation. Serum nitric oxide (NO), endothelial nitric oxide synthase (eNOS), and endothelin (ET-1) was measured in duplicates using ELISA (BD Biosciences) according to manufacturer’s specifications. Thirty-two of the 39 HTN-HLP patients and all 25 of the healthy adults consented to examine NO, eNOS, and ET-1.

2.7. Culture of HUVEC
Human umbilical vein endothelial cells (HUVEC) were collected from human umbilical cord veins obtained from Peking University Third Hospital Obstetrics and Gynecology department. HUVECs were cultured in Endothelial Cell Medium (ECM) (ScienCell, American) which contained essential and non-essential amino acids, vitamins, Penicillin, organic and inorganic compounds, hormones, growth factors, streptomycin, trace minerals, and a low concentration of fetal bovine serum (FBS) (5%) at 37°C in humidified air containing 5% CO2. The cells were expanded and frozen to provide enough cells. The cells were used from 3 to 5 passages in this experiment.

2.8. Examination of VCAM-1 and ICAM-1 expression on HUVEC
HUVECs were cultured in 96-well plates and cultured to ~80% confluence. After 12 hours of starvation with serum-free ECM, the cells were treated with 100 µL fresh ECM plus 100 µL pooled plasma from HEALTHY or HTN-HLP groups and cultured for 6 hours. Expression of VCAM-1 or ICAM-1 on the surface of HUVECs was examined by ELISA as previously described. Briefly, cells were washed with PBS twice and fixed with PBS containing 4% paraformaldehyde at room temperature. The plates were blocked with 2% BSA at 37°C for 2 hours. Expression of VCAM-1 or ICAM-1 were determined by means of primary binding with specific antibody (sc-8304& sc-7891, Santa Cruz), followed by secondary binding with an HRP-conjugated goat anti-rabbit IgG antibody. Quantification was performed by
determination of colorimetric conversion at OD at 450 nm of 3,3',5,5'-tetramethylbenzidine using a TMB peroxidase H2A substrate kit (Bio-Rad).

2.9. Framingham risk score

The Framingham risk score was calculated according to the literature based on the clinical characteristics listed above for each patients and healthy adults.[22]

2.10. Statistical analysis

Descriptive data are presented as the mean ± standard deviation (SD) for continuous variables, as medians (minimal, maximal) for discontinuous variables, and as frequencies for categorical variables. The clinical and laboratory data were analyzed with an independent t test for continuous variables and nonparametric test (Mann–Whitney test or Kruskal–Wallis test) for discontinuous variables, chi-square tests for categorical data. Correlation between the MIF and other study variables were evaluated by Spearman analysis. Significance was assumed at a 2-sided P value <0.05. Statistical analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, IL).

Statistical analysis was performed by using SPSS for Windows (version 16.0).

3. Results

3.1. The clinical characteristics of hypertension–hyperlipidemia and healthy groups

The demographic, biochemical, and clinical data as well as endothelial function data of hypertension–hyperlipidemia (HTN-HLP) and healthy control (HEALTHY) groups were listed in Table 1. Two groups did not differ in regard to gender, age, BMI (body mass index), smoking, heart rates, blood HCT, WBC, PLT, Scr, BUN, UA, FBG, HbA1c, HDL-C, ApoA1, Lp-a, and left ABI. However, SBP (systolic blood pressure), DBP (diastolic blood pressure), TCHO, LDL-C, TG, ApoB, Hs-CRP, left and right average IMT, left and right baPWV, right ABI and Framingham risk score were significantly higher in the HTN-HLP group compared with the HEALTHY group.

3.2. Plasma MIF was elevated and endothelial function was impaired in HTN-HLP patients

Plasma MIF was measured using ELISA kits as described previously.[23] As shown in Fig. 1A, MIF was significantly elevated in the HTN-HLP group compared with the HEALTHY group (65.60 ± 44.35 ng/mL vs 26.63 ± 10.85 ng/mL, P < 0.001). Key markers of endothelial function were also examined in the serum of both groups. As shown in Fig. 1B and C, serum NO (19.10 ± 1.71 mmol/mL vs 33.82 ± 2.50 mmol/mL, P < 0.001) and eNOS (17.68 ± 1.85 U/mL vs 31.25 ± 2.77 U/mL, P < 0.001) levels were significantly lower in the HTN-HLP group compared with the HEALTHY group. Serum ET-1 levels were significantly higher in the HTN-HLP group compared with the HEALTHY group (95.44 ± 3.16 ng/mL vs 43.15 ± 5.09 ng/mL, P < 0.001).

3.3. Plasma MIF was correlated with blood pressure, PWV, cholesterol levels, and endothelial function

In order to find the influencing factor of MIF, we performed correlation analysis between plasma MIF levels and clinical characteristics in general population (including HTN-HLP and HEALTHY groups). As shown in Table 2 and Fig. 2, SBP (R² = 0.198, P < 0.001), DBP (R² = 0.216, P < 0.001), left baPWV (R² = 0.122, P = 0.007), right baPWV (R² = 0.129, P = 0.003), and ET-1 (R² = 0.248, P < 0.001) were significantly positively correlated with plasma MIF levels, NO (R² = −0.184, P < 0.001) and eNOS (R² = −0.230, P < 0.001) were significantly negatively correlated with plasma MIF levels in general population.

To further distinguish the affecting factor of MIF in HTN-HLP patients, we performed correlation tests between plasma MIF levels and clinical characteristics in the HTN-HLP group. As shown in Table 3 and Fig. 3, TCHO (R² = −0.200, P = 0.006),
LDL-C ($R^2 = -0.131$, $P = 0.03$), ApoB ($R^2 = -0.114$, $P = 0.04$) were all significantly negatively correlated with plasma MIF levels in HTN-HLP patients.

3.4. Plasma from HTN-HLP patients promoted endothelial adhesion molecules expression

To explore the functional significance of elevated plasma MIF in HTN-HLP patients, we treated HUVECs with pooled plasma from HTN-HLP and HEALTHY groups. The protein levels of adhesion molecules VCAM-1 and ICAM-1 were determined by ELISA as described previously.[21] As shown in Fig. 4, plasma from HTN-HLP patients significantly stimulated VCAM-1 ($P = 0.002$) and ICAM-1 ($P = 0.01$) protein expression, comparing with plasma from healthy adults.

4. Discussion

Hypertension and hyperlipidemia as independent risk factors for coronary heart disease (CHD) could cause endothelial dysfunction by upregulating adhesion molecules ICAM-1 and VCAM-1.[9–12,25,26] MIF has been found elevated in acute myocardial infarction and CHD patients[13,15,23]; recent reports also indicated potential roles of MIF in the pathology of metabolic syndrome.[16] However, the impacts of HTN-HLP on endothelial function and underlying mechanism has not been fully elucidated; also there is no report on the serum level of MIF in HTN-HLP patients. Here in this article we hypothesized HTN-HLP patients may have elevated plasma MIF levels, which may stimulate the expression of ICAM-1 and VCAM-1, thus causing endothelial dysfunction.

We found that MIF was significantly elevated in the plasma of HTN-HLP patients (Fig. 1A). It was reported that MIF promoted endothelial expressions of ICAM-1 and VCAM-1 and monocyte adhesion.[17,18] Thus, we asked whether treatment with plasma...

**Table 2**

Correlation between plasma MIF, clinical characteristics, and endothelial function in general population.

|                  | Pearson correlation | $P$  |
|------------------|---------------------|------|
| Gender           | $-0.005$            | 0.87 |
| Age              | $-0.054$            | 0.68 |
| Smoking          | 0.048               | 0.71 |
| BMI              | 0.328               | 0.51 |
| SBP              | 0.445               | $<0.001$ |
| DBP              | 0.465               | 0.66 |
| HR               | 0.226               | 0.19 |
| HCT              | $-0.058$            | 0.66 |
| TCHD             | 0.032               | 0.81 |
| LDLC             | $-0.016$            | 0.90 |
| HDLC             | $-0.060$            | 0.65 |
| TG               | 0.172               | 0.18 |
| ApoA             | 0.170               | 0.20 |
| ApoA1            | 0.028               | 0.83 |
| Lp-a             | $-0.039$            | 0.77 |
| Hs-CRP           | 0.205               | 0.12 |
| Average (MT R)   | 0.137               | 0.30 |
| Average (MT L)   | 0.098               | 0.46 |
| baPWV (R)        | 0.359               | 0.005 |
| baPWV (L)        | 0.349               | 0.007 |
| ABI (R)          | 0.206               | 0.11 |
| ABI (L)          | 0.176               | 0.18 |
| Framingham score | 0.190               | 0.14 |
| NO               | $-0.429$            | 0.101 |
| eNOS             | $-0.479$            | $<0.001$ |
| ET-1             | 0.498               | $<0.001$ |

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**Figure 1.** Plasma MIF and serum NO, eNOS and ET-1 levels in HTN-HLP and HEALTHY groups. The plasma levels of MIF (A) and serum levels of NO (B), eNOS (C) and ET-1 (D) were measured using ELISA and compared between HTN-HLP and HEALTHY groups. $**P < 0.001$. eNOS = endothelial nitric oxide synthase, ET-1 = endothelin, HEALTHY = healthy adults, HTN-HLP = hypertension–hyperlipidemia, MIF = migration inhibitory factor, NO = nitric oxide.
from HTN-HLP patients could promote endothelial expression of ICAM-1 and VCAM-1. We found that plasma from HTN-HLP patients significantly promoted ICAM-1 and VCAM-1 protein levels on the surface of HUVECs. To our best knowledge, no study has reported the influence of plasma from HTN-HLP patients on endothelial adhesion molecule expression. Our findings indicated elevated plasma MIF levels may be responsible for impaired endothelial function in HTN-HLP patients.

In this study, we also discussed the correlation of plasma MIF with clinical characteristics, endothelial function, and atherosclerosis parameters. In general population, we found that SBP, DBP, left baPWV, right baPWV, and ET-1 levels were significantly positively; NO and eNOS levels were significantly negatively correlated with plasma MIF levels. These results indicated that plasma MIF may be elevated in patients with hypertension, especially with target organ damage (arterial stiffness) and impaired endothelial function. To our surprise, we
found that TCHO, LDL-C, and ApoB were all significantly negatively correlated with plasma MIF levels in HTN-HLP patients. These results indicated that in HTN-HLP patients higher cholesterol levels may not necessarily elevate plasma MIF levels. In fact, report showed that MIF gene variation rather than plasma MIF level was correlated with cholesterol levels in human,[27] whereas animal study found that knockdown of MIF gene did not change serum cholesterol levels.[28]

MIF is widely expressed by different cell types, including monocytes, macrophages, T-cells, dendritic cells, mast cells, mesenchymal cells, endothelial cells, and cardiomyocytes.[29] Thus, MIF released from cardiomyocytes (cardiogenic MIF) or immune plasma and endothelial cells (noncardiogenic MIF) could both be detected in plasma.[10] Cardiogenic MIF was detected in the plasma of acute myocardial infarction patients, accompanied with elevated levels of cardiac injury markers.[23] Here we detected elevated plasma MIF levels but not cardiac injury markers in HTN-HLP patients, which was probably non-cardiogenic MIF. However, the current technique could not determine the cell-origin of plasma MIF, which was 1 limitation of this search. Another limitation of this work was that this was a mono-center retrospective study involving only Chinese population, which needs to be examined in other centers of different races.

### Table 3

|                          | Pearson correlation | P     |
|--------------------------|--------------------|-------|
| Gender                   | -0.023             | 0.89  |
| Age                      | -0.220             | 0.20  |
| Smoking                  | -0.151             | 0.38  |
| BMI                      | 0.069              | 0.70  |
| SBP                      | 0.069              | 0.70  |
| DBP                      | 0.185              | 0.30  |
| HR                       | 0.113              | 0.53  |
| HCT                      | -0.187             | 0.28  |
| WBC                      | -0.056             | 0.75  |
| PLT                      | 0.144              | 0.41  |
| Scr                      | -0.248             | 0.15  |
| BUN                      | -0.023             | 0.90  |
| UA                       | -0.072             | 0.68  |
| FPG                      | 0.245              | 0.16  |
| HbA1c                    | 0.100              | 0.58  |
| TCHO                     | -0.448             | 0.006 |
| LDL-C                    | -0.362             | 0.03  |
| HDL-C                    | -0.126             | 0.47  |
| TG                       | 0.006              | 0.98  |
| ApoB                     | -0.339             | 0.04* |
| ApoA1                    | -0.034             | 0.85  |
| Lip-a                    | -0.607             | 0.70  |
| Hs-CRP                   | -0.085             | 0.63  |
| Average IMT (R)          | -0.202             | 0.25  |
| Average IMT (L)          | -0.128             | 0.47  |
| baPWV (R)                | 0.068              | 0.61  |
| baPWV (L)                | 0.007              | 0.97  |
| ABI (R)                  | 0.089              | 0.61  |
| ABI (L)                  | 0.124              | 0.48  |
| Framingham score         | -0.201             | 0.24  |
| NO                       | 0.254              | 0.18  |
| eNOS                     | -0.112             | 0.56  |
| ET-1                     | 0.021              | 0.91  |

A10 = ankle brachial index, ApoA1 = apolipoprotein A-1, ApoB = apolipoprotein B, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, BUN = blood urea nitrogen, DBP = diastolic blood pressure, eNOS = endothelial nitric oxide synthase, ET-1 = endothelin, HbA1c = glycated hemoglobin, HCT = red blood cell specific volume, HDL-C = high density lipoprotein-cholesterol, Hs-CRP = high sensitivity-C reactive protein, LDL-C = low density lipoprotein-cholesterol, Lip-a = lipoprotein-a, MIF = migration inhibitory factor, NO = nitric oxide, PLT = platelet, SBP = systolic blood pressure, Scr = serum creatinine, TCHO = total cholesterol, TG = triglyceride, UA = uric acid, WBC = white blood cell.

**Figure 3.** Correlation of plasma MIF and clinical characteristics in HTN-HLP groups. The plasma levels of MIF were measured using ELISA and correlated with clinical characteristics in HTN-HLP groups. The coefficient of determinant ($R^2$) and P value were listed on each panel. HTN-HLP = hypertension— hyperlipidemia, MIF = migration inhibitory factor.
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Figure 4. Impacts of plasma from HTN-HLP and HEALTHY groups on adhesion molecules. HUVECs were treated with plasma from HTN-HLP and HEALTHY groups; the expressions of ICAM-1 and VCAM-1 were measured using ELISA and compared between HTN-HLP and HEALTHY groups. *P<0.05, **P<0.01. HEALTHY = healthy adults, HTN-HLP = hypertension-hyperlipidemia, HUVEC = human umbilical vein endothelial cells, ICAM-1 = intercellular adhesion molecule-1, VCAM-1 = vascular cell adhesion molecule-1.

5. Conclusion

Although our results need to be confirmed by large-scale studies, we found that plasma MIF was elevated in HTN-HLP patients and correlates with impaired endothelial function. MIF may act as a potential marker for endothelial function in hypertension and hyperlipidemia patients in future.

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