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# Relationship between plasma resistin concentrations, inflammatory chemokines, and components of the metabolic syndrome in adults

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**Abstract**

Recent data suggest that resistin, an adipocyte-derived cytokine, has a putative role in inflammatory processes and metabolic derangements. In vitro data suggest that resistin stimulates the production of inflammatory chemokines, yet the relationship in vivo is largely unknown. The purpose of this study was to determine if a relationship exists between plasma resistin concentrations, plasma inflammatory chemokine aged concentrations (ie, monocyte chemoattractant protein 1 [MCP-1] and epithelial neutrophil activator 78 [ENA-78]), and components of the metabolic syndrome in nondiabetic subjects without known cardiovascular disease (CVD). Plasma samples were obtained from nondiabetic subjects (N = 123) aged 18 to 55 years without known CVD or CVD risk equivalents. The presence of the metabolic syndrome was assessed using consensus guidelines. Fasting plasma resistin, MCP-1, ENA-78, and high-sensitivity C-reactive protein (hs-CRP) concentrations were analyzed. The study population consisted of 67.5% women and 68.3% Caucasians (mean age = 44 ± 7 years and mean body mass index = 33.3 ± 6 kg/m$^2$). The metabolic syndrome was present in 46.3% of study participants. Resistin concentrations were significantly correlated with white blood cell count ($r$ = 0.326, $P$ < .001), hs-CRP concentrations ($r$ = 0.293, $P$ = .005), MCP-1 concentrations ($r$ = 0.251, $P$ = .005), body mass index ($r$ = 0.193, $P$ = .033), and high-density lipoprotein cholesterol ($r$ = −0.182, $P$ = .044). Resistin concentrations were 1.21 times higher in subjects with the metabolic syndrome compared with those without the metabolic syndrome ($P$ = .003). In stepwise regression analysis, white blood cell count ($P$ < .001) and MCP-1 concentrations ($P$ = .002) were significantly associated with resistin concentrations, independent of hs-CRP, sex, body mass index, presence of the metabolic syndrome, and high-density lipoprotein cholesterol. Data from our cross-sectional study demonstrate that plasma resistin concentrations are associated with circulating chemokine markers of inflammation, namely, MCP-1, and white blood cell count in nondiabetic adults without CVD. Future studies examining the causal relationship between plasma resistin concentrations, chemokine markers of inflammation, CVD, and diabetes are warranted.


## 1. Introduction

Resistin is an adipocyte-derived cytokine with a putative role in insulin resistance, inflammation, obesity, and cardiovascular disease (CVD). Resistin is also thought to play a role in the pathogenesis of the metabolic syndrome, a clustering of metabolic, proinflammatory, and prothrombotic health risks that increases a person's risk of developing CVD and type 2 diabetes mellitus. Based on animal and in vitro data, resistin was originally thought to be a hormone linking obesity with insulin resistance [1]. However, the association between resistin, obesity, and insulin resistance has not been consistently replicated in clinical studies. Instead, resistin has emerged as a protein that appears to be more closely tied to inflammation, rather than insulin resistance or obesity [2]. The relationship between resistin and inflammation has been further supported by mice and human data showing that resistin levels are suppressed by thiazolidinediones, which are peroxisome proliferator–activated receptor $\gamma$ agonists with known anti-inflammatory effects [1,3].

Resistin is a member of the FIZZ (found in inflammatory zones) family of secretory proteins. Resistin is expressed at high levels in human monocytes and macrophages and at low

The University of Florida has filed a patent for ENA-78 concentrations as a diagnostic and prognostic tool with Dr Zineh as a co-inventor.

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levels in adipose tissue, and has been found in human atherosclerotic lesions [4-6]. In various patient populations, circulating resistin levels have been positively correlated with inflammatory cytokines, adhesion molecules, and circulating leukocytes [7-13]. Despite intense interest in resistin as an inflammatory mediator underlying the pathogenesis of the metabolic syndrome and CVD, few data exist on the association between circulating resistin, inflammatory chemokines, and components of the metabolic syndrome in humans.

Chemokines promote leukocyte recruitment and migration and are key mediators of the atherosclerotic disease process [14]. Monocyte chemoattractant protein 1 (MCP-1) is a member of the CC chemokine family and plays a prominent role in the recruitment of monocytes into the vascular endothelium and the activation of macrophages in atherosclerotic plaques. In terms of the relationship between resistin and MCP-1, recombinant resistin has been shown to increase the expression of MCP-1 in endothelial cells and adipocytes in vitro [15,16]. However, few data exist regarding the relationship between circulating resistin concentrations and circulating MCP-1 concentrations in humans. In addition to monocytes and macrophages, neutrophils play an important role in CVD pathogenesis. Epithelial neutrophil activating peptide 78 (ENA-78) is a CXC chemokine produced by monocytes, neutrophils, platelets, and endothelial cells (among others) [17,18], which functions as a neutrophil activator and attractor [17,19]. Epithelial neutrophil activating peptide 78 is thought to be a mediator in inflammatory processes [20,21]. However, to date, the relationship between circulating resistin levels and ENA-78 levels in humans has not been elucidated.

Given that inflammation is involved in the pathophysiology of the metabolic syndrome, we sought to determine if plasma resistin concentrations are correlated with plasma inflammatory chemokine concentrations (ie, MCP-1 and ENA-78) and components of the metabolic syndrome in nondiabetic subjects without known CVD.

## 2. Methods

### 2.1. Subjects

Blood samples were collected from nondiabetic subjects between 18 to 55 years of age who were screened for a metabolic syndrome clinical study at the University of Colorado Denver. The clinical study was approved by the University of Colorado Multiple Institutional Review Board, and all subjects provided written consent that their samples could be used in future research. A clinical diagnosis of the metabolic syndrome was made using the criteria outlined in the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [22]. Subjects were considered to have the metabolic syndrome if they had 3 or more of the following criteria: increased waist circumference (men, ≥40 in; women, ≥35 in), elevated triglycerides (≥150 mg/dL), reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men, <50 mg/dL in women), elevated blood pressure (≥130 mm Hg systolic and/or ≥85 mm Hg diastolic and/or on drug treatment for hypertension), or elevated fasting plasma glucose (≥100 mg/dL). Although the American Heart Association/National Heart, Lung, and Blood Institute criteria account for subjects on fibrate or niacin lipid-lowering therapy, individuals on any cholesterol medications (including hydroxymethylglutaryl–coenzyme A reductase inhibitors, fibrates, and niacin) were excluded from our analysis to avoid any potential confounding effects of these drugs on metabolic or inflammatory parameters. Participants were also excluded if taking systemic glucocorticoids, daily (ie, chronic) anti-inflammatory medications (eg, ibuprofen, naproxen, aspirin), HIV antiretroviral drugs, immunosuppressant drugs, atypical antipsychotics, phenytoin, and prescription or over-the-counter weight loss medications. Clinical exclusion criteria were history of type 1 or type 2 diabetes mellitus, documented fasting plasma glucose ≥126 mg/dL, clinically significant hepatic or renal disease, history of known coronary artery disease, stroke, congestive heart failure, polycystic ovary syndrome, Cushing syndrome, self-reported HIV positivity, or ≥10% weight change in the previous 2 months.

### 2.2. Laboratory measurements

Plasma resistin concentrations were analyzed in duplicate by enzyme-linked immunosorbent assay (Linco Research, St Louis, MO). The MCP-1 and ENA-78 were analyzed in duplicate by multiplex cytometric fluorescence detection (R&D Systems, Minneapolis, MN). Plasma concentrations of high-sensitivity CRP (hs-CRP) were determined in duplicate by an immunoturbidimetric method (Olympus America, Melville, NY). Plasma hs-CRP levels were only available for 91 of the 123 subjects in the study population. All blood samples were drawn in the fasting state between 7:00 AM and 11:00 AM.

### 2.3. Statistical analyses

Data are presented as mean ± standard deviation or median (range). Where appropriate, variables were natural log-transformed (ln) to achieve normal distributions before statistical analysis. Pearson correlations were used to analyze the relationship between ln-resistin concentrations, inflammatory chemokine concentrations, white blood cell count, and continuous variables that make up the metabolic syndrome. After natural log transformation, Student *t* tests were used to compare mean plasma concentrations of resistin, MCP-1, ENA-78, and hs-CRP between subjects with vs without the metabolic syndrome and between men vs women. Stepwise linear regression was used to determine the effects of covariates on natural log-

transformed resistin concentrations. Variables identified as significantly correlated with resistin concentrations in univariate analyses that were subsequently included in the stepwise multiple regression analysis were ln MCP-1 concentrations, ln hs-CRP concentrations, white blood cell count, HDL cholesterol, sex, body mass index (BMI), and presence of the metabolic syndrome. All data were analyzed with a 2-sided significance level of .05. Data were analyzed using SPSS 14.0 for Windows (SPSS, Chicago, IL).

## 3. Results

### 3.1. Population characteristics

The study population consisted of 123 nondiabetic subjects without CVD. Baseline demographics are presented for the entire study cohort and the subsets of women, men, presence of the metabolic syndrome, and no metabolic syndrome in Table 1. The ethnic distribution of the entire study population was 68.3% white, 14.6% African American, 11.4% Hispanic, 2.4% American Indian, 1.6% Asian American, and 1.6% other. Smoking status was available for 121 subjects in the population, and 33 subjects were smokers. The medians and corresponding ranges of plasma concentrations of resistin, MCP-1, ENA-78, and hs-CRP in the entire study cohort were 9.64 ng/mL (range, 3.51-23.67 ng/mL), 79.5 pg/mL (range, 32.1-333.0 pg/mL), 244.0 pg/mL (range, 32.20-2010.0 pg/mL), and 3.05 mg/L (range, 0.12-20.5 mg/L), respectively.

### 3.2. Relationship between resistin, inflammatory markers, and metabolic variables

In univariate analyses, resistin concentrations were significantly correlated with (in rank order) white blood cell count (Fig. 1A), hs-CRP concentration (Fig. 1B), MCP-1 concentration (Fig. 1C), BMI (Fig. 1D), and HDL cholesterol (Fig. 1E). There was a nonsignificant trend for a correlation between resistin and ENA-78 concentrations (Fig. 1F).

Stepwise linear regression analysis revealed that variables significantly associated with resistin concentrations were white blood cell count and plasma MCP-1 concentration. These data are shown in Table 2. Associations between resistin concentrations and white blood cell count and MCP-1 were independent of hs-CRP concentration, sex, BMI, presence of the metabolic syndrome, and HDL cholesterol. White blood cell count and plasma MCP-1 concentrations accounted for 28.6% of the variability in plasma resistin concentrations.

### 3.3. Evaluation of resistin and inflammatory markers by metabolic syndrome phenotype and sex

Plasma resistin concentrations were 1.21 times higher in subjects with the metabolic syndrome compared with subjects without the metabolic syndrome ($P$ = .003, Fig. 2A). In terms of the relationship between the other inflammatory markers and the metabolic syndrome, MCP-1 concentrations were 1.20 times higher in those with the metabolic syndrome compared with those without the metabolic syndrome ($P$ = .009, Fig. 2B). Furthermore, hs-CRP concentrations were 1.89 times higher in individuals with the metabolic syndrome compared with those without the metabolic syndrome ($P$ = .003, Fig. 2C). The ENA-78 concentrations did not differ significantly between those with vs without the metabolic syndrome ($P$ = .41, Fig. 2D).

Resistin concentrations were 1.15 times higher in women compared with men ($P$ = .026, Fig. 3A). When correlation analysis was conducted separately by sex, resistin concentrations in women were significantly correlated with (in rank order) hs-CRP concentration ($r$ = 0.335, $P$ = .011), MCP-1 concentration ($r$ = 0.28, $P$ = .01), white blood cell count ($r$ = 0.272, $P$ = .013), HDL cholesterol ($r$ = −0.256, $P$ = .02), and triglyceride level ($r$ = 0.229, $P$ = .037). In men, resistin concentrations were significantly correlated with white blood cell count ($r$ = 0.382, $P$ = .015) and MCP-1 concentration ($r$ = 0.308). In terms of the other inflammatory mediators, ENA-78 concentrations were 1.39 times higher in women compared with men ($P$ = .021, Fig. 3B). However, neither

Table 1
Baseline demographics of study population

| Baseline characteristics | Total population (N = 123) | Women (n = 83) | Men (n = 40) | Metabolic syndrome (n = 57) | No metabolic syndrome (n = 66) |
|---|---|---|---|---|---|
| Age (y) | 44 ± 7 | 44 ± 7 | 43 ± 8 | 44 ± 7 | 44 ± 8 |
| BMI (kg/m$^2$) | 33.3 ± 6.0 | 34.0 ± 6.3 | 32.0 ± 5.2 | 35.3 ± 5.8 | 31.6 ± 5.6 |
| Weight (kg) | 94.0 ± 17.0 | 91.0 ± 16.2 | 100.2 ± 17.3 | 98.7 ± 16.6 | 89.9 ± 16.4 |
| Systolic blood pressure (mm Hg) | 132 ± 16 | 130 ± 16 | 137 ± 13 | 137 ± 15 | 128 ± 15 |
| Diastolic blood pressure (mm Hg) | 77 ± 12 | 75 ± 13 | 80 ± 11 | 79 ± 11 | 74 ± 13 |
| Total cholesterol (mg/dL) | 208 ± 39 | 212 ± 41 | 201 ± 35 | 209 ± 43 | 207 ± 35 |
| HDL cholesterol (mg/dL) | 50 ± 13 | 53 ± 13 | 44 ± 10 | 44 ± 9 | 56 ± 13 |
| LDL cholesterol (mg/dL) | 128 ± 33 | 131 ± 34 | 124 ± 29 | 129 ± 37 | 128 ± 29 |
| Triglycerides (mg/dL) | 152 ± 108 | 139 ± 80 | 177 ± 148 | 186 ± 94 | 121 ± 111 |
| Fasting plasma glucose (mg/dL) | 93 ± 11 | 93 ± 11 | 94 ± 11 | 99 ± 11 | 89 ± 8 |
| White blood cell count (×10$^9$/L) | 6.7 ± 2.1 | 7.0 ± 2.2 | 6.2 ± 1.7 | 7.3 ± 2.4 | 6.3 ± 1.7 |

Data are presented as mean ± standard deviation. LDL indicates low-density lipoprotein.

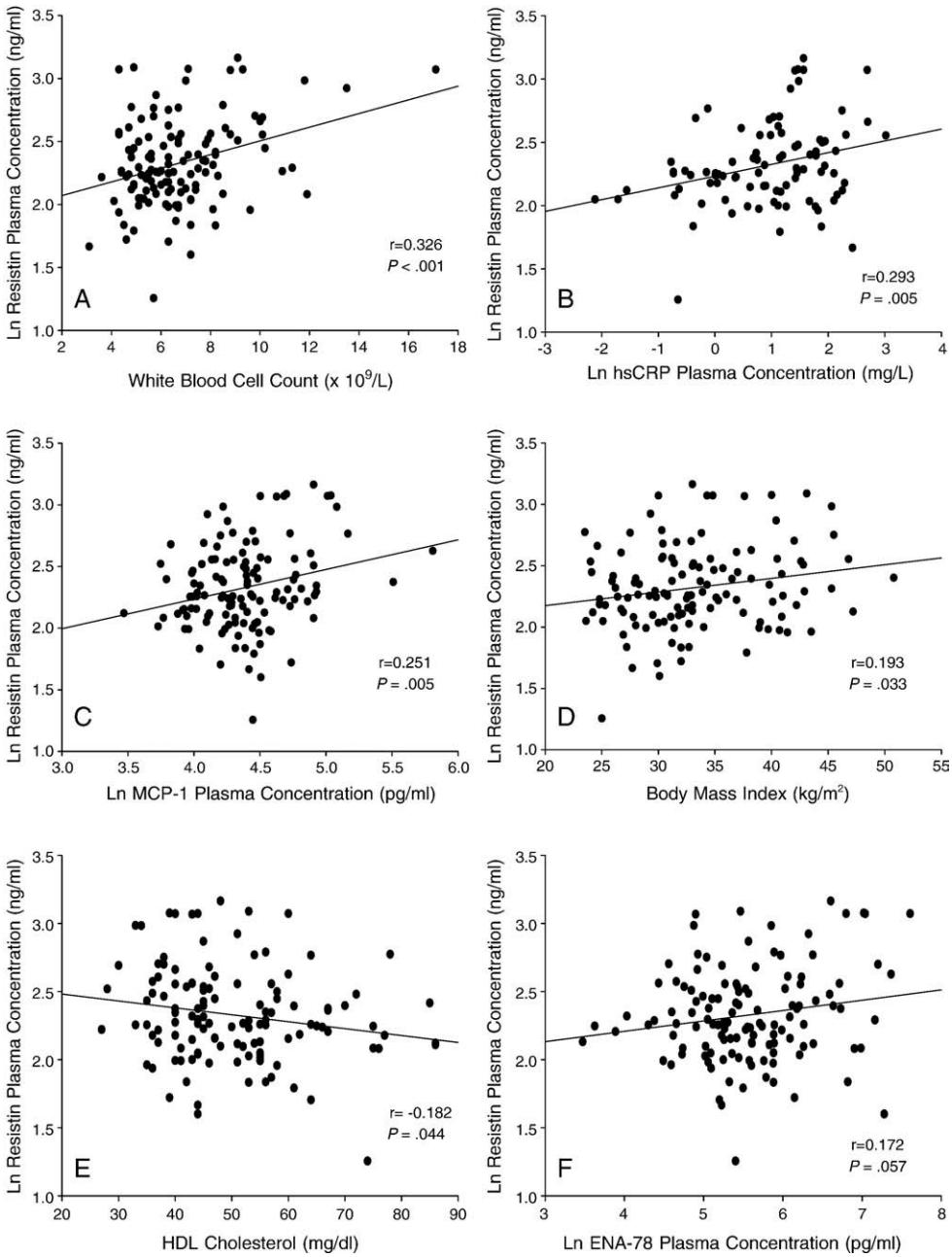


Fig. 1. Scatter plots with regression lines for correlations between plasma resistin concentrations and major outcome variables. A, The ln resistin plasma concentration and white blood cell count. B, The ln resistin plasma concentration and ln hs-CRP plasma concentration. C, The ln resistin plasma concentration and ln MCP-1 plasma concentration. D, The ln resistin plasma concentration and BMI. E, The ln resistin plasma concentration and HDL cholesterol. F, The ln resistin plasma concentration and ln ENA-78 plasma concentration.

MCP-1 concentrations ($P$ = .07, Fig. 3C) nor hs-CRP concentrations ($P$ = .15, Fig. 3D) differed significantly between women and men.

## 4. Discussion

Resistin is proposed to play a role in inflammation and the pathogenesis of CVD. We sought to determine if plasma resistin concentrations were associated with circulating concentrations of the monocyte and neutrophil chemokines MCP-1 and ENA-78, respectively, as well as components of the metabolic syndrome in nondiabetic subjects without known CVD. We found that resistin levels were significantly correlated with circulating levels of the inflammatory chemokine MCP-1, nonspecific markers of inflammation (ie, hs-CRP and white blood cell count), and some individual components of the metabolic syndrome (ie, obesity and HDL cholesterol). The pattern of correlations between circulating resistin levels and inflammatory and metabolic variables

Table 2
Variables independently associated with plasma resistin concentrations in stepwise linear regression analysis

| Independent variable | Parameter estimate | Standard error | *P* |
|---|---|---|---|
| White blood cell count ($\times 10^9$/L) | 0.067 | 0.014 | <.001 |
| Ln MCP-1 concentration (pg/mL) | 0.256 | 0.079 | .002 |

Dependent variable: ln resistin plasma concentration. Independent variables: white blood cell count, ln MCP-1 plasma concentrations, ln hs-CRP plasma concentration, sex, HDL cholesterol, BMI, and presence of the metabolic syndrome (yes/no). Overall model significance = $P < .001$; model $R^2$ value = 28.6%.

appeared to differ between women and men, with resistin levels being associated with metabolic variables (ie, HDL cholesterol and triglycerides) in women but not in men. However, neither sex nor metabolic variables were significantly associated with circulating resistin concentrations in linear regression analysis. We also found that plasma resistin concentrations were higher in nondiabetic individuals with a clinical diagnosis of the metabolic syndrome compared with those without the metabolic syndrome. However, after controlling for covariates in stepwise regression analysis, we found that circulating levels of MCP-1 and white blood cell count were the only variables significantly associated with plasma resistin concentrations. These data suggest that plasma resistin levels are more closely tied to inflammation, rather than individual metabolic parameters or a clinical diagnosis of the metabolic syndrome, in our study population.

Recently, numerous studies have emerged showing associations between resistin and circulating inflammatory markers in various patient populations [9-11,13,23,24]. For example, Kunnari and colleagues [13] showed that plasma resistin levels were positively correlated with circulating leukocyte levels and C-reactive protein levels in a large population-based cohort of Finnish subjects. These findings were independent of age, sex, BMI, glucose, and insulin levels. Like Kunnari and colleagues, we also found plasma resistin concentrations to be positively correlated with white blood cell count and CRP levels in our study population. Our correlation data are also consistent with 2 large population-based cohort studies of Italian and Japanese subjects that revealed a positive correlation between circulating resistin levels and serum CRP levels [12,25]. In terms of other inflammatory markers, a study of patients with type 2 diabetes mellitus showed that serum resistin levels were positively associated with interleukin 6 (IL-6), soluble vascular cell adhesion molecule 1, and serum amyloid A [26]. Data from the Study of Inherited Risk of Coronary Atherosclerosis showed that circulating resistin levels were

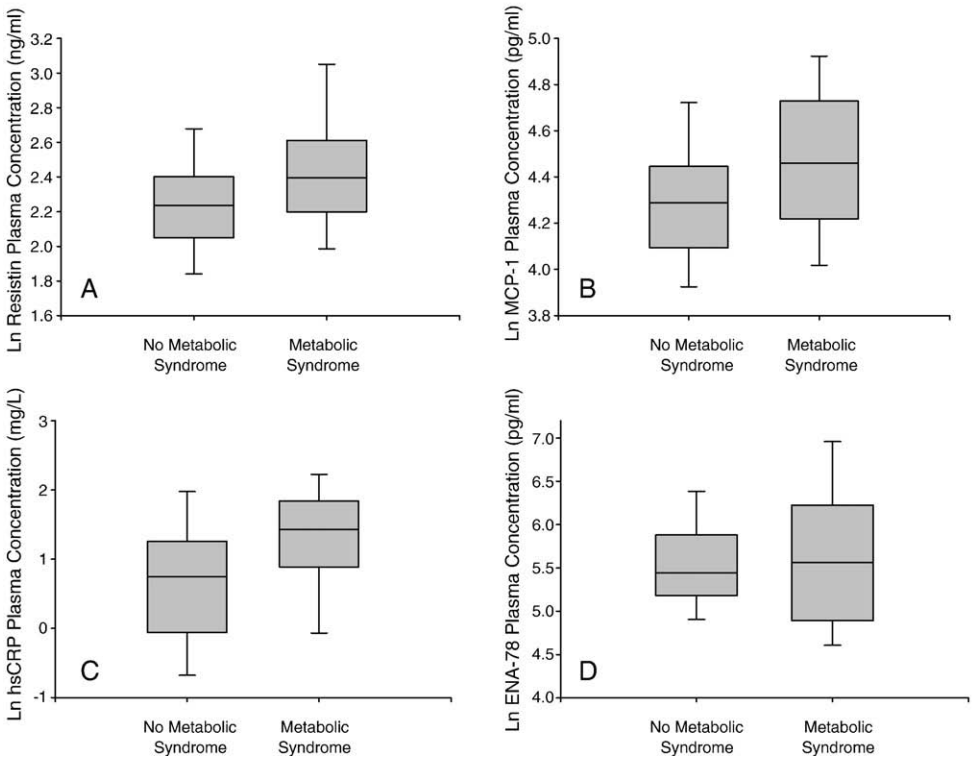


Fig. 2. Box plots comparing natural log-transformed plasma concentrations of resistin (A), MCP-1 (B), hs-CRP (C), and ENA-78 (D) in subjects without the metabolic syndrome vs subjects with the metabolic syndrome. The vertical gray rectangle contains the interquartile range. The horizontal solid line in the vertical gray rectangle represents the median value of the data. The whiskers extending from the top and bottom of the box indicate the 90th and 10th percentiles of the data, respectively.

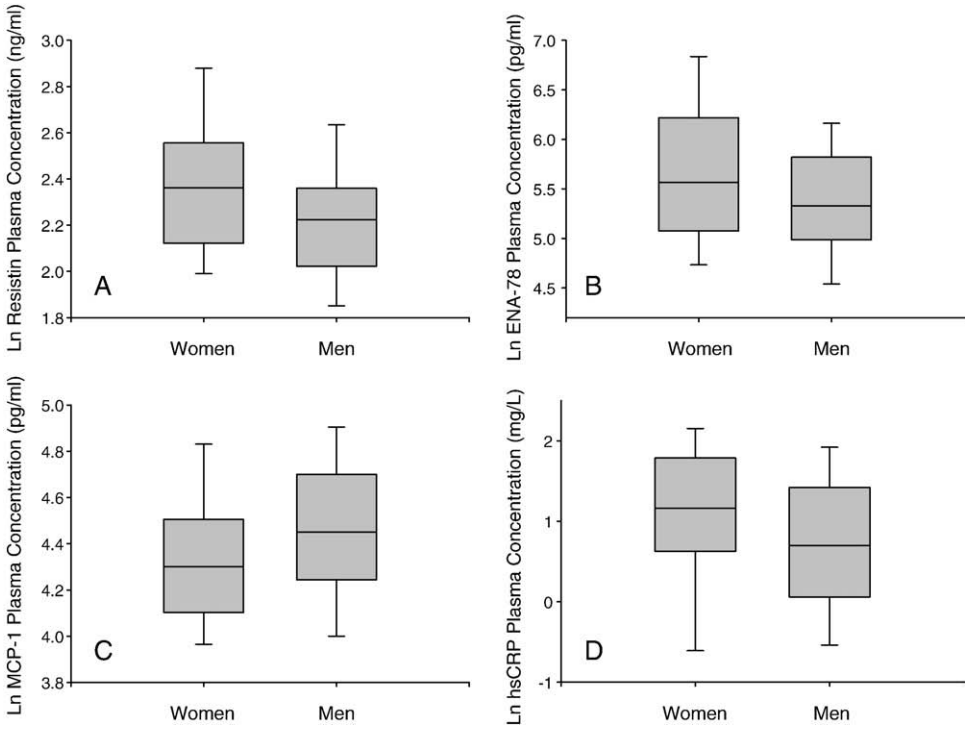


Fig. 3. Box plots comparing natural log-transformed plasma concentrations of resistin (A), ENA-78 (B), MCP-1 (C), and hs-CRP (D) in women vs men. The vertical gray rectangle contains the interquartile range. The horizontal solid line in the vertical gray rectangle represents the median value of the data. The whiskers extending from the top and bottom of the box indicate the 90th and 10th percentiles of the data, respectively.

positively correlated with soluble tumor necrosis factor α receptor 2, IL-6, and lipoprotein-associated phospholipase A2 [7]. Furthermore, plasma resistin levels were predictive of coronary atherosclerosis, as measured by coronary artery calcification, independent of CRP levels in their study. Taken together, these data show that resistin has been associated with myriad inflammatory markers, namely, CRP, IL-6, and cellular adhesion molecules in clinical studies, and may play a role in the development of atherosclerosis.

To our knowledge, few data exist on the association between circulating resistin levels and circulating levels of inflammatory chemokines, particularly MCP-1 and ENA-78, in humans. Inflammatory chemokines are involved throughout the continuum of the atherosclerotic disease process-from early fatty streak formation to advanced development of fibrous plaques within the vessel wall [14]. Monocyte chemoattractant protein 1 is one of the most intensely studied inflammatory chemokines because of its role in monocyte recruitment and macrophage activation in the endothelium. In terms of the relationship between resistin and MCP-1, recombinant resistin has been shown to activate human endothelial cells in vitro, with a corresponding increase in the expression of MCP-1 [15]. Furthermore, overexpression of resistin increased concentrations of MCP-1 in 3T3-L1 adipocytes [16]. In obese humans, it is known that peripheral blood mononuclear cells are in a proinflammatory state; and it has been observed that elevated circulating MCP-1 levels are present in obesity [27,28]. In addition, previous studies have shown that circulating MCP-1 levels are elevated in patients with coronary artery disease and that elevated MCP-1 concentrations in patients with acute coronary syndromes increase the risk for myocardial infarction [29,30]. Our study provides evidence of an in vivo association between plasma resistin levels and plasma MCP-1 concentrations, independent of hs-CRP levels, sex, BMI, presence of the metabolic syndrome, and HDL cholesterol. Furthermore, we found that circulating MCP-1 levels are increased in persons with a clinical diagnosis of the metabolic syndrome. Knowledge that plasma resistin concentrations are correlated with chemokine markers of inflammation, such as MCP-1, may have important implications for delineating the role of resistin in CVD risk and progression and the pathophysiology of the metabolic syndrome.

Reports such as ours that show higher circulating levels of resistin, MCP-1, and hs-CRP in patients with the metabolic syndrome suggest that resistin may be indicative of the proinflammatory state that is thought to underlie the pathophysiology of the metabolic syndrome rather than the metabolic derangements associated with the syndrome [22]. Our resistin data are consistent with a study by Norata and colleagues [31] that found that plasma resistin concentrations were 17% higher in those individuals with the metabolic syndrome compared with those without the metabolic syndrome. Despite our finding of a univariate association between resistin and the presence of the metabolic syndrome, the metabolic syndrome variable was not a significant

predictor of resistin concentrations in stepwise regression analysis in our study population. Instead, only white blood cell count and MCP-1 concentrations were significantly associated with the plasma resistin concentrations. This finding suggests that the proinflammatory state of the metabolic syndrome, rather than the clinical diagnosis of the metabolic syndrome itself, may be governing elevated plasma resistin concentrations in this population.

There are limitations of our study that deserve to be acknowledged. Because of our cross-sectional study design, the causal relationship between plasma resistin levels and MCP-1 levels could not be examined. Thus, we were unable to determine whether circulating resistin concentrations increase circulating MCP-1 concentrations or vice versa. It may also be that during inflammatory processes, circulating levels of resistin and MCP-1 increase in an independent, yet parallel, fashion. In terms of the metabolic syndrome phenotype, we did not prospectively obtain insulin measurements as part of our study. As such, we are unable to provide associations between resistin, inflammatory chemokines, and surrogate measures of insulin resistance in our study population. Lastly, we only found a trend toward a significant association between circulating resistin concentrations and ENA-78 concentrations in our population. However, sample size may have limited our power to detect such correlations; and our observation warrants further study in a larger sample size.

In summary, plasma MCP-1 concentrations and white blood cell count are associated with plasma resistin concentrations in nondiabetic adults without known CVD. These data provide further evidence that resistin is associated with an inflammatory state, even in persons with a perceived low cardiovascular risk. The relationship between resistin and inflammatory chemokines and their role in vascular biology and the pathogenesis of atherosclerosis merit further consideration in both in vitro and in vivo studies.

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