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Elevations in C-reactive protein and endothelin-1 system activity in humans

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Abstract

Aims—C-reactive protein (CRP) is an inflammatory cytokine that has been shown to be an independent predictor of future atherothrombotic events. Hyperactivity of endothelin-1 (ET-1), a potent vasoconstrictor peptide produced by the endothelium, is linked with cardiovascular disease development and progression. ET-1 is sensitive to inflammatory stimuli, though the influence of CRP on ET-1 system activity is unknown. We tested the hypothesis that ET-1-mediated vasoconstrictor tone is enhanced in adults with elevated plasma CRP concentrations.

Materials and Methods—Sixty non-obese adults (43–70 years) were studied: 20 with hsCRP <1.0 mg/dL (low CRP; 0.5 ± 0.1 mg/L); 20 with hsCRP 1.0–3.0 mg/dL (moderate CRP; 2.0 ± 0.1 mg/L); and 20 with hsCRP >3.0 mg/dL (high CRP; 6.3 ± 0.5 mg/L). Forearm blood flow (FBF; plethysmography) was determined in response to intra-arterial infusions of ET-1 (5 pmol/min for 20 min) and selective ET_A receptor blockade (BQ-123, 100 nmol/min for 60 min).

Key Findings—In response to ET-1, FBF decreased ~10% in the low ($-10.0 \pm 2.3\%$), moderate ($-10.7 \pm 4.0\%$), and high ($-6.6 \pm 5.2\%$) CRP groups, with no significant differences between groups. Additionally, all groups demonstrated a marginal, though significant (~10%), vasodilator response to BQ-123; however, there were no differences in the FBF response to BQ-123 across CRP groups. There were no significant correlations between plasma CRP concentrations and peak FBF response to either ET-1 or BQ-123.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

Significance—These results indicate that ET-1 system activity is not influenced by elevations in CRP. Enhanced ET-1 system activity may not be involved in the increased cardiovascular disease risk associated with elevations in plasma CRP concentrations.

Keywords

C-reactive protein; endothelin-1; endothelium; plethysmography

INTRODUCTION

C-reactive protein (CRP) is an acute phase cytokine that is considered an important biomarker of cardiovascular disease risk [1]. For example, data from the Physician's Health Study [2] indicated that CRP was the strongest non-lipid predictor of peripheral artery disease and provided additional prognostic value over standard lipid measures. CRP is also a mediator of inflammation and is thought to have a direct negative impact on endovascular health and function [3, 4]. Indeed, CRP is an active participant in lesion formation by inducing foam cell propagation [5] and promoting endothelial cell expression of adhesion molecules and chemokines [6, 7]. From a clinical perspective, our laboratory and others have previously demonstrated that plasma CRP concentrations are inversely associated with endothelial fibrinolytic capacity [8] and endothelium-dependent vasodilation [9].

An important contributor to vascular health is endothelin-1 (ET-1). ET-1 is a potent vasoconstrictor peptide that is synthesized and released from endothelial cells and plays a key role, along with nitric oxide, in the regulation of vascular tone. In addition to its vasomotor influences, there is considerable evidence supporting the involvement of ET-1 in the pathogenesis of atherosclerotic vascular disease [10, 11]. Upregulation of ET-1 and ET-1 receptors have been reported in atherosclerotic plaques in human and animal models [12, 13]. ET-1 receptors have also been identified at regions of neovascularization in atherosclerotic coronary arteries and failed saphenous vein grafts [14, 15]. Lerman et al. [16] demonstrated that early coronary atherosclerosis in humans is characterized by increased ET-1 immunoreactivity. Importantly, ET-1 transcription is regulated by inflammatory stressors [17, 18]. Of particular note, Verma, et al. [18] showed that treatment of endothelial cells with CRP significantly increases ET-1 protein levels. Despite the apparent importance and potential interaction between CRP and ET-1 in vascular health and disease, the influence of CRP on ET-1 system activity has not been evaluated clinically.

Accordingly, we tested the hypothesis that ET-1-mediated vasoconstrictor tone is enhanced in adults with elevated plasma CRP concentrations, independent of other cardiometabolic risk factors. To test this hypothesis, we employed an isolated forearm model to assess the response to exogenous ET-1 and ET_A receptor antagonism in middle-aged and older adults.

MATERIALS AND METHODS

Subjects

Sixty non-obese, sedentary adults (age: 43-70 years) were studied: 20 with CRP concentrations <1.0 mg/L (low CRP; 13M/7F); 20 with CRP concentrations of 1.0-3.0 mg/L

(moderate CRP; 13M/7F); and 20 with CRP concentrations >3.0 mg/L (high CRP; 13M/7F). CRP classification tertiles were based on published guidelines regarding plasma CRP concentrations and associated cardiovascular risk [19, 20]. All subjects were nonsmokers, non-medicated, normotensive (arterial pressure 140/90 mmHg) and free of overt metabolic or cardiovascular diseases. Women were at least one year postmenopausal and had never taken or discontinued hormone replacement therapy at least one year prior to study start. Subjects provided written informed consent according to the guidelines of the University of Colorado, Boulder.

Body Composition

Body mass index (BMI) and minimal waist circumference were measured according to published guidelines [21]. Percent body fat was determined by dual-energy X-ray absorptiometry (Lunar Radiation, Madison, WI).

Metabolic and CRP Measurements

Fasting plasma lipid, lipoprotein, glucose, and insulin concentrations were determined using standard techniques [22]. Blood samples for the determination of circulating levels of CRP were collected in chilled EDTA tubes with minimal venostasis, after an overnight fast. As previously described, plasma concentrations of high sensitivity CRP were determined in duplicate by enzyme immunoassay (Alpco Diagnostics, Windham, NH) [8]. The intra- and inter-assay coefficients of variation were <6% and <5%, respectively. In order to avoid confounding effects from potential infection or acute inflammation on ET-1 system activity, all subjects were free of recent infection/inflammation (>2 weeks) as determined by questionnaire [23].

Intra-arterial Infusion Protocol

All measurements were performed in a temperature-controlled room between 7 and 10 AM after a 12-hour overnight fast, as previously described [24]. A 5-cm, 20-gauge catheter was inserted into the brachial artery of the non-dominant arm under local anesthesia (1% lidocaine). Forearm blood flow (FBF) was measured using strain-gauge venous occlusion plethysmography (D.E. Hokanson, Bellevue, WA). Due to limited drug availability, a subgroup of subjects (11 low CRP / 9 moderate CRP/ 8 high CRP) were first infused with ET-1 (Cinalfa, AG) at a rate of 5 pmol/min for 20 minutes. FBF was measured during the last three minutes and allowed to return to baseline levels (30 minutes). All subjects were infused with the selective ET_A receptor antagonist, BQ-123 (Clinalfa, AG), at a rate of 100 nmol/min for 60 minutes. FBF was measured every 10 minutes throughout the infusion of BQ-123.

Statistical Analysis

Differences in subject characteristics as well as group differences in the FBF response to ET-1 were determined by one-way analysis of variance (ANOVA). Group differences in FBF response to BQ-123 were determined by repeated-measures ANOVA. There were no significant gender interactions in any of the primary outcome variables; therefore, the data were pooled and presented together. Because of the skewed distribution of plasma CRP

concentrations, the data were log transformed to satisfy basic assumptions for parametric testing. However, per joint American College of Cardiology and Centers for Disease Control recommendations [20], the absolute values for CRP are presented to facilitate clinical interpretation. Relations between log-transformed CRP and peak FBF to ET-1 and BQ-123 were assessed by linear regression analysis. All data are expressed as mean $\pm$ SEM. Statistical significance was set *a priori* at $P < 0.05$.

RESULTS

Physical and metabolic characteristics are shown in the Table. Anthropometric, hemodynamic, and metabolic variables were not significantly different between the three groups. By design, plasma CRP concentrations were ~4-fold higher in the moderate (2.0 ± 0.1 mg/L) compared with the low (0.5 ± 0.1 mg/dL) CRP group and 3-fold and 12-fold higher in the high (6.3 ± 0.5 mg/L; $P < 0.05$) CRP group compared with the moderate and low CRP groups, respectively (Figure 1).

Figure 2 shows the vasoconstrictor response to ET-1. There were no significant group differences in the FBF response to ET-1. FBF decreased ~10% in the low ($-10.0 \pm 2.3\%$), moderate ($-10.7 \pm 4.0\%$), and high ($-6.6 \pm 5.2\%$) CRP groups ($P > 0.05$). Figure 3 shows the FBF response to selective ET_A receptor blockade. In response to BQ-123, all three CRP groups demonstrated a marginal, albeit significant, vasodilator response. FBF increased by ~10% in all three groups to BQ-123. There were no significant univariate correlations between circulating CRP concentrations and peak FBF response to either ET-1 ($r = 0.11$) or BQ-123 ($r = 0.16$) (Figure 4).

DISCUSSION

The primary new finding of the present study is that elevations in circulating CRP concentrations are not associated with enhanced ET-1 system activity. To our knowledge, this is the first study to evaluate the relation between circulating CRP concentrations and ET-1 system activity in humans.

Several large population cohort studies indicate that plasma CRP concentrations are highly and independently predictive of cardiovascular events [1]. The exact mechanisms by which CRP exerts such negative influence on the cardiovascular system have not been fully elucidated. However, a number of cellular [6, 18], animal [4, 25, 26], and clinical [8, 9] studies have implicated adverse effects of CRP on endothelial cell health and function as a contributing factor. Most studies evaluating the role of CRP on endothelial function have focused on vasodilator regulation; as the ability of the endothelium to facilitate dilation is essential to the maintenance of vascular tone and vasodilator dysfunction is linked to the development and progression of atherothrombotic disease and vascular events [27, 28]. For example, Fichtlscherer and colleagues [9] demonstrated that FBF response to acetylcholine, an endothelium-dependent vasodilator, is blunted to a greater extent in men with coronary artery disease with elevated circulating CRP concentrations compared to those with lower CRP concentrations. It is interesting to note, however, that while some studies corroborate these findings [29, 30], others have shown no association between vasodilation and CRP [31,

32]. The reasons for these discrepancies are unclear, though differing populations, measurement techniques (i.e. FBF or flow mediated dilation) and circulating CRP cutpoints may explain the differential findings. In addition to vasodilation, CRP may influence other properties of the endothelium. We have demonstrated that the ability of the endothelium to release tissue type plasminogen activator (t-PA), the primary activator of fibrinolysis, is markedly impaired in adults with CRP concentrations ≥ 1.0 mg/L, suggesting that endothelial fibrinolytic dysfunction may play a role in the increased atherothrombotic risk associated with elevated plasma CRP concentrations [8].

The results of the present study complement and significantly extend these previous studies. While the ET-1 system plays an important role in maintaining vascular tone, ET-1 system hyperactivity is linked to atherosclerotic vascular disease, hypertension and coronary artery disease [11]. Herein we demonstrate, for the first time, that elevations in circulating CRP concentrations are not associated with ET-1 system activity. Indeed, there were no significant differences in the FBF responses to either ET-1 or selective ET_A receptor blockade amongst the CRP groups. Moreover, there was no correlation between plasma CRP concentrations and peak FBF response to either ET-1 or BQ-123. These findings are not consistent with *in vitro* studies demonstrating an impact of CRP on endothelial ET-1 production [18]. Lack of group differences in the FBF responses to both ET-1 and ET_A receptor blockade across the three CRP groups suggests that neither endogenous ET-1 production nor ET-1-mediated vasoconstrictor tone is influenced by elevations in circulating CRP concentrations in healthy adults. Although the present study is cross-sectional in nature, precluding any interpretation regarding the direct effect of CRP on ET-1 system activity, it is important to emphasize that we studied nonsmoking, sedentary, middle-aged and older adults who, aside from differences in CRP concentrations, were remarkably healthy and free of cardiometabolic risk factors and diseases. As such, we are confident in our notion that circulating CRP concentrations do not directly and independently influence ET-1 system activity. It is possible that interaction with risk factors and/or underlying disease is needed to illuminate a relation between circulating CRP and the ET-1 system.

The impact of circulating CRP concentrations on endothelial function is clearly complex and, in some cases, equivocal depending upon the functional characteristic in question [8, 9, 29-32]. The mechanisms underlying the apparent differential influence of CRP on endothelial vasomotor and fibrinolytic function are unclear. We previously demonstrated a strong inverse relation between elevations in CRP concentration and endothelial fibrinolytic function in a similar population of healthy middle-aged adults, whereas, to our surprise, no such correlation was observed in the present study with the ET-1 system. Future studies are needed to differentiate the effects of CRP on specific aspects of endothelial cell function in order to gain greater mechanistic insight on the role of CRP in endothelial dysfunction, and in turn, cardiovascular risk.

There are a few experimental considerations of the present study that should be mentioned. First, the CRP concentrations reported were from a single plasma sample from each subject, limiting our ability to account for changes in plasma CRP concentrations over time. However, all subjects were free of known chronic inflammatory conditions as well as recent inflammatory/infectious events, thus minimizing the potential impact of acute inflammation

on fasting CRP concentrations. Second, we did not measure circulating ET-1 concentrations and assess any potential relation with circulating CRP concentration. Considering >80% of ET-1 is released abluminally towards the vascular smooth muscle [11], circulating concentrations represent only a minor fraction of ET-1 production and are not indicative of ET-1 activity at the vessel wall but rather variable spillover into, and clearance from, the bloodstream. Thus, any observed relations between circulating levels of CRP and ET-1 would lack plausible physiological relevance.

CONCLUSION

In conclusion, the results of the present study demonstrate that ET-1-mediated vasoconstrictor tone is not influenced by circulating CRP concentrations in healthy adults. Alterations in ET-1 system activity may not be involved in the increased cardiovascular risk associated with elevations in plasma CRP concentrations.

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REFERENCES

1. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: Moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol.* 2007; 49:2129–38. doi: 10.1016/j.jacc.2007.02.052. [PubMed: 17531663]
2. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: A comparison of c-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA.* 2001; 285:2481–5. doi: [PubMed: 11368701]
3. Jialal I, Devaraj S, Venugopal SK. C-reactive protein: Risk marker or mediator in atherothrombosis? *Hypertension.* 2004; 44:6–11. doi: 10.1161/01.HYP.0000130484.20501.df. [PubMed: 15148294]
4. Bian F, Yang X, Zhou F, Wu PH, Xing S, Xu G, et al. C-reactive protein promotes atherosclerosis by increasing ldl transcytosis across endothelial cells. *Br J Pharmacol.* 2014; 171:2671–84. doi: 10.1111/bph.12616. [PubMed: 24517733]
5. Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: Implications for atherosclerosis. *Circulation.* 2001; 103:1194–7. [PubMed: 11238260]
6. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of c-reactive protein on human endothelial cells. *Circulation.* 2000; 102:2165–8. [PubMed: 11056086]
7. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of c-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. *Circulation.* 2001; 103:2531–4. [PubMed: 11382718]
8. Weil BR, Greiner JJ, DeSouza CA, Stauffer BL. Relation of c-reactive protein to endothelial fibrinolytic function in healthy adults. *Am J Cardiol.* 2011; 108:1675–9. doi: S0002-9149(11)02304-6 [pii] 10.1016/j.amjcard.2011.07.026. [PubMed: 21890088]
9. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated c-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation.* 2000; 102:1000–6. [PubMed: 10961964]
10. Levin ER. Endothelins. *N Engl J Med.* 1995; 333:356–63. doi: 10.1056/NEJM199508103330607. [PubMed: 7609754]

11. Luscher TF, Barton M. Endothelins and endothelin receptor antagonists: Therapeutic considerations for a novel class of cardiovascular drugs. *Circulation*. 2000; 102:2434–40. [PubMed: 11067800]
12. Jones GT, van Rij AM, Solomon C, Thomson IA, Packer SG. Endothelin-1 is increased overlying atherosclerotic plaques in human arteries. *Atherosclerosis*. 1996; 124:25–35. [PubMed: 8800491]
13. Fan J, Unoki H, Iwasa S, Watanabe T. Role of endothelin-1 in atherosclerosis. *Ann N Y Acad Sci*. 2000; 902:84–93. discussion 93–4. [PubMed: 10865828]
14. Dashwood MR, Jeremy JY, Mehta D, Izzat MB, Timm M, Bryan AJ, et al. Endothelin-1 and endothelin receptors in porcine saphenous vein-carotid artery grafts. *J Cardiovasc Pharmacol*. 1998; 31(Suppl 1):S328–30. [PubMed: 9595472]
15. Dashwood MR, Barker SG, Muddle JR, Yacoub MH, Martin JF. [125i]-endothelin-1 binding to vasa vasorum and regions of neovascularization in human and porcine blood vessels: A possible role for endothelin in intimal hyperplasia and atherosclerosis. *J Cardiovasc Pharmacol*. 1993; 22(Suppl 8):S343–7. [PubMed: 7509983]
16. Lerman A, Holmes DR Jr, Bell MR, Garratt KN, Nishimura RA, Burnett JC Jr. Endothelin in coronary endothelial dysfunction and early atherosclerosis in humans. *Circulation*. 1995; 92:2426–31. [PubMed: 7586341]
17. Marsden PA, Brenner BM. Transcriptional regulation of the endothelin-1 gene by tnfr-alpha. *Am J Physiol*. 1992; 262:C854–61. [PubMed: 1566813]
18. Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of c-reactive protein. *Circulation*. 2002; 105:1890–6. [PubMed: 11997273]
19. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of c-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002; 347:1557–65. doi: 10.1056/NEJMoa021993. [PubMed: 12432042]
20. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the american heart association. *Circulation*. 2003; 107:499–511. [PubMed: 12551878]
21. Lohman, TG.; Roche, AF.; Mortorelli, R. Anthropometric standardization reference manual. Human Kinetics; Champaign, IL: 1988.
22. Van Guilder GP, Hoetzer GL, Greiner JJ, Stauffer BL, DeSouza CA. Metabolic syndrome and endothelial fibrinolytic capacity in obese adults. *Am J Physiol Regul Integr Comp Physiol*. 2008; 294:R39–44. doi: 10.1152/ajpregu.00564.2007. [PubMed: 17959703]
23. Macko RF, Ameriso SF, Gruber A, Griffin JH, Fernandez JA, Barndt R, et al. Impairments of the protein c system and fibrinolysis in infection-associated stroke. *Stroke*. 1996; 27:2005–11. [PubMed: 8898806]
24. Hoetzer GL, Stauffer BL, Greiner JJ, Casas Y, Smith DT, DeSouza CA. Influence of oral contraceptive use on endothelial t-pa release in healthy premenopausal women. *Am J Physiol Endocrinol Metab*. 2003; 284:E90–5. doi: 10.1152/ajpendo.00333.2002. [PubMed: 12388132]
25. Hein TW, Singh U, Vasquez-Vivar J, Devaraj S, Kuo L, Jialal I. Human c-reactive protein induces endothelial dysfunction and uncoupling of enos in vivo. *Atherosclerosis*. 2009; 206:61–8. doi: 10.1016/j.atherosclerosis.2009.02.002. [PubMed: 19268941]
26. Yu Q, Li Y, Wang Y, Zhao S, Yang P, Chen Y, et al. C-reactive protein levels are associated with the progression of atherosclerotic lesions in rabbits. *Histol Histopathol*. 2012; 27:529–35. doi: [PubMed: 22374730]
27. Yasue H, Matsuyama K, Matsuyama K, Okumura K, Morikami Y, Ogawa H. Responses of angiographically normal human coronary arteries to intracoronary injection of acetylcholine by age and segment. Possible role of early coronary atherosclerosis. *Circulation*. 1990; 81:482–90. doi: 10.1161/01.CIR.81.2.482. [PubMed: 2105173]
28. Vanhoutte PM, Shimokawa H, Tang EH, Feletou M. Endothelial dysfunction and vascular disease. *Acta Physiol (Oxf)*. 2009; 196:193–222. doi: 10.1111/j.1748-1716.2009.01964.x. [PubMed: 19220204]

29. Tondi P, Santoliquido A, Di Giorgio A, Sestito A, Sgueglia GA, Flore R, et al. Endothelial dysfunction as assessed by flow-mediated dilation in patients with cardiac syndrome x: Role of inflammation. *Eur Rev Med Pharmacol Sci.* 2011; 15:1074–7. [PubMed: 22013731]
30. Cleland SJ, Sattar N, Petrie JR, Forouhi NG, Elliott HL, Connell JM. Endothelial dysfunction as a possible link between c-reactive protein levels and cardiovascular disease. *Clin Sci (Lond).* 2000; 98:531–5. [PubMed: 10781383]
31. Sampaio RR, Ladeia AM, Meneses RB, Lima Mde, L, Guimaraes AC. C-reactive protein is not correlated with endothelial dysfunction in overweight and obese women. *J Clin Med Res.* 2013; 5:294–9. doi: 10.4021/jocmr1418w. [PubMed: 23864919]
32. Verma S, Wang CH, Lonn E, Charbonneau F, Buithieu J, Title LM, et al. Cross-sectional evaluation of brachial artery flow-mediated vasodilation and c-reactive protein in healthy individuals. *Eur Heart J.* 2004; 25:1754–60. doi: 10.1016/j.ehj.2004.06.039. [PubMed: 15451155]

Figure 1.

Plasma CRP concentrations in the low, moderate, and high CRP groups. Values are mean ± SEM. *P<0.05 vs low CRP. †P<0.05 vs moderate CRP.

Figure 2. FBF response to ET-1 in the low, moderate, and high CRP groups. Values are mean $\pm$ SEM.

Figure 3. FBF response to the ET_A receptor antagonist, BQ-123, in the low, moderate, and high CRP groups. Values are mean $\pm$ SEM.

Figure 4. Correlations between plasma CRP concentrations and peak FBF response to ET-1 (Panel A) and BQ-123 (Panel B) in the overall study population.

Table

Select physical and metabolic characteristics

Variable	Low CRP (<1.0 mg/L) (n=20)	Moderate CRP (1.0-3.0 mg/L) (n=20)	High CRP (>3.0 mg/L) (n=20)
Men/Women	13/7	13/7	13/7
Age (years)	55 ± 2	56 ± 3	56 ± 2
Body mass (kg)	78.4 ± 2.8	80.2 ± 2.8	84.6 ± 3.3
BMI (kg/m ²)	26.5 ± 0.5	26.4 ± 0.6	27.9 ± 0.8
Body fat (%)	31.1 ± 2.1	32.9 ± 1.8	34.1 ± 2.1
Waist Circumference (cm)	88.8 ± 2.5	91.1 ± 2.7	94.9 ± 2.3
Systolic BP (mmHg)	122 ± 2	123 ± 2	125 ± 2
Diastolic BP (mmHg)	77 ± 1	75 ± 2	79 ± 1
Total cholesterol (mg/dL)	198 ± 4	198 ± 7	197 ± 5
HDL cholesterol (mg/dL)	49 ± 3	52 ± 3	53 ± 3
LDL cholesterol (mg/dL)	127 ± 5	123 ± 5	125 ± 5
Triglycerides (mg/dL)	111 ± 10	118 ± 14	101 ± 8
Glucose (mg/dL)	91 ± 2	94 ± 2	95 ± 2
Insulin (μU/L)	6 ± 1	7 ± 1	7 ± 1

CRP, C-reactive protein; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Values are mean ± SEM.