Kocatepe Tıp Dergisi
Kocatepe Medical Journal
20: 201-207/2019 Özel Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

MONOCYTE COUNT TO HDL-CHOLESTEROL RATIO MAY BE A NOVEL CARDIOMETABOLIC MARKER IN PATIENTS WITH FUNCTIONAL ADRENAL TUMORS

MONOSİT SAYISININ HDL-KOLESTEROLE ORANI FONKSİYONEL ADRENAL TÜMÖRLÜ HASTALARDA YENİ BİR KARDİYOMETABOLİK BELİRTEÇ OLABİLİR

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ÖZ

AMAÇ: Monosit sayısının HDL-Kolesterole oranı (MHO), kardiyovasküler hastalığı olan hastalarda yüksek bulunmuş ve kardiyovasküler risk faktörleri için belirteç olduğu gösterilmiş. Fonksiyonel adrenal tümör ve fonksiyonel olmayan adrenal adenomlu hastalarda bile kardiyovasküler hastalık riski artmaktadır. Bu çalışmada ilk olarak, MHO'nun adrenal tümörlü hastalarda yüksek olup olmadığı ve kardiyometabolik risk faktörleri ile ilişkisi araştırıldı.

GEREÇ VE YÖNTEM: Çalışmaya fonksiyonel adrenal tümürü olan 24 hasta (10 Cushing sendromu, 12 feokromositoma ve 2 primer hiperaldosteronizm), fonksiyonel olmayan adrenal adenomlu hasta (n=33) ve kontrol olgusu (n=50) alındı. Antropometrik inceleme, hormon ve biyokimyasal sonuçlar, lipid paneli, açlık kan şekeri (AKŞ), kan basıncı (KB), tam kan sayımı, C-reaktif protein (hs-CRP) ve karotis intima-media kalınlığı (KIMK) karşılaştırıldı.

BULGULAR: Ortalama yaş (51.14±2.03'e karşın 54.01±9.37 yıl), cinsiyet dağılımı (kadın 66.7 %'a karşın 73.8 %) ve vücut kitle indeksi (31.12±3.38'a karşın 30.46±2.96 kg/m2) adrenal tümör ve kontrol grubu arasında benzerdi (sırasıyla, p>0.05). MHO değeri fonksiyonel tümör grubunda, fonksiyonel olmayan adenom ve kontrol grubuna göre, yüksek bulundu (13.79±3.14, 10,19±2,84 vs 10.08±1.82, sırasıyla, p<0.05). MHO değeri fonksiyonel olmayan adenom ve kontrol grubu arasında benzer bulundu (p>0,05). MHO değeri sistolik KB (r=0.480; p<0.001), diyastolik KB (r=0.452; p<0.001), AKŞ (r=0.333; p=0.001), hs-CRP (r=0.538, p=0.001) ve idrar normetanefrin düzeyi (r=0.302; p=0.043) ile pozitif korele idi. Kardiyovasküler hastalığı olan fonksiyonel adrenal tümörlü hastalarda, kardiyovasküler hastalığı olmayan fonksiyonel adrenal tümörlü hastalara göre, MHR değeri yüksek bulundu (14.69±2.67'e karşın 11.84±2.57, p<0.05).

SONUÇ: Monosit sayısının HDL-Kolesterole oranı fonksiyonel adrenal tümörlü hastalarda yüksek bulunurken; fonksiyonel olmayan adenomlu hastalarda yüksek değildi. Monosit sayısının HDL-Kolesterole oranı kardiyometabolik risk faktörleri olan AKŞ, KB ve hs-CRP ile korele idi. Monosit sayısının HDL-Kolesterole oranı, fonksiyonel adrenal tümörlü hastalarda kardiyovasküler risk faktörleri için prediktif belirteç olabilir.

ANAHTAR KELİMELER: Monosit sayısının HDL-Kolesterol oranı, Kardiyometabolik risk faktörleri, Adrenal tümör

ABSTRACT

OBJECTIVE: The monocyte count to HDL-Cholesterol ratio (MHR) was increased in patients with cardiovascular disease and, showed as an indicator of cardiovascular risk factors. Functional adrenal tumor and even nonfunctional adrenal adenomas are associated with an increased risk for cardiovascular disease. This is the first study to evaluate the MHR value in patients with adrenal tumors, and examine its relation with cardiometabolic risk factors.

MATERIAL AND METHODS: Twenty-four patients with functional adrenal tumor (10 Cushing syndrome, 12 pheochromocytoma, and 2 primary hyperaldosteronism), patients with non-functional adrenal adenoma (n=33) and, control subjects (n=50) were included. Anthropometric, hormonal and biochemical results, lipid panel, fasting plasma glucose (FPG), blood pressure (BP), blood cell counts, high-sensitivity C-reactive protein (hs-CRP), and carotid intima-media thickness (CIMT) were compared.

RESULTS: Mean age (51.14±2.03 vs 54.01±9.37 years), sex distribution (female 66.7 % vs 73.8 %), and body mass index (31.12±3.38 vs 30.46±2.96 kg/m2) were similar between adrenal tumor and control group (respectively, p>0.05). The MHR value was higher in the functional tumor group compared with the non-functional adenoma and control group (13.79±3.14, 10.19±2.84 vs 10.08±1.82, respectively, p<0.05). MHR value was similar between the non-functional adenoma and controls (p>0.05). MHR value was positively correlated with systolic BP (r=0.480, p<0.001), diastolic BP (r=0.452, p<0.001), FPG (r=0.333, p=0.001), hs-CRP (r=0.538, p=0.001) and, urinary normetanephrine concentrations (r=0.302, p=0.043). Functional adrenal tumor with cardiovascular disease had higher MHR value compared with those without cardiovascular disease (14.69±2.67 vs 11.84±2.57, p<0.05).

CONCLUSIONS: The MHR value was increased in patients with functional adrenal tumor; however it did not increase in patients with nonfunctional adenoma. MHR value was correlated with cardio-metabolic risk factors such as FPG, BP, and hs-CRP. The MHR value suggests as a predictive marker for cardiometabolic risk factors in functional adrenal tumors.

KEYWORDS: Monocyte count to HDL-C ratio, Cardiometabolic risk factors, Adrenal tumor

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Kabul Tarihi / Accepted: 22.07.2019
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INTRODUCTION

Monocytes are major source of pro-inflammatory and pro-oxidant cytokines (1, 2). Monocytes interact with platelets and endothelial cells, which initiates pro-thrombotic and pro-inflammatory process (3). Monocytes differentiate into macrophages at the site of inflammation (4). Macrophages remove oxidized low-density lipoproteins (LDLs) and release inflammatory cytokines and metalloproteinases in the inflamed tissue (5). Circulating monocytes and macrophages initiates the pathogenesis of cardiovascular disease (CVD), through this atherosclerosis and inflammatory process (6). High-density lipoproteins cholesterol (HDL-C) decreases atherosclerosis by inhibiting pro-inflammatory and pro-oxidant effects of monocytes (2, 4). Hence, decreased of HDL-C and accumulation of monocyte may participate in CVD and atherosclerosis (1). Previous studies have reported that the monocyte-to-HDL ratio (MHR) increased in the inflammatory disorders (3, 7), and atherosclerosis (8, 9). From these studies, monocytes and HDL-C have functions in inflammation and atherosclerosis rather than individual monocyte counts or an individual HDL-C value, the MHR value may be a marker for the assumption of cardiometabolic risk factors (8, 10, 11). Evidence suggests that cardio-metabolic derangements observe in patients with adrenal tumors (12, 13). Cushing syndrome (14), pheochromocytoma (15), and primary hyperaldosteronism (16) are associated with increased risk for cardiovascular events and mortality. Furthermore, even patients with non-functional adrenal adenoma increase risk for developing cardiovascular deteriorations (17, 18). Both non-functional and functional adrenal adenoma has alterations in endothelial dysfunction, which contributes to atherosclerosis (19).

The elevated MHR value was suggested as a novel prognostic marker to predict patients who have a greater risk for CVD (1). Patients with functional and nonfunctional adrenal adenoma are at higher risk of CVD, than in general population (12, 13). Hence, we aimed to investigate the MHR value, and its relation to cardiometabolic risk in patients with functional and non-functional adrenal tumors. This is the first study to evaluate the association between the MHR value and cardiovascular risk factors in patients with adrenal tumor.

MATERIALS AND METHODS

Patients

Functional adrenal tumors and non-functional adrenal adenoma were diagnosed at the Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Training and Research Hospital. Fifty-seven patients with adrenal tumors and 50 healthy controls were included in this study. The adrenal tumor group was divided into two categories based on functionality. The nonfunctional adrenal adenoma group consisted of 33 patients, and the functional group comprised 24 patients. All subjects were underwent medical history and physical examination. Specific symptoms and signs of hormone excess were not shown in patients with adrenal adenoma, and subjects were not treating with hormonal therapy. Overproduction of glucocorticoids, mineralocorticoids and catecholamines was not observed in all subjects with nonfunctional adrenal adenoma. Patients with infectious disease, liver or renal failure or autoimmune diseases were not included in the group of adrenal tumor. The functional adrenal tumor group consisted of 10 patients with Cushing syndrome, 12 with pheochromocytoma and 2 with primary hyperaldosteronism. Sex- and age-matched healthy subjects with normal adrenal imaging were included as control group.

All subjects underwent abdominal computed tomography, which was confirmed to have an adrenal tumor by the same radiologist. Benign adrenal mass was defined as regularity of margins, pre-contrast Hounsfield units (≤10 HU), and 15-minute washout after contrast infusion (≥50 %). Subjects having radiologic appearance of malignant disease, infiltrative disease and cysts were not included. Serum blood electrolytes, lipids and glucose concentrations, complete blood counts, high-sensitivity CRP (hs-CRP), liver and kidney functions tests were measured from all subjects. The hypothalamic-pitui-

tary-adrenal axis was examined in all patients with adrenal tumor. Primary hyperaldosteronism was suspected when patients had an aldosterone to renin ratio > 30 (ng/dL)/(ng/mL/hour) and plasma aldosterone>15 ng/dL in an erect position. Primary hyperaldosteronism was diagnosed when patients without an aldosterone suppression (<10 ng/dl) after an intravenous saline infusion. Patients who suspected primary hyperaldosteronism underwent adrenal venous sampling for diagnosing the idiopathic adrenal hyperplasia and aldosterone-producing adenoma. After successful adrenalectomy, serum renin and aldosterone level were measured as normal range. Pheochromocytoma was diagnosed when patients presented with hypertension, dizziness, flushing, palpitations, headache, high value of 24-hour urinary catecholamines and serum metanephrines or normetanephrines, and imaging of adrenal tumors. All subjects with functional adrenal tumors underwent surgery, and histopathologic verification was confirmed.

Anthropometric measurements were performed from all subjects. Weight, height, waist circumferences, waist to hip circumference ratio, body mass index (BMI) and systolic and diastolic blood pressure (BP) were measured. Carotid intima-media thickness (CIMT) measurement was performed to investigate having carotid atherosclerosis. CIMT was calculated as the distance between the blood-intima and media-adventitia boundaries on high-resolution B-mode ultrasound (EUB 7000 HV; Hitachi, Tokyo, Japan) with a 13-MHz linear array transducer.

ETHIC APPROVAL

The study protocol was approved by the local ethics committee of Diskapi Yildirim Beyazit Training and Research Hospital (05.10.2016-15/41), and written informed consent was obtained from all subjects.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 18.0 (SPSS, Inc) soft-ware. Variables are presented as mean±standard deviation (SD) and percentages (%). Normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk W test. Categorical variables were analyzed with Chi-square test or Fisher's exact test, where appropriate. Student's t test was used for normally distributed continuous variables or log-transformed variables between two groups. Logarithmic transformation was used on continuous variables that were not normally distributed. Correlation was performed using Spearman's and Pearson's tests. Statistical significance was defined as a $p < 0.05$.

RESULT

Fifty-seven patients with adrenal tumor (n=24 functional adrenal adenoma, and n=33 non-functional adrenal adenoma) and healthy control subjects (n=50) were included. Mean age (51.14±2.03 vs 54.01±9.37 years), gender (female 66.7 % vs 73.8 %), and BMI (31.12±3.38 vs 30.46±2.96 kg/m2) were similar between adrenal tumor and control group (respectively, p>0.05). Mean age was lower in patients with functional tumor (p<0.05). Systolic and diastolic BP, glucose, triglyceride, total cholesterol, hs-CRP and, CIMT value were significantly higher in the functional and non-functional adenoma compared with control group (p<0.05). Serum creatinine, sodium and, potassium were similar between groups (p>0.05). Characteristics of subjects in both groups are shown in **(Table1)**.

Table 1: Characteristics of subjects

	Control group (n=50)	Nonfunctional adenoma (n=33)	Functional tumor (n=24)	P*	P**	P***
Age (years)	51.14±2.03	58.48±7.83	47.02±8.12	**0.003**	**0.001**	**0.001**
BMI (kg/m²)	30.46±2.96	31.78±4.08	30.78±5.34	**0.010**	0.996	0.069
Waist circumference (cm)	98.48±3.86	101.87±6.54	98.76±7.28	**0.034**	0.174	0.064
White blood cell (x10³/µL)	7935.72±2481.82	8177.48±2344.31	8838.14±2404.89	0.675	0.174	0.328
Monocyte count (x10³/µL)	524.28±124.40	513.15±136.86	670.61±64.58	0.121	**0.001**	**0.005**
Monocyte/HDL-C ratio	10.08±1.82	10.19±2.84	13.79±3.14	0.580	**0.001**	**0.001**
Systolic BP (mmHg)	116.67±8.97	138.26±14.73	170.71±20.15	**0.001**	**<0.001**	**0.003**
Diastolic BP (mmHg)	77.56±5.52	90.14±7.27	108.57±13.88	**0.002**	**<0.001**	**0.002**
Glucose (mg/dl)	93.09±9.23	99.21±22.47	115.95±64.84	**0.001**	**0.002**	0.178
Triglyceride (mg/dL)	141.13±20.39	169.05±38.70	285.95±361.19	**0.018**	**0.012**	0.070
Total cholesterol (mg/dL)	193.78±9.66	223.63±25.69	218.52±26.51	**0.002**	**0.008**	0.485
LDL-C (mg/dL)	120.39±5.63	131.93±15.09	141.68±15.27	0.064	**0.001**	**0.026**
HDL-C (mg/dL)	51.42±2.35	50.47±2.98	49.10±4.32	0.132	**0.008**	0.173
hs-CRP (mg/L)	2.28±1.91	4.66±2.45	6.79±1.24	**0.005**	**0.001**	**0.001**
CIMT (cm)	0.56±0.14	0.78±0.09	0.74±0.56	**0.004**	**<0.001**	**0.010**

p* control vs nonfunctional p** control vs functional p*** nonfunctional vs functional

Bolds represents p-significant value

Abbreviations: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; hs-CRP, high-sensitivity C-reactive protein; CIMT, carotid intima-media thickness.

The functional adrenal tumor group included 10 patients with Cushing syndrome, 12 with pheochromocytoma, and 2 with primary hyperaldosteronism **(Table 2)**.

Table 2: Clinics of Patients with Adrenal Tumor

	Nonfunctional adrenal adenoma (n=33)	Functional adrenal tumor (n=24)	P
Female (%)	60.6	75.0	0.255
Cushing syndrome (%)	-	41.7	-
Pheochromocytoma (%)	-	50.0	
Primary hyperaldosteronism (%)	-	8.3	
Co-morbidity (%)			0.064
Diabetes	19.4	25.0	
Hypertension	41.9	54.2	
Heart disease	6.9	8.3	
Obesity	54.8	38.7	
Clinical presentation at diagnosis (%)			**<0.001**
Asymptomatic	82	6.8	
High blood pressure	18	5.9	
Uncontrolled hypertension	-	45.6	
Cushing syndrome	-	41.7	

Bold represents significant p-value.

Percentage of diabetes, hypertension, obesity, and heart disease were similar between non-functional and functional adenoma group, respectively (p>0.05). White blood cell count

were similar between groups (p>0.05). Monocyte count was significantly higher in the functional adrenal group (p<0.05). The MHR value was significantly higher in the functional group compared with non-functional and control group (13.79±3.14, 10.19±2.84 vs 10.08±1.82, p<0.05), but it was similar between non-functional group and control group (p>0.05). The MHR value was positively correlated with systolic and diastolic BP, glucose, hs-CRP and urinary normetanephrine concentrations. MHR was not correlated with other cardio-metabolic risk factors including lipids and, CIMT **(Table 3)**.

Table 3: Correlations of monocyte to HDL-C ratio with various variables

	r^2	p
BMI	-0.049	0.635
Age	-0.227	0.126
Systolic blood pressure	**0.480**	**<0.001**
Diastolic blood pressure	**0.452**	**<0.001**
Glucose	**0.333**	**0.001**
Triglyceride	0.192	0.060
LDL-C	0.294	0.034
Total cholesterol	0.044	0.673
CIMT	0.202	0.052
hs-CRP	**0.538**	**0.001**
Urinary normetanephrine	**0.302**	**0.043**

Bold represents significant p-value.

Abbreviations: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; CIMT, carotid intima-media thickness.

Functional adrenal tumor with CVD had higher MHR value compared with those without CVD (14.69±2.67 vs 11.84±2.57, p<0.05).

DISCUSSION

This is the first study to show an association between the MHR value and cardiovascular risk factors in adrenal tumors. Our results reported that MHR value increased in patients with functional adrenal tumor; however it did not increase in nonfunctional adrenal adenoma. Elevated MHR value positively correlated with cardiometabolic risk factors, such as blood pressures, glucose, and hs-CRP. MHR value may be a potential marker for functional adrenal tumor patients at higher risk for developing CVD.

Pheochromocytoma (20), primary hyperaldosteronism (16), and Cushing's syndrome (21) are associated with increased prevalence of metabolic and cardiovascular disease. Our results reported that higher values of MHR were shown in patients with functional adrenal tumor; whereas it did not increase in patients with non-functional adenoma. Previous studies have reported that functional adrenal tumor autonomously secrete hormones, and increase the risk for metabolic and cardiovascular deteriorations (12, 21-23); which might support the findings of this study. Park et al reported that patients with autonomous cortisol secretion presented obesity, glucose intolerance, arterial hypertension, and, increased CIMT compared with patients with nonfunctional adrenal adenoma (21). A grater prevalence of diabetes, insulin resistance, dyslipidemia, and increased inflammation was observed in patients with Cushing's syndrome (24, 25). Low-grade inflammation participates in an increased cardiovascular risk in patients with Cushing's syndrome (24). Primary hyperaldosteronism patients had higher blood pressures, increased CIMT (26), greater incidence of cardiovascular risk (27), and cardiovascular events (22) than in patients with essential hypertension. Pheochromocytoma and primary hyperaldosteronism have shown to be associated with an increased inflammation (28) compared with patients with essential hypertension (29). Zelinka et al showed that pheochromocytoma was associated with endothelial dysfunctions and, established further atherosclerosis (23). However; previous studies reported that nonfunctional adrenal adenoma was associated with an increased cardio-metabolic disturbance (30) including hypertension (31), insulin resistance or diabetes (12, 17). Nonfunctional adrenal adenomas have shown to be associated with increased risk of cardiovascular events (17), and mortality (14). Inconsistence to previous studies, the MHR value did not increase in patients with nonfunctional adrenal adenoma in our study. Previous studies reported that increased atherosclerosis, altered cardiac functions (31, 32), and elevated CIMT value (33) were observed in patients with nonfunctional adrenal adenoma. Non-functional adrenal adenoma showed worse endothelial alterations rather than established atherosclerosis (34, 35). Akkus reported that nonfunctional adrenal adenoma was associated with increased adipocytokines levels, which affect the insulin resistance and cardiovascular risk factors (36). Our patients with non-functional adrenal adenoma may possibly present in the early stage of inflammation and atherosclerosis, which might be explained why MHR does not associate with non-functional adrenal adenoma. Evidence suggests that CRP value, as a biomarker of systemic inflammation, predicts cardiovascular events and mortality (9, 10, 37, 38). Serum hs-CRP value was reported to be increased in both patients with functional and non-functional adrenal tumor (19, 34).

Similarly, our study showed that hs-CRP levels were elevated both in patients with functional and non-functional adenoma, and hs-CRP was positively related to the MHR value in patients with adrenal tumor. A significant correlation of high MHR value with high CRP levels in patients with infective endocarditis (37), acute coronary syndrome (10), coronary artery disease (9, 38), and hypertensive patients (39). MHR with its positively relation to CRP, as a biomarker of inflammation, therefore using MHR with CRP would be a predictor of clinical cardiometabolic outcomes (1). Hypertension causes to developing asymptomatic atherosclerosis in heart and vessels and, promoting subclinical organ dysfunction (16, 20, 23). MHR value was positively correlated with systolic and diastolic BP and serum glucose in our study. Similarly, Aydin et al reported that MHR value was observed to be increased in asymptomatic organ damage in primary hypertension (40).

Previous studies have showed that an elevated value of MHR correlated with the features of asymptomatic organ damage such as CIMT (40) and, aortic stiffness index (39). Inconsistence to this result, we observed that MHR value was not related to CIMT in patients with adrenal tumors. In our study, functional adrenal tumor patients with diabetes, hypertension and CVD had higher MHR value in comparison those without such co-morbidities. Previous studies have demonstrated that even non-functional adrenal tumors were associated with an increased incidence of insulin resistance and diabetes (12, 17), which supports our findings.

MHR value was reported to be increased in patients with CVD, and postulated as a predictor of future CVD (1, 8). Elevated values of MHR have observed in patients with coronary artery disease (38) and acute coronary syndrome (10), with an independently increased risk of cardiovascular mortality (37, 41).

The accumulation of monocytes and reduction of HDL-C at site of inflammation and endothelium upon different disease is similar to the observation of higher MHR value in patients with cardiovascular disorders (1). Elevated MHR values were shown in patients with acute ischemic (6) and hemorrhage stroke (8), with an increased risk of death. Inonu Koseoglu reported that MHR values were higher in obstructive sleep apnea syndrome patients with CVD, in comparison those without CVD (42). A rise in MHR value was shown to be associated with a higher risk of fatal cardiovascular events in patients with chronic renal failure (43). Higher value of MHR was shown in subjects with metabolic syndrome at higher risk of CVD compared with general population (44). Monocytes differentiate into tissue macrophages in interaction with platelet and endothelium, which is an immune-mediated process (1).

This process induces inflammation, subsequently participates in the beginning and progression of atherosclerosis (7); therefore, monocytes count suggests as a predictor of premature occurrence of cardiovascular events (2). HDL-C possesses anti-oxidant, anti-inflammatory, anti-thrombotic, and anti-atherosclerotic effects by inhibiting the migration of macrophage, suppressing the LDL oxidation, and interrupting the cholesterol efflux from macrophages (1, 2, 8, 37). HDL-C interrupts the activation of monocytes and inhibits the differentiation of monocytes to macrophages (1). HDL-C inhibits the pro-inflammatory and pro-oxidant effect of monocytes, which decreases inflammation and atherosclerosis (8, 37). MHR measurement has practical and economic advantage compared with other inflammatory markers, such as interleukin, and tumor necrosis factor-α (1). This study was a single-center study with a small sample size. This is limitation of our study. In conclusion, this study showed that MHR value increased in patients with functional adrenal tumor; whereas it did not increase in nonfunctional adrenal adenoma. Elevated MHR value was positively correlated with systolic and diastolic BP and, glucose, and hs-CRP; however it was not associated with other cardio-metabolic risk factors including lipids, and CIMT. MHR was not associated with nonfunctional adrenal adenoma due to possibly the early stage of inflammation. We suppose that elevated value of MHR predicts inflammation, which contributes to atherosclerosis. Elevated MHR value may also be a novel marker of future CVD in patients with functional adrenal tumor. More comprehensive studies need to enlighten this association.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

ABBREVIATIONS

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; hs-CRP, high-sensitivity C-reactive protein; CIMT, carotid intima-media thickness.

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