

Impact of metabolic syndrome and systemic inflammation on endothelial function in postmenopausal women

Postmenopozal kadınlarda metabolik sendrom ve sistemik inflamasyonun endotel fonksiyonu üzerindeki etkisi

ABSTRACT

Objective: Data on the impact of metabolic syndrome (MetS) and systemic inflammation on endothelial function remains scarce. In this study, we aimed to investigate the combined effects of MetS and systemic inflammation on endothelial function in postmenopausal women.

Methods: We identified 423 postmenopausal women from February 2019 through July 2020. MetS was diagnosed according to the International Diabetes Federation (IDF) criteria, and high sensitivity C-reactive protein (hs-CRP) was measured to assess the degree of underlying inflammation. The measurement of endothelial function was using digital arterial tonometry by assessing reactive hyperemia-induced vasodilation in one arm and adjusting for changes in the contralateral arm (reactive hyperemia index, RHI).

Results: There were 156 patients with MetS and 267 without MetS. Compared to the group without MetS, patients with MetS had significantly lower natural logarithmic RHI (0.66 ± 0.29 versus 0.91 ± 0.31 ; $p < 0.001$), but higher levels of hs-CRP (0.98 [$0.31, 3.54$] versus 0.53 [$0.20, 2.14$]; $p < 0.001$). In sequential multivariable analysis, the presence of hs-CRP ($\Delta R^2 = 0.047$, $p = 0.004$) had a significant and independent influence on natural logarithmic RHI. Furthermore, the interaction of hs-CRP*MetS was synergistically associated with endothelial dysfunction even in the fully adjusted model ($\beta = -0.107$, 95% CI $[-0.161 \sim -0.053]$, $p = 0.009$).

Conclusion: MetS and systemic inflammation are synergistically associated with endothelial dysfunction in postmenopausal women. Postmenopausal women with both these conditions appear to be at a significantly higher risk for adverse cardiovascular events.

Keywords: Postmenopausal, metabolic syndrome, systemic inflammation, endothelial function

ÖZET

Amaç: Metabolik sendromun (MetS) ve sistemik inflamasyonun endotel fonksiyon üzerindeki etkisine ilişkin veriler yetersizdir. Bu çalışmada, postmenopozal kadınlarda MetS ve sistemik inflamasyonun endotel fonksiyonu üzerindeki kombine etkilerini araştırmayı amaçladık.

Yöntemler: Şubat 2019 ile Temmuz 2020 arasında 423 postmenopozal kadın belirlendi. MetS, Uluslararası Diyabet Federasyonu (IDF) kriterlerine göre teşhis edildi ve altta yatan inflamasyonun derecesini değerlendirmek için yüksek hassasiyetli C-reaksiyon proteini (hs-CRP) ölçüldü. Endotel fonksiyonunun ölçümü, bir kolda reaktif hipereminin neden olduğu vazodilatasyonu değerlendirerek ve karşı koldaki değişiklikleri (reaktif hiperemi indeksi, RHI) ayarlayarak dijital arteriyel tonometri kullanılarak yapıldı.

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Hongju Zhang, M.D.¹ 
Tao Sun, M.D.² 
Yutong Cheng, M.D.² 
Jing Zhang, M.D.³ 
HaiXia Zhang, M.D.³ 
Chayakrit Krittanawong, M.D.⁴ 
Edward El-Am, M.D.⁵ 
Roukoz Abou Karam, M.D.⁶ 
Su Wang, M.D.² 
Qian Wang, M.D.² 
Ning Ma, M.D.¹ 

¹Department of Echocardiography, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

²Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

³Department of Ultrasound, Shunyi Maternal and Children's Hospital of Beijing Children's Hospital, Beijing, China

⁴Section of Cardiology, Baylor College of Medicine, Houston, TX, USA

⁵Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

⁶The Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center Harvard Medical School, Boston Massachusetts, USA

Corresponding Author:

Ning Ma
✉ maning_echo@163.com

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Bulgular: MetS'li 156 ve MetS'siz 267 hasta vardı. MetS'i olmayan grupla karşılaştırıldığında, MetS'li hastalarda anlamlı olarak daha düşük doğal logaritmik RHI (0.66 ± 0.29 'a karşı 0.91 ± 0.31 ; $p < 0.001$), ancak daha yüksek hs-CRP seviyeleri ($0.98 [0.31, 3.54]$ 'e karşı $0.53 [0.20, 2.14]$; $p < 0.001$) vardı. Sıralı çok değişkenli analizde, hs-CRP'nin varlığı ($\Delta R^2 = 0.047$, $p = 0.004$) doğal logaritmik RHI üzerinde anlamlı ve bağımsız bir etkiye sahipti. Ayrıca, hs-CRP*MetS etkileşimi, tam olarak ayarlanmış modelde bile endotel disfonksiyonu ile sinerjistik olarak ilişkiliydi ($\beta = -0.107$, %95 CI $[-0.161 \sim -0.053]$, $p = 0.009$).

Sonuç: MetS ve sistemik inflamasyon, postmenopozal kadınlarda endotel disfonksiyonu ile sinerjik olarak ilişkilidir. Bu koşulların her ikisine de sahip olan postmenopozal kadınlar, olumsuz kardiyovasküler olaylar açısından önemli ölçüde daha yüksek risk altında görünmektedir.

Anahtar Kelimeler: Postmenopozal, metabolik sendrom, sistemik inflamasyon, endotel fonksiyonu

Endothelial function is considered a marker of vascular health and therefore may provide important insights into mechanisms contributing to the development and progression of atherosclerosis.^[1] Endothelial stress can trigger a low level of inflammation, leading to heightened plaque instability and platelet activation,^[2] which facilitates the propensity for thrombosis in coronary arteries.

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors that significantly contributes to the development of cardiovascular disease (CVD).^[3–5] In addition, systemic inflammation and MetS frequently coexist and tend to be associated with CVD.^[6–9] Prior studies have demonstrated a remarkable increase in the prevalence of CVD in women after menopause. This is mainly secondary to the loss of protective effects of estrogen,^[8] increased inflammation, and the prevalence of MetS after menopause. However, little is known about whether endothelial dysfunction and increased cardiovascular risk could be explained by the combined effects of MetS and systemic inflammation.^[9–13]

Therefore, in this study, we aimed to determine whether the combination of MetS and systemic inflammation is associated with worse endothelial function and to

explore the potential role of systemic inflammation in the prediction of endothelial dysfunction in postmenopausal women.

METHODS

Study population

In this retrospective study, patient information was collected from a registry on screening of endothelial dysfunction using EndoPAT 2000 (Itamar Medical Inc, Caesarea, Israel), a noninvasive testing device used at Shunyi Maternal and Children's Hospital and Beijing Anzhen Hospital from February 2019 through July 2020. Of the 983 patients identified, 356 were outpatients of the preventive cardiology clinic, 324 were inpatients of the cardiology clinic, 176 were volunteers, and 127 were outpatients of the internal medicine clinic. Postmenopausal status was defined by amenorrhea ≥ 12 months and was confirmed by a reproductive hormone panel. Exclusion criteria included congestive heart failure, coronary artery disease (CAD), valvular heart disease, non-sinus rhythm, chronic obstructive pulmonary disease, peripheral vascular disease, rheumatologic disease, inflammatory disorders, diabetes mellitus (DM), and hyperthyroidism. In addition, as smoking could increase systemic inflammation, patients who smoked were excluded from the study.^[10,11] Although coronavirus disease 2019 (COVID-19) has been reported since December 2019, when an outbreak of pneumonia cases emerged in Wuhan, Hubei province in China. However, in Beijing, only approximately 500 people (the presence of COVID-19 was 2.4/105) had been infected with COVID-19 until July 2020. Moreover, there were no patients with COVID-19 at Shunyi Maternal and Children's Hospital and Beijing Anzhen Hospital from December 2019 through July 2020; and once diagnosed, patients with COVID-19 could be transferred to the infectious diseases hospital immediately. However, because COVID-19 could aggravate endothelial dysfunction owing to excessive inflammation,^[12] patients with COVID-19 were also excluded from our study.

ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
BMI	Body mass index
CAD	Coronary artery disease
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
DM	Diabetes mellitus
FMD	Flow-mediated vasodilation
HDL-c	High-density lipoprotein cholesterol
hs-CRP	High sensitivity C-reaction protein
MetS	Metabolic syndrome
OSA	Obstructive sleep apnea
PCOS	Polycystic ovary syndrome
RHI	Reactive hyperemia index

The protocol of this study was approved by the human research ethical committee of Capital Medical University (Approval Date: December 2018; Approval Number: IR.IEC-C-008-A08-V.05.1), and written informed consent was obtained from all the participants. The study involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Metabolic syndrome

MetS was defined according to the International Diabetes Federation criteria.^[13] Patients were considered to have MetS if they fulfilled three or more of the following five cardiometabolic risk factors: 1) abdominal obesity with a waist circumference ≥ 88 cm in women, 2) elevated triglyceride level of 150 mg/dL or higher or specific treatment for this lipid abnormality, 3) reduced high-density lipoprotein cholesterol (HDL-c) level of less than 50 mg/dL in women or specific treatment for this lipid abnormality, 4) elevated systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, 5) impaired glucose regulation with a fasting plasma glucose ≥ 110 mg/dL.

Demographic, clinical, and laboratory parameters

Demographics and clinical characteristics, medications, and laboratory parameters were extracted from the medical records. Hypertension was defined as blood pressure $> 140/90$ mm Hg or a history of hypertension and current antihypertensive medications. Patients with obstructive sleep apnea (OSA) were defined as having an Epworth Sleeping Scale score ≥ 11 .^[14] Fasting blood samples were obtained for plasma lipids including HDL-c, low density lipoprotein cholesterol, blood triglycerides, and blood glucose. Peripheral venous blood samples were obtained before endothelial function assessment at the same visit. Serum high sensitivity C-reaction protein (hs-CRP) was measured using a latex particle-enhanced immunoturbidimetric assay.^[15]

Peripheral endothelial function evaluation

The patients were instructed to start fasting at least 12 h before the measurement and abstain from coffee or tobacco use on the day of the examination. The use of all vasoactive medications was discontinued at least 24 h before testing. Peripheral artery tonometry signals were obtained using the EndoPAT 2000 device. A peripheral artery tonometry finger probe was placed on each index finger. Pulsatile volume changes of the distal digit induced pressure alterations in the finger cuff, which were sensed by pressure transducers and transmitted to and recorded by the EndoPAT 2000 de-

vice. Endothelial function was measured via the reactive hyperemia index (RHI), as described earlier.^[16] The ratio of the peripheral artery tonometry signal after cuff release compared with the baseline was calculated with a computer algorithm automatically normalizing for baseline signal and indexed to the contralateral arm. RHI is a validated measure of endothelial function, and a higher RHI value correlates with better endothelial function (RHI > 1.67 is considered normal).^[15] RHI is not normally distributed, and thus, a logarithm transformation is performed.

Statistical analysis

The normality of each variable was assessed with the Kolmogorov-Smirnov test. Categorical data were expressed as numbers (n) and percentage (%), whereas quantitative data were given as mean \pm standard deviation and median (interquartile range). Continuous variables were compared using unpaired t-test; categorical variables were compared using the Fisher exact test or χ^2 tests as appropriate. Three multivariate regression models were constructed. The following procedure was used to assess the difference in how much variation is explained by the covariates among each of the three models. The dependent variable was the natural logarithmic RHI. In model 1, all covariates with a significant influence on endothelial function in the univariate linear regression model (p value < 0.15) or those with a known influence on endothelial function were included; age, OSA, family history of CAD, hypertension, body mass index (BMI), and the intake of angiotensin-converting enzyme inhibitor (ACEI). Model 2 included these covariates and MetS, and model 3 included these covariates, MetS, and hs-CRP. R2 values were calculated in a different regression model, and subsequent $\Delta R2$ were obtained. $\Delta R2$ represents the endothelial function variation that could be explained by the additional parameter.^[15] The MetS and hs-CRP interaction models were constructed in different models to assess whether MetS modified and enhanced the impact of hs-CRP on endothelial function. A value of $p < 0.05$ was considered statistically significant.^[17] Statistical analyses were performed using the SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and cardiometabolic characteristics

During the study period, 423 postmenopausal women met the inclusion criteria, and their cardiometabolic characteristics are summarized in Table 1. The mean age of the study population was 64 ± 9 years.

Table 1. Demographic and clinical characteristics in the MetS and no MetS groups

	MetS group (n=156)	No MetS group (n=267)	p
Age (years)	64±9.3	64±11.2	0.432
Body mass index (kg/m ²)	35±4.5	25±4.6	<0.001
SBP (mm Hg)	132±15	125±17	0.012
DBP (mm Hg)	75±11	75±10	0.983
Heart rate (beats/min)	71.3±10.4	69.2±11.4	0.123
Waist circumference (cm)	102.4±11.5	93.8±10.6	0.005
Family history of CAD, n (%)	23 (14.7%)	25 (9.4%)	0.127
Hypertension, n (%)	110 (70.5%)	126 (47.2%)	<0.001
Obstructive sleep apnea, n (%)	25 (16.0%)	51 (19.1%)	0.427
Hemoglobin (g/dL)	13±1.48	13±1.45	0.614
Erythrocytes (10 ¹² /L)	4.54±0.43	4.56±0.49	0.348
Leukocytes (10 ⁹ /L)	6.89±0.96	6.45±1.70	0.109
Platelet count (10 ⁹ /L)	241±54	243±56	0.817
Total cholesterol (mg/dL)	179±65	192±56	0.078
Triglycerides (mg/dL)	130 (84, 188)	99 (74, 146)	0.018
LDL (mg/dL)	100±17	110±16	0.157
HDL (mg/dL)	48.3±12.8	56.3±13.9	0.003
TC/HDL	4.03±1.18	3.73±1.20	0.232
FBG (mmol/L)	4.65±0.89	4.72±0.93	0.142
Hs-CRP (mg/dL)	0.98 (0.31, 3.54)	0.53 (0.20, 2.14)	<0.001
Medications, n (%)			
ACEI	66 (42.3%)	44 (16.5%)	<0.001
β-blocker	54 (34.6%)	60 (22.5%)	0.007
Calcium blocker	35 (22.4%)	30 (11.2%)	0.003
Lowering lipid	86 (55.1%)	87 (32.6%)	<0.001
Natural logarithmic RHI	0.66±0.29	0.91±0.31	<0.001

ACEI: angiotensin-converting enzyme inhibitor; CAD: coronary artery disease; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL: high-density lipoprotein; hs-CRP: high sensitive C-reaction protein; LDL: low density lipoprotein; MetS: metabolic syndrome; RHI: reactive hyperemia index; SBP: systolic blood pressure; TC: total cholesterol.

There were 156 (36.9%) patients with MetS and 267 (63.1%) without MetS. Compared to the group without MetS, the MetS group had a higher level of hs-CRP (0.98 [0.31, 3.54] versus 0.53 [0.20, 2.14]; $p<0.001$), more prevalent hypertension (70.5% versus 47.2%; $p<0.001$), and were more frequently prescribed ACEI (42.3% versus 16.5%; $p<0.001$), β-blocker (34.6% versus 22.5%; $p=0.007$), calcium channel blocker (22.4% versus 11.2%; $p=0.004$), and lipid lowering medication (55.1% versus 32.6%; $p<0.001$). In addition, the MetS group had higher BMI (35±4.5 versus 25±4.6 kg/m²; $p<0.001$), systolic blood pressure (132±15 versus 125±17 mm Hg; $p=0.012$), waist circumference (102.4±11.5 versus 93.8±10.6 cm; $p=0.005$), and higher level of triglyceride (130 [84,188] versus 99 [74, 146] mg/

dL; $p=0.018$), but lower levels of HDL-c (48.3±12.8 versus 56.3±13.9 mg/dL; $p=0.003$) and significantly lower natural logarithmic RHI (0.66±0.29 versus 0.91±0.31; $p<0.001$) than the group without MetS. However, there were no significant differences in age (64±9.3 versus 64±11.2; $p=0.432$), fasting blood glucose (4.65±0.89 versus 4.72±0.93; $p=0.142$), family history of CAD (14.7% versus 9.4%; $p=0.127$), and the prevalence of OSA (16.0% versus 19.1%; $p=0.371$).

Sequential multivariable analysis and the interaction of hs-CRP*MetS

The sequential multivariable regression analysis for the relationship between hs-CRP, MetS, and endothelial dysfunction is shown in Table 2. The R² values resulting from models 1, 2, and 3 were 0.109, 0.124, and 0.171,

Table 2. Sequential multivariate regression for the relationship between hs-CRP, MetS, and endothelial dysfunction

Variables	Model 1	Model 2	Model 3						
	β (95% CI)	p	VIF	β (95% CI)	p	VIF	β (95% CI)	p	VIF
Age	0.086 (0.037~0.135)	0.197	1.036	0.091 (0.043~0.139)	0.184	1.029	0.076 (0.028~0.125)	0.236	1.029
Obstructive sleep apnea	-0.097 (-0.145~-0.048)	0.152	1.025	-0.129 (-0.176~-0.082)	0.064	1.031	-0.094 (-0.143~-0.046)	0.131	1.042
Family history of CAD	-0.158 (-0.206~-0.107)	0.034	1.041	-0.173 (-0.221~-0.126)	0.019	1.043	-0.138 (-0.187~-0.089)	0.056	1.048
Hypertension	-0.105 (-0.154~-0.056)	0.086	1.039	-0.098 (-0.146~-0.049)	0.152	1.032	-0.116 (-0.165~-0.067)	0.075	1.043
Body mass index	-0.083 (-0.132~-0.034)	0.219	1.028	-0.123 (-0.171~-0.072)	0.072	1.041	-0.106 (-0.156~-0.057)	0.082	1.037
ACEI	0.071 (0.022~0.121)	0.258	1.032	0.068 (0.021~0.117)	0.315	1.019	0.062 (0.013~0.114)	0.317	1.028
MetS				-0.168 (-0.217~-0.119)	0.021	1.045	-0.141 (-0.192~-0.093)	0.053	1.019
Hs-CRP							-0.197 (-0.246~-0.145)	0.007	1.016
R2	0.109	0.124	0.171						
Δ R2		0.015	0.047						
F change		1.613	8.749						
p	<0.001	0.307	0.004						

ACEI: angiotensin-converting enzyme inhibitor; CAD: coronary artery disease; hs-CRP: high sensitive C-reaction protein; MetS: metabolic syndrome; VIF: variance inflation factor.

Table 3. Multivariate models of natural logarithmic RHI predicted by interaction of MetS*hs-CRP

Models	β (95% CI)	p	VIF
1	-0.107 (-0.161~-0.053)	0.009	1.025
2	-0.086 (-0.137~-0.036)	0.041	1.032
3	-0.093 (-0.141~-0.045)	0.029	1.015
4	-0.074 (-0.128~-0.029)	0.063	1.021

BMI: body mass index; CAD: coronary artery disease; hs-CRP: high sensitivity C-reaction protein; MetS: metabolic syndrome; OSA: obstructive sleep apnea; RHI: reactive hyperemia index; VIF: variance inflation factor.
 Model 1: Adjusted by age, OSA, BMI, family history of CAD, hypertension.
 Model 2: Adjusted by age, OSA, BMI, family history of CAD.
 Model 3: Adjusted by age, OSA, BMI.
 Model 4: Adjusted by age, OSA.

respectively. The Δ R2 between model 2 and model 1 was equal to 0.015 ($p=0.307$), which indicates that model 2 does not add new information from that of

model 1. The Δ R2 between model 3 and model 2 was equal to 0.047 ($p=0.004$), suggesting that the change in natural logarithmic RHI might be explained by the addition of hs-CRP as a covariate used in model 3; thus, the presence of systemic inflammation has additional independent information on endothelial function. The interaction of hs-CRP*MetS was synergistically associated with endothelial dysfunction even in the fully adjusted model ($\beta=-0.107$, 95% CI [-0.161~-0.053], $p=0.009$) (Table 3).

DISCUSSION

This is the first study to evaluate endothelial function and to examine the association between MetS, systemic inflammation, and endothelial function. The major findings of our study were as follows: 1) The presence of systemic inflammation had a significant and independent influence on endothelial function;

2) MetS and systemic inflammation were synergistically associated with endothelial dysfunction in postmenopausal women.

Atherosclerosis develops over decades and has a prolonged asymptomatic phase during which functional and structural abnormalities of the arteries can occur. Multiple efforts have been focused on the development and improvement of novel noninvasive methods to detect early, subclinical atherosclerosis.^[18] Flow-mediated vasodilation (FMD) allows evaluation of the response of endothelium to shear stress increase after transient ischemia. Irace C and colleagues demonstrated that temporal patterns are associated with the degree of atherosclerosis of the carotid arteries. Patients with delayed vasodilation had a higher degree of atherosclerosis than those with early vasodilation.^[19] Rubinshtein et al.^[16] reported that endothelial dysfunction detected by noninvasive peripheral arterial tonometry could predict late cardiovascular events. MetS is a constellation of abnormalities that together increase the risk of CVD. Consistent with a previous study,^[3] we found that patients with MetS had worse endothelial function than those in the group without MetS. One possible explanation for this finding is that MetS, high blood pressure, and insufficient physical activity have been identified as major contributors to atherosclerotic plaque formation. These factors increase the risk of atherosclerosis regardless of ethnicity and geography.^[20]

Several studies have shown that hs-CRP was increased in patients with CAD,^[1,21] and it was an independent marker of abnormal coronary vasoreactivity in patients with non-obstructive CAD.^[22] Consistent with a study by Jeon et al.,^[23] our results also showed that hs-CRP level was significantly higher in patients with MetS than those without MetS. This study also found that hs-CRP was associated with endothelial dysfunction only in patients with MetS. This may be explained by the fact that during MetS, persistent presence of various atherogenic molecules instigates a hypoxic environment along with oxidative stress. This is followed by a cascade of biochemical and molecular events that may progressively lead to systemic inflammation, foam cell formation, and endothelial dysfunction, which are all important factors in the pathogenesis of atherosclerosis.^[2,24] However, hs-CRP is not currently included in the definition of MetS despite epidemiological studies^[2] indicating that chronic subclinical inflammation is part of MetS, and the

predictive power of MetS for CVD may be enhanced by the presence of inflammation manifested by high levels of hs-CRP.^[25] These findings support the assumption that MetS can cause systemic inflammation and, therefore, the combination confers a higher risk of CVD.

The complex interplay between MetS, systemic inflammation, and vascular injury poses several clinical challenges.^[26,27] Both MetS and systemic inflammation are associated with an increased risk of CVD, making it difficult to assess the individual impact of these conditions on CAD risk.^[2] In this study, the interaction of hs-CRP*MetS showed a synergistic association with endothelial dysfunction even in our fully adjusted model. This indicates that the combined effects of both disease processes have a significant deleterious impact on endothelial function. Moreover, because of age-related decaying of endoplasmic reticulum molecular chaperones, endothelial dysfunction is characterized by chronic inflammatory markers, which are associated with increased risk of cardiovascular events, especially in patients with MetS^[28,29] as the combination of MetS and systemic inflammation synergistically increases the risk of CVD. Therefore, in postmenopausal women with MetS, systemic inflammation should be further addressed.

Postmenopausal women with a combination of MetS and systemic inflammation have repeated hypoxic events and release of reactive oxygen species, which could secondarily lead to blood pressure elevation, higher cholesterol levels, and endothelial dysfunction.^[24,26] A similar pathophysiology also exists in women with polycystic ovary syndrome (PCOS). Women with PCOS, even at an early age, have a clustering of cardiometabolic risk factors, such as insulin resistance, hypertension, and low-grade systemic inflammation. It is well known that the initial activation of systemic inflammation in patients with PCOS is associated with an increased production of reactive oxygen species, which in turn plays a key role in the development of oxidative stress and further vicious cycle activation of inflammatory response. Furthermore, according to the available data from the literature and meta-analyses, women with PCOS have a higher level of hs-CRP not due to obesity, rather due to the presence of the disease itself, which highlights activation of systemic inflammation in patients with PCOS complicated by cardiometabolic disorders and insulin resistance.^[30,31]

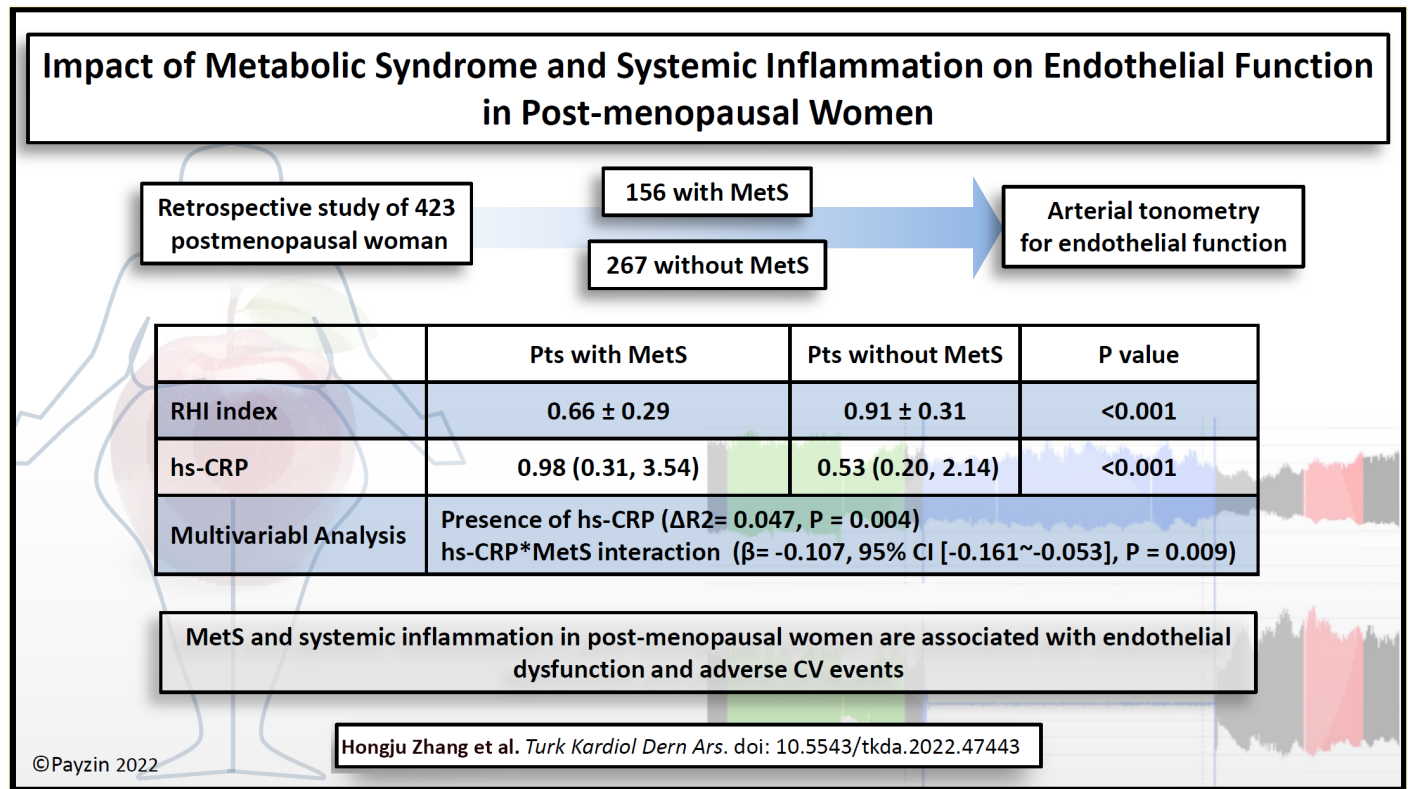


Figure 1. Visual summary of the article

Limitations

Our study had some limitations, including the fact that it was a cross-sectional and retrospective study, subject to the limitations of retrospective analyses. In addition, the sample size was relatively small; therefore, studies with a larger number of patients should be conducted to further confirm our conclusion. Another limitation is that we did not take the predictive value of the severity of MetS on endothelial dysfunction into account in our analyses. Finally, several factors that are known to affect endothelial function were not included in this study.

CONCLUSION

Among postmenopausal women with MetS, the presence of systemic inflammation is associated with endothelial dysfunction. The significant interaction between hs-CRP*MetS suggests that the combined effects of MetS and systemic inflammation have a worse impact on endothelial function and synergistically increase CVD risk. Diagnosis and management of MetS in postmenopausal women should also address systemic inflammation to create a more effective treatment for these often concomitant conditions.

Visual summary of the article can be seen in Figure 1.

Ethics Committee Approval: Ethics committee approval was received for this study from the Human Research Ethical Committee of Capital Medical University (Approval Date: December 2018; Approval Number: IR.IEC-C-008-A08-V.05.1).

Informed Consent: Written informed consent was obtained from the participants of the study.

Peer-review: Externally peer-reviewed.

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