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Enzyme and lipid markers in relation to cardiovascular risk in postmenopausal women

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Abstract

Postmenopausal women are at an increased risk of cardiovascular disease (CVD), the leading cause of death worldwide, compared with younger women. Gamma-glutamyl transferase (GGT) and high-density lipoprotein cholesterol (HDL-c) are linked with oxidative stress, inflammation, insulin resistance, and CVD risk factors. However, there have been no studies that examined the relationship between GGT/HDL-c and CVD exclusively in women who are not of reproductive age. Therefore, we aimed to examine this potential relationship in a cohort of CVD-free postmenopausal women. A total of 150 disease-free postmenopausal women were consecutively included. CVD risk was defined according to high sensitivity C-reactive protein (hsCRP) concentration (hsCRP < 1 mg/L defines low risk and hsCRP ≥ 1 mg/L defines intermediate and high risk). The GGT/HDL-c was independently associated with intermediate and high CVD risk in postmenopausal women. As this enzyme/lipid index increased by 1 unit, the probability of intermediate and high CVD risk rose by 10.3% (OR = 1.103, p = 0.024). The GGT/HDL-c ratio was independently associated with higher CVD risk, as measured with hsCRP in postmenopausal women. This cost-effective, easily measured, and widely available index could be used in everyday clinical practice for estimating CVD risk in postmenopausal women.

Key words: cardiovascular risk, gamma-glutamyl transferase, lipoproteins, postmenopausal

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Introduction

Postmenopausal women are at an increased risk of cardiovascular disease (CVD), the leading cause of death worldwide, compared with younger women (1). This is mostly due to changes in hormonal milieu, predominantly resulting in estrogen deficiency and relative hyperandrogenemia in women in whom the reproductive period is over (2).

Given the paramount importance of this public health concern, one of the major strategies in the primary care setting is the timely recognition of postmenopausal women at increased CVD risk, as well as the development of preventive and therapeutic strategies in this population cohort, since they usually do not exhibit symptoms before a cardiovascular event occurs (3).

Weight gain and the redistribution of adipose tissue towards the abdominal region are the accompanying phenomena in this period of life (2, 3). Obesity is a well-established risk factor for CVD, even in the young population (4). Since women in postmenopause are more susceptible to abdominal adiposity, a lot of research has been done so far to examine the pathophysiological mechanisms, with a special focus on oxidative stress and inflammation processes underlying obesity-related disorders (5, 6). Namely, adipose tissue secretes a variety of pro-inflammatory cytokines and adipokines, and joint increase in the production of reactive oxygen/nitrogen species disrupts homeostasis towards a chronic pro-oxidant and low-grade pro-inflammatory environment (7, 8).

Although a lot of biomarkers of oxidative stress have emerged in the last decades, the majority of them have not yet found their application in routine clinical practice (9). Similarly, the availability of many novel inflammation biomarkers is still limited in clinical laboratories, since they are only used in experimental research and are time-consuming due to the impossibility of measuring these biomarkers on automatic analyzers (10).

Hence, there is an urgent need for cost-effective, easily measured and widely available biomarkers for timely diagnosis of increased CVD risk.

Gamma-glutamyl transferase (GGT) and high-density lipoprotein cholesterol (HDL-c) are linked with oxidative stress, inflammation, insulin resistance, and CVD risk factors (11).

GGT is widely used as a biomarker that serves as an indicator of liver function, being closely linked with fatty liver disease-related complications (12). Furthermore, it is a part of an algorithm called the fatty liver index (FLI), which is widely used in epidemiological studies and highly correlates with liver steatosis diagnosed by ultrasound (2). It was also shown that GGT was positively correlated with higher CVD risk in the female, but not in the male population (13).

HDL exerts anti-inflammatory, antioxidant, antithrombotic, fibrinolytic (14) and cholesterol flux properties (12). The monitoring of changes in HDL quality and quantity can be a reliable indicator of the onset/progression of many disorders (15, 16).

Recently published data have shown that the GGT/HDL-c ratio has a better diagnostic ability for type 2 diabetes mellitus (T2D) (17, 18) and fatty liver disease (12, 19) than each single biomarker (i.e., GGT or HDL-c). Moreover, a recent study examined the sex-dependent relationship of GGT/HDL-c and CVD, with such an association observed only in women but not in men (20).

However, there have been no studies that examined the relationship between GGT/HDL-c and CVD exclusively in women who are not of reproductive age. Therefore, we aimed to examine this potential relationship in a cohort of CVD-free postmenopausal women.

Patients and Methods

Patients

A total of 150 disease-free postmenopausal women who had experienced natural menopause were consecutively included in the research after obtaining the approval of the Institutional Ethics Committee. All women signed an informed consent regarding their willingness to participate in the study. The research was conducted following the ethical principles of the Helsinki Medical Declaration.

CVD risk is roughly estimated with high-sensitivity C-reactive protein (hsCRP). The levels of hsCRP lower than 1 mg/L indicate low CVD risk; hsCRP levels between 1.0 mg/L and 3.0 mg/L indicate intermediate CVD risk, and hsCRP levels higher than 3.0 mg/L indicate higher CVD risk. Since a total of 72 postmenopausal women had hsCRP < 1.0 mg/L, 57 postmenopausal women exhibited 1.0 mg/L ≤ hsCRP ≤ 3.0 mg/L, and only 21 postmenopausal women had hsCRP values higher than 3.0 mg/L, for simplicity reasons, all postmenopausal women were divided into 2 groups, i.e., women with low CVD risk (hsCRP < 1mg/L) and women with intermediate and high CVD risk (hsCRP ≥ 1mg/L).

Blood sampling and anthropometric measurements were taken the same morning, after overnight fasting, while questionnaires were filled in with demographic data, lifestyle habits-smoking, alcohol consumption, diseases, and medication use. The inclusion criterion was postmenopausal status, confirmed by self-reported absence of menstrual bleeding for more than 1 year.

The exclusion criteria were diagnosis of diabetes mellitus, other endocrine diseases, gout, CVD, stroke, malignant and autoimmune diseases, acute/chronic infection, pregnancy, anti-inflammatory, antidiabetic, hypolipemic, hormone replacement therapy or any other drugs in the last 3 months. Women with hsCRP equal to or higher than 10.0 mg/L were further excluded from the next phase of the study since these values indicate a high probability of a sign of an acute infection (6).

Methods

All biochemical analyses [i.e., gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), high density lipoprotein cholesterol (HDL-c), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), and triglycerides (TG)] were performed on a Roche Cobas 6000 c501 chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany) using standardized procedures.

TC/HDL-c, LDL-c/HDL-c, TG/HDL-c, Non-HDL-c, ALP/HDL-c, and GGT/HDL-c ratios were calculated.

The participants' blood pressure [i.e., systolic (SBP) and diastolic (DBP)] and anthropometric measurements [i.e., body weight and height, and waist circumference (WC)] were taken, and the body mass index (BMI) was calculated.

Statistical analysis

The Kolmogorov-Smirnov test was applied for the assessment of data normality. Normally distributed continuous variables were given as the mean ± standard deviation and compared by the Student *t*-test. Skewed distributed data were given as median (25^{th}–75^{th} percentiles) and compared by the Mann-Whitney *U*-test. Categorical data were reported as absolute and relative frequencies. The Chi-square test for contingency tables was used for intergroup difference testing in categorical variables. The associations between dependent categorical variables (i.e., CVD risk, dichotomous variable) and independent continuous variables were analysed using binary logistic regression analysis. CVD risk was defined according to hsCRP concentration (hsCRP < 1 mg/L defines low risk and hsCRP ≥ 1 mg/L defines high risk). Multivariate logistic regression was used to evaluate possible independent associations between lipid and enzyme markers and CVD risk. Data from association analysis were given as odds ratio (OR) and 95% Confidence Interval (CI). Multivariate regression models included confounding factors which were significantly different between tested groups and associated with CVD risk in univariate analysis ($p < 0.05$).

The area under the Receiver Operating Characteristic (ROC) curve (AUC) was determined in order to test the diagnostic performance of single lipid and enzyme markers, as well as models to discriminate menopausal women with intermediate/high CVD risk from those who had low CVD risk. The results were given as AUC and 95% CI.

Significance in statistical testing was set for p less than 0.05. Statistical analyses were performed using the SPSS statistical program Version 21 (IBM, New York, United States).

Results

The general data of the studied population are presented in Table I. Postmenopausal women with intermediate and high CVD risk had higher weight, WC, and BMI than women with low CVD risk. Additionally, SBP and DBP were also higher in women with intermediate and high CVD risk, and more hypertensive women were in this group as well. The postmenopausal women were of the same age and had a similar period of time in postmenopause.

Table I Demographic and clinical data in postmenopausal women according to CVD risk

Tabela I Demografski i klinički podaci žena u postmenopauzi prema kardiovaskularnom riziku

	Low CVD risk (hsCRP < 1mg/L)	**Intermediate/high CVD risk (hsCRP ≥ 1mg/L)**	**p**
Age, years	57 (53–60)	56 (54–60)	0.608
Weight, kg*	65.8 ± 9.9	78.4 ± 11.5	< 0.001
Height, m*	167.0 ± 5.8	166.5 ± 5.0	0.628
BMI, kg/m^2*	24.5 ± 3.7	28.2 ± 4.1	< 0.001
WC, cm	79 (75–89)	95 (87–102)	< 0.001
SBP, mmHg	125 (98–145)	135 (120–150)	0.008
DBP, mmHg	82 (67–92)	88 (80–95)	0.024
Hypertension, n (%)	26 (36%)	41 (53%)	0.043
Menopausal duration, years	5 (2–10)	4 (2–9)	0.880

Data are given as median (interquartile range) and compared by the Mann Whitney *U*-test.

*Data are given as mean ± SD and compared by the Student *t*-test.

Postmenopausal women with intermediate and high CVD risk had lower HDL-c levels, but higher TG/HDL-c, ALP, GGT, ALP/HDL-c, and GGT/HDL-c than women with low CVD risk (Table II). As expected, hsCRP levels were higher in women with intermediate and high CVD risk.

Table II Laboratory markers in postmenopausal women according to CVD risk

Tabela II Laboratorijski parametri žena u postmenopauzi prema kardiovaskularnom riziku

	Low CVD risk (CRP < 1mg/L)	Intermediate/high CVD risk (CRP ≥ 1mg/L)	p
TC, mmol/L*	6.6 ± 1.0	6.4 ± 1.1	0.219
HDL-c, mmol/L*	1.8 ± 0.4	1.6 ± 0.4	**0.005**
LDL-c, mmol/L	4.2 (3.6–4.8)	4.1 (3.7–5.0)	0.861
TG, mmol/L	1.2 (0.8–1.6)	1.3 (1.0–1.9)	0.118
TC/HDL-c	3.57 (2.95–5.15)	3.99 (3.30–5.14)	0.087
LDL-c/HDL-c	2.32 (1.81–3.48)	2.58 (2.09–3.62)	0.098
TG/HDL-c	0.62 (0.43–1.07)	0.84 (0.54–1.50)	**0.029**
Non-HDL-c, mmol/L	4.65 (3.95–5.37)	4.59 (4.08–5.56)	0.685
AST, U/L	18 (17–20)	18 (15–21)	0.298
ALT, U/L	18 (14–22)	20 (15–24)	0.184
ALP, U/L	68 (24–79)	72 (61–88)	**0.035**
GGT, U/L	11 (9–13)	13 (9–17)	**0.009**
ALP/HDL-c	36.54 (29.75–53.06)	46.43 (36.07–61.47)	**0.007**
GGT/HDL-c	6.51 (5.03–12.60)	8.33 (5.56–12.61)	**0.001**
HsCRP, mg/L	0.46 (0.26–0.66)	2.00 (1.32–3.39)	**<0.001**

Data are given as median (interquartile range) and compared by the Mann Whitney *U*-test.

*Data are given as mean ± SD and compared by the Student *t*-test.

Our further goal was to test associations of lipid and enzyme markers with CVD risk. For that purpose, we performed a binary logistic regression analysis (Table III). In univariate analysis, each lipid and enzyme marker was used as an independent continuous variable, and the dichotomous categorical variable CVD risk (0 – low CVD risk; 1 – intermediate and high CVD risk) was used as a dependent variable. HDL-c, GGT, ALP/HDL-c, and GGT/HDL-c were associated with CVD risk. As HDL-c decreased by 1 mmol/L, the probability of intermediate and high CVD risk rose by 63.3% (OR=0.312, p=0.006). As GGT increased by 1 U/L, and ALP/HDL-c and GGT/GDL-c by 1 unit, the probability of intermediate and high CVD risk rose by 9.5% (OR=1.095, p<0.004), 2.8 times (OR=2.842, p<0.010) and 14.9% (OR=1.149, p=0.001), respectively.

These predictors were adjusted for other markers that differed significantly between the tested groups and were significantly associated in univariate binary regression analysis. Multivariate logistic regression analysis showed that only GGT/HDL-c kept an independent prediction for intermediate and high CVD risk in postmenopausal women (Table III). As this enzyme/lipid index increased by 1 unit, the probability of intermediate and high CVD risk rose by 10.3% (OR=1.103, p=0.024). The adjusted R^2 for the Model was 0.287, which means that 28.7% of variation in CVD risk could be explained with this Model (Table III).

Table III Univariate and multivariate binary logistic regression analysis for lipid and enzyme markers predicting intermediate and high CVD risk

Tabela III Univarijantna i multivarijantna binarna logistička regresiona analiza za markere lipida i enzima koji predviđaju srednji i visoki kardiovaskularni rizik

	Unadjusted		
	OR (95% CI)	P	Nagelkerke R^2
HDL-c, mmol/L	0.312 (0.136–0.716)	**0.006**	0.071
TC/HDL-c	1.194 (0.913–1.560)	0.196	0.015
LDL-c/HDL-c	1.199 (0.875–1.643)	0.258	0.012
TG/HDL-c	1.519 (0.921–2.504)	0.102	0.025
ALP, U/L	1.019 (0.999–1.040)	0.066	0.034
GGT, U/L	1.095 (1.028–1.165)	**0.004**	0.085
ALP/HDL-c	2.842 (1.277–6.326)	**0.010**	0.064
GGT/HDL-c	1.149 (1.059–1.246)	**0.001**	0.115
	Adjusted		
Models	OR (95% CI)	P	Nagelkerke R^2
HDL-c, mmol/L	1.015 (0.348–2.957)	0.979	0.310
GGT, U/L	1.072 (0.999–1.149)	0.061	0.310
ALP/HDL-c	1.708 (0.719–4.058)	0.226	0.300
GGT/HDL-c	1.103 (1.013–1.202)	**0.024**	0.287

Data are given as OR (95% CI)

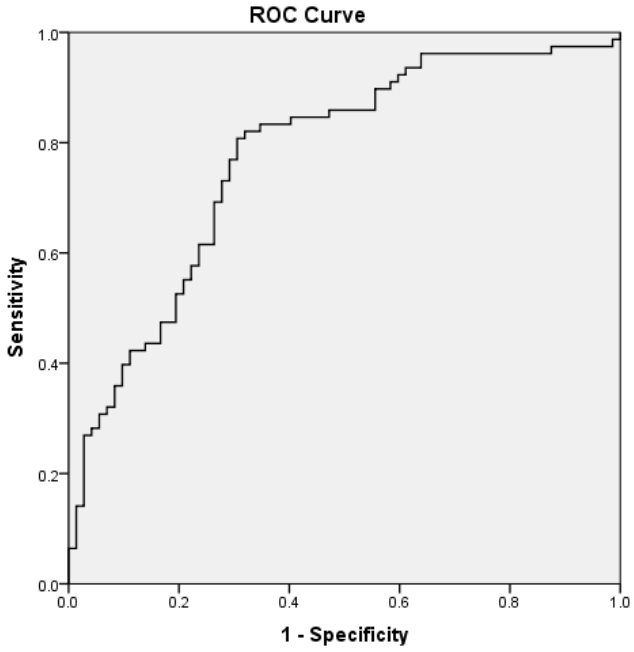
HDL-c was adjusted for hypertension presence, ALP, GGT and BMI

GGT was adjusted for hypertension presence, ALP and BMI

ALP/HDL-c was adjusted for hypertension presence, GGT and BMI

GGT/HDL-c was adjusted for hypertension presence and BMI

ROC analysis was used to discriminate women with intermediate/high from women with low CVD risk (Figure 1). The calculated AUCs for the models of HDL-c, GGT and ALP/HDL-c ranged from 0.600 to 0.700, indicating that the clinical accuracy of each diagnostic marker was low (data not presented). However, the AUC for the model with GGT/HDL-c was AUC = 0.773 (0.698–0.849), $p < 0.001$ with standard error of 0.038. The calculated AUC for this model indicated good clinical accuracy in discriminating menopausal women with low from those with intermediate/high CVD risk.



Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.773	.038	.000	.698	.849

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 1. ROC curve and area under the curve to discriminate women with intermediate/high risk from women with low CVD risk

Slika 1. ROC kriva i površina ispod krive za diskriminaciju žena sa srednjim/visokim kardiovaskularnim rizikom od žena sa niskim rizikom

Discussion

As far as we are informed, no previous study has examined the association between the GGT/HDL-c ratio and CVD risk in postmenopausal women. The findings of the current study reveal that the GGT/HDL-c ratio is independently associated with higher CVD risk (i.e., as determined with hsCRP ≥ 1 mg/L) in the cohort of CVD-free postmenopausal women. Moreover, this index showed better correlations with higher CVD risk than any single biomarker (i.e., GGT or HDL-c) in this study. GGT and HDL-c lost their independent correlations with CVD risk after adjustment for confounding variables, especially for BMI and hypertension.

These findings are in accordance with the recently published data on the superiority of the GGT/HDL-c ratio in the population with T2D and NAFLD, respectively, to a single biomarker, i.e., GGT or HDL-c (12, 17–19). Moreover, the AUCs for the model of HDL-c and GGT ranged from 0.600 to 0.700, indicating low clinical accuracy of each diagnostic marker, whereas the AUC for the model with GGT/HDL-c had AUC = 0.773, indicating good clinical accuracy in discriminating menopausal women with low from those with intermediate/high CVD risk.

To the best of our knowledge, only one study has examined the associations of GGT/HDL-c ratio and the incident risk of CVD (20). This large longitudinal study included 27,643 CVD-free Korean adults. After a 50-month follow-up, the researchers concluded that the GGT/HDL-c ratio may be a reliable predictor of CVD in women but not in men (20). However, in order to diminish the confounding effect of sex hormone variation in women across their life span, we excluded young girls and women of reproductive age, thus encompassing the postmenopausal cohort, since these women are at an increased CVD risk (1).

We searched for low-cost and easily obtained biomarkers that could be measured in everyday clinical practice to serve as reliable CVD risk parameters in this population group, and tried to emphasize a new outlook on the relatively old biomarkers.

GGT is an enzyme which plays a major role in the processes of oxidative stress by facilitating the breakdown of glutathione (which is an antioxidant) in extracellular compartments, thus enabling an amino acid’s precursor to be transported for intracellular re-synthesis of glutathione (21). However, higher GGT activity is connected with insulin resistance-related disorders, CVD risk and all-cause mortality (22). This could, in part, be explained by the different properties of GGT (i.e., its dual activity) depending on its concentrations. Namely, if it is within the normal range, GGT combats oxidative stress by restoring intracellular glutathione. However, at higher concentrations, GGT exerts pro-inflammatory and pro-oxidant properties, thus accelerating atherosclerosis onset (23) by catalyzing the LDL oxidation, and being directly included in the atheromatous plaque formation (24).

HDL is well-known for its beneficial properties in atherosclerosis due to its antioxidant, anti-inflammatory, fibrinolytic, and antithrombotic effects (14). HDL inhibits the pathological endothelial adherence of monocytes, thus playing a role in the

mechanisms of endothelial repair (25). However, similarly to GGT, HDL exhibits a dual nature (26). In the absence of inflammation, the proteins linked with HDL exert anti-inflammatory effects, but in case of increased inflammation, these proteins act in a pro-inflammatory manner (26). Indeed, we have previously shown lower HDL-c levels in patients with T2D (15), but higher HDL-c levels have been independently correlated with liver fibrosis (i.e., BARD score) (16). Moreover, previous findings assumed that cholesterol flux, rather than an unfluctuating HDL-c level, may be a significant determinant of coronary artery disease (27).

Our results point out the reliability of the GGT/HDL-c ratio in relation to CVD risk (as determined by hsCRP) compared to a single biomarker, i.e., GGT or HDL-c. Hence, we assume that the GGT/HDL-c ratio, given that it is cost-effective and easily available, could be used in everyday clinical practice for estimating CVD risk in postmenopausal women, especially in low-income countries where hsCRP measurement can be limited.

The strength of our study lies in the fact that we have encompassed exclusively postmenopausal women free of cardiometabolic diseases and excluded several confounding factors that might significantly affect the results of the study, such as smoking, alcohol consumption, and any medication use. On the other hand, this cross-sectional study does not enable us to determine causality between the examined variables. CVD risk was estimated using hsCRP as a well-established biomarker for CVD. Imaging methods, such as the measurement of carotid intima-media thickness, would be of great significance in addition to the biomarkers measured in the current study. Moreover, we have included only women who experienced natural menopause, and their postmenopausal status was not confirmed by sex hormone levels; these data were self-reported, which might cause bias in the interpretation of the results. Hence, we were unable to further examine the role of sex hormones in relation to CVD risk. Future studies that would include a larger sample size, with longitudinal design, and with the measurement of lipoprotein subclasses, could be valuable in further examining the obtained results.

Conclusion

The GGT/HDL-c ratio was independently associated with higher CVD risk, as measured with hsCRP in postmenopausal women. On the other hand, GGT and HDL-c lost their independent correlations with CVD risk after adjustment for confounding variables. The GGT/HDL-c ratio is a cost-effective, easily measured, and widely available index, which could be used in everyday clinical practice for estimating CVD risk in postmenopausal women.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

AK-Writing - original draft; Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; FM- Review & editing; MB-Review & editing; AN-Software; Supervision; Validation; Review & editing.

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Enzimski i lipidni markeri u proceni rizika za nastanak kardiovaskularnih bolesti kod žena u menopauzi

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Kratak sadržaj

Žene u postmenopauzi su pod povećanim rizikom od kardiovaskularnih bolesti (KVB), vodećeg uzroka smrti širom sveta, u poređenju sa mlađim ženama. Gama-glutamil transferaza (GGT) i koncentracija holesterola u lipoproteinima visoke gustine (HDL-c) povezani su sa oksidativnim stresom, upalom, insulinskom rezistencijom i faktorima rizika za KVB. Međutim, ne postoje studije koje su ispitivale odnos između GGT/HDL-c i KVB isključivo kod žena koje nisu u reproduktivnom dobu. Stoga smo imali za cilj da ispitamo pomenuti potencijalni odnos u kohorti žena u postmenopauzi bez KVB. Ukupno je uključeno 150 zdravih žena u postmenopauzi. Rizik od KVB je definisan prema koncentraciji visokosenzitivnog C-reaktivnog proteina (hsCRP) (hsCRP < 1 mg/L definiše nizak rizik, a hsCRP ≥ 1 mg/L definiše srednji i visoki rizik). GGT/HDL-c je bio nezavisno povezan sa srednjim i visokim rizikom od KVB kod žena u postmenopauzi. S povećanjem ovog enzimskog/lipidnog indeksa za 1 jedinicu, verovatnoća srednjeg i visokog rizika od KVB porasla je za 10,3% (OR = 1,103, p = 0,024). Odnos GGT/HDL-c je nezavisno povezan sa većim rizikom od KVB, merenim pomoću hsCRP kod žena u postmenopauzi. Ovaj isplativ, lako merljiv i široko dostupan indeks mogao bi se koristiti u svakodnevnoj kliničkoj praksi za procenu rizika od KVB kod žena u postmenopauzi.

Ključne reči: kardiovaskularni rizik, gama-glutamil transferaza, lipoproteini, postmenopauza