European Review for Medical and Pharmacological Sciences 2020; 24: 10126-10133

Total oxidant status and oxidative stress index as indicators of increased Reynolds risk score in postmenopausal women

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Abstract. – OBJECTIVE: Considering the knowledge gap between underlying pathophysiological mechanisms of oxidative stress and increased cardiovascular risk, the present study aimed to examine the potential relationship between total oxidant status (TOS), total antioxidant status (TAS) and oxidative stress index (OSI) and the Reynolds Risk Score (RRS) in the cohort of postmenopausal women.

PATIENTS AND METHODS: A total of 126 postmenopausal women participated in this cross-sectional study. Blood pressure, anthropometric and biochemical markers were determined. OSI was calculated as the TOS/TAS ratio. Associations of biochemical parameters with RRS were tested using univariable and multivariable logistic ordinal regression analysis.

RESULTS: TOS and OSI were the highest in women in high RRS category compared to moderate and low risk ones (p<0.001, for both). There was no difference in TAS level across RRS categories (p=0.370). Multivariable ordinal regression analysis showed independent association of TOS and OSI with RRS when tested with other clinical variables [OR=2.45; 95% CI (1.08-5.53); p=0.031 and OR=2.84; 95% CI (1.27-6.36); p=0.011, respectively].

CONCLUSIONS: TOS and OSI are associated with the RRS in the cohort of postmenopausal women. Longitudinal studies are needed to confirm whether adding the TOS and OSI to the standard RRS algorithm could improve its potential to predict cardiovascular event.

Key Words:
Oxidative stress, Total oxidant status, Total antioxidant status, Cardiovascular risk.

Introduction

Despite the fact that cardiovascular diseases (CVDs) still represent the common cause of death in both genders[1] much more studies have been conducted in men than in women, so far[2]. This can often lead to late diagnosis, misdiagnosis, undertreatment or inadequate treatment in female population, especially in women whose reproductive period is over[3]. Women who experience menopause, apart from changes in body fat distribution, accompanied with typically re-distribution of adipose tissue toward abdominal region, exhibit many other metabolic disturbances[4]. Not only lipid and hormonal profile shift to unfavorable ones, but diminished insulin sensitivity, increased low-grade inflammation and oxidative stress (OS) are often reported in that period[4,5]. Accordingly, in parallel with these changes cardiovascular risk increases. It is higher in postmenopausal than that in premenopausal period, and equal or even higher in women in that period than in men[3]. Therefore, coping strategies with the CVD in any cohort start with the recognition of CVD risk and its reduction. Having all these concerns in mind, it is crucial to develop the best approach to the mentioned population in order to evaluate CVD risk and to distinguish those women who have higher burden to be adequately treated. Many easily-obtained CVD risk scores were proposed[6-8]. Among them, Framingham Risk Score (FRS) and Reynolds Risk Score (RRS) are the best validated ones and have been included in the treatment guidelines. Although both these CVD risk scores have been widely established, the RRS showed its superiority over FRS in many studies[6,7] and proved to be a strong predictor of CVD events. This is partly due to implementation of the inflammation level [i.e., determined as high sensitivity C-reactive protein (hsCRP)] in the overall scoring algorithm, since inflammation markers highly correlate with endothelial disfunction[9,10]. However, there is still space for the evaluation of some novel biomark-

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ers that can add significant contribution to RRS scoring system and risk stratification. This is especially the case with OS as the major underlying pathophysiological feature of the broad spectrum of cardiometabolic disorders[11-15].

Representing the imbalance between pro-oxidants [i.e., reactive oxygen/nitrogen species (ROS/RNS)] and antioxidants in favor of pro-oxidants, OS is regarded as a trigger in many signaling pathways that precede inflammation, vasoconstriction, platelet aggregation and endothelial dysfunction[16,17]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, nitric oxide synthase (NOS) and xanthine oxidase (XO) are enzymes that produce ROS/RNS in a variety of pathophysiological processes[16]. However, ROS/RNS molecules express high reactivity and short half-life, which limits their measurement[16]. Therefore, it is of the utmost importance to promptly identify their secondary products, before the occurrence of advanced irreversible cell damages.

OS occurs and progresses from either a decrease in an antioxidant defense system and/or an increase in ROS/RNS generation. Therefore, it is more convenient that the evaluation of OS includes determination of not only secondary products of ROS/RNS, but also antioxidant status simultaneously[18]. Hence, total oxidant status (TOS) and total antioxidant status (TAS) are parameters that have been recently studied in several chronic diseases[19-21] involved with OS. While TOS represents the measure of the overall pro-oxidant state, the TAS reflects the overall antioxidant state[22,23]. Their ratio (i.e., TOS/TAS), the so-called oxidative stress index (OSI), is regarded as a comprehensive marker that reflects the overall OS[21].

However, there is still a knowledge gap between underlying pathophysiological mechanisms of OS and increased CVD risk. As far as we are aware, there are no studies that examined the effect of TOS, TAS and OSI on RRS. In order to overcome these inquiries, we aimed to further explore this issue and to evaluate the potential relationship between these mentioned OS markers and RRS in the cohort of postmenopausal women.

Patients and Methods

Patients

A total of 126 postmenopausal women were included consecutively during their visit to Primary Health Care Center, after the Institutional Ethics Committee approved the Research Protocol. The study was conducted according to Ethical principles of Helsinki Medical Declaration and Good Clinical Practice. Each woman has completed questionnaire which included inquiries about demographic data, illnesses, history of parental coronary heart disease/stroke, drugs use, smoking habits, alcohol consumption.

Women that self-reported absence of menstrual bleeding for more than 1 year were considered to be postmenopausal. Other inclusion criterion was voluntary and signed informed consent to participate in the research. Women that were premenopausal or reported irregular menstrual bleeding for less than 1 year, that used hormone replacement therapy, antioxidant supplements, with a history of CVD, stroke, malignancies, ethanol consumption >20 g/day, or acute or chronic inflammatory diseases other than type 2 diabetes were excluded from the study. Additionally, women with hsCRP equal or higher than 10.0 mg/L were also excluded from the further research.

Methods

Blood pressure and anthropometric data were obtained from each participant, as previously described[5]. Venipuncture for laboratory testing was performed in the morning, after an overnight fast of at least 8 hours. About 10 mL of venous blood were collected in tubes with K_2EDTA and in tubes with serum separator and clot activator. The samples in the latter ones were centrifuged after being left to clot for 30 minutes, as described elsewhere[11]. Routine biochemical parameters [i.e., lipid parameters, glucose, urea, uric acid, liver enzymes, total bilirubin, hsCRP and glycated haemoglobin (HbA1c)] were determined on Roche Cobas c501 chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Measurement of TAS and TOS were performed spectrophotometrically by using o-dianisidine[23] and an ABTS as a chromogen[22], respectively. The key components of serum TOS are lipid hydroperoxide and H_2O_2[22], whereas the main components of TAS are vitamin C and thiol groups[23]. Also, a variety of other biomolecules in serum (urea, creatinine, bilirubin, uric acid, vitamin E, reduced glutathione, lipoic acid, b-carotene, proteins, etc.) display antioxidant properties making the measurement of TAS as a reliable tool for determination of total antioxidative status[20].

OSI was calculated as follows: OSI (arbitrary unit) = TOS (μmol H_2O_2 equivalent/L)/TAS (μmol Trolox equivalent /L) × 100[21].

The RRS was determined according to proposed algorithm of Ridker at al[6] who involved a total of 16,000 initially CVD-free women ≥45 years old in the Women's Health Study and followed them for 10 years. Accordingly, assessment of a10-year CVD includes age, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), systolic blood pressure (SBP), HbA1c (for those patients with diabetes), smoking, hsCRP, family history of premature myocardial infarction/stroke. All women were categorized into low-risk (RRS<5%), moderate-risk (5%≤RRS<10%) and high-risk group (RRS≥10%), respectively[6].

Statistical Analysis

Shapiro-Wilk test was employed for data distribution testing. Continuous data were shown as median and interquartile range (25th percentile-75th percentile) and compared by Kruskal-Wallis test with *post-hoc* Mann-Whitney U tests. Categorical data were presented as relative frequencies and compared by Chi-square test for contingency tables. Correlation between RRS and other demographic and biochemical data were tested with Spearman's correlation analysis. Data from that analysis were given as correlation coefficient (ρ).

Univariable ordinal regression analysis was performed to determine possible associations of TOS and OSI levels with RRS categories. Dependent variable RRS was defined as 0-low, 1-moderate, 2-high risk. TOS levels which corresponded to the fourth quartile of distribution in low-risk postmenopausal women were used as a cut-off to classify participants, as follows: less than 8.45 μmol/L as 0 and equal or higher than 8.45 μmol/L as 1. Also, OSI levels which corresponded to the fourth quartile of distribution in low-risk postmenopausal women were used as a cut-off to classify participants, as follows: less than 0.78 as 0 and equal or higher than 0.78 as 1. Multivariable ordinal regression model was used to test possible independent associations of TOS and OSI with RRS. Covariates significantly correlated with RRS in Spearman's correlation analysis but were not used for RRS calculation entered the models. In multivariable ordinal regression analysis, there was no multicollinearity between covariates and also all of them had an identical effect at each cumulative split of the ordinal dependent variable (RRS categories). In addition, we calculated the additive effects of obesity [i.e., body mass index (BMI)] and oxidative stress (i.e., TOS or OSI) on risk for cardiovascular event presented as RRS. Obese patients (i.e., BMI ≥30 kg/m^2) with TOS or OSI values higher than 75th percentile of their distribution were coded as 1. Those with BMI <30 kg/m^2 and with TOS or OSI less than 75th percentile of their distribution were coded as 0. Data from ordinal regression analyses were given as odds ratio (OR) and 95% confidence intervals (CIs). The variation in RRS was explained by Nagelkerke R^2. Significance was set at the probability level of 0.05. All the calculations were performed using IBM® SPSS® Statistics version 22 software (SPSS Inc., IBM, Armonk, NY, USA).

Results

According to the Table I, the youngest postmenopausal women were in group with low cardiovascular risk. Postmenopausal women with high risk had higher BMI, waist circumference (WC) and longer diabetes duration compared to women with low and moderate risk. Hip circumferences were lower in low-risk compared to high-risk postmenopausal women. Women with RRS ≥10% had higher SBP than those with low risk. Unequal number of menopausal women using antihyperglycemic, insulin and antihypertensive therapies were distributed in risk groups. Glucose, HbA1c, triglycerides (TG), uric acid, TOS and OSI were the highest in women with high cardiovascular risk compared to moderate-risk and low-risk group. However, HDL-c were the lowest in high-risk women. Total bilirubin was lower in high-risk compared to low-risk group. Women in low-risk group had the lowest urea concentration. Gamma-glutamyl transferase (GGT) activity was higher in women with moderate risk compared to those with low risk (Table II). Higher RRS was in positive correlation with older age, BMI, WC, hips circumference, SBP, glucose, HbA1c, TG, hsCRP, uric acid, urea, GGT, TOS and OSI. On the other side, lower RRS correlated significantly with higher HDL-c and total bilirubin (Table III). Ordinal regression analysis was used to examine independent associations of TOS and OSI with RRS. Both, TOS and OSI showed significant ORs for RRS categories in univariable analysis (OR=4.60, p<0.001 and OR=4.48, p<0.001, respectively) (Table IV). Nagelkerke R^2 for TOS

Table I. Basic demographic characteristics of postmenopausal women according to Reynolds risk score.

	RRS < 5% N = 55	5% ≤ RRS < 10% N = 28	RRS ≥ 10% N = 43	p**
Age, years	58 (54-61)	65 (60-70)[a†]	69 (64-75)[a†]	< 0.001
BMI, kg/m^2	27.9 (24.7-31.1)	27.0 (25.9-30.5)	30.8 (27.4-32.9)[a*,b*]	0.036
WC, cm	93 (85-99)	94 (89-98)	101 (97-110)[a#,b#]	0.006
Hips circumference, cm	106 (102-112)	108 (104-112)	110 (106-116)[a*]	0.006
SBP, mmHg	136 (126-146)	128 (119-141)	137 (127-152)[b*]	0.044
DBP, mmHg	85 (77-92)	81 (75-86)	86 (78-96)	0.166
Diabetes, %	5	32	70	< 0.001
Duration of diabetes, years	0 (0-0)	0 (0-1)[a#]	2 (0-6.5)[a†,b#]	< 0.001
Smokers, %	10	28	23	0.105
Family history of CVD, %	0	7.1	9.3	0.073
Antihyperglycemics, %	3	28	86	< 0.001
Insulin therapy, %	0	14	21	0.002
Hypolipidemics, %	36	25	42	0.347
Antihypertensives, %	47	61	86	< 0.001
-Angiotensin converting enzyme inhibitors, %	73.1	82.3	67.6	
-Calcium channel blockers, %	11.5	11.8	18.9	
-Angiotensin receptor blockers, %	0	0	13.5	
-Beta-blockers, %	15.4	17.6	13.5	
-Thiazide diuretics, %	0	17.6	27.0	

Data are presented as median (interquartile range) and compared by Kruskal-Wallis test with *post hoc* Mann-Whitney test. Categorical data are given as relative frequencies and compared by Chi-square test for contingency tables. ***p* for Kruskal-Wallis test. [a]Significantly different from group of patients with RRS<5%. [b]Significantly different from group of patients with 5% ≤ RRS < 10%. **p*<0.05; [#]*p* <0.01; [†]*p*<0.001.

and OSI levels were 0.161 and 0.154, respectively. Multivariable analysis revealed independent associations of TOS and OSI with RRS when tested with other clinical variables (Table IV, Model 1 and 2). As demonstrated by Model 1 and 2, an increase in TOS or OSI by 1 unit, increased the probability for RRS rise for more than 2 times. Nagelkerke R^2 for TOS was 0.338, which means that regression Model 1 could explain 33.8% variation in calculated RRS and 0.344, which means that Model 2 could explain 34.4% variation in RRS (Table IV).

Table II. Clinical characteristics of postmenopausal women.

	RRS < 5% N = 55	5% ≤ RRS < 10% N = 28	RRS ≥ 10% N = 43	p**
Glucose, mmol/L	5.6 (5.2-6.1)	5.7 (5.5-6.7)	7.5 (6.1-8.6)[a†,b#]	< 0.001
HbA1c, %	5.5 (5.1-5.8)	5.7 (5.4-6.1)[a*]	6.8 (6.0-7.2)[a†,b†]	< 0.001
TC, mmol/L	6.0 (5.1-6.7)	6.2 (5.1-7.2)	6.4 (5.3-7.2)	0.610
HDL-c, mmol/L	1.6 (1.4-1.9)	1.5 (1.1-1.7)	1.2 (1.1-1.3)[a†,b#]	< 0.001
LDL-c, mmol/L	3.5 (2.8-4.2)	3.7 (2.7-5.0)	4.0 (2.9-4.8)	0.473
TG, mmol/L	1.4 (1.1-2.2)	2.0 (1.2-2.4)	2.4 (1.9-3.3)[a†,b*]	< 0.001
hsCRP, mg/L	1.0 (0.5-2.5)	1.5 (0.7-2.3)	1.4 (0.8-3.1)	0.152
Total bilirubin, µmol/L	8.6 (6.6-10.4)	7.6 (6.9-9.8)	7.1 (5.4-9.1)a*	0.052
Uric acid, µmol/L	249 (221-305)	257 (225-281)	295(245-394)[a#,b#]	< 0.001
Urea, mmol/L	5.2 (4.4-6.2)	5.7 (5.4-7.0)[a#]	5.6 (4.9-7.5)[a*]	0.014
AST, U/L	19 (17-22)	21 (16-25)	20 (17-23)	0.504
ALT, U/L	18 (13-24)	18 (16-26)	21 (15-26)	0.273
GGT, U/L	14 (10-21)	18 (14-25)[a*]	16 (11-22)	0.034
TOS, µmol/L H_2O_2 equivalent/L	5.6 (3.5-8.4)	5.6 (3.8-13)	10.6 (7.3-18.6)[a†,b*]	< 0.001
TAS, µmol/L Trolox equivalent/L	1178 (1084-1249)	1157 (1038-1257)	1193 (1095-1334)	0.370
OSI, arbitrary unit	0.5 (0.3-0.8)	0.5 (0.3-1.2)	0.9 (0.6-1.4)[a†,b*]	< 0.001

Data are presented as median (interquartile range) and compared by Kruskal-Wallis test with *post hoc* Mann-Whitney test. ***p* for Kruskal-Wallis test. [a]Significantly different from group of patients with RRS < 5%. [b]Significantly different from group of patients with 5% ≤ RRS < 10%. **p*<0.05; [#]*p*<0.01; [†]*p*<0.001.

Table III. Correlation coefficients of RRS with other tested markers.

	ρ	*p*
Age, years	0.616	< 0.001
BMI, kg/m^2	0.286	0.001
WC, cm	0.323	< 0.001
Hips circumference, cm	0.278	0.002
SBP, mmHg	0.176	0.049
DBP, mmHg	0.129	0.151
Glucose, mmol/L	0.532	< 0.001
HbA1c, %	0.647	< 0.001
TC, mmol/L	0.080	0.372
HDL-c, mmol/L	-0.521	< 0.001
LDL-c, mmol/L	0.102	0.254
TG, mmol/L	0.432	< 0.001
hsCRP, mg/L	0.260	0.003
Total bilirubin, µmol/L	-0.228	0.010
Uric acid, µmol/L	0.280	0.001
Urea, mmol/L	0.220	0.013
AST, U/L	0.005	0.955
ALT, U/L	0.106	0.236
GGT, U/L	0.226	0.011
TOS, µmol/L H_2O_2 equivalent/L	0.400	< 0.001
TAS, µmol/L Trolox equivalent/L	0.146	0.104
OSI, arbitrary unit	0.363	< 0.001

Due to high Spearman's correlation significance between BMI, TOS and OSI with RRS (Table III) and the fact that obesity and oxidative stress do not enter RRS calculation, additive effects of TOS and BMI, as well as OSI and BMI on RRS were analyzed. Beside its independent associations with TOS and RRS, TOS levels higher than 75th percentile of low-risk women distribution in mutual effects with obesity increased the probability for higher RRS [OR=8.25; 95% CI (3.16-21.54); p<0.001, R^2=0.264]. As well, OSI levels higher than 75th percentile of low-risk women distribution together with obesity increased the probability for higher RRS [OR= 8.41; 95% CI (3.13-22.64); p<0.001, R^2=0.262].

Discussion

As far as we are aware, this is the first study that investigated the relationship between TAS, TOS and OSI with CVD risk (as determined by RRS). In line with this, we have shown that TOS and OSI independently and positively correlated with the RRS in the cohort of postmenopausal women.

A few recent studies[18,19,21,24] also explored the ratio between the overall pro-oxidant and anti-oxidant status by using different OS markers and anti-oxidants, in various diseases. Nsonwu-Anyanwu et al[24] reported higher OSI, measured as the ratio of total plasma peroxide levels (TPP), as a marker of lipid peroxidation and total antioxidant capacity (TAC), in patients with type 2 diabetes, relative to controls. Seyedsadjadi et al[18] demonstrated an inverse association between the ratio of plasma TAC and lipid hydroperoxide levels (HPX), and the FRS in both genders, confirming that TAC/HPX is a more reliable measure of redox status than measuring either HPX or TAC alone.

Lower levels of TAS were reported in many diseases[20,21]. Brunelli et al[25] reported strong association between lower antioxidant capacity and CVD risk factors in a cohort comprised of healthy individuals. However, we did not report any difference in TAS across CVD risk categories of examined women. Our results are in accordance with that of Kucukaydın et al[26] who

Table IV. Estimated odds ratios after ordinal regression analysis with RRS as dependent variable.

	Unadjusted		
	OR (95% CI)	*p*	Nagelkere R^2
TOS	4.60 (2.29-9.30)	< 0.001	0.161
OSI	4.48 (2.21-9.03)	< 0.001	0.154
	Adjusted		
Model	OR (95% CI)	*p*	Nagelkere R^2
TOS	2.45 (1.08-5.53)	0.031	0.338
OSI	2.84 (1.27-6.36)	0.011	0.344

Model TOS or OSI (given as categorical variables) and continuous variables: BMI, uric acid, total bilirubin, TG and GGT.

also reported higher plasma TOS levels in women with polycystic ovary syndrome, but found no difference in TAS levels, as compared to controls. On the contrary, Čolak et al[27] demonstrated surprisingly increased TAS in the group of adolescents with increased CVD risk compared to the controls. Our results, showing no difference in TAS level across CVD risk groups, might be attributed to the antioxidant properties of medications that majority of our postmenopausal women used (i.e., angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, statins and metformin)[28,29]. Moreover, various other factors might influence the TAS, such as diminished synthesis of enzymatic antioxidants; an increased utilization of antioxidant as an attempt to cope with deleterious effects of increased ROS/RNS production; as well as decreased intake of antioxidants[16,25].

Having in mind that there is a broad spectrum of antioxidants and that they act in synergic and fine-tuned manner, measurement of the activity of each one alone is complex and time consuming and might not represent the overall pathophysiological state. Therefore, TAS may be an early sign of modification of biomolecules and a reliable indicator of the overall antioxidant imbalance[21].

Another important finding in our study is the reported additive effect of obesity and OS on RRS. Namely, due to the fact that several risk factors often co-exist and can generate the mutual impact on endothelial dysfunction[29] we have explored the additive effects of obesity and OS on CVD risk. Accordingly, women with BMI $\geq$30 kg/m^2 who presented TOS levels higher than 75th percentile (i.e., $\geq$8.45 μmol/L) of low-risk distribution increased the probability for higher RRS (OR=8.25; p<0.001). In addition, women with BMI $\geq$30 kg/m^2 who presented OSI levels higher than 75th percentile (i.e., $\geq$0.78) of low-risk distribution increased the probability for higher RRS (OR= 8.41; p<0.001).

It is assumed that OS and inflammation may be the important link between obesity and endothelial dysfunction[15,29,30]. In our recent study[31] we demonstrated that increased BMI independently correlated with high XO activity in overweight/obese population. Moreover, XO controls the vascular tone by influencing the bioavailability of nitric oxide (NO), which might in part explain the link between XO and CVD pathogenesis[16]. Furthermore, we have also previously shown that obesity indices (e.g., BMI or WC) were independently associated with the increased CVD risk, both in young[32,33] and adult population[34,35]. Adipose tissue, particularly visceral one, appears to be significant source of pro-oxidant and pro-inflammatory species and concomitant reduction in antioxidant enzymes[5,31,36]. Increased secretion of adipokines and pro-inflammatory cytokines, such as interleukine-6 and tumor necrosis factor-alpha, may have an impact on insulin signaling pathways, thus leading to consequent insulin resistant state. Insulin resistance promotes increased lipolysis of TG in adipose tissue. Associated excess of free fatty acids flow to the liver and enhanced oxidative phosphorylation, leading to a rise in ROS/RNS production and liver fat peroxidation, increased lipogenesis, and promotion of atherogenic dyslipidemia[17]. The latter includes change in HDL composition and its increased clearance, increased synthesis of small dense low-density lipoproteins (sdLDL), as well as increased oxidation of LDL particles. Moreover, hyperinsulinemia promotes increased glucose autoxidation and production of advanced glycation end products, thus further leading to increased ROS and consequently increased CVD risk[17,28].

In addition, ROS/RNS diminishes the activity of endothelial NOS, with concomitant reduction in NO synthesis, causing vasoconstriction[16]. ROS further aggravate endothelial inflammation, by stimulating the secretion of pro-inflammatory cytokines. The latter ones promote the upregulation of expression of adhesion molecules, as well as monocytes/macrophages migration. All these complex mechanisms previously mentioned, along with injury of glycocalyx, increased endothelial permeability and stiffness, and increased platelet aggregation are the first signs of endothelial dysfunction that precede atherosclerotic plaque formation[17,29].

We demonstrated for the first time the evaluation of overall redox balance in relation to RRS in the cohort of postmenopausal women. Moreover, we examined the additive effect of obesity and OS on RRS, since the co-existence of both risk factors can produce the additive influence on endothelial dysfunction. Indeed, our results confirmed that increase in TOS or OSI by 1 unit, increased the probability for higher RRS for more than 2 times. However, when the additive effect of obesity is included, the probability for higher RRS raises for more than 8 times. The limitations of our study are in its cross-sectional design and the inability to exclude the medications use in some patients which may represent a source of

bias when examining the OS status in this cohort. Prospective studies are needed to confirm if adding the OSI to the standard RRS could improve its potential to predict cardiovascular event.

Conclusions

A non-invasive, cost-effective and comprehensive marker of the ratio between the overall oxidative stress and the antioxidant status, such as TOS/TAS ratio was independently associated with increased CVD risk (determined with RRS) in postmenopausal women. Longitudinal studies are warranted to confirm whether adding the OSI, as a measurement of redox balance to the standard RRS could improve its potential to predict cardiovascular event. If so, it would enable to evaluate the reliability of new target treatment therapy based on decreasing the OS, and concomitantly lowering CVD risk.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

This work was financially supported in part by a grant from the Ministry of Science, Montenegro and the Ministry of Education, Science and Technological Development, Republic of Serbia (project number 451-03-68/2020-14/200161).

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