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ORIGINAL ARTICLE

Body mass index is independently associated with xanthine oxidase activity in overweight/obese population

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Abstract

Purpose The pathophysiological mechanism of the relationship between xanthine oxidase (XO) activity and obesity has not been completely elucidated. Since inflammation and oxidative stress are regarded as key determinants of enlarged adipose tissue, we aimed to investigate the association between oxidative stress (as measured with XO activity), inflammation [as measured with high-sensitivity C-reactive protein (hsCRP)] and obesity [as measured with body mass index (BMI)]. In addition, we wanted to examine whether hsCRP itself plays an independent role in XO activity increase or it is only mediated through obesity.

Methods A total of 118 overweight/obese volunteers (mean age 54.76 ± 15.13 years) were included in the current cross-sectional study. Anthropometric, biochemical parameters, and blood pressure were obtained.

Results Significant differences between age, BMI, waist circumference, concentrations of uric acid and hsCRP, as well as xanthine dehydrogenase (XDH) activities were evident among XO tertile groups. Multiple linear regression analysis revealed that BMI (beta = 0.241, $p = 0.012$) and XDH (beta = − 0.489, $p < 0.001$) are the independent predictors of XO activity (R^2-adjusted = 0.333), whereas hsCRP lost its independent role in XO activity prediction.

Conclusion Obesity (as determined with increased BMI) is an independent predictor of high XO activity in overweight/obese population.

Level of Evidence Level V: cross-sectional descriptive study.

Keywords Inflammation · Obesity · Oxidative stress · Xanthine oxidase

Introduction

It is well known that increased oxidative stress and inflammation are the major underlying features of obese state, and consequently obesity-related disorders [1–6].

For that reason, many biomarkers of oxidative stress and inflammation have been widely explored so far, searching for the best therapeutical target approach for such cardiometabolic disorders [7–10].

The enzyme xanthine oxidase (XO) has been gaining a lot of attention recently, especially concerning the beneficial role of XO inhibitors in cardiometabolic diseases [11]. This enzyme is an oxidant form of xanthine oxidoreductase (XOD), which converts purine bases to uric acid [12]. Under normal physiological conditions XOD predominates in the form of xanthine dehydrogenase (XDH). However, in the state of hypoxia, when antioxidant defense system can no longer cope with increased free radical production, increased oxidative stress occurs [12] and XOD converts into XO, which is regarded as the main source of reactive oxygen species liberation in circulation [13]. These processes might explain the increased XO activity in inflammatory states such as familial hypercholesterolemia [14], metabolic syndrome [15], and cardiovascular disease (CVD) [11]. In addition, several recent studies, although in a small sample size, have confirmed the influence of obesity on increased

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activity of this enzyme [15–17]. However, the pathophysiological mechanism on the relationship between XO activity and obesity has not been completely elucidated. Importantly, inconsistent results concerning the independent relationship between some inflammation biomarkers and XO activity have been demonstrated so far [14, 15, 18].

Since inflammation and oxidative stress are regarded as the key determinants of enlarged adipose tissue, we aimed to investigate the association between oxidative stress (as measured with XO activity), inflammation [as measured with high-sensitivity C-reactive protein (hsCRP)] and obesity [as measured with body mass index (BMI)]. In addition, we wanted to examine whether hsCRP itself plays an independent role in XO activity increase or it is only mediated through obesity.

Subjects and methods

Study population

A total of 118 overweight/obese volunteers (mean age 54.76 ± 15.13 years) were recruited in the Center for Laboratory Diagnostics of the Primary Health Care Center in Podgorica, Montenegro, for their regular biochemical analyses check-up in a period from October 2015 to May 2016. Clinical examinations and medical history for each participant were carried out on the same day.

Participants that were eligible to enter the study met the inclusion criteria: overweight/obese otherwise healthy volunteers, that had not used any medicament therapy in the last 6 months. Subjects with $25 \leq BMI < 30$ and $BMI \geq 30$ kg/m^2, were regarded as overweight and obese, respectively.

Exclusion criteria were: normal weight or underweight participants (i.e., $18.5 \leq BMI < 25$ kg/m^2, $BMI < 18.5$ kg/m^2, respectively), acute inflammatory disease, hsCRP > 10 mg/L, diabetes mellitus, liver disease other than steatosis, gout, ethanol consumption > 20 g/day, pregnancy, malignant diseases, as well as unwillingness to enter the study.

All procedures performed in the current study involving overweight/obese subjects were in accordance with the ethical standards of the Research Committee of Primary Health Care Center in Podgorica, Montenegro which approved the research protocol, and with the 1964 Helsinki Declaration and its later amendments. All the participants included in this examination provided written informed consent.

We have selected exclusively overweight/obese population, since it is well known that this group is at increased cardiometabolic risk compared to normal weight individuals [1, 2]. In addition, enlarged adipose tissue in overweight/obese individuals is characterized with increased reactive oxygen species production, as well as with increased inflammation level through enhanced secretion of pro-inflammatory adipocytokines, compared with adipose tissue in normal-weight individuals [1, 2]. Therefore, we aimed to examine if BMI influences XO activity, to come up with better targeted treatment for this vulnerable group.

Aiming to get better insight into the relationship between obesity and inflammation with XO, participants were grouped into the three tertile groups according to the levels of XO activity (i.e., < 122.50, 122.51–144.55, and > 144.56 U/L, respectively).

Anthropometric measurements

Basic anthropometric measurements [i.e., body weight, body height, waist circumference (WC) and BMI], as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained, as described elsewhere [6].

Biochemical analyses

Biochemical analyses were performed after an over-night fasting of at least 8 h. Cubital venous blood sample was collected from each participant. The blood samples were taken between 7 and 9 o'clock a.m. Samples were left to clot for 30 min and then centrifuged at 3000 rpm for 10 min. Fasting glucose and lipid parameters were measured immediately, and other aliquots of serum were frozen until the analyses. In addition, a whole blood in K_2EDTA was used for determination of glycated hemoglobin (HbA1c).

Serum malondialdehyde (MDA) level and catalase (CAT), XOD, and XO activity were measured spectrophotometrically, as described previously [8, 13]. The determination of XOD and XO in serum was based on the liberation of uric acid using xanthine as substrate in the presence of NADH (for XOD) or absence of NADH (for XO) when only molecular oxygen was electron acceptor. The XDH activity was calculated by subtracting XO activity from XOD activity [13], and the results in XOD, XO and XDH, respectively, were expressed in U/L.

Lipid parameters [e.g., total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG)], glucose, creatinine, uric acid, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), were measured using standardized enzymatic procedure, while HbA1c was measured with immunoturbidimetric assay (Roche Cobas 400, Mannheim, Germany). HsCRP levels were measured nephelometrically (Behring Nephelometer Analyzer, BN II, Marburg, Germany).

Statistical analysis

Continuous variables with normal Gaussian distribution were expressed as arithmetic mean ± standard deviation. In

the case of non-Gaussian distribution, logarithmic transformation of data was carried out to reach normality and those data were expressed as geometrical mean (95% confidence interval). If Gaussian distribution was not accomplished after logarithmic transformation, data were expressed as median (interquartile range). Categorical data are presented as absolute frequencies. Comparisons of continuous parameters were performed using the ANOVA with Bonferroni post hoc test (for normally or log-normally distributed data) and Kruskal–Wallis with post hoc test (for skewed distributed data). Differences between categorical variables were tested by Chi-square test. To assess the correlation between clinical parameters, bivariate Spearman's correlation analysis was executed. Data are presented as Spearman's correlation coefficient (ρ). If p values for Spearman's ρ correlation coefficient had been <0.10, those variables (confounders) with normal and log-normal distribution were included in multiple linear regression analysis. Multiple linear regression analysis was performed to estimate the independent contributions of clinical parameters on XO activity. The F-ratio of ANOVA test in multiple linear regression analysis was used to determine whether the overall regression model is good fit of data. Multicollinearity between independent variables was also tested. A $p<0.05$ was set as statistical significant. Statistical analyses were carried out using PASW® Statistic version 18 (Chicago, Illinois, USA).

Results

The basic demographic characteristics according to XO tertiles are summarized in Table 1. There were significant differences in age, BMI and WC between XO activity tertile groups. Participants in the third XO tertile group were older than those in the first one ($p<0.05$). BMI of participants in the third tertile group was significantly higher than those in the first ($p<0.01$) and the second XO activity tertile group ($p<0.05$). In addition, participants in the third XO activity tertile group had significantly higher WC than those in the first ($p<0.05$) and the second XO tertile group ($p<0.05$). There were no significant differences in SBP and DBP between XO activity tertile groups. Chi-square analysis demonstrated equal distribution of both, gender ($p=0.094$) and smoking habits ($p=0.416$) in each of the XO activity tertile groups.

Significantly different concentrations of uric acid and hsCRP, as well as XDH activities were evident among XO activity tertile groups (Table 2). Uric acid concentration washigher in the third than in the second XO tertile group ($p<0.05$) and those tertile groups were not significantly different from the first XO tertile group. HsCRP concentration was higher in the third than in the first and the second XO tertile group ($p<0.01$ for both). Opposite to this, XDH activities were lower in the third than in the first and

Table 1 Basic demographic characteristics of examined population according to XO activity tertiles

	First XO activity tertile (≤ 122.50 U/L)	Second XO activity tertile (122.51–144.55 U/L)	Third XO activity tertile (≥ 144.56 U/L)	*p*
N (male/female)	42 (18/24)	38 (8/30)	38 (15/23)	0.094
Age, years	50.10 ± 16.21	55.08 ± 14.56	59.61 ± 13.08[a]*	0.018
BMI, kg/m^2	26.70 ± 4.84	27.68 ± 5.57	30.41 ± 4.47[a]**,[b]*	0.004
WC, cm[c]	94.50 (86.50–107.00)	97.00 (91.00–104.00)	103.00 (97.00–111.00)[d]*,[e]*	0.005
SBP, mmHg[c]	134 (127–141)	135 (129–145)	140 (130–146)	0.243
DBP, mmHg[c]	78 (70–83)	76 (70–84)	80 (73–85)	0.388
Smoking habits, (smoker/non-smoker)	31/11	26/12	31/7	0.416

Data are presented as arithmetic mean ± SD and compared by one-way ANOVA

Categorical variables are presented as absolute frequencies and compared by Chi-square test for contingency tables

BMI body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *XO* xanthine oxidase

[a]Significantly different from the first XO tertile using post hoc Bonferroni test

[b]Significantly different from the second XO tertile using post hoc Bonferroni test

[c]Skewed distributed data are presented as median (interquartile range) and compared by Kruskal–Wallis test

[d]Significantly different from the first group using Kruskal–Wallis post hoc test

[e]Significantly different from the second group using Kruskal–Wallis post hoc test

*$p<0.05$; ** $p<0.01$

Table 2 Laboratory and clinical parameters of examined population according to XO activity tertiles

	First XO activity tertile (≤ 122.50 U/L)	Second XO activity tertile (122.51–144.55 U/L)	Third XO activity tertile (≥ 144.56 U/L)	*p*
TC, mmol/L	5.28 ± 1.23	5.84 ± 1.31	5.76 ± 1.18	0.101
HDL-c, mmol/L	1.47 ± 0.46	1.51 ± 0.42	1.34 ± 0.37	0.206
LDL-c, mmol/L[a]	2.92 (2.61–3.26)	3.44 (3.10–3.82)	3.45 (3.13–3.80)	0.091
TG, mmol/L[a]	1.50 (1.26–1.77)	1.45 (1.26–1.68)	1.64 (1.43–1.88)	0.513
Glucose, mmol/L[b]	5.20 (4.90–6.10)	5.40 (5.00–6.00)	5.60 (5.20–6.10)	0.239
HBA1c, %	5.05 ± 0.67	5.08 ± 0.55	5.31 ± 0.47	0.090
AST, U/L[b]	20 (17–24)	20 (17–22)	20 (18–24)	0.700
ALT, U/L[b]	21 (16–27)	20 (14–27)	22 (16–28)	0.580
GGT, U/L[b]	15 (12–30)	16 (12–19)	15 (12–24)	0.710
Total bilirubin, µmol/L[b]	7.90 (5.90–10.00)	6.35 (5.60–9.90)	6.65 (5.10–8.70)	0.535
Creatinine, µmol/L[b]	69.50 (60.00–81.00)	63.00 (56.00–75.00)	70.00 (63.00–82.00)	0.058
Uric acid, µmol/L	278.43 ± 67.10	265.32 ± 72.38	312.47 ± 81.97[c]*	0.018
HsCRP, mg/L[a]	1.17 (0.88–1.54)	1.23 (0.92–1.66)	2.50 (1.96–3.20)[c]**,[d]**	< 0.001
XOD, U/L	328.94 ± 72.40	343.77 ± 64.69	338.16 ± 73.69	0.636
XO, U/L[a]	92.70 (82.96–103.58)	132.36 (130.44–134.75)	186.32 (175.14–198.22)	< 0.001
XDH, U/L	231.70 ± 81.07	210.89 ± 63.25	148.35 ± 75.86 [c]**,[d]**	< 0.001
MDA, µmol/L	50.63 ± 7.45	53.59 ± 8.02	52.83 ± 9.28	0.249
CAT, U/L	82.41 ± 40.58	62.08 ± 38.48	67.41 ± 49.34	0.092

Data are presented as arithmetic mean ± SD and compared by one-way ANOVA

TC total cholesterol, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *TG* triglycerides, *HbA1c* glycated hemoglobin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *HsCRP* high-sensitivity C-reactive protein *XOD* xanthine oxidoreductase, *XO* xanthine oxidase, *XDH* xanthine dehydrogenase, *MDA* malondialdehyde, *CAT* catalase

[a]Log-normal distributed data are presented as geometric mean (95% CI) and compared by one-way ANOVA after logarithmic transformation

[b]Skewed distributed data are presented as median (interquartile range) and compared by Kruskal–Wallis test

[c]Significantly different from the second XO tertile using post hoc Bonferroni test

[d]Significantly different from the first XO tertile using post hoc Bonferroni test

*$p < 0.05$; ** $p < 0.01$

the second XO tertile group ($p < 0.01$ for both). There were no significant differences in lipid profile and other clinical parameters between tested XO activity tertile groups. In addition, one-way ANOVA showed no significant differences in MDA concentrations and CAT activities between tested groups.

Significant positive correlations were determined between XO activity and age, BMI, hsCRP ($\rho = 0.202$, $p = 0.028$; $\rho = 0.328$, $p < 0.001$ and $\rho = 0.325$, $p < 0.001$). Significant negative correlations between XO activity and XDH, CAT activities ($\rho = -0.447$, $p < 0.001$ and $\rho = -0.190$, $p = 0.039$, respectively) were determined in this group of examinees (Table 3). No significant correlations were determined between XO activity and lipid parameters, HbA1c, XOD and MDA.

In further statistical analysis, we applied multiple linear regression analysis to identify the parameters independently associated with XO activity. Independent normal and log-normal distributed variables that correlated with XO activity in Spearman's correlation analysis with significance of $p < 0.10$ (Table 3) were grouped into the Model. These independent variables statistically significantly predicted XO activity ($F = 10{,}726$, $p < 0.001$). This also demonstrated the Model as a good fit of the data. An adjusted $R^2 = 0.333$ for the Model demonstrated that 33.3% variation in XO activity could be explained by this Model. BMI was independently associated with increase in XO activity ($\beta = 0.241$, $p = 0.012$) and XDH activity was independently associated with decrease in XO activity ($\beta = -0.489$, $p < 0.001$). The multiple regression unstandardized coefficient (B), its standard error (SE), standardized coefficient (β), t value and significance (p) are presented in Table 4.

Discussion

The finding of the current study reveals that increased XO activity is independently associated with BMI in overweight/obese population (Table 4). Our results are in accordance with some previous studies which also found the association

Table 3 Bivariate Spearman's correlation analysis between XO activity and other clinical parameters

	XO, U/L	
	ρ	*p*
Age, years	0.202	0.028
BMI, kg/m^2	0.328	< 0.001
TC, mmol/L	0.104	0.265
HDL-c, mmol/L	− 0.106	0.255
LDL-c, mmol/L	0.161	0.081
TG, mmol/L	0.070	0.454
HbA1c, %	0.105	0.255
Uric acid, µmol/L	0.089	0.363
HsCRP, mg/L	0.325	< 0.001
XOD, U/L	0.071	0.445
XDH, U/L	− 0.447	< 0.001
MDA, µmol/L	0.082	0.377
CAT, U/L	− 0.190	0.039

BMI body mass index, *TC* total cholesterol, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *TG* triglycerides, *HbA1c* glycated hemoglobin, *HsCRP* high-sensitivity C-reactive protein, *XOD* xanthine oxidoreductase, *XO* xanthine oxidase, *XDH* xanthine dehydrogenase, *MDA* malondialdehyde, *CAT* catalase

Table 4 Multiple regression analysis for the association of examined parameters with XO activity

Predictors	Dependent variable XO activity; $F = 10{,}726$, $p < 0.001$, $R^2 = 0.367$, Adjusted $R^2 = 0.333$				
	Unstandardized		Standardized coefficient		
	B	Standard error	*β*	*t*	*p*
Age, years	0.103	0.089	0.097	1.153	0.252
BMI, kg/m^2	0.749	0.292	0.241	2.566	0.012
LDL-c, mmol/L	− 0.015	0.094	− 0.013	− 0.155	0.877
HsCRP, mg/L	0.002	0.038	0.005	0.056	0.955
XDH, U/L	− 0.966	0.157	− 0.489	− 6.145	< 0.001
CAT, U/L	− 0.015	0.030	− 0.040	− 0.503	0.616

BMI body mass index, *LDL-c* low-density lipoprotein cholesterol, *TG* triglycerides, *HsCRP* high-sensitivity C-reactive protein, *XDH* xanthine dehydrogenase, *CAT* catalase

between XO activity and BMI in patients with metabolic syndrome [15] and diabetes [19], explaining the another interesting role of XO, in addition to purine metabolism. Namely it has been reported that XO plays a pivotal role in adipocytes differentiation through regulation of the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) activity [20], which is a determining factor for controlling the development of adipocytes [21]. In line with this, an increased expression and activity of XO was observed in adipose tissue of obese mice, whereas decrease in XO activity was correlated with reduction in fat mass [20].

Indeed, clinical studies also demonstrated increased XO activity even in obese young population, although in smaller sample size than in the current study [16, 17]. Chiney et al. [17] examined 16 normal weight and 9 obese children, whereas Tamm et al. [16] evaluated 22 normal weight and 20 obese children, and in both of these studies obese children displayed higher XO activity than their normal weight counterparts. The activity of XO even correlated with CVD risk factors [16], thus suggesting that increased XO activity may influence on increased cardiovascular risk even at young age. Conversely, reduction in fat mass lead to decreased XO activity [22, 23].

In the current study, we have also shown that subjects in the highest XO activity tertile group had significantly higher WC than those in the lower XO activity tertile groups (Table 1). This is in accordance with previous findings of visceral adipose tissue as significant pro-oxidant and pro-inflammatory milleu with a broad spectrum of increased mediators of inflammation [2, 24] and reactive oxygen species, but low antioxidant defense [6]. In line with this, although no differences were observed in the CAT activity between the three XO activity tertiles groups (Table 2), we demonstrated a negative correlation between XO and CAT (Table 3), showing a tight relationship between increased oxidative stress and decreased antioxidant defense. Similarly, the inverse association between XO and another antioxidant defense enzyme, such as superoxide dismutase was reported in the previous study [15]. In contrast, a significant decrease in XDH activities were observed in the third XO activity tertile group in comparison to the first and second tertile groups. The possible explanation for such finding may lay in the predomination of XOD in the form of XDH under normal physiological conditions, but in the state of hypoxia and increased oxidative stress, when antioxidant defense system can not combat with the increased free reactive oxygen species any more [12], XOD becomes converted into XO at the expense of reducing XDH [13]. Given the increased hypoxia in the obese adipose tissue [25], which leads to further adipose tissue dysfunction, accompanied with increased oxidative stress, our results of increased XO activity parallel with decreased XDH activity are not surprising.

In the current study, we have also shown the increase in hsCRP parallel with the increment in XO activity tertiles (Table 2), and its correlation with XO activity (Table 3). However, this association lost its independence in multiple linear regression analysis (Table 4).

Similarly, Feoli et al. [15], although in a smaller sample size than ours ($n = 17$) showed that XO activity correlated positively with hsCRP. Furthermore, in a study of participants with familial combined hyperlipidemia,

Martinez-Hervas et al. [18] confirmed a relationship between XO activity and hsCRP, but that association was not independent, which is in accordance with the results of our study. However, they reported the independent relationship between XO activity and some other inflammation biomarkers, such as nuclear factor kappa beta (NF-kB) activity and interleukin-6 [18]. On the contrary, Real et al. [14] showed that XO was independently associated with both, hsCPR and NF-kB in patients with familial hypercholesterolemia. The possible explanation for such discrepancies between studies might be explained by different study groups, as well as different sample size of the examined groups. However, this can at least in part explain the important link between obesity and CVD through increased inflammation and oxidative stress, since it has been shown that XO plays a pivotal role in inflammatory states leading to monocyte chemoattractant protein-1 production in macrophages [11]. In addition, increased expression of XO in endothelial cells and production of reactive oxygen species by XO further inactivate nitric oxide, which may be another contributing factor to vascular damage and consequent CVD [11].

The relationship between XO activity and cardiometabolic risk was confirmed by some other studies, as well as that XO inhibition can have beneficial effect on reducing cardiometabolic risk. Namely Kushiyama et al. [26] showed that XO is involved in macrophage foam cell formation and atherosclerosis development, thus suggesting that XO inhibitors may have beneficial role in prevention of CVD. In line with this, El-Bassossy et al. [27] showed that XO inhibition has led to decrease in the low-grade inflammation and oxidative stress associated with insulin resistance through amelioration of hypertriglyceridemia.

On the other hand, Murakami et al. [28] demonstrated that the reduction in XO gene expression in mice enhanced the accumulation of lipids in adipocytes, leading to an increased oxidative stress, and induced obesity with concomitant insulin resistance in older age mice groups. Tsushima et al. [25] also suggested a possible involvement of XO in lipid homeostasis. Even though they reported that adipose tissue in obese mice displayed higher XO activity than those in control group, they speculated that enlarged adipose tissue is accompanied with active fatty acid synthesis, which is closely related to de novo purine synthesis through the activation of the pentose phosphate pathway.

Additionally, we have observed significant increase in the age of the participants in the third XO activity tertile group in relation to the first tertile group (Table 2), as well as positive correlation between XO and advanced age (Table 3). However, although similar association between XO activity and age was found in human plasma in previous report [29], in our current study age was not an independent predictor of higher XO activity, but was one of the confounders (Table 4).

The cross-sectional design represents the limitation of the current study. However, unlike several previous studies [15–17], we have included a larger sample size of participants when estimating the complex relationship between obesity, oxidative stress and inflammation. However, new studies with longitudinal design are needed to examine the causal link between the mentioned entities, as well as to reveal the best therapeutic target approach for the obesity-related diseases.

Conclusion

Obesity (as determined with increased BMI) is an independent predictor of high XO activity in overweight/obese population. New studies are needed to explore the better pharmacological target treatment to reduce obesity-related oxidative stress and its consequences.

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Compliance with ethical standards

Conflict of interest The authors declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee of Primary Health Care Center in Podgorica, Montenegro and with the 1964 Helsinki Declaration and its later amendments.

Informed consent All the participants included in this study provided written informed consent.

References

1. Savini I, Catani MV, Evangelista D, Gasperi V, Avigliano (2013) Obesity-associated oxidative stress: strategies finalized to improve redox state. Int J Mol Sci 14(5):10497–10538. https://doi.org/10.3390/ijms140510497
2. Papaetis GS, Papakyriakou P, Panagiotou TN (2015) Central obesity, type 2 diabetes and insulin: exploring a pathway full of thorns. Arch Med Sci 11(3):463–482. https://doi.org/10.5114/aoms.2015.52350
3. Laaksonen DE, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT (2004) C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. Diabetologia 47(8):1403–1410. https://doi.org/10.1007/s00125-004-1472-x
4. Chedraui P, Escobar GS, Ramírez C, Pérez-López FR, Hidalgo L, Mannella P, Genazzani A, Simoncini T (2012) Nitric oxide and pro-inflammatory cytokine serum levels in postmenopausal women with the metabolic syndrome. Gynecol Endocrinol 28(10):787–791. https://doi.org/10.3109/09513590.2012.671395
5. Farah R, Gilbey P, Grozovski M, Asli H, Khamisy-Farah R, Assy N (2016) Antioxidant enzyme activity and cognition

in obese individuals with or without metabolic risk factors. Exp Clin Endocrinol Diabetes 124(9):568–571. https://doi.org/10.1055/s-0042-113125
6. Klisic A, Kotur-Stevuljevic J, Kavaric N, Martinovic M, Matic M (2018) The association between follicle stimulating hormone and glutathione peroxidase activity is dependent on abdominal obesity in postmenopausal women. Eat Weight Disord 23(1):133–141. https://doi.org/10.1007/s40519-016-0325-1
7. Venturini D, Simão AN, Scripes NA, Bahls LD, Melo PA, Belinetti FM, Lozovoy MA, Dichi I (2012) Evaluation of oxidative stress in overweight subjects with or without metabolic syndrome. Obesity (Silver Spring) 20(12):2361–2366. https://doi.org/10.1038/oby.2012.130
8. Klisic A, Isakovic A, Kocic G, Kavaric N, Jovanovic M, Zvrko E, Skerovic V, Ninic A (2017) Relationship between oxidative stress, inflammation and dyslipidemia with fatty liver index in patients with type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. https://doi.org/10.1055/s-0043-118667
9. Petelin A, Tedeschi P, Maietti A, Jurdana M, Brandolini V, Pražnikar ZJ (2017) Total serum antioxidant capacity in healthy normal weight and asymptomatic overweight adults. Exp Clin Endocrinol Diabetes 125(7):470–477. https://doi.org/10.1055/s-0043-107783
10. Miyata S, Noda A, Hara Y, Ueyama J, Kitaichi K, Kondo T, Koike Y (2017) Nitric oxide plasma level as a barometer of endothelial dysfunction in factory workers. Exp Clin Endocrinol Diabetes 125(10):684–689. https://doi.org/10.1055/s-0043-110054
11. Kushiyama A, Nakatsu Y, Matsunaga Y, Yamamotoya T, Mori K, Ueda K, Inoue Y, Sakoda H, Fujishiro M, Ono H, Asano T (2016) Role of uric acid metabolism-related inflammation in the pathogenesis of metabolic syndrome components such as atherosclerosis and nonalcoholic steatohepatitis. Mediat Inflamm 2016:8603164. https://doi.org/10.1155/2016/8603164
12. Vida C, Rodríguez-Terés S, Heras V, Corpas I, De la Fuente M, González E (2011) The aged-related increase in xanthine oxidase expression and activity in several tissues from mice is not shown in long-lived animals. Biogerontology 12(6):551–564. https://doi.org/10.1007/s10522-011-9351-6
13. Boban M, Kocic G, Radenkovic S, Pavlovic R, Cvetkovic T, Deljanin-Ilic M, Ilic S, Boban MD, Djindjic B, Stojanovic D, Sokolovic D, Jevtovic-Stoimenov T (2014) Circulating purine compounds, uric acid, and xanthine oxidase/dehydrogenase relationship in essential hypertension and end stage renal disease. Ren Fail 36(4):613–618. https://doi.org/10.3109/0886022X.2014.88224014
14. Real JT, Martínez-Hervás S, García-García AB, Civera M, Pallardó FV, Ascaso JF, Viña JR, Chaves FJ, Carmena R (2010) Circulating mononuclear cells nuclear factor-kappa B activity, plasma xanthine oxidase, and low grade inflammatory markers in adult patients with familial hypercholesterolaemia. Eur J Clin Invest 40(2):89–94. https://doi.org/10.1111/j.1365-2362.2009.02218.x
15. Feoli AM, Macagnan FE, Piovesan CH, Bodanese LC, Siqueira IR (2014) Xanthine oxidase activity is associated with risk factors for cardiovascular disease and inflammatory and oxidative status markers in metabolic syndrome: effects of a single exercise session. Oxid Med Cell Longev 2014:587083. https://doi.org/10.1155/2014/587083
16. Tam HK, Kelly AS, Metzig AM, Steinberger J, Johnson LA (2014) Xanthine oxidase and cardiovascular risk in obese children. Child Obes 10(2):175–180. https://doi.org/10.1089/chi.2013.0098
17. Chiney MS, Schwarzenberg SJ, Johnson LA (2011) Altered xanthine oxidase and *N*-acetyltransferase activity in obese children. Br J Clin Pharmacol 72(1):109–115. https://doi.org/10.1111/j.1365-2125.2011.03959.x
18. Martinez-Hervas S, Real JT, Ivorra C, Priego A, Chaves FJ, Pallardo FV, Viña JR, Redon J, Carmena R, Ascaso JF (2010) Increased plasma xanthine oxidase activity is related to nuclear factor kappa beta activation and inflammatory markers in familial combined hyperlipidemia. Nutr Metab Cardiovasc Dis 20(10):734–739. https://doi.org/10.1016/j.numecd.2009.06.003
19. Miric DJ, Kisic BM, Filipovic-Danic S, Grbic R, Dragojevic I, Miric MB, Puhalo-Sladoje D (2016) Xanthine oxidase activity in type 2 diabetes mellitus patients with and without diabetic peripheral neuropathy. J Diabetes Res 2016:4370490. https://doi.org/10.1155/2016/4370490
20. Cheung KJ, Tzameli I, Pissios P, Rovira I, Gavrilova O, Ohtsubo T, Chen Z, Finkel T, Flier JS, Friedman JM (2007) Xanthine oxidoreductase is a regulator of adipogenesis and PPAR gamma activity. Cell Metab 5(2):115–128. https://doi.org/10.1016/j.cmet.2007.01.005
21. Hallenborg P, Petersen RK, Kouskoumvekaki I, Newman JW, Madsen L, Kristiansen K (2016) The elusive endogenous adipogenic PPARγ agonists: lining up the suspects. Prog Lipid Res 61:149–162. https://doi.org/10.1016/j.plipres.2015.11.002
22. Tam HK, Kelly AS, Fox CK, Nathan BM, Johnson LA (2016) Weight loss mediated reduction in xanthine oxidase activity and uric acid clearance in adolescents with severe obesity. Child Obes 12(4):286–291. https://doi.org/10.1089/chi.2015.0051
23. Richette P, Poitou C, Manivet P, Denis J, Bouillot JL, Clément K, Oppert JM, Bardin T (2016) Weight loss, xanthine oxidase, and serum urate levels: a prospective longitudinal study of obese patients. Arthritis Care Res (Hoboken) 68(7):1036–1042. https://doi.org/10.1002/acr.22798
24. Klisic AN, Vasiljevic ND, Simic TP, Djukic TI, Maksimovic MZ, Matic MG. Association between C-reactive protein, anthropometric and lipid parameters among healthy normal weight and overweight postmenopausal women in Montenegro. Lab Med 45:12–16. PMID: 24719979
25. Tsushima Y, Nishizawa H, Tochino Y, Nakatsuji H, Sekimoto R, Nagao H, Shirakura T, Kato K, Imaizumi K, Takahashi H, Tamura M, Maeda N, Funahashi T, Shimomura I (2013) Uric acid secretion from adipose tissue and its increase in obesity. J Biol Chem 288(38):27138–27149. https://doi.org/10.1074/jbc.M113.485094
26. Kushiyama A, Okubo H, Sakoda H, Kikuchi T, Fujishiro M, Sato H, Kushiyama S, Iwashita M, Nishimura F, Fukushima T, Nakatsu Y, Kamata H, Kawazu S, Higashi Y, Kurihara H, Asano T (2012) Xanthine oxidoreductase is involved in macrophage foam cell formation and atherosclerosis development. Arterioscler Thromb Vasc Biol 32(2):291–298. https://doi.org/10.1161/ATVBAHA.111.234559
27. El-Bassossy HM, Watson ML (2015) Xanthine oxidase inhibition alleviates the cardiac complications of insulin resistance: effect on low grade inflammation and the angiotensin system. J Transl Med 13:82. https://doi.org/10.1186/s12967-015-0445-9
28. Murakami N, Ohtsubo T, Kansui Y, Goto K, Noguchi H, Haga Y, Nakabeppu Y, Matsumura K, Kitazono T (2014) Mice heterozygous for the xanthine oxidoreductase gene facilitate lipid accumulation in adipocytes. Arterioscler Thromb Vasc Biol 34(1):44–51. https://doi.org/10.1161/ATVBAHA.113.302214
29. Aranda R, Doménech E, Rus AD, Real JT, Sastre J, Viña J, Pallardó FV (2007) Age-related increase in xanthine oxidase activity in human plasma and rat tissues. Free Radic Res 41(11):1195–1200. https://doi.org/10.1080/10715760701481461