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Oxidative stress, depression, and risk of recurrence of stable coronary heart disease

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SOUHRN

Souvislosti a cíle: Záměrem této studie je objasnit vztah mezi úrovní oxidačního stresu (OS), depresí (D) a rizikem opakovaného výskytu stabilní ischemické choroby srdeční (sICHS).
Metody: Retrospektivní studie se zúčastnilo 174 osob ve věku 45+: 86 hospitalizovaných pacientů kardiologického oddělení s rekurentní sICHS a 88 hospitalizovaných pacientů kardiologického oddělení s primární sICHS. Vážnost symptomů deprese byla hodnocena za použití 30bodového dotazníku Geriatrické škály deprese (GDS), platné lotyšské verze GDS-LAT. Každému pacientovi byly odebrány vzorky krve za účelem změření parametrů oxidačního stresu malondialdehydu (MDA) a glutathionu peroxidázy (GPx).
Výsledky: 83,9 % vzorků mělo vysokou koncentraci MDA. V 72,4 % byl vzorek hodnoty GPx normální, v 17,8 % byla hodnota vysoká a v 9,8 % nízká. O něco více než polovina pacientů má depresi (44,3 % mírnou D a 6,9 % těžkou D). GPx se statisticky lišila u primární a rekurentní sICHS (p = 0,003). Pacienti s D a vysokým GPx měli 10,6krát vyšší pravděpodobnost opakované sICHS ve srovnání s pacienty bez D a s normální GPx (p = pacienti s D měli obě hodnoty MDA a GPx vysoké častěji než účastníci bez D, ale nebylo to statisticky významné [p = 0,51]).
Závěr: V uvedené studii bylo zjištěno, že koncentrace antioxidačního (AO) enzymu GPx byla podstatně vyšší u depresivních pacientů s opakovanou sICHS ve srovnání s pacienty bez D a s pacienty s primární ICHS a pacienti s D i s vysokým GPx měli vyšší pravděpodobnost opakované sICHS ve srovnání s těmi bez D a s normálním GPx. Dá se předpokládat, že GPx je významnější marker rizika D a opakované sICHS. Koncentrace MDA ve většině z obou skupin (primární a opakovaná sICHS) pacientů by mohla dokazovat, že zvýšená koncentrace OS je všeobecně rizikový faktor ischemické choroby srdeční. Monitorování biomarkerů OS se zdá být významné ve zvládání komorbidity sICHS s D. Bylo by vhodné provést další studie, které by potvrdily tyto nálezy.

ABSTRACT

Aim: The aim of the study was to investigate the relationships between a level of oxidative stress (OS), depression (D) and risk of recurrence of stable coronary heart disease (SCHD).
Methods: A retrospective study was conducted on 174 participants, at the age 45+ years: 86 in-patients of the cardiology department with a recurrent SCHD and 88 in-patients of the cardiology department with primary SCHD. The severity of depressive symptoms was assessed using the long 30-item form of Geriatric Depression Scale (GDS), valid Latvian version of GDS-LAT. The blood samples were taken from each patient to measure oxidative stress parameters malondialdehyde (MDA) and glutathione peroxidase (GPx).
Results: 83.9% of the sample had high level of MDA. In 72.4% of the sample the GPx level was normal, in 17.8% it was high and in 9.8% low. Slightly more than a half of the patients were experiencing depression (44.3% – mild D and 6.9% – severe D). GPx was found statistically differing between primary and recurrent SCHD (p = 0,003). Patients with both D and high GPx had 10.6 times higher chances of recurrent SHCD compared to those without D and normal GPx (p = patients with present D were experiencing both – high levels

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of MDA and GPx – more often than responders with no D, but this wasn't statistically significant [$p = 0.51$]). **Conclusion**: In the present study it was found that level of antioxidant (AO) enzyme GPx was significantly higher in depressed patients with recurrent SCHD compared to patients without D and to patients with primary SCHD and patients with both D and high GPx had higher chances of recurrent SCHD compared to those without D and normal GPx. It could be supposed that GPx is a more significant marker of risk of D and recurrence of SCHD. The high level of MDA in most of both (primary and recurrent SCHD) groups patients could evidence that increased OS is a risk factor for CHD in general. Monitoring OS biomarkers seems to be important in the management of SCHD comorbidity with D. Further studies are warranted to confirm these findings.

Introduction

The public health sector faces a huge challenge as a result of the high prevalence and burden of disability caused by ischemic cardiovascular disease (CVD) and depression (D). Accumulating evidence reveals that CVD and D are correlated and share common risk factors, particularly obesity, diabetes, and hypertension. They also share common mechanisms, including oxidative stress (OS), inflammation, and immune response, cell death signaling pathway, and microbiome-gut-brain axis.[1] According to the World Health Organization data CVDs are the number 1 cause of death globally, taking an estimated 17.9 million lives each year, an estimated 31% of all deaths worldwide.[2] Cardiovascular disease is a group of diseases that include both heart and blood vessels, thereby including coronary heart disease (CHD) and coronary artery disease (CAD), and several other conditions.[3] CAD is usually used to refer to the pathologic process affecting the coronary arteries (usually atherosclerosis) whilst CHD includes the diagnoses of angina pectoris, MI and silent myocardial ischemia. In turn, CHD mortality results from CAD.[4]

D in cardiac disease is common, persistent, underrecognized, and deadly. Over the past 20 years, research has found that not only is D more common in cardiac patients than in the general population, but D is also a risk factor for cardiac morbidity and mortality, independent of traditional risk factors.[5] The prevalence of D is, compared with the general population, significantly higher in patients with CHD.[6] More than one fifth of all patients with CHD are depressed (with the risk of D highest in the most severe CHD cases), and up to one third of them report elevated depressive symptoms. These are prevalence figures that are at least 4 times greater than in the general population.[7] A meta-analysis has demonstrated that the overall risk of depressed but otherwise healthy individuals developing heart disease is 64% higher than for those without D.[8] Five meta-analyses reported a 60–80% increased risk of CHD in participants with D.[1]

Depressive symptoms are diagnosed in less than 15% of cases and only 25% of patients with CHD and severe D are diagnosed with psycho-emotional disorder and approximately only half of them receive adequate antidepressant (AD) therapy.[9,10] Another 30–45% of patients with CHD suffer from clinically significant symptoms consistent with a minor D, and this is a risk factor for the future of a major depressive episode in patients with CHD, associated with an increased risk of secondary acute ischemic events, lower interventions and increased mortality regardless of traditional cardiac risk factors.[11–15]

In addition, major D worsens the cardiovascular prognosis, particularly for CHD, by significantly increasing the risk of recurrent CHD. The relative risk of death in depressed patients during the 18 months following the cardiac event is twice that in non-depressed patients. Recent studies have also shown the harmful nature of D after myocardial infarction in terms of rehospitalization or getting access to cardiac rehabilitation, which is particularly beneficial in this context.[16] Although CVD and D are very different pathologies, they share some common pathophysiological characteristics and risk factors, such as the increased production of pro-inflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels and disorder in vitamin D metabolism.[17]

D is associated not only with inflammatory reactions taking place in the body, but also with an increased amount of pro-inflammatory cytokines and increased lipid peroxidation.[18] D is connected with current inflammatory reactions in the body and an increased level of lipid peroxidation, leading to OS. Moreover, OS is considered an important mechanism for the development of CVD.[19] OS is an emergency mechanism that relates to both CVD and D pathophysiology.[20] Inflammation, OS, and activation of the hypothalamic-pituitary-adrenal (HPA) axis is D and cardiac co-morbidities. The inflammatory hypothesis as a common physiopathological pathway in mood disorders and CVD is being put forward more and more frequently. The hypothesis that inflammatory and OS are factors in both mood disorders and CHD seems to be growing stronger.[16]

Malondialdehyde (MDA) is one of the most commonly used indicators of lipid peroxidation, it can also be more resistant than other markers of the late stage (4-HNE, 8-ISO) of lipid peroxidation.[21,22] Heart failure under both acute and chronic conditions is associated with increased levels of OS markers (e.g. MDA, GPx). These findings suggest that CHD status may be determined by OS activity rather than the degree of coronary stenosis.[23] And being a marker of lipid peroxidation, the MDA level increases significantly with D.[24] The main biological role of GPx in the body is a protection against damage caused by free radicals and active forms of oxygen.[18] The higher GPx activity could have been a compensatory mechanism for the excess production of free radicals in depressed patients.[25]

Despite the potentially important role of the OS in pathogenesis of CHD and D, according to available research results, by 2015, the role of OS in the development of D in patients with CHD has not been studied.[18] Normalization of the levels of reactive oxygen species and antioxidant (AO) activity after successful AD therapy sug-

gests that OS mechanisms can be especially important in the study of pathophysiology and prognosis of D. [20,26] Therefore, there is a need to understand the underlying mechanisms and find effective therapies to control CVD and D.[1] The role of OS in stable CHD (SCHD) recurrence in patients with SCHD and D has not been studied previously. At the moment, there is insufficient evidence that routine screening of D in patients with SCHD will ultimately help improve the patient's condition, that is why the study of the relationship between SCHD, D, and OS is very important.[27]

Based on the foregoing, the aim of the present study was to investigate the relationships between OS level, prevalence of D, and risk of recurrent SCHD. The hypothesis was that in recurrent SCHD patients with D would be higher level or OS than in patients with primary SCHD without D.

Materials and methods

A retrospective case-control study was conducted on 174 participants, at the aged 45+ years old:

1) 86 in-patients of the cardiology department of the Paul Stradins Clinical University Hospital (Riga, Latvia) at the age of 45+ years, with a recurrence of SCHD and
2) 88 in-patients of the cardiology department of the same hospital at the age of 45+ years, with a primary SCHD. Each participant was a patient and was examined before discharge from the hospital. There were no statistically significant differences between two groups by gender and age (Chi-square test, p = 0.1 and p = 0.2, OR p< 0.05).

Inclusion criteria in research group were: Patients with SCHD (I20–I25) – by classification ICD-10: I20 angina pectoris; I21 acute myocardial infarction; I22 subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction; I23 certain current complications following STEMI and NSTEMI myocardial infarction (within the 28 day period); I24 other acute ischemic heart diseases; I25 chronic ischemic heart disease; primary hospitalization related to CHD; re-hospitalization related to CHD; patients are stable; age ≥45 years; non-smokers; not vegetarian; do not drink alcohol at least during the last 1 year; use prescribed drugs on regular base.

Exclusion criteria in research group were: Age >45 years; approved diabetes mellitus type 1 and 2; glucose tolerance disturbances; any acute illnesses; irregular usage of prescribed drugs; any F diagnosis; obesity (BMI ≥30).

Ethical aspects

Information about the nature and course of the study was provided to all study participants. The patients filled an informed consent form and a questionnaire. To ensure anonymity of personal data, all patient personal data (name, surname) were coded. All procedures complied with the ethical standards on human experimentation (World Medical Association Helsinki Declaration). The approval for this study was obtained from the Ethics Committee of Riga Stradins University. RSU Ethics Committee's decision to "agree for a study" was received on October 29, 2015 (No. 22).

Investigation methods

Diagnoses of SCHD were confirmed using medical records and by a psychotherapist using a structured interview. The severity of depressive symptoms was assessed using the long 30-item form of Geriatric Depression Scale (GDS), valid Latvian version of GDS-LAT.[28,29]

The blood samples were taken from each patient to measure OS parameters: MDA and GPx.

MDA determination method: manual, spectrophotometric. MDA determines the color intensity of the reaction with thiobarbituric acid (TBA) in an acid medium at 95 °C, after optical density in butanol extract at 532 nm. MDA is calculated from the standard curve using the MDA reference substance 1,1,3,3-tetraethoxypropane.[30–32]

GPx – determination method: automatic spectrophotometric. Glutamate peroxidase catalyzes the oxidation of glutathione (GSH) in the presence of opaque hydroperoxide. Oxidative glutathione (GSSG) under the influence of glutasereductase (GR) and NADPH transforms into a reduced form – GSH, simultaneously oxidising NADPH to NADP+. GPx activity corresponds to an absorption drop at 340 nm due to oxidation of NAPH. One unit corresponds to the amount of enzyme produced by 1.0 μMNADPH oxidation atNADP+1 minute at 340 nm at 37 °C.33

Statistical analysis

Data were analyzed using SPSS 23.0 software. Statistical significance of the prevalence of dependent variables between the strata of independent variables was tested using Chi square test. Normal distribution of parametric variables was checked using Kolmogorov–Smirnov test. In case of normal distribution, the means of dependent variables were compared between strata of independent variables using T-test of ANOVA. If the criteria of normal distribution were not met, the alternative tests (Mann–Whitney U test and Kruskal–Wallis test) were used. For detection of correlations between parametric variables Spearman correlation analysis was used (correlation considered as week if r< 0.3, mean, if r is ranged from 0.3–0.8 and as strong if r >0.8). For multivariate analysis linear, binary and multinomial logistic regressions were applied. Results are considered as statistically significant if p< 0.05.

Results

Descriptive statistics

174 responders participated in the study – 49.4% (n = 86) of them have experienced recurrent SCHD and 50.6% (n = 88) of them formed a control group (patients of primary SCHD). There were no differences between distribution of patients in the primary and the recurrent groups by gender and mean age. A half of the total sample (53.4%) were males. Majority of the sample (83.9%) has high level of MDA and for the rest of them the MDA level was considered as normal (i.e. low level of MDA was detected for none of the patients). For majority of the patients (72.4%) the GPx level was normal, for 17.8% it was high

Table 1 – Description of the sample (total and stratified by SCHD status)

Independent variable	Total		Primary SCHD		Recurrent SCHD		p^*
	n	%	n	%	n	%	
Sex							
Male	93	53.4	43	48.9	50	58.1	0.22
Female	81	46.6	45	51.1	36	41.9	
Age							
81+	13	7.5	7	8.0	6	7.0	0.34
71–80	48	27.6	27	30.7	21	24.4	
61–70	71	40.8	30	34.1	41	47.7	
≤ 60	42	24.1	24	27.3	18	20.9	
MDA							
Low	–	–	–	–	–	–	
High	146	83.9	76	86.4	70	81.4	0.37
Normal	28	16.1	12	13.6	16	18.6	
GPx							
Low	31	17.8	17	19.3	14	16.3	**0.003**
High	17	9.8	2	2.3	15	17.4	
Normal	126	72.4	69	78.4	57	66.3	
GDS							
Severe	12	6.9	6	6.8	6	7	0.65
Mild	77	44.3	36	40.9	41	47.7	
No	85	48.9	46	52.3	39	45.3	

* Statistically significant if $p < 0.05$

and for 9.8% low. Slightly more than a half of the patients are experiencing D (44.3% mild D and 6.9% severe D) (see Table 1).

As it can be seen in Table 1, groups of recurrent and primary SCHD did not differ according to none of the afore mentioned variables except the GPx level – among patients of recurrent SCHD there was lower proportion of individuals with normal level of GPx when compared to primary SCHD patients (66.3% and 78.4%, respectively) ($p = 0.003$).

Correlation between OS markers

Correlation of OS factors (MDA and GPx indicators) was found to be positive and statistically significant but yet weak (r = 0.18, $p = 0.017$).

Factors associated with the recurrent SCHD

When the independent variables are analyzed as parametric values, it was found that the only factor statistically differing between primary and recurrent SCHD patients, was GPx, i.e. among patients of recurrent SCHD mean GPx value is significantly higher than among patients of primary SCHD (8329.8 and 7474.5 U/g Hb respectively) ($p = 0.01$) (see Table 2). Mean age was slightly higher among patients of primary SCHD as well as the median MDA, whereas the median GDS value was higher among patients of recurrent SCHD. But, as it has been mentioned already before, these tendencies cannot be considered as statistically significant. The multivariate analysis hasn't changed the conclusion. After the adjustment the only factor significantly associated with recurrent status of SCHD was GPx ($p = 0.008$). But as regards the measure of OR, the increase in GPx per one unit is making so small changes in OR that it was not detectable within two decimal figures. This was the reason why in the further data analysis the parametric measures were categorized and analyzed as nonparametric variables.

As it's seen in Table 2, there is a tendency for odds of recurrent SCHD to be higher among males, older patients and persons with mild D. Interestingly that the odds of recurrent SCHD are lower among patients with high levels of MDA. But these observations are not statistically significant in univariate, or multivariate analyses. The only factor showing stable and statistically significant association with recurrent SCHD is GPx level, i.e. in multivariate analysis independently from other factors high levels of GPx is associated with 11.29 times higher odds of having recurrent SCHD status ($p = 0.003$).

Factors associated with the D

Patients with present D were experiencing both – high levels of MDA and GPx – more often than responders with no D (11.2% and 8.2%, respectively). But this trend cannot be considered as statistically significant ($p = 0.51$). And vice versa – among patients with simultaneously high levels of MDA and GPx the prevalence of D is higher

Table 2 – Factors associated with recurrent SCHD in univariate and multivariate analysis (if independent variables are nonparametric measures)

Independent variable	Primary SCHD		Recurrent SCHD		OR*	95% CI	*p***	Adjusted OR*	95% CI	*p***
	n	%	n	%						
Sex										
Male	43	46.2	50	53.8	1.45	0.80–2.65	0.22	1.63	0.85–3.12	0.14
Female	45	55.6	36	44.4	1			1		
Age										
81+	7	53.8	6	46.2	1.14	0.33–3.99	0.83	1.48	0.35–6.28	0.60
71–80	27	56.3	21	43.8	1.04	0.45–2.39	0.93	1.34	0.52–3.43	0.55
61–70	30	42.3	41	57.7	1.82	0.84–3.94	0.13	2.25	0.96–5.31	0.06
≤ 60	24	57.1	18	42.9	1			1		
MDA										
Low	–	–	–	–	–	–	–	–	–	–
High	76	52.1	70	47.9	0.69	0.31–1.56	0.37	0.53	0.22–1.27	0.15
Normal	12	42.9	16	57.1	1			1		
GPx										
Low	17	54.8	14	45.2	1.00	0.45–2.20	0.99	0.96	0.42–2.19	0.92
High	2	11.8	15	88.2	**9.10**	**1.99–41.37**	**0.004**	**11.29**	**2.31–55.06**	**0.003**
Normal	69	54.8	57	45.2	1			1		
GDS										
Severe	6	50.0	6	50.0	1.18	0.35–3.95	0.79	0.82	0.18–3.67	0.80
Mild	36	46.8	41	53.2	1.34	0.72–2.49	0.35	1.31	0.66–2.60	0.44
No	46	54.1	39	45.9	1			1		

* OR – odds ratio; ** statistically significant if $p < 0.05$.

Table 3 – Factors associated with recurrent SCHD in univariate and multivariate analysis among patients with D

Independent variable	Primary SCHD		Recurrent SCHD		OR*	95% CI	*p***	Adjusted OR*	95% CI	*p***
	n	%	n	%						
Sex										
Male	20	44.4	25	55.6	1.25	0.54–2.88	0.60	1.16	0.46–2.91	0.76
Female	22	50.0	22	50.0	1			1		
Age										
81+	7	70.0	3	30.0	0.32	0.06–1.79	0.20	0.56	0.09–3.71	0.55
71–80	17	51.5	16	48.5	0.71	0.20–2.49	0.59	1.43	0.33–6.15	0.63
61–70	12	37.5	20	62.5	1.25	0.34–4.49	0.73	2.60	0.58–11.78	0.22
≤ 60	6	42.9	8	57.1	1			1		
MDA										
Low	–	–	–	–	–	–	–	–	–	–
High	34	47.9	37	52.1	0.87	0.31–2.46	0.79	0.64	0.21–1.97	0.44
Normal	8	44.4	10	55.6	1			1		
GPx										
Low	5	35.7	9	64.3	2.23	0.68–7.40	0.19	3.04	0.80–11.60	0.10
High	1	10.0	9	90.0	**11.18**	**1.34–93.37**	**0.03**	**12.76**	**1.34–121.84**	**0.03**
Normal	36	55.4	29	44.6	1			1		

* OR – odds ratio; ** statistically significant if $p < 0.05$.

than among patients with normal levels of MDA and GPx or with high or low levels of just one of the indicators (58.8% and 50.3%, respectively). And the level of statistical significance of the mentioned observation is surely the same, i.e. not reaching the level of significance (p = 0.51).

Factors associated with the recurrent SCHD in relation to the presence of D

If only people with D were analyzed (n = 89), the findings remained the same as for the total sample – the only factor significantly increasing the odds of experiencing recurrent SCHD was the high level of GPx (OR 12.76; p = 0.03). As regards the other factors there was a tendency that higher odds of experiencing recurrent SCHD are for males and people aged 61–71 (compared to the younger ones). People with high levels of MDA have almost 40% lower odds of experiencing recurrent SCHD. But the mentioned tendencies cannot be considered as statistically significant (see Table 3).

Further – switching D and SCHD from being the dependent variables to be independent ones (and making markers of OS as the dependent variables), it was found that MDA and GPx are more frequent among patients of recurrent SCHD regardless of the status of D. And the observation can be considered as statistically significant (p = 0.006). But when the four strata are further compared pairwise, it is concluded that the high levels of MDA and GPX were significantly more frequent within the group "D and recurrent SCHD" (19.1%) than within the groups "no D and primary SCHD" (2.2%; p = 0.03) or within the group "D and primary SCHD" (2.4%; p = 0.04) (see Table 4).

Analyzing the for strata pairwise it was found that the prevalence of recurrent SCHD was significantly higher among patients with D and high levels of GPx (90.0%) when compared to people with no D and normal or low levels of GPx (42.3%; p = 0.02) or patients with D but normal or low levels of GPx (48.1%; p = 0.04).

The levels of MDA were not giving any additional impact on the relation between status of D in combination with levels of GPx and the status of SCHD. The conclusions were identical to the ones described above for the combination of the D and GPx alone (see Table 5).

Further, cross tabulation analysis revealed that the group "D + high GPx" had 10.6 times higher chances of recurrent SHCD compared to "no D + normal GPx" group (see Table 6).

Table 4 – Prevalence of simultaneously high levels of MDA and GPx in relation to the presence of D and recurrent SCHD

Status of D in relation to SCHD	High both – MDA and GPx		Normal MDA and GPx or high one of them	
	n	%	n	%
D + recurrent SCHD*^	9	19.1	38	80.9
D + primary SCHD^	1	2.4	41	97.6
No D + recurrent SCHD	6	15.4	33	84.6
No D + primary SCHD*	1	2.2	45	97.8

* p = 0.03, ^ p = 0.04. Statistically significant if p< 0.05.

Table 5 – Prevalence of simultaneously high levels of MDA and GPx in relation to the presence of D and recurrent SCHD

Independent variable Status of D, MDA and GPx	Recurrent SCHD		Primary SCHD	
	n	%	n	%
D + high MDA + high GPx*	9	90.0	1	10.0
No D + high MDA + high GPx^	6	85.7	1	14.3
D + normal MDA + normal or low GPx^	38	48.1	41	51.9
No D + normal MDA + normal or low GPx*	33	42.3	45	57.7

* p = 0.02, ^ p = 0.04. Statistically significant if p< 0.05.

Table 6 – Prevalence and odds of recurrent SCHD stratified by the presence of depression and the level of GPx

Dependent variables	OR (95% CI)	p
D, low GPx	2.12	0.22
D, high GPx	**10.61**	**0.03**
D, normal GPx	0.95	0.89
No D, low GPx	0.49	0.23
No D, high GPx	7.07	0.08
No D, normal GPx	1	

Statistically significant if p < 0.05

Discussion

As mentioned above, the aim of the present study was to investigate the relationships between OS level, prevalence of D, and risk of recurrent SCHD. The hypothesis was that in recurrent SCHD patients with D would be higher level or OS than in patients with primary SCHD without D.

Prevalence of D

The result of the research revealed that prevalence of D was in 51.2% of all patients what is in accordance with previous research. Based on the literature, between 31–45% of patients with CHD, including those with stable CAD, unstable angina, or myocardial infarction, suffer from clinically significant depressive symptoms.[11]

In accordance with our expectations in the recurrent SCHD patients prevalence of D was higher (47.7% in primary group and 54.7% in recurrent group), though the difference between primary and recurrent patients wasn't statistically significant (p = 0.44). Multivariate logistic regression results indicated that as the D indicators increase by 1 unit, the chances of recurrent SCHD increase 1.04 times or 4%, but it wasn't statistically significant.

A small difference between groups could be explained with :1) presence of D long time before primary hospitalization, not only after cardiac event; 2) all the patients were enrolled in the research before hospital discharge, that means sometimes after 7–10 days of treatment and adherence to sleep and nutrition. In a study of hospital-

ized patients with a variety of cardiac conditions, those who met criteria for clinical D during admission had improvement of adherence (to diet, exercise, and medication) if their D improved following hospitalization. This suggests that reduced adherence to key secondary prevention behaviors in depressed cardiac patients may be modifiable with treatment of the depressive symptoms.[34]

OS level

There were analyzed two markers of OS: MDA – lipid peroxidation product that shows OS level and AO enzyme GPx – marker of the body defense against OS.

In the most of all patients high MDA level was found (in 146 patients or in 83.9 %) from 174, what is similar with the literature. Results of the studies of Pezeshkian et al. (2001) showed that MDA levels increased significantly in heart diseases.[35] Some other investigates have also reported increase of MDA and GPx levels in patients with CAD.[31] In spite of our expectations, in primary SCHD group MDA level was slightly higher, though there was no statistically significant difference between the subgroups. Moreover, cross tabulation analysis indicates that higher MDA level was in patient with primary SCHD without D (in 91.3% of patients). Though there weren't statistically significant differences between subgroups (p = 0.38), this tendency could be taken into account.

In turn, GPx level was significantly higher in recurrent SCHD subgroup (p = 0.01). Multivariate analysis showed that higher GPx level 11.29 fold increased risk of SCHD. Kaya et al. (2012) also reported an increase of MDA and GPx levels in patients with CAD. GPx enzyme activation was significantly higher in patients with CAD than healthy controls.[36] The result of present research revealed also that GPx level in patients with recurrent SCHD is slightly lower than in patients with primary SCHD. It has been demonstrated that AO enzyme activities are reduced in CHD, and this is linked to the increased disease risk. Many studies have indicated that free radical generation increases and AO defenses decrease in response to increased OS in CHD patients. Activity levels of the AO enzymes GPx, and non-enzymatic AO, are considered as predictors of CHD.[37]

The discrepancies – higher MDA level in patients with primary SCHD – can be explained by several factors. First, OS may be an early causative factor in CVD pathology rather than a late consequence and OS and inflammation develops long before the onset of the first symptoms.[38] We could suppose that OS in recurrent SCHD patients was longer than in primary, but activation of AO enzymes partially compensated high OS level. The fact that GPx level was higher in the patients with recurrent SHCD, that means antioxidative system defense activation, could confirm this assumption. Second, use of beta-blockers. All of both groups' patients took a beta-blocker therapy during hospitalization. In previous researches was found that treatment with beta-blockers such as metoprolol, carvedilol and bisoprolol reduces the levels of OS.[39,40] Unfortunately, in the present study we didn't have information of use of beta-blockers before hospitalization. We could assume that patients with recurrent SCHD used beta-blockers longer than patients with primary SCHD – long time before hospitalization. The longer duration of beta-blocker therapy could explain lower MDA level in recurrent SCHD group. Third, we did not have data on psychoactive drug use or psychological support of the patients before they were enrolled in the study or other factors that could affect the MDA level.

Interesting finding in the present research was the cross tabulation analysis indicating that both OS markers (MDA and GPx) together was significantly higher in recurrent SCHD subgroup, and, moreover, compared pairwise, it was found that the high levels of MDA and GPx are significantly more frequent within the group "D and recurrent SCHD" than within the groups "no D and primary SCHD" (p = 0.03) or within the group "D and primary SCHD" (p = 0.04). Analyzing for strata pairwise it was found that the prevalence of recurrent SCHD is significantly higher among patients with D and high levels of GPx (90.0%) when compared to people without D and normal or low levels of GPx (p = 0.02) or patients with D but normal or low levels of GPx (p = 0.04). Moreover, as it's the group "D + high GPx" had 10.6 times higher chances of recurrent SHCD compared to "no D + normal GPx" group. Hence, we can suppose that OS indeed is a risk factor of SCHD recurrence, especially in patients with D. Although the division into groups of combinations entailed a small number of people in each subgroup, we suggest taking into account these finding in further studies. As mentioned above, there only in-patients before discharge were included in the study who already observed a certain sleep regimen and diets, and received appropriate treatment and care, which could reduce the symptoms of both D and OS. That could explain small number of patients with both D and OS in each primary and recurrent SCHD subgroups.

There is need to add that it's the first research comparing OS and D in primary and recurrent patients with SCHD. Previous studies compared OS level in CHD patients and in healthy controls. Cheraghi et al. (2019) found that serum GPx and MDA were significantly greater in CHD patients than in healthy controls.[37] Moreover, other researches confirm that the OS directly increases the risk of D in patients with CVDs, whereas it increases the risk of CVDs in depressed people. In summary, the common risk factors increase the production of OS and reduce antioxidant defenses, thereby promoting the occurrence and development of interacted ischemic CVD and D.[1]

D, a frequently occurring disease, has a bidirectional relationship with ischemic CVD and partially shares common risk factors (such as obesity and diabetes) and mechanisms (such as inflammation and OS) with CVD, providing a new direction for future research. Based on the literature in patients with CVD, D is often chronic and recurrent. Among patients with CVD hospitalized for acute cardiac events and found to meet criteria for D during or shortly after admission, approximately 50–70% had ongoing depressive symptoms that preceded their cardiac event. This finding is consistent with literature that describes persistent D in patients with stable CAD. Depressed patients with unstable CAD appear to be at even greater risk for poor cardiac outcomes. OS can independently and directly affect stroke, CHD and D. Furthermore, OS acts as a link between ischemic CVD and D.[1] Several lines of evidence indicate that different cardiovascular consider-

ations should be inspected in patients who need to take AD medications.[41] There is an increasing body of evidence supporting that D may be associated with changes in OS markers and that AD agents (especially long-term treatment) may increase AO defenses. It is possible that augmentation of AO defenses may be one of the mechanisms underlying the neuroprotective effects of ADs observed in the treatment of D.[11] It has been shown that the depressed patients have elevated level of platelet adhesion and aggregation leading increased risk for cardiovascular events. In fact, the use of SSRIs may prevent developing atherosclerotic plaques and also arterial thrombosis.[42] Patients who respond to AD therapy within the first year of treatment have shown to experience significantly lower rates of morbidity and mortality.[41]

In summary, there is a need to find effective therapies to control CVD and D. When D screening is paired with a management protocol or system of care (e.g., a care management program) to treat D in patients with CVD, there has been consistent evidence for improved patient outcomes (including, in some studies, improved adherence, reduced cardiac symptoms, reduced cardiac events and improved blood pressure and lipids). Patients who meet full criteria for D should be treated, whether cardiac events are recent or remote.[11] OS directly increases the risk of D in patients with CVD, whereas it increases the risk of CVD in depressed people. The common risk factors increase the production of OS and reduce AO defenses, thereby promoting the occurrence and development of interacted ischemic CVD and D.[1]

Limitations of the study

1) There were rather heterogenous groups as concerns age and gender in both groups, that could influence the results. MDA appears to be sensitive to both gender and age. It is significantly lower and shows a greater age-dependence in women than in men. The age-dependent slope of the steady state concentration is maximal at the age between 50 and 55 years, indicating that it may be attributed to the change of metabolism in the postmenopausal period. Interestingly, total glutathione decreased with age simultaneously with the increase in MDA.[43]
2) In the current study patients' anthropometric dates weren't take into account there, only people with BMI >30 were excluded, based on literature, that there was no clear association between obesity and systemic OS in subjects with BMI less than 30 kg/m^2.[44]
3) In the present research authors couldn't exclude other factors that affect D and/or OS in patients in relations to SCHD recurrence (dietary intake, substance use disorder, chronic somatic disorder, difficult life events no relationships, no family, poor social life, lower socioeconomic status etc.)

Conclusions

In the present study was found that AO enzyme GPx significantly higher in depressed patients with recurrent SCHD compared to patients without D and to patients with primary SCHD. Patients with both D and high GPx had 10.6 times higher chances of recurrent SHCD compared to those without D and normal GPx. It could be supposed that GPx is more significant marker of risk of D and recurrence of SCHD. Though MDA level was slightly higher in primary SCHD group without D, the high level of MDA in most of both (primary and recurrent SCHD) groups patients evidences that increased OS is a risk factor for SCHD in general, but not for recurrence of SCHD. Monitoring OS biomarkers seems to be important in the management of SCHD comorbidity with D. Further studies are warranted to confirm these findings.

Conflict of interest
None.

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Ethical statement
The article was written in accordance with ethical standards.

Informed consent
All the patients filled an informed consent form.

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