OXIDATIVE STRESS INDICATORS, DEPRESSION AND QUALITY OF LIVE LEVELS IN CORONARY HEART DISEASE PATIENTS

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Depression (D) is 3-4 times more common in patients with coronary heart disease (CHD) than the prevalence in the population. D increases the risk of cardiac mortality, and is associated with an increased risk of secondary acute ischemic events.Pathophysiological mechanisms such as activity of inflammatory reactions, circulating inflammatory mediators, dysfunction of the endothelium influence the relationship between these diseases. Reconsidering the attitude towards the use of antidepressants and antioxidants can be particularly useful in the prevention of CHD and depends from understanding of interactions between D and CHD.

To identify and examine the relationship between the severity of symptoms of depression, quality of live level and indicators of OS in primary stable CHD (SCHD) patients and in patients with recurrent SCHD.

A retrospective case-control study, ambulatory patients at the age 45+ years: 100 patients with recurrent SCHD and 100patients with primary SCHD. It is assessed in both target groups: manifestations of SCHD; OS parameters in the blood (MDA, GPx); quality of life level; D.

The valid data obtained from 88 patients with primary SCHD and 86 relapses of SCHD: in patients with primary SCHD, D was established in 42 cases (mild - 36, severe - 6), in patients with recurrent SCHD - at 47 (mild - 41, severe - 6). The mean score of the QlesQ parameters in patients with primary SCHD is 64 % but in patients with recurrent SCHD 63 %.
Conclusions. The primary data obtained indicate an increased level of OS – MDA in both groups, and negative correlation between QlesQ and D. GPx does not have any significant changes in both groups. It is necessary to continue the study in randomized groups, taking in account level of D, cardiovascular risk and the therapy received.

Key words: oxidative stress markers, depression in CHD patients.

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INTRODUCTION

Depression (D) is a complex phenomenon that is associated with various pathophysiological processes, which, in turn, makes it difficult to identify clinically useful diagnostic and prognostic markers, as well as treatment options (Adifbair 2016).
D, the most common mood disorder (Adibhatla, 2008), is a leading contributor to the global burden of disease affecting more than 120 million individuals worldwide (Barth 2004).

Major depressive disorder (MDD) lifetime prevalence is 10-15% (Carney 2005) and *World Health Organization* predicts that MDD would be the leading disease burden worldwide by 2030 (Barth 2004, Carney 2005).

MDD is 3-4 times more common in patients with CHD (Adibhatla, 2008), and depressed patients have a 2-4 times increased risk of sudden CHD (Frasure-Smith, 1999), as well as the same overestimated risk of sudden death due to heart problems, which suggests bi-directional connection between these two states (Adifbair 2016).

A large proportion of patients also suffer from subclinical depression (Blankenberg 2001, Bruunsgaard 2000), which shares diagnostic criteria with MDD, but corresponds to smaller criteria (Carney 2004).

Researchers (Capuron L., Maier S.F., Matthews K.A., et al.) suggest a hybrid model like the hybrid dependence of depression and CHD, in which there is a bi-directional relationship between depression and inflammation (Capuron 2004, Maier 1998, Matthews 2010).

According to the World Health Organization data CHD is currently the leading cause of death and ranks first in the world among diseases in the developed world (WHO 2011).

Various pathophysiological mechanisms underlie the risk of cardiovascular diseases in patients with D: increased activity of inflammatory processes; increased susceptibility to blood coagulation due to changes in several stages of the coagulation cascade, including activation and aggregation of platelets; oxidative stress; subclinical hypothyroidism; hyperactivity of the sympathetic-adrenomedullary system and hypothalamic-pituitary-adrenal axis; decrease in the number of circulating endothelial progenitor cells and associated processes of arterial reconstruction; increased variability of heart rate; and the presence of genetic factors (Nemeroff 2012).

The relationship between D and CHD is complex and can be complicated by genetic, metabolic factors and lifestyle (deJonge 2010), which can contribute to temporary or persistent depressive episodes.

This significantly complicates the diagnosis of D. Depressive symptoms are diagnosed in less than 15% of cases (Guck, 2001) and only 25% of patients with CHD and severe D are diagnosed with psychoemotional disorder and approximately only half of them receive adequate antidepressant (AD) therapy (Steeds 2000); (Moryś 2016).

D is widely distributed in patients with congestive heart failure (May 2009, Kato 2009, Lesman-Leegte 2009) or atrial fibrillation (Frasure-Smith, 2009), as well as in patients with myocardial infarction (Frasure-Smith 1993); (Glassman 2009) or who underwent bypass coronary artery grafting (CABG), and has a significant adverse effect on morbidity and mortality in these settings (Tully 2008, Dao 2010, Kende 2010).

Up to 20% of patients with CHD experience a major depressive episode within the first year after an acute coronary syndrome, the incidence of MDD in this case is 2-3 times higher than in the adult population as a whole (Sowden 2009, Celano 2011).

Another 30-45% of patients with CHD suffer from clinically significant symptoms consistent with a minor D (Sowden 2009, Celano 2011), 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 (Barth 2004, Januzzi 2000, Carney 2004, vanMelle 2004).

Anhedonia is an inability to experience pleasure, is a symptom of D, which is most strongly associated with adverse cardiac events and increased mortality after myocardial infarction (Davidson 2010, Leroy 2010).

D also has a significant effect on the outcome of cardiovascular diseases in patients with stable CHD (Frasure-Smith 2010, Hoen 2010).

Considering the negative cardiac and cognitive effects of persistent D in patients with CHD, adequate treatment with antidepressants is a clinically important need in the case of CHD (Carney 2004, Freiheit 2012).

CHD is characterized by inflammation with extravasation of immune cells in the subendothelial space, which contributes to the formation and / or progression of atherosclerotic plaques and thickening of artery walls. Accordingly, circulating inflammatory mediators in combination with vascular risk factors, including hypertension, dyslipidemia and diabetes, are associated with the presence of vascular endothelial dysfunction, atherogenesis in coronary and peripheral vessels, and an increased risk of thrombosis (Mizuno 2011). This leads to a progressive incidence associated with CHD and an increased risk of acute ischemic events, such as myocardial infarction or stroke (Mizuno 2011). Although a depressive episode can often be temporary in patients with CHD, it can also become chronic and may persist for one year or even longer (Frasure-Smith 1999, Lauzon 2003).

It is worth noting that chronic inflammation of low degree is an inalienable component of D (Adifbair 2016).

Inflammation is involved in the pathophysiology of CHD by stimulating myocardial contractility and apoptosis of cells (Swardfager 2011).

Increased inflammation can also contribute to both cardiovascular diseases and depression in all age groups (Nemeroff 2012).

D is characterized by a stable inflammatory condition (Currier 2010, Raison 2009, Raedler 2011) and elevated concentrations of various inflammatory markers, such as C-reactive protein, interleukin 6 (IL-6) and soluble intercellular adhesion molecule-1, can serve as a link in increasing the risk of developing CBC in patients with D (Currier 2010, Raison 2009, Raedler 2011).

Arterial inflammation is caused by harmful irritants, which damage the arterial wall, such as LDL cholesterol, cigarette smoke and hypertension. The internal recovery process, which probably includes the selection of local arterial cells and stem cells from reservoirs, such as the bone marrow, maintains the integrity of the arterial wall. Inflammatory activity caused in response to arterial damage can coordinate the response and once the recovery is complete, the inflammation will stop (Goldschmidt-Clermont 2003, Goldschmidt-Clermont 2003, Asahara 1997). However, if the arterial recovery is impossible or incomplete, the inflammatory response will continue, leading to further destruction of the arterial wall (Goldschmidt-Clermont 2003, Goldschmidt-Clermont 2003, Asahara 1997).

Activated macrophages can induce apoptosis of smooth muscle cells and other cells in arterial layers (Seshiah 2002). This apoptosis leads to a weakening of the arterial wall and the production of growth factors and free radicals that convert smooth muscle cells from normal, contractile phenotype to a proliferative phenotype.

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 (Vaváková 2015). In this connection, oxidative stress (OS) is of importance.

OS is the shift in the balance between pro-oxidants and oxidants, mostly uncompensated, towards peroxidants. A condition that traditionally causes damage to cells in separate organs and in the body and disrupts many functions (Voicehovskis 2012).

The body's antioxidant system (AOS) is the one that regulates and protects cells and organs from oxidative damage. Normal AOS can ensure the integrity of cells, normal, physiological function of the organs. At the same time, in an organism or in the environment conditions can be formed in which the AOS cannot fully implement adequate protective mechanisms, in this connection the organism approaches the state of OS (Voicehovskis 2012).

The OS can unite all possible types of stress, for example, physicochemical (large temperature changes, ultraviolet radiation, radiation, chemical agents, noise, vibration, electromagnetic radiation, etc.), as well as psychoemotional stress (pain, fear, emotional tension, etc.) (Voicehovskis 2012).

Oxidative stress (OS) is an emergency mechanism that relates to both cardiovascular and D pathophysiology (Adifbair, 2016). Active forms of oxygen (ROS) are highly unstable compounds that participate in various physiological processes due to non-reactivity with neighboring biomolecules (Vichova 2013). ROS-induced toxicity is balanced by the recovery functions of endogenous and exogenous antioxidants (Vichova 2013). However, increasing the production of free radicals with reduced antioxidant activity can lead to OS, in which excess ROS exerts a direct toxic effect in the immediate environment (Sun 2009) in addition to changes in the final regulated signaling pathways in which they participate (Zweier 2006). The resulting oxidative damage leads to the stabilization of protein, DNA and lipid oxidation products that can be measured in the blood and used as potential biomarkers (Zhang 2014).

Endothelium plays a key role in linking inflammation to depression and heart disease (Adifbair 2016, Celano 2011). Nitroxide (NO) supports a healthy vasculature, stimulating vasodilation and inhibiting contraction and growth of smooth muscle cells, platelet aggregation, and adhesion of leukocytes to the endothelium (Higashi 2009).

Inflammatory or vascular risk factors, such as hypertension, can increase the production of superoxide, which, combined with NO, reduces its bioavailability (Hinderliter 2003, Forstermann 2006) and instead of forming a longer-lived oxidizing / nitrosating agent peroxynitrite. This can aggravate the damage to the vascular endothelium, which further worsens the endothelial function (Forstermann 2006).

Patients with CHD have significantly higher level of circulating complex protein oxidation products, which also correlates with the severity of CHD (Kaneda 2002).

OS can also contribute to depressive disorder by acting on established etiopathological components of D, including lipid signaling, monoamine regulation and inflammation (Moylan 2014, Maes 2011, Maes 2011). Thus, many clinical studies are associated with D and with an increase in the level of OS markers and lower overall antioxidant activity (Black 2015, Cumurcu 2009, Frey 2006).

Normalization of the levels of ROS and antioxidant activity after successful antidepressant therapy (Cumurcu, 2009) suggests that OS mechanisms can be especially important in the study of pathophysiology and prognosis D (Adifbair 2016).

ROS initiates damage to lipids (proteins and DNA) and leads to mitochondrial dysfunction, dysregulation of ion balance and loss of integrity and destabilization of the membrane, which is the factor that causes cellular necrosis (Vanlangenakker 2008).

Lipid peroxidation products, such as malondialdehyde (MDA), cause changes in the metabolism of dopamine, induce the synthesis of

protein reactive dopaminergic toxins (Rees 2007) and have an inhibitory effect on the reduction of nucleotide excision by direct interaction with cellular repair proteins (Feng 2006).

In MDA reactions with DNA, deoxyguanosine and deoxyadenoside are involved, they form adducts of DNA, while simultaneously releasing the intermediate product-formaldehyde (Del Rio, 2005). Formaldehyde, even at low concentrations, can cause protein folding (aggregation of high toxicity). The MDA molecule is stable and relatively inactive, compared with free radicals, however, it can not only significantly affect the stability and function of cells, but can also be indirectly involved in the OS reaction (Voicehovskis 2012).

MDA is one of the most commonly used indicators of lipid peroxidation (Del Rio 2005, Moore 1998, Li 2008), it can also be more resistant than other markers of the late stage (4-HNE, 8-ISO) of lipid peroxidation (Mazereeuw 2017). And being a marker of lipid peroxidation, the MDA level increases significantly with D (Frey 2006).

The main biological role of glutathione peroxidase (GPx) in the body is protection against damage caused by free radicals and active forms of oxygen. One of the biological functions of GPx is the conversion of hydrogen peroxide to alcohol and its subsequent neutralization up to water (Miyamoto, 2003). The function GPx also includes neutralization of the processes of catalysis of per- and hydroxides of fatty acids, because of which aggressive products are converted to alcohols (Voicehovskis 2012).

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 (Adifbair 2016).

Aim of the study

To identify and examine the relationship between the severity of symptoms of depression, quality of live level and indicators of OS in primary stable CHD (SCHD) patients and in patients with recurrent SCHD.

MATERIALS AND METHODS

A retrospective case-control study, where two target groups were surveyed.
1) Patient group - 100 in-patients of the cardiology department of the Pauls Stradiņš Clinical University Hospital(Riga, Latvia) at the age of 45+ years, with a recurrence of CHD with a stable course (SCHD);
2) Control group - 100 in-patients of the cardiology department of the Pauls Stradiņš Clinical University Hospital(Riga, Latvia) at the age of 45+ years, with a primary SCHD.

Inclusion criteria in research group
1. Patients with stable Coronary Heart Disease (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 ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period);
• I24 Other acute ischemic heart diseases;
• I25 Chronic ischemic heart disease;
2. Primary hospitalizationconnectes with CHD;
3. Re-hospitalization connected with CHD;
4. Patients are stable;
5. Age > 45 years;
6. Stradins Clinical University Hospital, Latvian Cardiology Center in-patients;
7. Non-smokers;
8. Not vegetarian;
9. Do not drink alcohol at least during the last 1 year;
10. Use prescribed drugs on regular base.

Exclusion criteria in research group
1. Age < 45 years;
2. With approved diabetes mellitus type 1 and 2;
3. With glucose tolerance disturbances;
4. With any acute illnesses;

5. Irregular usage of prescribed drugs;
6. There are no F diagnoses:
• F00-F09With confirmed organic psychiatric disorders;
• F20-F29With approved schizophrenia, schizotypal disorders and delusions;
• F70-F79With confirmed mental retardation;
• F80-F89With confirmed mental disorders;
• F10-F19With confirmed psychiatric and behavioral disorders due to use of psychoactive substances.

Investigation methods

In target groups, the following were assessed:
• manifestations of SCHD – using structured interviews;
• blood OS parameters (MDA, 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. 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 transformes into reduced form - GSH, simultaneously oxidizing NADPH to $NADP^+$. Glutathione peroxidase 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 at$NADP^+$1 minute at 340 nm at 37 ° C (Paglia, 1967).

• level of Quality of life – pleasure and satisfaction (short form Q-les-Q questionnaire, author J. Endicott **(Endicott, 1993)**, valid Latvian version Q-les-Q-LAT (Voicehovskis, 2010);

• D level – long 30-item form of Geriatric Depression Scale, by J.A. Yesavage et al. **(Yesavage, 1982-1983)**, valid Latvian version of GDS-LAT (Voicehovskis 2013).

Ethical aspects

Information about the nature and course of the study was provided to all study participants.

Patients filled an informed consent form and a questionnaire. To ensure anonymity of personal data, all patient personal data (name, surname) was coded except patient's consent form.

RSU Ethics Committee's decision to "agree for a study" received on October 29, 2015 (No. 22).

RESULTS

26 patients have been excluded from this study due to the following reasons: refusal from interview or blood sample taking, hemolysis of blood sample.

The data obtained from 88 patients with primary SCHD and 86 relapses of SCHD: in patients with primary SCHD, D was established in 42 cases (mild - 36, severe - 6), in patients with recurrent SCHD - at 47 (mild - 41, severe - 6).

Study results presented in tables Tab.1 – 4 and in figures Fig.1 – 4:

The mean score of the Q-les-Q parameters in patients with primary SCHD is 64 % but in patients with recurrent SCHD 63 %.

At the moment, there is insufficient evidence that routine screening of D in patients with SCHD will ultimately help improve the patient's condition (Hasnain, 2011), which is why the study of the relationship between CHD, D and OS is very important.

About markers of inflammation: only a few of them can be used to predict the association of CHD and D and possible interaction. Overall, evidence supporting the use of inflammatory cytokines as biomarkers is unconvincing and requires further study. There is conflicting information about the usefulness of IL-6 as

Table 1. Patients with primary and reccurent CHD

		Age	Oxidative Stress (MDA)	Geriatric Depression Scale	Q-les-Q	Oxidative Stress (GPx)
N	Valid	174	174	174	174	174
	Missing	0	0	0	0	0
Mean		66,44	10,4170	9,64	,6311	7914,05
Median		66,00	9,6550	10,00	,6400	7831,50
Std. Deviation		8,788	3,61769	5,766	,16750	2179,596
Minimum		48	5,23	0	,20	3210
Maximum		87	39,53	25	1,00	15286

Table 2. Patients with primary CHD

		Age	Oxidative Stress (MDA)	Geriatric Depression Scale	Q-les-Q	Oxidative Stress (GPx)
N	Valid	88	88	88	88	88
	Missing	0	0	0	0	0
Mean		66,50	10,7607	9,30	,6352	7494,20
Median		67,00	10,0600	9,00	,6400	7608,50
Std. Deviation		8,821	4,23270	5,367	,15952	1844,191
Minimum		48	5,76	0	,23	3210
Maximum		83	39,53	23	,91	10981

Table 3. Patients with reccurent CHD

		Age	Oxidative Stress (MDA)	Geriatric Depression Scale	Q-Les-Q	Oxidative Stress (GPx)
N	Valid	86	86	86	86	86
	Missing	0	0	0	0	0
Mean		66,37	10,0653	10,00	,6269	8343,66
Median		65,00	9,3250	10,00	,6400	8058,00
Std. Deviation		8,805	2,83770	6,159	,17613	2412,188
Minimum		50	5,23	0	,20	3468
Maximum		87	19,21	25	1,00	15286

biomarker (Pizzi 2009, Vaccarino 2007, Schins 2005). It has also not been established that IL-1β is significantly associated with D (Hekler, 2007). From IL-8, IL-2, IL-4, IL-10, monocyte chemoattractant protein-1, interferon-y, as well as soluble cytokine receptors sIL-6R, sTNF-RI and sTNF-RII- with concomitant CHD.

The possibility of using C-reactive protein also has limitations: its levels exceeding 10 mg / L should be excluded to avoid the inclusion of significant infections or damage to non-cardiac origin (Clyne, 1999).

TNF-α has shown some perspectives as a marker in recent studies (Shang, 2014), but the results only indicate that it needs further study of it as a biomarker.

Available data on the use of leukocytes (WBC) as

biomarkers were controversial (Whooley, 2007). Some results indicate a strong connection between thyroid function and pathophysiology of D; however, the generalizability of thyroid hormones as D markers can be limited due to gender differences (Adifbair 2016).

Leukotrienes are powerful inflammatory mediators (Henderson 1994, Peters-Golden, 2007, Jala 2004), which are necessary for normal brain function (Chiba 2006, Andoh 2005), may also affect susceptibility to D, and haplotypes of leukotrienes were previously associated with cardiovascular disease (Helgadottir 2006). Nevertheless, sex differences in the metabolic pathway of leukotriene biosynthesis (Pergola, 2008)indicate that it can be a gender marker of D. Changes in the serotonin 5-HT receptor system play an important role in the pathophysiology of CHD (Adifbair 2016). 5-HT plays a role in the development and progression of arterial stenosis and atherosclerosis, promoting vasoconstriction and vasodilation of the vasculature (Miyata 2000); (Nilsson 1999, Musselman 1998, Ashton 1986), thrombosis and platelet aggregation (Musselman 1998, Ashton 1986), the growth of

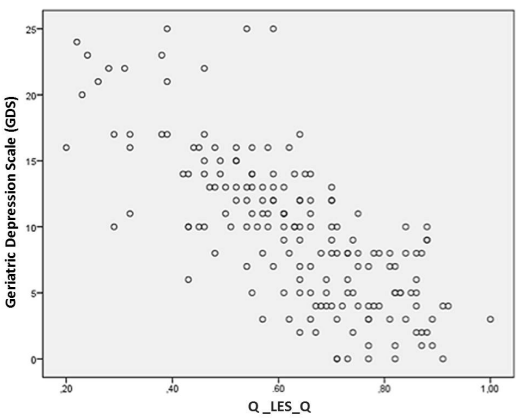

Fig.1. Relation between depression level expresed in Geriatric depression score points andlevelof life Quality.

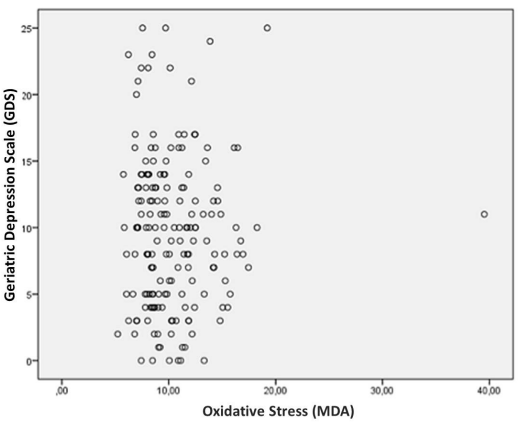

Fig.2. Relation between depression level expresed in Geriatric depression score points and oxidative stress parameter (MDA).

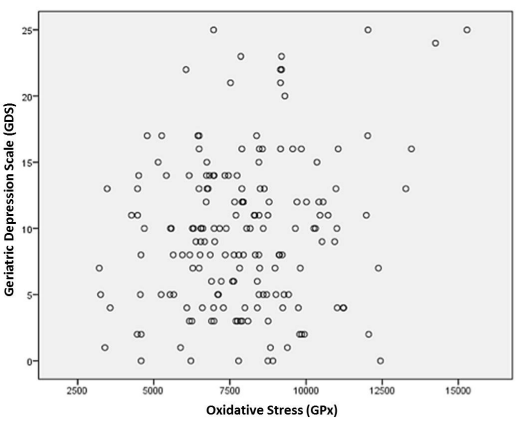

Fig.3. Relation between depression level expresed in Geriatric depression score points and oxidative stress parameter (GPx)

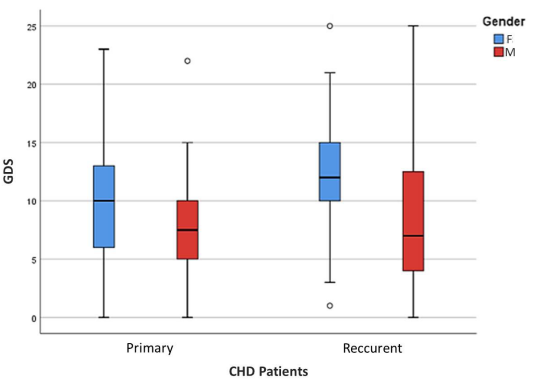

Fig.4. Box plot displaying the distribution of the data showing differences in Geriatric depression score points in primary and recurrent SCHD patients according to gender.

vascular smooth muscle and endothelial cells (Ruzicka, 1994); (Willerson, 1991). Accordingly, an increased concentration of 5-HT in the blood was associated with CHD and subsequent cardiac events (Vikenes, 1999). The reports on the binding of 5-HT2A receptors are inconsistent, further studies of the status of the 2A receptor of 5-HT relative to D should be further studied (D'Haenen 1992, Biver 1997, Attar-Levy 1999).

There are promising biomarkers such as endothelin-1, platelet activating factor (FAT), ferritin. Endothelin-1 (ET-1) is largely regulated by NO, and it has been found that patients with severe depressive symptoms exhibit significantly higher levels of ET -1 than in patients with any other severity of the depressive symptom, which present a high risk for events of acute coronary syndrome (Katayama, 2005). Unfortunately, these studies were limited to their transverse nature, which made it impossible to draw any conclusions about the direction of the causal relationship between endothelial dysfunction, OS and D (Nemeroff, 2012). FAT is a phospholipid, a powerful inflammatory mediator that is elevated in the case of CHD, which is associated with the main mechanisms underlying D in the CHD (Mazereeuw 2015). Excess ferritin reflects pro-inflammatory disorders of iron metabolism (Maes 1996), and transferrin can promote chronic inflammation, promoting the formation of free radicals (vanRensburg 2004).

The study of the general mechanisms underlying D and other concomitant conditions, such as CHD, may have the potential to identify relevant biomarkers of etiological and prognostic value (Adifbair 2016).

Among patients with CHD, mental health treatment and cardiac rehabilitation can each, individually, reduce D and the consequences of CHD; moreover, cardiac rehabilitation is more important in reducing the risk of mortality. The results confirm the subsequent importance of mental health treatment and the greater role of mental health professionals in cardiac rehabilitation (Rutledge 2013).

CONCLUSIONS

The primary data obtained indicate an increased level of OS – MDA in both groups, as well as a negative correlation between Q-les-Q and D. Indicators of Q-les-Q and D: correlation coefficient -0.75 (negative moderate correlation) is statistically significant: $p<0.001$. The higher rate of D according to GDS patients have, the lower level of life quality according to Q-les-Q questionnaire they have.

None of the analyzed features is statistically significantly different in primary and recurrent SCHD patient groups, since p is anywhere greater than 0,05. Only tendencies can be described now – MDA parameters are increased in both groups, slightly higher in the group of primary SCHD. While GDS is slightly higher in patient group with recurrent SCHD. GPx does not have any significant changes in both groups.

It is necessary to continue the study in randomized groups, taking in account level of D, cardiovascular risk and the therapy received.

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The protocol of the study, informative consent and the protocol of participation were approved by Ethics committee of RigaStradins university (Riga, Latvia) – on October 29, 2015 (No. 22), and corresponds to the Helsinki declaration on principles of humanity in medicine.

The present study protects the rights and welfare of all participants in the spirit of ethical guidelines outlined under the Declaration of Helsinki. The study further respects the ethical principles of the RSU and the Law on personal data protection rules.

Personal information obtained in this study course will be strictly secured and coded to avoid external leaks of information.

Opinions expressed in the work belong to the author and do not reflect Latvian government and RSU position or politics.

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