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Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: A 24-week follow-up study

Vahap Ozan Kotan [a,*], Emre Sarandol [b], Emine Kirhan [b], Guven Ozkaya [c], Selcuk Kirli [d]

[a] Department of Psychiatry, Seydisehir State Hospital, Konya, Turkey
[b] Department of Biochemistry, Uludag University Medical Faculty, Bursa, Turkey
[c] Department of Biostatistics, Uludag University Medical Faculty, Bursa, Turkey
[d] Department of Psychiatry, Uludag University Medical Faculty, Bursa, Turkey

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ABSTRACT

Purpose: Major depressive disorder (MDD) is a devastating disease that afflicts large populations and has also been accepted to be an independent risk factor for cardiovascular disease (CVD). Oxidative stress seems to play an essential role in the relationship of MDD and CVD. We aimed to determine the level of oxidative stress in patients with MDD and to investigate the effects of long-term antidepressant (AD) treatment on the oxidative-antioxidative system parameters and CVD risk factors.

Method: Fifty patients who fully met the fourth Diagnostic and Statistical Manual of Mental Disorders criteria for MDD and 44 healthy control subjects were included in the study. Control visits of the patients were repeated 6 weeks, 12 weeks and 24 weeks after beginning of the AD treatment. Lipid profiles, oxidation and oxidizability of apolipoprotein B-containing lipoproteins (expressed as apo B-b-MDA and apo B-Δ-MDA, respectively), levels of plasma malondialdehyde (p-MDA), total antioxidative capacity (TAOC), antioxidant molecules and antioxidant enzyme activities including paraoxonase/arylesterase, red blood cell superoxide dismutase (RBC-SOD) and glutathione peroxidase were determined during 24-week of follow-up period.

Results: According to the results of the study, p-MDA, apo B-b-MDA and RBC-SOD activity were increased and arylesterase activity was decreased in MDD patients. Body mass index (BMI), vitamin A and total cholesterol levels in MDD patients increased after 24-weeks of AD treatment. RBC-SOD activity, TAOC, p-MDA and apo B-b-MDA levels were decreased; paraoxonase/arylesterase activities and apo B-Δ-MDA were increased at the end of 24th week.

Conclusion: Oxidative stress, demonstrated in MDD patients, was partly improved during 24 weeks of AD treatment. Increase in paraoxonase/arylesterase activities and decrease in p-MDA and apo B-b-MDA levels after 24 weeks seem to be beneficial for reduction of CVD risk in MDD patients. However increased BMI and apo B-Δ-MDA levels are negative cardiovascular effects of long-term AD treatment.

1. Introduction

Oxidative stress, the imbalance between the oxidative–antioxidative systems, plays role in the pathophysiology of several disturbances, including mental health diseases and atherosclerotic vascular diseases (Delimaris et al., 2008; Holvoet, 2004; Maes et al., 2000, 2010; Tsuboi et al., 2006). Major depressive disorder (MDD) is a devastating disease that afflicts large populations and has also been accepted to be an independent risk factor for cardiovascular disease (CVD). Whether oxidative stress primarily or secondarily plays a role in the pathophysiology of MDD and/or CVD, there seems to be an association between these three situations. Genetic factors, such as polymorphism of the oxidative genes in MDD, are also able to help understanding the diseases and clarifying their associations (Galecki et al., 2009a; Maes et al., 2010). Oxidative–antioxidative system indicies and CVD risk factors of MDD patients were investigated in a number of studies. Although there is a general consensus that MDD is associated with oxidative stress, there are discrepencies in the findings of the studies. These discrepencies might be related to the differences in the variations in laboratory methods, test samples, study populations and etc.

There are several indicies of oxidative stress in the human body. Malondialdehyde (MDA), a by-product of polyunsaturated fatty acid

Abbreviations: MDD, major depressive disorder; CVD, cardiovascular disease; MDA, malondialdehyde; LDL, low density lipoprotein; VLDL, very low density lipoprotein; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; GR, glutathione reductase; CAT, catalase; AD, antidepressant; CMS, chronic mild stress; TAOC, total antioxidative capacity; PON1, paraoxonase; HDL, high density lipoprotein; oxLDL, oxidized LDL; p-MDA, plasma MDA; apo B-b-MDA, oxidation of apolipoprotein B-containing lipoproteins; apo B-Δ-MDA, oxidizability of apolipoprotein B-containing lipoproteins; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; RBC, red blood cell; Cu,Zn-SOD, cupper, zinc SOD; CVs, coefficients of variation; BMI, body mass index; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acid.

* Corresponding author at: Tel.: +90 533 225 28 22; fax: +90 224 442 88 52.
E-mail address: ozankotan79@yahoo.com (V.O. Kotan).

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peroxidation and arachidonic acid, is the most widely investigated parameter of oxidative status and has been accepted to be an indicator of lipid peroxidation and oxidative stress (Holvoet, 1999; Maes et al., 2010). Lipoprotein oxidation, particularly low density lipoprotein (LDL) oxidation, has been associated with atherosclerosis formation and CVD risk (Holvoet, 1999; Matsuura et al., 2008; Tsimikas and Witztum, 2008). However, Esterbauer et al. (1992) suggested that not only LDL, but all apolipoprotein B-containing lipoproteins play role in the pathogenesis of atherosclerosis. Oxidized LDL (oxLDL) and very low-density lipoproteins (VLDLs) exert several common biological effects that may contribute to the initiation and progression of atherosclerosis (Jong et al., 2000; Whitman et al., 1998). The evaluation of the oxidative status and susceptibility of serum lipoproteins to oxidation have been reported as an accurate indicator for oxidative status and CVD risk in humans (Holvoet, 2004).

Antioxidative system consists of several enzymes and molecules. Enzymatic and non-enzymatic systems that are synchronized with free radical processes protect cells from damage caused by the free radicals. Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), glutathione reductase (GR) and catalase (CAT) are among the major antioxidant enzymes. Bilirubin, albumin, uric acid, glutathione, vitamin E, vitamin C and vitamin A are among the major non-enzymatic antioxidants (Galecki et al., 2009b; Valko et al., 2007).

Most of the human studies searching oxidative stress parameters in MDD show increased MDA and SOD activity, and decreased antioxidant molecules like vitamins C and E (Bilici et al., 2001; Galecki et al., 2009b,c; Khanzode et al., 2003; Maes et al., 2000; Owen et al., 2005; Sarandol et al., 2007). Antidepressant (AD) treatment was able to improve such changes in the studies of Bilici et al. (2001) and Khanzode et al. (2003); whereas no improvement due to AD treatment was shown in the studies of Sarandol et al. (2007) and Galecki et al. (2009b). MDD patients in the study of Herken et al. (2007) showed decreased SOD activity, which increased after AD treatment.

Animal studies also support the role of oxidative stress in depression. In the olfactory-bulbectomized rats, a depression model, GSH-Px activity was decreased (Song et al., 1994). In male Wistar rats, depression induced by chronic mild stress (CMS) was accompanied by lowered cortical GSH-Px activity (Eren et al., 2007a,b). In another study, CMS reduced total antioxidative capacity (TAOC), glutathione contents, and SOD and CAT activities in mice (Zhang et al., 2009). Lucca et al. reported that rats with CMS-induced depression showed lower SOD activity in the prefrontal cortex, the hippocampus and the striatum (Lucca et al., 2009a, 2009b). Increased vitamin A levels in rat brain by escitalopram treatment, was also shown in the study of Eren et al. (2007a). Zafir and Banu (2007) showed that fluoxetine was able to restore the depletion of antioxidant enzymes like SOD in restraint-stressed rats and prevent the oxidative damage. The severely accumulated MDA and protein carbonyl contents and decreased activities of SOD, CAT, glutathione S-transferase and GR in stressed rodents were significantly normalized by fluoxetine, venlafaxine and imipramine treatments (Zafir et al., 2009).

Paraoxonase (PON1), a high density lipoprotein (HDL) associated antioxidant enzyme exerting both paraoxonase and arylesterase activities, is able to prevent LDL and HDL oxidation and cholesterol efflux (Mackness et al., 2003). Low serum paraoxonase and arylesterase activities were reported in CVD patients (Mackness et al., 2003; Serdar et al., 2006). Some gene polymorphisms of PON1 were also shown to be associated with atherosclerosis in recent studies (Mohamed et al., 2010; Sapian-Raczkowska et al., 2010; Wang et al., 2010). Serum paraoxonase and arylesterase activities were found to be unchanged in MDD patients, but were reduced by AD treatment in the study of Sarandol et al. (2006).

Studies investigating the oxidative stress may help us to understand the mechanism of MDD-CVD relationship and thus find out clues for the prevention of the disease or develop new treatment strategies, such as supportive (antioxidant) treatment or monitoring the progression of the disease or the treatment. There are limited number of studies investigating the effects of AD treatment on oxidative status of MDD patients, which revealed discrepent results as mentioned above. Furthermore, duration of the treatment periods were relatively short (between 6 – 12 weeks) in these studies. In the present study, our aim is to follow up the effects of long term (24 weeks) AD treatment on oxidative–antioxidative system parameters and CVD risk factors in patients with MDD. Considering the relationship between oxidative stress and MDD, we hypothesize that long-term AD treatment will improve oxidative stress in MDD patients.

2. Methods

2.1. Subjects

Seventy-three patients diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994) were included in the study. Patients with an Axis I disorder other than MDD or with an Axis II disorder, as well as patients having MDD with psychotic features and alcohol/substance users were excluded by a semi-structured psychiatric interview. Other exclusion criteria were: diagnosis of a physical disease or syndrome such as chronic fatigue syndrome or fibromyalgia, presence of early CVD in first-degree relatives and pregnancy. Subjects with body mass indices over 30 kg/m^2 and subjects on any regular drug treatment including oral contraceptives, antioxidants or omega-3 polyunsaturated fatty acids were also excluded. Heavy smokers, who smoke $\geq$15 cigarettes/day (Godtfredsen et al., 2005), were also excluded. The patients had been drug-free for at least three months. Controls were recruited from the university staff and were also assessed by a semi-structured psychiatric interview. The control group comprised 44 healthy individuals matched for age, sex, smoking status and body mass indices. Informed consents were obtained from all of the participants. The protocol for the trial was submitted to the ethical committee of Uludag University and the trial was started after approval (Number of bioethics commission agreement: B.30.2.ULU.0.01.00.01.02.020/ 14073).

Laboratory examinations, including complete blood count, serum electrolyte assay, liver function tests, thyroid function tests and electrocardiography were performed to all subjects. Control evaluations of the patients took place on the 6th, 12th and 24th weeks of the follow-up period.

Due to early compliance problems (12 patients), emerged physical illnesses including allergic and inflammatory reactions (7 patients), non-response to given AD treatments (4 patients); 23 MDD patients dropped out in the follow-up period. Patients who did not complete 24 weeks of treatment were excluded from the final data analysis.

17-item Hamilton Depression Rating Scale (HDRS) (Akdemir et al., 1996) and Hamilton Anxiety Rating Scale (HARS) (Yazici et al., 1998) were applied to patients at every visit. A decrease of 50% in HDRS was accepted as the response to treatment. Forty-three MDD patients responded to treatment at the end of 6 weeks, 7 patients at the end of 12 weeks.

2.2. Antidepressant treatment

Proper AD drugs were tried to be chosen for each patient according to her/his psychiatric examination. Chosen drugs were venlafaxine 125 ± 43.3 mg/day (n = 21), paroxetine 25 ± 7.6 mg/day (n = 8), escitalopram 16.3 ± 5.2 mg/day (n = 8), sertralin 80 ± 27.4 mg/day (n = 5), citalopram 33.3 ± 11.5 mg/day (n = 3), milnacipran 100 ± 0 mg/day (n = 2), fluoxetine 20 mg/day (n = 1), tianeptin 37.5 mg/day (n = 1), moclobemid 600 mg/day (n = 1), all of which were used in standard AD doses. Drug change had to be made at the 6th week visit in two patients because of untolerated side effects.