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Levels of nitric oxide, asymmetric dimethyl arginine, symmetric dimethyl arginine, and L-arginine in patients with obsessive-compulsive disorder

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Background/aim: We aimed to investigate and compare to healthy controls the variations in the levels of nitric oxide (NO), asymmetric dimethyl arginine (ADMA), symmetric dimethyl arginine (SDMA), and L-arginine levels in patients with obsessive-compulsive disorder (OCD).

Materials and methods: We enrolled 30 patients with OCD and 30 healthy controls in the study consecutively. Diagnostic interviews of all participants were conducted with the Structured Clinical Interview for Axis I Disorders (SCID-I), and sociodemographic data of the participants were recorded. Patients scoring 10 points or more on the Yale–Brown Obsessive-Compulsive Scale were enrolled in the study.

Results: The NO levels of patients with OCD were increased compared to the control group, but the increase was not statistically significant ($P > 0.05$). However, patients with OCD had significantly lower levels of ADMA, SDMA, and L-arginine compared with the controls ($P < 0.001$).

Conclusion: We found a significant decrease in ADMA, SDMA, and L-arginine as NO inhibitors between the groups, possibly because of an increase in NO. However, the insignificant increase in NO suggests that ADMA, SDMA, and L-arginine play direct and potentially important roles in OCD biology.

Key words: Obsessive-compulsive disorder, nitric oxide, asymmetric dimethyl arginine, symmetric dimethyl arginine, L-arginine

1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder of unknown etiology with a prevalence of 1.9%–3.3% and a usually chronic trend that can significantly impair patients' quality of life (1). It is known that the oxidative mechanisms in OCD are unbalanced, but at the same time, nitric oxide (NO) level can be an important factor in OCD biology (2,3).

Synthesized by the nitric oxide synthase (NOS) enzyme from the L-arginine amino acid, NO is a lipophilic compound with a very short half-life, small molecular structure, and key functions. LN-monomethyl arginine (L-NMMA), symmetric dimethyl arginine (SDMA), and asymmetric dimethyl arginine (ADMA), as natural analogs of the L-arginine amino acid, may competitively inhibit NO synthesis. The neuronal NOS (nNOS) enzyme undertaking NO synthesis is found at higher concentrations in the cerebellum, cerebral cortex, and cerebral areas associated with anxiety and memory such as the hypothalamus, hippocampus, and amygdala (4).

According to a few studies, NO is effective in brain development and realization of brain function (5,6). In addition to the release of noradrenaline and dopamine, NO plays a role in the regulation of numerous physiological functions such as memory and learning, regulation of nociceptive sensory neurons, balance, transmission of stimuli, smelling, and eating (7,8). In addition to affecting various enzyme activities and neurotransmitter release and reuptake in neuropsychiatric diseases, NO plays a role in many physiological and pathological phenomena

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such as regulation of the cerebrovascular system, cerebral ischemia, paralysis, pain perception, cerebral damage related to alcohol consumption, and neurotoxicity in Alzheimer and Huntington diseases (9,10).

The results of a few clinical and experimental studies suggest that NO, which has important biological activity in the central nervous system (CNS) and its periphery, and it may have a role in psychiatric disorders such as alcohol and drug addiction, schizophrenia, mood disorders, and OCD (11,12). Another study reported that neurons regulating nNOS release in suprachiasmatic nuclei in the CNS are reduced by 40% in depression, NMDA receptors effective in NO synthesis play an important role in anxiety and affective disorders, and NMDA receptor antagonist treatments have effective anxiolytic and antidepressant efficacy (13).

Most studies pertaining to NO inhibitors in the literature employed ADMA. ADMA is a natural amino acid present in cells and tissues; it can circulate freely in the plasma and it is removed from the body via urination. Because it is a natural NOS inhibitor, ADMA as a molecule has been addressed significantly in various studies (14). According to previous reports, ADMA may serve as a mortality indicator in cardiovascular diseases. Furthermore, it may be associated with coronary heart diseases and hypercholesterolemia, as well as stroke and ischemic attacks in cerebrovascular diseases (15). ADMA levels increase and NO levels decrease in major depression (13). Moreover, some studies have indicated that various NOS-inhibiting agents generate antidepressant effects in laboratory animals (16,17). Ferreira et al. observed that 7-nitroindazole, a central selective NOS inhibitor, potentiates the anxiolytic effects of alcohol in experimental anxiety created in rats (18). The anxiolytic effects of NOS inhibitors are supported by other studies as well (19).

Our literature review revealed no study collectively addressing the relationship between NO and its inhibitors, namely ADMA, SDMA, and L-arginine, in OCD. Based on the assumption that in OCD neurobiology there may be differences among NO levels and ADMA, SDMA, and L-arginine levels, which are natural NO inhibitors, it is aimed to investigate the roles of NO, ADMA, SDMA, and L-arginine levels in OCD.

2. Materials and methods

2.1. Participants

The Ethics Committee of the Faculty of Medicine of Fırat University approved the study. All participants were informed about the study, and blood samples were taken with their informed consent.

Thirty inpatient and outpatient OCD patients (13 males, 17 females) admitted to the Istanbul Erenköy Training and Research Hospital for Mental and Neurological Diseases during April–June 2010 and 30 healthy controls (12 males, 18 females) were sequentially included as participants in the study. Diagnostic interviews of all participants were conducted according to the Diagnostic and Statistical Manual of Psychiatry 4th version (DSM IV) Structured Clinical Interview for Axis I Disorders (SCID-I) (20), and the sociodemographic data of the participants were recorded.

Criteria for inclusion in the study were as follows:

1) Patient age greater than 18 years
2) Clinically diagnosed with OCD as per the DSM-IV
3) Ten or more points on the Yale–Brown Obsessive-Compulsive Scale
4) Reading and signing the informed consent form

Criteria for exclusion in the study were as follows:

1) Patient age less than 18 years
2) Currently diagnosed with psychiatric disorders other than OCD
3) Currently having a cardiovascular disease
4) Currently having a cerebrovascular disease
5) Diagnosed with diabetes mellitus
6) Having defects in renal functions

2.2. Clinical scales

2.2.1. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

This interview was developed in 1987 to diagnose subjects/patients according to the DSM III-R criteria, followed by DSM-IV adaptation in 1997 (20). A validity and reliability study of its Turkish form was performed (21).

2.2.2. Yale–Brown Obsessive-Compulsive Rating Scale (Y-BOCS)

Goodman et al. developed this scale for clinicians to rate the severity of obsessive-compulsive symptoms (22). Items 1–5 on the scale reflect obsession points, and items 6–10 reflect compulsion points. The sum of both types of points yields the total obsessive-compulsive score. Two independent studies have tested the validity and reliability of the Turkish form of this scale (23,24).

2.3. Biochemical measurements

We took 4 mL of fasting blood samples from each participant by venipuncture after 12 h of fasting, between 0800 and 0900 hours, and collected the samples in anticoagulant-free vacuum tubes. The samples were allowed to clot and then centrifuged at 3000 × *g* for 10–15 min. The serum aliquots were stored at –80 °C until we assayed and thawed them immediately before the measurement of the biochemical parameters. Routine biochemical parameters and lipid levels were measured in an autoanalyzer with appropriate commercial kits (Abbot Brand kits and Abbott Architect C8200I, Abbott Corp., USA).

2.3.1. Measuring total nitric oxide (NO_X) levels of the serum

Nitric oxide produced in biological systems is oxidized into nitrite (NO_2) and nitrate (NO_3) in a very short period of 2–30 s. Therefore, by measuring NO_2 and NO_3 levels, we determined the total nitric oxide levels.

We authors employed a spectrophotometric method modified by Cortas et al. (25) for NO_2 and NO_3 measurements.

2.3.2. Measuring serum arginine, ADMA, and SDMA

In this study, L-arginine, ADMA, and SDMA levels were measured by high-performance liquid chromatography (HPLC) using a EUREKA kit (EUREKA, Italy) and a fluorescence detector (26).

2.4. Statistical analysis

The data collected in the study are presented as average ± standard deviation. For comparisons between groups, we applied Student's t-test, the chi-square test, and Fischer's exact chi-square test with $P < 0.05$ as the lowest significance level.

3. Results

The sociodemographic data related to the groups are presented in Table 1. In Table 1, we summarize the results of a comparison of age made using Student's t-test and those of the other parameters using chi-square and Fischer's exact chi-square tests.

The biochemical parameters of both groups were compared with Student's t-test and no significant difference was found between the control group and the OCD group in terms of glucose, urea, and creatinine levels ($P > 0.05$, $P > 0.05$, $P > 0.05$) (Table 2).

In contrast, based on the respective lipid parameters of the groups, total cholesterol values were significantly higher in the OCD patient group compared to the control group ($P < 0.05$). Moreover, triglyceride values were found to be significantly different between the groups ($P < 0.05$) (Table 2).

An increase in NO level (51.58 ± 8.30 μmol/L) was observed in the control group compared to that (54.01 ± 6.52 μmol/L) in the OCD group, not reflecting a statistically significant difference ($P > 0.05$).

Table 1. Sociodemographic data of control and OCD patient groups (Student's t-test, chi-square test, Fischer's exact test).

	Groups		P
	Control (n = 30)	OCD (n = 30)	
Age (years)	35.19 ± 9.99	33.26 ± 10.38	NS
Sex (M / F)	12 / 18	13 / 17	NS
Educational status			
Not literate	-	1	P < 0.05
Primary school	6	6	
Secondary school - high school	15	19	
University	9	4	
Marital status			
Married	22	14	P < 0.05
Single	8	16	
Residence			
Provincial center	18	26	NS
District	6	3	
Village or town	1	1	
Status of employment			
Yes	27	14	P < 0.001
No	3	16	
History of disease in the family			
Yes	-	5	P < 0.001
No	30	25	
Y-BOCS score	0.00 ± 00	21.53 ± 5.25	P < 0.001

OCD: Obsessive-Compulsive disorder, Y-BOCS: Yale–Brown Obsessive-Compulsive Rating Scale, NS: not significant.

Table 2. Biochemical parameters of control and OCD patient groups (Student's t-test).

	Groups		P
	Control (n = 30)	OCD (n = 30)	
Glucose (mg/dL)	91.61 ± 7.96	98.06 ± 9.68	P < 0.05
Urea (mg/dL)	28.00 ± 6.37	27.41 ± 5.37	P > 0.05
Creatinine (mg/dL)	0.78 ± 0.09	0.81 ± 0.13	P > 0.05
Total cholesterol (mg/dL)	166.94 ± 17.07	186.83 ± 44.98	P < 0.05
Triglyceride (mg/dL)	86.00 ± 22.64	115.81 ± 59.38	P < 0.05
HDL (mg/dL)	47.96 ± 12.22	47.66 ± 12.78	P > 0.05
LDL (mg/dL)	101.31 ± 18.03	118.16 ± 38.96	P < 0.05
NO (μmol/L)	51.58 ± 8.30	54.01 ± 6.52	P > 0.05
L - Arginine (μmol/L)	74.75 ± 9.19	45.74 ± 9.42	P < 0.001
ADMA (μmol/L)	5.72 ± 1.81	2.31 ± 0.59	P < 0.001
SDMA (μmol/L)	3.67 ± 0.98	0.27 ± 0.06	P < 0.001

OCD: Obsessive-compulsive disorder, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NO: nitric oxide, ADMA: asymmetric dimethyl arginine, SDMA: symmetric dimethyl arginine.

A comparison of serum L-arginine level in the OCD group (45.74 ± 9.42 μmol/L) with that in the control group (74.75 ± 9.19 μmol/L) revealed a highly significant decrease in patients with OCD (P < 0.001).

In contrast, the level of serum ADMA, a natural NOS inhibitor in NO metabolism, decreased significantly in the OCD group (2.31 ± 0.59 μmol/L) compared to the control group (5.72 ± 1.81 μmol/L) (P < 0.001).

The average SDMA level of 0.27 ± 0.06 μmol/L in the OCD group was significantly lower than the value of 3.67 ± 0.98 μmol/L in the control group (P < 0.001).

4. Discussion

According to a few studies, in several neuropsychiatric disorders, free oxygen radicals effectively influence disease onset and prognosis, as well as changes occurring in blood circulation of brain (15,27). NO's role in CNS-related diseases is believed to be mediated by an excessive release mechanism (28,29).

In the present study, which is the first to collectively investigate the levels of NO, ADMA, SDMA, and L-arginine, we found that NO level was insignificantly higher in patients with OCD compared to the control group, while ADMA, SDMA, and L-arginine levels were significantly lower.

The findings in the literature indicate that as ADMA level increases, NO level decreases (10,30,31). In our study, although NO level was determined to increase, the increase was not statistically significant. This finding might result from the fact that the sample group was not large enough. In addition, Zincir and Zincir (32) claimed that abnormalities in NO and ADMA production in schizophrenia patients can be related to disease chronicity. Similarly, abnormalities in the production of NO and ADMA in OCD patients can vary with the chronicity of OCD.

In recent years, free oxygen radicals have come to be known as a risk factor in pathogenesis and systemic complications of many diseases, including neuropsychiatric disorders, and many studies have attempted to inhibit and treat cell damage caused by free oxygen radicals (33,34). NO is a neuromodulator highly addressed in recent psychiatry studies (34–36). Symptoms caused by neuronal damage associated with changes in NO levels in the CNS have attracted increased research attention toward the role of NO metabolism in diseases causing psychiatric disorders. Here, in addition to the relationship of NO with cerebral regions known to be associated with a variety of symptoms and mental disorders, NO is known to play a critical role in combination with a few structures to give rise to neuronal damage (28). Moreover, a few compounds, which are natural NO inhibitors, released in an organism with NO may play a role in this condition. ADMA, SDMA, and L-arginine are the most important examples of such compounds (37). In combination with free oxygen radicals, NO forms highly toxic peroxynitrite radicals

that cause destruction, particularly by damaging cell membranes (38). Because of reactions with heavy metals, severe cellular damage may occur from lipid peroxidation and nitrosylation of various molecules (39).

Studies report that changes in NO levels play an important role in conditions such as behavioral development, changes in appetite, and disorders such as brachial ischemia, schizophrenia and bipolar disorders, depression, and eating disorders (4,32,40,41).

The authors of an investigation of NO levels in bipolar disorders found higher NO levels in patients compared to the control group (42). Another study proved that the average plasma ADMA concentration in schizophrenia patients is 3 times higher than that in healthy subjects (43). Two separate studies found higher NO levels in patients with depression compared to those in the control groups (44,45). Yet another study found lower NO levels in patients compared with the control group (46). In a study performed on a control group composed of 21 pregnant women with depression and 42 participants, lower plasma levels of ADMA and L-arginine as NO inhibitors were found in pregnant women with depression (47). In studies measuring NO levels on cerebellar Purkinje fiber synapses in rats under depression, the authors reported that changes in NO levels were associated with psychomotor failure (48,49). One study showed that fluoxetine and tianeptine as antidepressant agents inhibit nNOS in the CNS to suppress NO activity (50). In one study where NO, nesfatin-1, and ghrelin levels were investigated in patients with major depression after venlafaxine treatment, posttreatment nesfatin-1 and ghrelin levels decreased significantly, contrary to the NO level, which increased significantly. The findings of that study suggest that decreasing nesfatin-1 and increasing NO towards normal values constitutes a major criterion in the evaluation of treatment response (51).

In a study of Alzheimer patients, the increase in ADMA levels in the plasma and the decrease in ADMA levels in the cerebrospinal fluid were highly significant (52). In another study, ADMA eased the response to acetylcholine by affecting cerebral blood flow in the resting condition (37).

In a study, it was found that NO level was higher in OCD patients compared to that in controls, and the authors of that study stated that NO might be an important factor in OCD biology (3). In our study, NO level was found to be insignificantly higher in the patient group compared to that in the control group. The higher NO level in OCD patients compared to that in the controls might be ascribed to the fact that in the mentioned study, plasma NO levels were studied, whereas we investigated NO levels in serum samples. In addition, we thing that this difference could be due to the difference in case numbers in both studies. Increase in the levels of NO as an antioxidant may be in response to a pathology in OCD biology. However, despite the insignificant increase in NO levels, we found highly significant increases in the levels of ADMA, SDMA, and L-arginine as NO inhibitors between the groups. Although a possible interpretation is that an increase in NO led to a decrease in inhibitors, the insignificant increase in NO suggests direct, potentially important roles of ADMA, SDMA, and L-arginine in NO biology. Our review of the literature reveals that these findings have not been reported hitherto in OCD patients. Moreover, according to the literature, increase in NO level, despite it being an antioxidant, may have direct neurotoxic effects (53,54).

It is known that ADMA increases oxidative stress, especially causing damage in lipid levels and weakening the enzymatic antioxidant system (55,56). According to a study on metabolic syndrome (MS) patients, fluvastatine given to cure the disorders in the lipid profile causes recovery in the lipid profile while causing a significant decrease in serum ADMA levels, and, in this way, it is effective on endothelial functions in MS patients (57,58). In our study, when considering the lipid parameters together with increased ADMA levels in OCD patients, we observed that there were significant increases, especially in LDL cholesterol and triglyceride levels. According the literature, an increase in ADMA levels increases vascular risk factors, especially in patients with coronary heart disease (59). Lundman et al. also reported that ADMA levels increased significantly together with the increase in triglyceride levels (60). This shows that the increase in ADMA levels, especially abnormalities in lipid levels together with irregularities in NO metabolism resulting from vascular structure dysfunction, can be more risky for OCD patients with regard to cardiovascular and cerebrovascular complications. In the etiopathogenesis of OCD patients, complex mechanisms are effective, in which free radicals are also held responsible for, in addition to serum ADMA levels and abnormalities in lipid levels, risk factors that play important roles in endothelial structure degeneration. Therefore, to prevent cardiovascular and cerebrovascular system complications, new treatment approaches effective on these parameters should be developed.

There are some limitations to our study. In addition to the limited number of participants, several publications in the literature suggest that a few metabolic disorders, insulin resistance, glucose tolerance, diabetes mellitus, hyperlipidemia, chronic kidney disease, hypertension, and coronary heart diseases may be associated with increased ADMA levels (61,62). Moreover, in this study, we found that total cholesterol and triglyceride levels in OCD patients were higher compared to those in the control group, but there was no difference between the groups

in terms of blood glucose, urea, and creatinine levels. In addition, most of our patients were medicated with SSRI group antidepressants. Data from the literature suggest that antidepressant agents are effective for oxidative stress and NO (63,64).

All these data indicate the need to carry out further studies on the relationship among NO, ADMA, SDMA, and L-arginine in OCD neurobiology with greater numbers of participants to obtain deeper statistics.

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