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Relationship between Oxytocin Level and Major Depressive Disorder

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ABSTRACT

Background: major depressive disorder is one of the most common medical disorders worldwide, having huge impact on physical and mental health in the society and is considered an extended life-threatening psychiatric disorder. Abnormalities in the neurohypophyseal system, neuroendocrine, and immune systems have been reported in depression. **Aim of the Work:** this study was carried out to identify the relationship between plasma oxytocin level and the severity of major depressive disorder. **Patients and Methods:** this case control observational study was started from July 2016 till March 2018. The subjects were selected from inpatient and outpatient clinics of Institute of Psychiatry, Faculty of medicine, Ain Shams University. Twenty two female patients were enrolled and fourteen female healthy subjects were considered as controls. Both groups were subjected to Arabic version of Structured Clinical Interview for DSM-IV-TR Axis I Disorders and sampling of serum Oxytocin. Moreover the female patients were subjected to Hamilton rating scale for depression and state trait anxiety inventory to assess the presence of anxiety symptoms. **Results:** our study revealed reduced serum oxytocin levels in depressed female patients with cutoff point ≤25.6 denoting that below this level shows probability for major depressive disorder in females. **Conclusion:** our study revealed reduced serum oxytocin levels in depressed female patients. Consistently with the hypothesis of dysregulated OXT biology may serve as a biomarker for major depression.

Keywords: Oxytocin, major depressive disorder, Hamilton Rating Scale for Depression, state trait anxiety inventory.

INTRODUCTION

Major depressive disorder (MDD), is associated with substantial deficits in quality of life, considered to be the leading cause of disability globally as it affects nearly 350 million people worldwide [(1,2)]. Importantly, the quality of life deficits revealed to persist beyond the clinical resolution of symptoms. Placing patients at an increased risk for relapse and rising direct and indirect costs [(3)]. In the last decades several neuropeptide families were discovered having modulatory roles on neurotransmission in synapses. This in turn evoked the interest of psychoneuro-endocrinologists predicting potential significant clinical relevance in the treatment of stress-related mood disorders [(4)]. Oxytocin (OXT) is a neuropeptide produced in the hypothalamus, involved in a broad range of physiological and behavioral processes [(5)]. A few data suggest a link between Oxytocin and neuropsychiatric disorders, especially obsessive-compulsive disorder, addiction, post-traumatic stress disorder, anxiety, depression, schizophernia and autism which elevates the need for further research [(6)]. A recent perspective added the possible role for oxytocin in depressive disorders. Oxytocin is involved in prosocial behaviors such as attachment, affiliation, trust, and social support [(7)]. Moreover, several studies have reported a significant association between plasma OXT levels and major depressive disorders in both humans and animals. An increased concentration of OXT in plasma is negatively correlated with symptoms of depression [(8)]. There has been unprecedented interest in the prosocial effects of the neuropeptide oxytocin in humans over the last decade. A range of studies have shown correlations between basal oxytocin levels and the strength of social and bonding behaviors in both healthy individuals and in those suffering from psychiatric disorders[(9)]. It was found that plasma OXT levels are reduced in patients suffering from major depression. In animal models of depression, OXT has been shown to act as a potent antidepressant. It has been suggested that one of the mode of actions of selective serotonin reuptake inhibitors (SSRIs) is through increased OXT release[(10)]. Clinical reports suggest OXT to be a promising drug for psychiatric diseases such as depression, anxiety disorders, schizophrenia, and autism. OXT may also have therapeutic potential in the treatment of major depressive disorders [(11)].

AIM OF THE WORK

To measure plasma oxytocin level in major depressive disorder patients. To identify the relationship between plasma oxytocin level and the severity of major depressive disorder by Hamilton Rating Scale for Depression (HRSD). To compare between plasma oxytocin level in major depressive

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disorder patients versus healthy control not suffering from depression. To determine whether there is difference in oxytocin level in patients with Major depressive disorder versus patients experiencing Major depressive disorder with comorbid anxiety symptoms.

PATIENTS AND METHODS

A. Study design: Case control study; comparative study.

B. Study Proper: The research study was started from July 2016 till March 2018.

C. Site of the study: The subjects were selected from inpatient and outpatient clinics of Institute of Psychiatry, Faculty of medicine, Ain Shams University. Ain Shams

D. Approval and consent: 1. Approvals and Ethical consideration: All procedures were reviewed and approved by the Ethical Committee of Ain Shams University. **2. To access the Hospitals:** After taking the approval of the Ethical committee. **3. Consent:** A written informed consent was obtained from all participants involved in the study. **4. Ethical considerations:** Confidentiality of the participants was ensured and none of the collected data was revealed; unless it was asked by the candidate. All the participants had the right to withdraw from research at any time without giving reasons, and without any negative consequences. No direct benefits or risks were expected from this study except for the psychological discomfort with lengthy interview. That was minimized by dividing it into more than one interview; according to the participant's capacity.

E. Study Procedure: 1. Selection of patients: Forty patients were recruited to this study, selected from inpatient and outpatient clinic of the Institute of Psychiatry, Faculty of Medicine, Ain Shams University, fulfilling the diagnosis of Major Depressive Disorder according to DSM-IV TR and according to the inclusion and exclusion criteria which are mentioned afterwards. **a) Inclusion criteria of the patient group:** Patients diagnosed with major depressive disorder, in which depressed patients were allowed to remain on their psychotropic medications provided the dose has not been adjusted in the last week. Patients having active episode, having scores above 17 by Hamilton rating scale for depression. Sex: Both males and females. Age: 18-45. **b) Exclusion criteria of the patient group:** Patients with Medical disorders, history of seizures, major head trauma and abnormal clinical laboratory tests. Patients receiving any hormonal therapy or steroids. Females with menstrual irregularities or using hormonal contraceptives. Pregnancy and lactation. Past history of diagnosis with schizophrenia, bipolar affective disorder and delusional disorder. Substance abuse problems in the last 6 months. **3. Selection of controls:** According to Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-**I,**) Forty healthy age-matched and sex-matched individuals were enrolled in this study as a control group collected from relatives of the patients and workers at the Institute of Psychiatry، Faculty of Medicine، Ain Shams University fulfilling the inclusion and exclusion criteria which are mentioned afterwards. **a) Inclusion Criteria of the control group:** Sex and age should be matching with the patient group. **b) Exclusion criteria of the control group:** as the exclusion criteria of the patients with exclusion of past history of diagnosis with any psychiatric disorder

Patients group were subjected to the following: 1. Full history taking: by using designed sheet for personal history and for assessment of the following domains: Personal data. Social and income status. Employment status. Family history of psychiatric disorder. **2. Arabic version of Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) [(12)]:** for clinical assessment and diagnosis of Major depressive disorder and to exclude other psychiatric disorders. **3. Hamilton Rating Scale for Depression (HRSD) [(13)]:** To rate the severity of depressive symptoms. **4. State trait anxiety inventory (STAI) [(14)]:** to assess the presence of anxiety symptoms. **5.** Morning Serum levels of oxytocin was measured at 8:00 a.m. from all patients, Blood samples were centrifuged within 2 hours and the serum was immediately frozen and kept at -20 °C until analyzed by using Human Oxytocin ELISA Kit with detection range from 10 ng/ml-450 ng/ml.

Control group were subjected to the following: 1. Arabic version of Structured Clinical

Interview for DSM-IV-TR Axis I Disorders (SCID-I) [12]: for exclusion of psychiatric disorders. 2. Morning Serum levels of oxytocin was measured. **Statistical analysis:** The collected data of the present study were revised, coded, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS®); software program version 17.0. Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

RESULTS

Comparing between patients and controls: OXT level: On comparing the OXT level between the female patients group and the female controls group, we found a statistical significant difference P-value (<0.001). Denoting that group A has lower level of oxytocin than group B **(Table 1)**.

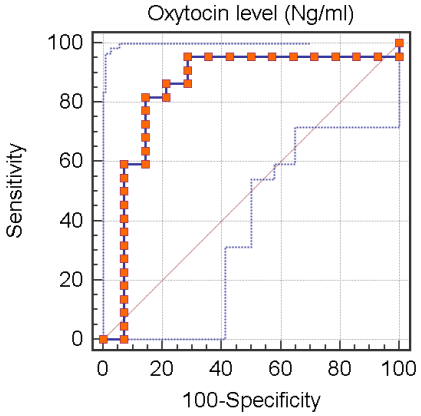
Table (1): Comparison between patients group and the controls group regarding the oxytocin level.

		Oxytocin level (ng/ml)			Mann-Whitney Test	
		Range	Median	IQR	Z	P-value
Female	Patients	14.8 - 450	19.9	7.425	3.440	<0.001*
	Controls	14.5 - 404.3	38.15	95		

Receiver operator curve (ROC) was done between the female patients group and female controls groups for the evaluation of the serum oxytocin test. Sensitivity recorded 81.82 while specificity was 85.71with accuracy 84.4 %and having a cutoff point ≤ 25.6 denoting that below this level shows probability for major depressive disorder **(Table 2)**.

Table (2): ROC curve between female Patients and female Controls.

Cutoff	Sensitivity	Specificity	Postive predictable value	negative predictable value	Accuracy
≤ 25.6	81.82	85.71	90.0	75.0	84.4 %



Relation between OXT level and Psychometric scales in female patients: Non-significant correlation was present between Hamilton score, STAI (state) and STAI (traits), in addition no significant difference was observed when comparing SCID-I diagnosis with OXT level (P-value= 0.453, 0.351, 0.594, 0.195 respectively) **(Tables 3,4) and (figure 1).**

Table (3): Correlations between Hamilton score and STAI (state and trait) in female patients with the oxytocin level.

Correlations		
Female Patients	Oxytocin level (Ng/ml)	
	r	P-value
Hamilton score	0.169	0.453
STAI (state)	0.209	0.351
STAI (traits)	0.120	0.594

Table (4): Relation between SCID-I diagnosis and oxytocin level.

SCID diagnosis	Oxytocin level (Ng/ml) (Female patients)			Mann-Whitney Test	
	Range	Median	interquartile range	Z	P-value
MDD	14.8 - 28.8	18.75	7.53	1.297	0.195
MDD and GAD	17 - 450	21.35	10.23		

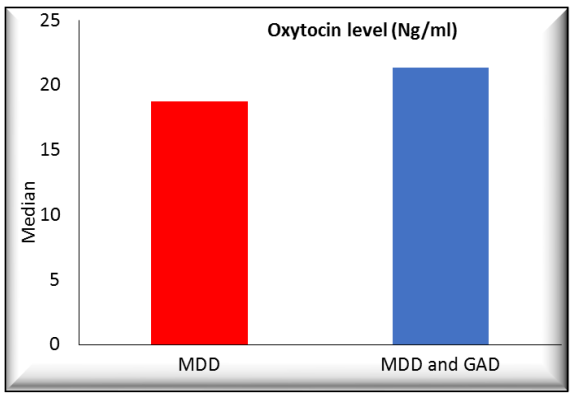


Figure (1): Oxytocin level.

DISCUSSION

Depression is now a leading cause of disability worldwide and it is a major contributor to the overall global burden of disease [15]. The relationship between oxytocin and psychiatric disorders has been a major concern in many studies. We hypothesized that that plasma oxytocin (OXT) level is altered in female patients with major depressive disorder. The study involved 80 participants. 22 patients were females diagnosed

with MDD and 14 healthy controls were females. All the participants in the study were assessed after taking an oral and a written consent. On comparing both oxytocin level in the female patients and female control groups, it revealed high statistical significance among the two groups (P- value= 0.001) this was similar to that found by ***Yuen et al. study*** [16] ***and Ozsoy et al. study*** [17] in which P-value =0.0093, 0.015 respectively. Cutoff point was ≤ 25.6 denoting that below this level shows probability for major depressive disorder, specificity 85.71and sensitivity 81.82 with accuracy 84.4 % which were measured in our study, yet no studies measured the cutoff point for the evaluation of the serum oxytocin test. Females may be more sensitive to the effect of stress on oxytocin. Recent research suggested that oxytocin plays a role in stress responses by inhibiting HPA-axis activity and that this role is modulated by ovarian hormones, especially estrogen [18, 19]**.** In Addition, females OXT plays its role of promoting social bonding [20, 21]**,** and when females experience social isolation or loss, as frequently occurs prior to onset of depression [22]**,** they experience diminished OXT release. This finding is in accordance with previous results that reported a negative association between plasma oxytocin levels and depression scores [8], yet the current study showed non-significant correlation between OXT level and the severity of depression on the HRSD which could be related to small sample size. The conclusion of the present study, together with the findings of earlier reports might suggest dysfunction of the neurohypophyseal system in depression. The function and physiological regulation of the oxytocin system are probably related to the HPA axis. Oxytocin has been shown to have stress-attenuating and anxiolytic effects and to act as an antidepressant in animal models of depression [23, 24]. Oxytocin, on the other hand, inhibits adrenocorticotropic hormone (ACTH) [25]**.** Increased HPA activity in depression is probably associated with decreased oxytocin levels [17]**.** On the other side, some earlier studies found no alteration in basal oxytocin levels in depressive patients as shown in the study of ***Scantamburlo and colleagues*** [26] **as well as indicated through the results of** ***van Londen and colleagues*** [27]**,** who compared 52 MDD patients with 37 healthy controls**.** This discrepancy between the studies may be the result of differences between the patient populations, enrolling of both genders or between the kits used. Regarding the HRSD, non-significant correlation was present between HRSD score and OXT level (r = 0.169, P-value=0.453). This was in agreement with that revealed by ***Ozsoy et al.*** [17] **who found** non-significant correlation between serum oxytocin levels and scored symptoms of depression. In the contrast with ***Scantamburlo et al.*** [8], the mean score of HRSD was 30.9 and their results showed a significant negative correlation between the symptom depression and plasma OXT levels (r=-0.58, P- value =-0.003). This difference may be due to the difference in the sample size, age, inclusion of both genders and different cultures. In addition, the Current study measured the STAI (state) and (traits) in female patients who showed non significance correlation between both STAI (state); STAI (traits) and oxytocin level (**r =** 0.209**,** 0.120 respectively, P-value= 0.351, 0.594 respectively). This was in aligning with the conclusion of ***Ozsoy et al.*** [17] in which no significant correlation was found between serum oxytocin levels and scored symptoms of anxiety on the clinical anxiety scale. However, in the study of Scantamburlo ***et al.*** [8]**, it was found that the correlations** between OXT and STAI (State) showed a significant negative correlation between anxiety and OXT levels (r =-0.61, P-value = 0.005) yet in our study we failed to find any significant correlations between both STAI and OXT level, This difference between both studies may be due to different cultures, recruiting both genders and different sample size.

CONCLUSION

In conclusion, our study revealed reduced serum oxytocin levels in depressed female patients with cutoff point ≤ 25.6 denoting that below this level shows probability for major depressive disorder. Consistently with the hypothesis of dysregulated OXT biology may serve as a biomarker for major depression with statistical significance on comparing matching gender between patients and controls. No correlation was found with on comparing OXT with the severity of depression on HRSD and associated anxiety symptoms on STAI. Further studies with a larger number of subjects would be recommended. Moreover, there is a suggestion that intranasal OXT "replacement" therapy may be efficacious in patients with known impairments in OXT signaling.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. **Rapaport MH, Clary C, Fayyad R *et al.* (2005):** Quality-of-life impairment in depressive and anxiety disorders. The American Journal of Psychiatry, 162:1171–1178.
2. **Ishak WW, Balayan K, Bresee C *et al.* (2013):** A descriptive analysis of quality of life using patient-reported measures in major depressive disorder in a naturalistic outpatient setting. Quality of life research: an international journal of quality of life aspects of treatment, Care and Rehabilitation, 22:585–596.
3. **Ishak WW, Mirocha J, James D *et al.* (2015):** Quality of Life in Major Depressive Disorder Before/After Multiple Steps of Treatment and One-year Follow-up. Acta Psychiatr Scand., 131: 51–60.
4. **Paschos KA, Veletza S, Chatzaki E (2009):** Neuropeptide and sigma receptors as novel therapeutic targets for the pharmacotherapy of depression. CNS Drugs, 23: 755–772.
5. **McQuaid RJ, McInnis OA, Stead JD *et al.* (2013):** A paradoxical association of an oxytocin receptor gene polymorphism: early-life adversity and vulnerability to depression. Original Research Article, 7: 128.
6. **Marazziti D & Dell'Osso MC (2008):** The Role of Oxytocin in Neuropsychiatric Disorders. Current Medicinal Chemistry, 15: 698-704.
7. **McQuaid RJ, McInnis OA, Abizaid A *et al.* (2014):** Making room for oxytocin in understanding depression. Neuroscience and Biobehavioral Reviews, 45: 305–322.
8. **Scantamburlo G, Hansenne M, Fuchs S *et al.* (2007):** Plasma oxytocin levels and anxiety in patients with major depression. Psychoneuroendocrinology, 32: 407–410.
9. **Striepens N, Kendrick KM, Maier W *et al.* (2011):** Prosocial effects of oxytocin and clinical evidence for its therapeutic potential. Frontiers in Neuroendocrinology, 32: 426–450.
10. **Ishak WW, Kahloon M, Fakhry H (2011):** Oxytocin role in enhancing well-being: A literature review. Journal of Affective Disorders, 130: 1–9.
11. **Matsuzaki M, Matsushita H, Tomizawa H *et al.* (2012):** Oxytocin: a therapeutic target for mental disorders. J Physiol Sci., 62:441–444.
12. **First M, Spitzer R, Williams J *et al.* (1995):** Structured Clinical Interview for DSM-IV (SCID-I) (User's Guide and Interview) Research Version. New York, Biometrics Research Department, New York Psychiatric Institute. Available at: http://www.scid4.org/info/refscid.html.
13. **Hamilton M (1967):** "Development of a rating scale for primary depressive illness." Br J Soc Clin Psychol., 6:278-296.
14. **Spielberger CD, Gorsuch RL, Lushene RE (1970):** Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press. Available at: https://www. researchgate. net/ publication/ 235361542_ Manual_ for_ the_State-Trait_ Anxiety_ Inventory_Form_Y1_-_Y2
15. **World Health Organization (2016):** Depression: Fact Sheet No. 369. www.who.int › News › Fact sheets ›
16. **Yuen KW, Garner JP, Carson DS *et al.* (2014):** Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. Journal of Psychiatric Research, 51:30-36.
17. **Ozsoy S, Esel E, Kula M (2009):** Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. Psychiatry Research, 169: 249-252.

18. **Taylor SE, Gonzaga GC, Klein LC *et al.* (2006):** Relation of oxytocin to psychological stress responses and hypothalamic–pituitary–adrenocortical axis activity in older women. Psychosomatic Medicine, 68: 238–245.

19. **Ochedalski T, Subburaju S, Wynn PC *et al.* (2007):** Interaction between oestrogen and oxytocin on hypothalamic–pituitary–adrenal axis activity. Journal of Neuroendocrinolgy, 19: 189–197.

20. **Lim MM and Young LJ (2006):** Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Hormones and Behavior, 50:506-517.

21. **Witt DM, Winslow JT, Insel TR (1992):** Enhanced social interactions in rats following chronic, centrally infused oxytocin. Pharmacology Biochemistry and Behavior, 43:855-861.

22. **Bruce ML and Hoff RA (1994):** Social and physical health risk-factors for 1st-onset major depressive disorder in a community sample. Social Psychiatry and Psychiatric Epidemiology, 29:165-171.

23. **Anderberg UM ,Uvnas-Moberg K (2000):** Plasma oxytocin levels in female fibromyalgia syndrome patients. Zeitschrift für Rheumatologie, 59: 373–379.

24. **Arletti R , Bertolini A (1987).** Oxytocin acts as an antidepressant in two animals models of depression. Life Sci., 41:1725–1730.

25. **Legros JJ (2001):** Inhibitory effect of oxytocin on corticotrope function in humans: are vasopressin and oxytocin ying-yang neurohormones? Psycho-neuroendocrinology, 26:649–655.

26. **Scantamburlo G, Hansenne M, Fuchs S *et al.* (2005):** AVP- and OT-neurophysins response to apomorphine andclonidine in major depression. Psychoneuroendocrinology, 30: 839–845.

27. **Van Londen L, Goekoop JG, Van Kempen GM *et al.* (1997):** Plasma levels of arginine vasopressin elevated in patients with major depression. Neuropsycho-pharmacology, 17: 284–292.