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Association Between MKP-1, BDNF, and Gonadal Hormones with Depression on Perimenopausal Women

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Abstract

Background: Studies suggest that brain-derived neurotrophic factor (BDNF) exerts effects on the neuronal function of hippocampal neurons and increases hippocampal mitogen-activated protein kinase phosphatase-1 (MKP-1) expression, which causes depressive behaviors in rat or mouse. Here we focus on the change of serum MKP-1, BDNF, testosterone (T), and estradiol (E_2) levels, in order to test the hypothesis that dysregulation of MKP-1, BDNF, T, and E_2 are associated with depression in perimenopausal women.
Methods: Women with depression, after meeting criteria in the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, for mental and behavioural disorders and the 17-item Hamilton Depression Rating Scale (HDRS), were included in the study. Psychosocial data and blood samples were obtained from the subjects in the study, including 38 perimenopausal and 32 young women with depression, 26 healthy control perimenopausal women, and 34 young women.
Results: Serum MKP-1 levels were higher and T was lower in the women with depression compared to controls ($p < 0.05$), and depressed perimenopausal women exhibited the highest serum MKP-1 levels and lowest T levels. Logistic regression analyses showed that MKP-1 levels were positively correlated with HDRS scores in the women, and T levels were inversely correlated with HDRS scores in the perimenopausal women ($p < 0.05$).
Conclusions: This study suggests that high serum MKP-1 levels are associated with depression in women, and this association did not appear to be confounded by age. Further, the results provide evidence of association between depressive symptom severity and increasing serum MKP-1 levels in women, and decreasing T levels in perimenopausal women.

Introduction

Epidemiological and clinical data have unequivocally supported the notion that women experience more psychiatric problems during their lives, particularly mood and anxiety symptoms, compared with men. For some women, the increased risk is associated with fluctuating ovarian hormone levels that occur during reproductive cycle events, particularly during the menopausal transition. Estrogens have a mood-enhancing effect in depression arising during the transitional phase of menopause. Recent data show that hormone therapy may prevent mood disorders or even serve as a treatment regimen for women with diagnosed mood disturbances via estrogen regulation.[1,2,3] Although estrogen has greater effects on the behaviors and mood of women, androgens such as testosterone also have important effects.[4] Women with major depressive disorder or certain types of anxiety disorder express lower levels of salivary testosterone compared with emotionally healthy women.[5] In more senior men and women, lower levels of testosterone are associated with an increased prevalence of major depressive disorder.[6] Clinical evidence also suggests that testosterone has anxiolytic and antidepressant benefits, with the potential to promote improved mood and mental health in both women

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and men.[7] However, the neurobiological mechanisms underlying the protective effects of estrogens and testosterone in females remain poorly understood.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin abundantly expressed in several areas of the central nervous system. BDNF plays a crucial role in numerous aspects of vertebrate brain development and function, including neurogenesis, cell survival, growth of axonal projections, synaptogenesis, and processes linked to learning and memory. Several studies have shown altered BDNF production and secretion in a variety of neurodegenerative diseases like Alzheimer's and Parkinson's diseases and also in mood disorders like depression and schizophrenia.[8] These observations stimulated us to investigate a putative coregulation between BDNF and gonadal hormones as well as their relationship to the incidence of depression.

BDNF influences cellular function via activation of the tyrosine kinase receptor B as well as the mitogen-activated protein kinase (MAPK) cascade that includes extracellular signal-regulated kinase (ERK) signaling.[9,10] The MAPK cascade plays a pivotal role in depression. Activated MAPK is dephosphorylated and inactivated by MAPK phosphatases (MKPs). MAPK phosphatase-1 (MKP-1) is a multispecific MKP that dephosphorylates ERK2, JNK, and p38.[11] A previous study reported that expression of MKP-1 is increased in the hippocampus of depressed humans and chronically mildly stressed mice.[12] Recent reports show that chronically defeated rats using the resident-intruder paradigm induced depressive-like physiological, behavioral, and molecular changes have increased expression of MKP-1 in the hippocampus.[13] Both testosterone and estradiol can exert cellular effects by activating a number of intracellular signaling pathways, notably the MAPK pathway. Recently, the Kabbaj lab has implicated this pathway in the antidepressant actions of testosterone in the hippocampus of male rats.[7] Testosterone or estradiol may activate one or more of these MAPK pathways in brain regions mediating mood and emotion. This may be one potential mechanism whereby androgens or estradiol promote antidepressant actions. The purpose of this study is to assess the relationships between estradiol, testosterone, BDNF, and MKP-1 in depression in young and perimenopausal women. This report also investigates whether fluctuating E_2 levels cause any change in levels of BDNF and MKP-1.

Subjects and Methods

Subjects

Thirty-eight perimenopausal women aged 45–55 years and 32 young women aged 20–35 years with depression coming from First Affiliated Hospital of Xi'an Jiaotong University, Shaanxi Province, China, were enrolled in the depression group from September 1, 2011, to February 1, 2013. Depression was defined as diagnosis code F32 according to the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision after fulfilling a 17-item Hamilton Depression Rating Scale (HDRS) assessment criteria for depressive disorders (more than 17 points). Perimenopausal stage was determined by using the Stages of Reproductive Aging Workshop staging system, which is based on the day of the last menstrual cycle and self-reported cycle length variability in the past 12 months. Women were considered perimenopausal if they reported menstrual cycle length variability (change in menstrual cycle length of longer than 7 days, ≥60 days amenorrhea, or ≥2 skipped cycles in the last 12 months). The average ages of these women were 51.07 ± 4.43 years for perimenopausal and 31.21 ± 3.21 years for young women. All of the young women examined had a regular menstrual cycle and early follicular phase follicle-stimulating hormone (FSH) levels (mean: 7.82 ± 4.10 IU/L). Twenty-six perimenopausal women aged 45–55 years and 34 young women aged 20–35 years with normal physical examination results, no evidence of systemic disease or any history of drug use, and scored lower than 17 points on the HDRS were included as the control group. The average ages of perimenopausal and young women in the control group were 49.19 ± 3.92 years and 29.75 ± 2.99 years, respectively.

All of the women tested had the cognitive capacity to read and comprehend the tests and the ability to read and write. Exclusion criteria for the study were as follows: (1) diagnosis with a somatic disease (hypertension or diabetes mellitus); (2) presence of a hypothalamic-pituitary-adrenal axis or thyroid disease; (3) presence of dementia or other organic mental disorders; (4) use of oral contraceptives or hormone therapy within 3 months of entering the study; (5) a history of mental diseases including nondepressive disorders experienced by the participant or a family member (including lineal relation by blood and collateral blood relatives within three generations); or (6) smoking and/or dependence on alcohol. Data on the age, marital status, educational level, employment status, residence, methods of contraception, and menstrual cycle duration of the women in the depression group and the control group were recorded. The study protocol was approved by the Ethics Committee in First Hospital Affiliated of Xi'an Jiaotong University, and all procedures were carried out with the adequate understanding and written consent of the subjects.

Serum gonadal hormone, BDNF and MKP-1 assays

A fasting blood specimen (3 mL) was collected into 5-mL sterile plain tubes without anticoagulant at 9:00–11:00 a.m. on the second to third day of menstrual cycle in 66 young women and 64 perimenopausal women. However, if a timed sample could not be obtained (as was especially the case for the late perimenopausal women), a fasting sample was taken when the endometrium was <5 mm thick as staged by a transvaginal Doppler ultrasound scan. After centrifugation for 10 minutes at 3000 rpm at room temperature, the sera were stored at −80°C. Before assaying, all samples were thawed to room temperature and assayed on the same day to avoid interassay variation. The serum levels of E_2, testosterone (T), progesterone (P), FSH, and luteinizing hormone (LH) were measured using electrochemiluminescence assay kits (Roche Group) and an automatic electrochemiluminescence immunoassay analyzer (Roche Group). The serum levels of BDNF and MKP-1 were measured with human BDNF ELISA kit and human MAP phosphatase dual specificity plaosplaatase ELISA kit (CUSABIO Biotech Co. Ltd.). Biological samples were blinded prior to analyses.

Statistical analysis

Continuous data are presented as mean ± standard deviation (range) and categorical data as number (%); *t*-tests and chi-square analyses were used to compare continuous and categorical demographic data, respectively, between women

with depression and control women. Data that are normally distributed were analyzed with the factorial analysis of variance and one-way analysis of variance (ANOVA) (including perimenopausal and young women in the depression and control group comparisons of BDNF levels). Data that are not normally distributed were analyzed with the Mann-Whitney U-test for pairwise comparisons (including perimenopausal and young women in the depression and control group comparisons of E_2, T, and MKP-1 levels). Pearson's correlation (correlation coefficient) test was used for testing correlations between HDRS score and E_2, T, BDNF, and MKP-1, given that all variables involved are continuous. Differences in protein expression data and hormone concentrations were analyzed by logistic regression in order to obtain any independent predictive factors correlated with perimenopausal depressive disorder. All statistical analyses were performed using SPSS software version 13.0. A p-value of 0.05 was considered statistically significant.

Table 1. Sociodemographic Characteristics of Depression and Control Groups

	Depression		*Control*	
Characteristic	*%*	*Mean*	*%*	*Mean*
Perimenopausal women				
HDRS[a]		24.47		5.85
Age, years[b]		51.07		49.19
Marital status[c]				
Married	84.21		84.62	
Widowed	15.79		15.38	
Educational level[d]				
College or more	15.79		23.08	
High school	52.63		53.84	
Less than high school	31.58		23.08	
Employment status[e]				
Employed full-time	63.16		65.38	
Homemaker	36.84		34.62	
Residence[f]				
City	57.89		69.23	
Village	42.11		30.77	
Young women				
HDRS[g]		21.41		5.00
Age, years[h]		31.21		29.75
Marital status[j]				
Married	82.35		81.25	
Widowed	17.65		18.75	
Educational level[j]				
College or more	41.18		46.88	
High school	58.82		50.00	
Less than high school	0		3.12	
Employment status[k]				
Employed full-time	88.23		90.63	
Homemaker	11.76		9.37	
Residence[m]				
City	70.59		75.00	
Village	29.41		25.00	

[a] $t = 15.95$, $p < 0.001$; [b] $t = 0.91$, $p = 0.52$; [c] chi-squared = 0.002, $p = 0.965$; [d] chi-squared = 0.838, $p = 0.658$; [e] chi-squared = 0.033, $p = 0.855$; [f] chi-squared = 0.846, $p = 0.358$; [g] $t = 21.34$, $p < 0.001$; [h] $t = 1.917$, $p = 0.06$; [i] chi-squared = 0.363, $p = 0.547$; [j] chi-squared = 1.170, $p = 0.557$; [k] chi-squared = 0.216, $p = 0.642$; [m] chi-squared = 0.074, $p = 0.786$.

HDRS, Hamilton Depression Rating Scale.

Results

Distributions of sociodemographic characteristics between the depression and control groups

As shown in Table 1, the depression group and control group in this sample had no significant differences with regard to covariates of the distributions of sociodemographic characteristics including age, marital status, educational level, employment status, and residence. It appeared that healthy women were more likely to have a college degree and more likely to engage in a job, but this observation did not reach statistical significance.

Relationship between depression and T, E_2, BDNF and MKP-1 levels

The T, E_2, BDNF, and MKP-1 levels were evaluated in all women in the study. The serum levels of T, E_2, and BDNF were significantly lower in the perimenopausal women than that in the young women (T: median 0.41 nmol/L vs. 0.96 nmol/L, $Z = -3.612$, $p < 0.000$; E_2: median 39.09 pmol/L vs. 238.8 pmol/L, $Z = -7.585$, $p < 0.001$; BDNF: 1.12 ± 0.11 ng/mL vs. 1.64 ± 0.15 ng/mL, $t = -2.855$, $p < 0.000$), but the MKP-1 levels were significantly higher in the perimenopausal women than that in the young women (median 295.22 pg/mL vs. 224.94 pg/mL, $Z = -1.391$, $p = 0.041$). The depression group had a statistically significant lower T (median 0.38 nmol/L vs. 0.82 nmol/L, $Z = -3.069$, $p = 0.039$) and E_2 levels (median 52.52 pmol/L vs. 103.30 pmol/L, $Z = -1.689$, $p = 0.047$) and higher MKP-1 levels (median 303.64 pg/mL vs. 213.86 pg/mL, $Z = 3.532$, $p = 0.000$) than that of the control group. There was no significant difference in BDNF levels between the depression group and control group (1.25 ± 0.12 ng/mL vs. 1.55 ± 0.15 ng/mL, $t = -1.550$, $p = 0.124$). The Spearman correlation tests between HDRS scores with T, E_2, MKP-1, and BDNF levels were performed and the HDRS scores were significantly correlated with E_2 ($r = -2.170$, $p = 0.042$), T ($r = -0.100$, $p = 0.003$), and MKP-1 ($r = 0.273$, $p = 0.009$), but not with BDNF levels.

The serum levels of BDNF, MKP-1, T, and E_2 between the depression and control groups in perimenopausal and young women

The factorial analysis of variance of BDNF revealed that statistically significant differences exist between perimenopausal women and young women ($F = 7.499$, $p = 0.007$), and no significant differences between depression and control groups ($F = 1.947$, $p = 0.165$). No significant interaction was found between age and depression ($F = 0.801$, $p = 0.165$). Further one-way ANOVA analysis revealed that the perimenopausal women had lower levels of BDNF than young women in the control group ($p < 0.01$). The perimenopausal women in the depression group also exhibited higher MKP-1 levels and lower T levels than women in the control group ($Z = -3.144$, $p = 0.002$; $Z = -2.624$, $p = 0.009$), the young women in depression and control groups ($Z = -3.608$, $p = 0.000$, $Z = -3.133$, $p = 0.002$; $Z = -3.712$, $p = 0.000$, $Z = -3.811$, $p = 0.000$). Also, the young women had higher serum MKP-1 levels in the depression group than those in the

Table 2. Comparison of Estradiol, Testosterone, Brain-Derived Neurotrophic Factor, and Mitogen-Activated Protein Kinase Phosphatase Values

Characteristic	*Depression perimenopausal women* (n = *38*)	*Control perimenopausal women* (n = *26*)	*Depression young women* (n = *32*)	*Control young women* (n = *34*)
E_2, pmol/L median (range)	20.17 (18.35–233.80)	38.55 (18.35–202.60)	208.80 (26.77–558.00)	158.10 (47.81–743.80)
T, nmol/L median (range)	0.30[a] (0.09–1.08)	0.52 (0.09–1.05)	0.67 (0.38–2.84)	1.05 (0.52–1.98)
BDNF, ng/mL Mean (SD)	1.07 (0.15)[b]	1.18 (0.16)[b]	1.46 (0.20)	1.84 (0.22)
MKP-1, pg/mL median (range)	319.18[c] (88.08–2292.91)	213.86 (90.96–575.49)	277.17[d] (36.35–792.57)	199.91 (100.06–465.01)

[a]Significantly lower compared with the control group and young women in the depression and control group ($Z = -2.624$, $p = 0.009$; $Z = -3.133$, $p = 0.002$; $Z = -3.811$, $p = 0.000$).
[b]Significantly lower compared with young women in the control group ($p = 0.003$, $p = 0.019$).
[c]Significantly higher compared with the control group and young women in the depression and control group ($Z = -3.144$, $p = 0.002$; $Z = -3.608$, $p = 0.000$; $Z = -3.712$, $p = 0.000$).
[d]Significantly higher compared with the control group ($Z = -2.194$, $p = 0.010$).
E_2, estradiol; MKP, mitogen-activated protein kinase phosphatase; SD, standard deviation; T, testosterone.

control group ($Z = -2.194$, $p = 0.010$) (Table 2). However, there was no significant difference in E_2 levels of the perimenopausal women between the depression group and control group ($Z = -2.236$, $p > 0.05$). The logistic regression analyses showed that MKP-1 levels were significantly positively correlated with HDRS scores ($F = 3.562$, $p = 0.001$), T levels were significantly inversely correlated with HDRS scores ($F = 0.141$, $p = 0.008$), and serum E_2 levels were significantly positively correlated with BDNF levels ($F = 4.878$, $p = 0.009$). In contrast, serum E_2 levels were significantly inversely correlated with MKP-1 levels ($F = 0.604$, $p = 0.048$). Thus, progressively reduced serum E_2 was associated with increased MKP-1 serum quantity and with decreased BDNF serum quantity in the women. When the data was analyzed with logistic regression in perimenopausal women and young women, MKP-1 levels were still significantly positively correlated with HDRS scores in perimenopausal women ($F = 6.414$, $p = 0.011$) and young women ($F = 4.597$, $p = 0.032$), but T levels were only significantly inversely correlated with HDRS scores in perimenopausal women ($F = 5.413$, $p = 0.020$).

Discussion

Perimenopausal depression and E_2, T levels

The perimenopause is a period of marked hormone instability, with intense and irregular fluctuations in the levels of E_2, which tend to decline up to the postmenopausal stage.[14] Contrary to our initial hypothesis and evidence in the literature which suggests that the rapid change in circulating E_2 concentrations may have a deleterious impact on mood in some but not all women,[15] E_2 levels in perimenopausal women with depression were not significantly different in comparison to perimenopausal women without depression in this study. The majority of previous studies also failed to show an association between perimenopausal depression and total plasma E_2 levels.[16,17,18] However, Ryan et al. found that the risk of depressive symptoms increased 3-fold with a decline in E_2 levels over a 2-year period, and the risk was associated with changes in E_2 rather than the absolute levels of the hormone.[19] Freeman and colleagues found that the varying hormone milieu experienced by women during the menopause transition had an important negative effect on their mood.[20] However, the design of our study did not allow us to test this phenomenon.

In this study, five types of sex hormones, including E_2, T, P, LH, and FSH, in young and perimenopausal women were analyzed and the relationship between them was assessed with consideration of the development of depression. There were no difference in the levels of P, LH, and FSH between women with depression and healthy control women in the investigation, so we did not discuss them. However, women with depression exhibited significantly lower T levels compared with controls, and depressed perimenopausal women had the lowest T levels. Furthermore, the logistic regression analyses showed that T levels are significantly inversely correlated with HDRS scores in the perimenopausal women participating in the survey. This finding may reflect an age-related reduction of T levels, but it also shows that depression severity increases as the testosterone levels decreased in perimenopausal women.

The results obtained from this study examining the possible relation between depression and testosterone in women are consistent with others. In a separate report that has similar features to our study, including the relationship between testosterone levels in serum and depression disorders, it was observed that testosterone levels in the serum of depressed women were low in comparison with the control group. That study also found that the serum testosterone levels of the depressed women increased and the HDRS scores of the depressed women decreased significantly following antidepressant treatment.[21] Furthermore, depressed women with Huntington's disease (HD) had significantly lower levels of plasma total testosterone (TT) and dehydroepiandrosterone sulfate (DHEAS) compared with controls. While TT and DHEAS seemed to decline with age in female patients with HD to the same extent as in healthy females, the presence of depression in the authors' symptomatology is connected to lower ovary–adrenal androgen levels.[22] Additionally, transdermal application of testosterone in women experiencing age-related declines in androgens resulted in substantially

improved mood and psychological well-being compared with placebo-treated individuals.[23]

Similarly, several reports suggest that testosterone-replacement therapy in men greatly improves mood and mitigates symptoms of depression,[24,25] and indeed, hypogonadal men exhibit a significantly higher prevalence of anxiety disorders and major depressive disorder, compared with those with normal physiological levels of androgens.[26] In another study, elderly men with depressive symptoms had lower total testosterone levels. A significant inverse correlation was found between testosterone levels and depressive symptoms such that depression scores were lower with increased testosterone levels.[27] However, this is not the case in all clinical studies. For example, one study reported that neither testosterone nor free testosterone is associated with depression symptom severity in polycystic ovary syndrome women after controlling for body dissatisfaction and age.[28] Another study reported that testosterone replacement therapy in androgen-deficient men did not significantly alleviate symptoms of major depressive disorder compared with placebo-treated controls.[29] However, despite a few inconsistent reports, the majority of studies support the case that testosterone yields beneficial effects on mood in men and women, especially in those with lower than normal levels. Further evaluation via prospective studies, laboratory experiments, and patient studies are needed.

Perimenopausal depression and MKP-1

MKP-1 has been identified as a key factor in the pathophysiology of major depressive disorder in rodent models.[12] To investigate the correlation between serum level of MKP-1 and depression, serum MKP-1 was measured in our cohort of depressed and nondepressed women. The highest MKP-1 levels were observed in the perimenopausal women with depression. Specifically, the perimenopausal women with depression exhibited higher MKP-1 levels than nondepressed perimenopausal women, young women with depression, and the nondepressed young women. In addition, a significant increase in MKP-1 levels was detected in the young women with depression compared with nondepressed young women. Also, MKP-1 levels were significantly positively correlated with HDRS scores and serum E_2 levels, and inversely correlated with MKP-1 levels in women. These results indicate that MKP-1 may be associated with depressive disorder in women, and our study also found an association between high serum MKP-1 and severity of depression, with MKP-1 levels increasing with reduced E_2.

Studies to date indicate that MKP-1 expression is elevated in the brains of rodents in a model of major depressive disorder.[30] The increased expression of hippocampal MKP-1 in rats suppressed body weight gain, enlarged the adrenal glands, and increased the immobility time in a forced swim test.[13] Targeted viral expression of MKP-1 in the dentate gyrus subfield of nonstressed rats produced profound depressive-like responses similar to the effect of chronic unpredictable stress. The MKP-$1^{-/-}$ mice had no obvious behavioral or histological abnormalities and exhibited normal locomotor activity. Conversely, chronic antidepressant treatment normalizes stress-induced MKP-1 expression and behavior.[8] MKP-1 is a major negative regulator of the neurotrophic factor-MAPK cascade that contributes to the expression of depressive symptoms.[12] Previous studies have showed that p44/42 MAPK activity was significantly decreased in the prefrontal cortical areas and the hippocampus of depressed suicide subjects,[31] and the acute blockade of MAPK signaling produces a depressive-like phenotype in mouse.[32] In our study, the higher MKP-1 levels in serum were positively associated with the presence of depression in women. Interestingly, we found serum MKP-1 levels increasing with reduced levels of E_2. Indeed, Swartz et al.[33] found that the expression of MKP-1 was lower in E_2-treated uterine leiomyoma cells than in the ethanol treated cells *in vitro*. We were not able to test for an increase in the expression of MKP-1 as a result of estrogen reduction in brain tissues in this study. However, we postulate that functional (phosphorylated) MAPK levels may be decreased because of the increased inhibition by MKP-1 regulated by E_2 in perimenopausal women.

Perimenopausal depression and BDNF

Studies in rats show that BDNF is involved in the pathophysiology of stress-related mood disorders, and BDNF expression decreases after exposure to stress, including social-defeat stress.[34,35] The infusion of BDNF into the hippocampus shows antidepressant effects.[36] Studies in humans show decreased plasma levels of BDNF in bipolar disorder, mania, and depression.[37,38] However, not all studies report differences in plasma BDNF levels between individuals with depression and controls.[39,40] It may be the case that relationships between BDNF and depression are more complex, such as the involvement of gene × environment interactions[41] or the duration of the depression.[42] The data in our study do not suggest an association between plasma BDNF levels and perimenopausal depression. However, we found that serum E_2 levels were significantly positively correlated with BDNF levels, which means that progressively reduced serum E_2 is associated with decreased BDNF serum quantity in the women. Studies suggest that BDNF mediates several of the effects of estrogen in the hippocampus and that these interactions play a role in the normal brain as well as in disease.[43] In addition, increased endogenous BDNF signaling in the ventromedial nucleus of hypothalamus of rats may mediate E_2-induced inhibitory effect on feeding.[44] In both mammalian and zebra finch systems, expression of BDNF protein can be modulated by E_2.[45] Therefore we hypothesize that coregulation may exist between BDNF and E_2 and this relationship influences perimenopausal depression.

Conclusion

This study provides a gender-specific investigation of serum MKP-1, BDNF, and gonadal hormone levels and depression. Our results suggest that high serum MKP-1 levels are associated with depression in women. This association did not appear to be confounded by age. The study also supports previous reports of the association between depression and reduced serum T levels in women. Furthermore, the current findings provide evidence of association between depressive symptom severity and increasing serum MKP-1 levels in women, and decreasing serum T levels in perimenopausal women. Our study also found that progressively reduced serum E_2 was associated with increased MKP-1 serum quantity and with decreased BDNF serum quantity in the women. The results did not suggest differential serum BDNF and E_2 levels

across perimenopausal women with depression in comparison to healthy controls. Studies with larger samples of both genders are needed to further delineate these relationships.

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Author Disclosure Statement

No competing financial interests exist.

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