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THE CORRELATION BETWEEN TENASCIN-C AND SEX HORMONE LEVELS IN DEPRESSIVE PATIENTS: A POTENTIAL DIAGNOSTIC TOOL

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ABSTRACT

Objective: The current research was performed to investigate the association between serum testosterone and Tenascin-C levels in people with depressive disease, and assess the potential significance of Tenascin-C as a predictive parameter for the assessment of depressive symptoms. **Method:** The levels of Tenascin-C were detected in the serum of 117 clinically depressive patients and matched 104 healthy blood donors by enzyme-linked immune-absorbance assay tests. Concentrations of estradiol, testosterone, free thyroxine, free triiodothyronine, thyroid-stimulating hormone and high-sensitivity C-reactive protein were also analyzed. **Results:** We found that patients with depression had lower levels of testosterone, free triiodothyronine, thyroid-stimulating hormone and testosterone/estradiol ratios than healthy controls, while Tenascin-C and hs-CRP levels were higher in patients compared with control subjects. The sensitivity of Tenascin-C in detecting depression was 83% at a specificity of 64%. Multiple linear regression analysis displayed that testosterone, testosterone/estradiol ratios and Tenascin-C levels were negatively correlated in male depressive patients. Increased Tenascin-C serum levels are associated with depression severity (p=0.003) and suicidal ideation (p=0.013). **Conclusion:** the progression of depressive disorder is potentially influenced by the up-regulation of TNC in the presence of low hormone concentrations in male patients.

KEYWORDS: Tenascin-C; Sex hormone; Depression; Thyroid hormones.

INTRODUCTION

Depressive disorder is a complex, detrimental psychiatric disorder with a lifetime prevalence of approximate 16%.[1] The pathogenesis, presentation, course and response to treatment are highly variable. Extensive investigations have reported that neurotrophy disorder, dysregulation of monoamine, dysfunction of hypothalamic-pituitary-adrenal (HPA) and inflammatory occurrence are found to relate to MDD.[2,3] However, the exact pathophysiology of MDD is not easily understood. The results reported by Hisashi et al[4] have found that there was a negative correlation among serum testosterone levels and the number of depressive episodes in male depressive patients, while serum testosterone levels in either male or female depressive patients remained unchanged compared with healthy controls. In addition, a review by Amore et al[5] suggests that partial androgen deficiency (PADAM) in aging males is related to various behavioral symptoms, including weakness, depressive mood, anxiety and memory impairment, and that testosterone treatment might give rise to antidepressant effects. Increasing evidence also indicated that low testosterone abundances should be regarded as an independent depressive risk factor in male patients.[6,7]

Tenascin-C (TNC) is an extracellular matrix glycoprotein expressed during the development of multiple organisms and in pathological progress, including inflammation and tissue impairment as well as psychiatric disorders. An earlier study indicated that functional suppression of TNC plays an important role in Alzheimer's disease (AD), indicating that TNC might be a potential therapeutic target for AD.[8]A recent study also showed that TNC was induced in the brain during the development of brain edema and blood-brain barrier (BBB) disruption following subarachnoid hemorrhage (SAH), suggesting a potential for TNC as a molecular target in SAH- stimulated brain damages.[9] Up-regulation of TNC occurs spatially and temporally during angiogenesis, while TNC is not measured when neovascularization had ceased in the central nervous system (CNS).[10] A study related to serum proteomic profiling of major depressive disorder suggested that

TNC may be a biomarker for depression and that it may participate in its pathophysiology.[11] These results suggest that TNC responds to the presence of common psychopathic risk factors and predicts psychopathic events. Moreover, proinflammatory cytokines promote HPA-axis activation, associate with TNF-α, cytokines plays an important role in the development of wider depression.[12] In addition, TNC plays an essential role in the inflammatory response to the brain and may increase the development of depression.

Earlier studies suggested that estrogen and androgen regulate the expression of TNC in vitro,[13,14] suggesting a potential role of these sex hormones in TNC- mediated signaling pathways. The functions of TNC- mediated pathways, and its role in inflammation, apoptosis and oxidative stress may particularly relate to depression in humans. Nevertheless, the clinical value of TNC and the relationship among TNC levels and sex hormones in male depressive patients remain to be unknown. This study was performed to reveal these issues using a cross-sectional research in male depressive individuals. In the current study, we analyzed the diagnostic value of TNC in depressive disorder and the association among TNC levels and sex hormones with other parameters that are changed in male patients with depression.

MATERIALS AND METHODS

Characteristics of male patients and healthy controls

Serum samples of 127 male depressive patients, age ranging 18 to 72 years (median 36.48 years) with a clinical diagnosis of depressive disorder and blood sera of 109 male healthy volunteers, age ranging 21 to 76 years (median 33.29 years), were recruited in the current study. All depressive patients and healthy volunteers underwent a Structure Clinical Interview for DSM-IV (SCID) and their essential information were collected from Department of Psychiatry at Zhongnan Hospital of Wuhan University. The non inclusion criteria of healthy controls were as follows: if they had recently taken medication, refused to provide informed consent, had diseases that might interfere with the study, including hyperthyroidism, other mental disorders, or neurological disease. These participants did not suffer from bipolar depression, although some of them suffer from recurrent depression. Sociodemographic information, cigarette consumption, alcohol use, symptom duration and the status of drug treatment were also recorded at the beginning of hospitalization. Hamilton Depression Scale (HAMD) was performed to assess depression severity, hopelessness, impulsivity, and suicidal ideation of depressive patients. All depressive patients had no antecedent of antidepressants for at least one prior to research. The research was approved and performed in accordance with the principals of the Medical Ethics Review Committee of Zhongnan Hospital, Wuhan University. All participants provided written informed consent before recruited this study.

Sample collection

Antecubital vein blood of each individual was drawn between 8 and 9 o'clock in the morning after without food consumption for at least 8 hours. Blood serum were recovered, aliquoted into 1.5-ml tubes and stored at -80℃ until analysis.

Analytical methods

The levels of TNC in depressive patients were measured using an available commercial enzyme-linked immunosorbent assay kit (CusaBio, Wuhan, China) according to the manufacturer's guidance. All serum samples were also used to determine the levels of high-sensitivity C-reactive protein (hs-CRP) using a Siemens Advia 2400 automatic biochemistry analyzer (Siemens, Erlangen, Germany). The levels of estradiol (E2), testosterone (T), free thyroxine (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) were measured by a Siemens Advia Centaur CP (Siemens, Erlangen, Germany).

Statistical analysis

The statistical analysis was carried out using IBM SPSS version 19.0 statistics software (Chicago, IL, USA). The normality of distribution variables is displayed as averages±standard deviation (SD). The normality of distribution variables and homogeneous analysis of all variables were evaluated using Levene's test. Group differences of cigarette consumption, alcohol use, symptom duration, T, E2, T/E2 ratio, TSH, and drug treatment were assessed by independent t-test. Group differences of age, TNC, FT3, FT4 and hs-CRP were analyzed by Mann-Whitney test. Correlations among TNC and T, E2, T/E2 ratio, TSH, FT3, FT4, hs-CRP were assessed using Spearman's analysis. The relationships between the depressive incidence and the measured values were carried out using univariate and multivariate logistic regression analysis. The association between TNC levels and depressive risk factors was carried out by multiple linear regression analysis. The cut-off concentration of TNC quantification was determined by the Youden-index. All variables achieving a P value ≤ 0.05 were regarded as statistically significant.

RESULTS

Characteristics of the study population

The levels of sex hormone and thyroid hormone in control and depressive groups were summed up in Table 1. Depressive patients had lower TSH and FT3 levels than did the control individuals, while the hs-CRP levels in the depressive group significantly increased compared with control group (all $p<0.01$). Table 1 and Figure 1 show that serum testosterone level and testosterone/estradiol ratio were significant lower in depressive subjects than the control individuals (all $p<0.001$). In addition, estradiol and FT4 levels unchanged in depressive group when compared to healthy controls. The antidepressants treatment for patients before at least one prior to research are summarized in Table 1.

Tenascin-C (TNC) concentrations in depressive was significantly increased (mean ± SD=11.79 ± 6.06 ng/ml) compared with control subjects (mean ± SD=6.92 ± 2.87 ng/ml, p<0.001; Figure 2). The results of receiver operating characteristic curves analysis displayed that TNC have a high diagnostic value for depression. The area under curve (AUC) was 0.764. The cut-off level determined by the Youden index was 8.33 ng/ml. The sensitivity of TNC in diagnosing depression was 64% at a specificity of 83% compared with healthy controls.

Correlation among TNC levels and variables in depressive patients

The association between TNC levels and the concentrations of thyroid and sex hormones were carried out using Spearman partial correlation analyses. After adjustment for age, serum TNC concentrations were negatively associated with estradiol, testosterone levels and estradiol/testosterone ratios, while were positively correlated with FT4 levels (Figure 2). The data indicated that depressive patients with higher serum testosterone levels and estradiol/testosterone ratios appeared to have lower serum TNC levels.

Logistic regression analyses for depression

Univariate and multivariate logistic regression analyses were carried out to evaluate the variables predicting the incidence of depression (Table 2). Univariate analyses indicated that testosterone, estradiol/testosterone ratios, TNC, TSH, FT3, and hs-CRP were correlated with the incidence of depression. Multivariate analyses showed that estradiol/testosterone ratios, TNC, TSH, and FT3 levels were predictors for the incide.

Association between TNC and the main depressive risk factors in patients

The relationship among TNC and depressive risk variables was further evaluated using multivariate regression analyses. The results from Table 3 showed that TNC was negatively correlated to testosterone levels and estradiol/testosterone ratios in male patients with depression.

Association of TNC serum levels and clinical symptoms

Depressive patients were divided into two groups, including high-concentration (≥8.33 ng/ml) and low-concentration (<8.33 ng/ml) TNC groups. The association of clinical symptoms and TNC levels using cross table displayed a significant relationship elevated TNC levels and depression severity (severe depression compared with medium and mild depression; p=0.003) and suicidal ideation (no versus yes; p=0.013), respectively (Table 4). The clinical parameter (age) did not display a significant difference in these two groups. However, there are no significant associations between TNC levels and hopelessness, impulsivity in high- and low-level groups.

DISCUSSION

The purpose of the current research was to investigate the relationship between serum sex hormone concentrations and TNC levels in male patients, and assess the potential of TNC as a diagnostic and prognostic value in patients with depressive disorder. Until now, only a few studies have evaluated the functional role of TNC in the occurrence of depression. The data in this study displayed that serum TNC concentrations were significantly increased compared with control subjects (p<0.001). The AUC indicated an available discriminatory ability of TNC (AUC=0.764; Figure 2). The sensitivity (64%) and specificity (83%) of TNC were significantly higher than the serum biomarkers for depressive episodes reported by Gottschalk.[15] These results remind us to accept that TNC might be an appropriate diagnosing marker for the depressive disorder due to the fact that the over-expression of TNC was found to suppress the regeneration of the nervous tissue.[16] In our research, the results found that serum testosterone levels and testosterone/estradiol ratios were significantly lower in male depressive patients than in healthy controls. Serum TNC levels were negatively correlated with testosterone levels and testosterone/estradiol ratios. Multiple linear regression analyses indicated that serum levels of TNC and testosterone were closely correlated in male depressive patients. Moreover, serum TSH and FT3 levels significantly decreased compared with the control group, which is consistent with the results reported by Jia et al.[17] In addition, TNC levels were positively associated with FT4 levels in male depressive patients, indicating that the over-expression of TNC is associated with the functional turbulence of the hypothalamic-pituitary-thyroid (HPT) axis in depressive patients. In this study, the level of alcohol in the control group was higher than in the patient group, but the difference of the two groups has no statistical significance. However, the alcohol used, might also have affected the levels of TNC and hormones, so further prospective researches with large populations are needed to assess our results.

Serum proteomic profiling of major depressive disorder has demonstrated that TNC may help to diagnose the disease. Additionally, TNC improves our understanding of its pathophysiology.[11] An earlier study has reported that TNC deficiency can weaken climbing fibers (CF) paired-pulse depression and augment parallel fibers (PF) paired-pulse facilitation, which indicates that TNC may suppress the regenerative ability of the nervous tissue.16 In addition, TNC is considered to play important functional roles during neural development, axonal regeneration, and synaptic plasticity.[18] Moreover, our results showed that TNC levels are positively correlated with FT4 levels in male patients with depressive disorder, suggesting that the over-expression of TNC in depressive patients leads to the functional turbulence of the hypothalamic-pituitary-thyroid (HPT) axis. However, the mechanism of this hypothesis needs to be further studied. We also observed the association of TNC serum

levels and depressive clinical symptoms, which found significant correlations of increased TNC levels with depression severity and suicidal ideation (p=0.003 and p=0.013, respectively), suggesting a relatively increased TNC levels in patients with severe depression. TNC was reported to not only inhibit neurite outgrowth and binding with neuritogenic substrates,8 but also promote inflammatory response, neuronal apoptosis, and oxidative stress injury.[10] Therefore, these effects of TNC may exacerbate depression severity and suicidal ideation.

Previous studies have demonstrated that estrogen improves depression-like behavior by suppressing inflammation, activating ndoleamine- 2,3-dioxygenase (IDO) and maintaining serotonin (5-HT) levels.[19] Similar research has also shown that testosterone has antidepressant effects through activating the extracellular signal-regulated kinase 2 (ERK2) signaling pathway within the dentate gyrus area of the hippocampus.[20] A review by Amiaz et al.[21] states that most studies do not support testosterone treatment or replacement as more efficacious than antidepressant for depressive disorder, but it may be efficacious in certain groups, including hypogonadal male patients, antidepressant-resistant men, male patients with early onset depression, and HIV-infected men. The conclusions from another review also demonstrated that testosterone may not be regarded as a broadly effective drug for depression, but it may produce antidepressant effects.[22] Earlier research has reported that testosterone ablation stimulates TNC expression in the rat prostate,[14] and our study showed that the testosterone levels and testosterone/estradiol ratios are significant lower than in healthy controls, while the TNC concentrations significantly increased compared with control subjects. Furthermore, the correlation analysis demonstrated that TNC levels are negatively associated with testosterone levels and testosterone/estradiol ratios, indicating that the synergistic effect of exogenous testosterone/estradiol may suppress the expression of TNC via androgen/estrogen receptor and further improve the symptoms. Our data also suggest that reduced testosterone level may play an important role in up-regulating the expression of TNC and stimulating depression.

The current research does, however, have limitations. The depressive individuals were blind to the antidepressants used and it may impact the serum TNC levels and multiple hormones levels. Although every participant in this study had no antecedent of drug treatment for at least one month prior the recruitment, the current research did not investigate the influence of antidepressants on serum TNC and hormones levels. Another limitation is the lack of power to observe the impact of other possible risk factors. In addition, the mean values of the measured parameters in both groups: control group and depressive group, respectively, while those include T, E2, TSH, FT3, FT4, hs-CRP, were within standard values due to the confined populations and the undemanding inclusion criteria. Further prospective research with large populations is needed to assess the prognostic power of TNC serum concentrations and the association between TNC and testosterone levels in patients with depressive disorder. Furthermore, the functional roles of TNC and testosterone in depression are poorly understood and need to be observed in in vivo and in vitro studies. In addition, the mechanism of the influence of testosterone/estradiol synergistic effect on TNC expression needs to be further investigated in vitro. Collectively, the results of the present research are the first time to report that TNC levels are correlated with testosterone/estradiol ratios and TNC could be used as a predictive factor for depression.

Authors' Contributions

Christian Cedric Bongolo Moukeila.Y.M.Bassirou and Jian-Cheng Tu designed the study. Moukeila.Y.M.Bassirou collected samples and provided assistance for data acquisition .Christian Cedric Bongolo and Yan-Lin Feng performed all the experiments. Tapara D.M. Souraka analyzed the data .Christian Cedric Bongolo and Moukeila.Y.M.Bassirou wrote this paper. Linzy Elton and Terence.O.O.Etsaka revised the manuscript.All authors have read and approved the final manuscript.

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Table 1.

Characteristics	Controls (n=104)	Depressive Patients (n=117)	p
Age (year)	33.29 ± 10.71	36.48 ± 15.73	0.584
Cigarette consumption (%)	39 (30.7%)	44 (34.6%)	0.546
Alcohol use (%)	26 (23.9%)	16 (12.6%)	0.054
Symptom duration (months)	-	36.47 ± 31.72	
TNC (ng/ml)	6.92 ± 2.87	11.79 ± 6.06	<0.001
T (241-376.72 ng/ml)	441.47 ± 142.96	336.28 ± 150.53	<0.001
E2 (19.5-144.2 pg/ml)	30.28 ± 11.51	28.80 ± 12.87	0.354
T/E2 ratio	15.74 ± 6.01	12.74 ± 5.81	<0.001
TSH (0.55-4.78 µIU/ml)	2.26 ± 0.93	1.75 ± 1.03	<0.001
FT3 (2.3-4.2 pg/ml)	3.50 ± 0.30	3.38 ± 0.43	0.006
FT4 (0.89-1.80 ng/ml)	1.23 ± 0.14	1.27 ± 0.22	0.310
hs-CRP (0-3.0 mg/l)	0.39 ± 0.41	1.22 ± 3.14	0.008
Treatment			
Imipramine		44 (34.6%)	
Mirtazapine		31 (24.4%)	
Fluoxetine		27 (21.3%)	
Other antidepressants		25 (19.7%)	

TNC: Tenascin-C; T: testosterone; E2: estradiol; TSH: thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; hs-CRP: high-sensitivity C-reactive protein

Table 2.

Factor	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	1.018	0.998-1.037	0.077			
E2	0.990	0.970-1.011	0.352			
T	0.995	0.993-0.997	<0.001	1.002	0.999-1.005	0.180
T/E2 ratios	0.916	0.873-0.960	< 0.001	1.090	1.019-1.166	0.012
TNC	1.312	1.204-1.429	< 0.001	0.757	0.686-0.836	<0.001
TSH	0.578	0.433-0.772	<0.001	1.818	1.286-2.570	0.001
FT3	0.421	0.205-0.862	0.018	3.332	1.232-9.017	0.018
FT4	3.455	0.821-14.539	0.091			
hsCRP	1.542	1.095-2.171	0.013	0.762	0.524-1.108	0.154

TNC: Tenascin-C; T: testosterone; E2: estradiol; TSH: thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; hs-CRP: high-sensitivity C-reactive protein

Table 3.

	T	T/E2	TSH	FT3	hs-CRP
B-coefficient	-0.244	-0.187	-0.075	-0.074	0.041
p	<0.001	0.007	0.094	0.512	0.241

T: testosterone; E2: estradiol; TSH: thyroid-stimulating hormone; FT3: free triiodothyronine; hs-CRP: high-sensitivity C-reactive protein.

Table 4.

		All (n)	TNC high (n and %)	TNC low (n and %)	Significance (p)
Age (cut 40)	<40	80	28 (35%)	52 (65%)	0.543
	≥40	47	14 (30%)	33 (70%)	
Depression severity	Mild	44	19 (43%)	25 (57%)	0.003
	Medium	57	37 (65%)	20 (35%)	
	Severe	26	21 (81%)	8 (19%)	
Hopelessness	No	89	53 (60%)	36 (40%)	0.151
	Yes	38	26 (68%)	12 (32%)	
Impulsivity	No	74	43 (58%)	31 (42%)	0.109
	Yes	53	29 (55%)	24 (45%)	
Suicidal ideation	No	92	41 (45%)	51 (55%)	0.013
	Yes	35	21 (60%)	14 (40%)	

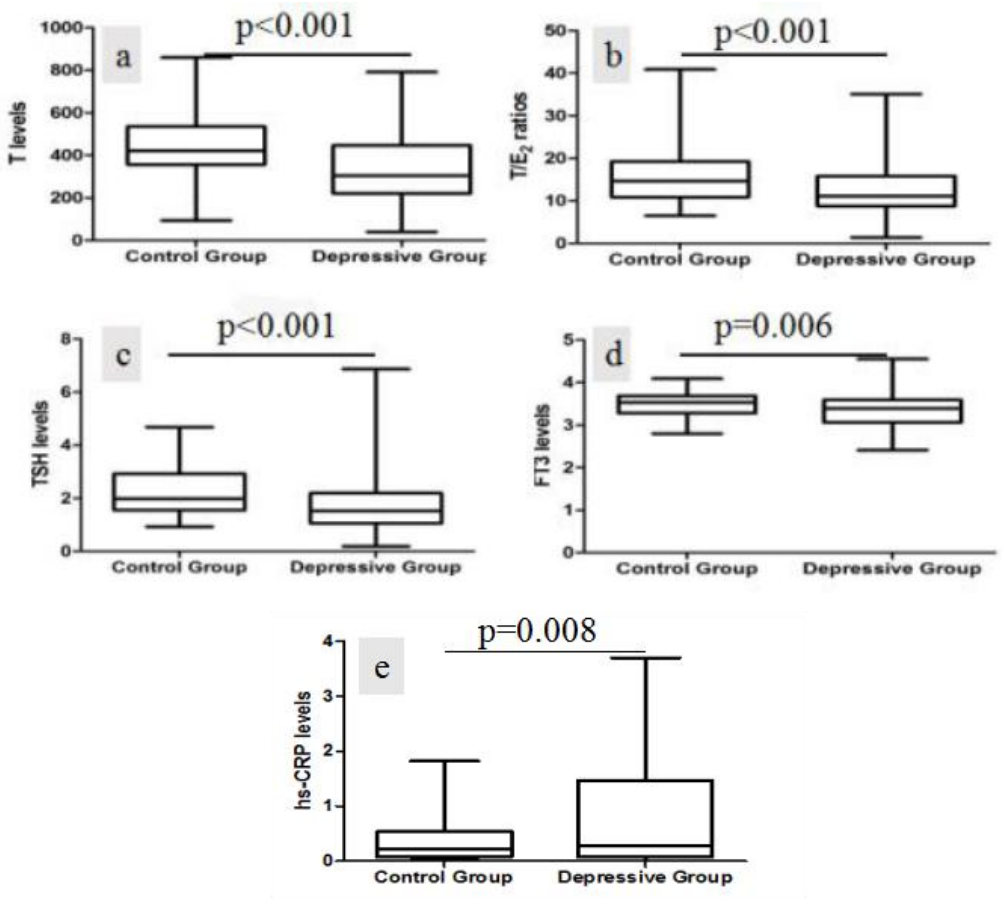

Figure 1.

Figure1 Serum levels of T (a), T/E2 ratio (b), TSH (c), FT3 (d), hs-CRP (e) in control and depressive groups

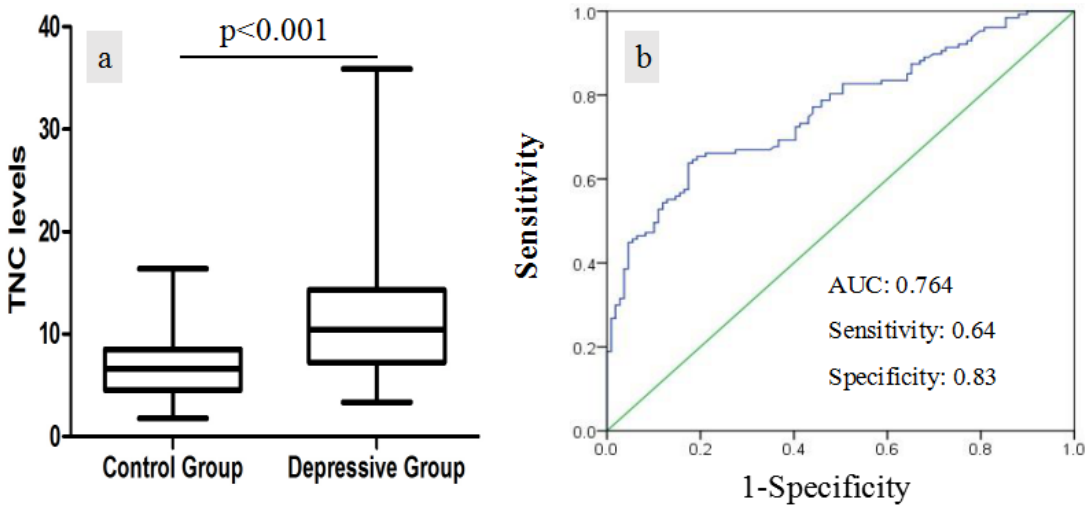

Figure 2.

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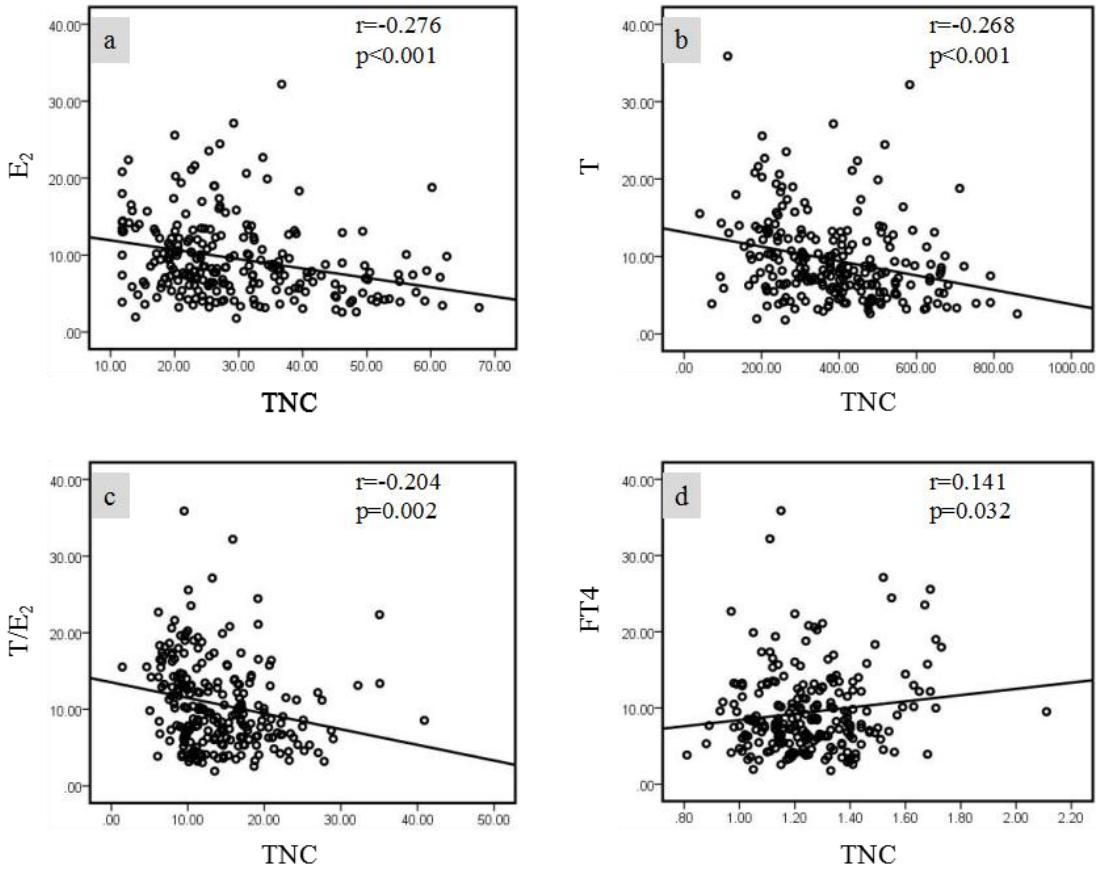

Figure 3.

Scatter diagram depicting the association among TNC levels and E2 levels(a), T levels (b), T/E2 ratio (c), and FT4 levels (d).

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Conflict of Interests

All authors declare no competing interests.

REFERENCES

1. Müller S, Rohde P, Gau JM, et al. Moderators of the effects of indicated group and bibliotherapy cognitive behavioral depression prevention programs on adolescents' depressive symptoms and depressive disorder onset. Behav Res Ther, 2015; 75(11): 1-10.
2. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature, 2008; 455(21): 894-902.
3. Belmaker RH, Agam G. Mechanisms of disease: major depressive disorder. N Engl J Med, 2008; 358(7): 55-68.
4. Hisashi M, Hitoshi M, Sayaka K,et al. Gender differences in serum testosterone and cortisol in patients with major depressive disorder compared with controls. Int J Psychiatry Med, 2013; 46(18): 203-21.
5. Amore M, Scarlatti F, Quarta AL, et al. Partial androgen deficiency, depression and testosterone treatment in aging men. Aging Clin Exp Res, 2009; 21(19): 1-8.
6. Kawato S. Role of androgen in the elderly. Modulation of synaptic plasticity by brain-synthesized androgens. Clin Calcium, 2013; 23(17): 1141-50.
7. Sankar JS, Hampson E. Testosterone levels and androgen receptor gene polymorphism predict specific symptoms of depression in young men. Gend Med, 2012; 9(26): 232-43.
8. Xie K, Liu Y, Hao W, et al. Tenascin-C deficiency ameliorates Alzheimer's disease-related pathology in mice. Neurobiol Aging, 2013; 34(23): 2389-98.
9. Fujimoto M, Shiba M, Kawakita F, et al. Deficiency of tenascin-C and attenuation of blood-brain barrier disruption following experimental subarachnoid hemorrhage in mice. J Neurosurg, 2016; 124(24): 1693-702.
10. Zagzag D, Capo V. Angiogenesis in the central nervous system: a role for vascular endothelial growth factor/vascular permeability factor and tenascin-C. Common molecular effectors in cerebral neoplastic and non-neoplastic "angiogenic diseases". Histol Histopathol, 2002; 17(19): 301-21.

11. Bot M, Chan MK, Jansen R, et al. Serum proteomic profiling of major depressive disorder. Citation: Transl Psychiatry, 2015, 5(14): e599.
12. Piotr G, Monika T, George A, et al. Mechanisms underlying neurocognitive dysfunctions in recurrent major depression. Med Sci Monit, 2015; 21(21): 1535-1547.
13. Francesca V, Elena DB, Paola T, et al. Effect of adipose-derived mesenchymal stromal cells on tendon healing in aging and estrogen deficiency: an in vitro co-culture model. Cytotherapy, 2015; 0(4): 1-9.
14. Giinter V, Horst M, Grsten E, et al. Androgen Ablation Induces Tenascin expression in the rat prostate. The Prostate, 1994; 258(24): 1-90.
15. Gottschalk MG, Cooper JD, Chan MK, et al. Discovery of serum biomarkers predicting development of a subsequent depressive episode in social anxiety disorder. Brain Behav Immun, 2015; 48(3): 123-31.
16. Andjus PR, Bajić A, Zhu L, et al. Short-term facilitation and depression in the cerebellum: some observations on wild-type and mutant rodents deficient in the extracellular matrix molecule tenascin C. Ann N Y Acad Sci, 2005; 1048(7): 185-97.
17. Jia Y, Zhong S, Wang Y, et al. The correlation between biochemical abnormalities in frontal white matter, hippocampus and serum thyroid hormone levels in first-episode patients with major depressive disorder. J Affect Disord, 2015; 18(2): 162-9.
18. Evers MR, Salmen B, Bukalo O, et al. Impairment of L-type Ca2+ channel-dependent forms of hippocampal synaptic plasticity in mice deficient in the extracellular matrix glycoprotein tenascin-C. J Neurosci, 2002; 22(16): 7177-94.
19. Xua YJ, Sheng H, Tang ZP, et al. Inflammation and increased IDO in hippocampus contribute to depression-like behavior induced by estrogen deficiency. Behavioural Brain Research, 2015; 288(3): 71–78.
20. Carrier N, Kabbaj M. Extracellular signal-regulated kinase 2 signaling in the hippocampal dentate gyrus mediates the antidepressant effects of testosterone. Biol Psychiatry, 2012; 71(14): 642–651.
21. Amiaz R, Seidman SN. Testosterone and depression in men. Curr Opin Endocrinol Diabetes Obes, 2008; 15(8): 278-83.
22. Johnson JM, Nachtigall LB, Stern TA. The effect of testosterone levels on mood in men: a review. Psychosomatics, 2013; 54(11): 509-14.