Altered Circulating GDF-15 Level Predicts Sex Hormone Imbalance in Major Depressive Disorder

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Research

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Abstract

Background: It has been hypothesized that higher growth differentiation factor 15 (GDF15) level and lower testosterone/ estradiol (T/E) ratio are associated with major depressive disorder (MDD), yet the underlying effect of serum GDF15 on hinting the T/E ratio imbalance are not fully understood. We observed the correlations between serum T/E ratio and circulating GDF15 in depressed cohort.

Methods: The sample consisted of participants (aged 18~65 years) from the Renmin Hospital of Wuhan University with MDD (n=412) defined according to a Structured Clinical Interview for DSM-IV (SCID), and healthy controls (n=137). Serum levels of testosterone, estradiol, and depression risk indicators (thyroid hormone, lipids, hs-CRP, Tenascin-C [TNC], GDF15, KLF4, Gas6, and sgp130) were measured. The associations among loge-transformed T/E ratio and these indicators were analyzed using univariate correlation analysis, category analyses, and linear regression adjusting for standard risk factors.

Results: Of the sample, 36.89% had lower T/E ratio (<10:1) and 10.20% had higher T/E ratio (>20:1). After multivariable adjustment, T/E ratios were negatively associated with GDF15 (-0.095 [95% CI -0.170~-0.023] standard deviation [SD] change per SD increase in lg[T/E], $P=0.015$) and inversely related to TNC (-0.085 [95% CI -0.167~0.003] standard deviation [SD] change per SD increase in lg[T/E], $P=0.048$). Serum T/E ratio was negatively associated with GDF15 level in both FT3, TSH and HDL strata, whereas this association was not observed in TNC. In T/E ratio strata analyses, there is a significant and negative correlation among T/E ratio and GDF15 in depressive patients with sex hormone imbalance, yet this relationship was not investigated in patients with sex hormone balance.

Conclusion: In our community-based observation, circulating GDF-15 level was greatly and inversely associated with serum T/E ratio, indicating that higher GDF-15 alerts sex hormone imbalance in patients with MDD.

Trial registration: All subjects did not provide written informed consent due to the using the remaining specimens.

Background

Major depressive disorder (MDD) is considered as a major public healthy challenge and is predicted to the significant cause of disability worldwide in 2020 [1]. This disorder leads to the soaring costs for treatment and heavy mental pressure for patients [2]. Depressive etiology and pathophysiology have been poorly demonstrated. Research advances in recent decade demonstrated the potential effect of new biomarkers which may impact mood in combination with the more neuroendocrine mechanisms. A large number of observations have proposed that dysregulation of neurotransmitter, dysfunction of hypothalamic-pituitary-thyroid (HPT) and inflammatory response are closely associated with the development of MDD [3–5]. Furthermore, extensive investigations have demonstrated that sex hormone deficiency may be involved in the pathogenesis of depression [6–8]. A basic study has shown that both testosterone and estradiol have anxiolytic- and antidepressant-like effects in gonadectomized male

animals, and the protective effects of testosterone are mediated by its aromatization [9]. The excess aromatase activity could lead to low testosterone and relatively increased estradiol levels (sex hormone imbalance) in men [10], and sex hormone imbalance was found to be correlated with the occurrence of depressive disorder [11].

Recent studies have displayed that many serum biomarkers, such as Tenascin-c (TNC), GDF-15, growth arrest-specific 6 (Gas6), kruppel like factor 4 (KLF4), and soluble glycoprotein 130 (sgp130), were found to be potential associated with MDD. Some researchers demonstrated that serum elevated TNC and GDF15 levels may be inflammatory biomarkers for depressive pathophysiology [12, 13]. Gas6 deficiency may be a potential mediator for MDD via increasing oligodendrocyte loss and microglial activation [14]. Whereas KLF4 could induce microglial activation through increasing the production of inflammatory cytokines [15]. An earlier study also reported that sgp130 may be a therapeutic target in chronic depression [16]. Moreover, related studies have demonstrated that gonadal hormone are closely associated with these serum biomarkers. Our research team have confirmed that testosterone is significantly and positively associated with serum Gas6 level [17], and serum sgp130 was positively correlated with estradiol and testosterone/estradiol ratio in male patients with coronary atherosclerotic disease [18]. TNC, KLF4 and GDF15 were also found to be associated with sex hormone levels in earlier studies [19–21]. However, the associations between sex hormone and these biomarkers in depressive patients remain poorly demonstrated, and the alteration in which marker could alert sex hormone imbalance in MDD is unclear.

In the current study, we explored the associations among serum T/E ratio and circulating depression risk indicators in depressed cohort. The main aim of this study was to select a biomarker to alert the sex hormone imbalance in depressive patients.

Material And Methods

Study population

Participants (412 depressive patients and 137 healthy controls) were enrolled from Department of Psychiatry at Renmin Hospital of Wuhan University. All subjects received a Structured Clinical Interview for DSM-IV (SCID). In addition, Hamilton Depression Rating Scale (HDRS) and the Beck's Suicidal Ideation Scale (SSI) were also performed to assess the severity of depressive symptoms. Depressed symptoms were evaluated basing on SCID score at the first day of admission, and the background materials were recorded simultaneously. Sociodemographic characteristics contained age and years of education. The following lifestyle and health indicators were evaluated: smoking status, alcohol use, and body mass index. Clinical characteristics (duration of symptoms and age of onset) were also recorded. To determine a potential pathophysiological effect of treatment, antidepressants use was evaluated according to consulting the patients and family members, and medicine were included selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA). The Medical Ethics Review Committee of Renmin Hospital of Wuhan University approved this study

protocol, and all subjects did not provide written informed consent due to the using the remaining specimens.

Sample Collection

Blood specimens were drawn from antecubital vein of all participants after an overnight fast. Serum samples were immediately centrifuged, recovered into 2 ml cryogenic vials and frozen at -80 °C until assays for various analyses.

Depression Risk Biomarkers

Circulating concentrations of TNC, GDF15, KLF4, Gas6 and sgp130 were detected along with a panel of other indicators, including testosterone, estradiol, thyroid hormone, lipids, and hs-CRP, as detailed previously [23]. In brief, the concentrations of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hs-CRP) were measured using a Siemens Advia 2400 automatic biochemistry analyzer (Siemens, Erlangen, Germany). Free thyroxine (FT4), free triiodothyronine (FT3), thyroid-stimulating hormone (TSH), testosterone (T), and estradiol (E) concentrations were determined using a Siemens Advia Centaur CP (Siemens, Erlangen, Germany). The T/E ratio was calculated according to the values of testosterone and estradiol. TNC concentration was detected using an enzyme-linked immunosorbent assay with a detection limit of 0.78 ng/ml (Wuhan, China, CUSABIO), GDF15 level was measured by an enzyme-linked immunosorbent assay with a detection limit of 7.8 pg/ml (Wuhan, China, CUSABIO), KLF4 concentration was detected using an enzyme-linked immunosorbent assay with a detection limit of 18.75 pg/ml (Wuhan, China, CUSABIO), Gas6 content was measured by an enzyme-linked immunosorbent assay with a detection limit of 0.78 ng/ml (Wuhan, China, CUSABIO), sgp130 concentration was determined by an enzyme-linked immunosorbent assay with a detection limit of 0.25 ng/ml (Wuhan, China, Elabscience).

Statistical Analyses

Variables were described as mean $\pm$ s.d. or percentages. All indicators were natural logarithmically transformed (to normalize their skewed distribution) and standardized. Differences in clinical characteristics were analyzed using χ^2 -tests or analyses of variance as appropriate. Difference in depression risk indicators were tested according to classification of T/E ratio using ANOVA. The associations among T/E ratio and depression risk indicators were assessed using single-factor correlation analysis and multivariable linear regression analysis. Stratified analysis was performed to further analyze the correlations between T/E ratio and GDF15, TNC in age, duration, FT3, TSH, HDL and hs-CRP strata.

Results

Study population

A total of 547 subjects, with a average age of 35.89 years (± 13.57 of s.d.), had complete epidemiologic inquiry and biomarkers measurements from the case-control study. Depressive patients were more likely to be older and less education. Lifestyle and health indicators for depressed individuals were worse than healthy controls. The mean of duration of disease in depressive patients was 36.47 months (± 31.72 of s.d.), the average age of onset was 29.34 years (± 13.52 of s.d.), and 41.01% of the depressed patients comorbided anxiety. The analyses of depressive severity showed that more than half the patients suffered from moderate depression (Table 1).

The biochemical variables of the participants are displayed in Table 1. The values of serum T, T/E ratio, FT3, TSH, HDL, KLF4 and Gas6 level in depressed patients were significantly decreased compared with healthy controls (all $P < 0.05$). Whereas the serum levels of hs-CRP, TG, TNC and GDF15 in depressed subjects were higher than healthy controls (all $P < 0.05$). The serum levels of E, FT4, TC, LDL and sgp130 unchanged in patients when compared to controls (all $P > 0.05$).

Table 1
Characteristics of the study population.

Characteristics	Controls (n = 137)	Depressive patients (n = 412)	P
Sociodemographic			
Age (years) (mean $\pm$ s.d.)	33.29 $\pm$ 10.71	36.48 $\pm$ 15.73	0.584
Education (years) (mean $\pm$ s.d.)	14.05 $\pm$ 3.41	12.92 $\pm$ 3.26	0.492
Lifestyle and health indicators			
Smoking status (%)			0.546
Non smoker	70.07	67.96	
Current smoker	29.93	32.04	
Alcohol use (%)	12.41	18.70	0.054
Body mass index (%)			0.037
Normal	67.15	59.47	
Overweight	23.36	30.10	
Obesity	9.49	10.43	
Clinical characteristics			
Duration (month) (mean $\pm$ s.d.)	-	36.47 $\pm$ 31.72	
Age of onset (years) (mean $\pm$ s.d.)	-	29.34 $\pm$ 13.52	
Comorbid anxiety (%)	-	41.01	
Antidepressant use (%)			
No antidepressant	-	72.33	
SSRI	-	10.68	
SNRI	-	12.62	
TCA	-	4.37	
Severity of depression			
Mild	-	29.61	
Moderate	-	51.21	
Severe	-	19.18	
Testosterone (T, ng/ml)	439.53 $\pm$ 136.08	331.64 $\pm$ 149.37	< 0.001

Characteristics	Controls (n = 137)	Depressive patients (n = 412)	<i>P</i>
Estradiol (E, pg/ml)	31.08 ± 10.34	29.34 ± 11.82	0.367
T/E ratio	16.32 ± 5.94	12.17 ± 5.62	< 0.001
FT3 (pg/ml)	3.48 ± 0.31	3.24 ± 0.39	0.006
FT4 (ng/ml)	1.24 ± 0.13	1.26 ± 0.23	0.426
TSH (μIU/ml)	2.28 ± 0.88	1.71 ± 0.96	< 0.001
hs-CRP (mg/l)	0.38 ± 0.36	1.16 ± 3.06	0.009
TC (mmol/l)	4.11 ± 0.79	4.23 ± 0.83	0.392
TG (mmol/l)	1.16 ± 0.49	1.51 ± 0.57	< 0.001
HDL (mmol/l)	1.28 ± 0.26	1.16 ± 0.24	0.024
LDL (mmol/l)	2.24 ± 0.62	2.31 ± 0.71	0.604
TNC (ng/ml)	6.92 ± 2.87	11.79 ± 6.06	< 0.001
GDF15 (pg/ml)	52.22 ± 42.86	74.60 ± 64.37	< 0.001
KLF4 (pg/ml)	23.51 ± 13.86	13.12 ± 6.84	< 0.001
Gas6 (ng/ml)	6.07 ± 3.12	4.88 ± 2.43	0.019
sgp130 (ng/ml)	14.04 ± 4.13	13.54 ± 4.39	0.297

Altered biomarkers concentrations in different classification of serum T/E ratio

Based on extensive investigations, many researchers proposed a cut-point of 10 as the lower limit of normal T/E ratio, and a cut-point of 20 as the higher limit of normal T/E ratio in male [22]. In this study, one third of the depressed patient (36.89%) had lower T/E ratio (< 10:1) and 10.20% had higher T/E ratio (> 20:1). The proportion of participants with with lower T/E ratio increased from healthy controls (13.14%) to those with depression (36.89%) (Fig. 1). Table 2 shows the changes of depression risk indicators among lower, normal, and higher T/E ratio assessed by one-way analysis of variance. As shown in Table 2, the significant changes of FT3, GDF15 and Gas6 levels between lower, normal, and higher T/E ratio were observed ($P < 0.05$), whereas the levels of other risk factors unchanged significantly ($P > 0.05$). Higher levels of FT3 and Gas6 were investigated for increasing T/E ratio, and lower level of GDF15 was observed for increasing T/E ratio.

Table 2
Unadjusted means of different biomarkers according to T/E status

Variable	lgT/E status			<i>F</i>	<i>P</i>
	T/E < 10:1 (n = 152)	10:1 ≤ T/E ≤ 20:1 (n = 218)	20:1 < T/E (n = 42)		
Age	36.87 ± 15.90	35.19 ± 14.02	32.57 ± 12.26	0.996	0.370
FT3	3.22 ± 0.45	3.29 ± 0.42	3.48 ± 0.42	5.616	0.004
FT4	1.22 ± 0.18	1.23 ± 0.21	1.27 ± 0.18	1.139	0.321
TSH	1.90 ± 1.16	1.95 ± 1.34	1.98 ± 0.86	0.541	0.582
hs-CRP	0.80 ± 1.85	0.94 ± 2.61	0.60 ± 2.64	2.697	0.069
TC	4.07 ± 0.84	4.21 ± 0.96	4.31 ± 0.98	0.928	0.396
TG	1.31 ± 0.86	1.44 ± 1.28	1.80 ± 1.42	1.685	0.187
HDL	1.18 ± 0.30	1.15 ± 0.30	1.19 ± 0.30	0.415	0.660
LDL	2.22 ± 0.68	2.31 ± 0.77	2.20 ± 0.73	0.270	0.763
TNC	9.40 ± 5.18	8.75 ± 5.15	8.18 ± 4.49	1.752	0.175
GDF15	107.52 ± 62.15	83.55 ± 61.44	69.36 ± 61.67	8.827	< 0.001
KLF4	213.17 ± 258.73	210.41 ± 252.37	212.06 ± 311.12	0.197	0.821
Gas6	3.64 ± 2.51	4.34 ± 2.58	4.88 ± 3.30	3.458	0.033
sgp130	12.83 ± 4.38	14.06 ± 4.26	14.31 ± 4.04	0.617	0.542

Correlations among loge-transformed T/E ratio and biomarkers in MDD

Univariate correlation analysis was performed to study the associations between loge-transformed T/E ratio and depression risk indicators in depressive participants. The results in Table 3 demonstrate that T/E ratio is positively and significantly associated with FT3 ($\beta=0.381$, $P<0.05$) and Gas6 ($\beta=0.061$, $P<0.05$); whereas T/E ratio is negatively and significantly associated with TNC ($\beta=-0.075$, $P<0.05$) and GDF15 ($\beta=-0.113$, $P<0.001$).

Table 3
Correlations of loge-transformed T/E ratio
and biomarkers

Variable	T/E		
	β	T	P
Age	0.023	0.378	0.706
FT3	0.381	2.173	0.030
FT4	0.048	0.311	0.756
TSH	0.013	0.348	0.728
hs-CRP	0.001	0.096	0.923
TC	0.045	0.020	0.731
TG	0.076	1.547	0.123
HDL	-0.150	-1.363	0.174
LDL	-0.056	-0.661	0.509
TNC	-0.075	-2.011	0.045
GDF15	-0.113	-4.161	< 0.001
KLF4	-0.012	-0.713	0.477
Gas6	0.061	1.980	0.048
sgp130	0.029	0.241	0.810

Logistic regression analyses for loge-transformed T/E ratio and GDF15

Results from multivariate linear regression models relating loge-transformed T/E ratio to depression risk indicators are displayed in Table 4. According to the results of univariate correlation analysis, we incorporated the age, FT3, HDL, TG, Gas6, GDF15 and TNC to perform the multivariable logistic regression analyses. Upon multivariable adjustment for age, FT3, HDL, TG and Gas6, higher T/E ratio remained statistically significantly related to lower GDF15 level (estimate-0.095 [95% *CI*-0.170~-0.023] standard deviation [SD] change per SD increase in lg[T/E], $P=0.015$) and TNC (estimate-0.085 [95% *CI*-0.167 ~ 0.003] standard deviation [SD] change per SD increase in lg[T/E], $P=0.048$). In addition, upon multivariable adjustment for only age, higher T/E ratio remained statistically significantly related to lower GDF15 level (estimate-0.118 [95% *CI*-0.168~-0.075] standard deviation [SD] change per SD increase in lg[T/E], $P=0.001$) and TNC (estimate-0.087 [95% *CI*-0.157~-0.019] standard deviation [SD] change per SD increase in lg[T/E], $P=0.009$).

Table 4
Adjusted associations between loge-transformed T/E ratio, GDF15 and TNC

	GDF15			TNC		
	β	95% CI	P	β	95% CI	P
Model1	-0.095	-0.170~-0.023	0.015	-0.085	-0.167 ~ 0.003	0.048
Model2	-0.095	-0.169~-0.025	0.009	-0.081	-0.158~-0.001	0.041
Model3	-0.118	-0.168~-0.075	0.001	-0.087	-0.157~-0.019	0.009

Model 1: adjusted for age, FT3, HDL, TG and Gas6; Model 2: adjusted for age, FT3 and HDL; Model 3: adjusted for age.

Associations between loge-transformed T/E ratio and GDF15 across risk categories

Table 5 presents correlation coefficient for the association among loge-transformed T/E ratio and GDF15, TNC levels, stratified by age, duration, FT3, TSH, HDL and hs-CRP. Inverse associations among T/E ratio and GDF15 level were found for all FT3, TSH and HDL strata, whereas the negative relations between T/E ratio and GDF15 level were noted for partial age, duration and hs-CRP strata. However, the inverse relations among T/E ratio and TNC level in all age, duration, FT3, TSH, HDL and hs-CRP strata were not observed.

Table 5
Correlations of loge-transformed T/E ratio, GDF15 and TNC across categories of age, duration, FT3 level, TSH level, HDL level and hsCRP level.

	GDF15			TNC		
	β	T	P	β	T	P
Age						
≥ 45	-0.090	-1.739	0.085	-0.059	-0.945	0.347
45 ~ 25	-0.144	-3.925	< 0.001	-0.025	-0.449	0.654
≤ 25	-0.081	-1.391	0.167	-0.143	-1.882	0.062
Duration						
≥ 3	-0.043	-0.855	0.394	-0.089	-1.426	0.156
<3	-0.124	-2.511	0.013	-0.040	-0.769	0.443
FT3						
≥ 3.32	-0.084	-2.232	0.027	-0.086	-1.530	0.128
<3.32	-0.126	-2.961	0.003	-0.089	-1.794	0.074
TSH						
≥ 1.717	-0.135	-3.105	0.002	-0.064	-1.254	0.211
<1.717	-0.092	-2.639	0.009	-0.084	-1.503	0.134
HDL						
≥ 1.01	-0.126	-2.795	0.006	-0.062	-1.253	0.212
<1.01	-0.067	-2.053	0.042	-0.129	-2.304	0.022
hs-CRP						
≥ 0.11	-0.037	-0.084	0.286	-0.051	-1.224	0.222
<0.11	-0.180	-4.480	< 0.001	-0.098	-1.506	0.133

Altered Gdf-15 Level Alerts Sex Hormone Imbalance In Mdd

In order to further demonstrate whether the altered serum GDF15 level could alert sex hormone imbalance in depressive subjects, we analyzed the associations between loge-transformed T/E ratio and depression risk indicators across the strata of T/E ratio. Based on the earlier report [22], the normal T/E ratio in men was defined as 10:1 ~ 20:1 (sex hormone balance), and the T/E ratio lower than 10:1 or more than 20:1 were considered as abnormal (sex hormone imbalance). As shown in Table 6, there is a significantly and

negatively correlation between T/E ratio and GDF15 level in depressed patients with sex hormone imbalance. These findings further verify that increased circulating GDF15 level could alert sex hormone imbalance in MDD.

Table 6
Correlations of loge-transformed T/E ratio and biomarkers across categories of sex hormone balance and unbalance.

	Balance			Unbalance		
	β	T	P	β	T	P
FT3	-0.090	-0.815	0.416	0.808	2.615	0.010
FT4	-0.238	-2.740	0.007	0.495	1.619	0.107
TSH	-0.001	-0.047	0.963	0.052	0.674	0.501
hs-CRP	0.005	0.607	0.544	-0.021	-0.813	0.418
TC	-0.124	-1.564	0.120	0.116	0.522	0.602
TG	-0.032	-1.039	0.301	0.166	2.136	0.034
HDL	-0.042	-0.606	0.546	-0.163	-0.911	0.364
LDL	-0.092	-1.832	0.069	-0.083	-0.575	0.566
TNC	-0.012	-0.549	0.584	-0.126	-1.656	0.099
GDF15	0.006	0.355	0.723	-0.193	-4.001	<0.001
KLF4	-0.018	-1.686	0.094	-0.006	-0.207	0.836
Gas6	0.006	0.316	0.752	0.056	1.102	0.272
sgp130	-0.094	-1.192	0.239	0.168	0.618	0.541

Discussion

In a host of depressive patients and healthy controls, to our knowledge the first of its kind, we demonstrated that after adjusting a large number of potential confounding factors, high serum abundance of GDF15 was associated with sex hormone imbalance in MDD. Not only the overall correlation between T/E ratio and GDF15 level was of significant effect size, but also the effect size was more pronounced in depressed patients with the sex hormone imbalance. Clinically higher GDF15 level was more likely to be observed in depressive individuals with lower T/E ratio. In addition, the association among T/E ratio and TNC level was of rather small effect size relative to GDF15. In the current study, we also observed that being depression was correlated to lower FT3 and TSH levels, in line with previous studies [23, 24]. Hyperparathyroidism has been regarded as the most important mechanism whereby inflammatory response could lead to the development of MDD.

At the molecular level, GDF15 was found to be a stress-responsive cytokine which is secreted by multiple cells, such as macrophages, endothelial cells, and neurons in response to oxidative stress, injury, and inflammation [25, 26]. GDF15 acts as a growth factor as well as immunomodulator, and has been thought to be involved in cognitive decline [27, 28]. Our study demonstrated that GDF15 level in depressed subjects was significantly higher than healthy controls, as well as increased GDF15 could alter sex hormone imbalance in patients with MDD. In prior studies, GDF15 was significantly and inversely associated with testosterone level in subjects with anaemia [21], as well as estradiol could activate GDF15 expression in the tamoxifen resistant cell systems [29]. These previous investigations confirm our results that T/E ratio was closely significantly and negatively associated with circulating GDF15 level in depressed patients. There was a demonstration that GDF15 may participant in the etiology of Parkinson's disease through the activation of chemokine receptor 4 (CXCR4) [30].

The present research possesses several limitations. First, as the research design was mainly cross-sectional, on deduction on the directionality of the correlation could be performed. We could not adjust the determined correlation for dietary intake of cholesterol, which can be metabolized into testosterone and estradiol, because nutritional information can not be collected. Whereas only small part of serum testosterone is detected by dietary intake, and high intake of saturated fat could result in the elevation of estradiol [31]. Furthermore, soy intake was found to impact the secretion or metabolism of sex steroids and further alter the circulating levels of testosterone and estradiol [32]. Then the the medicine used for 1–2 months prior to recruitment may affect the aex hormone and depression risk indicators. Therefore, we were also not able to adjust the relationship for drug treatment of antidepressants. In addition, this research has several crucial superiorities, such as adjustment for possible confounders, multilevel analyses for observed association.

Collectively, our results afford compelling evidence to previous studies, which mainly investigated the alterations in sex hormone or single risk indicators in MDD. Remarkably, after adjustment for multiple risk factors, serum T/E ratio was closely and inversely associated with GDF15, suggesting that the sex hormone imbalance in vivo may contribute to the increased circulating GDF15 level. Adjusting for those confounders did not attenuate the correlation among serum T/E ratio and GDF in MDD. This finding should induce further longitudinal and basic experimental test stating consistent time-sequenced correlations to investigate causality in the sex hormone-GDF15 link in DMM. Confirming an involvement of GDF15 in the pathway to depressive development due to sex hormone imbalance may have important implications. GDF15 could possesses positive and negative roles depending on the status of cells and their environment [33]. We speculate that individuals with sex hormone imbalance could stimulate GDF15 expression, and it shows a negative effect to promote the development of depression, including the induction of inflammation and oxidative stress [34, 35]. Addressing these problem successfully could help us to thought whether normalization of serum T/E ratios may become a possible future strategy to prevent or treat MDD. Furthermore, normalization of serum GDF15 level may be considered as a potential biomarker to hint sex hormone imbalance in vivo.

Conclusion

In summary, circulating GDF-15 level was greatly and inversely associated with serum T/E ratio, indicating that higher GDF-15 alerts sex hormone imbalance in patients with MDD.

Abbreviations

MDD

Major depressive disorder; TNC:Tenascin-c; GDF15:Growth differentiation factor 15; Gas6:Growth arrest-specific 6; KLF4:Kruppel like factor 4; sgp130:Soluble glycoprotein 130; E:Estradiol; T:Testosterone; TSH:Thyroid-stimulating hormone; FT3:Free triiodothyronine; FT4:Free thyroxine; hs-CRP:High-sensitivity C-reactive protein; LDL-C:Low density lipoprotein cholesterol; HDL-C:How density lipoprotein cholesterol; TG:Triglyceride; TC:Total cholesterol; TCA:Tricyclic antidepressants; SNRI:Serotonin-norepinephrine reuptake inhibitors; SSRI:Selective serotonin reuptake inhibitors; SCID:Structured clinical interview for DSM-IV; HDRS:Hamilton depression rating scale; SSI:Beck's suicidal ideation scale.

Declarations

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Authors' contributions

RP carried out literature searches, prepared figures, did data interpretation and writing; DL did writing and editing; YL conceptualized the paper, prepared figures, did writing and editing. The authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The Medical Ethics Review Committee of Renmin Hospital of Wuhan University approved this study protocol and all subjects provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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Figures

Figure 1

Clinical classification of serum T/E ratio in control and depressive groups