

The Association Among Serum Growth Differentiation Factor 15 Level and Suicidal Ideation is Dependent on Testosterone Deficiency in Depressive Patients

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Background: Elevated levels of growth differentiation factor (GDF)-15 and reduced levels of testosterone have been linked to depressive disorder, but whether they are also linked to suicidal ideation in patients with depression is unclear.

Methods: This retrospective study involved 301 patients ≥ 22 years old hospitalized for depression between July 2018 and November 2020 at Renmin Hospital of Wuhan University, of whom 120 had suicidal ideation. Serum levels of GDF-15 and testosterone were compared between patients with or without suicidal ideation.

Results: GDF-15 levels were significantly higher among patients with suicidal ideation than among those without, regardless of whether testosterone levels were above or below the median of 314 ng/dL. In multivariate logistic regression involving all patients, serum GDF-15 level was associated with low testosterone level ($P=0.001$). Among patients with testosterone < 314 ng/dL, an increase of 1 standard deviation in serum GDF-15 level translated to a 1.3-fold increase in the risk of suicidal ideation ($P=0.007$). This relationship was not observed in all population or patients with testosterone levels ≥ 314 ng/dL.

Conclusion: High serum GDF-15 level may be associated with an increased risk of suicidal ideation in patients with depression, and this association appears to be partly mediated by low testosterone levels.

Keywords: growth differentiation factor-15, testosterone, suicidal ideation, major depressive disorder

Introduction

Major depressive disorder (MDD) is a common mental illness that negatively affects daily living of people globally, and it is a leading cause of disability worldwide.¹ MDD is associated with high healthcare costs, resulting in economic burden on patients and their families.² Considering the economic burden and disability caused by depression, identification of MDD-related biomarkers might guide early diagnosis or targets for the treatment of MDD. Suicide-related event in patients with MDD is a leading cause of death in adolescents worldwide. Epidemiologic observations indicate that nearly 20% of adolescents with MDD consider suicide, more than 15% have formulated plans for suicide, and nearly 10% attempt suicide annually.³ Furthermore, it is well known that psychological, somatic, and psychosocial sequelae are the risk factors for suicidal ideation.⁴

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While the etiology and mechanism of MDD are unclear, it may involve dysregulation of neurotransmitters, dysfunction of the hypothalamic-pituitary-thyroid axis, and inflammatory responses.⁵ Patients with long-term MDD have high levels of the peripheral inflammatory markers interleukin-6, tumor necrosis factor- α and C-reactive protein (CRP).^{6,7} A useful inflammatory biomarker for MDD might be growth differentiation factor-15 (GDF-15), a well-known inflammatory cytokine that has been associated with several diseases, including major bleeding, mortality, stroke, and diabetes.^{8–10} GDF-15 is associated with neuroinflammation in a mouse model of Parkinson's disease, and its deficiency compromises dopaminergic neuron survival and microglial response.¹¹ Serum GDF-15 levels are significantly increased in patients with depression who have suffered acute ischemic stroke.¹² In view of this association, we speculated that GDF-15 may be a useful inflammatory biomarker for MDD.

In addition, MDD affects male and female differently. In fact, low testosterone is associated with higher risk of MDD.^{13,14} Interestingly, levels of GDF-15 may correlate with levels of testosterone: in cancer cells, testosterone directly regulates the expression of GDF-15.^{15,16} If this link also exists in depression, it may affect clinical manifestations of the disorder, since low testosterone levels are associated with greater risk of suicidal behavior among men with MDD.¹⁷ Thus, the present study explored whether levels of GDF-15 and testosterone are associated with suicidal ideation among men with depression.

Methods

Patients

This was a retrospective clinical study involving 301 men with MDD at least 22 years old who were hospitalized in the Department of Psychiatry at Renmin Hospital of Wuhan University between July 2018 and November 2020. All patients underwent Structured Clinical Interview for DSM-IV (SCID), Hamilton Depression Rating Scale (HDRS) and the Beck's Suicidal Ideation Scale (SSI). Suicidal ideation was defined as a conscious intent of the depressive subjects to end their life; however, ambivalent, through means that the patient thought could lead to death. To be included, patients had to be diagnosed with MDD with symptoms of depression for at least 4 weeks prior to the study. Patients were excluded if they reported using illegal drugs, or substance abuse during the preceding 3 months. Patients were also excluded if they had a history of heart disease, kidney or inflammatory disease; any infection; current cancer; or major somatic

disorders. Ethics approval was obtained from the Medical Ethics Review Committee of Renmin Hospital of Wuhan University. The clinical trial registration number is 20200988. Patients, at the time of admission, provided written consent for their anonymized medical data to be analyzed and published for research purposes. This study was also conducted in accordance with the Declaration of Helsinki.

Data Collection

Data were collected at the time of hospitalization on sociodemographic information (age, sex), lifestyle and health factors [current smoking and packs of cigarettes smoked per week, current alcohol consumption and quantity of alcohol consumed, and body mass index (BMI)], and clinical characteristics (duration of depression and antidepressant use). Smoking and alcohol use were evaluated by asking the subjects whether they smoked or drank, and if they did, they were asked to show the numbers of cigarettes smoked or drinking in present. BMI was evaluated by measuring the weight and height of both individuals on the same scale and calculated by dividing weight (in kilograms) by the square of height (in meters).

Blood Sampling and Assays

Patients were sampled after admission. They had to have been free of antidepressants or antipsychotic agents for at least one week prior to blood sampling, since these drugs can alter cytokine levels in serum.

Blood samples were drawn at 8 a.m. after overnight fasting. Samples were centrifuged, and the serum was stored at -70°C until assay. GDF-15 levels were measured using a commercial enzyme-linked immunosorbent assay kit (CusaBio, Wuhan, China). The manufacturer-specified detection range was 9.6–500 ng/mL GDF-15. All serum samples were diluted 10-fold before assay. Coefficients of variation for intra- and inter-assay reproducibility were, respectively, $<8.0\%$ and $<10.0\%$.

Blood samples were also assayed for the following routine parameters using an Advia Centaur CP system (Siemens): total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), Lipoprotein-a (Lp(a)), high-sensitivity C-reactive protein (hs-CRP), free thyroxine (FT4), free triiodothyronine (FT3), thyroid-stimulating hormone (TSH), and testosterone.

Statistical Analyses

Statistical analyses were performed using SPSS 20.0 (IBM, Chicago, IL, USA). Statistical tests were two-tailed, and $P < 0.05$ was defined as significant. Categorical data were shown as numbers (percentages), and continuous variables were shown as medians [inter-quartile range (IQR)]. Patients with or without suicidal ideation were categorized into groups of low testosterone or high testosterone, based on whether they had <314 or ≥ 314 ng/dL, which was the median testosterone levels observed in this study. Differences among the four groups were analyzed using the χ^2 test or Mann–Whitney U -test. Spearman correlation was performed to analyze associations of GDF-15 levels with other biochemical factors, and multiple stepwise regression was carried out to identify factors associated with serum GDF-15 levels. Logistic regression was used to identify predictors of decreased testosterone levels. Associations between a change in serum level of GDF-15 [per 1 standard deviation (SD)] and suicidal ideation were explored using logistic regression.

Results

Patient Characteristics

A total of 301 male patients with depression with a median age of 43 years (IQR 22 to 65 years) were included. MDD patients with suicidal ideation (39.87%) were compared with patients without suicidal ideations. Irrespective of testosterone levels, patients with suicidal ideation had significantly higher levels of TG, hsCRP and FT4, longer depressive duration, and a higher usage of antidepressants compared to those without suicidal ideation (Table 1). The median GDF-15 level in serum was 112.01 (11.63–376.46) ng/mL across all patients, and it was significantly lower among those without suicidal ideation (90.16 ng/mL, IQR 11.63–253.04 ng/mL) than among those with suicidal ideation (132.49 ng/mL, IQR 32.07–376.46 ng/mL; Figure 1).

Comparison of Serum GDF-15 Levels Between Those with Low or High Testosterone

The subgroup of patients with high testosterone, defined as levels ≥ 314 ng/dL, had a median testosterone GDF-15 level of 129.41 ng/mL (IQR 27.59–376.46 ng/mL), significantly higher than the median of 95.22 ng/mL (IQR 11.63–316.92 ng/mL) among patients with low testosterone. In both the low- and high-testosterone subgroups, GDF-15 levels were significantly lower among subjects without suicidal ideation than among those with ideation.

Univariate logistic regression showed that serum TG, HDL-c, hsCRP, FT3, TSH, and GDF-15 levels were related to low testosterone levels in patients with depression (Table 2). Multivariate logistic regression identified serum HDL-c, TSH, and GDF-15 levels as independent predictors of low testosterone levels (Table 2).

Associations Between Serum GDF-15 Level and Testosterone Level in Patients with Depression

Serum GDF-15 level was negatively associated with testosterone level ($r = -0.218$, $P = 0.003$), HDL-c ($r = -0.183$, $P < 0.001$) and TSH ($r = -0.196$, $P = 0.002$), but positively associated with TC ($r = 0.153$, $P < 0.001$), TG ($r = 0.251$, $P = 0.013$), hsCRP ($r = 0.218$, $P = 0.009$) and FT4 ($r = 0.187$, $P < 0.001$). In multivariate stepwise regression, serum GDF-15 level was defined as the dependent variable, while the independent variables were age, BMI, TC, TG, HDL-c, LDL-c, Lp(a), hs-CRP, FT3, FT4, TSH, Glu, testosterone, current smoking status, and current alcohol consumption status. This regression showed three variables to independently predict serum GDF-15 levels through a negative relationship: HDL-c, TSH, and testosterone (Table 3).

Association Between Serum GDF-15 Level and Suicidal Ideation in Patients with Depression

A 1-SD increase in serum GDF-15 level was not associated with an increased risk of suicidal ideation in the entire sample of patients with depression, or in the subgroup of patients with high testosterone. Such an association was, however, observed in the subgroup of patients with low testosterone [odds ratio (OR) 1.452, 95% confidence interval (CI) 1.078–2.062, $P = 0.003$; Table 4]. Similar results were obtained after correcting for several potential confounders in the multivariate model. Logistic regression showed that the use of antidepressants was negatively associated with suicidal ideation across all patients as well as separately in the low- and high-testosterone subgroups (all $P < 0.05$).

Discussion

Although the mechanism of MDD is unclear, it has been associated with microglial activation, neuroinflammation and low testosterone in men. Given the medical burden and health-care costs of depression, early detection and exploration of

Table 1 Patient Characteristics

Characteristic	Testosterone <314 ng/dL		Testosterone ≥314 ng/dL	
	With Suicidal Ideation (n=67)	Without Suicidal Ideation (n=84)	With Suicidal Ideation (n=53)	Without Suicidal Ideation (n=97)
Age (years)	47 (25–65)	43 (28–63)	39 (22–59)	46 (28–62)
BMI (kg/m ²)	21.76 (18.92–23.76)	20.47 (17.45–22.94)	18.93 (16.96–24.52)	20.68 (17.84–23.79)
TC (mmol/L)	4.13 (2.67–7.56)	4.02 (2.45–6.87)	3.97 (2.78–7.01)	4.21 (2.55–6.84)
TG (mmol/L)	1.58 (0.84–2.27)**	1.05 (0.76–1.95)	1.44 (0.79–2.19)*	1.16 (0.94–2.23)
HDL-c (mmol/L)	1.09 (0.93–1.38)**	1.42 (0.89–1.85)	1.13 (0.89–1.41)*	1.37 (1.01–1.75)
LDL-c (mmol/L)	2.36 (1.45–3.17)	2.29 (1.62–2.86)	2.31 (1.62–3.01)	2.23 (1.46–2.82)
Lp(a) (mg/L)	201.36 (128.02–295.42)	189.33 (104.37–304.28)	218.53 (112.93–316.39)	204.12 (95.47–295.43)
hsCRP (mg/L)	2.58 (1.08–5.04)**	1.79 (1.18–3.72)	2.25 (0.99–4.72)*	1.75 (1.06–4.28)
FT3 (pg/mL)	3.08 (1.47–5.93)	3.14 (1.52–5.45)	3.19 (1.48–4.92)	3.11 (1.08–4.78)
FT4 (ng/dL)	1.32 (0.79–1.63)**	1.17 (0.82–1.85)	1.28 (0.84–1.79)*	1.09 (0.79–1.88)
TSH (uIU/mL)	1.43 (0.79–2.13)*	1.97 (0.97–2.87)	1.52 (0.82–2.28)*	1.87 (0.96–2.21)
Glucose (mmol/L)	5.02 (4.03–6.16)	5.09 (4.15–5.89)	5.11 (4.11–6.02)	5.07 (4.47–5.84)
Duration of depression (year)	2.13 (0.56–5.03)*	1.24 (0.36–4.27)	1.97 (0.44–4.48)*	1.32 (0.41–4.03)
Current smoking	35 (52.23)	41 (48.81)	35 (66.04)	56 (57.73)
Current alcohol consumption	21 (31.34)	33 (39.29)	21 (39.62)	37 (38.14)
Anti-depressant therapy	39 (58.21)*	22 (26.19)	33 (62.26)*	31 (31.94)

Notes: Values are n (%) or median (interquartile range). Compared with patients without suicidal ideation, * $P < 0.05$, ** $P < 0.01$.

Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); hs-CRP, high-sensitivity C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

biomarkers in patients with depression are needed. Therefore, this study explores whether the inflammatory factor, GDF-15, is linked to the suicidal ideation in male depressive patients. The present study appears to be the first to investigate the relationship between serum GDF-15 level and suicidal ideation in male patients with depression. We found that serum GDF-15 levels were higher in patients with suicidal ideations than in those without suicidal ideation, regardless of their testosterone levels. More detailed analyses revealed that serum GDF-15 level was associated with suicidal ideation only in patients with testosterone levels below the median (314 ng/dL), but not in those with levels at or above the median. After adjusting for confounding factors, each 1-SD increase in serum GDF-15 level in low-testosterone patients was associated with a 1.3-fold increase in risk of suicidal ideation.

Many patients with long-standing MDD show an increased concentration of peripheral inflammatory cytokines, which has been linked to endocrine disturbances and deficiency of sex hormones.¹⁸ In fact, low testosterone has been associated with depression,^{13,14} and testosterone may protect against the disorder.^{19,20} We found here that GDF-15 levels correlated negatively with testosterone levels in patients with depression, similar to what has been reported for patients with coronary artery disease.²¹ GDF-15 has been demonstrated to be associated with the activation of microglia, which showed that GDF-15 deficiency compromises microglial response in the 6-hydroxydopamine mouse model of Parkinson's disease.²² These findings showed that GDF-15 might contribute to the development of MDD and lead to the disease exacerbation. Previous study have also reported that severity of

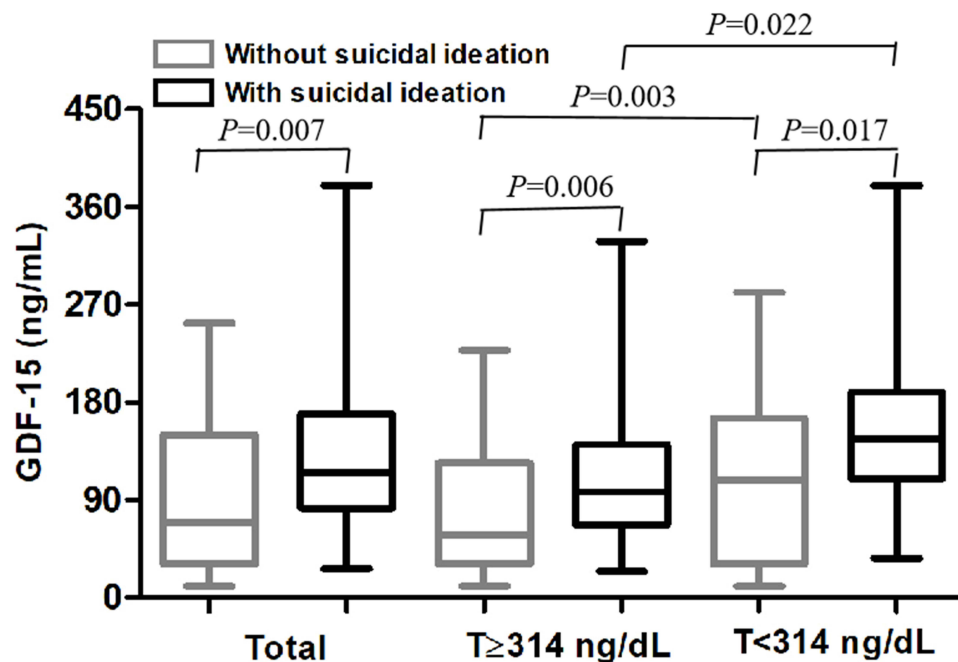


Figure 1 Tukey plot comparing serum GDF-15 levels between patients with or without suicidal ideation.
Abbreviations: GDF-15, growth differentiation factor (GDF)-15; T, testosterone.

MDD is significant with a clear association of increased suicidality.²³ Moreover, we also found that higher GDF-15 levels were associated with suicidal ideation. Similarly, serum GDF-15 levels have been shown to predict mood

disorders in patients.²⁴ High circulating GDF-15 levels have been associated with the development and progression of multiple disorders, such as cardiovascular and neurological disorders as well as cancer.^{25–27}

Table 2 Univariate and Multivariate Logistic Regression to Identify Factors Associated with Low Testosterone

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	1.062	0.953–1.103	0.129			
BMI	1.183	0.916–1.394	0.285			
TC	1.051	0.887–1.396	0.317			
TG	1.692	1.205–2.671	0.000	1.542	0.933–2.051	0.215
HDL-c	0.447	0.102–0.875	0.004	0.572	0.117–0.932	0.009
LDL-c	1.562	0.992–2.183	0.572			
Lp(a)	0.932	0.827–1.436	0.361			
hsCRP	1.105	1.024–1.562	0.014	1.057	0.873–1.657	0.226
FT3	0.673	0.219–0.965	0.006	0.772	0.336–1.014	0.451
FT4	0.329	0.184–1.163	0.417			
TSH	0.782	0.418–0.972	0.000	0.673	0.375–0.991	0.014
Glucose	1.426	0.893–2.107	0.219			
Duration of depression	0.762	0.395–1.301	0.527			
Current smoking	1.306	0.707–1.946	0.225			
Current alcohol consumption	0.956	0.672–1.548	0.362			
Anti-depressant therapy	1.062	0.783–1.422	0.421			
GDF-15	1.217	1.007–1.753	0.000	1.107	1.002–1.683	0.001

Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); hs-CRP, high-sensitivity C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; OR, odds ratio; CI, confidence interval.

Table 3 Multivariate Regression to Identify Factors Associated with Serum GDF-15 Levels in Patients with Depression

Variable	Standardized β	t	P
HDL-c	-0.318	5.273	0.005
TSH	-0.267	4.093	0.013
Testosterone	-0.484	7.892	0.000

Abbreviations: HDL-c, high-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone.

Table 4 Associations Between Serum GDF-15 and Suicidal Ideation in Patients with Depression

Groups	OR	95% CI	P
All patients			
Unadjusted	0.782	0.492–1.105	0.372
Adjusted	0.815	0.439–1.152	0.417
Patients with testosterone ≥ 314 ng/dL			
Unadjusted	1.106	0.874–1.782	0.218
Adjusted	1.206	0.905–1.864	0.269
Patients with testosterone < 314 ng/dL			
Unadjusted	1.452	1.078–2.062	0.003
Adjusted	1.338	1.062–1.995	0.007

Abbreviations: CI, confidence interval; OR, odds ratio.

Serum GDF-15 levels were significantly and negatively associated with testosterone in patients with coronary artery disease or HBV-associated hepatocellular carcinoma.^{28–30} Thus, the present research was to investigate the association among serum GDF-15 level and testosterone levels in depressive patients with or without suicidal ideation. Our data confirmed depressed subjects with suicidal ideation showed much higher serum GDF-15 levels than those without suicidal ideation, regardless of whether they had a testosterone < 314 ng/dL or ≥ 314 ng/dL. The testosterone was authenticated as an independent factor negatively correlated with serum GDF-15 level. The increased GDF-15 level was closely associated with an increasing risk of suicidal ideation, and this correlation was dependent on testosterone deficiency. This phenomenon may be explained that the decreased of testosterone levels have direct effects on central nervous system functions and neuroinflammation, which regulate the suicidal ideation.

Our findings suggest a close relationship among serum GDF-15 level, testosterone level and suicidal ideation in male patients with depression. The mechanisms underlying this relationship remain to be explored, preferably in larger, prospective studies. GDF-15 may exert its damaging effects, in part, by activating microglia.¹¹ Autopsy studies of patients with depression who commit suicide have detected activation of

microglia in many.³¹ High levels of GDF-15 and other inflammatory cytokines in the circulation of patients with depression may injure the nervous system.³² Conversely, testosterone may protect against depression by decreasing neuroinflammation.³³ Our study leads us to suggest that GDF-15 functions as a pro-inflammatory factor in the development and progression of depressive disorder, and that its activity may depend on testosterone levels, perhaps because testosterone regulates GDF-15 expression in the brain. Given that sex hormone deficiency contributes substantially to depressive and other health risks,³⁴ and is also an important regulatory factor associated with serum GDF-15 levels.

In summary, serum GDF-15 level was significantly increased in depressive patients with testosterone deficiency. The elevated GDF-15 level was also significantly associated with an increasing risk of suicidal ideation in depressed patients, and this correlation was dependent on testosterone deficiency. Our results indicate that GDF-15 may be a potential biomarker to identify patients with depression who are at higher risk of suicidal behavior.

Data Sharing Statement

Data are available with the consent of the corresponding author.

Acknowledgments

This study was supported by the Fundamental Research Funds for the Central Universities (2042020kf0064). We thank Renmin Hospital of Wuhan University for providing technical consultation.

Disclosure

The authors declare that they have no conflicts of interest.

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