The contribution of type 2 diabetes mellitus to hypothalamic inflammation and depressive disorders in young patients with obesity

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Background: To explore the contribution of type 2 diabetes mellitus (T2DM) to hypothalamic inflammation and depressive disorders in young patients with obesity.

Methods: According to the diagnostic criteria for T2DM, all of patients with obesity were divided into the diabetic and the non-diabetic groups. The severity of depressive disorders was assessed by self-rating depression scale (SDS). The signal intensity (SI) ratio of the T2-weighted phase of the superior hypothalamus/amygdala (H/A) was measured using a quantitative magnetic resonance imaging (MRI) technique to evaluate hypothalamic inflammation. Univariate and multivariate logistic regression analysis was used to find the influencing factors of depressive disorder. The prediction equation's sensitivity and specificity for the depressive disorder were calculated based on the receiver operating characteristic (ROC) curve.

Results: In young patients with obesity and diabetes, the incidence of depression is 79.49%, which was much higher than that in patients without diabetes (P<0.001). The SI of the left H/A in young patients with obesity and diabetes is significantly higher than that in non-diabetic patients (P<0.001). The relative risks of depression are fasting blood glucose (FBG) (OR 1.60; CI: 1.26–2.05), HbA1c (OR 1.94; CI: 1.40–2.68) and triglycerides (OR 1.40; CI: 1.03–1.90). Only FBG enters the predictive equation for depressive disorder, with a 52.8% sensitivity and 84.5% specificity.

Conclusions: In young diabetic patients with obesity, the incidence of depressive disorder is high, a mechanism possibly related to the left hypothalamus inflammation. Elevated FBG can be an independent predictor of depressive disorder in young patients with obesity.

Keywords: Type 2 diabetes mellitus (T2DM); obesity; hypothalamic inflammation; depressive disorder

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Introduction

The latest research shows that more than half of Chinese adults are overweight (34.3%) or obese (16.4%). In absolute terms, 600 million people are already overweight or obese, more than any other country (1). Patients with obesity often have multiple comorbidities, such as various cardiovascular and cerebrovascular diseases. Type 2 diabetes mellitus (T2DM) is one of the most common comorbidities in patients with obesity. One of the key study indicate the bidirectional associations between T2DM and obesity (2). Of the 1,389,016 eligible patients, the most common conditions in patients with T2DM included overweight/obesity in 78.2% (3).

In addition to causing various cardiovascular and cerebrovascular diseases, obesity is also associated with mood disorders, such as anxiety and depression. Many studies have investigated the relationship between obesity and mood disorders. It was found that obesity can cause emotional distress (4), especially depression (5), as confirmed in our previous clinical outcomes of patients with obesity (6). Further studies have found that depression has a bidirectional association with obesity (7). Depressed people have a 37% increased risk of obesity, and obese people have an 18% increased risk of depression. People with depression may experience significant weight gain due to irregular eating patterns and sedentary lifestyles triggered by clinical symptoms and/or treatment medications. This tendency to overeat under negative emotions, known as emotional eating, is closely associated with weight gain (8).

The link between diabetes and depression has long been noted and also works both ways, according to recent studies. The risk of depression in diabetes mellitus is 2.0–4.71 times higher than that in the general population (9). Conversely, depression also increases the risk of type 2 diabetes mellitus (T2DM) by 60% (10). Depression is a result of and a risk factor for T2DM (11). Their relationship is complex. This also suggests possible common pathophysiological mechanism between them (9). Chronic low-level inflammatory processes throughout the body are an essential feature of T2DM and obesity. However, the role of systemic inflammation in the central nervous system (CNS) (especially the hypothalamus and hippocampus) remains unclear. Previous studies also found that depressive disorder in young patients with obesity is related to hypothalamic inflammation (6). Still, this research result does not exclude the influence of diabetes on hypothalamic inflammation.

To study the influence of diabetes on hypothalamic inflammation and depressive disorder, we conducted a cross-sectional study design using quantitative imaging technology to explore the contribution of T2DM to hypothalamic inflammation and depressive disorders in young patients with obesity. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-192/rc).

Methods

Participants and procedures

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (No. 2020KY204-01). Informed consent was obtained from all participants. All participants underwent magnetic resonance imaging (MRI) and a clinical assessment using the self-rating depression scale (SDS) within a week of admission. All subjects fasted for more than 8 hours, taking blood samples from 6:00 a.m. to 8:00 a.m. The oral glucose tolerance test (OGTT) was 75 g of the glucose taken orally. A second blood sample was obtained 2 hours after glucose ingestion. All research data were registered, checked and verified by two professionally trained graduate students.

The inclusion criteria were as follows: (I) aged between 18 and 45 years, (II) body mass index (BMI) above 28 kg/m^2, (III) at least 4 years of school education, and (IV) informed consent provided by either the patient or an authorised relative.

Exclusion criteria were as follows: (I) neurological or psychological disease diagnosis, (II) procalcitonin level ≥0.05 ng/mL, (III) contraindications or inability to undergo an MRI scan, or (IV) severe hearing or vision impairment resulting in a failure to undergo assessment.

All criteria were determined by two experts from the Psychology Department of Changzhou No. 2 People's Hospital. A professional radiologist, blinded to participant information, analysed the images and excluded ineligible cases.

Demographic information and biochemical indexes

Demographic information (age, gender, height, weight, education and renal function) were collected. IBM's calculation was to divide weight in kilograms by height in

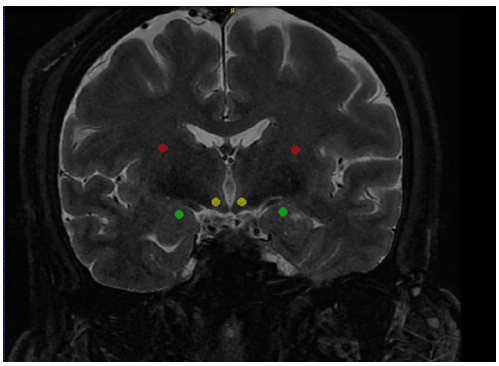

Figure 1 ROIs in coronal T2-weighted images. Representative coronal T2-weighted MRI scan through the hypothalamus. The zoomed image shows the placement of the right and left ROIs. The yellow-, green-, and red-stained areas represent the regions of interest in the hypothalamus, amygdala, and putamen. ROIs, regions of interest; MRI, magnetic resonance imaging.

metres squared. In addition, clinical chemistry parameters (glucose, blood lipid, renal function and procalcitonin) were determined on an ADVIA XPT Clinical Chemistry System (Siemens Healthineers). HbA1c was determined using the Tosoh G8 HPLC Analyzer (Tosoh Bioscience, Sursee, Switzerland).

Diagnostic criteria for T2DM

Typical symptoms of diabetes are any of the following: (I) random blood glucose ≥11.1 mmol/L, (II) FBG ≥7.0 mmol/L, (III) blood glucose ≥11.1 mmol/L at OGTT 2 hours and (IV) HbA1c ≥6.5%. In the absence of typical diabetes symptoms, it is necessary to recheck for confirmation on another day. Type 1 diabetes, special type diabetes and gestational diabetes were excluded (12).

According to the diagnostic criteria for T2DM, all of patients with obesity were divided into the diabetic and the non-diabetic groups.

Image pre-processing and quality control

Cranial MRI was performed in the Department of Radiology, the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, using a 3.0 Tesla MRI system (GE Discovery MR750W, GE Healthcare, Chicago, IL, USA). The scanning parameters and methods were based on previous publications (6). All scans were performed by the same radiologist. ITK-SNAP, the imaging analysis software developed by the University of Pennsylvania, is used to pre-process images and collect the average grey intensity (*Figure 1*). Two trained neurologists independently analysed imaging data of 175 patients with obesity. The average value from the two neurologists was taken as the grey intensity value. H/A ratio was then calculated.

Clinical assessments

The Zung SDS (https://psychology-tools.com/test/zung-depression-scale), consisting of 20 items with an original score of 20–80 points, was used for self-assessment based on patients' full understanding of the guide language. A standard score is an integral part of the original score multiplied by 1.25. According to the Chinese SDS norm scoring standard, SDS standard score under 50 is classified as 'no depressive disorder' and ≥50 as 'depressive disorder' (13).

Statistical analyses

The SPSS 24.0 statistical software was used for data analysis. A P value of 0.05 on both sides was considered statistically significant. The statistical description of the measurement data was expressed as mean ± standard deviation. The Shapiro-Wilk test was used to verify the normal distribution of continuous variables. *T*-test was used for normal distribution data. Non-normal distribution, expressed by the median, was used as the rank-sum test. The chi-square test was used for counting data.

Univariate unconditional logistic regression analysis was used to determine the correlation between depressive disorder and age, sex, education level, etc. The independent variable of 0.2 was used as a potential influencing factor for the multifactor unconditional logistic regression analysis, determining each variable's absolute risk and 95% confidence interval.

We plotted characteristic ROC curves to estimate the discernability of predicted variables for the occurrence of depressive disorder in young patients with obesity and to test the model's accuracy and sensitivity.

Results

Participant characteristics

A total of 179 patients with obesity hospitalised in the Gastrointestinal Surgery Department of Changzhou No. 2

Table 1 Participant characteristics

Variable	Non-diabetic group (n=136)	Diabetic group (n=39)	t or χ^2	P
Age, M (P25, P75)	29.5 [25, 36]	29 [27, 34]	–0.34	0.732
Gender (%)			0.96	0.092
Male	38 (27.94)	14 (35.90)		
Female	98 (72.06)	25 (64.10)		
Education level (%)			1.86	0.331
Junior college and below	46 (33.83)	12 (30.77)		
Undergraduate and above	90 (66.17)	27 (69.23)		
BMI (kg/m^2), M (P25, P75)	37.55 (33.19, 40.65)	40.36 (35.58, 45.54)	2.57	0.242
LDL-C ($\bar{x}$±s)	2.95±0.73	3.06±0.85	–0.80	0.422
HDL-C (mmol/L), M (P25, P75)	1.06 (0.94, 1.21)	1.00 (0.86, 1.10)	2.00	0.056
TG (mmol/L), M (P25, P75)	1.50 (1.11, 2.08)	2.21 (1.63, 2.56)	3.78	<0.001
TC (mmol/L), M (P25, P75)	4.47 (4.04, 5.31)	4.63 (4.25, 5.31)	1.31	0.189
UA (mmol/L), M (P25, P75)	369.5 (312.5, 439.5)	372.0 (298.0, 459.0)	–0.13	0.898
Scr (mmol/L), M (P25, P75)	54.0 (46.0, 63.7)	51.0 (45.0, 62.0)	–0.82	0.415
BUN (mmol/L), M (P25, P75)	3.90 (3.05, 4.70)	3.60 (2.70, 4.70)	–1.11	0.267

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; UA, uric acid; Scr, serum creatinine; BUN, blood urea nitrogen.

People's Hospital affiliated to Nanjing Medical University from January 2019 to June 2021 were selected for elective bariatric surgery. Four patients were excluded for not meeting inclusion criteria. There were 175 patients with obesity (BMI 38.18±6.10 kg/m^2) enrolled in this study and divided into the diabetic [39] and the non-diabetic [136] groups according to the diagnostic criteria for T2DM. There were no significant differences in age, sex, education level, BMI, high- and low-density lipoprotein, cholesterol, uric acid, creatinine and urea nitrogen (P>0.05). Triglycerides were statistically significant between the groups (P<0.05; *Table 1*).

Incidence of depressive disorder

The incidence of depressive disorder in young obese patients was 41.14%. In young patients with obesity and diabetes, it was much higher than that in obese patients without diabetes (P<0.001; *Figure 2*).

H/A SI ratio

The SI ratio of the H/A can be used as a substitute marker for studying hypothalamic inflammation (14). There was no significant difference in the right H/A SI in young obese patients with or without diabetes (P>0.05). The intensity of the left H/A signal in young diabetic patients with obesity was significantly higher than that in non-diabetic patients (P<0.001; *Table 2*).

Influencing factors of depressive disorder

In young patients with obesity, the relative risk of depressive disorder was associated with FBG (OR 1.60; CI: 1.26–2.05), HbA1c (OR 1.94; CI: 1.40–2.68) and triglycerides (OR 1.40; CI: 1.03–1.90), but not age, sex, education level, renal function, and cholesterol. Taking depression disorder as the dependent variable, the seven factors with P value under 0.2 were independent variables. The multifactor unconditional logistic regression analysis results showed that only FBG was included in the logistic regression equation (*Table 3*).

Predictive equations of depressive disorders

According to the receiver operating characteristic (ROC) curve of FBG for depressive disorder, the area under ROC was calculated to be 0.679. Sensitivity evaluation

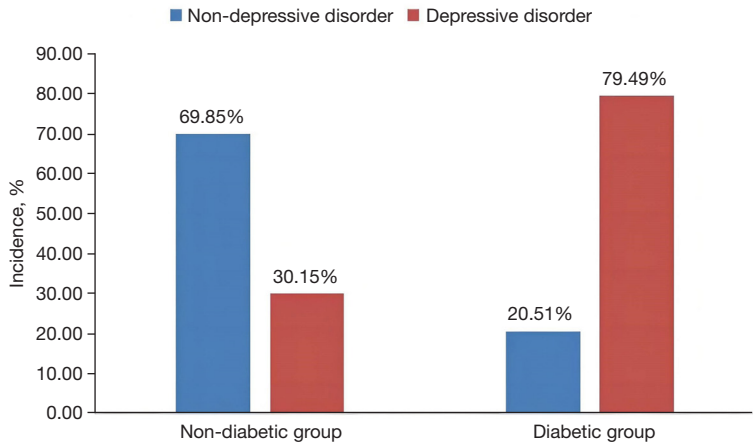

Figure 2 Incidence of depressive disorder in young patients with obesity.

Table 2 H/A SI ratio

Variable	Non-diabetic group	Diabetic group	t	P
Right H/A ratio, M (P25, P75)	1.07 (0.97, 1.15)	1.09 (1.01, 1.21)	1.27	0.206
Left H/A ratio, M (P25, P75)	1.05 (0.90, 1.17)	1.21 (1.17, 1.31)	5.60	<0.001

H/A, hypothalamus/amygdala.

across different FBG level thresholds showed that FBG ≥6.03 mmol/L had a 52.8% optimal sensitivity, with an 84.5% specificity, in predicting postpartum glucose intolerance (*Figure 3*).

Discussion

This study revealed that young diabetic patients with obesity had a higher incidence of depressive disorder, with significantly increased left H/A SI ratio. The relative risk of depressive disorder in young patients with obesity was related to FBG, glycated haemoglobin and triglycerides, whereas the absolute risk was only related to FBG.

Obesity, depression and T2DM are complex pictures (15). As the BMI increases, the risk of depression also increases (16). A meta-analysis showed that overweight patients had a risk of depression of 1.07 (95% CI: 1.04–1.11), whereas patients with obesity had an increased risk of depression of 1.32 (17). Our previous studies also showed that the incidence of depression in patients with obesity was higher than that in the normal population (6). Generally, the incidence of depressive disorder in obese people is 1.7–50% (2,18). In this study, the incidence of depression in patients with obesity was 41.14%. Obesity can lead to low self-evaluation, inferiority complex and social isolation, inducing depressive disorder. T2DM is one of the most common comorbidities in patients with obesity, and induce depression through common HPA axis dysfunction, insulin resistance, immune-inflammatory activation and other mechanisms. Among diabetics, obesity is associated with an increased risk of depressive disorder or severe depressive symptoms (OR 1.63; 95% CI: 1.40–1.92) (19), especially among the White population. This study also confirmed that depressive disorder incidence in young diabetic patients with obesity was significantly higher than that in obese patients without diabetes. This suggests a possible common anatomical basis and pathophysiological process among T2DM, obesity and depression (15). Inflammation (20) and intestinal flora (21) have been proposed successively, which need to be confirmed by further experimental studies.

Obesity and T2DM are both low-level inflammation processes throughout the body. This low-grade systemic inflammation causes the release of inflammatory factors in the peripheral tissues, affecting the CNS, such as the thalamus, resulting in energy regulation and obesity imbalance. Animal experiments have shown that short-term feeding of high-fat food can cause activation and infiltration of hypothalamic inflammatory cells, which is earlier

Table 3 Univariate and multivariate unconditional logistic regression analyses of depressive disorder

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.04	0.99–1.08	0.117	0.96	0.91–1.00	0.958
Education level	1.58	0.79–3.14	0.194	0.64	0.33–1.25	0.192
FBG	1.60	1.26–2.05	<0.001	1.31	1.04–1.66	0.023
HbA1c	1.94	1.40–2.68	<0.001	1.13	0.64–1.42	0.096
UA	1.00	0.99–1.01	0.140	0.99	0.96–1.01	0.104
BUN	0.82	0.62–1.09	0.166	1.16	0.89–1.48	0.257
TG	1.40	1.03–1.90	0.032	0.98	0.67–1.44	0.933
Gender	1.05	0.54–2.02	0.895	NA		
BMI	1.03	0.98–1.08	0.214	NA		
TC	1.61	0.45–5.76	0.462	NA		
LDL-C	1.29	0.87–1.92	0.213	NA		
HDL-C	1.52	0.24–9.83	0.660	NA		
Scr	1.00	0.96–1.03	0.817	NA		

BMI, body mass index; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; UA, uric acid; Scr, serum creatinine; BUN, blood urea nitrogen; NA, not included in the multivariate analysis.

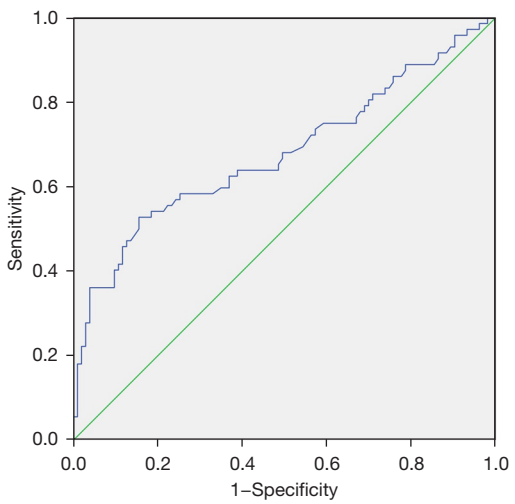

Figure 3 Receiver operating characteristic curve for prediction of depressive disorder intolerance.

than obesity occurrence, suggesting that hypothalamic inflammation is not the result of obesity, but a key trigger factor of obesity pathogenesis (22). Hypothalamic inflammation can lead to energy imbalance and aggravate central insulin resistance and leptin resistance. This causes fat accumulation in surrounding tissues, leading to the obesity occurrence and development (23). In clinical experiments, quantitative imaging technology was used to study hypothalamic inflammation. It was confirmed that BMI was correlated with hypothalamic inflammation (24), but only with the left hypothalamic inflammation (25). We used this technique to study the relationship between diabetes and hypothalamic inflammation. It was found that T2DM in young patients with obesity was only related to the H/A SI ratio in the left hypothalamus. This left-right asymmetry has also been observed in previous studies. Data from animal and human studies (25,26) suggest that the left and right hypothalamus asymmetrically adjust the HPA axis, circadian rhythms, reproductive and immune systems, release of thyroid function and satiety status—all of which are involved in emotional regulation. Left hypothalamus inflammation may be one of the possible mechanisms of depressive disorder among young diabetic patients with obesity. Anti-inflammatory therapy may be one way to control blood sugar, reduce weight and improve depression in the future.

There are many influencing factors for the occurrence of

depression among young patients with obesity. We screened FBG, glycated haemoglobin and triglyceride as relative risk factors by univariate logistic regression analysis. Different models were established, and the multiple factor stepwise logistic regression analysis was used to determine if FBG may be an independent predictor of depressive disorder in young patients with obesity. Haleem *et al.* (27) measured FBG, leptin levels, depression scores in patients with different BMI and found that leptin and fasting glucose levels in obese patients with depressive disorder were higher than those in obese patients without depressive disorder, related to leptin's influence on the CNS in diabetic patients with obesity (28). Furthermore, leptin and FBG levels were consistent with the depressive disorder's severity, suggesting that leptin in the blood has a strong inhibitory effect on insulin release in obese patients with depressive disorder. Domestic studies have also reached similar conclusions. Depression and FBS (OR 1.5; 95% CI: 1.00–2.20) were associated with T2DM (OR 1.5; 95% CI: 1.01–2.20) (29), suggesting that HPA axis dysfunction, insulin resistance, immune-inflammatory activation and other pathways are common between the two. However, this association's mechanism and direction are unclear. Depressive disorders may be the cause or consequence of hyperglycemia (30), which needs to be explored in high-quality randomised, double-blind, multi-centre longitudinal studies with a large sample size. We also used the ROC curve to calculate FBG's sensitivity and specificity in predicting the occurrence of depressive disorder in young patients with obesity, conducive to the early detection of depressive disorder and patients' early treatment and recovery.

Our study has certain limitations. First, it was designed to be a cross-sectional survey and could only produce a correlational analysis, not a causal relationship between obesity, T2DM and depressive disorders. Second, we did not assess variables, such as environment and family income, which may cause these three diseases. They should be included in future studies.

Conclusions

The high incidence of depressive disorder in young diabetic patients with obesity may be related to the left hypothalamus inflammation. Anti-inflammatory therapy may be a way to control blood glucose, reduce body weight and even improve mood in the future. Elevated fasting glucose can be an independent predictor of depressive disorder in young patients with obesity.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-192/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-192/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-192/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (No. 2020KY204-01). Informed consent was obtained from all participants.

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