Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Gender Differences of Antioxidant System and Thyroid Function in Depressed Adolescents with Non-Suicidal Self-Injury

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Purpose: The aim of our study was to explore the relation between serum levels of non-enzymatic antioxidants, thyroid function with the risk of non-suicidal self-injury (NSSI) in depressed adolescents.

Patients and Methods: We retrospected the electronic records of 454 hospitalized patients aged 13–17 years old with a diagnosis of major depressive disorder (239 patients with NSSI and 215 subjects without NSSI), and collected their demographic and clinical information, including serum levels of total bilirubin (Tbil), uric acid (UA), free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH).

Results: The incidence of NSSI was 52.6% among depressed adolescents aged 13–17, 57.1% in female and 38.5% in male. After using the propensity scoring method to exclude the influence of age between the two groups, it was found that patients with NSSI showed lower levels of Tbil (P=0.046) and UA (P=0.015) compared with those without NSSI. Logistic regression results showed that serum UA was associated with NSSI behavior in female patients (OR=0.995, 95% CI: 0.991–0.999, P=0.014), and TSH was associated with NSSI in male participants (OR=0.499, 95% CI: 0.267–0.932, P=0.029).

Conclusion: Female and male may have different pathological mechanisms of NSSI. NSSI is more likely to be related to antioxidant reaction in female adolescent patients, while more likely to be related to thyroid function in male depressed adolescent patients.

Keywords: antioxidant system, depressed adolescents, incidence, non-suicidal self-injury, thyroid function

Introduction

Non-suicidal self-injury (NSSI) means any deliberate action that leads to destruction of tissues without any intention of committing suicide.[1,2] The prevalence of occasional NSSI in adolescents is 19.7% and the lifetime prevalence of NSSI is 27.6%.[3] One occurrence of NSSI behavior is likely to indicate that the behavior will happen again.[4] The number of adolescents who reported participating in repetitive NSSI was approximately 7.8%.[3] Adolescents with major depressive disorder (MDD) exhibited greater and more stable involvement in NSSI than non-MDD adolescents.[4] NSSI can also cause physical injuries such as bleeding, bruising and infection, and it also increases the risk of other high-risk behaviors, including suicide.[5–7]

NSSI is influenced by many factors, such as psychosocial,[8] behavioral,[9] neurobiological and genetic factors.[10] Multiple studies focused on the psychosocial factors related to NSSI, such as adverse childhood events,[11,12] bullying and media influence.[13] However, investigations focusing on biological factors possibly correlating to NSSI are few, as the mechanism of NSSI is still unclear. Neurobiological studies have suggested that the hypothalamic-pituitary-adrenal (HPA) axis[14,15] and endogenous opioids[16] probably participated the pathogenesis of NSSI.

Received: 2 December 2023
Accepted: 4 June 2024
Published: 20 June 2024

Oxidative stress is important in clinical neuroscience, the brain is especially vulnerable to oxidative stress for its enormous consumption of oxygen, moderate antioxidant defense system and rich in lipid cosmetics.[17] The imbalance between reactive oxygen species and antioxidant defense leads to relaxation of brain function and abnormal neuronal signaling.[18] Oxidative stress played a key role in normal brain function and the pathogenesis of neuropsychiatric diseases such as depression,[19] bipolar disorder[20,21] and Alzheimer's disease.[22,23] Previous studies have shown that serum bilirubin[24] and uric acid (UA)[25–27] could be involved in the pathophysiology process of depression by regulating oxidative stress. In addition, one study indicated patients with suicide attempts had higher levels of nitrogen oxides (products of nitrates and nitrites), lipid hydroperoxides (biomarkers of oxidative damage to lipids / lipid peroxidation) and lower TRAP (biomarkers of total antioxidant defense system) than those who had no history of suicide attempts.[28] Bartoli et al attempted to examine whether the level of UA associated with specific clinical and behavioral features in patients with mood disorders, though no behavioral/clinical features were found to be associated with changes in blood uric acid.[29]

It is well established knowledge that the thyroid hormone plays a role in neuronal differentiation, migration, myelination and synaptic formation during brain development.[30] The link between thyroid function and MDD has long been recognized. Most of the existing studies have reported that the prevalence and incidence of hypothyroidism in patients with depression are higher than those within the general population.[31] The dysregulated levels of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4), even within the normal range, correlated with the severity of depression.[32,33] Suicide attempts were associated with reduced activity in the hypothalamic-pituitary-thyroid (HPT) axis in depressed patients. Lack of TSH response to TRH can be a risk factor for suicide[34]. The serum FT4 levels in individuals with depression or who had attempted suicide were lower than those who had not attempted suicide, while there was no significant variation in TSH and FT3 levels.[35] Mouri et al study focusing on thyrotropin receptor knockout murine models demonstrated phenotypes within murines such as hyperactivity, impulsiveness and increase in aggression.[36] It is generally considered that NSSI behaviour is impulsive.[37] However, the relationships between thyroid hormone and NSSI behavior in depressive patients have not been reported yet.

At present, a close relationship between antioxidant level and thyroid function had been reported.[38] Thyroid hormones regulate cellular oxidative stress through mitochondrial oxygen consumption. Changes in thyroid hormone levels lead to subtle variations in the degree of antioxidant enzyme presence, resulting in an imbalance for the removal of reactive oxygen species. From one perspective, hyperthyroidism can lead to increased oxidative metabolism and reduced glutathione peroxidase in rats, thus leading to increased lipid peroxidation level.[39] Following another perspective, hypothyroidism is related to increased reactive oxygen species production, enhanced oxidative stress, and then enhance lipid peroxidation.[40]

In view of the lack of studies on biochemical and hormone levels related to NSSI, the present study investigated biological correlations between clinical biochemical indicators and NSSI, to explore the potential pathophysiological mechanisms associated with the occurrence and development of NSSI. Total bilirubin (Tbil) and UA are important endogenous antioxidants in the body,[41,42] that can reflect the antioxidant capacity of individuals. FT3, FT4 and TSH are the main indicators reflecting thyroid function. Previous studies have confirmed that females are more likely to engage in NSSI behaviors than males.[43] Moreover, there are differences in the levels of antioxidants and thyroid function between males and females.[44–46] Therefore, we speculate that there are gender differences in the association between antioxidant stress system and thyroid function and adolescent depression. The results of this study are expected to enhance our understanding of the relationship between NSSI behavior and serum indicators of oxidative and thyroid hormone levels in adolescent depression, thereby improving the treatment of NSSI behavior associated with adolescent depression.

Materials and Methods

Patient Study Groups

We conducted a retrospective study that included 454 patients with MDD, with individual age ranging from 13 to 17 years old. All participants admitted to hospital between February 2016 and June 2022 from the In-patient Department of Psychiatry, University Town Hospital Affiliated to Chongqing Medical University. The diagnosis of MDD was determined in accordance with the International Statistical Classification of Diseases and Related Health Problems - 10th Revision (ICD-10) for depression by two experienced psychiatrists. Moreover, the 9-item Patient Health Questionnaire

(PHQ-9) score of all patients was ≥10. Patients were excluded for the following reasons: co-diagnosis with kidney disease (chronic renal failure, nephritis, etc.), liver disease, allergic diseases (asthma), metabolic diseases (metabolic syndrome, dyslipidemia, gout, etc.), hypertension, thyroid dysfunction and other physical diseases, co-diagnosis for schizophrenia spectrum bipolar disorder, psychoactive substance use disorder and suicide attempts (self-harm behavior with the purpose of ending one's life) history. All patients were diagnosed by two senior doctors.

This current study was conducted according to the Helsinki Declaration. In addition, our study was approved by the Ethics Committee of University Town Hospital Affiliated to Chongqing Medical University (LL-202161). As our study was a retrospective study, we had obtained permission from the Ethics Committee of University Town Hospital Affiliated to Chongqing Medical University to waive informed consent. All patient information included was strictly confidential.

Data Collection

The customized electronic report questionnaire was used for data collection. We collected sociodemographic and clinical information in the database of the Case-data Management Platform, including demographic characteristics, lifestyle and personal history. The database recorded the basic information, disease progress and treatment process for all patients. Data quality control was conducted by two trained researchers, and independently confirmed by two researchers. The calculation formula for Body mass index (BMI) is as follows: BMI = weight(kg)/height(m)^2.

PHQ-9 was used to assess the severity of depressive symptoms.[47] The PHQ-9 consisted of 9 items, all of which were rated on a 4-point scale (0: not present; 3: almost every day). 7-item Generalized Anxiety Disorder scale (GAD-7) was used to assess the severity of anxiety symptoms.[48] The GAD-7 consisted of 7 items, all of which were rated on a 4-point scale (0: not present; 3: almost every day).

All personnel involved in blood collection had undergone standardized training. Blood collection was carried out according to standard specifications and procedures. All blood samples were collected between 06:30–07:00 after overnight fasting. Blood samples were sent to the laboratory for testing within 30 minutes after collection. UA and Tbil were measured by a Mindray BS-800® automatic biochemistry analyzer [mindray, made in Shenzhen, China]. Thyroid functions, including FT3, FT4 and TSH, were measured by the Roche® automatic electrochemical luminescence immune analyzer [Roche, made in Basel, Switzerland]. All tests were conducted by skilled doctors in the laboratory department according to standardized procedures. Finally, 454 antioxidant index data and 397 thyroid function data were collected.

Non-Suicidal Self-Injury Evaluation

In the present study, NSSI refers to behaviour involving self-injury with no suicidal intent.[1] Participants who had repeatedly committed self-harm in the year prior to admission were assigned to the "self-harm group" (MDD/NSSI), if they never did not assign to the "non-self-harm group" (MDD/non-NSSI).

Statistical Analysis

SPSS 26.0 ® was used for statistical analysis. The propensity scoring method (PSM) was used to eliminate age differences between the two groups. Enumeration data was expressed in percentiles (%) and measurement data was expressed in medians (IQR) or mean ± standard deviation (SD). Shapiro–Wilk test was used to conduct normality analysis. Difference between two groups of measurement data was determined by Mann–Whitney *U*-test or independent *t* test. Difference between two groups of counting data was assessed by Chi-square tests. Spearman correlation analysis was used to assess the correlation between thyroid function and antioxidant factors. Logistic regression was used to explore the relationship between antioxidant factor, thyroid function and NSSI. NSSI was as dependent variable, Tbil, UA, FT3, FT4, TSH as independent variables, respectively. The factors that may affect NSSI were controlled as covariates, and the variable selection adapted the enter method. Statistical significance was defined as $p<0.05$.

Results

Characteristics of Adolescent Non-Suicide Self-Injury Behavior

We identified 705 MDD patients aged 13–17 years old. We excluded 28 patients for lacked PHQ-9 score. We excluded 17 patients because they had physical diseases, such as hypertension, asthma, urticaria, thyroid disease, etc. In addition, we excluded 206 patients who had attempted suicide. Finally, a total of 454 MDD patients aged 13–17 years were included, including 239 patients with NSSI and 215 patients without NSSI (see Figure 1). Table 1 lists the demographic data and clinical variations between MDD/NSSI group and MDD/non-NSSI group. Univariate analysis elucidated differences in age (P<0.001), gender (P=0.001), age of onset (P<0.001), antidepressant use (P<0.001), PHQ-9 score (P<0.001) and GAD-7 score (P=0.003) in the two groups. However, there was no significant difference in BMI (P=0.190), history of smoking (P=0.971), family history of mental illness (P=0.533) or duration of illness (P=0.252) between the two groups.

The incidence of NSSI in adolescents with depression was 52.6%. There were 345 female MDD patients, 197 of whom had NSSI behaviour, and the incidence of NSSI in female adolescents with depression was 57.1%. In addition, there were 109 male MDD patients, 42 of whom had NSSI behavior and the incidence of NSSI in male adolescents with depression was 38.5%. The incidence of NSSI in female patients was significantly higher than that in male patients in this study (χ^2=11.457, P=0.001) (See Figure S1).

As age was one of the main factors affecting non suicidal self injury, PSM was conducted between the two groups using age as a covariate. After PSM, there were 158 patients in each group. Differences were found only in gender (P=0.047), antidepressant use (P<0.001), PHQ-9 scores (P<0.001), and GAD-7 scores (P=0.011) between the two groups after PSM (Table 1).

In addition, considering the discrepancy in the incidence of NSSI between male and female patients, we conducted a stratified analysis based on the data after PSM.

In female participants, univariate analysis showed that there were differences in anti-depressant use (P=0.022), PHQ-9 score (P<0.001) and GAD-7 score (P=0.006) between the MDD/NSSI group and the MDD/non-NSSI group (See Table S1). In male MDD patients, univariate analysis elucidated that there was no significant differences in age, BMI, smoking, family history of mental illness, age of onset, duration of illness, anti-depressant use, PHQ-9 scores and GAD-7 scores between the two groups(P>0.05) (See Table S2).

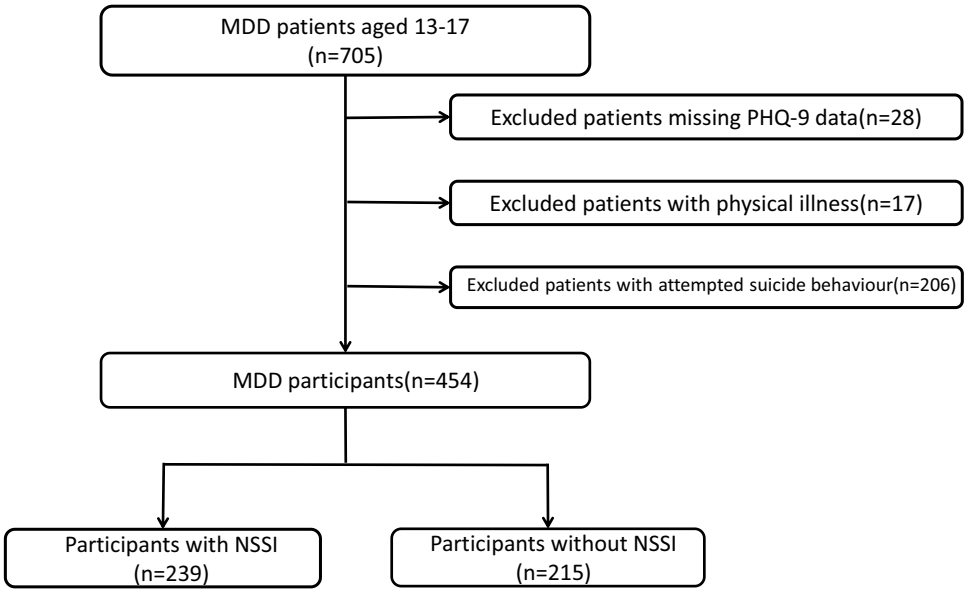

Figure 1 The selection process for this study.

Table 1 Demographic and Clinical Characteristics of the Participants

Characteristics	Before PSM				After PSM			
	MDD/NSSI (n=239) N (%) Median (IQR) Mean ± SD	MDD/non-NSSI (n=215) N (%) Median (IQR) Mean ± SD	Statistic	P	MDD/NSSI (n=158) N (%) Median (IQR) Mean ± SD	MDD/non-NSSI (n=158) N (%) Median (IQR) Mean ± SD	Statistic	P
Gender (% female)	197 (82.43)	148 (68.84)	χ^2=11.457	0.001[b]	128 (81.01)	113 (71.52)	χ^2=3.934	0.047[b]
Age	15 (14–16)	16 (15–17)	z=−6.239	<0.001[a]	16 (14–16)	15 (14–16)	z=−1.238	0.216[a]
BMI	20.00 (18.21–21.98)	20.30 (18.73–22.40)	z=−1.310	0.190[a]	20.15 (18.39–21.90)	20.30 (18.73–22.63)	z=−0.781	0.435[a]
Smoking	18 (7.53)	16 (7.44)	χ^2=0.001	0.971[b]	12 (7.59)	7(4.43)	χ^2=1.400	0.237[b]
Family history of mental illness	29 (12.13)	22 (10.28)	χ^2=0.388	0.533[b]	19 (12.03)	17 (10.83)	χ^2=0.112	0.738[b]
Age of onset	13 (12–15)	14 (13–15)	z=−3.845	<0.001[a]	14 (12.75–15)	14 (13–15)	z=−1.016	0.309[a]
Duration of illness (months)	12 (6–24)	12 (6–26)	z=−1.145	0.252[a]	12 (7–24)	12 (6–24)	z=−0.415	0.678[a]
Antidepressant use	150 (62.76)	98 (44.79)	χ^2=13.120	<0.001[b]	108 (68.35)	69 (43.95)	χ^2=19.054	<0.001[b]
PHQ-9 (scores)	21 (17–24)	18 (14–22)	z=−5.806	<0.001[a]	20 (17–23.25)	18 (14–22)	z=−5.009	<0.001[a]
GAD-7 (scores)	16 (12–18)	14 (9–18)	z=−3.002	0.003[a]	16 (12–18)	13 (9–18)	z=−2.538	0.011[a]
Tbil (μM)	8.43 (6.24–11.57)	9.66 (7.03–12.60)	z=−3.211	0.001[a]	8.70 (6.67–11.87)	9.53 (7.03–12.56)	z=−1.999	0.046[a]
UA (μM)	312.12 (265.57–377.12)	336.11 (288.40–390.66)	z=−3.137	0.002[a]	312.75 (265.96–380.18)	328.46 (283.62–383.33)	z=−2.422	0.015[a]
FT3 (p M)	4.86±0.75	4.90±0.76	t=−0.415	0.678[c]	4.76±0.72	4.90±0.76	t=−1.575	0.116[c]
FT4 (p M)	14.91 (13.49–16.52)	15.47 (14.04–17.08)	z=−2.277	0.023[a]	15.03±2.47	15.39±2.27	t=−1.247	0.213[a]
TSH (μ IU/mL)	1.80 (1.24–2.60)	1.90 (1.25–2.83)	z=−0.719	0.472[a]	1.79 (1.30–2.67)	1.90 (1.26–2.85)	z=−0.814	0.416[a]

Notes: [a]Median (interquartile range). Mann–Whitney Test. [b]Number (percentage). Level of significance of the chi-squared test. [c]Mean ± s.d. Two independent samples *t*-test.

Abbreviations: PSM, propensity score method; MDD/non-NSSI=Major depressive disorder without non-suicidal self-injury group; MDD/NSSI=Major depressive disorder with non-suicidal self-injury; IQR=inter quartile range; BMI, body mass index; PHQ-9, 9-item Patient Health Questionnaire; GAD-7, 7-item Generalized Anxiety Disorder scale; Tbil, total bilirubin; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

https://doi.org/10.2147/NDT.S452643

The Relationship Between Antioxidant System and Thyroid Function and Non-Suicide Self-Injury Behavior in the Total Sample

Compared to MDD/non-NSSI group, the levels of serum Tbil (P=0.046) and UA (P=0.015) in the MDD/NSSI group were lower. However, there were no significant differences in the levels of FT3 (P=0.116), FT4 (P=0.213) and TSH (P=0.416) between the MDD/NSSI and MDD/non-NSSI group (see Table 1).

Relativity analyses were employed to evaluate the relationship between antioxidant factor and thyroid function in patients. Datasets from total sample revealed a significant positive correlation between serum Tbil level and FT3 (r=0.127, P=0.034) and FT4 (r=0.364, P<0.001) levels. Serum UA was positively correlated with FT3 (r=0.155, P=0.010) and FT4 (r=0.170, P=0.005) levels. In MDD/non-NSSI group, serum Tbil was positively associated with FT4 (r=0.341, P<0.001). In MDD/NSSI group, serum Tbil was positively associated with FT4 (r=0.366, P<0.001). Serum UA was positively associated with FT3 (r=0.208, P=0.016) and FT4 (r=0.181, P=0.036)(See Table S3).

Binary logistic regression analysis was used to evaluate whether the antioxidant factors and thyroid function were associated with NSSI. It was found that serum UA (OR=0.997, 95% CI: 0.994–0.999, P=0.017) was associated with NSSI in patients with MDD. After adjusted gender, antidepressant use, PHQ-9 and GAD-7, no correlation was found between antioxidant factor, thyroid function and NSSI (Table S4).

The Relationship Between Antioxidant System and Thyroid Function and Non-Suicide Self-Injury Behavior in Female Participants

Compared to MDD/non-NSSI group, the levels of UA (P=0.026) in the MDD/NSSI group were significantly lower. However, the levels of Tbil (P=0.237), FT3 (P=0.179), FT4 (P=0.434) and TSH (P=0.755) did not significantly differ within the MDD/NSSI and the MDD/non-NSSI groups (See Figure S2).

Binary logistic regression analysis highlighted that serum UA was associated with NSSI in female patients with MDD (OR=0.996, 95% CI: 0.992–1, P=0.028). After adjusted antidepressant use, PHQ-9 and GAD-7, serum UA (OR=0.995, 95% CI: 0.991–0.999, P=0.014) was negatively associated with NSSI in female patients (Table 2).

The Relationship Between Antioxidant System and Thyroid Function and Non-Suicide Self-Injury Behavior in Male Participants

Compared to MDD/non-NSSI group, the levels of TSH (P=0.019) in the MDD/NSSI group was significantly lower. The serum levels of Tbil (P=0.509), UA (P=0.719), FT3 (P=0.791) and FT4 (P=0.519) did not show statistical significance within the MDD/NSSI and MDD/non-NSS group (See Figure S3).

Binary logistic regression analysis highlighted that the level of TSH was associated with NSSI in male patients with MDD (OR=0.499, 95% CI: 0.267–0.932, P=0.029) (see Table 3).

Table 2 Binary Logistic Regression of Related Factors of NSSI in Female MDD Patients

Factor	B[a]	Wald[a]	OR[a]	95% CI[a]	P	B[b]	Wald[b]	OR[b]	95% CI[b]	P
Tbil	−0.023	0.028	0.978	0.925–1.033	0.423	0.007	0.052	1.007	0.948–1.070	0.819
UA	−0.004	4.850	0.996	0.992–1.000	0.028	−0.005	6.026	0.995	0.991–0.999	0.014
FT3	−0.250	1.644	0.778	0.531–1.142	0.200	−0.085	0.159	0.919	0.606–1.393	0.690
FT4	−0.047	0.616	0.954	0.847–1.074	0.432	0.020	0.084	1.020	0.891–1.168	0.773
TSH	−0.012	0.011	0.915	0.800–1.221	0.915	0.034	0.080	1.034	0.820–1.303	0.777

Notes: [a]Uncorrected. [b]Corrected the difference factors, including: antidepressant use, PHQ-9 and GAD-7.
Abbreviations: Tbil, total bilirubin; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Table 3 Binary Logistic Regression of Related Factors of NSSI in Male MDD Patients

Factor	B	Wald	OR	95% CI	P
Tbil	−0.009	0.068	0.991	0.926–1.060	0.794
UA	0.001	0.133	1.001	0.996–1.006	0.715
FT3	−0.103	0.073	0.902	0.426–1.908	0.787
FT4	−0.071	0.428	0.932	0.754–1.152	0.513
TSH	−0.695	4.749	0.499	0.267–0.932	0.029

Abbreviations: Tbil, total bilirubin; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Discussion

This is the first research to examine the relationship between serum non-enzymatic antioxidant levels, thyroid hormone and NSSI behavior in adolescents with MDD. We found that the incidence of NSSI behavior was 52.6% in depressive adolescents aged 13–17 years old. Among them, the female NSSI incidence is 57.1%, and the incidence of male NSSI is 38.5%. According to our findings, serum Tbil and UA levels in MDD participants with NSSI were significantly lower than MDD participants without NSSI. Controlling for confounding variables, these factors were not related to NSSI. In female participants, serum UA was associated with NSSI. In addition, serum TSH correlated with NSSI in male participants.

This study found that the incidence of NSSI in adolescents with depression was 52.6%, which is lower than that observed in other studies (about 70%) reporting the incidence of NSSI in inpatient samples.[49,50] This may be because our focus was on NSSI behavior, and patients who had previously attempted suicide were excluded. Co-occurrence of NSSI and previous attempted suicide is highly likely.[51] In addition, in the present research, we found that NSSI associated with adolescent depression was more common in females rather than in males. A meta analysis including 116 articles revealed that a higher prevalence of NSSI in females,[43] but some studies believed there was no difference between the females and males.[52] The reasons for the inconsistency of the results could be related to the selected sample size, sample source and the inconsistency in the assessment of NSSI. Girls who self-injure were more likely to be hospitalized than boys because their injuries were sometimes taken more seriously than boys'.[43]

Animal studies have revealed that psychomotor stimulants such as methamphetamine[53] and amphetamine[54] can cause intense dopamine release in mice, inducing the production of reactive oxygen species and reactive nitrogen, leading to oxidative stress and ultimately resulting in long-term neuronal damage and NSSI. However, dopamine receptor antagonists[55] and free radical scavenging agents[53] could significantly reduce methamphetamine-induced NSSI. Therefore, we speculated that due to the low antioxidant capacity of the body, reactions associated with oxidative stress may lead to the production of many harmful substances that cause nerve dysfunction, ultimately increasing the incidence of NSSI. Unfortunately, although our study found differences in Tbil and UA levels between the MDD/NSSI group and MDD/non-NSSI group, regression analysis did not show any association between them and NSSI after adjusting for confounding factors.

Our study investigated the correlation between thyroid hormone and non-enzymatic antioxidant serum levels, where we elucidated that UA is correlated to FT3 and FT4, together with Tbil being correlated to FT3 and FT4 in depressed patients. Oxidative stress is closely related to thyroid hormone serum level, as the former can affect thyroid hormone synthesis. The synthesis of thyroid hormones requires hydrogen peroxide (H_2O_2) as the substrate, so the production of reactive oxygen species (ROS) is a physiological requirement of thyroid hormones.[56,57] Chao et al found a linear correlation between uric acid levels and FT3 and FT4 through the presence of normal thyroid function.[58] It is speculated that thyroid hormone can dysregulate cytokine levels produced by oxidative stress and inflammation. Dysregulated thyroid hormone levels lead to variations in the production of related cytokines and enzyme levels, and ultimately affect uric acid levels. The results of this investigation were consistent with previous studies.

UA is an important antioxidant factor, which can well reflect the antioxidant capacity. According to the results of our study, the serum level of UA is associated with NSSI in female adolescent MDD patients. In addition, our previous study has shown that lower serum uric acid levels have a significant relationship with female's suicide risk.[59] Suicide and self-injury have common characteristics in some aspects. Therefore, we speculate that UA, an important antioxidant factor,

may participate in the pathological mechanism of female suicide and self-injury at the same time. However, we did not observe this relationship in males. On the one hand, the relatively small proportion of male participants may be one of the reasons. On the other hand, differences in sex hormones between female and male may explain a part of this discrepancy. The level of UA in females is lower than that in males, because the sex hormone estrogen reduces the level of UA by increasing its excretion of UA and reducing the production simultaneously,[44] but testosterone has been proven to grow the level of UA through increasing its renal reabsorption.[60] Individuals who have low level of UA may have disappeared some of the antioxidant protection from the UA. Furthermore, a research found that the treatment for UA can improve clinical prognosis in female stroke patients.[61] All of these suggest that serum level of UA might be an important clinical indicator of antioxidant stress in females.

The present study also found that NSSI behavior was related to TSH level in male patients with MDD, although we did not find this association in females with MDD. One possible reason is that men and women have different levels of TSH. Researches reported that the serum TSH level in males was lower than females.[45,46] This gender difference in TSH levels may be due to males being more blunted in response to TRH stimulation.[62] In addition, a study reported that the level of TSH is negatively correlated with male depression.[63] To sum up, serum TSH level may be an important clinical indicator related to male NSSI behaviour.

The limitations of the current study should be noted. Firstly, this is a retrospective study, therefore no causal deductions can be made. Secondly, the results of this study was limited by the recall bias of NSSI over the past 12 months. Future research on the relative changes of NSSI can overcome this issue by using techniques such as ecological momentary assessment.[64] Thirdly, only peripheral blood antioxidant system was analyzed in this study. Although peripheral blood can reflect the antioxidant capacity of the central system to a certain extent, this contribution is still limited since the central and peripheral antioxidant systems are not completely consistent. Forthly, only TSH/FT3/FT4 was detected, thyroxine-binding globulin (TBG) was not detected. In further studies, we can detect the level of TBG and conduct further research. Fifthly, in essence the etiology of NSSI behavior is multi-factorial in nature, encompassing complex interactions between psychological, environmental and biological factors. Consequently, it is difficult to unravel fully the knowledge concerning the development of NSSI behavior by investigating one isolated factor - future studies need to integrate multi-factorial analyses. Sixthly, only MDD patients were analyzed in this study and lack of data for healthy controls. In future studies, it is essential to add the normal control group and conduct a cohort study to confirm our findings.

Conclusion

Collectively, we found that the incidence of NSSI was higher in female adolescents with depression than that in male adolescents with depression. Serum UA is associated with female NSSI behavior, and serum TSH is associated with male NSSI behavior. This suggests that there are complex pathophysiological mechanisms in adolescents' NSSI behavior, which may be related to gender. Females may be involved in antioxidant defense system disorders, and males may be involved in thyroid dysfunction. In future clinical practice and scientific research, we should pay attention to the different effects of gender differences in NSSI behavior. In future study, we need a large sample of prospective research design to further prove our findings. It is also necessary to conduct in-depth basic research to explore the exact pathological mechanism of NSSI in different genders.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Acknowledgments

Thanks to all those who participated in this study.

Funding

This work was supported by the [National Natural Science Foundation of China] under Grant [NO. 82101615]; [National Natural Science Foundation of China] under Grant [NO. 81971286]; and [The Natural Science Foundation of Chongqing,

China] under Grant [NO. cstc2021jcyj-msxmX0349]; and [The Science and Health Joint Medical Research Project Fund of Chongqing] under Grant [NO. 2022QNXM001].

Disclosure

The authors report no conflicts of interest in this work.

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