Article

Xiaomei Chen[1,2,*,†]
Shiping Shi[3,†]
Chao Sun[4]
Shuang Li[1]

A Study of the Relationship between Inflammatory Immune Function and Intestinal Flora in Adolescent Patients with First-Episode Depression

[1]School of Educational Sciences, Ludong University, 246025 Yantai, Shandong, China
[2]Correction Center, Shandong Women's Prison, 250013 Jinan, Shandong, China
[3]Student Affairs Office, North China Electric Power University, 071003 Baoding, Hebei, China
[4]Department of Gastroenterology, Nanshan Hospital of Shandong Province, 250309 Jinan, Shandong, China

Abstract

Background: Depression has become one of the most common mood disorders in adolescents, with an increasing incidence each year. Abnormal activation of peripheral immunity causes an increase in pro-inflammatory factors, which in turn affects neuroendocrine dysfunction and alters neurobiochemistry, leading to depression. In this study, we aimed to explore the relationship between inflammatory immune function and intestinal flora in adolescents with first-episode depression.

Methods: A total of 170 cases of adolescent patients with first-episode depression who attended our hospital from January 2020 to March 2023 were retrospectively selected as the observation group. Simultaneously, 170 individuals who underwent a healthy physical examination during the same period were chosen as the control group. The enzyme-linked immunosorbent assay (ELISA) was employed to quantify the levels of monoamine neurotransmitters 5-hydroxytryptamine (5-HT), substance P (SP), neuropeptide Y (NPY), serum tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 in the patients. Flow cytometry was utilized to assess the levels of T-lymphocytes CD3$^+$, CD4$^+$, and CD8$^+$ cells. The levels of 16S ribosomal RNA (16SrRNA) method were used to determine the intestinal flora of the subjects in both groups. Inflammatory factor levels, immune function, and intestinal flora expression were observed, and correlation analysis was performed.

Results: The levels of 5-HT and NPY in the observation group were lower than those in the control group. The SP level was significantly higher in the observation group compared to the control group ($p < 0.05$). The observation group demonstrated significantly higher TNF-α, IL-1β, and IL-6 levels than the control group ($p < 0.05$). The values of CD3$^+$, CD4$^+$, CD4$^+$/CD8$^+$ in the observation group were lower than those in the control group ($p < 0.05$), whereas the CD8$^+$ values were notably higher ($p < 0.05$). *Bifidobacterium*, *Escherichia coli*, *Lactobacillus*, and *Bacteroides* in the observation group were less than those in the control group ($p < 0.05$). The content of *Bifidobacterium* was negatively correlated with the level of TNF-α (r = –0.358, $p < 0.001$), positively correlated with the level of CD3$^+$, CD4$^+$, CD4$^+$/CD8$^+$ (r = 0.490, 0.169, 0.165, $p < 0.05$), and negatively correlated with the level of CD8$^+$ (r = –0.154, $p < 0.05$). The level of *Escherichia coli* content was negatively correlated with the levels of IL-6, CD3$^+$, CD4$^+$, CD4$^+$/CD8$^+$ (r = –0.483, –0.548, –0.317, –0.328, $p < 0.001$), and positively correlated with the levels of CD8$^+$ (r = 0.325, $p < 0.001$). The content of *Lactobacillus* was positively correlated with the levels of CD3$^+$, CD4$^+$, CD4$^+$/CD8$^+$ (r = 0.552, 0.188, 0.194, $p < 0.05$), and negatively correlated with the level of CD8$^+$ (r = –0.186, $p < 0.05$). The content of *Bacteroides* was positively correlated with the level of CD3$^+$, CD4$^+$, CD4$^+$/CD8$^+$ (r = –0.570, –0.183, –0.193, $p < 0.05$), and negatively correlated with the level of CD8$^+$ levels were positively correlated (r = 0.187, $p < 0.05$).

Conclusions: The intestinal flora is related to the level of inflammatory factors and immune function. Further study on the relationship between intestinal flora, inflammatory immune function, and depression could offer novel insights for the prevention and treatment of depressive disorders.

*Corresponding author details: Xiaomei Chen, School of Educational Sciences, Ludong University, Yantai, 246025, Shandong, China; Correction Center, Shandong Women's Prison, Jinan, 250013, Shandong, China. Email: chenxiaomei9777@163.com
[†]These authors contributed equally.

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Keywords

first episode depression; adolescents; inflammatory immune function; intestinal flora

Introduction

Depression is the more common type of mental disorder, characterized by low mood, relatively slow thinking, decreased appetite, decreased volitional activity, and cognitive impairment [1]. As adolescents are at the peak of physiological changes and facing the ensuing social development challenges, depression has shown a trend in younger people in recent years, and the incidence of depression in adolescents has increased year by year [2]. The treatment of adolescents with depression has become a significant concern for society and families [3,4]. Similarly, patients with gastrointestinal disorders are more likely to experience depressive symptoms [5]. Depression is more common in patients with irritable bowel syndrome (IBS) and abdominal pain. It has been suggested that depressive symptoms and gastrointestinal symptoms in patients with depression may share common pathophysiologic mechanisms, which may involve neuroendocrine, neuroimmune, intestinal flora, and neuroplasticity [6].

The microbe-gut-brain axis is an essential pathway for signaling between the gut and brain, forming a complex network with the autonomic nervous, neuroendocrine, enteric, and immune systems [7]. The microbial-gut-brain axis hypothesis suggests that gut flora plays a role in the onset of neurological and psychiatric disorders by regulating immune responses that affect brain function [8]. Signaling between the gut and the brain is bidirectional. The brain can influence the motility, sensation, and secretion of the gastrointestinal tract. At the same time, the gut also influences brain function, particularly in areas of the brain involved in the stress response. Alterations in the gut microbiota have the potential to stimulate inflammatory responses in the gut and peripheral nerves, which in turn can lead to neuroinflammation or neurodegeneration in the central nervous system [9]. Inflammatory biomarkers are elevated in patients with depression [10]. The clinical state of depression is associated with immune dysfunction [11]. Immune system activity enhances the link between the gut flora and the brain, and dysbiosis of the gut flora can compromise the integrity of the intestinal epithelium, leading to defective defense against pathogenic microorganisms, which, in turn, results in neuroinflammation and a series of inflammatory responses. Abnormal activation of peripheral immunity causes an increase in pro-inflammatory factors, which, in turn, affects neuroendocrine dysfunction and alters neurobiochemistry, leading to depression [12,13]. It is important to conduct relevant clinical studies on the outcomes of adolescent patients with first-episode depression. In this study, we used a case-control analysis to observe the levels of inflammatory factors and immune function in adolescent patients with first-episode depression and their relationship with changes in intestinal flora.

Materials and Methods

Research Subjects

One hundred and seventy cases of adolescent patients with first-episode depression who attended the Nanshan Hospital of Shandong Province from January 2020 to March 2023 were retrospectively selected as the observation group. This study was approved by the Nanshan Hospital of Shandong Province's Medical Ethics Committee [2020-214-01(2)]. The entire experimental procedure was explained to the patient or their family, and the study complied with the Declaration of Helsinki.

Inclusion criteria: ① All patients meet the Diagnostic and Statistical Manual of Mental Disorders (5th edition) [14] Diagnostic Criteria of Depressive Disorders; ② Age 16–30 years old, gender is not limited; ③ First time onset, no prior antidepressant or psychiatric treatment. Exclusion criteria: ① Combination of infectious and autoimmune diseases; ② Combination of organic brain diseases or other types of mental disorders; ③ Combination of serious physical diseases; ④ Combination of organic gastrointestinal diseases or functional gastrointestinal diseases; ⑤ Combination of diabetes mellitus, coronary artery disease, hypertension, and other diseases; ⑥ History of previous intestinal surgery; ⑦ History of depression before enrollment; ⑧ Three months prior to enrollment, antidepressant medications, antibiotics or drugs affecting intestinal flora; ⑨ Body mass index (BMI) $\geq$18.5 kg/m^2; ⑩ Inclusion or proposed inclusion in other clinical studies and history of antidepressant drug treatment. One hundred and seventy cases of healthy physical examination during the same period were chosen to constitute the control group; None of the control group had depressive symptoms, and the exclusion criteria were the same as above.

The control group comprised 71 males and 99 females, aged 17–29 years old, mean (23.21 $\pm$ 3.68) years old; BMI 18.57–27.31 kg/m^2, mean (22.95 $\pm$ 2.40) kg/m^2. The observation group comprised 66 males and 104 females; Age 16–27 years old, mean (21.78 $\pm$ 3.45) years old; BMI 18.70–27.66 kg/m^2, mean (23.45 $\pm$ 2.63) kg/m^2. The general data, such as gender, age, and BMI, were not statis-

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tically significant ($p > 0.05$) when compared between the two groups. This study was approved and passed by the hospital's Medical Ethics Committee.

Assessment of Depressive Symptoms

The Hamilton-Depression Scale-17 (HAMD-17) [15] was assessed with a score of 7 or more, and a higher overall HAMD-17 scale score indicated a more severe degree of depression in the patients. And a score of 50 or more on the Self-rating Depression Scale (SDS) was considered. The assessment is done by trained neurologists, and the rating is rigorous.

Detection of Monoamine Neurotransmitter Levels

After enrollment, fasting venous blood was drawn from the patients. The plasma specimens mentioned above were taken to determine the levels of 5-hydroxytryptamine (5-HT) (ml057425, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China), substance P (SP) (ml057693, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) and neuropeptide Y (NPY) (ml037876, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) by enzyme-linked immunosorbent assay.

Inflammatory Factor Detection

Fasting venous blood was drawn from patients, and the serum was left at room temperature for one hour, centrifuged at 4000 r/min for 10 minutes at 4 °C with an effective centrifugation radius of 15 cm, separated, and stored at –80 °C. Enzyme-linked immunosorbent assay (ELISA) was utilized to quantify the levels of serum tumor necrosis factor-α (TNF-α) (ml077385, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China), interleukin (IL)-1β (ml058059, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China), and IL-6 (ml058097, Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China) following the provided instructions.

Immune Function Tests

5 mL venous blood was extracted from the patient on an empty stomach, shaken in an ethylenediamine tetraacetic acid (EDTA) anticoagulant tube, then added into a flow tube, thoroughly mixed with monoclonal antibody, and incubated for 10 minutes. Add red blood cell lysate (R7757, Sigma-Aldrich, Saint Louis, MO, USA) 500 µL and mix well. Then, five mL of phosphate-buffered saline (PBS) buffer (11666789001, Roche, Melbourne, VIC, Australia) was added and centrifuged at 3000 r/min for 5 minutes. The supernatant was carefully poured out, and 300 µL PBS (LSKCRS500, Millipore, Bedford, MA, USA) was added to the suspended cells. $CD3^+$, $CD4^+$, and $CD8^+$ T cells were detected by flow cytometry (Agilent 2100 Bioanalyzer, Agilent Technologies, Inc., Santa Clara, CA, USA), and $CD4^+/CD8^+$ were calculated.

Intestinal Flora Testing

Fresh feces were collected using fecal nucleic acid preservation tubes (11901-50, Shanghai Biotechnology Corporation, Shanghai, China) and stored at –80°C. The genomic deoxyribonucleic acid (DNA) in the feces was extracted using a fecal DNA extraction kit (18820ES08, Yeasen Biotechnology (Shanghai) Co., Ltd., Shanghai, China), amplified using a Polymerase Chain Reaction (PCR) kit (10184ES50, Yeasen Biotechnology (Shanghai) Co., Ltd., Shanghai, China), and then the bacterial DNA quantity was determined by quantitative polymerase chain reaction (qPCR). After amplifying the V4 highly variable region of 16S ribosomal RNA (16SrRNA), the amount of DNA amplified in each sample was quantified using the double-stranded DNA 910 (dsDNA910) kit (DNF-910-K1000, Agilent Technologies, Santa Clara, CA, USA) on the fragment analyzer (Agilent 5200, Agilent Technologies, Santa Clara, CA, USA). After obtaining the PCR products, 16SrRNA sequencing was completed on the Illumina MiSeq platform (MiSeq, Illumina, San Diego, CA, USA). The obtained data were assigned to operational taxonomy units (OTUs) pairwise matched according to a 97% threshold and categorized using the Ribosomal Database Project (RDP) reference database.

Statistical Methods

SPSS 21.0 software (IBM, Amenk, NY, USA) statistics was used for data analysis. The measurement information was expressed as mean ± standard deviation ($\bar{x} \pm s$), group comparisons were performed using independent sample *t*-tests, and comparisons between multiple groups were analyzed using one-way ANOVA. LSD-*t* test was used for further pairwise comparison. The counting information was expressed as the number of cases and the percentage, and the χ^2 test was used. The correlation analysis was performed using Pearson's analysis. Differences were considered statistically significant at $p < 0.05$.

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Table 1. Comparison of depressive symptom assessment scores between the two groups ($\bar{x} \pm s$).

Groups	Number of examples	HAMD-17 (score)	SDS (score)
Control Group	170	2.23 ± 0.97	14.70 ± 3.91
Observation Group	170	24.78 ± 6.15	56.92 ± 6.77
t-value		47.224	70.412
p-value		<0.001	<0.001

Note: HAMD-17, Hamilton-Depression Scale-17; SDS, Self-rating Depression Scale.

Table 2. Comparison of changes in monoamine neurotransmitter levels between the two groups ($\bar{x} \pm s$).

Groups	Number of examples	5-HT (μg/L)	SP (μg/mL)	NPY (μg/mL)
Control Group	170	49.63 ± 7.11	3.37 ± 0.71	8.81 ± 1.50
Observation Group	170	25.18 ± 4.53	6.02 ± 0.97	5.42 ± 0.65
t-value		37.814	28.743	27.037
p-value		<0.001	<0.001	<0.001

Note: 5-HT, 5-hydroxytryptamine; SP, substance P; NPY, neuropeptide Y.

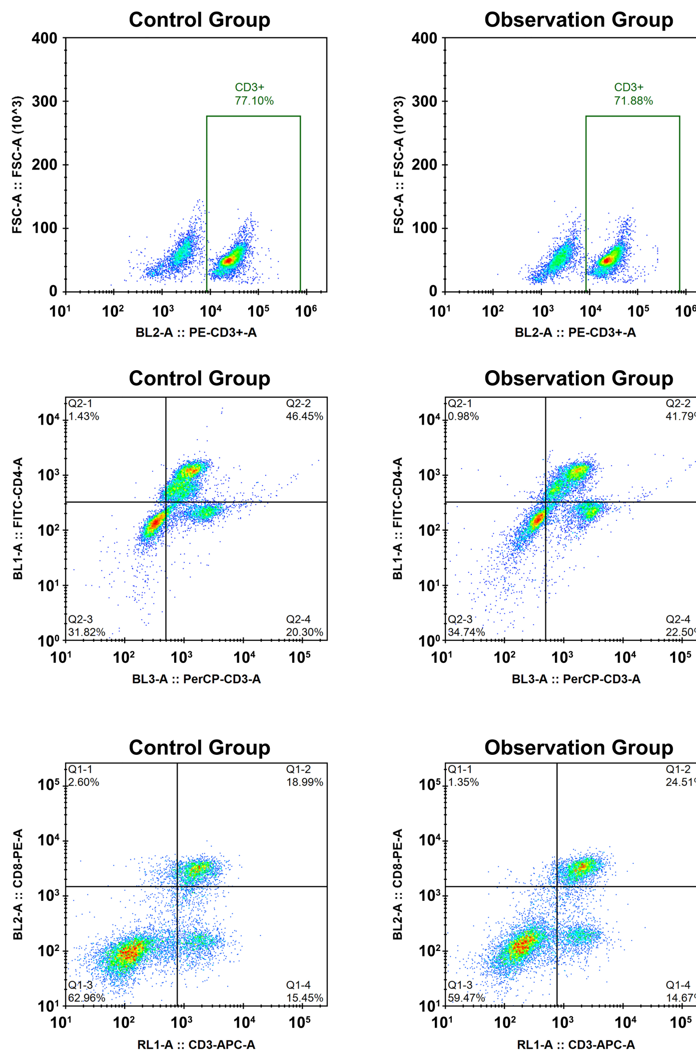

Fig. 1. Comparison of immune function between the two groups.

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Table 3. Comparison of inflammatory factor levels between the two groups (ng/L, $\bar{x} \pm s$).

Groups	Number of examples	TNF-α	IL-1β	IL-6
Control Group	170	23.98 $\pm$ 2.41	44.72 $\pm$ 3.11	26.81 $\pm$ 5.10
Observation Group	170	28.02 $\pm$ 1.93	49.31 $\pm$ 3.43	30.42 $\pm$ 6.01
t-value		17.060	12.926	5.971
p-value		<0.001	<0.001	<0.001

Note: TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

Table 4. Comparison of immune function between the two groups.

Groups	Number of examples	$CD3^+$ (%)	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$
Control Group	170	77.83 $\pm$ 6.32	46.31 $\pm$ 5.77	18.93 $\pm$ 3.50	2.38 $\pm$ 1.02
Observation Group	170	71.16 $\pm$ 8.49	41.73 $\pm$ 7.41	24.37 $\pm$ 6.34	1.63 $\pm$ 0.33
t-value		8.217	6.358	9.794	9.122
p-value		<0.001	<0.001	<0.001	<0.001

Results

Comparison of Depressive Symptom Assessment Scores between the Two Groups

The total scores of HAMD-17 and SDS in the observation group were significantly higher than those in the control group ($p < 0.05$, Table 1).

Comparison of Changes in Monoamine Neurotransmitter Levels between the Two Groups

The levels of 5-HT and NPY of the observation group were lower than those in the control group, and the level of SP was significantly higher compared to the control group ($p < 0.05$, Table 2).

Comparison of Inflammatory Factor Levels between the Two Groups

The levels of TNF-α, IL-1β and IL-6 in the observation group were higher than in the control group, and the differences were all statistically significant ($p < 0.05$, Table 3).

Comparison of Immune Function between the Two Groups

See Fig. 1 for representative flow cytometry plots. In the observation group, the values of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ were significantly lower compared to the control group ($p < 0.05$, Table 4), and the values of $CD8^+$ were significantly higher in the observation group compared to the control group ($p < 0.05$, Table 4).

Comparison of Intestinal Flora Content between the Two Groups

Bifidobacterium, *Escherichia coli*, *Lactobacillus*, and *Bacteroides* in the observation group were fewer than those in the control group, and the differences were all statistically significant ($p < 0.05$, Table 5).

Correlation Analysis of Intestinal Flora and Inflammatory Factor Levels and Immune Function

Bifidobacterium content exhibited a negative correlation with TNF-α level (r = –0.358, $p < 0.001$, Table 6), no correlation with IL-1β and IL-6 levels, a positive correlation with $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ levels (r = 0.490, 0.169, 0.165, $p < 0.05$, Table 6) and a negative correlation with $CD8^+$ levels (r = –0.154, $p < 0.05$). *Escherichia coli* levels were negatively correlated with IL-6 levels (r = –0.483, $p < 0.001$), did not correlate with TNF-α and IL-1β levels, and were negatively correlated with $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ levels (r = –0.548, –0.317, –0.328, $p < 0.001$, Table 6), and positively correlated with $CD8^+$ levels (r = 0.325, $p < 0.001$). *Lactobacillus* content did not correlate with TNF-α, IL-1β, and IL-6 levels but had a positive correlation with the levels of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ (r = 0.552, 0.188, 0.194, $p < 0.05$, Table 6), and a negative correlation with $CD8^+$ levels (r = –0.186, $p < 0.05$, Table 6). The content of *Bacteroides* did not correlate with TNF-α, IL-1β, and IL-6 levels ($p > 0.05$, Table 6). It exhibited a negative correlation with $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ levels (r = –0.570, –0.183, –0.193, $p < 0.05$, Table 6), and a positive correlation with $CD8^+$ levels (r = 0.187, $p < 0.05$, Table 6).

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Table 5. Comparison of intestinal flora levels between the two groups (lg copies/g, $\bar{x} \pm s$).

Groups	Number of examples	*Bifidobacterium* genus (bifidobacteria)	*Escherichia coli* (E. coli)	*Lactobacillus* genus	*Mycobacterium* (genus of saccharomyces cerevisiae)
Control Group	170	7.68 ± 0.89	7.31 ± 0.61	8.47 ± 0.50	7.67 ± 0.79
Observation Group	170	7.13 ± 0.81	6.72 ± 0.78	7.91 ± 0.55	7.35 ± 0.71
t-value		5.959	7.769	9.823	3.192
p-value		<0.001	<0.001	<0.001	0.002

Table 6. Correlation analysis of intestinal flora and inflammatory factor levels and immune function.

Intestinal flora		*Bifidobacterium*	*Escherichia coli*	*Lactobacillus*	*Bacteroides*
TNF-α	r-value	–0.358	0.064	–0.094	0.016
	p-value	<0.001	0.409	0.223	0.840
IL-1β	r-value	–0.062	–0.095	–0.050	0.110
	p-value	0.419	0.218	0.516	0.154
IL-6	r-value	–0.130	–0.483	0.060	–0.040
	p-value	0.090	<0.001	0.438	0.601
$CD3^+$	r-value	0.490	–0.548	0.552	–0.570
	p-value	<0.001	<0.001	<0.001	<0.001
$CD4^+$	r-value	0.169	–0.317	0.188	–0.183
	p-value	0.027	<0.001	0.014	0.017
$CD8^+$	r-value	–0.154	0.325	–0.186	0.187
	p-value	0.045	<0.001	0.015	0.015
$CD4^+/CD8^+$	r-value	0.165	–0.328	0.194	–0.193
	p-value	0.031	<0.001	0.011	0.012

Discussion

Adolescent depression is often accompanied by changes in cognitive function, such as decreased attention and memory loss, which has a serious impact on the completion of school, the execution of work, the development of family relations, and intimate relationships. Therefore, if we can find the level of inflammatory factors and the functioning of the immune system, and the relationship between them and the changes of intestinal flora in the first episode of adolescent depression, subsequent targeted intervention will benefit individual adolescents and their families. Depression is associated with abnormal central neurotransmitter activity, and the microbial-gut-brain axis largely depends on the interaction of gut flora with the immune system and neural pathways [16]. Substantial variations exist in the gut microbiota composition when comparing individuals with depression to those in a healthy population [17]. The imbalance of gut flora is a key factor driving the development of depression [18].

Depressed patients have functional, structural abnormalities at the level of neurotransmitters or neurotransmitter-related neural pathways, and the noradrenergic, dopaminergic, 5-hydroxytryptaminergic nervous systems and gamma-aminobutyric acid all play important roles in the pathogenesis of depression [19,20]. It has been found that some of the proteins produced by gut bacteria and fungi have similarities to substances such as neuropeptides synthesized by the body. The normal function of the immune system is ensured by normal immune cell function and the secretion of pro-inflammatory cytokines [21]. Both elevated levels of pro-inflammatory factors and environmental stresses can lead to the activation of the limbic system, primarily involved in memory, mood, and behavior. Immune cells are directly involved in the immune response, and pro-inflammatory cytokines induce the differentiation and maturation of immune cells, and enhance the inflammatory response [22]. Pro-inflammatory cytokines can decrease intracranial 5-HT levels and increase neurotoxicant accumulation by stimulating indoleamine-pyrrole 2,3-dioxygenase. 5-HT can activate immune cells, promote cytokine release from macrophages and T lymphocytes, and activate macrophage phagocytosis while suppressing natural killer cell levels [23].

In this investigation, serum inflammatory markers TNF-α, IL-1β, and IL-6 were detected by venous blood drawn from depressed patients and healthy controls. The findings indicated that adolescents experiencing depression had elevated serum levels of TNF-α, IL-1β, and IL-6 compared to their healthy adolescents. Many previous studies

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have demonstrated that TNF-α, IL-1β, and IL-6 are elevated in adolescents with depression and are closely related to the symptoms of adolescent depression [24,25], which is consistent with the outcomes observed in the current study. In the pathogenesis of depression, TNF-α inflammatory cytokines play an important role and serve as central regulators in initiating and regulating cytokine cascades during the neuroinflammatory response. IL-1β is a major regulator of the cascade of brain inflammation, which contributes to regulating the expression of TNF-α and IL-6 and controlling the onset of neuroinflammation. Serum IL-1β penetrates the blood-brain barrier, directly stimulates HPA, upregulates 5-HT transporter mRNA and protein levels, and reduces 5-HT reuptake in the synaptic cleft, leading to depressive symptoms [26]. IL-6 serves as a crucial multifunctional cytokine within the immune system, playing a role in inducing the production of additional metabolites in astrocytes during stress conditions [27]. Depressed patients have increased pro-inflammatory cytokines (including IL-6 and TNF-α) and reduced anti-inflammatory cytokines, skewing the immune response toward inflammation [28].

Aizawa *et al*. [29] showed decreased levels of *Lactobacillus* and *Bifidobacterium* in depressed patients, which aligns with the findings of this study. Activation of the HPA axis is associated with early microbial colonization, and excessive activation of the HPA axis results in an elevation of Gram-negative bacteria spp. and a reduction in *Bifidobacterium* [30]. Dysregulation of gut ecology and cellular components of gut microbes (e.g., lipopolysaccharides produced by Gram-negative bacteria) can cause gut barrier impairment and inflammatory responses [18]. Inflammatory responses, such as NF-κB and pro-inflammatory cytokine production, often cause intestinal permeability. Changes in the relative abundance of gut microorganisms between different phyla may also contribute to the development of chronic inflammation, where an increase in the number of Aspergillus spp. may lead to increased intestinal permeability and chronic inflammation [31]. The current research results demonstrated that *Bifidobacterium* genus levels were negatively correlated with TNF-α levels and a negative correlation between the levels of *Escherichia coli* genus and IL-6 levels. Studies at the genus level have found a decline in the abundance of *Lactobacillus* and *Bifidobacterium* [32], observed in the present study. T lymphocytes are the agents of maintaining intestinal immune homeostasis, and the gut flora and its metabolites can influence T lymphocytes in various ways. In contrast, the gut flora and their metabolites interact to maintain intestinal homeostasis. In this study, we found abnormal expression of $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ values in adolescents with first-episode depression. In adolescents with first-episode depression, $CD4^+$ T lymphocytes are significantly decreased, CD8+T lymphocytes are increased, $CD4^+/CD8^+$ values are decreased, and obvious immune imbalance is one of the reasons for a series of neuroendocrine disorders and one of the mechanisms leading to depression in patients. Further correlation analysis showed that the levels of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ in peripheral blood were positively correlated with the contents of *Bifidobacterium* and *Lactobacillus*, and negatively correlated with the contents of *Escherichia coli* and *Bacteroides*. $CD8^+$ levels in peripheral blood were negatively correlated with *Bifidobacterium* and *Lactobacillus*, and positively correlated with *Escherichia coli* and *Bacteroides*. Adolescents with first-episode depression have abnormal expression of intestinal flora and peripheral blood $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ levels, and peripheral blood $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ expression levels correlate with intestinal flora.

Limitation

The current study has some limitations. The sample size of this study is small, which may lead to bias in the obtained results. The next study will expand the sources of sample size to expand the sample size. This study explored the correlation between inflammatory immune function and intestinal flora in adolescents with first-episode depression without using intervention or experimental methods to study the causal relationship between the two further. To increase the reliability of the results, follow-up studies will seek similar references to reveal the molecular and cellular mechanisms of inflammatory immune function and intestinal flora affecting the occurrence and development of depression.

Conclusions

In conclusion, this study showed that inflammatory immune function in adolescent patients with first-episode depression was associated with gut flora. Further research on the relationship between intestinal flora, inflammatory immune function, and depression may offer novel insights for the prevention and treatment of depression.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

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Author Contributions

XMC and CS designed the research study. SPS and SL performed the research. CS provided help and advice on the experiments. XMC and CS analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of the Nanshan Hospital of Shandong Province [2020-214-01(2)]. The entire experimental procedure was explained to the patient or their family, and the study was carried out in compliance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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