Effect of Inhibited T lymphocyte Function on Depressive Symptoms in Breast Cancer Patients with Depression

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Research Article

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Abstract

Background: Depression has a high incidence among patients with breast cancer, but the relationship between depression and cancer-related physiological changes is not clear.

Objectives: To explore the effect of T lymphocytes on breast cancer depression and the patient's quality of life.

Methods: This is a cross-sectional study. A total of 93 breast cancer patients with depression were recruited, 46 of whom underwent T lymphocyte, cortisol, BDNF, TNF-α, and IL-1β collection. We analysed the correlation between the indicators in these 46 participants and constructed two intermediary structural equations between their T lymphocytes and depression, as well as their T lymphocytes and their quality of life.

Results: The results showed that $CD4^+$ had a positive correlation with BDNF (r=0.334, P=0.023) and that BDNF had a negative correlation with HAMD-24 (r=-0.390, P=0.007). Both $CD3^+$ and $CD8^+$ cells were negatively correlated with cortisol (r=-0.358, P=0.015, r=-0.411, P=0.005), and cortisol was positively correlated with FACT-B (r=0.435, P=0.003). The equations including $CD4^+$, BDNF, and HAMD-24, as well as the equations including $CD3^+$, $CD8^+$, cortisol, and FACT-B, were established. BDNF was the mediating variable between $CD4^+$ and HAMD-24. Cortisol was the mediating variable between $CD3^+$, $CD8^+$ and FACT-B. Neither HAMD-24 nor FACT-B could form a direct path with T lymphocytes.

Conclusion: T lymphocytes may be involved in the depression of breast cancer patients since a poor quality of life could inhibit T lymphocytes, and this may be the underlying physiological cause of breast cancer-related depression.

Introduction

The incidence of depression among breast cancer patients has been increasing [1, 2], but the physiological basis of depression in specific populations is still insufficient. Immune function suppression based on changes in T lymphocytes is a common physiological change in breast cancer patients [3]. In the cancer microenvironment, T lymphocytes may be involved in the depression of breast cancer patients.

Studies have found that T lymphocytes play an important role in nerve repair, neurotrophic factor secretion, and inflammatory factor regulation [4]. Cancer cells can suppress the function of T lymphocytes through cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD- L1) [5]. This may affect the nerve repair function of T lymphocytes in depression and other psychiatric diseases. The onset of depression may be caused by changes in hormones and inflammation caused by stress, which affect the release of neurotransmitters (such as 5-HT and BDNF), inflammation (such as IL6 and CRP), and ultimately lead to damage to the

synaptic structure and induce depression [6]. However, the mechanism of depression in certain cancer populations may be different from this model.

We hypothesized that changes in T lymphocytes might be involved in depression in breast cancer patients as a physiological basis of their depression due to the cancer. T lymphocytes may be involved in the release of BDNF, thereby affecting nerve repair and ultimately leading to aggravation of their depression. In addition, cortisol and cancer cells inhibit the function of T lymphocytes and also aggravate depression.

This study included patients with depression and breast cancer from April 2018 to December 2018 and analysed their data on HAMD-24, FACT-B, BDNF, IL-1β, TNF-α, T lymphocytes, and cortisol. We analysed the correlations among the variables and constructed a structural equation connecting T lymphocytes with depression.

Methods

Study setting

This is a cross-sectional study. From April 2018 to December 2018, all patients with breast cancer and depression who were admitted to the Guangdong Provincial Hospital of Traditional Chinese Medicine were recruited. Information and blood samples were collected from any participants who met the inclusion criteria.

Inclusion criteria

Women between 18 and 75 years old who were pathologically diagnosed with primary malignant breast tumours were considered for inclusion. Participants had to meet the DSM-5 diagnostic criteria for depressive disorders, and their HAMD-24 score needed to be between 9 and 35. All of the participants voluntarily participated after total or partial breast resection while not receiving chemotherapy.

Exclusion criteria

Participants who suffered from a mental illness such as depression, mania, or suicidal tendencies before the diagnosis of breast cancer or had a family history of mental illness were excluded, as were participants who were currently taking drugs that could cause depression-like symptoms. Women who were pregnant or lactating, had high blood pressure, heart disease, hepatitis, kidney disease, or autoimmune disease were excluded.

Variables

Our study chose HAMD-24 as the primary outcome. To evaluate the impact of immune function on depression in people with breast cancer, we selected the number of T cells in the peripheral blood as a predictor of depression. In addition, hormones, neurotrophic factors, inflammation, quality of life and other factors were considered in the analysis of the onset of depression and the immune cell status. Therefore, this study collected information on HAMD-24, FACT-B, T-cell, cortisol, BDNF, and inflammatory factors.

HAMD-24 and FACT-B scales

The HAMD-24 scale is one of the most commonly used clinical scales for evaluating depression. It evaluates depression from the dimensions of somatization, weight, cognitive impairment, retardation, day and night changes, sleep disturbance, and despair. FACT-B is one of the scales of the Functional Assessment of Cancer Therapy. It is one of the main scales for assessing the quality of life of breast cancer patients. The assessment is mainly based on social and family status, emotional status, functional status, physiological status, and personal status.

T-cell

In this study, peripheral blood samples were collected for T cell evaluation from participants who agreed to provide blood samples. We mainly observed the content of CD3, CD4, and CD8 cells. The collection of T cells was carried out on an empty stomach around 8:00-8:30 in the morning.

Cortisol

Cortisol is one of the main hormones that affects the expression of human immune function, and it has a certain inhibitory effect on T lymphocytes. The secretion of cortisol fluctuates in response to people's living conditions and stress. Therefore, this study selected subjects' fasting peripheral blood cortisol at 8:00-8:30 in the morning as the observation index.

BDNF

Brain-derived neurotrophic factors promote synaptic plasticity. In depressed people, the content of peripheral blood BDNF is reduced, and the degree of depression is inversely related to BDNF. BDNF and other neurotrophic factors will also change in response to immune function. In this study, we collected BDNF from the peripheral serum of the subjects for evaluation, and the collection time was 8:00-8:30 in the morning on an empty stomach.

Inflammatory factors

Inflammatory factors are highly expressed in depressed people, and there is a positive correlation between inflammatory factors and the severity of depression. We selected TNF and IL-1β for evaluation, which are closely related to tumours, as indicators of peripheral inflammation. The collection time was 8:00-8:30 in the morning on an empty stomach.

Bias

To reduce bias, we established strict inclusion criteria, selected patients who only developed mild to moderate depression after breast cancer. The time and place of data collection for all subjects were unified to ensure data consistency.

Sample size

Recruitment of participants in this study was limited to breast cancer patients who were admitted to the Guangdong Provincial Hospital of Traditional Chinese Medicine from April 2018 to December 2018. All of the participants experienced their first episode of depression after a diagnosis of breast cancer. During this period, a total of 93 breast cancer patients with depression were included in this study, including 46 participants who agreed to blood testing.

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics version 24.0) and MPLUS (version 8.0). The quantitative data are expressed as the mean ± SD and the categorical data are described in terms of quantity and proportion. Correlation analysis was performed for the HAMD-24 score, FACT-B score, BDNF, T lymphocytes, inflammatory factors, and cortisol levels of 46 participants. We chose Pearson's or Spearman's correlation according to the variable type and recorded the correlation coefficient between the variables. $P<0.05$ was considered to be statistically significant. In addition, we used a structural equations model (SEM) to test the mediation relationship among the variables. The structural equation model was developed by using MPLUS (version 8.0). The model fit was assessed with the comparative fit index (CFI, critical value$\geq$0.9), the Tucker Lewis Index (TLI, critical value$\geq$0.9), the root mean square error approximation (RMSEA, value blew 0.08).

Results

Baseline

There were a total of 93 eligible participants in this study. Among the 93 participants, 46 agreed to undergo blood tests such as BDNF, cortisol, and T lymphocytes, but the remaining 47 refused to be tested. The demographic and clinical data of all participants are shown in Table 1.

Table 1

Demographic and clinical data.

Variable	Category	AP group (N = 93)	BT group (N = 46)
Age		52.12±8.58	50.93±7.51
Education	High School Degree	49 (52.69%)	21 (45.65%)
	University Degree	40 (43.01%)	22 (47.83%)
	Graduate Degree	4 (4.30%)	3 (6.52%)
Course (year)		3.20±2.10	2.75±2.09
Chemotherapy	Yes	22 (23.66%)	14 (30.43%)
	No	71 (76.34%)	32 (69.57%)
Cancer Stage	□	68 (73.12%)	30 (65.22%)
	□	22 (23.66%)	14 (30.43%)
	□	3 (3.23%)	2 (4.35%)
Breast Resection	Mastectomy	61 (65.59%)	31 (67.39%)
	Partial Mastectomy	32 (34.41%)	15 (32.61%)
Molecular Stage	Luminal A	28 (30.11%)	15 (32.61%)
	Luminal B	43 (46.24%)	20 (43.47%)
	Her - 2	18 (19.35%)	8 (17.39%)
	TNBC	4 (4.30%)	3 (6.52%)
HAMD-24		23.02±3.62	23.17±3.77
FACT-B		86.30±5.98	85.43±5.50
TNF-α (ng/L)		NA	11.14±5.38
IL-1β (ng/L)		NA	11.71±6.91
Cortisol (nmol/L)		NA	425.56±160.20
BDNF (pg/ml)		NA	17.78±3.71
$CD3^+$ (%)		NA	66.13±10.25
$CD4^+$ (%)		NA	36.74±6.80
$CD8^+$ (%)		NA	24.65±8.61

AP: All 93 participants. BT: The 46 participants who agreed blood test.

Correlation analysis

To explore the potential factors that affect the severity of depression in people with breast cancer, we used correlation analysis of HAMD-24, FACT-B, TNF-α, IL-1β, cortisol, BDNF, $CD3^+$, $CD4^+$, and $CD8^+$ among the 46 participants who completed all tests. The correlation analysis shows that the proportion of T lymphocytes was correlated with the content of BDNF and cortisol. Among them, $CD4^+$ and BDNF were positively correlated, and $CD3^+$ and $CD8^+$ were all negatively correlated with cortisol. In addition, BDNF and cortisol were related to HAMD and FACT-B, respectively. The results are shown in Fig. 1.

Structural equation model

To explore whether T lymphocytes mediate the severity of depression and whether T lymphocytes are affected by the quality of life of breast cancer patients, we constructed three chain intermediary intermediate structure equation model paths: CD4, BDNF, and HAMD-24 and CD3, CD8, cortisol, and FACT-B. The results showed that $CD4^+$ cells pointed to BDNF (r=-0.207, *P*=0.037, [95% CI, 0.017 to 0.418]) and the BDNF cells pointed to HAMD-24 (r=-0.269, *P*=0.012, [95% CI, -0.471 to -0.036]), but the $CD4^+$ cells could not directly point to HAMD-24 (r=-0.099, *P*=0.485, [95% CI, -0.353 to 0.217]). In another two model paths, cortisol pointed to $CD3^+$ and $CD8^+$ (r=-0.333, *P*=0.037, r=-0.348, *P*=0.041), FACT-B pointed to cortisol (r=0.435, *P*=0.001), but FACT-B could not directly point to $CD3^+$ and $CD8^+$ (r=0.095, *P*=0.511, r=0.194, *P*=0.161). See Fig. 2.

Discussion

$CD4^+$ cells used BDNF as a mediator variable to predict the HAMD-24 score. As the proportion of $CD4^+$ cells decrease, peripheral BDNF will also decrease, and the HAMD-24 score will be higher. FACT-B uses cortisol as a mediating variable to affect the ratio of $CD3^+$ to $CD8^+$. The worse the quality of life, the higher the level of cortisol, and the lower the proportion of $CD3^+$ to $CD8^+$. The physiological basis of depression in cancer patients may be related to the proportion of T lymphocytes. T lymphocytes will be affected by the quality of life of cancer patients. In addition, BDNF and cortisol are mediators between T lymphocytes, depression, and quality of life.

Nerves and immunity are connected to each other [7, 8]. The activation of specific T lymphocytes can induce the secretion of BDNF, protect nerves, and promote nerve regeneration [4]. $CD4^+$ cells are a potential source of BDNF after nerve injury and are responsible for neuroprotection [9, 10]. After nerve injury, $CD4^+$ cells can secrete BDNF to facilitate nerve repair [11]. Normal levels of BDNF can promote neuroplasticity and synaptic remodelling [12]. After BDNF binds to the receptor TrkB, it activates the mitogen-activated protein kinase (MAPK) pathway and other pathways, and finally, the cAMP response

element binding protein is activated, which improves long-term potentiation by improving neuroplasticity [13-15], increasing the number of NMDA and AMPA receptors, and increasing the release of glutamate [16]. Multiple clinical studies have also confirmed that insufficient secretion of BDNF is associated with depression [17]. However, cancer cells may inhibit T lymphocytes through the immune checkpoint cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD- L1) pathways [5, 18]. Eventually, the function and number of $CD4^+$ T cells are inhibited [19]. Inhibition of $CD4^+$ cells may slow down the expression of BDNF, leading to slower nerve repair, thereby aggravating depression. This is also consistent with the results of our equation model. Therefore, the decrease in the number and function of $CD4^+$ cells in the breast cancer environment may be the physiological basis for breast cancer-associated depression.

Most breast cancer patients will have negative emotions such as anxiety and depression during their illness [20]. The chronic stress stimulus of this negative emotion can induce depression and reduce their quality of life [2]. Negative emotions with reduced quality of life will affect the secretion of corticosteroids through the HPA axis of neuroendocrine and collaterals [21, 22], and the level of cortisol is also negatively correlated with the quality of life [23]. Many studies have reported that activation of the HPA axis will accelerate the secretion of cortisol under stress, and the imbalance of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) will lead to the occurrence of mood-related diseases [24]. Glucocorticoids have immunosuppressive functions on T cells, and hormones can inhibit the reproduction of T cells and induce T cell apoptosis [25]. Although there is a balance between endogenous cortisol and T lymphocytes, under the influence of negative emotions such as reduced quality of life, the imbalance of cortisol released by HPA may further inhibit the function of T lymphocytes. A breast cancer study also found that a worse quality of life and more clinical symptoms were related to lower levels of $CD4^+$ and $CD8^+$ T lymphocytes [26], which is consistent with the results of our study. The immune function of breast cancer patients will be affected by negative emotions caused by a poor quality of life, which may be mediated through the HPA axis affecting the secretion of cortisol.

There are some limitations of this study. The sample size of the study was insufficient, and there was no control group. The collection of neurotrophic factors should be expanded. In the future, the sample size should be increased, a control group should be established, the number of indicators should be increased, and longitudinal experiments should be designed.

Conclusion

T lymphocytes may be involved in the onset of depression in breast cancer patients. Poor quality of life and immunosuppression in the cancer environment will reduce the number and function of T lymphocytes. The release of neurotrophic factors and nerve repair are also impaired due to the inhibition of T lymphocytes, which aggravates depression. For the treatment of depression in breast cancer patients, T lymphocytes may be a potential therapeutic target.

Declarations

Acknowledgments

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Consent for Publication

All authors approved the final manuscript and gave consent for publication.

Conflict of interest

This research was funded by the Key-Area Research and Development Program of Guangdong Province, Shenzhen Bao'an Research Center for Acupuncture and Moxibustion, and Sanming Project of Medicine in Shenzhen, and there is no conflict of interest with any of the authors. Wen-bin Fu has 3 patents, Jun-He Zhou has 1 patent, and none of the patent holders have received any economic benefits from this article. None of the authors hold any stocks or funds that are related to this research and have economic returns.

Availability of data and material

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of the research participants, but the data could become available after Wen-Bin Fu agrees to authorize its release.

Authors' contributions

Jun-He Zhou and Wei-Han Li were responsible for the data analysis and the writing of this article. Jun-He Zhou and Wei-Han Li are co-first authors. De-Long Zhang and Bai-Le Ning were responsible for making corrections to the paper and guiding the analysis methods. Lin Zhao was responsible for preparing the

figures. Wen-Bin Fu was in charge of this research. The other authors participated in all stages of the research.

Ethics approval

The Institutional Ethics Committee of GUANGDONG Provincial Hospital of Traditional Chinese Medicine provided ethics approval (YF2018-041-01).

Consent to participant

Patients included in the study were required to sign an informed consent form and they participated in the study on a voluntary basis.

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Figures

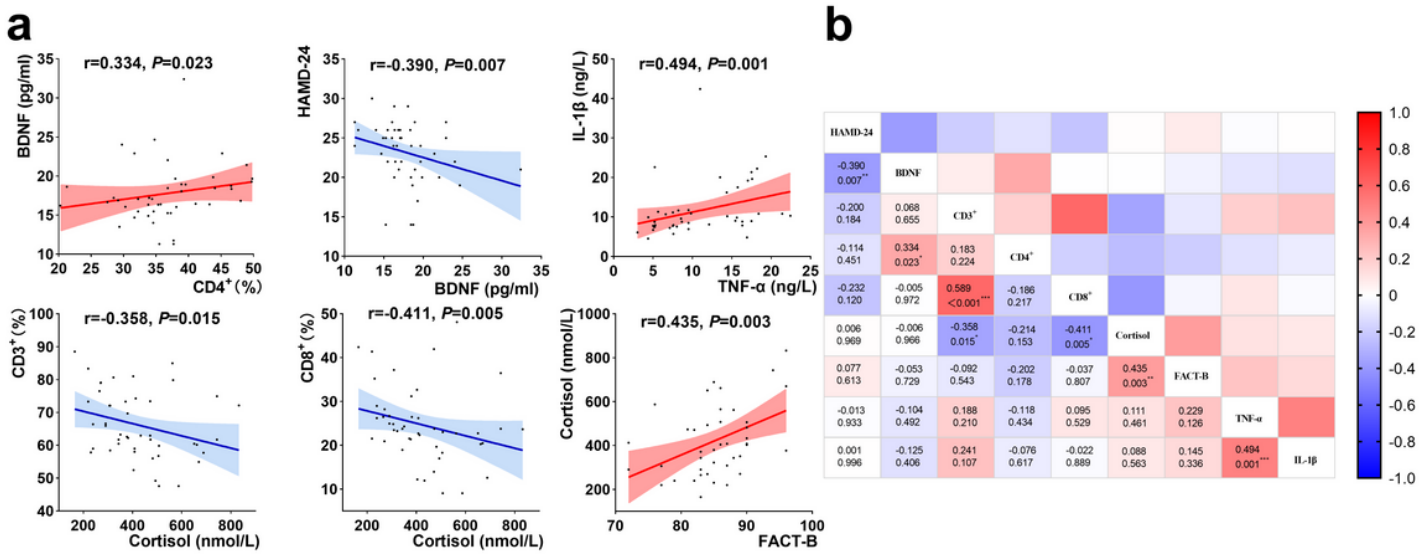

Figure 1

Correlation analysis between variables. a The proportion of T lymphocytes is correlated with the content of BDNF and cortisol. CD4+ and BDNF are positively correlated, CD3+ and CD8+ are all negatively correlated with cortisol. BDNF and cortisol are related to HAMD and FACT-B respectively. IL-β and TNF-α are positively correlated. b The results of correlation analysis of all variables. In this figure, the red background box represents the positive correlation between variables, and the blue represents the negative correlation. The darker the color, the greater the correlation. The numbers in each box represent the correlation coefficient and the P-value.

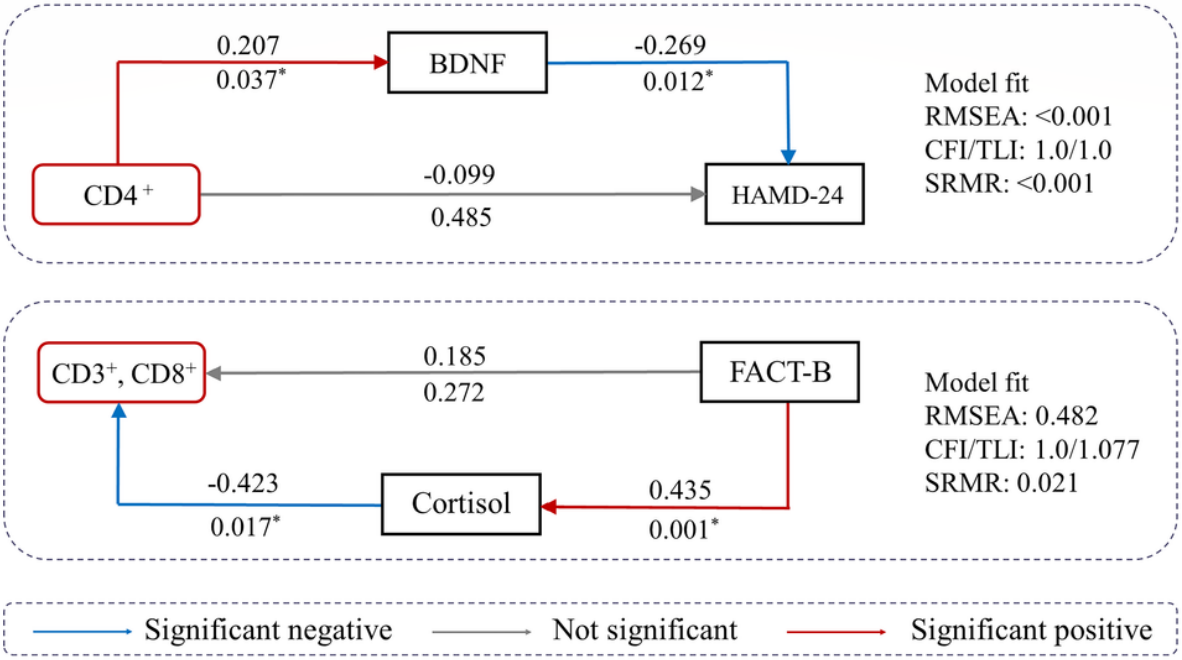

Figure 2

Two chain intermediary intermediate structure equation model paths.

Supplementary Files

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