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The Correlation between Free Triiodothyronine, Free Thyroxine and Hypertension in Depression Patients with Hypothyroidism and Its Clinical Guiding Value

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Abstract

Background: Cardiovascular diseases, such as hypertension and coronary heart disease, are often accompanied by thyroid and mental diseases, the harm of which poses great threats to patients' health. Objective: To explore the correlation between free triiodothyronine (FT_3), free thyroxine (FT_4) and hypertension in depression patients with hypothyroidism and its clinical guiding value. Methods: A total of 548 patients diagnosed with hypothyroidism in Wuxue First People's Hospital of Hubei Province from January 2018 to September 2022 were enrolled. According to whether complicated with depression, they were divided into hypothyroidism without depression group (group A) and hypothyroidism with depression group (group B). The gender, age, comorbidities (such as depression, hypertension, diabetes, dyslipidemia, acute myocardial infarction), FT_3, FT_4, and thyroid stimulating hormone (TSH) levels were recorded. Spearman rank correlation was used to analyze hypertensive patients with hypothyroidism. Multivariate binary Logistic regression was used to analyze the influencing factors of hypertension in patients with hypothyroidism. Results: The TSH level, the number of hypertension, coronary heart disease and hyperlipidemia in group B were statistically significantly higher than those in group A ($P < 0.05$). The FT_3 level in group B was statistically significantly lower than that in group A ($P < 0.05$). Correlation analysis of hypertensive patients with hypothyroidism showed that hypertension was positively correlated with depression ($r_s = 0.092$), coronary heart disease ($r_s = 0.000$), hyperlipidemia ($r_s = 0.000$), diabetes ($r_s = 0.000$), and age ($r_s = 0.000$), and negatively correlated with FT_3 ($r_s = 0.000$) ($P < 0.05$).

Logistic regression analysis showed that coronary heart disease, hyperlipidemia, FT_3 and FT_4 were the influencing factors of hypertension. The risk of hypertension in patients with coronary heart disease and hyperlipidemia significantly increased by 3.425 and 1.761 times ($P < 0.01$), respectively. With the decrease of FT_3, the risk of hypertension increased ($P < 0.01$); With the increase of FT_4, the risk of hypertension significantly increased ($P < 0.01$). Conclusions: Depression patients with hypothyroidism are more likely to suffer from hypertension, coronary heart disease and hyperlipidemia. Coronary heart disease and hyperlipidemia can increase the risk of hypertension in patients with hypothyroidism. FT_3 and FT_4 are the influencing factors of hypertension. The lower the FT_3 level, the higher the FT_4 level, the higher the risk of hypertension. FT_3 and FT_4 may be potential biomarkers of depression in hypertensive patients. Thyroid function assessment is recommended in patients with hypertension.

Keywords

Hypothyroidism, Depression, Hypertension, Coronary Heart Disease, Correlation Analysis, FT_3, FT_4

1. Introduction

Cardiovascular disease and mental disease have become two major public health diseases threatening national health. According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [1], depression is defined as a mental illness with core symptoms such as low mood, loss of interest, and lack of energy, and may be accompanied by cognitive, physiological, and behavioral symptoms, such as inattention, insomnia, slow reaction, decreased behavioral activity, and fatigue for at least 2 weeks. Hypertension [2] is characterized by a continuous increase in blood pressure in blood vessels. According to its source of disease, it is mainly divided into two types: essential hypertension and secondary hypertension. Depression and hypertension have a common pathogenesis [3]: a large number of studies have suggested that hypertension and depression are accompanied by increased sympathetic nerve activity, increased norepinephrine level, decreased norepinephrine transporter activity, and dysfunction of the renin-angiotensin system. Depression can lead to increased blood pressure [4]: the blood pressure of the human body is affected by various factors, and the psychological state can significantly affect the blood pressure, especially when depression causes insomnia, which will cause or aggravate the increase in blood pressure. In addition, tricyclic antidepressants (such as amitriptyline) [5], serotonin and norepinephrine reuptake inhibitors [6] (such as venlafaxine, duloxetine) in antidepressant drugs can also lead to blood pressure increase. At the same time, patients with hypertension are prone to anxiety and depression [7], accompanied by symptoms such as headache, dizziness and insomnia, which make pa-

tients feel anxiety and depression, and thus promote the occurrence and development of depression in people with potential risks of depression. In addition, reserpine, an antihypertensive drug, can cause the depletion of monoamine neurotransmitters in the brain [8], and long-term use can lead to depression and even suicide in severe cases. Therefore, reserpine and reserpine-containing compound preparations are not recommended. In addition, guanethidine, hydralazine, propranolol hydrochloride, and methyldopa can also cause depression [9]. Cardiovascular diseases, such as hypertension and coronary heart disease, are often accompanied by thyroid and mental diseases. At present, the interaction mechanism of thyroid disease with depression and anxiety is not completely clear. Studies have shown that hypothalamic-pituitary-thyroid (HPT) axis plays a certain role in depression and anxiety disorders, and its mechanism may be related to the TSH level in patients, and there is a negative correlation between them [10]. Several researches explored the mechanisms of arterial hypertension in depressive and hypothyroid patients [11] [12]. Diastolic dysfunction was associated with subclinical atherosclerosis, as expressed by altered arterial stiffness, and appeared to be strongly correlated with the intensity and duration of depressive symptoms. The last two factors, together with an increased pulse wave velocity, appear to be strong predictors for the occurrence of diastolic dysfunction. Endothelial dysfunction, documented in hypothyroid patients by means of three noninvasively methods, was strongly related to the severity of thyroid disease. Endothelial dysfunction was improved consistently after restoring the euthyroid state. The incidence of hypertension with depression is high, and the treatment is more difficult than that of simple hypertension, and depression patients generally have thyroid hormone disorders.

Studies have shown that felodipine sustained-release tablets combined with escitalopram oxalate tablets [13] have good efficacy in the treatment of hypertension with depression, and can effectively correct thyroid hormone disorders, control blood pressure, reduce depressive symptoms, and have good safety. At present, for hypertension combined with depression, the most evidence-based antidepressant treatment is selective serotonin reuptake inhibitors [6], including fluoxetine, paroxetine, sertraline and citalopram, etc, which are the first-line drugs. Central nervous system inhibitors and β-blockers with high lipophilicity should be avoided as far as possible in antihypertensive drugs [14]. The comorbidity of hypothyroidism, depression and hypertension may have some common pathological mechanisms, and the hypothalamic-pituitary-thyroid (HPT) axis system is related to the development and response of depression. However, the mechanism of HPT axis in hypertensive patients with depression is still unclear, and the characteristics of thyroid-related hormones are still lacking.

Therefore, it is of great clinical significance to evaluate the depression state and explore the thyroid function of patients with depression and hypertension. The study intends to explore the correlation between FT_3, FT_4 and hypertension

in depression patients with hypothyroidism and its clinical guiding value, which has important clinical significance for the practice of "Psycho-cardiology". In the future, the mechanism of low FT_3 and high FT_4 in the comorbidity of the three will be further studied. It may reduce the incidence of depression in hypertensive patients and improve the prognosis of cardiovascular disease by controlling the levels of FT_3 and FT_4, so as to achieve the complete physical and psychological rehabilitation of patients.

2. Objects and Methods

2.1. Subjects

A total of 548 patients diagnosed with hypothyroidism in Wuxue First People's Hospital, in Hubei Province from January 2018 to September 2022 were enrolled, including 177 males and 372 females; The average age was 60.11 ± 15.78 years old, ranging from 18 to 97 years old. Inclusion criteria: 1) Patients with clinical diagnosis of hypothyroidism; 2) Patients were newly diagnosed and had not been treated with any antidepressant, antihypertensive, cardiovascular drugs, and thyroid drugs (including levothyroxine, etc.); 3) All study subjects participated voluntarily and oral informed consent was obtained. Exclusion criteria: 1) Patients unable to cooperate with the investigation due to critical illness such as disturbance of consciousness or cardiac function grade IV; 2) Patients with severe mental illness or cognitive impairment.

2.2. Research Methods

The gender, age, comorbidities (such as depression, hypertension, diabetes, dyslipidemia, acute myocardial infarction and so on), free triiodothyronine (FT_3), free tetraiodothyronine (FT_4), and thyroid stimulating hormone (TSH) levels were recorded.

2.3. Indicator Detection Methods

Thyroid function was detected by direct chemiluminescence method. Fasting venous blood was collected in the morning to detect FT_3, FT_4 and TSH. The reference ranges of FT_3, FT_4 and TSH were 3.53 - 7.37 pmol/L, 7.98 - 16.02 pmol/L and 0.56 - 5.91 mU/mL, respectively.

2.4. Statistical Methods

SPSS 22.0 was used for data statistical analysis. The measurement data in line with normal distribution were expressed as mean ± standard deviation, and the measurement data of non-normal distribution were expressed as M (P25, P75). The non-parametric rank sum test was used for comparison between the two groups. Chi-square test was used for comparison between groups. Because depression scores did not follow the normal distribution, Spearman rank correlation was used to analyze hypertensive patients with hypothyroidism. Multivariate binary Logistic regression was used to analyze the influencing factors of

hypertension in patients with hypothyroidism. A difference of 0.05 was considered statistically significant.

3. Results

3.1. Comparison of General Data between Hypothyroidism without Depression Group and Hypothyroidism with Depression Group

There were 234 patients (42.7%) in hypothyroidism without depression group (group A) and 314 patients (57.3%) in hypothyroidism with depression group (group B). There was no significant difference in age, gender, FT_4 level, and the number of diabetes between the two groups ($P < 0.05$). The TSH level, the number of hypertension, coronary heart disease, and hyperlipidemia in group B were statistically significantly higher than those in group A ($P < 0.05$). The FT_3 level in group B was statistically significantly lower than that in group A ($P < 0.05$), as shown in Table 1, Table 2.

3.2. Correlation Analysis in Hypertensive Patients with Hypothyroidism

Spearman rank correlation analysis showed that hypertension was positively correlated with depression ($r_s = 0.092$), coronary heart disease ($r_s = 0.000$), hyperlipidemia ($r_s = 0.000$), diabetes ($r_s = 0.000$), and age ($r_s = 0.000$) ($P < 0.05$). It was negatively correlated with FT_3 ($r_s = 0.000$) ($P < 0.05$), but not with gender ($r_s = 0.011$), TSH ($r_s = 0.051$) and FT_4 ($r_s = 0.014$) ($P > 0.05$), as shown in Table 3.

3.3. Influencing Factors of Hypertension Risk in Patients with Hypothyroidism

Multivariate binary logistic regression analysis showed that coronary heart disease, hyperlipidemia, FT_3 and FT_4 were the influencing factors of hypertension. The risk of hypertension in patients with coronary heart disease and hyperlipidemia significantly increased by 3.425 and 1.761 times ($P < 0.01$), respectively. With the decrease of FT_3, the risk of hypertension increased ($P < 0.01$); with the increase of FT_4, the risk of hypertension increased ($P < 0.01$). See Table 4, Figure 1.

Table 1. Comparison of general data between hypothyroidism without depression group (group A) and hypothyroidism with depression group (group B).

	TSH	FT_3	FT_4	Age
Group A	5.96 (1.83 - 20.59)	2.37 (1.92 - 2.88)	0.83 (0.61 - 1.08)	63 (50 - 72)
Group B	8.14 (2.515 - 38.59)	2.24 (1.51 - 2.765)	0.77 (0.54 - 1.03)	63 (50 - 72)
Z-value	−2.062	−3.494	−1.842	−0.120
P-value	0.039	0.000	0.066	0.904

Table 2. Comparison of general data between hypothyroidism without depression group (group A) and hypothyroidism with depression group (group B).

	Gender	Hypertension	Coronary heart disease	Hyperlipidemia
Group A	85 (36.3%)	111 (47.4%)	109 (44.6%)	82 (35%)
Group B	92 (29.3%)	178 (56.70%)	173 (55.1%)	147 (46.8%)
Pearson's Chi-square value	3.026[a]	4.605[a]	3.891[a]	7.639[a]
P-value	0.082	0.032	0.049	0.006

a: Actual observations of Pearson Chi-square values.

Table 3. Correlation analysis between hypothyroidism patients with hypertension and influencing factors.

Variables of interest	r_s	P
Depression	0.092*	0.032
Coronary heart disease	0.382**	0.000
Hyperlipidemia	0.283**	0.000
Diabetes	0.442**	0.000
Gender	0.011	0.806
Age	0.153**	0.000
TSH	0.051	0.236
FT_3	−0.182**	0.000
FT_4	0.014	0.748

*: $P < 0.05$, **: $P < 0.01$.

Table 4. Influencing factors of hypertension risk in patients with hypothyroidism.

Variables of interest	OR (95%CI)	P
Depression	1.176 (0.758 - 1.823)	0.469
Coronary heart disease	4.425 (2.877 - 6.807)	0.000
Hyperlipidemia	2.761 (1.779 - 4.283)	0.000
Diabetes	1497920412.799	0.996
Gender	1.158 (0.731 - 1.832)	0.532
Age	1.014 (1.000 - 1.029)	0.052
TSH	1.001 (0.997 - 1.005)	0.803
FT_3	0.725 (0.549 - 0.956)	0.023
FT_4	1.257 (1.070 - 1.478)	0.006

OR: Odds Ratio, B: Beta.

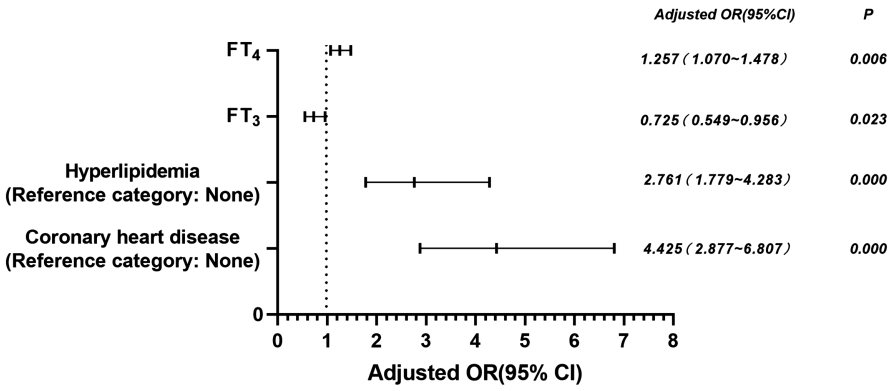

Figure 1. Influencing factors of hypertension risk in patients with hypothyroidism.

4. Discussion

4.1. Guide the Combination Therapy of Thyroid Function Disorders, Depression and Hypertension Complications

The mechanism of interaction between thyroid disease, depression and anxiety is not completely clear. The latest studies have shown that the hypothalamic-pituitary-thyroid (HPT) axis plays a role in depression and anxiety disorders, and its mechanism may be related to the TSH level in patients, and there is a negative correlation between them [10]. The main feature of subclinical hypothyroidism is that TSH is elevated, while FT_3 and FT_4 are normal. Compared with ordinary patients with anxiety and depression, it is more difficult for patients with subclinical hypothyroidism to relieve anxiety and depression under the treatment of anti-anxiety and depression drugs. Studies have shown that escitalopram oxalate combined with levothyroxine sodium can improve the anxiety and depression of patients with subclinical hypothyroidism and anxiety and depression, and its efficacy is better than that of single medication. The mechanism may be related to the enhancement of central serotonin activity, the reduction of TSH, and the improvement of FT_3 and FT_4 levels [13]. Escitalopram oxalate combined with levothyroxine sodium provides a new reference for the treatment of anxiety and depression in patients with subclinical hypothyroidism and anxiety and depression. Reducing thyroid hormone levels in patients with hyperthyroidism can effectively relieve the clinical symptoms of patients, but anxiety and other negative emotions of patients are often difficult to eliminate. Studies have found [15] that paroxetine combined with I^{311} can effectively relieve anxiety and depression in patients with hyperthyroidism and emotional disorders, improve the treatment effect of hyperthyroidism, and improve the levels of TSH, FT_4 and FT_3 in patients. Escitalopram combined with quetiapine has strong neurotransmitter antagonism, which can greatly reduce the impact of HPT dysfunction on patients, so as to alleviate thyroid dysfunction [16]. Studies have shown that compared with the control group, the serum TSH and FT_3 levels of the observation group were significantly increased, while the serum FT_4 level was significantly decreased after treatment, indicating that escitalopram

combined with quetiapine can improve the thyroid function of patients and reduce the negative emotional symptoms of patients [17]. The incidence of hypertension with depression is high, and the treatment is more difficult than that of simple hypertension, and depression patients generally have thyroid hormone disorders. Studies have shown that felodipine sustained-release tablets combined with escitalopram oxalate tablets have good efficacy in the treatment of hypertension with depression, and can effectively correct thyroid hormone disorders, control blood pressure, reduce depressive symptoms, and have good safety [18]. High serum FT_3 level and comorbidity of thyroid disease may increase the risk of readmission after hospitalization for major depressive disorder (MDD). Routine assessment and intervention of thyroid function during depression treatment is necessary to prevent re-hospitalization [19]. Studies have shown that the clinical use of T_3 can be used as an antidepressant enhancer in patients with major depression who do not respond to antidepressant monotherapy. Thyroid hormone-based antidepressants are recommended as a treatment option in cases where monotherapy fails, and clinicians also recommend the use of thyroid hormone supplements in unresponsive depressed patients, especially those with TSH levels in the high normal range [20]. In addition to its use as augmentation, evidence from multiple randomized controlled trials also supports the use of T_3 for accelerating the antidepressant response to tricyclic antidepressants (TCA).

Thyroid disease is often accompanied by psychiatric disorders, and even cardiovascular and endocrine diseases such as hypertension and diabetes. At present, there is still a lack of research on the combination of thyroid disease and depression complications. In the future, more extensive research on the combination of hyperthyroidism, hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism and depression, anxiety, dissociation and other mental disorders can be carried out.

4.2. Thyroid Function Analysis of Female Depression Patients at Different Stages

Some researchers analyzed the correlation between HAMD (Hamilton Depression Scale), HAMA (Hamilton Anxiety Scale) cores and thyroid function in female patients [21] and found that T_4 level was correlated with HAMA total score ($P < 0.05$), TSH level was associated with HAMD total score ($P < 0.05$). FT_3 and FT_4 levels were positively correlated with HAMA and HAMD scores ($P < 0.01$). FT_3 and FT_4 levels are more sensitive in female patients with depressive episode, and their changes are closely related to the severity of the disease. For women at different stages, some researchers have explored the relationship between hypothyroidism during pregnancy [22] and postpartum anxiety and depression, and found that the occurrence of postpartum anxiety and depression symptoms was correlated with hypothyroidism during pregnancy. Based on the study of anxiety and depression in menopausal women with diabetes and subclinical hypothyroidism, it has been shown that the course of diabetes is a risk factor for anxiety,

and the level of TSH is a risk factor for depression [23]. Postmenopausal women with type 2 diabetes mellitus complicated with subclinical hypothyroidism (SCH) often have anxiety and depression, especially those with longer duration of diabetes and higher TSH level. Psychological care should be given in time.

Depression and anxiety disorders in women are highly prevalent diseases, which are significantly higher than those in men, and are often accompanied by thyroid function diseases. Most of the current research is focused on female patients, and the correlation between depression and thyroid function in women can be subdivided into different stages such as menstruation, pregnancy, pregnancy, menopause, old age, etc.

5. Conclusion

Depression patients with hypothyroidism are more likely to suffer from hypertension, coronary heart disease, and hyperlipidemia. Coronary heart disease and hyperlipidemia can increase the risk of hypertension in patients with hypothyroidism. FT_3 and FT_4 are the influencing factors of hypertension. The lower the FT_3 level, the higher the FT_4 level, the higher the risk of hypertension. FT_3 and FT_4 may be potential biomarkers of depression in hypertensive patients. Thyroid function assessment is recommended in patients with hypertension.

6. Limitations and Strengths

There exist still some limitations of the present study. First, it is a cross-sectional study, and the causal relationship between low FT_3 level and high FT_4 level and hypertension in patients cannot be clearly defined. Next, it is not known whether depression occurs before or after the onset of hypertension. Social psychological factors such as smoking and drinking habits, interpersonal relationship (such as relationship with children or spouse), and economic status weren't combined to analyze these factors, which are important influencing factors for depression in elderly patients with chronic diseases. It also doesn't consider the physiological stages of women (such as menstruation, pregnancy, menopause and old age), which are important factors affecting the status of women with depression. Moreover, the study was a single-center study with a small sample size.

The study highlights the significant correlation between cardiovascular disease, thyroid dysfunction, and depression, emphasizing the considerable risk these comorbidities pose to patients' health, which medical professionals should closely monitor. However, such research is lacking, especially on the characteristics of thyroid hormones. Therefore, it has great clinical significance to evaluate the depression state and explore the thyroid function of patients with depression and hypertension. The study aims to explore the correlation between FT_3, FT_4 and hypertension in depression patients with hypothyroidism and its clinical guiding value, which has important clinical significance for the practice of "Psycho-cardiology". In the future, the mechanism of low FT_3 and high FT_4 in the comorbidity of the three will be further studied. It may reduce the incidence of

depression in hypertensive patients and improve the prognosis of cardiovascular disease by controlling the levels of FT_3 and FT_4, so as to achieve the complete physical and psychological rehabilitation of patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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