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Original Article

Correlation of GLUT1 and GLUT4 with prognosis of patients with hypothyroidism and cardiac insufficiency

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Abstract: Objective: Hypothyroidism is a disease with symptoms of collective metabolic dysfunction and systemic dysfunction due to the lack of serum thyroid hormones caused by various reasons. GLUT4 is over-expressed in monocytes of patients with hyperthyroidism, there are also studies suggesting that there is a certain regulatory relationship of GLUT1 and GLUT4 with thyroid function. This study is aimed to explore the correlation of glucose transporter 1 (GLUT1) and GLUT4 with prognosis of patients with hypothyroidism and cardiac insufficiency. Methods: From July 2016 to October 2019, totally 116 patients with cardiac insufficiency complicated with subclinical hypothyroidism treated in our hospital were enrolled in the research group (RG), and 110 patients with cardiac insufficiency but normal thyroid function were enrolled in the control group (CG). Serum GLUT1, GLUT4, free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were detected, and the correlation between them was analyzed. Then the predictive value and risk factors of GLUT1 and GLUT4 for poor prognosis of hypothyroidism complicated with cardiac insufficiency were analyzed. Results: The expression levels of GLUT1, GLUT4, FT3 and FT4 in serum of patients in RG was notably lower than that in CG, and TSH expression was remarkably higher than those in CG ($P<0.05$). In RG, GLUT1 and GLUT4 expression levels were positively correlated with FT3 and FT4 expression ($P<0.05$), but negatively correlated with TSH expression ($P<0.05$). ROC of GLUT1 and GLUT4 in RG in predicting poor prognosis of patients was over 0.8. Low expression of GLUT1 and GLUT4 and diabetes were independent risk factors for poor prognosis in patients with hypothyroidism complicated with cardiac insufficiency. Conclusion: GLUT1 and GLUT4 expression levels were significantly decreased in serum of patients with hypothyroidism complicated with cardiac insufficiency. Both of them have high predictive value for poor prognosis of patients, and are independent risk factors for poor prognosis of patients.

Keywords: GLUT1, GLUT4, hypothyroidism, cardiac insufficiency, prognosis prediction

Introduction

Hypothyroidism is a disease with symptoms of collective metabolic dysfunction and systemic dysfunction due to the lack of serum thyroid hormones caused by various reasons [1, 2]. There has been increasing concern in recent years about the cardiovascular risks associated with hypothyroidism because of the large base of patients currently suffering from hypothyroidism [3]. Epidemiological investigation [4] revealed that hypothyroidism is one of the risk factors for the occurrence and development of cardiovascular diseases. For older people who have many underlying medical conditions, hypothyroidism is often overlooked because of its insidious onset and slow progression [5]. Therefore, finding effective indicators to evaluate patients with hypothyroidism and cardiac insufficiency in a timely and effective way is of great clinical significance for the selection of follow-up treatment programs and the improvement of prognosis.

For patients with cardiac insufficiency caused by hypothyroidism, energy metabolism disorder of the heart is one of the important causes [6]. Glucose is one of the main substrates of energy metabolism in myocardial cells, and the utilization of glucose by the body needs the assistance of glucose transporters (GLUTs). Abnormal GLUTs on myocardial cell membrane will

Table 1. Primer sequence

Factor	Upstream primer 5'-3'	Downstream primer 5'-3'
GLUT1	TCAACACGGCCTTCACTG	CACGATGCTCAGATAGGACATC
GLUT4	GTAACTTCATTGTCGGCATGG	AGCTGAGATCTGGTCAAAAAACG
β-actin	GATTACTGCTCTGGCTCCTAG	GACTCATCGTACTCCTGCTTG

affect the normal intake and utilization of energy substances in myocardium [7]. GLUT1 and GLUT4 are mainly distributed in myocardial cells, which are mainly responsible for maintaining glucose intake of myocardial cells in the basic state, and are two of the most important glucose transporters in myocardial tissues. In the basic state, they are stored in cell vesicles and transferred to the cell membrane under the stimulation of insulin, which plays a part in mediating glucose transport [8, 9]. Previous studies [10] found that GLUT4 is over-expressed in monocytes of patients with hyperthyroidism, there are also studies suggesting that there is a certain regulatory relationship of GLUT1 and GLUT4 with thyroid function [11, 12], indicating that GLUT and thyroid function are related to each other.

At present, however, there is no relevant research to investigate the correlation of GLUT1 and GLUT4 with patients with hypothyroidism and cardiac insufficiency. To find new suitable indicators to improve the treatment and prognosis of the patients, we performed the following experiments.

Materials and methods

Clinical data

Totally 116 patients with cardiac insufficiency complicated with subclinical hypothyroidism treated in our hospital from July 2016 to October 2019 were prospectively chosen and enrolled in the research group (RG), and 110 patients with cardiac insufficiency but normal thyroid function treated in our hospital simultaneously were enrolled in the control group (CG). All patients included in the study met the diagnostic criteria of cardiac insufficiency [13], and the patients in RG met the diagnostic criteria of hypothyroidism [14]. Patients with severe hepatic or renal insufficiency, other malignant tumor diseases, or other serious endocrine diseases were excluded. All patients agreed to take part in the study and signed a written informed consent form. Hospital ethics committee authorized the study.

qRT-PCR detection of GLUT1 and GLUT4 expression

Venous blood (5 mL) of all subjects were drawn on an empty stomach, centrifuged at 1,500 × g for 10 min under 4°C to obtain supernatant for detection. TRIzol was put into the serum for total RNA extraction, and UV spectrophotometer and agarose gel electrophoresis were applied for determination of its purity, concentration and integrity. cDNA reverse transcription was performed in the light of the kit instructions. Power SYBR Green PCR Master Mix was adopted for quantitative RT-PCR. PCR reaction conditions were as follows: 95°C for 30 s, 95°C for 5 s, 60°C for 15 s, with a total of 40 cycles. β-actin was utilized as the internal reference. The primer sequence was shown in **Table 1**.

Detection of other relevant indicators

Echocardiography was utilized for assessment of cardiac function [left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD)] and heart rate. Free triiodothyronine (FT3), free thyroxine (FT4) (normal reference range: FT3: 3.5-6.5 pmol/L, FT4: 8.5-22.5 pmol/L), and thyroid stimulating hormone (TSH, normal reference range: 0.35-5.29 μIU/mL) were detected by chemiluminescence.

Statistical methods

Experimental data was statistical analyzed using SPSS20.0 [Bizinsight (Beijing) Co., Ltd.]. Counting data adopted Chi-square tese, and measurement data adopted mean standard deviation. T test was utilized for comparison between the two groups, and paired T test was utilized for comparison before and after treatment. Pearson was applied for correlation analysis. GraphPad Prism 6 software was applied for image rendering of the experimental pictures. When $P<0.05$, there was a statistical difference.

Results

General data

There were no significant differences in gender, age and BMI between RG and CG ($P>0.05$), but there were significant differences in the number of diabetes patients ($P<0.05$), as shown in **Table 2**.

Table 2. General data

Factors	Research group (n=116)	Control group (n=110)	t/χ^2	P
Gender			0.013	0.914
Male	62 (53.45)	58 (52.73)		
Female	54 (46.55)	52 (47.27)		
Age (years)	68.42±5.47	68.11±5.58	0.422	0.674
BMI (kg/m^2)	23.13±2.25	23.64±2.31	1.681	0.094
Type of heart disease			0.076	0.963
Coronary heart disease	71 (61.21)	68 (61.82)		
Dilated cardiomyopathy	31 (26.72)	30 (27.27)		
Other	14 (12.07)	12 (10.91)		
Drinking history			0.048	0.827
With	69 (59.48)	67 (60.91)		
Without	47 (40.52)	43 (39.09)		
Smoking history			0.001	0.970
With	55 (47.41)	51 (46.36)		
Without	63 (54.31)	59 (53.64)		
Hypertension			0.010	0.919
With	72 (62.07)	69 (62.73)		
Without	44 (37.93)	41 (37.27)		
Diabetes			4.383	0.036
With	79 (68.10)	60 (54.55)		
Without	37 (31.90)	50 (45.45)		

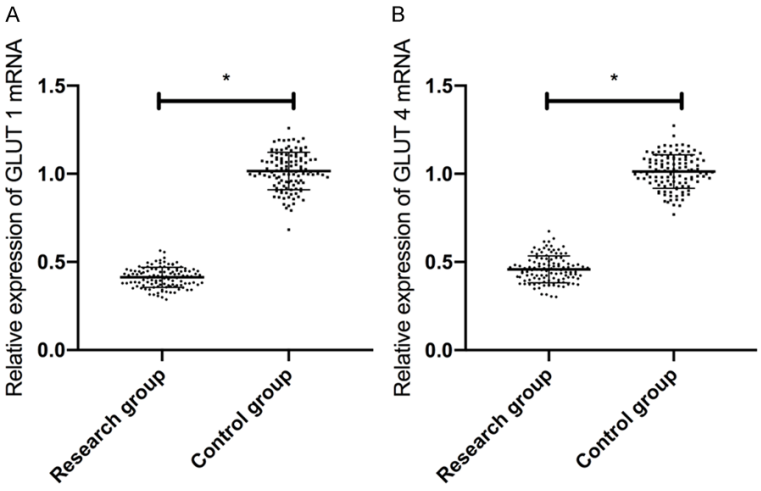

Figure 1. Expression of GLUT1 and GLUT4 in serum of two groups of patients. A: Comparison of serum GLUT1 expression. B: Comparison of serum GLUT4 expression. *denotes P<0.05.

GLUT1 and GLUT4 expression levels in serum of two groups of patients

We detected GLUT1 mRNA and GLUT4 mRNA in serum of patients in two groups by RT-PCR, and the results showed that GLUT1 mRNA and GLUT4 mRNA expression in the serum of RG was notably lower than that of CG, with statistically significant difference (P<0.05), as shown in **Figure 1**.

Expression of thyroid-related hormones in two groups of patients

TSH level in RG was notably higher than that in CG (P< 0.01). The levels of FT3 and FT4 in RG were remarkably lower than those in CG (P<0.01), as shown in **Figure 2**.

Correlation analysis of GLUT1 and GLUT4 with thyroid-related hormones

We analyzed the correlation of GLUT1 and GLUT4 with thyroid-related hormones. The results showed that GLUT1 and GLUT4 were inversely correlated with TSH, but positively correlated with FT3 and FT4 (P<0.05), see **Figure 3**.

Predictive value of GLUT1 and GLUT4 for poor prognosis of patients

Patients in RG were followed up for one year, and were divided into a MACE group (43 patients) and a non-MACE group (73 patients) according to whether they had major adverse cardiovascular events (MACE) during the follow-up period. By comparing serum GLUT1 and GLUT4 between two groups, it was found that the two patients in MACE group were evidently lower than those in non-MACE group (P<0.05). ROC analysis indicated that GLUT1 and GLUT4 had high predictive value for poor prognosis of patients with hypothyroidism and cardiac insufficiency. As shown in **Figure 4**.

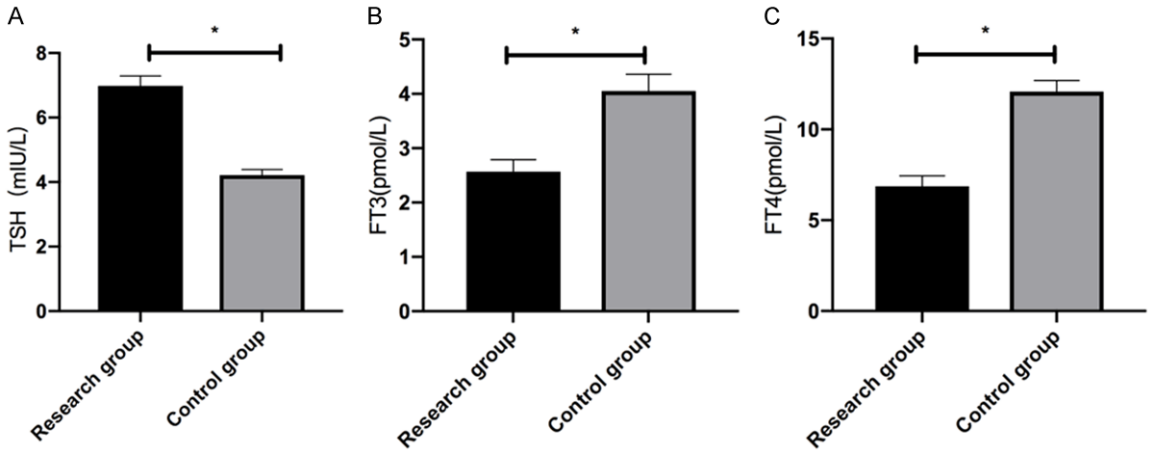

Figure 2. Expression of thyroid-related hormones in two groups of patients. A: Comparison of TSH expression. B: Comparison of FT3 expression. C: Comparison of FT4 expression. *denotes P<0.05. FT3: Free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone.

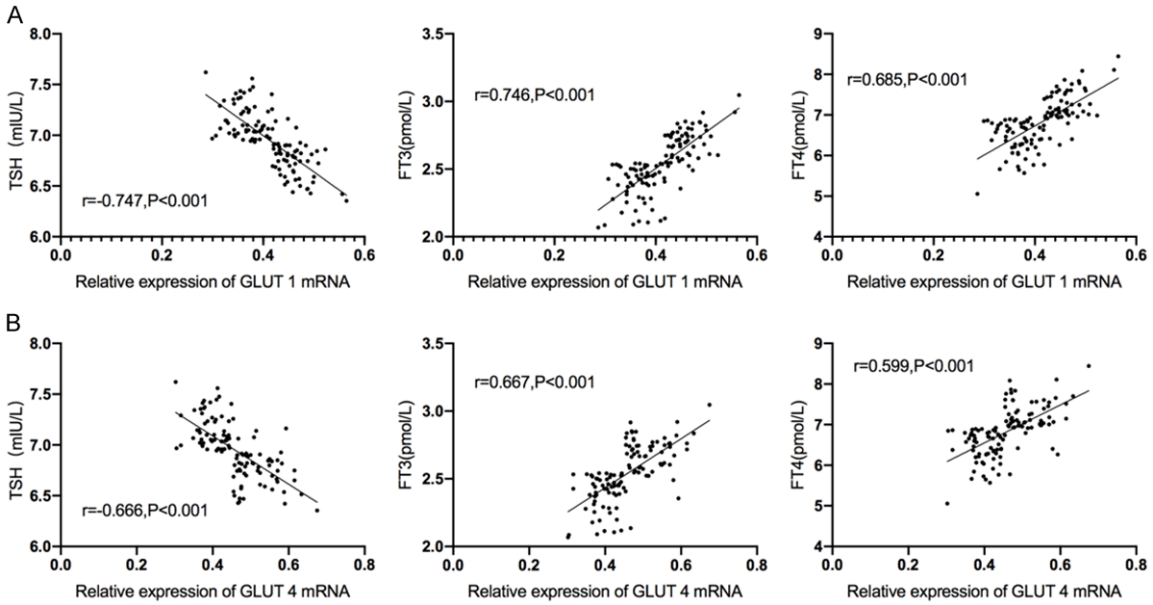

Figure 3. Correlation analysis of GLUT1 and GLUT4 with thyroid-related hormone. A: Comparison of the correlation of GLUT1 with TSH, FT3 and FT4. B: Comparison of the correlation of GLUT4 with TSH, FT3 and FT4.

Univariate analysis of poor prognosis in patients with hypothyroidism complicated with cardiac insufficiency

Univariate analysis of patients in MACE group and non-MACE group exhibited no significant difference in gender, age, drinking, etc. (P> 0.05), but significant difference in GLUT1, GLUT4, hypertension and diabetes (P<0.05). More details were shown in **Table 3**.

Multivariate analysis of poor prognosis in patients with hypothyroidism complicated with cardiac insufficiency

GLUT1, GLUT4 and diabetes were included in the analysis, whether MACE occurred or not was taken as the dependent variable, and Logistic regression model was adopted. The results showed that GLUT1, GLUT4 and diabetes were independent risk factors for

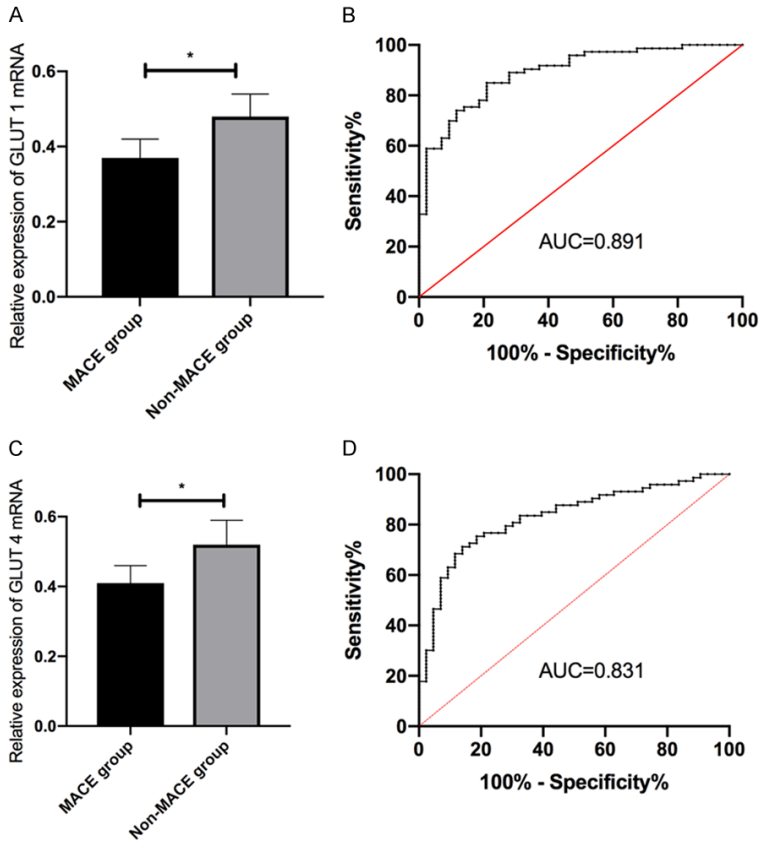

Figure 4. Predictive value of GLUT1 and GLUT4 for poor prognosis of patients. A: Low expression of GLUT1 in serum of patients with poor prognosis. B: Predictive value of GLUT1 for poor prognosis of patients with coronary heart disease. C: Low expression of GLUT4 in serum of patients with poor prognosis. D: Predictive value of GLUT4 for poor prognosis of patients with coronary heart disease. *denotes P<0.05.

Table 3. Univariate analysis of poor prognosis in patients with hypothyroidism complicated with cardiac insufficiency

Factors	MACE group (n=43)	non-MACE group (n=73)	t/χ^2	P
Gender [n, (%)]			0.154	0.695
Male	24 (55.81)	38 (52.05)		
Female	19 (44.19)	35 (47.95)		
Age (years)	68.11±5.32	68.52±5.37	0.576	0.565
BMI (kg/m^2)	23.22±2.15	23.17±2.26	0.170	0.865
Drinking				
Present	26 (60.47)	43 (58.90)		
Absent	17 (39.53)	30 (41.10)		
Hypertension			2.916	0.088
With	31(72.09)	41 (56.16)		
Without	12 (27.91)	32 (43.84)		
Diabetes			7.672	0.006
With	36 (83.72)	43 (58.90)		
Without	7 (16.28)	30 (41.10)		

poor prognosis in patients with hypothyroidism complicated with cardiac insufficiency (**Table 4**).

Discussion

As the largest endocrine gland of human body, thyroid hormone secreted by it is an important substance to regulate human growth and development, and produces a marked effect on regulating metabolism of various substances in human body [15, 16]. Thyroid hormone, as a vital neurohumoral endocrine hormone, can promote myocardial protein synthesis, enhance myocardial contractility, improve the responsiveness of heart and blood vessels to adrenaline, and reduce the resistance of peripheral blood vessels [17]. Therefore, some studies [18] believe that hypothyroidism can increase the risk of cardiovascular diseases.

In our study, we found that serum GLUT1 and GLUT4 in patients with hypothyroidism complicated with cardiac insufficiency were remarkably lower than those in cardiac insufficiency patients with normal thyroid function. Energy metabolism is crucial in the normal operation of heart function. When heart function is impaired, so is metabolic function [19]. However, for patients with cardiac insufficiency complicated with hypothyroidism, their metabolic function will appear more serious obstacles [20]. GLUT1 and GLUT4, as glucose transporters, mainly assist the transmembrane transport of glucose molecules inside and outside cells, thus supplying energy to the heart [21]. In the

Table 4. Multivariate analysis of poor prognosis in patients with coronary heart disease

Factor	β	S.E	Wald	OR	95% CI	P
GLUT1	0.463	0.215	4.655	1.627	1.033-2.409	0.011
GLUT4	0.904	0.377	6.064	2.538	1.742-3.605	<0.001
Diabetes	1.076	0.473	5.262	2.987	1.171-7.516	<0.001

past, there were relatively few studies on GLUT1 and GLUT4 in patients with hypothyroidism heart failure. In our study, we also found that the levels of GLUT1, GLUT4 and thyroid hormones were significantly correlated, suggesting that GLUT1 and GLUT4 might be important in the pathogenesis of hypothyroidism heart failure. Previous studies [22, 23] have revealed that there is obvious cardiac hypertrophy in the heart with GLUT4 deficiency, and the mechanism leading to GLUT4 deficiency is very complex, which may be related to hypertension or oxidative stress dysfunction.

Then we analyzed the prognostic value of GLUT1 and GLUT4 in patients with hypothyroidism and cardiac insufficiency. The results showed that patients with MACE had evidently lower GLUT1 and GLUT4 expression levels than patients without, and GLUT1 and GLUT4 had higher predictive value for poor prognosis. GLUT4 is abundantly expressed in normal myocardium [24]. In the past, some studies [25] pointed out that for patients with hypothyroidism, GLUT1 and GLUT4 can influence the heart function by regulating the insulin level in the heart, which is also consistent with our research. Finally, in order to further analyze the correlation of GLUT1 and GLUT4 with the prognosis of patients with hypothyroidism complicated with cardiac insufficiency, we first made a univariate analysis, and found that besides the differences in GLUT1 and GLUT4 expression levels, there were significant differences in hypertension and diabetes among patients with different prognosis. Subsequent multivariate analysis further proved that GLUT1, GLUT4 and diabetes were independent risk factors for poor prognosis of patients with hypothyroidism and cardiac insufficiency. GLUT1 and GLUT4 were generally considered to play a role in regulating insulin and glucose transport in the past [26], so the two expression in diabetic patients may be more obvious than that in patients without diabetes, which may be one of the reasons leading to diabetes becoming a risk factor for poor prognosis of patients. In the past, some studies [27] pointed out that diabetes alters the expression and transport of insulin sensitivity GLUT4 in the heart, which was consistent with some of our conjectures.

To sum up, GLUT1 and GLUT4 expression levels were significantly decreased in serum of patients with hypothyroidism complicated with cardiac insufficiency. Both of them have high predictive value for poor prognosis of patients, and are independent risk factors for poor prognosis of patients. However, there are some shortcomings in this study. For example, we do not know the specific mechanism between GLUT1, GLUT4 and hypothyroidism, which needs further basic experiments to explore.

Disclosure of conflict of interest

None.

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