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Correlation analysis of IGF-1, ZAG, nesfatin-1, HbA_{1c} levels, and type 2 diabetes mellitus complicated with hypothyroidism

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Abstract

To analyze the correlation between IGF-1, ZAG, nesfatin-1, HbA1c levels, and type 2 diabetes mellitus (T2DM) complicated with hypothyroidism.

Fifty-five patients with type-2 diabetes who were admitted to our hospital from August 2018 to February 2020 were selected as the control group, and 55 patients with type 2 diabetes combined with hypothyroidism who were admitted to the hospital at the same period were selected as the combined group, and 56 patients who came to our hospital for physical examination at the same period were selected as the healthy group. The general clinical data and relevant laboratory indexes of all patients in the three groups were collected and statistically analyzed. Besides, the correlation between IGF-1, ZAG, nesfatin-1, HbA1c levels, and T2DM complicated with hypothyroidism was analyzed.

Levels of FPG, FINS, TC, TG, LDL, 2hPBG, TPOAb, TgAb, and HOMA-IR in the diabetes group and combined group were all significantly higher than those in the healthy group, while HDL and T4 levels in the diabetes group and combined group were lower than those in the healthy group ($P < .05$). The levels of FPG, FINS, TC, TG, LDL, 2hPBG, TPOAb, and TgAb in the combined group were significantly higher than those in the diabetes group ($P < .05$), and the levels of HDL and T4 were lower than those in the diabetes group. In addition, the IGF-1 level was positively correlated with ZAG, nesfatin-1, and HbA1c levels in the combined group ($P < .05$), and IGF-1 (OR: 0.964, 95% CI: 0.943–0.983, $P = .001$), ZAG (OR: 1.298, 95% CI: 1.121–1.401, $P = .005$), nesfatin-1 (OR: 0.876, 95% CI: 0.751–0.901, $P = .002$), and HbA1c (OR: 1.321, 95% CI: 1.121–1.401, $P = .012$) were independent risk factors for T2DM complicated with hypothyroidism.

Regular detection of IGF-1, ZAG, nesfatin-1, and HbA1c levels are of great value for the diagnosis and treatment of patients with T2DM complicated with hypothyroidism.

Abbreviations: 2hPBG = 2 hours postprandial blood glucose, ADA = American Diabetes Association, BMI = body mass index, FINS = fasting insulin, FSG = fasting serum glucose, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, IGF-1 = serum insulin-like growth factor 1, LDL = low-density lipoprotein, LSD = least-significant difference, SD = standard deviation, T2DM = type 2 diabetes mellitus, T3 = triiodothyronine, T4 = thyroxine, TC = total cholesterol, TG = triglyceride, TgAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody, WHO = World Health Organization, ZAG = zinc-alpha2-glycoprotein.

Keywords: glycosylated hemoglobin, hypothyroidism, insulin-like growth factor 1, nesfatin-1, type 2 diabetes mellitus, zinc-alpha2-glycoprotein

1. Introduction

In recent years, the incidence of diabetes mellitus in the world has been increasing year by year, especially in China, where the prevalence rate is as high as 11.6%.[1] In addition, incidence of various complications of diabetes mellitus has also increased, such as diabetic macrovascular disease, diabetic peripheral

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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vascular disease, diabetes mellitus complicated with hypothyroidism, and so on. Diabetes mellitus and thyroid diseases are common diseases among the endocrine disorders. Many studies have confirmed that diabetes mellitus is closely related to thyroid diseases. Diabetes patients are in a state of high blood glucose for a long time, which can easily lead to catabolic disorders, resulting in abnormal secretion of thyroid hormones, and then affects thyroid function.[2–4] Therefore, the risk of thyroid disease in diabetic patients is several times higher than that in normal population. According to relevant epidemiological studies, the incidence of type 2 diabetes mellitus (T2MD) complicated with thyroid dysfunction is about 12.5%, of which T2DM complicated with hypothyroidism is the main type, while the incidence of thyroid dysfunction in non-diabetic population is about 5.9%.[2]

T2DM and hypothyroidism can interact with each other. Hypothyroidism not only exacerbates the duration of diabetes, but also promotes changes in the blood glucose of diabetic patients, thereby affecting the overall blood glucose control effect. In addition, the early hypothyroidism will affect various tissues and organs in the body. The American Diabetes Association (ADA) recommends that adult patients with T2DM should undergo thyroid function examination and thyroid color Doppler ultrasound examination every 5 years for at least 35 years.[5] However, the clinical characteristics of T2DM complicated with hypothyroidism are not obvious, which is difficult to judge only by clinical symptoms. Thus, the discovery of laboratory indexes of clinical significance is very important for the early diagnosis of diseases

Studies have indicated that abnormal lipid metabolism, high blood glucose were risk factors for T2DM complicated with hypothyroidism. Insulin-like growth factor 1 (IGF-1), zinc-alpha2-glycoprotein (ZAG), nesfatin-1, and glycosylated hemoglobin (HbA1c) play an important role in regulating glucose metabolism and lipid metabolism, and their levels may be related to the function of pancreas and thyroid. Research by Yan et al[6] suggested that the regular detection of serum IGF-1 level in patients with T2DM complicated with hypothyroidism was particularly important for clinical treatment. Research by Song et al[7] suggested that ZAG may be involved in the pathogenesis of T2DM complicated with hyperuricemia, but no relevant reports have been reported in patients with T2DM complicated with hypothyroidism. Research by Cai et al[8] suggested that nesfatin-1 may delay the occurrence and development of chronic complications in patients with T2DM. HbA1c is not affected by a single blood glucose fluctuation, and has become an effective standard for clinical monitoring of blood glucose control in diabetic patients, which can effectively reflect the average level of blood glucose control in 2 to 3 months.[9] However, research by Zhang et al[10] suggested that HbA1c alone could not be used as the criterion for determining the glucose metabolism level of patients with T2DM complicated with subclinical hypothyroidism. Based on these studies, we speculated that IGF-1, ZAG, nesfatin-1, and HbA1c may be associated with the occurrence of T2DM complicated with hypothyroidism. Herein, our study aimed to explore the correlation between IGF-1, ZAG, nesfatin-1, HbA1c levels and T2DM complicated with hypothyroidism, so as to provide potential targets for early diagnosis and early treatment of patients with T2DM complicated with hypothyroidism.

2. Materials and methods

2.1. Subjects

Fifty-five patients with type-2 diabetes who were admitted to our hospital from August 2018 to February 2020 were selected as the control group, and 55 patients with type 2 diabetes combined with hypothyroidism who were admitted to the hospital at the same period were selected as the combined group, and 56 patients who came to our hospital for physical examination at the same period were selected as the healthy group. This study was approved by the Ethics Committee of Affiliated Hospital of Jilin Medical University (approval number: JLMU-2018–07, approval date: July 4, 2018), and the informed consent forms were obtained from all patients. This study was conducted in accordance with the Helsinki Declaration of the World Medical Association.

The inclusion and exclusion criteria of the subjects were as follows. The inclusion criteria:

1. T2DM according to Diabetes Diagnosis and Classification Criteria by World Health Organization (WHO) in 1999[11];
2. hypothyroidism referred to the "Chinese Guidelines for the Diagnosis and Treatment of Thyroid Diseases"[12];
3. complete clinical data;
4. normal liver and kidney function;
5. no cardiovascular, cerebrovascular, or peripheral vascular disease;
6. the informed consent forms were obtained from all patients or their families.

Exclusion criteria:

1. elevated body temperature caused by infection;
2. acute and chronic respiratory diseases;
3. history of cardiac surgery;
4. malignant tumors, pregnancy, and lactation;
5. acute metabolic disorders such as diabetic ketoacidosis in the past 1 month;
6. extrapyramidal diseases;
7. patients who had taken drugs affecting thyroid function such as domperidone and phenytoin in the last 3 months.

2.2. Data collection

General data of all patients in the diabetes group, combined group and healthy group were collected, including gender, age, duration of diabetes, body mass index (BMI), smoking history, history of hypertension, history of coronary heart disease, and use of biguanides, statins, and insulin.

For each patient in the three groups, 3 to 5 mL elbow venous blood with fasting for more than 12 h was collected. After centrifugation, the serum was stored in a −30°C refrigerator for later use. The levels of fasting serum glucose (FSG), fasting insulin (FINS), fasting C-peptide, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), 2 h postprandial blood glucose (2hPBG), triiodothyronine (T3), thyroxine (T4), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), HbA1c, IGF-1, ZAG, nesfatin-1 were detected. Among them, FPG and 2hPBG were determined by glucose oxidase method using automatic biochemical analyzer; TgAb, TPOAb, T4, T3, IGF-1, fasting C-peptide, FINS, IGF-1 were detected by chemiluminescence method; LDL, HDL, TC and TG were measured by automatic biochemical

analyzer; HbA1c was determined by latex-enhanced immunosuppression; nesfatin-1 and ZAG were detected by enzyme-linked immunosorbent assay (ELISA). Nesfatin-1 kit was purchased from TSZ, United States, and the ZAG kit was purchased from Ray Biotech, United States, and the operation steps should be strictly in accordance with the instructions.

1. The reagents were recovered to room temperature of 20 to 23°C and mixed thoroughly.
2. The ELISA plate was taken out from the sealed tin foil bag. The A6 was set as a blank well, and 100 uL sample diluent was added. The A1 to A5 were set as standard wells; 50 uL of standard sample was added to each row of the wells, and 50 uL of sample solution (diluted with sample diluent) was added to each of the sample well.
3. The orifice plate was sealed with a sealing film and placed in a water bath with a constant temperature at 37°C for 30 min. After the reaction, the sealing film was removed; the liquid in the wells was shaken off. Each well was filled with washing solution and cleaned and shaken off for 5 times.
4. Fifty microliters of enzyme-labeled reagent was added to each well except for the blank well, and incubated in the water bath with a constant temperature at 37°C for 30 min.

   This step was repeated once.

5. For each well, 50 uL of developer A was added first and 50 uL of developer B was then added, shaken gently to mix well, and incubated at 37°C for 20 min in the dark room.
6. The plate was taken out, 50 μL of stop solution was added to each well, detection was conducted immediately after the reaction was terminated, and the OD value of each well at 450 nm on the plate reader was recorded.

The homeostasis model assessment of insulin resistance (HOMA-IR) = FPG (mmol/L) × FINS (mU/L)/22.5.[13] The quality control of the above biochemical index determination was carried out by professionals in the laboratory.

2.3. Statistical analysis

All the data collected in this study were analyzed using SPSS 21.0 software. Normally distributed measurement data were expressed as mean ± standard deviation (SD). One-way analysis of variance was used for the overall comparison of the data among three groups, and least-significant difference (LSD) was used for further pairwise comparison of the data between groups and within the group. Non-normally distributed measurement data were expressed as median (interquartile range) and rank-sum test was used for comparison between two groups. The categorical data was expressed as rate (%), and the chi-square test was used for comparison between groups. The correlation analysis was performed by Pearson correlation analysis or Spearman rank correlation analysis. The influencing factors of T2DM complicated with hypothyroidism were analyzed by non-conditional logistic regression analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. Comparison of general data among three groups

There were no significant differences in gender, age, and smoking history among three groups ($P > .05$). The duration of diabetes, BMI, number of cases with coronary heart disease, and number of cases taking biguanide in the combined group were significantly higher than those in the diabetes group ($P < .05$). There were no significant differences in number of cases with hypertension, number of cases taking statin, and number of cases using insulin between the combined group and the diabetes group ($P > .05$), as shown in Table 1.

3.2. Comparison of laboratory indexes among three groups

FPG, FINS, TC, TG, LDC, 2hPBG, TPOAb, TgAb, and HOMA-IR in the combined group were all higher than those in the diabetes group and the healthy group, while HDL and T4 in the combined group were significantly lower than those in the diabetes group and the healthy group ($P < .05$). FPG, FINS, TC, TG, LDL, 2hPBG, TPOAb, TgAb, and HOMA-IR in the diabetes group were significantly higher than those in the healthy group, HDL and T4 was significantly lower than that in the healthy group ($P < .05$). There were no significant differences in fasting C-peptide and T3 levels among the three groups ($P > .05$), as shown in Table 2.

3.3. Comparison of IGF-1, ZAG, nesfatin-1, and HbA1c levels among three groups

The levels of ZAG and HbA1c in the combined group were significantly higher than those in the diabetes group and the healthy group, and the levels of IGF-1 and nesfatin-1 were significantly lower than those in the diabetes group and the

Table 1

Comparison of general data among three groups.

General data	Diabetes group (n = 55)	Combined group (n = 55)	Healthy group (n = 56)	χ^2/Z	P
Number of cases (male/female) (n (%))	27 (49.09%)/28 (50.91%)	26 (47.27%)/29 (52.73%)	28 (50%)/28 (50%)	0.085	.958
Age (years)	48.2 ± 6.5	48.3 ± 6.6	48.2 ± 6.4	0.013	.987
Duration of diabetes (years)	10.2 ± 1.8	13.8 ± 2.1*	0	−9.653	<.001
BMI (kg/m^2)	27.21 ± 0.51	29.23 ± 0.62*	24.19 ± 0.49	1213.601	<.001
Number of cases with smoking history (n (%))	25 (45.45%)	18 (32.73%)	16 (29.09%)	3.737	.154
Number of cases with hypertension (n (%))	36 (65.45%)	34 (61.82%)	0	0.157	.692
Number of cases with coronary heart disease (n (%))	35 (63.64%)	45 (81.82%)*	0	4.583	.032
Number of cases taking biguanides (n (%))	20 (36.36%)	39 (70.91%)*	0	13.197	.000
Number of cases taking statins (n (%))	28 (50.91%)	23 (41.82%)	0	0.914	.339
Number of cases using insulin (n (%))	24 (43.64%)	40 (72.73%)	0	9.565	.001

* Compared with diabetes group, $P < .05$.

Table 2

Comparison of laboratory indexes among three groups.

Laboratory index	Diabetes group (n = 55)	Combined group (n = 55)	Healthy group (n = 56)	χ^2/Z	P
FPG (mmol/L)	8.86 ± 0.98†	9.87 ± 1.03*,†	6.63 ± 0.63	19.175	<.001
FINS (mU/L)	8.27 ± 0.76 †	9.51 ± 0.54*,†	6.62 ± 1.12	16.155	<.001
Fasting C-peptide (μg/L)	2.90 ± 0.43	2.81 ± 0.32	2.78 ± 0.28	1.774	.173
TC (mmol/L)	5.12 ± 0.93 †	9.73 ± 2.18*,†	5.01 ± 0.23	21.131	<.001
TG (mmol/L)	2.19 ± 0.23 †	4.12 ± 0.98*,†	0.83 ± 0.12	44.907	<.001
LDL (mmol/L)	3.19 ± 0.98 †	1.89 ± 0.23*,†	2.78 ± 0.31	68.613	<.001
HDL (mmol/L)	1.23 ± 0.24 †	1.93 ± 0.21*,†	1.19 ± 0.13	42.663	<.001
2hPBG [M (P_{25}, P_{75})] (ng/mL)	6.12 (3.02, 8.62)†	6.32 (3.31, 9.65)*,†	5.02 (3.9, 7.12)	9.876	<.001
T3 (μg/L)	1.50 ± 0.31	1.42 ± 0.23	1.40 ± 0.21	2.411	.093
T4 (μg/L)	85.37 ± 9.83 †	75.38 ± 7.62*,†	86.73 ± 8.73	27.566	<.001
TPOAb [M (P_{25}, P_{75})] (U/L)	5.2 (5.11, 7.28)†	6.33 (5.21, 7.63)*,†	4.62 (1.12, 8.86)	17.632	<.001
TgAb [M (P_{25}, P_{75})] (U/L)	36.07 (10.04, 76.09) †	200.23 (138.73, 399.73)*,†	8.87 (1.23, 58.76)	43.982	<.001
HOMA-IR [M (P_{25}, P_{75})]	4.73 (2.48, 8.92) †	7.01 (5.41, 9.98)*,†	1.03 (1.07, 2.45)	15.932	<.001

2hPBG = 2 hours postprandial blood glucose, FINS = fasting insulin, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein, T3 = triiodothyronine, T4 = thyroxine, TC = total cholesterol, TG = triglyceride, TgAb = thyroglobulin antibody, TPOAb = thyroid peroxidase antibody.

* Compared with diabetes group, $P < .05$.

† Compared with healthy group, $P < .05$.

Table 3

Comparison of IGF-1, ZAG, nesfatin-1 and HbA1c levels among three groups.

Laboratory index	Diabetes group (n = 55)	Combined group (n = 55)	Healthy group (n = 56)	Z	P
IGF-1 (μg/L)	193.73 ± 22.98 †	140.27 ± 12.27*,†	232.34 ± 9.63	462.726	<.001
ZAG (mg/L)	58.89 ± 4.17 †	85.38 ± 56.73*,†	38.73 ± 3.29	28.220	<.001
Nesfatin-1 (μg/L)	1.31 ± 0.51 †	1.00 ± 0.21*,†	1.57 ± 0.70	16.973	<.001
HbA1c (%)	8.01 ± 0.23 †	11.63 ± 0.46*,†	4.32 ± 0.32	6068.614	<.001

HbA1c = glycosylated hemoglobin, IGF-1 = serum insulin-like growth factor 1, ZAG = zinc-alpha2-glycoprotein.

* Compared with diabetes group, $P < .05$.

† Compared with healthy group, $P < .05$.

healthy group ($P < .05$). The levels of ZAG and HbA1c in the diabetes group were significantly higher than those in the healthy group, and the levels of IGF-1 and nesfatin-1 in the diabetes group were significantly lower than those in the healthy group ($P < .05$), as shown in Table 3.

3.4. Correlation analysis between IGF-1, ZAG, nesfatin-1, HbA1c levels, and type-2 diabetes with hypothyroidism

The spearman rank correlation analysis showed that the IGF-1, ZAG, nesfatin-1, and HbA1c levels were positively correlated with type 2 diabetes combined with hypothyroidism ($P < .05$, Table 4).

3.5. IGF-1, ZAG, nesfatin-1, and HbA1c were independent risk factors for the occurrence of T2DM complicated with hypothyroidism

With whether T2DM was complicated with hypothyroidism as dependent variables and with gender, the duration of diabetes, BMI, FPG, FINS, fasting C-peptide, TC, TG, LDL, HDL, 2hPBG, T3, T4, TPOAb, TgAb, HbA1c, IGF-1, ZAG, and nesfatin-1 as independent variables, the non-conditional logistic regression analysis was conducted to study the risk factors of T2DM complicated with hypothyroidism. The results showed that the independent risk factors for T2DM with hypothyroidism were IGF-1 (OR: 0.964, 95% CI: 0.943–0.983, $P = .001$), ZAG (OR: 1.298, 95% CI: 1.121–1.401, $P = .005$), nesfatin-1 (OR: 0.876, 95% CI: 0.751–0.901, $P = .002$), HbA1c (OR: 1.321, 95% CI: 1.121–1.401, $P = .012$), as shown in Table 5.

Table 4

Correlation analysis between IGF-1 level and ZAG, nesfatin-1 and HbA1c levels in the combined group.

Laboratory index	P	r
ZAG	.013	0.559
Nesfatin-1	.029	0.143
HbA1c	.031	0.081

HbA1c = glycosylated hemoglobin, ZAG = zinc-alpha2-glycoprotein.

4. Discussion

In patients with T2DM complicated with hypothyroidism, there are two endocrine and metabolic system imbalances in the body, which promote abnormal hypothalamus secretion. Research by Guo et al suggested that the hypoglycemic treatment increased

Table 5

The risk factors for T2DM complicated with hypothyroidism were analyzed by non-conditional logistic regression analysis.

Risk factor	OR	95% CI	P
IGF-1	0.964	(0.943, 0.983)	.001
HbA1c	1.321	(1.241.1.453)	.012
ZAG	1.298	(1.121, 1.401)	.005
Nesfatin-1	0.876	(0.751, 0.901)	.002

HbA1c = glycosylated hemoglobin, IGF-1 = serum insulin-like growth factor 1, ZAG = zinc-alpha2-glycoprotein.

nesstatin-1 level in patients with T2DM, improved insulin resistance, and promoted the functional recovery of pancreatic β cells.[14] Research by Pei et al suggested that when the body of diabetic patients was in a state of hyperglycemia, the energy utilization of thyroid follicular cells will be impaired, causing iodine dysfunction, so the hyperglycemia state of diabetes mellitus can directly affect thyroid function.[15] Therefore, hypothyroidism and diabetes mellitus can interact with each other, increasing the risk of fat, protein, glucose metabolism disorders and cardiovascular disease, which is not conducive to the prognosis of patients. Thus, study on the risk factors for T2DM complicated with hypothyroidism is of great significance for providing new targets for the diagnosis and treatment of disease.

The results of this study showed that the duration of diabetes, BMI, number of cases with coronary heart disease and the number of cases taking biguanides in the combined group were significantly higher than those in the diabetes group. Levels of FPG, FINS, TC, TG, LDL, 2hPBG, TPOAb, TgAb, and HOMA-IR in the diabetes group and combined group were all significantly higher than those in the healthy group, while HDL and T4 levels were lower than those in the healthy group. The levels of FPG, FINS, TC, TG, LDL, TG, 2hPBG, TPOAb, and TgAb in the combined group were significantly higher than those in the diabetes group, and the levels of HDL and T4 were lower than those in the diabetes group. There were no significant differences in fasting C-peptide and T3 levels among the three groups. Research conducted by Yang Hua et al[16] also confirmed that combination of subclinical hypothyroidism in patients with type 2 diabetes can lead to disorders of lipid metabolism in their bodies and increase their serum TC, TG, and LDL levels, and the serum HDL levels were decreased, leading to the combination of excessive lipoproteins and glycoproteins in the blood, blocking the blood vessels, thereby causing vascular complications of diabetes. Moreover, the level of IGF-1 was positively correlated with the levels of ZAG, nesfatin-1, and HbA1c in the combined group, and IGF-1, ZAG, nesfatin-1, HbA1c were independent risk factors for T2DM complicated with hypothyroidism. Therefore, we concluded that IGF-1, ZAG, nesfatin-1, and HbA1c may be involved in the pathogenesis of T2DM complicated with hypothyroidism, and regular detection of IGF-1, ZAG, nesfatin-1, and HbA1c levels is particularly important for the early diagnosis and treatment of patients with T2DM complicated with hypothyroidism.

IGF-1 is a cell regulatory factor, which is mainly synthesized by the liver and is regulated by growth hormone, insulin and thyroid hormone.[17] Research by Mancuso et al[9] suggested that IGF-1 had 48% amino acid sequence homology with insulin, so it had a hypoglycemic effect similar to insulin. IGF-1 can also promote the differentiation and proliferation of thyroid cells, directly or indirectly stimulating thyroid function.[18] Nesfatin-1 is a neuropeptide consisting of 82 amino acids, and its precursor is nesfatin/nucleobindin-2 (NUCB2). Insulin and NUCB2 are co-expressed in human and mouse pancreatic islet β-cells, which affect glucose metabolism in the body.[19] Hyperglycemia promotes the secretion of insulin and nesfatin-l by normal mouse pancreatic islet β-cells.[20] When the secretory function of pancreatic islet β-cells decreases, the level of nesfatin-l will decrease. In addition, nesfatin-1 inhibits food intake by promoting fat oxidation, increasing satiety, and affects fat metabolism by stimulating skeletal muscle.[21] Study by Cai et al suggested that nesfatin-1, thyroid hormone and TSH all affected lipid metabolism and food intake, and the level of nesstatin-1 decreased after hypothyroidism.[22] The decrease of nesfatin-1 in patients with T2DM complicated with hypothyroidism may be due to the fact that hypothyroidism may aggravate insulin resistance in T2DM, accelerate the apoptosis of pancreatic β cells, and further reduce nesfatin-1 level.[6] ZAG is a new type of adipokine, one of the members of the histocompatibility complex (MHC) class I family, it is composed of 276 amino acids and has a decomposing effect on fat, reducing fat mass and body weight. The mechanism is that ZAG activates the β_3 adrenergic receptors on the cell membrane and increases the content of cyclic adenosine monophosphate (cAMP) in adipocytes, thereby decomposing fat.[23] The study of Xie et al[24]suggested that the serum ZAG level of T2DM patients was highly expressed, and its level was related to HbA1c and insulin resistance.[25] It can be deduced from the results of our study that IGF-1, ZAG, nesfatin-1, and HbA1c were also risk factors for the type-2 diabetes. However, the underlying mechanisms needed to be further clarified. In clinical practice, physicians should carefully monitor the changes of IGF-1, ZAG, nesfatin-1 and HbA1c levels in patients with type 2 diabetes.

There were some limitations in our study as follows:

1. considering this was a single-center respective study, our sample size was limited. A prospective study with a larger sample size will be conducted for further investigation.
2. The mechanism of abnormal levels of IGF-1, ZAG, nesfatin-1, and HbA1 leading to the occurrence of T2DM complicated with hypothyroidism still needs further research.

In summary, the results of this study showed that in patients with T2DM complicated with hypothyroidism, the serum IGF-1 and nesfatin-1 levels were increased while the levels of ZAG and HbA1c were decreased, and IGF-1, nesfatin-1, ZAG, and HbA1c were independent risk factors for the occurrence of T2DM complicated with hypothyroidism. Therefore, it is necessary to pay close attention to the levels of IGF-1, nesfatin-1, ZAG, and HbA1c in patients with T2DM complicated with hypothyroidism in clinical practice, and the thyroid color ultrasound and thyroid function examination should be performed regularly on patients. With the development of molecular biology technology, especially the implementation and completion of the Human Genome Project, IGF-1, nesfatin-1, ZAG, and HbA1c are expected to be new targets for the treatment of T2DM complicated with hypothyroidism.

Author contributions

SH, YH, FJ, and YL collected and analyzed the data, drafted the initial manuscript and reviewed the manuscript. SH and YH conceptualized and designed the study, and supervised the conduct of the study. SH critically revised the manuscript. All authors gave their final approval for the version to be published.
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Writing – original draft: Shuangling He, Ying He, Fenghua Jin.
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