ORIGINAL ARTICLE

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Evaluation of Fibroblast Growth Factor Binding Protein 3 Level in Male Hyperthyroidism Iraqi Patients with and without Diabetes Mellitus

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ABSTRACT: *Background: FGFBP-3 plays a role in metabolic syndrome in mice by regulating fat and glucose metabolism. The FGFBP3 protein is secreted by adipose tissue and also functions in the central nervous system, similar to thyroid hormone. Thyroid dysfunction is the second most common endocrine disorder after diabetes mellitus (DM).* **Objective:** *This study evaluates FGFBP-3 levels in patients with hyperthyroidism, both with and without DM.* **Methods:** *The study included 90 participants divided into three groups: 30 patients with hyperthyroidism and DM, 30 patients with hyperthyroidism without DM, and 30 healthy individuals as controls. Thyroid hormones (TSH, total T3, and total T4) were measured using the Minividas device. FGFBP-3 levels were estimated by the enzyme-linked immunosorbent assay (ELISA) sandwich method. Additionally, lipid profile parameters (total cholesterol, triglycerides, HDL, LDL, and VLDL) were determined using enzymatic colorimetric methods.* **Results:** *The study found that TSH and HDL levels were significantly lower in both hyperthyroidism groups compared to controls. Conversely, FGFBP3, HbA1c, free T4, free T3, total cholesterol, triglycerides, LDL, and VLDL levels were significantly elevated in both hyperthyroidism groups relative to the healthy group. There were no significant differences in lipid profile levels between the hyperthyroidism with DM group and the hyperthyroidism without DM group. High serum FGFBP3 levels were observed in hyperthyroid patients regardless of DM status, whereas the control group exhibited lower FGFBP3 levels. Receiver operating characteristic (ROC) analysis indicated that FGFBP3 could serve as a biomarker for monitoring hyperthyroidism with and without DM.* **Conclusions:** *This study demonstrates a strong association between FGFBP3 levels and hyperthyroidism, irrespective of the presence of diabetes mellitus.*

KEYWORDS: *Fibroblast growth factor binding protein 3; Diabetes mellitus; Hyperthyroidism; Thyroid hormones; Dyslipidemia*

INTRODUCTION

Thyroid disease affects the thyroid gland, which is responsible for producing hormones that control metabolism [1]. The most important hormones generated by the thyroid gland are free triiodothyronine (FT3) and free thyroxine (FT4), which are essential for regulating growth, development, and metabolism [2]. Thyroid dysfunction (TD) is invariably caused by an imbalance between hypo- and hyperactive thyroid gland activity, which increases or decreases the thyroid's release of hormones [3]. Diabetes mellitus (DM) is a group of chronic diseases marked by elevated blood glucose levels caused by either an inability to produce insulin or an inability to use insulin effectively [4]. DM and TD are the two endocrine disorders that are most common in many populations [5]. Some studies consider insulin resistance (IR) to be a major risk factor for the development of the metabolic syndrome [6]. Fibroblast growth factor binding proteins (BP1, 2, and 3) are extracellular matrix-resident chaperones that can bind and release paracrine FGFs from their heparan sulfate (HS) stores [7], [8]. Because they both function as chaperones for heparin-binding, paracrine FGFs and

enhance FGF signaling, the methods of action and certain biological consequences of BP2, a gene missing in mice, and BP3 are comparable with the functions of BP1 [9]. These endocrine FGF3 are released into the bloodstream and regulate glucose metabolism [10]. Altered lipid metabolism was seen in BP3 knockout mice [11]. A metabolic disease-ridden animal model is due to dysregulated lipogenic and gluconeogenic genes [12], [13]. TD and DM are two endocrinopathies that are regularly observed in ordinary practice. Patients with diabetes, type 2 diabetes (T2 and DM) have a significant prevalence of TD [14]–[16]. The primary cause of hyperthyroidism is an overactive thyroid gland that produces an excessive amount of thyroid hormone through synthesis and secretion. The thyroid gland's radioactive iodine uptake is either high or normal in hyperthyroidism [17]. Overt or subclinical manifestations are the two ways that hyperthyroidism presents itself. T4 and T3 (or both of them) are the two thyroid hormones that are raised in the biochemical profile of overt hyperthyroidism and reduced in blood levels of thyroid-stimulating hormone (TSH). Serum levels of T4 and T3 are normal in subclinical hyperthyroidism, but they are noticeably lower in this condition [18]. Regardless of the increased activity of HMG-CoA reductase, total cholesterol and low-density lipoprotein (LDL-C) levels tend to decline in humans with clinical or subclinical hyperthyroidism. This occurs as a result of increased LDL receptor-mediated degradation of LDL particles brought on by heightened LDL receptor gene expression [19].

MATERIALS AND METHODS

This case-control study included (90) male patients at normal weight, divided into three groups: 30 of them were hyperthyroid with T2DM, 30 hyperthyroid patients were without DM, and 30 healthy controls were used for comparison, with their ages ranging between 40 and 60 years. The function of thyroid hormone tests included serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) using immunofluorescence (mini VIDAS-BIOMERIEUX-FRANCE). FGFBP3 was measured by the enzyme-linked immunoassay sandwich method (ELISA BT-Lab, China). Also, the enzymatic colorimetric method was used to determine (total cholesterol, triglyceride, HDL, LDL, and VLDL). The kit made available by (Linear chemicals, Spain).

Statistics Examination

The Prism 9.5.0 was used to carry out the needed data analysis. The independent sample one-way ANOVA was used to compare parameter means between groups; we used the more general descriptive statistics to give a high-level summary of our results. Significant statistics were defined as a P-value<0.001.

RESULTS AND DISCUSSION

The result showed that the thyroid hormones (FT3 and FT4), lipid profiles and HbA1c increased in hyperthyroidism with and without DM compared to the healthy group. Also, results showed that there is a significant increase in FGFBP3 in patients with and without DM when compared with the control group (P<0.001). While a significant decrease was found in thyroid-stimulating hormone (TSH), and high-density lipoprotein (HDL) in the two groups of patients when compared with the control group, as shown in Table 1.

TSH (Thyroid-stimulating hormone), FT3 (free triiodothyronine), FT4 (Free thyroxine), HbA1c (hemoglobin glycated A1c), HDL (high-density lipoprotein), LDL (low-density lipoprotein), VLDL (very low-density lipoprotein) and FGFBP3 (fibroblast growth factor binding protein 3).

The data in our study showed that TSH levels are low, which agrees with [20]. It was found that FT3 and FT4 levels were noticeably higher in individuals with (hyperthyroidism with and without DM) [21]. A previous study by [22] revealed that FT3 and FT4 levels were high when DM was uncontrolled. As shown in our results, TD and dyslipidemia were two conditions that have a close connection with DM [23]. On the other hand, our results showed that there was no significant difference in TD when comparing the hyperthyroidism with DM group to the hyperthyroidism without DM group. There was an important increase in lipid profile and HbA1c when comparing hyperthyroidism with DM and hyperthyroidism without DM with the healthy control group. The study conducted by [24] was in agreement with our findings that blood lipoproteins, including total cholesterol, triglyceride, LDL, and VLDL, were significantly higher in the hyperthyroidism with and without DM groups. In this study, the lipid profile was high in two patient groups compared to the healthy group, except for serum HDL level, which was lower in patients compared to the control group. In a recent investigation, individuals with and without DM had significantly higher levels of all lipid markers except

HDL [25], [26]. There is no data connecting FGFBP3 protein with hyperthyroidism with and without DM. The information that is currently available indicates that this study is the first to examine the connection between FGFBP3 protein concentrations and DM in individuals with hyperthyroidism. This study investigated potential associations between FGFBP3 protein and the condition in people with hyperthyroidism and DM. Patients with DM and hyperthyroidism exhibited increased lipid levels compared to the controls. The DM with hyperthyroidism and DM populations had considerably higher FGFBP3 protein levels than the control group. Alterations in lipid profiles in DM as a result of hyperthyroidism, these modifications impact fat tissue, glucose, and insulin [27]. The gene set comprised of genes such as FGFBP3, CERK, ETV5, E2F8, MAFB, and non-coding RNAs may be used to study and develop novel T2DM treatments in the future [28], [29]. This finding demonstrated that the administration of FGFBP3 with a single injection of this protein could regulate blood glucose level and keep it at the healthy stage for more than 24 hours [30].

Table 1: Distribution of the study parameters among the study groups

| Parameters	Groups	Mean ±SD	Dependent variable	P-value
TSH (uUI/L)	Control	2.60±1.63	Control vs. Hyperthyroidism without DM	<0.001
	Hyperthyroidism with DM	0.04±0.06	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	0.053±0.06	Hyperthyroidism without DM vs. Hyperthyroidism with DM	>0.999
F.T3 (Pg/mL)	Control	2.07±0.31	Control vs. Hyperthyroidism without DM	<0.001
	Hyperthyroidism with DM	4.31±0.99	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	4.26±0.89	Hyperthyroidism without DM vs. Hyperthyroidism with DM	>0.923
F.T4 (ng/mL)	Control	2.07±0.31	Control vs. Hyperthyroidism without DM	<0.001
	Hyperthyroidism with DM	3.86±0.78	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	3.16±0.64	Hyperthyroidism without DM vs. Hyperthyroidism with DM	>0.971
HbA1c %	Control	4.60±0.24	Control vs. Hyperthyroidism without DM	>0.998
	Hyperthyroidism with DM	8.05±1.40	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	5.43±0.46	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001
TC (mg/dl)	Control	146.5±27.22	Control vs. Hyperthyroidism without DM	<0.001
	Hyperthyroidism with DM	252±50.28	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	190.5±40.18	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001
TG (mg/dl)	Control	109.22±7.80	Control vs. Hyperthyroidism without DM	<0.001
	Hyperthyroidism with DM	227.1±35.68	Control vs. Hyperthyroidism with DM	<0.001

Table 1. Continued

	Hyperthyroidism without DM	165.5±40.86	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001
	Control	52.13±5.20	Control vs. Hyperthyroidism without DM	<0.001
HDL (mg/dl)	Hyperthyroidism with DM	35.01±1.57	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	40.32±1.66	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001
	Control	90.61±20.32	Control vs. Hyperthyroidism without DM	<0.001
LDL (mg/dl)	Hyperthyroidism with DM	166.4±42.88	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	129.5±36.48	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001
	Control	18.24±1.16	Control vs. Hyperthyroidism without DM	<0.001
VLDL (mg/dl)	Hyperthyroidism with DM	45.43±7.97	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	33.1±14.66	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001
	Control	1.54±0.79	Control vs. Hyperthyroidism without DM	<0.001
FGFBP3 (ng/mL)	Hyperthyroidism with DM	3.58±0.51	Control vs. Hyperthyroidism with DM	<0.001
	Hyperthyroidism without DM	2.33±0.49	Hyperthyroidism without DM vs. Hyperthyroidism with DM	<0.001

(Mean+SD) is the result given, P-values 0.05 are regarded as significant, P-values 0.001 are regarded as highly significant

Correlation

There was evidence of a correlation between the studied parameters, in accordance with the r-person statistical approach. When r approaches 1, there was a straight correlation between the two parameters, when r approaches -1, there was an inverse correlation. There was no correlation between the parameters when r gets closer to zero. In the Figure 1, HbA1c was showed positive correlation between TSH in hyperthyroidism with DM patients, but there was no correlation with hyperthyroidism without DM.
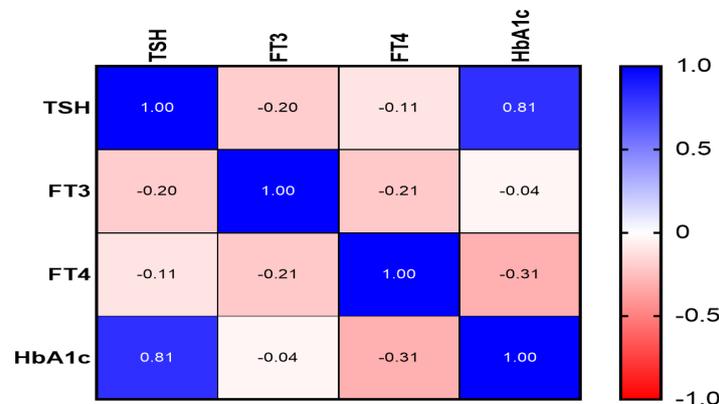
Figure 1. Correlation of HbA1c with TD in hyperthyroidism with DM

The results demonstrated that the FGFBP3 had a positive correlation with lipid profile in hyperthyroidism without DM group, except HDL, which showed no correlation in hyperthyroidism with DM group; a significant negative correlation was shown in FGFBP3 with TG and LDL and a positive correlation with HDL. There was no correlation between FGFBP3 with other parameters in the same group, as shown in Figure 2.

A	B	TC		TG		HDL		LDL		VLDL		FGFBP3	
TC		1.00	1.00	0.58	1.00	-0.34	-0.33	0.58	0.87	0.00	0.97	-0.03	0.53
TG		0.58	1.00	1.00	1.00	-0.96	-0.29	1.00	0.86	-0.58	0.97	-0.63	0.54
HDL		-0.34	-0.33	-0.96	-0.29	1.00	1.00	-0.96	-0.52	-0.96	-0.43	0.71	-0.03
LDL		0.58	0.87	1.00	0.86	-0.96	-0.52	1.00	1.00	0.66	0.96	-0.63	0.78
VLDL		0.00	0.97	-0.58	0.97	-0.96	-0.43	0.66	0.96	1.00	1.00	0.06	0.71
FGFBP3		-0.03	0.53	-0.63	0.54	0.71	-0.03	-0.63	0.78	0.06	0.71	1.00	1.00

Figure 2. Correlation of FGFBP3 with lipid profile in hyperthyroidism with and without DM

Area under the ROC curve for FGFBP3

The area under the ROC curve is a measure of accuracy. A perfect test has an area of 1, while a test with a value of 5 is meaningless. The diagnostic test's accuracy is roughly proven by the normal academic points system. The optimal cutoff value for circulating FGFBP3 to predict hyperthyroidism in patients with and without DM ware found to be >2.78 ng/ml, > 1.47ng/ml respectively. sensitivity: 82.41%, specificity: 100%, and AUC:0.1000) at a 95% confidence interval of (0.996~ 1.000) and P<0.001 in patients' hyperthyroidism without DM and (AUC 0.873, 95% confidence interval: 0.758 ~ 0.988), FGFBP3 was selected as the cutoff limit for the early diagnosis, and it showed a sensitivity of 82.41% and a specificity of 61.11 % at P-value<0.001 at patients' hyperthyroidism with DM, this illustrated in Figure 3. A novel biomarker for identifying and tracking hyperthyroidism with and without DM may be found in serum levels of FGFBP3
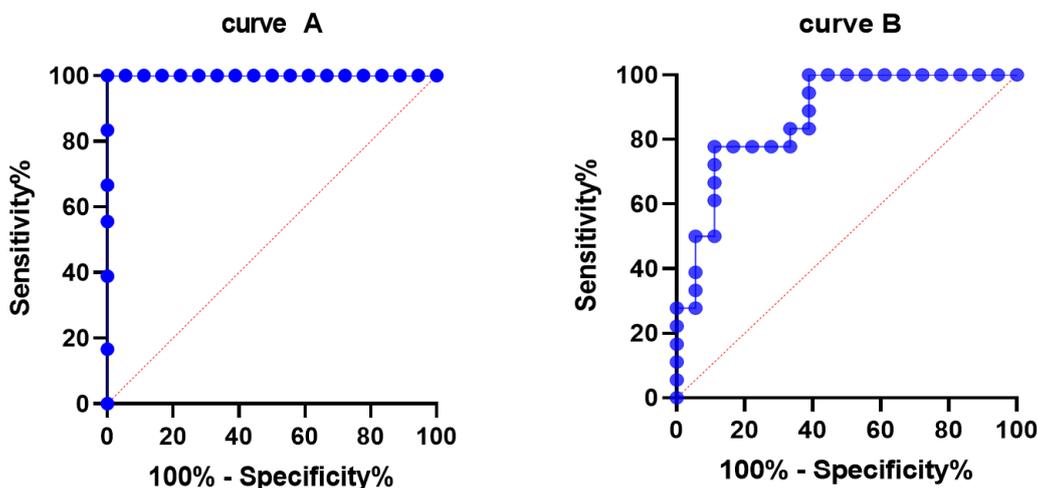

Figure 3. ROC-curve of control-hyperthyroidism with and without DM

CONCLUSION

According to the study's results, FGFBP3 had close ties with hyperthyroidism without DM in healthy subjects. In addition, the blood FGFBP3 level in the DM group is lower than that of the healthy group, compared to hyperthyroidism with and without DM. The ROC statistical results showed that FGFBP3 is predictive of DM in hyperthyroidism patients. In correlation, these findings presented that FGFBP3 is closely related to lipid profile in hyperthyroidism with and without DM. Hence, it

can be concluded that the investigation explores the probable connection between hyperthyroidism and the FGFBP3 protein to identify risk factors for TD with DM.

SUPPLEMENTARY MATERIAL

None.

AUTHOR CONTRIBUTIONS

Lamia H.A. Al-Sultan: Conceptualization, Writing - review, editing, Methodology, and visualization. Lubna A.A. Al-Assaf: Formal statistics examination.

DATA AVAILABILITY STATEMENT

Data are available from the authors upon reasonable request.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

This study has been compiled based on the National Center for Educational Laboratories at Medical City Hospital, Baghdad – Iraq (ID: CSEC/0423/0035). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the author.

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