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Evaluation of Fibroblast Growth Factor Binding Protein3 (FGFBP3) Level in Male Hyperthyroidism Iraqi patients with dyslipidemia

ABSTRACT: ***Background:*** *FGFBP-3 metabolic syndrome in mice showed that FGFBP-3 regulates fat and glucose metabolism. FGFBP3 protein is secreted by adipose tissues. It functions in the central nervous system like thyroid hormone. After Diabetes mellitus (DM), thyroid dysfunction is the second most common endocrine system problem;* ***Objective:*** *This study aimed to evaluate FGFBP-3 levels associated with hyperthyroidism without DM and hyperthyroidism with DM;* ***Methods:*** *The current included (90) patients, divided into three groups (30) of them had hyperthyroidism with DM, (30) hyperthyroidism without DM, and (30) were healthy individuals as a control group for comparison. The Minividas device was used to measure thyroid hormones (TSH, Tt3 and Tt4), while enzyme-linked immunoassay sandwich method was used to estimate FGFBP-3 (fibroblast growth factor binding protein-3), and the enzymatic colorimetric method was used to determine (total cholesterol, triglyceride, HDL, LDL, and VLDL);* ***Results:*** *The study's findings indicated that while TSH and HDL levels were lower in the healthy group, the concentrations of FGFBP3, HbA1c, FT4, FT3, total cholesterol, triglycerides, LDL, and VLDL were all significantly elevated in the hyperthyroidism with and without DM groups. Furthermore, the findings demonstrated that the lipid profile levels in the hyperthyroidism with DM group did not differ significantly from the hyperthyroidism without DM group. High serum FGFBP3 levels were observed in hyperthyroidism with and without DM patients but lower FGFBP3 level was detected in the control group. Form ROC, FGFBP3 can be used for monitoring hyperthyroidism with and without DM patients;* ***Conclusions:*** *In summary, this paper revealed that there was a close relationship between FGFBP3 levels and hyperthyroidism with and without DM diseases.*

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 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 thyroid dysfunction are the two endocrine disorders that are most common in many populations DM and thyroid dysfunction 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 have the ability to 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]. Ametabolic disease-ridden animal model is due to dysregulated lipogenic and gluconeogenic genes[12, 13]. Thyroid dysfunction (TD) and Diabetes mellitus (DM) are two endocrinopathies that are regularly observed in ordinary practice. Patients with diabetes, both type 1 (T1DM) and type 2 (T2DM), 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, T3, or both, are the two thyroid hormones that are raised in the biochemical profile of overt hyperthyroidism and reduced in the 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 people with clinical or subclinical hyperthyroidism. This happens 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, divided into three groups (30) of them were hyperthyroidism with DM, (30) hyperthyroidism without DM, and (30) were healthy controls for comparison, with their ages ranging between (40-60) years.

The function of thyroid hormone tests included serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) using immunofluoresence (mini VIDAS-BIOMERIEUX-FRANCE). FGFBP3 was measured by the enzyme-linked immunoassay sandwich method (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 was defined as a p-value < 0.001.

RESULTS AND DISCUSSION

The result showed that the thyroid hormones (FT3 and FT4), lipid profiles, HbA1c increased in hyperthyroidism with and without DM compared to the healthy group. Also, the 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).

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

Parameters	Groups	Mean ±SD	P-value
TSH (uUI/L)	Control	2.60±1.63	control vs. Hyperthyroidism without D.M P <0.001***
	Hyperthyroidism With D.M	0.04±0.06	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	0.053±0.06	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P>0.999
F.T3 (Pg/mL)	Control	2.07±0.31	control vs. Hyperthyroidism without D.M P <0.001***
	Hyperthyroidism With D.M	4.31±0.99	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	4.26±0.89	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P>0.923
F.T4 (ng/mL)	Control	2.07±0.31	control vs. Hyperthyroidism without D.M P <0.001***
	Hyperthyroidism With D.M	3.86±0.78	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	3.16±0.64	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P>0.971
HbA1c %	Control	4.60±0.24	control vs. Hyperthyroidism without D.M P>0.998
	Hyperthyroidism With D.M	8.05±1.40	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	5.43±0.46	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P< 0.001***
TC	control	146.5±27.22	control vs. Hyperthyroidism without D.M

(mg/dl)			P<0.001*
	Hyperthyroidism With D.M	252±50.28	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	190.5±40.18	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P <0.001***
TG (mg/dl)	control	109.22±7.80	control vs. Hyperthyroidism without D.M P<0.001*
	Hyperthyroidism With D.M	227.1±35.68	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	165.5±40.86	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P <0.001***
HDL (mg/dl)	control	52.13±5.20	control vs. Hyperthyroidism without D.M P<0.001***
	Hyperthyroidism With D.M	35.01±1.57	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	40.32±1.66	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P<0.001*
LDL (mg/dl)	control	90.61±20.32	control vs. Hyperthyroidism without D.M P<0.001*
	Hyperthyroidism With D.M	166.4±42.88	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	129.5±36.48	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P <0.001***
VLDL (mg/dl)	control	18.24± 1.16	control vs. Hyperthyroidism without D.M P<0.001*
	Hyperthyroidism With D.M	45.43 ±7.97	control vs. Hyperthyroidism with D.M P <0.001***
	Hyperthyroidism Without D.M	33.1±14.66	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P <0.001***
FGFBP3 (ng/mL)	Control	1.54±0.79	control vs. Hyperthyroidism without D.M P = P <0.001***
	Hyperthyroidism With D.M	3.58±0.51	control vs. Hyperthyroidism with D.M P = P <0.001***
	Hyperthyroidism Without D.M	2.33±0.49	Hyperthyroidism without D.M vs. Hyperthyroidism with D.M, P = P <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

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), **FGFBP3**(fibroblast growth factor binding protein3).

The data in our study showed that TSH levels are low, which agrees with[20]. It was found that FT3 and FT4 levels are noticeably higher in individuals with (hyperthyroidism with and without D.M)[21]. A previous study by[22] revealed that FT3 and FT4 levels are high when DM is uncontrolled. As shown in our results, thyroid dysfunction and dyslipidemia are two conditions that have a close connection with DM[23].On the other hand, our results showed that there was no significant difference in thyroid dysfunction when comparing the hyperthyroidism with DM group to the hyperthyroidisms without DM group. There was a significant increase in lipid profile and HbA1c when comparing between 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, lipid profile was lower compared to the healthy group, with the exception of 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 are results 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 the single injection of this protein could regulate blood glucose level and keep it at the healthy stage for more than 24 hours[30].

1correlation

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

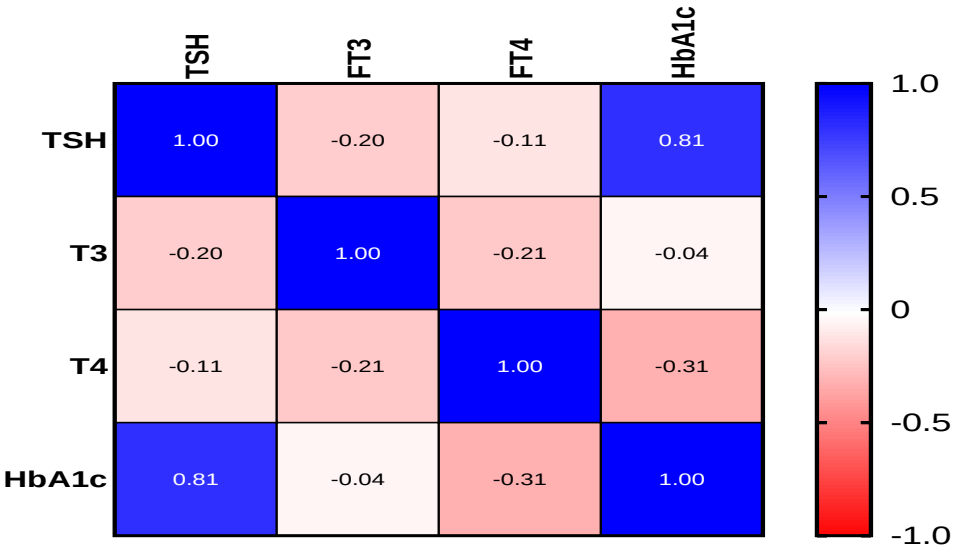

Figure (1): Correlation of HbA1c with thyroid dysfunction in hyperthyroidism with D.M

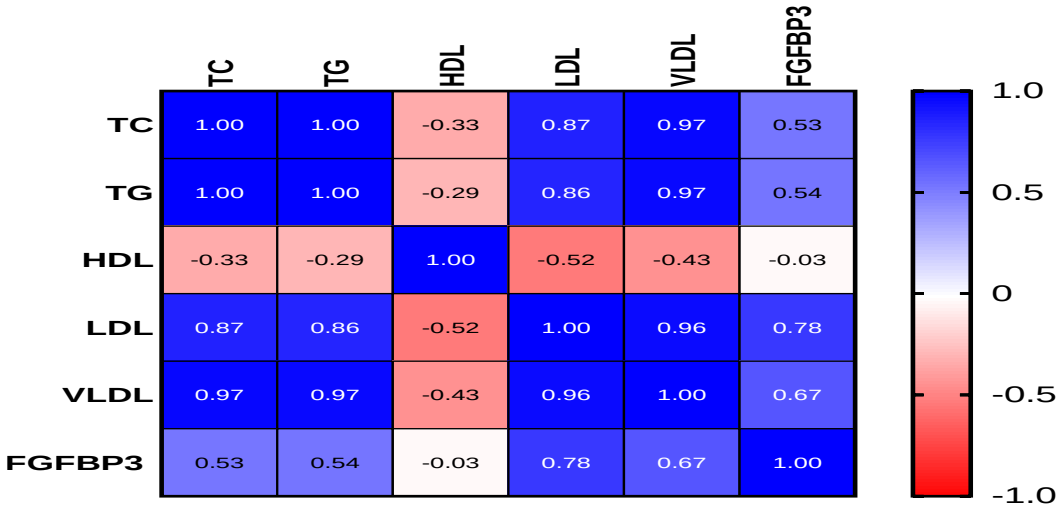

Figure (2): Correlation of FGFBP3 with lipid profile in hyperthyroidism without D.M

The results demonstrated that the FGFBP3 had positive correlation with lipid profile in hyperthyroidism without DM group except HDL, which showed no correlation, but in hyperthyroidism with DM group, negative significant correlation was shown in FGFBP3 with TG and LDL and positive correlation with HDL. There was no correlation between FGFBP3 with other parameters in the same group as shown in figures (2 and 3).

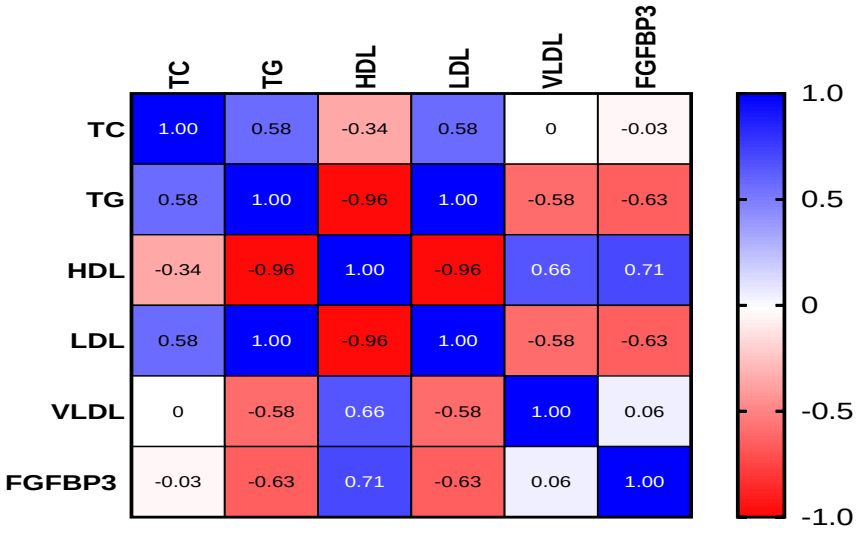

Figure (3): Correlation of FGFBP3 with lipid profile in hyperthyroidism with D.M

5.2Area under and the curve ROC for

The ROC curves were analyzed for FGFBP3 to investigate its predictive value. The optimal cutoff value for circulating FGFBP3 to predict hyperthyroidism in patients without DM was found to be > 1.47ng/ml (sensitivity: 82.41%, specificity: 61.11%, and AUC: 0.873) at a 95% confidence interval of (0.758 ~ 0.988) and P <0.001, as illustrated in figure (4).

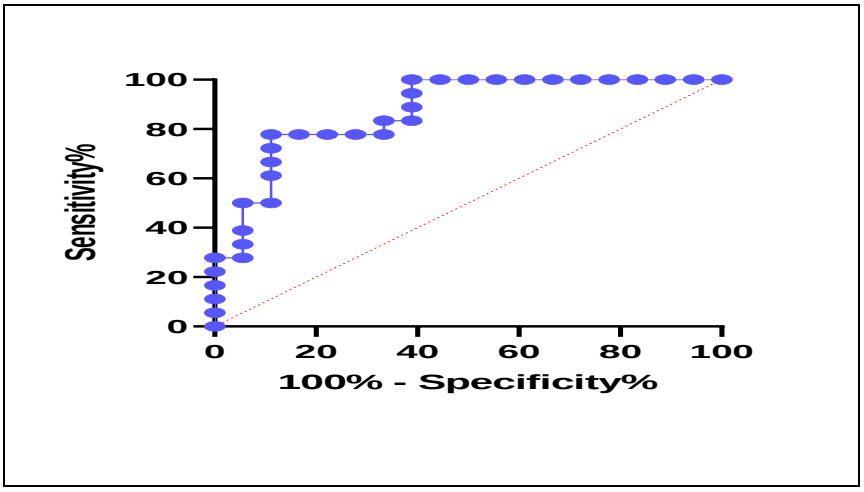

Figure (4): ROC-curve of Control-Hyperthyroidism without D.M

The association of serum FGFBP3 in hyperthyroidism with DM risk was observed (AUC 0.1000, 95% confidence interval: 0.996~ 1.000), of >2.78 ng/ml

FGFBP3 was selected as the cutoff limit for the early diagnosis, and it showed a sensitivity of 82.41% and a specificity of 100% at P value <0.001 as shown in figure (5).

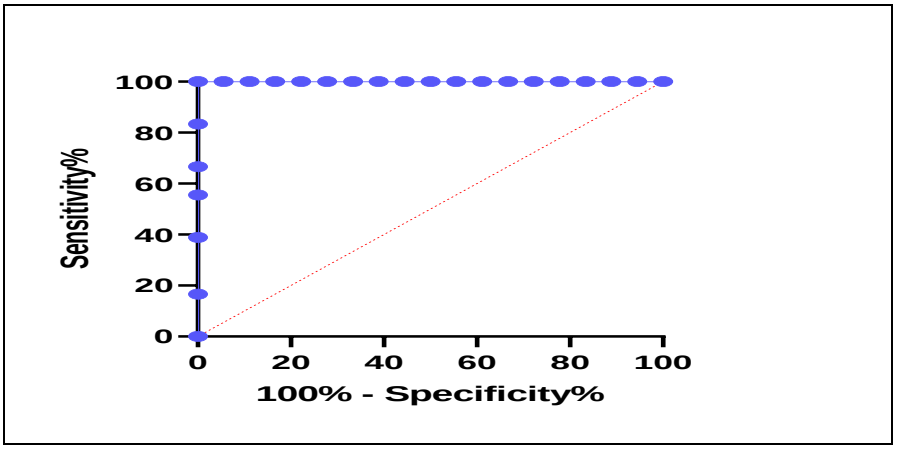

Figure (5): ROC-curve of Control-Hyperthyroidism with D.M

CONCLUSION

According to the study's results, FGFBP3 had close ties with hyperthyroidism without DM compared to healthy subjects and blood FGFBP3 level with DM group compared to the same group, which is the lower level of healthy group compared to hyperthyroidism with and without DM. The ROC statistical results showed that FGFBP3 predicted DM disease in hyperthyroidism patients. In correlation, the findings showed that FGFBP3 is closely related to lipid profile in hyperthyroidism with and without DM, so it can be concluded that investigation explores the probable connection between hyperthyroidism and FGFBP3 protein to identify risk factors for thyroid dysfunction with DM.

SUPPLEMENTARY MATERIAL

None

FUNDING

This study did not receive any funding in any form.

DATA AVAILABILITY STATEMENT

None

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Ethics Approval

This study has been compiled based on the national center for educational laboratories at the 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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