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A novel Score of Fibroblast Growth Factor 21 Level in Evaluation of Egyptian Diabetic Patients Suffering from Hypothyroidism.

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Abstract: Diabetes mellitus (DM) and thyroid diseases are two common endocrinopathies seen in the general population. Diabetes mellitus is one of the fundamental wellbeing fears in developing countries. Insulin resistance is interrelated to thyroid dysfunction. Hyper- and hypothyroidism have been correlated with insulin resistance which has been conveyed to be the key purpose of deficient glucose metabolism in T2DM. The Fibroblast growth factor 21(FGF-21) is a systemic metabolic modulator identified to regulate miscellaneous biological functions parallel to the actions of thyroid hormone. Thyroid hormone (TH) modulates FGF-21 levels in the liver and the adipose tissues. In opposing, peripheral FGF21 dispensation consequences in deficient circulating levels of thyroid hormone. These data suggest that FGF21 and TH could interrelate to schematize metabolism. In 50 hypothyroidism patients (25 T2DM and 25 without T2DM), 25 T2DM patients without hypothyroidism, and 25 healthy controls, the level of FGF21 was measured with ELISA. The differences in serum FGF21 concentrations were examined in patients with variable thyroid function. The results revealed that the mean frequency of circulating FGF21 was greatly significant to that in hypothyroidism patients than control, nonetheless, it was similar in T2DM patients without hypothyroidism. To sum up, Evaluation of FGF21 is related to the prediction of Hypothyroidism patients' grade.
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1. Introduction:

Diabetes is a metabolic disorder condition in human beings resulting due to elevated glucose levels in the human body for a prolonged period [1]. Indications of high glucose comprise recurrent urination, amplified thirst, and improved hunger. If gone untreated, diabetes can lead to several impediments [2]. In Egypt, the number of people affected with diabetes increased from 2,623,000 in the year 2000 to 6,726,000 in the year 2030 [3]. Diabetes mellitus may be a confusing syndrome discriminated by infinite or comparative insulin deficiency that leads to hyperglycemia and an altered glucose, fat, and protein metabolism. The deficiency of insulin could be due to the genetic defect of β- cell function or insulin, pancreatic diseases, drug-induced disease, viral infections, increased production of hormonal antagonist to insulin and specific syndrome [4].

Chronic hyperglycemia might lead to tissue damage by glycation of tissue proteins and other macromolecules thereby resulting in excess production of polyol compounds from glucose [5]. These metabolic dysfunctions are associated with various other characteristic long-term complications, such as diabetic nephropathy. Insulin resistance is linked to thyroid dysfunction. The association between diabetes and thyroid dysfunction was first published in 1979 [6]. Both thyroid disease and diabetes mellitus (DM) are two common endocrine disorders seen in the general population. Long term complications of diabetes with thyroid dysfunctions include retinopathy with a potential loss of vision; nephropathy with a risk of foot ulcers, amputation, and Charcot's joints, and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction [7].

Practically diabetes, thyroid disease is another common endocrine problem present in Egypt. It is second only to diabetes as the most common condition to affect the endocrine system [8]. The thyroid is a

butterfly-shaped gland located in the neck just below Adam's apple and above the collar-bone. It produces two hormones, thyroxin (T4) and triiodothyronine (T3) which enter the bloodstream and affect the metabolism of the heart, liver, muscles, and other organs [9]. The thyroid gland operates as a part of the feedback mechanism involving the hypothalamus and the pituitary gland which are located in the brain. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to secrete thyrotropin or thyroid-stimulating hormone (TSH). TSH increases iodide uptake and oxidation that leads to organification and coupling in the thyroid gland [10].

These are necessary steps to produce the thyroid hormones T4 and T3. Of thyroid hormones secreted 90% is T4 and 9% is T3. T3 is derived from the deiodination of T4; therefore 80% of circulating T3 is obtained from T4 [11]. Excessive T4 and to a small degree T3 circulating in the serum inhibits the secretion of TSH and TRH, thereby completing the feedback cycle (Johnson, 2006). Binding and transport of the thyroid hormones are carried out by thyroxin binding globulin (TBG) [12]. Thyroid hormones enter cells by diffusion and carrier-mediated transport and bind to nuclear TSH receptors. TSH receptors are found on the surface of the follicular cells within the thyroid as well as on the adipocytes, lymphocytes, fibroblasts, and gonads. Thyroid hormone exerts influence on numerous body systems, including growth and development, muscular function, sympathetic nervous system function, cardiovascular system, and carbohydrate metabolism [13].

Around are two main disorders of the thyroid gland, hypothyroidism, or an underactive thyroid gland and hyperthyroidism or an overactive thyroid gland [14]. Thyroid disorders are widely common with variable prevalence among the different populations [15]. The incidence of both hyper and hypothyroidism are very high in women as compared to men (Ratio 10:1 for hyper and 20:1 for hypothyroidism). About 7.5% of women are also having subclinical (T3 and T4 normal, TSH elevated) hypothyroidism [16].

Thyroid hormones play a vital role in typical fetal and neonatal brain development by regulating neuronal proliferation and differentiation, myelinogenesis, neuronal outgrowth, and synapse formation. The critical time for brain development starts in the uterus of the mother and continues to age two [17]. The deficiency of thyroid hormone during this important time can lead to structural and physiological impairment resulting in brain damage or severe neurological impairment [18]. This process cannot be reversed once completed, which is the reasoning behind universal screening for congenital hypothyroidism. The state-of-art evidence proposes a fundamental role of insulin resistance in assuring the connection between T2DM and thyroid dysfunction. 5′ adenosine monophosphate-activated protein kinase (AMPK) may be a principal target for an alteration of insulin sensitivity and feedback of thyroid hormones regarding appetite and energy expenditure [19].

Hashimoto's thyroiditis or thyroid overactivity (Graves' disease) has been examined to be correlated with diabetes mellitus. 11% of thyroid dysfunction in the patients of diabetes mellitus was reported. Fibroblast growth factor 21 (FGF21) acts in an endocrine fashion to regulate glucose and lipid metabolism and overall energy balance [20]. Despite the multiple beneficial effects of FGF21 on glucose and lipid homeostasis and insulin sensitivity, circulating FGF21 levels are elevated in obese humans with diet-induced and genetic obesity [21]. Circulating levels of FGF21 also are increased in patients with obesity-related disorders, involving the metabolic syndrome, type 2 diabetes. Insulin and thyroid hormone being intimately related to cellular metabolism and thus increment or deficit of these hormones lead to functional disturbance of the other [22].

Thyroid hormone (TH) regulates fibroblast growth factor 21 (FGF21) levels within the liver and the adipose tissue. On the contrary, peripheral FGF21 dispensation results in deficient circulating levels of TH [23]. These data propose that FGF21 and TH could interact to systematize metabolism, thyroid hormone regulates FGF21 expression in the liver and adipose tissue; however, until now, few reports regarding the correlation of thyroid function and FGF21 levels in humans have been generated [24]. This study intended to assess serum FGF21 levels in type 2 diabetic patients with or without hypothyroidism to study the association between insulin resistance, hypothyroidism, and FGF21.

2. Materials and Methods:

2.1 Study Design and Sample collection.

Seventy-five patients attending the National Institute of Diabetes and Endocrinology, Cairo, Egypt were included in this prospective study. They were divided into three groups: Group 1= Hypothyroidism patients without T2DM (n = 25), Group 2 = Hypothyroidism patients with T2DM (n = 25), and Group 3 = T2DM patients (n = 25). A control group (n= 25) of healthy volunteers consist of 5 males and 20 females were included in the FGF 21 evaluation analysis by ELISA. Exclusion criteria included patients with: decompensated liver disease, malignancy, organ transplantation, and co-infection with HIV or HBV, immunosuppression, renal disorder, and autoimmune comorbidities. Besides,

Diabetic patients with macro complications, Patients have active hepatitis C or B virus (HCV, HBV), Human Immunodeficiency Virus (HIV), or tuberculosis (TB), and Patients have Hyperlipidemia. All patients were positive to DM type 2 and hypothyroidism with detectable serum by ELISA test. Written informed consent for specimen use was obtained from all study subjects and the study protocol was approved by the ethics review committee of the General Organization for Teaching Hospitals and Institutes (GOTHI). Data and sample collection thorough history taking and full clinical assessment. Data for all study participants were collected from their medical files (grading and staging of thyroid disease). Blood sampling, 9 mL of peripheral blood was collected from each patient. Five mL were put on gel tubes to separate serum samples (used for ELISA), and 2 mL put on potassium ethylenediamine tetra-acetic acid (K3 EDTA) tubes for HbA1C. Two mL were collected into fluoride tubes to separate plasma samples (used in biochemical analysis of glucose levels). Serum samples for ELISA were stored at −80˚C until further processing.

2.2 Biochemical Investigations

Routine lab investigations including liver function tests (ALT, AST), Fasting Blood Glucose, HbA1c, and Lipid Profile were performed for each subject.

2.3 ELISA

The determination of TSH was done according to the method of The BioCheck by ELISA assay technique (Calbiotech Inc). The assay system utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the intact TSH molecule. This mouse monoclonal anti-TSH antibody is used for solid-phase immobilization (on the microtiter wells). A goat anti-TSH antibody is in the antibody-enzyme (horseradish peroxidase) conjugate solution. Determination of Free Triiodothyronine (FT3), FT3 ELISA kit is used for the quantitative measurement of Free Triiodothyronine (FT3) in human serum based on a solid phase competitive ELISA. The samples Anti-T3 Biotin and FT3 enzyme conjugate are added to the wells coated with Streptavidin. FT3 in the patient serum competes with a T3 enzyme conjugate for binding sites. Determination of Human Fibroblast Growth Factor 21 (FGF-21) by using a Sandwich-ELISA method as described in the material kit (Table 1). The Micro Elisa strip plate provided in this kit has been pre-coated with an antibody specific to FGF-21. Standards or samples are added to the appropriate Micro Elisa plate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP) – conjugated antibody specific for FGF-21 is added to each Micro Elisa well and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain FGF-21 and HRP conjugated FGF-21 antibody will appear blue and then turn yellow after the addition of the stop solution. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm. The OD value is proportional to the concentration of FGF-21.

Table 1: Materials of a specific method for evaluation of FGF21

SR	Materials provided with the kit	48 determinations	96 determinations	Storage
1	User manual	1	1	**R.T**
2	Closure plate membrane	2	2	**R.T**
3	Sealed bags	1	1	**R.T**
4	Micro Elisa strip plate	1	1	**2-8℃**
5	Standard: 135 pg/ml	0.5 ml x 1 bottle	0.5 ml x 1 bottle	**2-8℃**
6	Standard diluent	1.5 ml x 1 bottle	1.5 ml x 1 bottle	**2-8℃**
7	HRP-Conjugate reagent	3 ml x 1 bottle	6 ml x 1 bottle	**2-8℃**
8	Sample diluent	3 ml x 1 bottle	6 ml x 1 bottle	**2-8℃**
9	Chromogen solution A	3 ml x 1 bottle	6 ml x 1 bottle	**2-8℃**
10	Chromogen solution B	3 ml x 1 bottle	6 ml x 1 bottle	**2-8℃**
11	Stop solution	3 ml x 1 bottle	6 ml x 1 bottle	**2-8℃**
12	Wash solution	20ml (20X) x 1 bottle	20ml (20X) x 1 bottle	**2-8℃**

3. Statistics analysis:

The statistical analysis was performed using Statistical Package for Social Sciences **(SPSS Inc. Chicago, IL, V 21.0)** and **(Graph Pad software V 16)**. Quantitative variables were expressed by mean ± standard errors (SE). In all tests, P-value was considered to be statistically significant if less than 0.05. Comparisons of the results between the two methods were performed using One Way ANOVA Test with P values < 0.05 followed t-test was used for comparison of means.

4. Results:

4.1. Demographic Parameters.

Demographic data records are summarized in **(Table 2).** There were no significant differences in gender distribution among the four groups (P=0.9) with female predominance in diseased groups and they represented 92%, 76%, and 92% in hypothyroidism, T2DM without hypothyroidism and T2DM with hypothyroidism groups, respectively. There was no significant difference in BMI, age, systolic, and diastolic blood pressure.

Table 2: Comparison between patients and control groups regarding demographic data.

Group VARIABLE	Group 1 (Hypothyroidism) n=25	Group 2 (T2DM & Hypothyroidism) n=25	Group 3 (T2DM) n=25	Group 4 (Control) n=25	P-Value
Age (years) (mean±SD)	44.5±12.9	42.1±10.7	45±7.9	41.8 ±10.3	0.06
BMI (kg/m^2) (mean±SD)	29.9±4.2	33.4±5.6	32.9±4.2	30±5.2	0.06
SBP (mmHg) (mean±SD)	120.1±7.7	123.2±17.1	125.8±11.9	120.1±6.8	0.3
DBP (mmHg) (mean±SD)	79.4±5.9	78.9±9.9	79.9±7.4	77±6.2	0.6
Sex Male female	2(8.0%) 23(92%)	2 (8.0%) 23 (92%)	6 (24%) 19 (76%)	5 (20%) 20(80%)	0.9 0.9

4.2 Biochemical laboratory investigations of subjects.

Biochemical results are summarized in **(Table. 3)** and **(Figures 1. A, B, C, D)** showed that there is a highly statistically significant difference in the different patients' groups 2, 3 for FBG compared to the Control Group (P=0.00) as seen in (Fig.1.A). Furthermore, there is a poorly significant difference between the patients' groups for HbA1C (P-value = 0.04) as seen in (Fig.1.B). Also, there is a highly significant difference between all groups regarding Insulin, and HOMA-IR, compared to the Control group.

Table 3: Comparison of clinical data of Diabetes Marker's laboratory investigations in patients' type 2 diabetes mellitus, Hypothyroidism vs. control group.

Group Variables	Group 1 (Hypothyroidism) n=25	Group 2(T2DM & Hypothyroidism) n=25	Group 3 (T2DM) n=25	Group 4 (Control) n=25	P-value
FBG (mg/dL) (mean±SE)	113.8±4.2	239.2±23.8	207.7±20.7	99.3±2.6	0.000
HbA1c (%) (mean±SE)	6±0.1	8.5±2.9	8.7±0.4	5.4±0.1	0.04
Insulin (μlU/mL) (mean±SE)	13.1±2.6	30.6±5.5	17.8±3.5	12.1±1.2	0.001
HOMA-IR (mean±SE)	3.8±0.9	17.8±3.6	9.5±2.7	3±0.3	0.000
C-Peptide (ng/ml) (mean±SE)	2.3±0.2	2.1±0.05	2.3± 0.14	2.3±0.13	0.7

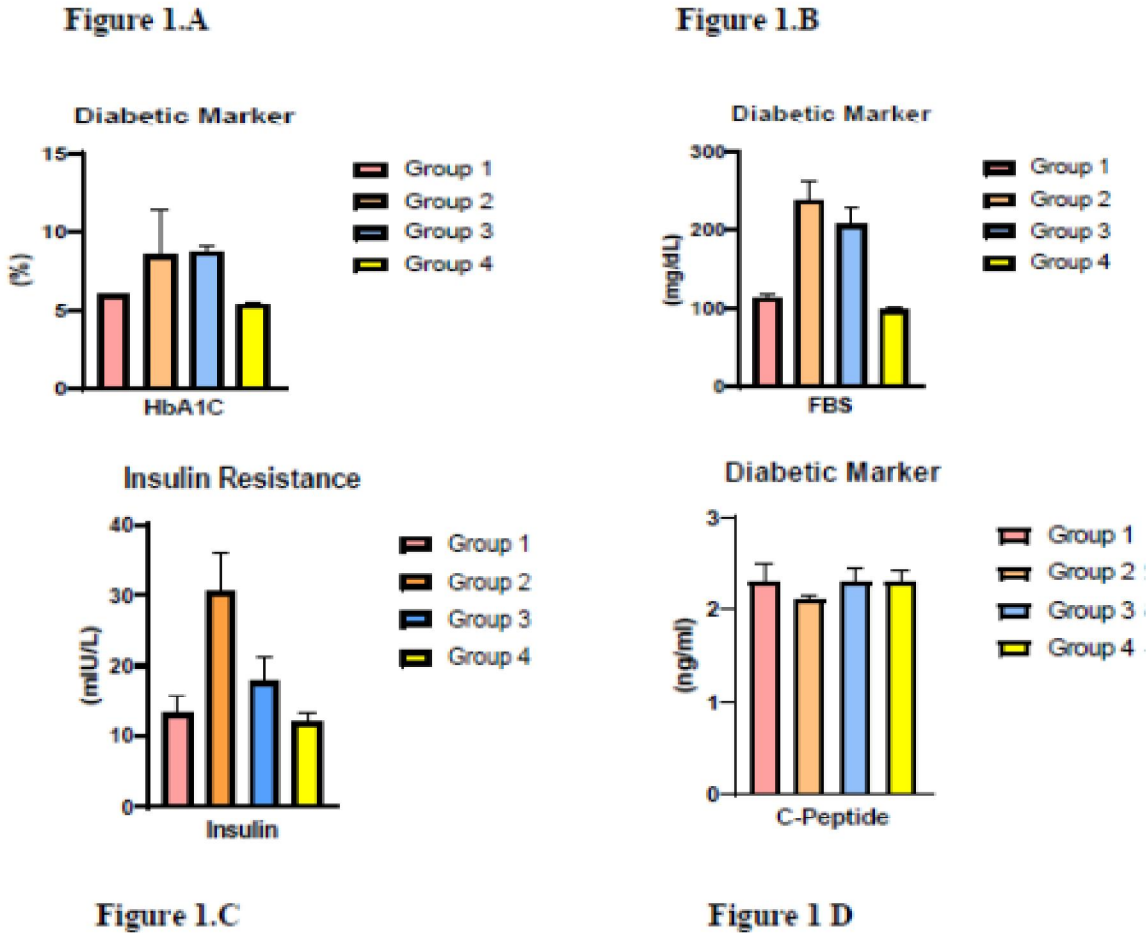

Figure 1. Glycosylated hemoglobin levels HbA1C (%), FBG (mg/dL), C-peptide (ng/ml) and Insulin Resistance in patient groups. Data are expressed by means ± standard error.

Following Thyroid and lipid results, the Data were summarized in **(Table 4)** and **(Figure 2)** which bard that there is a highly statistically significant difference in FT3 and FT4 between Hypothyroidism patients with T2DM and without T2DM patients groups as compared with the control group with (P-value = 0.00). Furthermore, there is a significant difference between all groups as compared with the control group as per the TSH level (P-value < 0.03). The levels and comparison of mean serum concentration of lipid profile in all group subjects were shown in (**Table 4)** and **(Figure 3)**. The mean serum cholesterol (188±14.2 mg/dl) in group hypothyroidism was very insignificantly (P=0.8) higher than the mean values in groups 2 and 3 respectively. The mean (122±17.1 mg/dl) triglycerides in group 1 were lower than the mean of other groups and the difference was statistically very significant (p=0.05). The mean serum HDL-cholesterol in diabetic and non-diabetic subjects was (39.3±2.00 mg/dl) and (37.3±2.2 mg/dl) respectively. Serum HDL value was lower in non-diabetic subjects as compared to diabetic subjects and this difference was statistically very significant (p=0.02). There were insignificant differences (p=0.6) between the mean (125.7±11.4 mg/dl) of LDL cholesterol in non-diabetic subjects compared with a mean (128±5.8mg/dl) in diabetic subjects.

Table 4: Comparison of thyroid hormones and lipid profile for patient groups regarding the control group.

Group	Group 1 (Hypothyroidism) n=25	Group 2 (T2DM & Hypothyroidism) n=25	Group 3 (T2DM) n=25	Group 4 (Control) n=25	P-value
TSH (uIU/ml) (mean±SE)	5.2±1.4	3.5±0.8	2.1±0.3	1.8±0.3	0.03
FT3 (pmol/L) (mean±SE)	2.1±0.1	2.2±0.1	3.1±0.1	3.2 ±0.1	0.000
FT4 (pmol/L) (mean±SE)	1.2±0.1	1.1±0.05	1.5±0.1	1.6±0.1	0.000
T-C (mg/dL) (mean±SE)	188±14.2	181.8±9.6	187.3±6.6	178.3±9.9	0.8
T.G (mg/dL) (mean±SE)	122±17.1	137±11.7	161.6±24.5	95.8±11.9	0.05
HDL-C (mg/dL) (mean±SE)	37.3±2.2	39.3±2.0	39.2±2.3	48.0±3.3	0.02
LDL-C (mg/dL) (mean±SE)	125.7±11.4	114.3±7.7	128±5.8	122.3±5.5	0.6

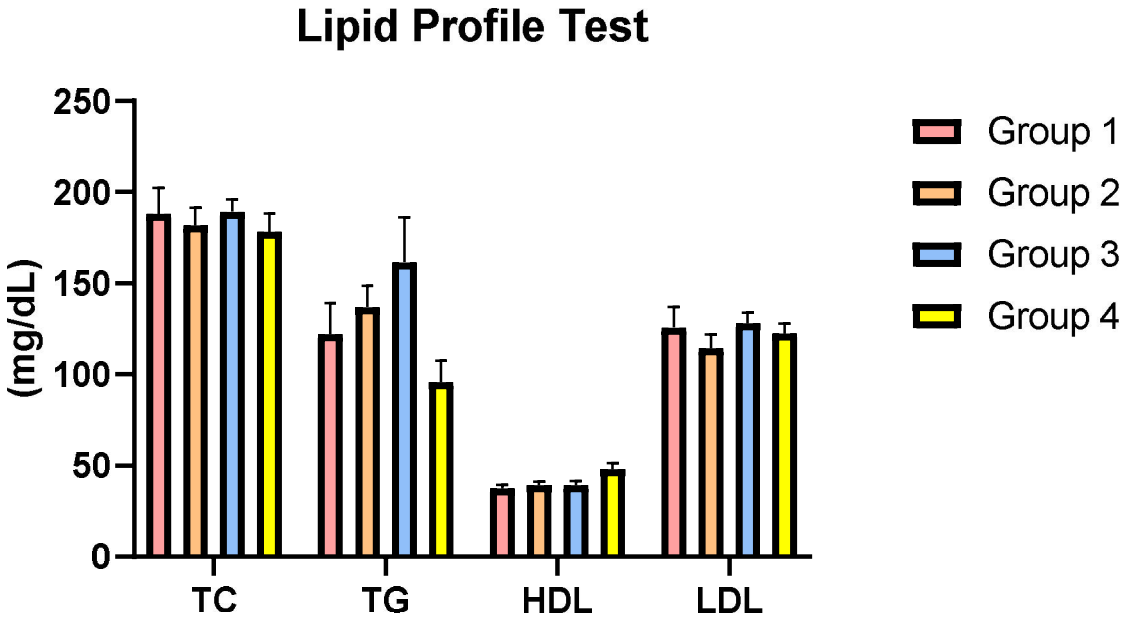

Figure 2. Mean of lipid profile in subjects groups. Values are represented as Mean ± SE.

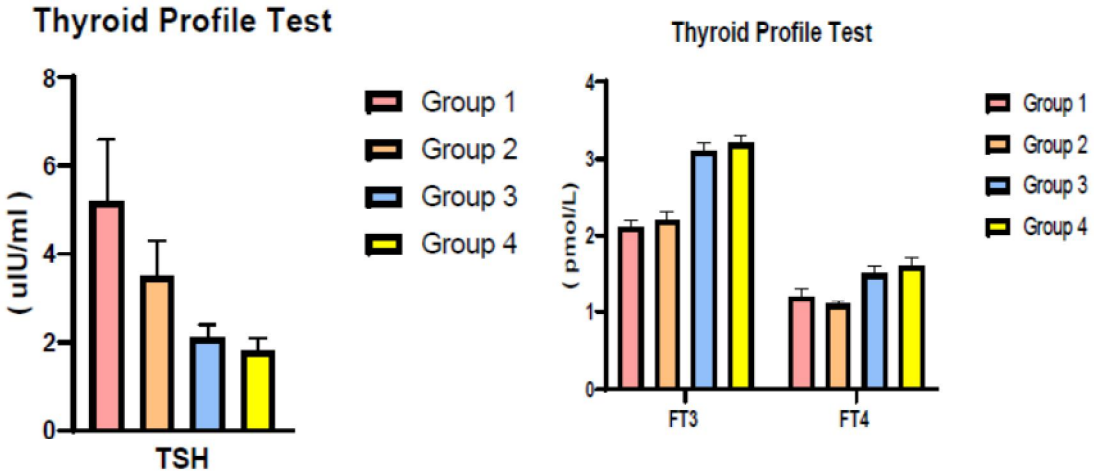

Figure 3. Levels of serum FT3, FT4, and TSH in subject groups. Values are represented as Mean ± SE.

4.3 Expression of Fibroblast Growth Factor 21 (FGF-21) in all subject groups

Kruskal–Wallis test results showed that in **(Table 5)** and **(figure 4)**, for the mean FGF21 levels in all groups, there were highly significant differences between all groups regarding control group (p=0.000), and the Mann– Whitney U test was used to authenticate these differences in the group 1 of hypothyroidism group and group 2 T2DM with hypothyroidism. The test results showed that the mean level of FG21 in patients without diabetes was significantly higher than those in patients with well-diabetes (p=0.01) and in group 2 (p=0.08) **(Table 6).**

According to Spearman correlation coefficient, results showed a significant positive relationship between FGF21 level with HDL, TSH, and FT3 as shown in **(Figure 5, A, B, C, D, E)** and did not show any significant correlation of cholesterol, and LDL with FGF-21 level as shown in **(Table 7).**

Table 5. Mean comparison of FGF21 in terms of four groups.

Group	Group 1 (Hypothyroidism) n=25	Group 2 (T2DM & Hypothyroidism) n=25	Group 3 (T2DM) n=25	Group 4 (Control) n=25	P-value
FGF-21 (pg/ml) (mean±SE)	85.7±16.5	51.1±3.7	36.2±0.5	37±0.5	0.000

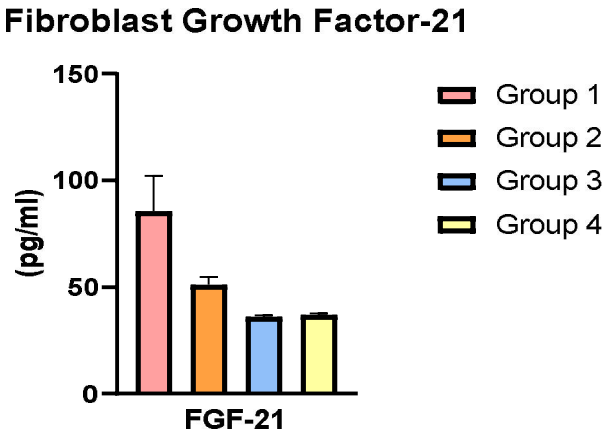

Figure 4. Comparison of FGF21 in subject groups

Table 6. Comparison **of** Fibroblast Growth Factor 21 Data concerning Hypothyroidism Group 1 and Hypothyroidism with diabetes mellitus Group 2.

Groups	Marker	Hypothyroid	Percent	N	mean±SE	P-value
Group 1	FGF21	Euthyroidism	32%	7	**150.3±30.7**	0.01
		Hypothyroidism	52%	11	**57.4±16.7**	
		Subclinical hypothyroidism	16%	3	**38.3±1.2**	
Group 2	FGF21	Euthyroidism	20%	4	**61.3±11.9**	0.08
		Hypothyroidism	64%	15	**45.7±0.9**	
		Subclinical hypothyroidism	16%	3	**64.7±22.1**	

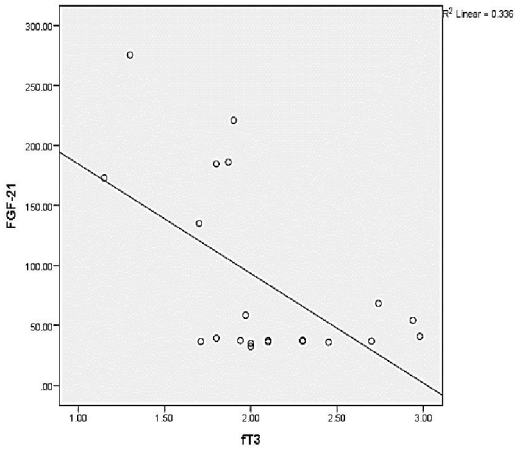

Figure 5, A

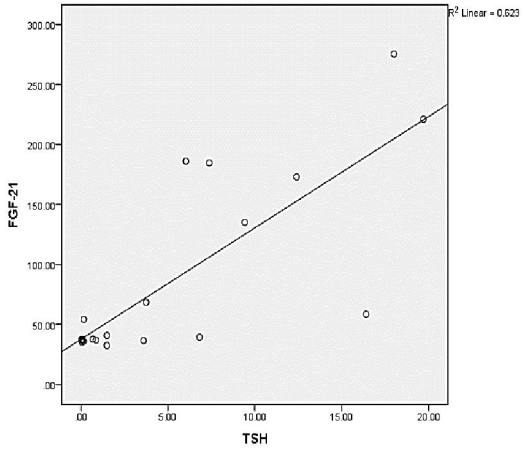

Figure 5, B

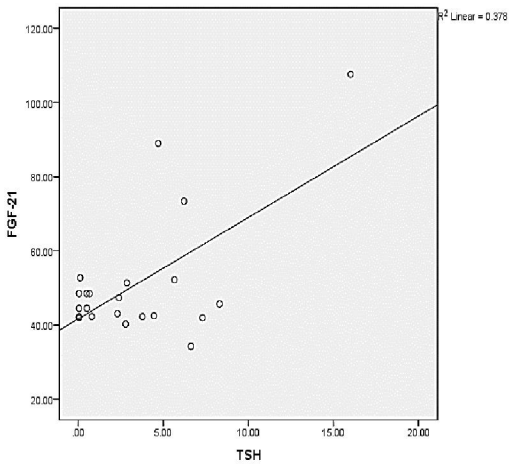

Figure 5, C

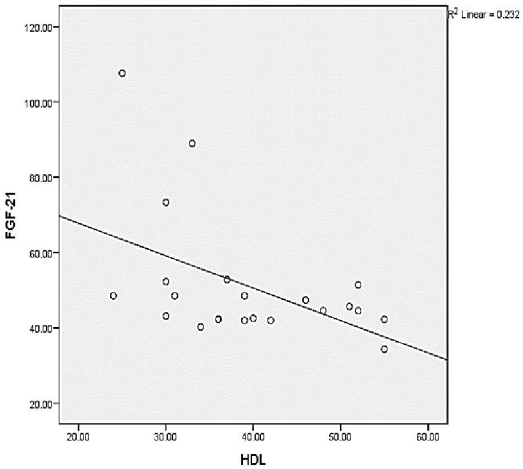

Figure 5, D

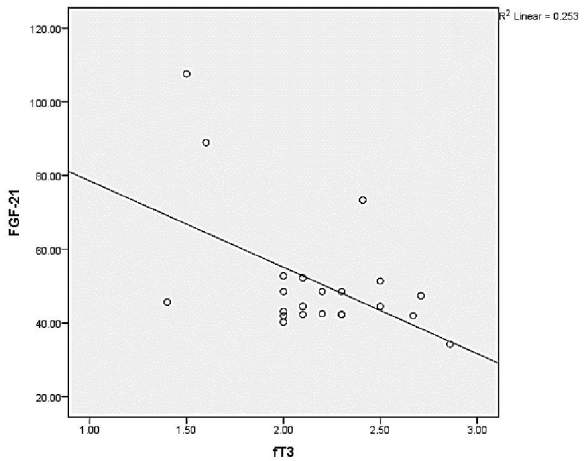

Figure 5, E

Figure 5. Correlation between FGF-21 level with lipid profiles, thyroid in the study groups.

Table 7. Correlation between FGF-21 level with lipid profiles and thyroid profiles in the study groups.

FGF-21 with all laboratory parameters	Group 1	Group 2
	Pearson coefficient (r)	Pearson coefficient (r)
Total Cholesterol	-0.033	-0.213
Triglycerides	0.177	0.234
High Density Lipoprotein	-0.119	-0.481
Low Density Lipoprotein	-0.061	-0.208
TSH	0.789	0.615
FT3	-0.579	-0.503
FT4	-0.289	-0.023

Note T2DM: Type 2 Diabetes mellitus; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TSH: thyroid-stimulating hormone; FT3; Free triiodothyronine, FT4; Free thyroxine; FGF21: human fibroblast growth factor 21; all the indexes in conformity with normal distributions were expressed in x± s.

5. Discussion

Generally speaking, the Fibroblast growth factor 21 is a systemic metabolic modulator recognized to normalize miscellaneous biological functions alike to the actions of thyroid hormone [25]. FGF21 is supposed to turn on its target tissues, relating liver and adipose tissue, to augment insulin sensitivity and reduce adiposity [26]. FGF21 seems to be predominantly produced by the liver, where its expression is partially under the control of the transcription factor peroxisome proliferator-activated receptor-α (PPARα) [27]. FGF21 expression is also induced by endogenous PPARα ligands, for instance, fatty acids, which upsurge after prolonged fasting, by a ketogenic diet in mice, or by fibrates, which are artificial PPARα ligands [28]. Nevertheless, while adipose tissue is an important target for the metabolic effects of FGF21, both βKlotho and FGF receptors, which are required for FGF21 action in vivo, are also present in the liver [29].

In the current study, the results exhibited that there was no significant difference between mean age or BMI and serum levels of FGF21 in any of the four groups. Because the groups were matched for age, and BMI, they did not have any differences in these variables. This was in incongruity with a study by Cheng et al., as they reported that fasting serum FGF21 levels significantly correlated with age and BMI [30]. Kralisch et al. found that the mean serum levels of FGF21 significantly correlated with BMI and age. Jin et al. reported a positive correlation among age, BMI, and serum levels of FGF21, but there was no significant relationship between sex and serum FGF21 levels [31].

In this contemporary study, the results revealed that the Serum FGF21 concentration was significantly raised in subjects with hypothyroidism. The

mechanism by which circulating FGF21 levels have been increased in patients with hypothyroidism was not clear. One possible explanation is that the increase in circulating FGF21 levels might be a substitutionary mechanism in response to altered metabolism by thyroid hormone [32]. The present findings are consistent with those reported by Lee et al [33]. They compared levels of FGF21 in groups' euthyroid, subclinical hypothyroid, and overtly hypothyroid groups and found that overtly hypothyroid patients' FGF21 levels are higher than other groups. The results of this present study are not consistent with study's findings reported by Y. Panahi et al., Chavez et al., Kralisch et al., they reported that FGF21 levels are increased in diabetic patients [34];[35];[31].

In the present study, there was no significant relationship among levels of triglycerides, cholesterol, or LDL, and FGF21 in groups 1 and 2. The present study in agreement with the study of Y. Panahi et al. which has been shown that there was no significant relationship among levels of triglycerides, cholesterol, HDL, or LDL and FGF21 in any of the groups [34]. In other studies, a positive association has been found between serum levels of triglycerides and FGF21, and FGF21 has been suggested to play a role in lipid metabolism [36]. Because FGF21 is known to exert beneficial effects on lipid profiles in animals, the independent association of serum FGF21 with triglycerides and LDL cholesterol in humans may represent a compensatory response to protect the body from the adverse effects of hyperlipidemia. Li and others reported that FGF21 has a relationship with TG and cholesterol [36].

Lee et al. [33] corrected FGF21 levels for serum triglyceride levels which have been repeatedly shown to be associated with serum FGF21 concentration. Jin et al., in 2014, reported a significant positive association between triglyceride levels and FGF21 [37]. Our findings disagree with previous reports on a positive correlation between serum FGF21 and triglyceride levels [37].

In this study, there was a significant positive correlation between HDL and FGF-21for group 2 only. This is disagreement with a study reported by Fu et al. they found that FGF21 had no relationship with HDL. Jin et al., in 2014, reported the association between HDL and FGF21 serum levels was not significant. Y. Panahi et al. reported that there was no significant relationship among levels of HDL and FGF21.

In the recent study, there was a significant positive correlation of TSH, FT3, and FGF-21 and a non-significant negative correlation of FT4 and FGF-21. This study's findings in agreement with those reported by Lee et al. showed that the FGF21 level of patients with elevated TSH (hypothyroidism) was increased when compared with euthyroid patients and FGF21 had a significant positive relationship with TSH [33]. on the other hand, our results are in disagreement with Fu et al. study's findings that FGF21 had no relationship with TSH [38].

In this current study, we illustrated, the relationship between serum FGF21 levels with the nearness of hypothyroidism in an Egyptian populace. Extra imminent examinations in different populaces are expected to help our speculation that FGF21 predicts the advancement of hypothyroidism, including the examination of the system by which flowing FGF21 levels are expanded in patients with hypothyroidism in people.

Technically speaking, various limitations professed to be noted for the current study. Our study was constrained by the moderate number of subjects with hypothyroidism and the possibility of our investigation was restricted to estimating biochemical profiles, lipid profiles, and serum FGF21 levels. In the top of that, Different factors, for example, thyroid autoantibodies, different adipocytokines, hormones, and quality articulation in tissues, and assessment of metabolic rates besides different parameters that may have influenced changed FGF21 were not analyzed surrendering the instrument by which coursing FGF21 levels are expanded in patients with hypothyroidism muddled. In conclusion, we investigated that serum FGF21 levels were significantly increased in subjects with hypothyroidism and predicted the development of hypothyroid disease in humans.

6. Conflict of interest

The authors declare that there were no conflicts of interest in this study.

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