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ORIGINAL ARTICLE

Serum Fibroblast Growth Factor 21 as a Marker of Pre-diabetes in Obese Egyptian Patients

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Abstract

Background: ***Serum Fibroblast Growth Factor 21 (FGF21) is a 210-amino acid polypeptide that is encoded by a human gene situated in the five ' region of the 1,2-fucosyltransferase gene on chromosome 19.***

Objectives: ***To assess the FGF21 serum levels as an indicator for prediabetes among obese Egyptian cases.***

Methods: ***Our case-control study involved 40 obese cases whose ages fell between 18 and 65 years, both genders, obese cases with body mass index (BMI) of 30 kg/m2 or above). Patients were categorized into two equal groups: Group A, prediabetic, and Group B, not prediabetic, but either impaired glucose tolerance (IGT) or impaired fasting glucose.***

Results: ***FGF-21 exhibited significantly greater values within the prediabetic group than the normal group (P <0.001). No association was documented among FGF-21, BMI, and waist-hip ratio (WHR). FGF21 can significantly predict prediabetes (P <0.001 and AUC (area under the curve) = 0.875) at cutoff>226 with 85% sensitivity, 75% specificity, 77.3% PPV and 83.3% NPV. In univariate regression, waist, triglyceride (TG), fasting plasma insulin (FPI), total cholesterol (TC), and FGF-21 exhibited independent prediabetes predictors (P <0.05). In multivariate regression, FPI and FGF-21 represented independent prediabetes predictors (P <0.05), while waist, TC, and TG were not. FPI, TC, TG, glycated hemoglobin (HbA1c), FGF-21, and waist exhibited significantly greater values within the prediabetic prediabetic group as opposed to the normal group (P <0.05).***

Conclusion: ***FGF-21 levels showed good predictive performance in distinguishing between prediabetes and normoglycemia in obesity. Additional metabolic risk factors like waist circumference, HbA1c, FPI, TG, and TC were also significantly elevated in the prediabetic prediabetic group.***

Keywords: Serum Fibroblast Growth Factor 21; Marker; Pre-diabetes; Obese; Egyptian

1. Introduction

Prediabetes potentially manifests as impaired glucose tolerance (IGT) or impaired fasting glucose levels .[1] These risk factors may lead to the development of type 2 diabetes mellitus (DMT2) and cardiovascular illnesses (CVDs). Prediabetes is predominantly caused by deficient pancreatic insulin production from beta cells in conjunction with insulin resistance (IR). [2]

The American Diabetes Association defines IGT as a plasma glucose level between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L) two hours after an oral glucose tolerance test involving 75 g of glucose. IFG is characterized by plasma glucose levels in the fasting state that vary between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L). Prediabetes is defined as an HbA1c concentration that falls within the interval of 5.7% to 6.4% (equivalent to 39–46 mmol/mol).[3,4]

DMT2 represents a persistent metabolic disorder marked by high blood glucose levels (hyperglycemia) and reduced sensitivity to insulin. It poses a substantial health issue and international burden, addressing a rising occurrence globally .[2, 5]

Fibroblast growth factor 21 (FGF21) is a 210-amino acid polypeptide that is encoded by a human gene situated in the 5′region of the 1,2-fucosyltransferase gene on chromosome 19.[6]

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FGF21 is mostly expressed in the liver, adipose tissue, skeletal muscle, and pancreas. It exhibits a strong positive impact on glucose and lipid metabolism and improves insulin sensitivity. By means of endocrine and autocrine mechanisms, the substance bonds to receptors and the coreceptor β-Klotho, a solitary transmembrane protein located in metabolic organs .[7]

FGI21's involvement in glucose and lipid metabolism has been well-researched in recent times. Research has addressed the possibility that human recombinant FGF21 may increase glucose uptake in mice and human fat cells, along with reducing blood glucose and triglyceride concentrations among obese and diabetic mice and diabetic monkeys .[8, 9]

Elevated levels of FGF21 are strongly linked to several conditions involving obesity, metabolic syndrome, DMT2, nonalcoholic fatty liver diseases (NAFLD), dyslipidemia, as well as coronary artery disorders .[10] Based on two prior studies with a follow-up period of five years, elevated FGF21 concentrations were shown to have a connection with impaired metabolism of glucose and DMT2 .[11, 12]

Multiple studies have shown that FGF21 enhances fatty acid oxidation and produces ketones while acids suppress lipogenesis. Additionally, FGF21 controls glucose-lipid metabolism .[13,14,15]

This work was aimed at assessing the FGF21 serum levels as an indicator for prediabetes among obese Egyptian cases.

2. Patients and methods

Our case-control study involved 40 obese cases whose ages fell between 18 and 65 years, both genders, obese subjects (body mass index (BMI) of 30 kg/m2 or above), and prediabetes was defined specifically as IGT and IFG. The American Diabetes Association defines impaired glucose tolerance (IGT) as a plasma glucose level between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L) two hours after a 75 g oral glucose tolerance test (OGTT) [16]; prediabetes was also defined as an HbA1c of 5.7-6.4% (39–46 mmol/mol). The research commenced following the Ethical Committee's approval at Al-Azhar University Hospitals, Cairo, Egypt. Participants were allowed to sign an informed consent.

We excluded cases developing overt diabetes, hepatic, renal, as well as CVDs, tumors, chronic inflammatory conditions, and others consuming steroids, statin, or fibrates.

All participants were equally categorized into two groups: Group A, which included obese subjects along with prediabetic prediabetic subjects, and Group B, which included obese subjects and non-prediabetic prediabetic subjects.

The subjects underwent a full medical history taking, clinical assessment, and lab testing [CBC, liver function testing (AST, and ALT), kidney function testing (Blood Urea Nitrogen (BUN), eGFR, and creatinine), HbA1c, FBS, RBS, as well as lipid profile testing Very low-density lipoprotein cholesterol (VLDLC), total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), triglyceride (TG), and low-density lipoprotein cholesterol (LDLc).

Venous samples (seven millimeters) were collected following an overnight fast. The sample underwent a split into (1) one milliliter of blood to an EDTA tube for analyzing HbA1c using the Immunoturbidimetric technique by Genius Diagnostics, and (2) six ml of the sample was divided equally between 2 serum separator gel tubes, with three ml within each. Samples underwent clotting for thirty minutes at 37 °C prior to being centrifuged for fifteen minutes at 3500 rpm. The produced serum was utilized for standard testing. The leftover serum, as well as plasma, was kept at -20 °C for analysis.

Commercially available test kits were utilized to measure HbA1c, LDL, HDL, cholesterol, AST, and ALT at the participating facilities. A BIOLABO kit (France) was utilized to measure TC. Additionally, TG was determined to utilize a BIOLABO kit from France. HDL-C was measured via the precipitation technique utilizing a BIOLABO kit from France. The LDL-C was determined using the Friedewald equation: LDL Concentration (mg/dL) = Cholesterol Concentration—HDL Concentration—(Triglyceride Concentration / 5).

VLDLC was calculated utilizing this equation: VLDL Conc. (mg/dL) = TG Conc./5b .[17] Intra- and intraassay CVs were below five percent within all approaches. HbA1c levels from various laboratories were adjusted using mathematical methods to align with the normal range established by the Diabetes Control and Complications Trial (4.05%–6.05%).

Quantitation of Human FGF21:

Serum FGF21 concentrations were determined using ELISA following the manufacturer's guidelines. The assay's standard curve range is 31.3–2000 pg./ml. Every sample underwent testing twice, and the two results were averaged for analysis.

Human FGF21 levels were quantified in all subjects using a Human FGF21 ELISA Kit supplied by the Shanghai, China-based Bioassay Technology Laboratory. A solution containing FGF-21 was introduced into wells that had been pre-coated with an FGF-21 monoclonal antibody. Following incubation, the biotin-conjugated anti-human FGF-21 antibody became selectively coupled to human FGF-21. Any unbound biotin-conjugated anti-human FGF-21 antibody is

eliminated via a rinsing step following incubation. Streptavidin-HRP was utilized to bind to the anti-human FGF-21 antibody conjugated with biotin. Any unbound Streptavidin-HRP was removed through rinsing following incubation. Following the integration of the substrate solution, pigment development occurred in proportion to the quantity of human FGF21 present. In order to terminate the process, an acidic halt solution was introduced. Moreover, at 450 nanometers, the absorbance was subsequently measured.

Statistical analysis:

The statistical analysis of the data was conducted using SPSS v28 (IBM Inc., Armonk, NY, USA). The quantitative variables were presented in both mean and standard deviation form. The presentation of qualitative variables consisted of frequency and percentage (%) values. The Pearson correlation method was implemented to conduct correlation analysis. In order to ascertain independent correlations and control for the influence of covariates, stepwise multiple linear regression analyses were performed, including as covariates all parameters that accounted for highly significant associations in the univariate analysis (P<0.01). Utilizing receiver operating characteristic (ROC) curve analysis, the TGF21 cutoff point for prediabetes diagnosis was determined. A P value with two tails that is less than 0.05 indicates statistical significance.

3. Results

Age, sex, weight, height, BMI, hip and WHR were insignificantly different among the two groups. Waist exhibited significantly higher values within prediabetic group as opposed to normal group (P= 0.037). Table 1

Table 1. Demographic data, waist, hip as well as WHR of the groups

		PREDIABETIC GROUP (N=20)	NORMAL GROUP (N=20)	P
AGE (YEARS)		44.8 ± 8.97	42.3 ± 10.88	0.433
SEX	Male	14 (70%)	12 (60%)	0.507
	Female	6 (30%)	8 (40%)	
WEIGHT (KG)		106.02 ± 9.8	101.6 ± 14.22	0.260
HEIGHT (CM)		167.51 ± 7.05	165.4 ± 4.97	0.282
BMI (KG/M^2)		37.88 ± 3.96	37.12 ± 4.85	0.591
WAIST (CM)		120.1 ± 12.26	110.8 ± 14.88	0.037*
HIP (CM)		126.9 ± 16.37	119.6 ± 14.27	0.141
WHR		0.96 ± 0.12	0.93 ± 0.1	0.466

Data are displayed as mean ± SD or frequency (%). *Significant p value <0.05, BMI: Body mass index, WHR: waist–hip ratio.

FPI, TC, TG as well as HbA1c exhibited significantly greater values within prediabetic group as opposed to normal group (P <0.001, <0.05, <0.001, <0.001 respectively). HDL and LDL exhibited insignificant variations among the two groups. Table 2

Table 2. Fasting plasma insulin, lipid profile and HbA1c of the groups

		PREDIABETIC GROUP (N=20)	NORMAL GROUP (N=20)	P
FPI (MIU/ML)		22.62 ± 7.48	11.31 ± 4.52	<0.001*
LIPID PROFILE	TC (mg/dl)	206.75 ± 23.74	180.69 ± 31.51	0.005*
	HDL (mg/dl)	53.37 ± 10.73	53.43 ± 6.79	0.983
	LDL (mg/dl)	113.95 ± 26.59	104.74 ± 17.7	0.205
	TG (mg/dl)	197.21 ± 55.92	153.57 ± 56.27	0.019*
HBA1C (%)		6.06 ± 0.24	4.82 ± 0.43	<0.001*

Data are displayed as mean ± SD or frequency (%). *Significant p value <0.05, FPI: Fasting plasma insulin, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, HbA1c: glycated hemoglobin, FGF-21: fibroblast growth factor.

FGF-21 exhibited significantly greater values within prediabetic group as opposed to normal group (P <0.001). Figure 1

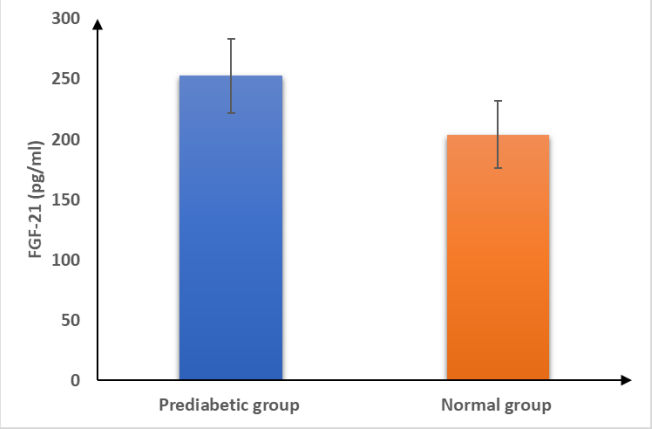

Figure 1. FGF-21 of the studied groups

FGF-21: Fibroblast Growth Factor 21

There was no relationship between FGF-21 and waist, hip, WHR and BMI. Table 3

Table 3. Association between FGF-21 and waist, hip, WHR as well as BMI

		FGF-21 (PG/ML)
WAIST (CM)	r	0.164
	P value	0.312
HIP (CM)	r	-0.027
	P value	0.866
WHR	r	0.208
	P value	0.197
BMI (KG/M^2)	r	0.153
	P value	0.346

r: Pearson Correlation. Significant p value <0.05, BMI: Body mass index, WHR: waist–hip ratio.

FGF21 can significantly predict prediabetes (P <0.001 and AUC = 0.875) at cut-off >226 with 85% sensitivity, 75% specificity, 77.3% PPV and 83.3% NPV. Figure 2

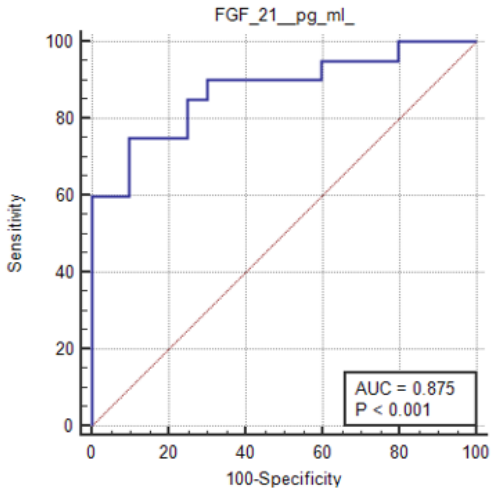

Figure 2. ROC curve of FGF21 for the diagnosis of prediabetes

FGF-21: Fibroblast Growth Factor 21

In univariate regression, waist, FPI, TC, TG and FGF-21 were independent prediabetes predictors (P value <0.05). In Multivariate regression, FPI and FGF-21 were independent prediabetes predictors (P value <0.05) while waist, TC and TG were not. Table 4

Table 4. Univariate and multivariate regression of age, TC, and fibroblast growth factor-21 as dependent variables for prediabetes

	UNIVARIATE			MULTIVARIATE		
WAIST (CM)	Odds ratio	95% CI	P	Odds ratio	95% CI	P
	1.052	1.001 - 1.107	0.045*	1.0676	0.96 to 1.17	0.181
FPI MIU/ML)	1.315	1.122- 1.541	<0.001*	1.3263	1.0299 to 1.7079	0.028*
TC (MG/DL)	1.034	1.007 - 1.06	0.012*	1.0455	0.9858 to 1.1088	0.138
TG (MG/DL)	1.0140	1.001 - 1.026	0.025*	0.9734	0.9373 to 1.0109	0.161
HBA1C (%)	247	--	0.998	--	--	--
FGF-21 (PG/ML)	1.0564	1.021 - 1.092	0.001*	1.0438	1.0001 to 1.0894	0.049*

CI: confident interval, * Significant p value <0.05, FPI: Fasting plasma insulin, TC: total cholesterol, TG: triglyceride, HbA1c: glycated haemoglobin, FGF-21: fibroblast growth factor.

4. Discussion

Treating prediabetes delays diabetes development. Detecting and treating prediabetes is a crucial tactic in preventing diabetes. Additionally, adults who are aware of their prediabetes are more inclined to participate in procedures that reduce diabetes risks as opposed to others who are uninformed of their condition .[18]

FGF21 is produced primarily by the liver, with skeletal muscle, adipocytes, pancreas, and thymus contributing to its synthesis to a lesser degree. Hepatokine is a biomarker that functions as an indicator for the timely identification of cardiometabolic disorders caused by metabolic imbalance .[19] FGF21 is predominantly recognized as a "favorable" cytokine due to its involvement in the regulation of glucose transport in cells that do not rely on insulin. FGF21 increases the expression of GLUT1 mRNA at the cellular membrane of adipocytes, resulting in enhanced glucose absorption in both an insulin-resistant model and obese (ob/ob) mice, according to animal research. [6]

FGF21 likely has a multifactorial impact on the development of MetS and T2DM. FGF21 requires binding to the β-Klotho complex, an FGF coreceptor found predominantly in metabolically active organs such as the liver, adipose tissue, and pancreas, in order to initiate FGF receptor-mediated signaling .[20] FGF21 initiates the metamorphosis of white adipose tissue (WAT) into brown adipose tissue, thereby promoting glucose uptake and improving glucose absorption in WAT.[21] FGF21 potentially mitigates glucolipotoxicity by inhibiting apoptosis of pancreatic β-cells, potentially through its effects on lipid and glucose homeostasis .[22] Prior research suggested that inflammation in adipocytes caused by obesity could inhibit tumor necrosis factor-alpha's production of β-Klotho, thereby causing dysfunction in FGF21 within adipose tissue and ultimately culminating in glucose intolerance .[23] FGF21 resistance could potentially arise from analogous mechanisms in conditions such as prediabetes and obesity, which are distinguished by subclinical inflammation .[24]

Obesity-related diseases may trigger an elevation in blood FGF21 levels as a protective mechanism to combat the metabolic strain caused by obesity. Obesity may result in resistance to the effects of FGF21, prompting an increase in its compensatory regulation. This situation resembles hyperinsulinemia and hyperleptinemia, which are believed to result from increased production to compensate for the resistance to insulin and leptin associated with obesity .[25]

Recent research demonstrated that therapeutic administration of FGF21 reduced serum lipids and blood glucose to nearly normal levels in ob/ob and db/db mice [26], indicating that the maximum effect of FGF21 is not altered in these organisms. However, it is important to note that these results do not rule out the possibility that the target tissues' sensitivity to physiological concentrations of FGF21 in these obese mice may have been diminished. Further extensive research is required to ascertain whether, in response to FGF21, animal models or obese individuals exhibit modified signaling in its target tissues and

decreased sensitivity, contingent upon the dosage.

In our study, FGF-21 exhibited significantly greater within the prediabetic prediabetic group in comparison with the normal group (P value <0.001). This agreed with Karamfilova et al.[10], who reported that mean FGF21 serum concentrations exhibited greater values within prediabetic cases than in patients without prediabetes. This also supported a large meta-analysis by Wang et al.[27] showed elevated FGF-21 levels within overt T2DM cases compared to controls. In addition, Jasim et al.[28] addressed hyperlipidemia cases exhibiting significantly greater FGF21 levels (108.05±4.03 pg/ml) as opposed to controls.

An association was seen between elevated FGF21 levels and obesity-related factors involving waist circumference, waist-to-hip ratio, BMI, and body fat percentage, even when factoring in age. FGF21 concentrations increased as the number of MetS components rose .[29] Elevated FGF21 in serum was found among cases developing obesity-related conditions along with others exhibiting insulin resistance [30], indicating FGF21 resistance, resulting in its compensatory upregulation. Renal function may also alter serum FGF21 levels. Amongst nondiabetic cases undergoing peritoneal dialysis, serum FGF21 concentrations were eight times greater than those of controls .[31]

In a previous study, FGF21 concentrations increased significantly in cases developing biopsy-proven NAFLD regardless of the confounding factors. Moreover, steatosis was associated with increased FGF21 levels rather than other histological parameters .[32]

The metabolic role of FGF21 in animal models is supported by increasing evidence, but the FGF21 role within human physiology remains controversial. FGF21 was first shown to affect nerve cells within the CNS, regulating circadian rhythm as well as stimulating the hypothalamic–pituitary–adrenal axis. This led to increased corticosterone release, promoting gluconeogenesis within the liver .[33] Several animal-based studies have addressed that FGF21 represents a strong metabolic regulator, possessing many positive effects regarding obesity and diabetes, hepatic lipogenesis, and fatty acid oxidation in hepatocytes .[34] Some studies indicate that in rodents, FGF21 increases the the glucose transporter glucose transporter 1 (GLUT-1) expression, thus increasing the uptake of glucose via an insulin-independent manner. [34]

In our study, FPI exhibited significantly higher values within the prediabetic prediabetic group in comparison with the normal group (P value <0.001). This is consistent with Karamfilova et al.[10] which demonstrated that, as expected, in the patients with prediabetes, there were more significant abnormalities in insulin sensitivity (QUICKI and Stumvoll Index) compared to the group of patients without prediabetes.

In our study, TC and TG exhibited significantly greater values within the prediabetic prediabetic group as opposed to controls (P value <0.05). HDL and LDL were insignificantly different between both groups.

This is in harmony with Karamfilova et al.[10] which demonstrated that lipid abnormalities were more significant in patients with prediabetes than in patients without prediabetes.

In our study, FGF21 can significantly predict prediabetes (P <0.001 and AUC = 0.875) at cutoff>226 with 85% sensitivity, 75% specificity, 77.3% PPV and 83.3% NPV. Karamfilova et al.[10] demonstrated that confirmation of the sensitivity of FGF21 from their results was that its values increase in direct proportion to the severity of carbohydrate disorders. Moreover, with respect to the FGF21 predictive value as regards prediabetes within obese NAFLD cases in those exhibiting FGF21 ≥ 320 pg/mL vs. those with lower values, the risk of prediabetes is about 4.2 times higher. Predictive FGF21 values were also found for the risk of MetS and IR, with levels ≥270 pg/mL linked to a four-times greater chance for MetS and ≥260 pg/mL with a 3.2-fold higher risk for IR.

In our study, there was no correlation between FGF-21 and waist, hip, WHR, and BMI. This disagrees with what Wang et al.[27] addressed regarding levels of FGF-21 linked to BMI. This is also contrary to Karamfilova et al.[10] who found correlations between serum levels of FGF21 and TG, VLDL, ALT, and WSR and surrogate markers for VAI.

Limitations: A relatively modest sample size along with a single-centered study. Lack of longitudinal follow-up. Potential confounding effects of comorbidities not evaluated. External validation is required prior to generalizability.

4. Conclusion

Significantly higher serum FGF-21 levels among obese prediabetic patients as opposed to obese normoglycemic controls. FGF-21 levels showed good predictive performance in distinguishing between prediabetes and normoglycemia in obesity. Additional metabolic risk factors like waist circumference, HbA1c, FPI, TGs, and TC were also significantly elevated in the prediabetic prediabetic group. Further research is warranted to establish reference ranges and validate the FGF-21 role as a screening biomarker for early identification of prediabetes in high-risk obese populations.

Disclosure

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