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Serum Fibroblast Growth Factor 21 as a Novel Biomarker in Prediction of Coronary Artery Disease Severity

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MMK and SF designed the study. Author TA wrote the protocol and collected all patients' data. Author SF wrote the first draft of the manuscript. Author MMK managed the literature searches, analyses of the study results and wrote the final manuscript. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: To evaluate serum FGF-21 concentrations in coronary heart disease patients (CHD) whether or not associated with diabetes and/or hypertension. It also investigated the possible association between serum FGF21 and the coronary angiographic findings in terms of number of coronary vessels affected.
Study Design: Cross-sectional observational comparative study.
Place and Duration of Study: Coronary angiography unit at the Critical Care Department with Biochemistry Department, Kasr Al Aini Medical Hospitals, from January 2013 to March 2014.
Methods: Seventy patients (47 Males and 23 females) were classified after coronary angiography into: Sub-group (A): Coronary Artery Disease patients without DM or hypertension; Sub-group (B): Coronary Artery Disease patients with DM and/or hypertension; Sub-group (C): Patients with normal angiography but suffering from DM and/ or hypertension. Twelve healthy individuals were

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also included in the present study as a control group. Body Mass Index (BMI) were matched for all groups, systolic and diastolic blood pressure (SBP&DBP) and fasting serum levels of FGF21, glucose, insulin and lipid profile were estimated.

Results: A significant increase in the levels of FGF-21 was detected in CHD patients compared to control group (325.8 ± 129.2 Vs 202.2 ± 65.8, *P* =.002) and significant increase was also found in those with multi-vessel disease affection compared to those with one-vessel affection group (392.1 ± 140.4 Vs 250.7 ± 83.8, *P* =.007), There was a highly significant positive correlation between serum levels of FGF-21 and each of BMI (r= .7, *P* < .001), SBP (r= .63, *P* < .001), and DBP (r= .67, *P* < .001). ROC curve analysis indicated that the optimum cut off value for plasma FGF 21 level in patients with CHD versus control was 236 pg/ml which gives 68.33% sensitivity and 75% specificity.

Conclusion: Circulating FGF21 level could be a biomarker for CHD and may be used for assessment of severity of CHD.

Keywords: FGF 21; CHD; BMI; metabolic syndrome and type 2 DM.

1. INTRODUCTION

Fibroblast growth factor 21 (FGF21) is considered as a metabolic regulator that plays an important endocrine role regulating insulin sensitivity and glucose and lipid metabolism [1]. Circulating levels of FGF-21 were found to increase in obese individuals with metabolic syndrome and type 2 DM [2].

FGF-21 has been proposed as a potential therapeutic target for type 2 diabetes in humans as it inhibits hepatic glycogen degradation, thus reducing levels of circulating glucagon. FGF21-mediated effects leads to maintain normal physiologic control of blood glucose and maintenance of the non-diabetic state [3,4].

Many studies reported significant relations between circulating serum levels of FGF21 and cardiovascular diseases such as myocardial hypertrophy, coronary atherosclerosis and acute myocardial infarction AMI; [5,6] and its level was also associated with thickness of carotid plaques [7].

All previous research studied the direct relation of FGF21 as a marker in CHD [5,6,8,9] but they didn't attribute FGF21 level in relation to severity of lesions in coronary artery disease CAD. The present work aimed to evaluate serum FGF-21 concentrations in coronary heart disease patients (CHD) (assessed by coronary angiography), whether or not associated with diabetes and \or hypertension. It also aimed to assess severity of CHD through investigating the possible association between serum FGF21 and the coronary angiographic findings in terms of number of coronary vessels affected.

2. PATIENTS AND METHODS

2.1 Patients Selection

Seventy patients (47 Males and 23 females) were recruited from individuals admitted to the Critical Care Unit, Kasr Al Aini Medical Hospital, for coronary angiography to assess Ischemic (or Coronary) Heart Disease (IHD, CHD). Twelve (age, sex and body mass index (BMI) matched apparently healthy individuals were also included in the present study.

Exclusion criteria included all factors or diseases that known to increase FGF21 serum level such as: pregnancy, liver or renal disease, thyroid patients, cancer patients and patients on steroid therapy.

2.2 Methodology

All patients were subjected to the following:

2.2.1 History and examinations

Full medical history, general and cardiological examinations and resting ECG (electrocardiogram) pre and post angiography.

Anthropometric measurement will be carried out including (weight and height). The body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters. [10]

2.2.2 Laboratory investigations

Blood samples were collected after overnight fasting by venipuncture and were divided into two

parts in: A- Empty centrifuge tubes: samples were allowed to clot for 30 minutes before centrifugation for 15 minutes at 1000 x g. Sera were separated and divided into aliquots and stored at – 800C till used. Haemolysed samples were discarded. B- Fluoride containing tubes: (for glucose estimation): which were incubated in water bath at 370C for 15 minutes then centrifuged at 3500 rpm. Sera were used for estimation of fasting blood glucose, the following laboratory measurements were included:

- Estimation of biochemical variables (fasting glucose, insulin, total cholesterol, triglycerides, LDL, HDL cholesterol and creatinine) after an overnight fasting of at least 10 hours.
- Serum FGF-21 was estimated by the Quantitative Enzyme Linked Immuno-Sorbent Assay (ELISA) kit provided by R&D system [11].
- Estimation of serum levels of insulin, this was done by Enzyme Linked Immuno-Sorbent Assay (ELISA) kit provided by DRG instruments GmbH, division of DRG International, Inc. Marburg, Germany [12].
- Homeostasis model assessment for insulin resistance (HOMA-IR) value were calculated on basis of fasting value of plasma glucose and insulin according to HOMA model formula; HOMA-IR = fasting insulin (mlU/L) X fasting glucose (mmol/L) ÷ 22.5, Insulin resistance was arbitrarily considered altered when it was > 2 [13].

2.2.3 Coronary angiography

Eligibility criteria for coronary angiography were based on electrocardiogram findings, elevation of serum enzymes, and chest discomfort consistent with myocardial infarction or recurrent chest discomfort related to exercise or excitement that lasted up to 15 minutes that was responsive to rest or nitroglycerin and together with objective evidence of myocardial ischemia (≥1 mm of ST-segment depression or ≥2 mm of T-wave inversion on an electrocardiogram at rest or inducible ischemia on exertion or pharmacologic stress testing) [14,15,16].

The Procedure was carried through the right femoral artery using the Seldinger's technique and using 6F. Left Judkins and right Judkins catheters [17].

Significant coronary stenosis was considered when the vessel lesion was higher than 50% stenosis and the number of coronary vessels affection were measured as: One vessel disease, two vessels disease and multi-vessel disease (affection of 3 vessels or more).

After coronary angiography for 70 patients (their age mean was 53.23 ± 7.14 and 47 patients; 67.2% were males, they were classified into;

- Sub-group (A): 15 patients (21.4%) were found to have significant coronary lesions but they had neither DM nor hypertension, (female/male ratio were 2/13; so males were 86.7%).
- Sub-group (B): 45 patients (64.3%) were found to have significant coronary lesions and had DM and/or hypertension, (female/male ratio were 13/32; so males were 71.1%).
- Sub-group (C): 10 Subjects (14.3%) were found to have normal angiographic findings but they had DM and/ or hypertension, (female/male ratio were 8 /2; so males were 20%).

In addition there was a group of 12 volunteers (50%; 6 patients were males) who were not diabetic, hypertensive or ischemic as a control group for the level of FGF-21, Fig. 1.

Sixty patients with CHD diagnosed by coronary angiography again were classified according to number of vessel affected (> 50% stenosis) into;

- Sub-group (1): 21 patients had one vessel disease (35%).
- Sub-group (2): 17 patients had two vessel diseases (28.3%).
- Sub-group (3): 22 patients had multi-vessel disease (36.7%), (Table 3).

2.3 Statistical Analysis

Analysis of data was performed using SPSS 21 (Statistical Package for Scientific Studies) for Windows. Description of variables was presented as follows:

- Description of quantitative variables were presented as the following: Normally distributed data were expressed as mean ± SD. Data that were not normally distributed, as determined using Kolmogorox-Smirnov test, were logarithmically transformed before analysis

and expressed as median with interquartile range.

- Description of qualitative variables was in the form of numbers (No.) and percents (%).
- Comparison between quantitative variables was carried out by student T-test of two independent samples Results were expressed in the form of P-values.
- Comparison between non parametric quantitative variables was carried out by Mann–Whitney U. kruskal-wallis test was used when comparing between more than two groups of independent variables. Results were expressed in the form of P-values.
- Comparison between qualitative variables was carried out by Chi-Square test (X2). Fisher exact test was used instead of Chi-square test when one expected cell or more were ≤ 5.
- Binary correlation was carried out by Spearman correlation test. Results were expressed in the form of correlation coefficient (R) and P-values. The following points are the accepted guidelines for interpreting the correlation coefficient:

  - 0 indicates no linear relationship.
  - +1 indicates a perfect positive linear relationship: as one variable increases in its values, the other variable also increases in its values via an exact linear rule.

- ROC (Receiver Operating Characteristic) curves were drawn for detection of reliability of markers as a diagnostic tool and their best cutoff values were calculated. AUC (area under the curve) was considered if > 0.60.

3. RESULTS AND DISCUSSION

70 patients (their age mean was 53.23 ± 7.14 and 47 patients; 67.2% were males) were subjected to coronary angiography then according to their results, they were classified into;

- Sub-group (A): 15 patients (21.4%) were found to have significant coronary lesions but they had neither DM nor hypertension, (female/male ratio were 2/13; so males were 86.7%).
- Sub-group (B): 45 patients (64.3%) were found to have significant coronary lesions and had DM and/or hypertension, (female/male ratio were 13/32; so males were 71.1%).
- Sub-group (C): 10 Subjects (14.3%) were found to have normal angiographic findings but they had DM and/ or hypertension, (female/male ratio were 8 /2; so males were 20%).

In addition there was a group of 12 volunteers (50%; 6 patients were males) who were not diabetic, hypertensive or ischemic as a control group for the level of FGF-21, Fig. 1.

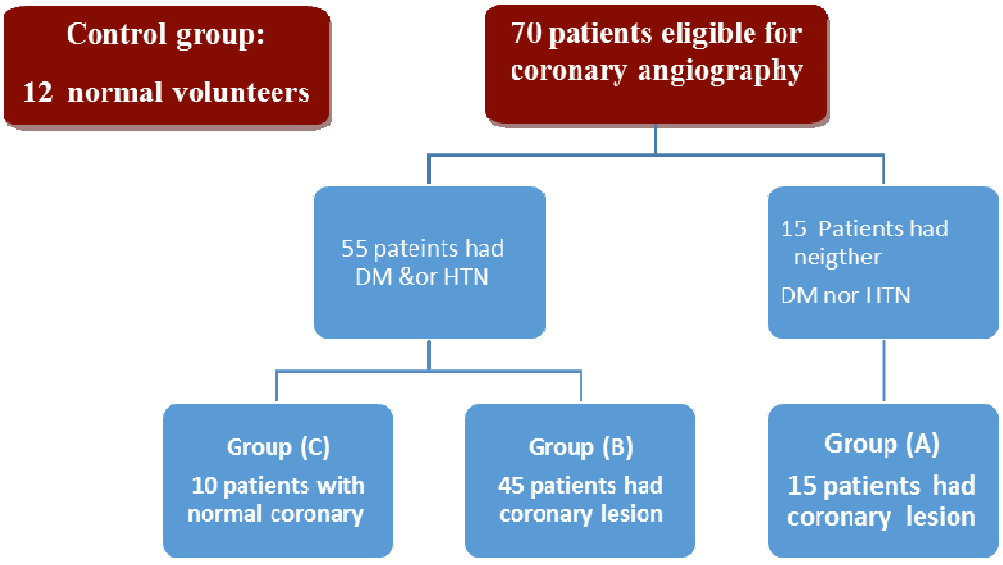

Fig. 1. Hierarchy of different groups of the study

Table 1. Comparison between the patient and control groups

	Patient group (n=70)	Control group (n=12)	P- value
Age (yrs)	53.2 ± 7.1	54.4 ± 6.6	0.70
BMI Kg/ m^2	27.6 ± 1.6	28.5 ± 1.7	0.12
Systolic bl. Press	141.8 ± 14.5	113.2 ± 7.8	0.001
Diastolic bl. Press	93.1 ± 15.3	73.3 ± 4.9	0.001
FBG mg/dl	133.0 ± 69.8	95.2 ± 11.6	0.91
Insulin µIU/mL	12.3 ± 7.1	14.4 ± 5.6	0.22
Cholesterol mg/dl	187.9 ± 44.5	166.7 ± 22.9	0.18
TG mg/dl	133.5 ± 55.1	101.2 ± 31.6	0.048
HDL-c mg/dl	37.8 ± 11.2	48.3 ± 5.8	**0.001**
LDL-c mg/dl	121.8 ± 38.6	102.1 ± 22.4	0.122
HOMA IR	4.16 ± 3.9	3.47 ± 1.6	0.77
FGF21 pg/mL	325.8 ± 129.2	202.2 ± 65.8	**0.002**

Table 2. Comparison between the 3 groups of patients subjected to coronary angiography

	Group A (n=15)	Group B (n=45)	Group C (n=10)	P- value
Age (yrs)	47.8 ± 5.2	55.0 ± 7.13	52.0 ± 5.9	0.002
BMI Kg/ m2	27.0 ± 1.6	27.8 ± 1.6	27.7 ± 1.6	0.45
Systolic bl. Press	129.0 ± 12.6	146.5 ± 11.0	145.0 ± 17.7	<0.001
Diastolic bl. Press	82.0 ± 8.8	97.2 ± 15.87	93.1 ± 12.8	0.001
FBG mg/dl	92.2 ± 12.4	144.1 ± 77.3	154.6 ± 71.3	0.007
Insulin µIU/mL	10.8 ± 7.41	12.5 ± 6.9	13.9 ± 7.5	0.56
Cholesterol mg/dl	179.0 ± 36.7	192.6 ± 42.9	162.4 ± 55.1	0.22
TG mg/dl	116.4 ± 51.0	144.9 ± 53.7	106.3 ± 63.8	0.011
HDL-c mg/dl	41.1 ± 8.56	36.7 ± 11.52	33.3 ± 10.2	0.22
LDL-c mg/dl	114.6 ± 32.8	124.5 ± 36.4	107.8 ± 55.4	0.43
HOMA IR	2.40 ± 1.6	4.5 ± 4.1	5.60 ± 5.2	0.03
FGF21 pg/mL	303.1 ± 119.6	334.9 ± 133.2	318.9 ± 132.8	0.04

When we compare the control group with the patients group who subjected to coronary angiography; 32.8% (23) patients were females, while 50% of the control group (6) were females, P-value=0.52, other general characteristics and laboratory findings between patient and control group are shown in Table 1.

Mean levels of serum HDL-c significantly decreased in the CHD patient versus the control group. The median levels of the DPB, SBP, serum TAG, and FGF-21 increased significantly in the CHD patient group as compared to the control group. However no significant differences were found in the CHD patient group versus the control group as regards the mean levels of the age, BMI, HOMA-IR, serum FBG, total cholesterol, serum LDL-c, and insulin (Table 1).

When we compared the results of the 3 groups of patients who did the coronary angiography according to their general characteristics and their laboratory findings, we found that there was a statistically significant relation between the 3 groups as regards the sex distribution with p-value= 0.008, other results are shown in Table 2:

The 60 patients with coronary lesions proved by coronary angiography were then classified according to number of affected vessels (showing more than 50% stenosis) into;

- Sub-group (1): 21 patients had one vessel disease (35%).
- Sub-group (2): 17 patients had two vessel diseases (28.3%).
- Sub-group (3): 22 patients had multi-vessel disease (36.7%).

Comparison between the 4 groups in relation to the general characteristics and laboratory findings as shown in Tables 3 and 4.

Mean levels of serum HDL-c significantly decreased in the subgroup with multi-vessel diseased patients (MVD) versus all other

Table 3. Comparison between different groups according to sex, DM and HTN

	MVD group (n=22)	Normal angio (n=10)	Single vessel (n=21)	Two vessels (n=17)	P- value
SEX	(4) 18.2%	(8) 80%	(6) 28.6%	(5) 29.4%	0.006
(F/M)	(18) 81.8%	(2) 20%	(15) 71.4%	(12) 70.6%	
DM	72.7%	40%	23.8%	29.4%	0.006
(yes/no)	27.3%	60%	76.2%	70.6%	
HTN	77.3%	80%	57.1%	47.1%	0.148
(yes/no)	22.7%	20%	42.9%	52.9%	

Table 4. Comparison between different groups according to different laboratory findings

	MVD group (n=22)	Normal angio (n=10)	Single vessel (n=21)	Two vessels (n=17)	p- value
Age (yrs)	55.2 ± 5.7	53.3 ± 5.9	53.6 ± 8.8	50.1 ± 6.5	0.17
BMI Kg/ m2	28.7 ± 1.5	27.6 ± 1.52	26.6 ±1.3	27.5 ± 1.3	0.001
Systolic bl. press	150.2 ± 10.4	140 ± 19.4	134.5 ± 12.6	141.2 ± 13.4	0.005
Diastolic bl.press	102.1 ± 20.45	91 ±12.2	86.4 ± 8.5	90.9 ± 10.5	0.002
DM duration	6.7 ± 4.6	6.7 ± 2.4	7.6 ± 5.2	3.3 ± 6.8	0.018
Htn duration	6.4 ± 3.0	8.1± 8.1	5.1 ± 5.7	4.3 ± 3.1	0.27
FBG mg/dl	155.3 ± 84.4	144.4 ± 66.5	104.1 ± 29.2	133.3 ± 79.4	0.07
Cholesterol mg/dl	179.4 ± 41.8	180.0 ± 61.2	189.2 ± 43.8	202.1 ± 37.1	0.38
TG mg/dl	124.6 ± 34.3	107.4 ± 56.9	148.1 ±73.3	142.1 ± 46.2	0.11
HDL-c mg/dl	31.3 ± 10.4	37.8 ± 13.2	41.7 ± 10.2	41.4 ± 8.8	0.006
LDL-c mg/dl	123.1 ± 40.7	120.7 ± 55.9	112.7 ± 31.3	132.3 ± 32.2	0.49
Insulin µIU/mL	12.6 ± 7.1	13.1 ± 7.6	12.9 ± 6.4	10.6 ± 7.9	0.72
FGF21 pg/mL	392.1 ± 140.4	318.9 ± 132.8	250.7± 83.8	336.8 ± 117.2	0.007
HOMA IR	4.74 ± 3.89	5.01 ± 4.84	3.4 ± 1.8	3.88 ± 5.2	0.41

subgroups and mean levels of BMI, DM duration and both systolic and diastolic blood pressure were significantly high in MVD group versus other groups. Significant increase was also found in those with multi-vessel disease affection compared to those with one-vessel affection group (392.1 ± 140.4 Vs 250.7± 83.8, *P* =.007), No significant differences in the mean levels of serum LDL-c, HOMA IR and insulin between the four groups Table 4.

Correlation of serum levels of FGF-21 with the other assessed parameters in CHD patients shows a highly significant positive correlation between FGF21 and each of BMI, DBP, and SBP. A weakly significant positive correlation was also found between FGF21 triacylglycerol and LDL-c. There was also a weakly significant negative correlation between FGF21and HDL-c. NO significant correlation between serum levels of FGF-21 and the rest of the studied parameters (Table 5).

Multivariate and univariate logistic regression analysis were performed for the factors that could affect and so predict CHD.

Table 5. Correlation of serum levels of FGF-21 with the other assessed parameters in CHD patients

Parameter	r - value	P- value
Age (years)	-0.115	0.304
BMI (Kg/m^2)	0.704	<0.001
DM duration (years)	-0.256	0.127
HTN duration (years)	-0.070	0.646
DBP (mmHg)	0.626	<0.001
SBP (mmHg)	0.672	<0.001
FBG mg/dL	0.052	0.646
Cholesterol mg/dL	0.152	0.173
Triacylglycerol mg/dL	0.223	0.044
HDL-c mg/dL	-0.231	0.037
LDL-c mg/dL	0.224	0.043
Creatinin mg/dL	-0.056	0.615
Insulin µIU/mL	-0.081	0.467
HOMA-IR	-0.086	0.440

r=0.7, P< .001, (n=60)

Serum levels of FBG, cholesterol, triacylglycerol, HDL-c, LDL-c, creatinine, insulin, HOMA-IR and FGF 21 & also BMI, DBP and SBP were selected as predictor variables for univariate analysis. Multivariate analysis was done stepwise. SBP was found to be the independent predictor for CHD (p =0.005, Odds Ratio (OR) = 1.396).

Table 6. Receiving operating curve (ROC) curve of serum concentration of FGF 21 for identification of patients destined to develop CHD compared to control

Variable	Cut-off value	Sensitivity %	Specificity %	AUC*	P value
FGF 21	236	68.33%	75%	.788	0.002

(AUC; area under the curve)

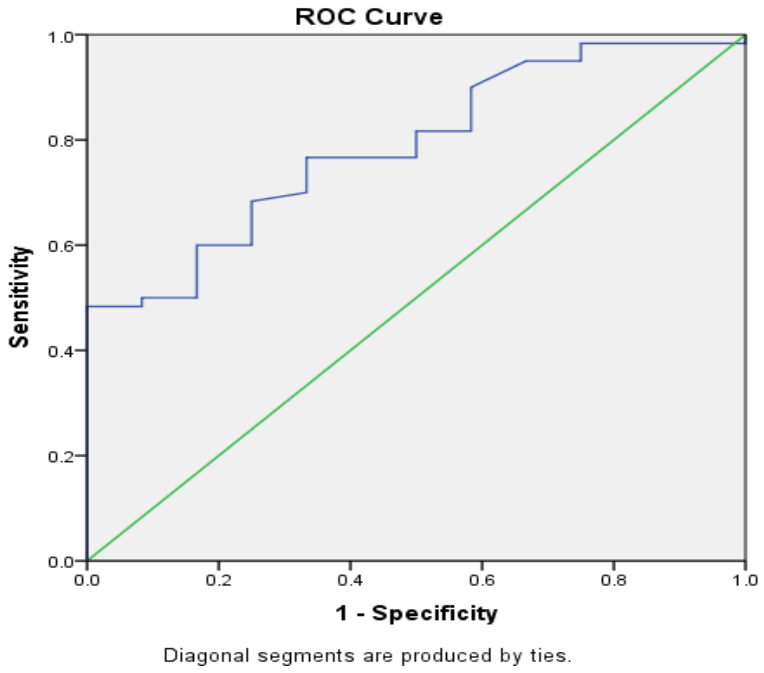

Fig. 2. ROC curve analysis to predict CHD versus normal control

ROC curve analysis indicated that the optimum cut off value for plasma FGF 21 level in patients with CHD versus control was 236 pg/mL which gives 68.33% sensitivity and 75% specificity.

3.1 Discussion

FGF21 are protein substances that are synthesized by the liver and adipose tissue. They are responsible for regulation of lipid and glucose metabolism and modifying insulin sensitivity through endocrine rather than paracrine pattern [18].

Some investigators described FGF21 substances as cytokines that released by the body as a protective response to inflammatory reaction secondary to metabolic syndrome [19], in type 2 DM and tissue ischemia, and this may explains high serum level of FGF21 in cases related to AMI, CAD [5,6,8,9] and in patients with thick atherosclerotic carotid plaques [7].

Other animal studies were concerned with the therapeutic role of FGF 21 in CHD that may be related to cardio-protective effect, through decreasing lipid metabolism in the cardiomyosites and prevention of oxidative stress and apoptosis by increasing other antioxidants like glutathione and superoxide dismutase. [20,21].

The present study investigated the associations between serum levels of FGF-21 in CHD subjects strictly matched for BMI. It also investigated the possible association between serum FGF21 and the coronary angiographic findings in terms of number of coronary vessels affected. Associations between serum FGF21, in CHD individuals, with diabetes, hypertension, or both were also addressed.

The present results illustrated an increase in the mean levels of serum FGF-21 in CHD patients versus the control group. There was a highly significant positive correlation between serum levels of FGF-21 and each of BMI ($r=0.7$, $p > 0.001$), SBP($r=0.63$, $P > 0.001$), and DBP ($r=0.67$, $P > 0.001$). A weakly significant positive

correlation was also found between serum levels of FGF-21 and each of TAG (r=0.223, P > 0.05) and serum levels of LDL-c (r=0.223, P > 0.05). A weakly significant negative correlation was also found between serum levels of FGF-21 and serum levels of HDL-c (r=0.23, P > 0.05).

In accordance to these results, a previous study done by Lin et al. showed that FGF-21 levels are 3-fold higher in CAD individuals, but they didn't describe FGF21 level in CHD in terms of severity [5].

The present study investigated the possible association between serum FGF21 and the coronary angiographic findings in terms of number of coronary vessels affected (> 50% stenosis). A significant increase in the mean levels of FGF-21 was detected in CHD patients with two vessel and multi-vessel affection compared to the control group and the one-vessel affecting group. These results indicate that serum levels of FGF-21 increase with the severity of the CHD condition. It is to be noted that the serum levels of FGf-21 correlated positively with SBP, DBP, serum levels of TAG and LDL-c and negatively with serum levels of HDL-c. All the fore-mentioned parameters are risk factors for CHD and may confound the relationships between FGF 21 and cardiovascular disease. Multi–variant logistic regression analysis revealed that the SBP was an independent risk factor for CHD.

In accordance with the present results, Semba et al. reported for the first time that elevated serum FGF-21 levels were associated with hypertension after adjustments with multiple explanatory variables in a community cohort. An inclusion of triglyceride levels as an explanatory variable substantially weakened the strength of association between the FGF-21 levels and hypertension [22]. In a previous report, Eto et al. postulated that elevated FGF-21 levels were also associated with higher systolic blood pressure in type 2 diabetic patients in a univariate analysis [23].

Logistic regression analysis demonstrated that FGF-21 showed an independent association with triglyceride and apolipoprotein A1. Apolipoprotein A1 is the major protein component of the high-density lipoprotein (HDL) particles, which promotes cholesterol efflux from tissues to the liver for excretion. Studies have shown inverse associations between apoA1 levels and CHD [24]. Direct administration of recombinant FGF21 has alleviated dyslipidemia in ob/ob and db/db mice and diabetic monkeys [25,26].

Consistent with our findings, a study showed a 2-fold increase of serum FGF21 in hypertriglyceridemic non-diabetic patients [27].

In vitro studies have shown that the over expression of FGF-21 suppressed triglyceride accumulation by inhibiting de novo lipogenesis [28], and interference with FGF-21 lead to dyslipidemia associated with the lower expression of enzymes related to fatty acid oxidation [29]. The elevation of FGF21 levels in patients showing high cardiometabolic risk can be viewed as a compensatory mechanism [25], or as indicative of an FGF21-resistant state. The latter interpretation is supported by a study of the short-term effects of exogenous FGF21 on diet-induced obese mice [30].

Lee et al. also reported that FGF21 levels correlate strongly with elevated triglycerides, and with ectopic fat accumulation, including pericardial fat, independent of the coronary artery status [6].

A progressive increase in serum FGF21 levels was also observed when an increasing number of components of the metabolic syndrome were found. More importantly, serum FGF21 was shown to be independently associated with the metabolic syndrome. This result suggests that serum FGF21 can be potentially used as a biochemical parameter for risk stratification of the metabolic syndrome. However, it is worthy to note that the association of serum FGF21 with the metabolic syndrome is not as strong as that of other biomarkers such as fasting insulin and C-peptide [2]. Further study is needed to evaluate whether serum FGF21 has any additive value to that of other classical biomarkers and/or risk factors in prediction of the metabolic syndrome.

Actually fasting blood sugar FBS, insulin level and insulin resistance HOMA IR were measured in all groups and subgroups but they didn't show significant statistical relation in different group comparisons, only HOMA IR showed significant relation between 3 subgroups A, B and C (P=.03).

Other studies are in accordance with our results as regards the correlation between serum levels of FGF-21 and any of FBG, insulin, or HOMA-IR. Li et al. [31] reported that serum levels of FGF21

are closely related to adiposity, lipid metabolism, and biomarkers of liver injury but not insulin secretion and sensitivity in humans.

Also, Matuszek et al. [19] confirmed that circulating FGF-21 is significantly and positively associated with weight, fasting glucose, and TG, whereas a negative correlation exists with HDL cholesterol. However, (as in our results) they failed to observe significant associations between markers of insulin resistance such as fasting insulin and HOMA-IR, which has been proven in research by others authors [32].

In the present study, ROC curve analysis indicated that the optimum cut off value for plasma FGF 21 level in patients with CAD versus non CAD was 236 which give 68.33% sensitivity and 75% specificity. This indicates that serum FGF21 may be potentially used as a biomarker of severity of CHD.

There are some limitations in this study. The large number of the confounders in relation to the rather small sample size of patients enrolled in this study. A large sample size may be needed for more comprehensive investigation. It may also, allow for better classification of CHD patients into diabetic only or hypertensive only or obese only. In addition, our study did not address the effect of diabetic control on the serum levels of FGF-21 nor the cause-effect relationship between FGF-21 and the onset and development of CHD. Further studies are needed to elucidate the precise mechanism by which CHD subjects elevate circulation FGF-21 levels and reveal the role of increased FGF-21 levels in CHD.

4. CONCLUSION

This study provides clinical evidence revealing that serum concentrations of FGF-21 are increased in CHD subjects with diabetes or hypertension in comparison to diabetic and hypertensive patients not suffering from CHD. Our data suggest that serum concentrations of FGF21 in humans are not related to insulin secretion, but rather to lipid metabolism. SBP appears to be strongly associated with serum FGF21 in CHD subjects. The consistent increase in FGF21 seen in human CHD patients and apparent significant difference between severely affected coronary lesion subgroups raises the intriguing possibility that FGF21 could be a biomarker for CHD and may be used for assessment of severity of CHD.

CONSENT

All patients were informed by all related details of the study and all patients signed detailed consent.

ETHICAL APPROVAL

This study was approved by both the local committee of Biochemistry Department and the ethical committee of Kasr Al-Aini medical hospital.

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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