International Journal Of

Recent Scientific Research

ISSN: 0976-3031

Volume: 7(4) April -2016

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 4, pp. 10232-10237, April, 2016

International Journal of Recent Scientific Research

Research Article

STUDY OF CIRCULATING FIBROBLAST GROWTH FACTOR – 21 AND INSULIN RESISTANCE IN PATIENTS WITH IMPAIRED FASTING, IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES

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ARTICLE INFO

Article History:

Received 06th January, 2016
Received in revised form 14th February, 2016
Accepted 23rd March, 2016
Published online 28th April, 2016

Keywords:

FGF-21, Type 2 diabetes, insulin resistance, adipocytokine.

ABSTRACT

Fibroblast growth factor -21 (FGF-21) is an adipocytokine with potent antidiabetic properties, that had been involved in the regulation of lipid and glucose metabolism. Aim: to assess the relationship between plasma levels of FGF-21 & Insulin resistance in cases with impaired fasting glucose, glucose intolerance and type 2 diabetes mellitus. Our case control study was conducted on eighty subjects, twenty with type 2 diabetes mellitus; twenty with impaired fasting glucose; twenty with impaired glucose tolerance; and twenty healthy subjects as our control group. All participants were subjected to full medical history thorough clinical examination and lab measuring of thorough clinical examination and lab measuring of serum FGF 21, FBG, 1hPPG, 2hPPG, HbA1c, FSI, HOMA-IR and lipid profile. Serum FGF-21 was higher in Type 2 diabetic patients, in impaired fasting glucose patients and in impaired glucose tolerance patients than in healthy group and highly significantly positively correlated with BMI, lipid profile (except HDL), indices of hyperglycemia, FSI and HOMA-IR. An inverse correlation was observed between Serum FGF-21 and HDL. FGF-21 might play a role in the development of diabetes and in dyslipidemia associated with insulin resistance.

INTRODUCTION

Diabetes is an increasing global health problem in recent years. The awareness of adipose tissue as a reservoir of fatty acids has been switchedyears by the assumption that adipose tissue is in charge of lipid and glucose metabolism and responsible for a large number of hormones and cytokines and thisleads to insulin resistance *(Beata et al., 2010)*.

IFG and IGT stand for intermediate states of abnormal glucose parameterthat is present between normal glucose homeostasis and diabetes. IFG is described as an elevated fasting plasma glucose (FPG) concentration (> 100 and < 126 mg/dl). IGT is demarcated as an elevated 2- h plasma glucose concentration (> 140 and < 200 mg/ dl) after a 75- g glucose load on the oral glucose test (OGTT) in the presence of FPG concentration <100 mg/dl *(Nathan et al., 2007)*.

Numerous adipose tissue hormones, adipokines, have revealed to predict and to be tangled in the pathogenesis of type 2 diabetes mellitus (T2DM). Data exposed an increasing proof that liver-derived hormones influence glucose and lipid metabolism. Among these "hepatokines," fibroblast growth factor FGF 21 has an increasing awareness *(Pradhan et al., 2001; Spranger et al., 2003)*.

Fibroblast growth factor -21 (FGF 21), a member of the FGF-19 subfamily, is an adipocytokine with a potent antidiabetic properties. FGF-21 is a metabolic regulator, and animal models has shown that FGF-21 improve glucose metabolism and insulin sensitivity *(Wente et al., 2006)*.

The present study aimed to assess the relationship between plasma level of FGF-21 & Insulin resistance in cases with impaired fasting glucose, glucose intolerance and type 2 diabetes mellitus.

SUBJECTS AND METHODS

Our case control study was conducted on eighty subjects, divided into four groups; **Group I:** Included twenty diabetic patients with type 2 diabetes mellitus aged 51.25±13.75 years and included 6 males and 14 females. **Group II:** Included twenty patients with impaired fasting glucose aged 46.5± 15.5 years and included 4 males and 16 females. **Group III:** Included twenty patients with impaired glucose tolerance aged 46 ±14years and included 8 males and 12 females.

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Table 1 Comparison between the different studied groups regarding the results of different variables

variables	Group I	Group II	Group III	Group IV	ANOVA		Sheffe's Test	
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	f	p-value	Comp.	p-value
BMI (kg/m^2)	31.4 ± 3.84	30.0 ± 1.94	30.05 ± 1.87	27.05 ± 2.76	**9.064**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	0.456 0.488 <0.001** 0.995 0.012* 0.010*
W/H ratio	0.90 ± 0.041	0.89 ± 0.018	0.88 ± 0.012	0.84 ± 0.017	**23.165**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	0.667 0.559 <0.001** 0.998 <0.001** <0.001**
FBS (mg/dl)	150.45 ± 48.1	116.85 ± 4.72	85.1 ± 11.45	71.7 ± 5.96	**39.404**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** <0.001 <0.001** <0.001** 0.419
1 hPPS (mg/dl)	252.05 ± 55.2	126.0 ± 3.04	121.15 ± 10.5	87.75 ± 7.49	**39.404**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** <0.001** 0.055 <0.001** 0.005*
2 hPPS (mg/dl)	321.0 ± 55.13	136.45 ± 1.66	156.2 ± 15.27	102.1 ± 11.02	**223.001**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** <0.001** <0.001** 0.005** <0.001**
HbA1c %	7.35 ± 0.793	5.52 ± 0.266	5.60 ± 0.302	5.22 ± 0.112	**92.270**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** <0.001** 0.965 0.220 0.073
FSI (µIU/ml)	16.25 ± 5.87	16.30 ± 3.18	15.30 ± 3.26	7.95 ± 1.57	**22.461**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	0.998 0.890 <0.001** 0.857 <0.001** <0.001**
HOMA-IR	5.86 ± 2.39	4.56 ± 0.986	3.16 ± 0.651	1.41 ± 0.324	**40.465**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	0.029 <0.001** <0.001** 0.017 <0.001** <0.001**
FGF 21 (pg/ml)	337.3 ± 151.7	294.1 ± 105.2	266.6 ± 94.86	182.15 ± 91	**7.801**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	0.678 0.024 <0.001** 0.301 0.022* 0.043*
S. creat (mg/dl)	0.950 ± 0.127	0.895 ± 0.135	0.905 ± 0.123	0.830 ± 0.130	**2.930**	**0.039***	I&II I&III I&IV II&III II&IV III&IV	0.615 0.751 0.042* 0.996 0.475 0.346
AST (U/L)	27.65 ± 7.67	24.8 ± 7.33	27.95 ± 7.28	22.95 ± 6.73	**2.168**	**0.099**	I&II I&III I&IV II&III II&IV III&IV	0.675 0.999 0.251 0.600 0.885 0.201

ALT (U/L)	28.75 ± 7.24	26.85 ± 7.60	29.40 ± 8.31	24.05 ± 6.47	**2.080**	**0.110**	I&II I&III I&IV II&III II&IV III&IV	0.884 0.994 0.271 0.759 0.703 0.169
TC (mg/dl)	168.7 ± 5.10	182.40 ± 5.14	182.55 ± 6.22	171.0 ± 8.63	**26.082**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** 0.735 0.998 <0.001** <0.001**
HDL (mg/dl)	35.8 ± 1.39	42.8 ± 2.64	43.25 ± 2.75	53.9 ± 4.01	**136.678**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** <0.001** 0.969 <0.001** <0.001**
LDL (mg/dl)	98.2 ± 4.23	115.8 ± 4.76	114.65 ± 4.88	103 ± 12.07	**28.672**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** 0.232 0.969 <0.001** <0.001**
TG (mg/dl)	163.85 ± 9.42	134.15 ± 6.80	138.7 ± 6.94	114.3 ± 11.08	**108.355**	**<0.001****	I&II I&III I&IV II&III II&IV III&IV	<0.001** <0.001** <0.001** 0.445 <0.001** <0.001**
eCcr	101.75 ± 22.2	112.85 ± 28	115.1 ± 22.76	116.85 ± 26.1	**1.487**	**0.225**	I&II I&III I&IV II&III II&IV III&IV	0.577 0.420 0.305 0.994 0.967 0.997

*; statistically significant, **; high statistical significant

Group IV: Included twenty normal subjects as a control group aged 40.5 ± 19.5 years and included 9 males and 11 females. Patients were recruited from diabetes out-patient clinic in Ain Shams University Hospital. This study was approved by the ethical committee. Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol.

All subjects were subjected to full medical history emphasizing on diabetic complications and other associated illnesses, thorough clinical examination including blood pressure and anthropometric measurements (Body Mass Index (BMI), Waist circumference and Hip circumference). Patients with type 1 diabetes mellitus, chronic illness like liver cell failure, renal failure, heart failure, cancer, autoimmune disease, pregnancy, and alcohol or drug abuse were excluded from our study. Also, patients with morbid obesity BMI ≥ 40 kg/m2 and on drugs that may affect insulin sensitivity as corticosteroids and thiazide diuretics for at least 6 months before were excluded.

Laboratory Measurements

Laboratory tests included fasting plasma glucose (FPG), 1h post oral glucose load (1hPPG), 2h post oral glucose load (2hPPG), fasting serum insulin (FSI), HbA1c, assessment of HOMA-IR, lipid profile, serum fibroblast growth factor -21 (FGF-21), ALT, AST, Serum creatinine and estimation of GFR.FPG, 1hPPG and 2hPPG were measured using an automated glucose oxidase method using Behring Diagnostics Reagents (SVR Glucose Test; Behring, La Jolla, CA). HbA1c Serum lipid concentrations were assayed by quantitative enzymatic colorimetric determination for total cholesterol, high-density lipoprotein cholesterol and triglycerides in plasma (Stanbio Cholesterol Liquicolor, Procedure NO. 1010). Immunoenzymatic assay was used for in vitro quantitative measurements of fasting serum insulin (BioSource INS-EASIA Kit; BioSource Europe SA, Belgium). Insulin resistance was estimated by HOMA-IR and was defined as fasting serum insulin (µU/mL) ×FPG (mmol/l)/22.5 *(Matthews et al, 1985)*. Estimation of GFR using Cockcroft Gault equation [ml/min]; eCcr = (140-age) ×Mass (in kilograms) × (0.85 if female)/ 72× serum creatinine (in mg/dl) *(Cockcroft et al, 1976)*. Serum fibroblast growth factor 21 is assayed by ELISA (Merck group, Millipore, Missouri 63304 U.S.A, Cat. # EZHFGF21-19K) using serum samples.

Statistical Analysis

Data analysis was performed using the SPSS program (version 20, 2012, IBM Corporation, USA). Data were expressed as mean ± standard deviation (SD), which was used for quantitative data, whereas number and percent (%) were used for qualitative data. According to the computer program SPSS for Windows. Parametric data was analyzed using one-way analysis of variance (ANOVA) test for comparison among different times in the same group in quantitative data. Post-hoc test (Tukey's) was used to detect the least significant difference (LSD) among the studied groups. Pearson's correlation coefficient (r) test was used for correlating data. Mann-Whitney U test was used to compare quantitative variables, in non-parametric data. Linear Correlation Coefficient [r] test was

used for correlating data. Scheffé's test is used for adjusting significance levels in a linear regression analysis to account for multiple comparisons. Standard student "t test", test of significance of the difference between two means was used when comparing between fibroblast growth factor-21 and different parameters. Probability (p-value) less than 0.05 was considered significant and less than 0.01 was considered as highly significant.

RESULTS

This study was conducted on 80 subjects, 27 (33.75%) were males and 53 (66.25%) were females. They were age and sex matched.

There was high statistical significant difference between all studied groups as regard BMI, W/H ratio, FPG, 1hPPS, 2hPPG, HbA1c, FSI, serum total cholesterol, serum triglycerides, HDL, LDL and HOMA-IR ($p < 0.01$). There was no statistical significant difference between all studied groups as regard eCcr, AST, ALT.

Serum FGF-21 levels were highly statistically significantly increased in Type 2 diabetic subjects, in impaired fasting glucose subjects and in impaired glucose tolerance subjects in comparison to control group ($p<0.01$). Also, Type 2 diabetic subjects had higher serum FGF-21than impaired glucose tolerance subjects ($p<0.05$), while there was no difference between Type 2 diabetic subjects and impaired fasting glucose subjects ($p=0.678$). Data were summarized in table 1.

Our results demonstrated that serum fibroblast growth factor 21 levels were highly significantly positively correlated ($p\leq0.001$) in Type 2 diabetic subjects, in impaired fasting glucose subjects and in impaired glucose tolerance subjects with BMI, W/H ratio, FPG, 1hPPG, 2hPPG, HbA1c, FSI, HOMA-IR, serum total cholesterol, serum triglycerides and LDL. An inverse correlation was observed between serum FGF-21 levels and HDL and eCcr but of no significant difference, as shown in table 2.

Table 2 Correlation coefficient between FGF21 and studied parameters in group I, group II and group III:

With	FGF 21					
	Group I		Group II		Group III	
	r	P	r	p	r	P
BMI	0.927	0.001**	0.929	0.001**	0.931	0.001**
W/H ratio	0.889	0.001**	0.969	0.001**	0.915	0.001**
FBS	0.915	0.001**	0.879	0.001**	0.898	0.001**
1 hpps	0.922	0.001**	0.955	0.001**	0.907	0.001**
2 hpps	0.949	0.001**	0.852	0.001**	0.950	0.001**
HBA1c	0.923	0.001**	0.904	0.001**	0.841	0.001**
FSI	0.909	0.001**	0.869	0.001**	0.895	0.001**
HOMA-IR	0.969	0.001**	0.943	0.001**	0.857	0.001**
S.creat	- 0.046	0.848	- 0.147	0.537	0.211	0.373
AST	0.178	0.453	0.067	0.777	0.172	0.469
ALT	0.206	0.384	0.050	0.836	0.257	0.274
TC	0.947	0.001**	0.938	0.001**	0.972	0.001**
HDL	- 0.356	0.125	- 0.276	0.236	- 0.191	0.419
LDL	0.878	0.001**	0.935	0.001**	0.875	0.001**
TG	0.860	0.001**	0.931	0.001**	0.966	0.001**
ECcr	- 0.140	0.555	- 0.122	0.609	- 0.076	0.751

DISCUSSION

According to our study, there was a statistically highly significant difference ($P<0.01$) between the four studied groups as regard FGF-21 (being highest in type 2 diabetic patients & lowest in control group).There is significant difference ($P<0.05$) between type 2 diabetic patients &impaired glucose tolerance patients, as regard FGF-21. Serum FGF-21 level was significantly higher in diabetic patients compared to impaired glucose tolerance patients and to control subjects. While there was no difference between impaired fasting glucose patients &impaired glucose tolerance patients ($p>0.05$) as regard FGF-21.

This result was a consistent finding with the study of *Alberto et al., 2009*, which found that serum FGF-21 is elevated in patients with T_2diabetes than healthy subjects (5.27 ±0.23 vs 3.88± 0.30 ng/ml $p< 0.05$). Also, in Impaired glucose tolerance subjects than healthy subjects (5.22 ±0.23 ng/ml $P < 0.05$) (*Alberto et al., 2009*). In addition, this is consistent with two other reports (*Chen et al., 2008; Zhang et al., 2008*) along with two previous studies in Asians, where FGF-21 levels were increased among newly diagnosed, drug-naïve diabetic subjects and treated type 2 diabetic subjects (*Li et al., 2008*).

Our results showed a significant positive correlation between serum FGF-21 and BMI &W/H ratio in diabetic patients, impaired fasting glucose patients and the impaired glucose tolerance patients ($p<0.05$). This result was consistent with a number of studies indicated that FGF-21 serum concentrations positively correlated with the BMI (*Christodoulides et al., 2009; Chavez et al., 2009; Mraz et al., 2009*). On the contrary to our results, *Beata et al., 2010*, found that there was no correlation between circulating FGF-21 with BMI. Increased FGF-21 serum levels have been found to be associated with obesity in both children (*Reinehr et al., 2012*) and adults, indicating a connection between FGF-21 and body fat mass (*Dushay et al., 2010*).

Furthermore, it had been shown that body weight was moderately decreased in FGF-21 treated animals (*Kharitonenkov et al., 2007; Xu et al., 2009*) and no evidence of augmented adiposity had been demonstrated (*Kharitonenkov et al., 2008*).

There was significant positive correlation between FGF-21 and fasting serum insulin (FSI) in diabetic group, impaired fasting glucose group and the impaired glucose tolerance group ($p<0.05$) in our work. This result was consistent with *Zhang et al. 2008*, who found that serum FGF-21 correlates positively with FSI. Some studies had shown that artificial hyperinsulinemia performed in healthy subjects is accompanied by an increase in FGF-21 levels (*Mai et al., 2009*). However, FGF-21 increases in hypoinsulinemic states (*Mai et al., 2010*).

FGF-21 level was found to be significantly positively correlated with FPG, 1hPPG and 2hPPG in diabetic group, impaired fasting glucose group and impaired glucose tolerance group ($p<0.05$). This result is consistent with *Chavez et al., 2009 and Cheng et al., 2011*. On the contrary to our study, there was no correlation between FGF-21 and FPG, 1hPPG and 2hPPG *(Galman et al., 2008)*. Glucose uptake induced by FGF21 is additive and independent of insulin. This glucose

entry into adipocytes results in its storage as TG. Moreover, the ability of FGF-21 for increasing the thermogenic capacity of white adipose tissue could, in part, lead to a greater clearance of glucose (*Hondares et al., 2010; Fisher et al., 2012*).

In the current study, there was a significant positive correlation between FGF-21and HbA1c in diabetic group, impaired fasting glucose group and impaired glucose tolerance group ($p<0.05$). This result is consistent with the study showed that plasma FGF-21 concentration to be correlated with A1C ($r = 0.325$, $P = 0.04$) (*Alberto et al., 2009*). But, *Beata et al., 2010* found that circulating FGF-21 levels were not correlated with HbA1c. Also, there was a significant correlation between FGF-21 and HOMA-IR in diabetic group, impaired fasting glucose group and impaired glucose tolerance group ($p<0.05$). FGF-21 correlates inversely with insulin sensitivity at muscle level and directly with the hepatic insulin resistance index, FPG, and 2hPPG after an oral glucose tolerance test and HbA1c, indicating an important relationship with hepatic and whole body insulin resistance in T2DM (*Cheng et al., 2011; Li et al., 2008*). FGF-21 is independently associated with insulin resistance and increased in T2DM in adults from the Baltimore longitudinal study of aging (*Semba et al., 2012*).

In addition, our study recorded a significant positive correlation between FGF- 21 and TG and LDL in diabetic group, impaired fasting glucose group and impaired glucose tolerance group ($p<0.05$) and non-significant correlation with HDL ($p>0.05$).This result was consistent with *Zhang et al., 2008* and *Lin et al., 2010* studies that found serum FGF-21 to be correlated positively with adiposity, TG and LDL.

Insulin resistance was closely linked with increased TG level as evidenced by *Chan et al*., 2002. In addition, *Chen et al., 2011*, demonstrated an independent association between serum FGF-21 levels on one hand and TG and HDL on the other hand in Chinese individuals. On the contrary to our result, it had been found that there was no significant correlation between FGF-21 and LDL and HDL by *Bobbert et al., 2013*. FGF21 had shown beneficial effects on lipid profile in animal models. Systemic administration of FGF-21 was also followed by a decrease in plasma TG, free fatty acids (FFA), and cholesterol in genetically compromised diabetic and obese rodents (*Kharitonenkov et al., 2005; Xu et al., 2009*).

Moreover, FGF-21 has a promise as a new therapeutic approach for type 2 diabetes. It results in a better lipid profile, which includes lowering LDL and raising HDL in diabetic rhesus monkeys (*Kharitonenkov et al., 2007*).

CONCLUSION

Serum FGF-21 was positively correlated to BMI, W/H ratio and to insulin resistance. FGF-21 may play a role in dyslipidemia associated with insulin resistance. Further studies are recommended to assess the role of FGF-21 in insulin resistance, hypertensive patients, in microvascular and macrovascular complications and also to assess the effect of antidiabetic drugs on FGF-21 level in type 2 diabetes mellitus as FGF-21 may show a promise as a new therapeutic approach for type 2 diabetes.

References

Alberto OC, Molina-Carrion M, Abdul-Ghani MA, Folli F, DeFronzo RA, and Tripathy D. Circulating FGF-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. Diabetes Care 2009; 32:1542–1546.

Beata M, Monika LL, Dariusz D, Janusz S, Andrzej N. Evaluation of concentrations of FGF-21 — a new adipocytokine in type 2 diabetes. Endokrynol Pol 2010; 61 (1): 50–54.

Bobbert T, schwarz F, Fischer-RosinskyA, Pfeiffer AFH, Möhlig M, Mai K andSpranger J. Fibroblast Growth Factor 21 Predicts the Metabolic Syndrome and Type 2 Diabetes in Caucasians. Diabetes Care 2013; 36:145–149.

Chan DC, Watts GF, Barrett PH,Mamo JC, Redgrave TG. Markers of triglyceride-rich lipoprotein remnant metabolism in visceral obesity. ClinChem 2002; 48:278–283.

Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, Defronzo RA, Tripathy D. Circulating fibroblast growth factor-21 (FGF-21) is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. Diabetes Care 2009; 32: 1542–1546.

Chen WW, Li L, Yang GY, Li K, Qi XY, Zhu W, Tang Y, Liu H, Boden G. Circulating FGF-21 levels in normal subjects and in newly diagnose patients with type 2 diabetes mellitus. Exp. Clin. Endocrinol. Diabetes 2008; 116: 65–68.

Chen W, Hoo RL, Konishi M, Itoh N, Lee PC, Ye HY, Lam KS, Xu A. Growth hormone induces hepatic production of fibroblast growth factor 21 through a mechanism dependent on lipolysis in adipocytes. Journal of Biological Chemistry 2011; 286: 34559–34566.

Cheng X, Zhu B, Jiang F, Fan H. Serum FGF-21 levels in type 2 diabetic patients. Endocrine Research 2011; 36: 142–148.

Christodoulides C, Dyson P, Sprecher D, Tsintzas K, Karpe F.Circulating FGF- 21 is induced by peroxisome proliferatoractivated receptor agonists but not ketosis in man. J Clin Endocrinol Metab 2009; 94:3594–601

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976, 16: 31-41.

Dushay J, Chui PC, Gopalakrishnan GS *et al*. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 2010; 139:456–463.

Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, *et al*. FGF21 regulates PGC-1a and browning of white adipose tissues in adaptive thermogenesis. Genes and Development 2012; 26: 271–281.

Galman C, Lundasen T, Kharinonekov A, Bina HA, Eriksson M*et al*. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPAR-a activation in man. Cell Metabolism 2008; 8: 169–174.

Hondares E, Rosell M, Gonzalez FJ, Giralt M, Iglesias R, Villarroya F. Hepatic FGF21 expression is induced at birth via PPARa in response to milk intake and

contributes to thermogenic activation of neonatal brown fat. Cell Metabolism 2010; 11: 206–212.

Kharitonenkov A and Shanafelt AB. Fibroblast growth factor-21 as a therapeutic agent for metabolic diseases. Bio Drugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy 2008; 22: 37–44.

Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R *et al*. FGF-21 as a novel metabolic regulator. Journal of Clinical Investigation 2005; 115: 1627–1635.

Kharitonenkov A, Wroblewski WJ, Koester A, Chen YF, Clutinger CK *et al*. The metabolic state of diabetic monkeys is regulated by FGF21. Endocrinology 2007; 148: 774–781.

Li L, Yang G, Ning H, Yang M, Liu H, Chen W. Plasma FGF-21 levels in type 2 diabetic patients with ketosis. Diabetes Res Clin Pract 2008; 82:209–213.

Lin Z, Wu Z, Yin X, Liu Y, Yan X *et al*. Serum levels of FGF-21 are increased in coronary heart disease patients and are independently associated with adverse lipid profile. PLoS ONE 2010; 5: e15534.

Mai K, Andres J, Biedasek K, Weicht J, Bobbert T *et al*. Free fatty acids link metabolism and regulation of the insulin-sensitizing fibroblast growth factor-21. Diabetes 2009; 58: 1532–1538.

Mai K, Bobbert T, Groth C, Assmann A, Meinus S*et al*. Physiological modulation of circulating FGF21: relevance of free fatty acids and insulin. *American Journal of Physiology*. Endocrinology and Metabolism 2010; 299: E126–E130.

Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC.Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412e419.

Mraz M, Bartlova M, Lacinova Z, Michalsky D, Kasalicky M*et al*. Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clin Endocrinol (Oxf) 2009; 71:369–375.

Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR *et al*. Impaired fasting glucose and impaired glucose tolerance- Implications for care. DiabetesCare2007; 30:753–759.

Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286:327–334.

Reinehr T, Woelfle J, Wunsch R, Roth CL. Fibroblast growth factor 21 (FGF-21) and its relation to obesity, metabolic syndrome, and nonalcoholic fatty liver in children: a longitudinal analysis. *Journal of Clinical Endocrinology and Metabolism* 2012; 97: 2143–2150.

Semba RD, Sun K, Egan JM, Crasto C, Carlson OD, Ferrucci L. Relationship of serum fibroblast growth factor 21 with abnormal glucose metabolism and insulin resistance: the Baltimore Longitudinal Study of Aging. *Journal of Clinical Endocrinology and Metabolism* 2012; 97: 1375–1382.

Spranger J, Kroke A, Möhlig M,Bergmann MM, Ristow M *et al*. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003; 361:226–228.

Wente W, Efanov AM, Brenner M, Kharitonenkov A, KösterA *et al*. Fibroblast growth factor-21 improves pancreatic β-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways. Diabetes 2006; 55: 2470–2478.

Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M*et al*. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 2009; 58:250 –259.

Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG*et al*. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 2008; 57:1246–1253.

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How to cite this article:

AbdEsatar E. Eldeeb., Enas M. Sabry and Meram M. Bekhet.2016, Study of Circulating Fibroblast Growth Factor – 21 And Insulin Resistance In Patients With Impaired Fasting, Impaired Glucose Tolerance And Type 2 Diabetes. *Int J Recent Sci Res.* 7(4), pp. 10232-10237.

TSSN 0976-3031