

High Circulating Fibroblast Growth Factor-21 Levels as a Prognostic Marker in Fatty Pancreas Patients

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Research article

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Abstract

Background: The study aimed to detect the serum levels of fibroblast growth factor-21 (FGF-21) in fatty pancreas (FP) patients and to investigate their potential clinical value.

Methods: We screened patients with FP using transabdominal ultrasound. The anthropometric, biochemical and serum levels of FGF-21 were compared between the FP group and the normal control (NC) group. A receiver operating characteristic (ROC) curve was used to evaluate the predictive value of serum FGF-21 for FP patients.

Results: Compared with the NC group, body mass index, fasting blood glucose levels, uric acid levels and cholesterol levels of the FP group were significantly higher, while the high-density lipoprotein level was lower. In addition, levels of serum FGF-21, resistin, leptin and tumor necrosis factor- α were significantly higher than those in the NC group, while the serum adiponectin level was lower. Pearson analysis showed serum FGF-21 levels in FP patients were negatively correlated with leptin and cholesterol. The ROC curve showed the best critical value of the serum FGF-21 level in FP patients was 187.85 pg/mL (AUC 0.716, $P=0.002$, 95% confidence intervals 0.611-0.820).

Conclusion: Serum FGF-21 was closely related to fatty pancreas. Detecting serum FGF-21 levels may help identify the population susceptible to FP.

Introduction

Adipose tissue, as the energy storage of the body, is mainly distributed throughout the body subcutaneously and around the abdominal organs. An imbalance in energy metabolism can lead to fat deposition in abnormal areas, such as the liver and muscle fascia, and these abnormal deposits are called ectopic fat deposits [1]. It has been found that fat can be deposited heterotopically in pancreatic tissue, which is usually referred to as fatty pancreas (FP) and this condition has a definite pathophysiological significance [2]. As early as 1933, Ogilvie [3] found via autopsy that there was a difference in pancreatic fat content between obese and nonobese people. Li et al. noted that the incidence of fatty pancreas varied from 16% to 69.7% in different countries [4]. Previously, our team found that the prevalence of fatty pancreas in the examined population was approximately 2.7% in Yangzhou, China [5]. The specific pathogenesis of fatty pancreas remains unclear.

Fibroblast growth factor-21 (FGF-21) is a member of the endocrine fibroblast growth factor subfamily [6]. The main physiological function of FGF-21 is to maintain the balance between glucose and lipid metabolism [6]. Animal experiments have shown that excessive expression of FGF-21 could lead to body fat reduction [7]. In addition, exogenous FGF-21 plays a clear role in promoting glucose uptake and reducing blood glucose and liver fat deposition [7]. Clinical studies have shown that the circulating FGF-21 level was closely related to metabolic diseases. Serum FGF-21 levels in patients with fatty liver, obesity, metabolic syndrome and diabetes were significantly higher than those in healthy volunteers [8, 9, 10, 11].

FGF-21 also plays an important role in pancreatic diseases. FGF-21 is highly expressed in pancreatic exocrine cells, and its expression can be significantly increased when acute pancreatitis occurs [12]. Johnson et al. showed that FGF-21 gene knockout mice experienced aggravated acute pancreatitis and that exogenous FGF-21 could significantly reduce the severity of caerulein-induced acute pancreatitis in mice [13]. Recent animal experiments have confirmed that recombinant human FGF-21 can reduce inflammation, pancreatic cysts high-grade intraepithelial neoplasia and pancreatic cancer in high-fat-diet-fed mice, suggesting that FGF-21 may be used for the prevention and treatment of pancreatic cancer [14]. Surprisingly, FGF-21-deficient mice exhibit a phenotype of pancreatic fat deposition [15]. However, there are no reports on the correlation between FGF-21 and fatty pancreas. Hence, in the present study, circulating FGF-21 levels in patients with fatty pancreas were detected for the preliminary assessment of their relationship.

Materials And Methods

Study population

The study was performed at the Affiliated Hospital of Yangzhou University in Yangzhou, China. We selected 99 fatty pancreas subjects and 19 healthy subjects from the physical examination center of Affiliated Hospital of Yangzhou University from August 2018 to June 2019. Fatty pancreas subjects who met the following criteria were excluded: (1) subjects aged < 18 years or > 65 years; (2) subjects with an acute or chronic inflammatory disease; (3) subjects with a previous diagnosis of chronic pancreatic, liver or kidney disease; (4) subjects with severe immune system disorders or pregnancy; (5) subjects with incomplete information or refusal to provide clinical blood samples.

This study conformed to the ethical principles of the Declaration of Helsinki. Consent from the subjects, as well as ethical approvals from our hospital ethics committees, was obtained.

Diagnosis of fatty pancreas and fatty liver

As previously described, all subjects underwent transabdominal ultrasonography to diagnose fatty pancreas and fatty liver [5]. Operations were performed by skilled surgeons with more than 10 years of experience using transabdominal ultrasonography (with an abdominal convex array probe, frequency: 3.5-5 MHz, LOGIQ E9, GE, USA). The ultrasound diagnostic criteria for fatty liver were as follows: the anterior echo of the liver was enhanced while the posterior echo was weakened, and the tubular structure of the liver could not be clearly displayed [16]. The characteristics of the ultrasonic image of fatty pancreas were as follows: diffuse strong echoes of pancreatic parenchyma, normal or slightly increased volume, similar or slightly higher echogenicity compared to the adipose tissue in the area of the superior mesenteric artery [5, 17].

Anthropometric and biochemical findings

Clinical information, including the subject's identity, age, body weight, height, blood pressure, past medical history, drug history, history of smoking and alcohol intake, was recorded using a standardized

questionnaire. Height and body weight were assessed using standardized and calibrated scales. Additionally, the body mass index (BMI) was calculated for each subject [BMI=body weight (kg)/square of height (m²)]. The subjects included “continuous smokers” (continuous or cumulative smoking for 6 months or more in a lifetime) and “nonsmokers” (including those who quit smoking ≥1 year ago). The subjects also included “continuous drinkers” (drinking volume ≥20g/d; drinking duration ≥2years) and “nondrinkers” (individuals who had not consumed alcohol for ≥half a year).

All subjects fasted for at least 8 hours the night before the visit, and blood samples were collected with the participants in a quiet state on an empty stomach the next morning. Blood samples were sent to the laboratory for uniform testing (dry chemical method), and the remaining unused serum was frozen in an ultralow temperature freezer for analysis using an enzyme linked immunosorbent assay (ELISA). Diabetes was defined as a fasting blood glucose (FBG) level ≥6.1 mmol/L or a previous diagnosis by a doctor.

Dyslipidaemia was defined as meeting any of the following: high serum total cholesterol (CHO) (≥5.17 mmol/L), high triglyceride (TG) levels (≥1.7 mmol/L), decreased high density lipoprotein (HDL) levels (<1.03 mmol/L), high low density lipoprotein (LDL) levels (≥4.1 mmol/L), or a previous diagnosis of dyslipidaemia by a doctor[5].

Measurement of FGF-21 and adipocytokine levels in human serum

Levels of serum FGF-21, adiponectin, leptin, resistin and tumor necrosis factor-alpha (TNF-α) were quantified using ELISA kits (USCN KIT INC, Wuhan, China). All operations were carried out in strict accordance with the kit instructions.

Statistical analysis

Statistical analysis was performed with IBM SPSS 19.0 software. Normality and homogeneity of variance tests were performed for each group of data. Continuous measurement data that were normally distributed are presented as the mean ± standard deviation (Mean±SD). Continuous variables that were not normally distributed are presented as medians (25th and 75th percentiles), and categorical variables are presented as percentages (n%). The differences between the fatty pancreas (FP group) and normal control (NC group) groups were determined using Student's t tests. The qualitative data were compared using the chi-square test. Pearson analysis was used to evaluate the correlation between FGF-21 and other factors. GraphPad Prism 7 was used to generate receiver operating characteristic (ROC) curve. A two-sided p value <0.05 was used to indicate statistically significant differences.

Results

Basic and clinical characteristics of the study population

In this study, 99 fatty pancreas patients (FP group) were enrolled, and 19 healthy subjects were enrolled as the normal control group (NC group). As shown in Table 1, the proportion of males in the FP group and NC group was 58.6% (58/99) and 47.4% (9/19), respectively. The average age and BMI in the FP group were significantly higher than those in the NC group. Moreover, there was no difference in the proportion of smokers or drinkers between the two groups.

Table 1
Demographic characteristics of participants

Characteristic	FP(n=99)	NC(n=19)	P value
Males,(n%)	58(58.6%)	9(47.4%)	0.37
Age,y	48.0±11.4	40.8±13.9	0.016*
BMI,kg/m ²	25.4±3.2	21.8±1.6	<0.001***
Smoking	18(18.2%)	3(15.8%)	0.805
Drinking	21(21.2%)	4(21.1%)	0.988
Fatty liver	25(25.3%)	0	<0.001***
Diabetes	24(24.2%)	0	<0.001***
Hypertension	28(28.3%)	2(10.5%)	0.045*
Obesity	14(14.1%)	0	<0.001***
Dyslipidemia	50(50.5%)	3(15.8%)	0.001**

Table 1: Values are expressed in the mean±SD or n%. FP, fatty pancreas; NC, normal control; BMI, body mass index; SD, standard deviation. *P<0.05, **P<0.01, ***P<0.001.

Then, clinical characteristics were compared between the FP and NC groups. As shown in Table 2, it is self-evident that some key metabolic indicators, including serum glucose, CHO, TG and uric acid (UA) were significantly higher in the FP group than in the NC group (all P<0.05), with the corresponding serum HDL was decreased (P<0.05).

Table 2
Biochemistry characteristics of participants

Characteristic	FP(n=99)	NC(n=19)	P value
TP,g/L	73.2±4.7	72.0±3.6	0.296
ALB,g/L	44.3±2.1	44.3±3.0	0.92
TB,umol/L	13.3(10.9,16.3)	16.1(12.5,19.1)	0.025*
DB,umol/L	3.7±1.2	4.2±1.7	0.066
ALT,U/L	21.0(15.2,33.0)	23.0(14.0,35.0)	0.946
AST,U/L	20.4(17.0,25.2)	20.0(16.0,25.9)	0.332
γ-GGT,U/L	27.0(18.6,39.6)	15.0(12.3,21.2)	0.129
Cr,umol/L	70.8±16.2	69.1±11.7	0.658
BUN,mmol/L	5.2±1.3	5.0±1.4	0.552
UA, umol/L	337.0(286.0,404.3)	279.0(248.2,299.0)	<0.001***
GLU,mmol/L	5.5(5.1,6.1)	5.0(4.8,5.1)	<0.001***
TG,mmol/L	2.6±2.4	1.5±0.8	0.045*
CHO,mmol/L	4.8±1.0	4.2±0.7	0.012*
HDL,mmol/L	1.2±0.3	1.4±0.3	0.012*
LDL,mmol/L	2.6±0.8	2.3±0.5	<0.001***
			0.125

Table 2: Values are expressed in the mean±SD or the medians (25th and 75th percentiles). FP, fatty pancreas; NC, normal control; TP, total protein; ALB, Albumin; TB, total bilirubin; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, gamma-glutamyl transpeptidase; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; GLU, glucose; TG, triglyceride; CHO, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation.

*P<0.05,**P<0.01,***P<0.001.

Comparison of serum FGF-21 and adipocytokine levels

We measured the levels of serum FGF-21 and adipocytokines (adiponectin, resistin, leptin and TNF-α) in the two groups. As shown in Figure 1, the serum levels of FGF-21, resistin and leptin in the FP group were significantly higher than that in the NC group, and adiponectin showed the opposite trend (all p<0.01). In addition, the serum TNF-α level in the FP group showed an upward trend in the FP group without a significant difference.

It is remarkable that serum FGF-21 levels were negatively correlated with leptin ($r=-0.323$, $P=0.001$) and CHO ($r=-0.205$, $P=0.042$) in the Pearson correlation analysis. In addition, there was no clear correlation with adipocytokines (adiponectin, resistin and TNF- α) or key metabolic clinical indicators (Glucose, LDL, TG and HDL) (Table 3).

Table 3
Correlation between FGF-21 and other clinical indicators

Characteristic	R	95% CI	P value
BMI,kg/m ²	-0.081	-0.274,0.119	0.428
Leptin,ng/mL	-0.323	-0.489,-0.134	0.001**
Adiponectin,ug/mL	0.053	-0.146,0.247	0.605
Resistin,ng/mL	-0.086	-0.279,0.114	0.398
TNF- α ,pg/mL	-0.024	-0.221,0.174	0.810
TG, mmol/L	-0.159	-0.346,0.040	0.116
CHO, mmol/L	-0.205	-0.387,-0.008	0.042*
HDL, mmol/L	-0.041	-0.237,0.157	0.685
LDL, mmol/L	-0.107	-0.298,-0.093	0.293
Glucose,mmol/L	-0.051	-0.246,0.148	0.619

Table 3: FGF-21, fibroblast growth factor 21; 95% CI, 95% confidence interval; BMI, body mass index; TNF- α , tumor Necrosis Factor-alpha; TG, triglyceride; CHO, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein. * $P<0.05$, ** $P<0.01$.

Fatty pancreas prediction analysis

Serum FGF-21 levels showed significantly greater discriminative ability for FP. Area under ROC curves (AUC) of FGF-21 were remarkably larger than adipocytokines (adiponectin, resistin, leptin and TNF- α) (Figure 2). To determine the critical value of FGF-21 for predicting FP, ROC curves were assessed and are presented in Table 4. The results showed that 187.85 pg/mL was the best critical value (AUC 0.716, $P=0.002$, 95% Confidence Interval (95% CI) 0.611-0.820). The corresponding sensitivity was 73.1%, and the specificity was 65.0% (Table 4).

Table 4
Performance of FGF21 and adipocytokines in predicting fatty pancreas patients

	AUC(95% CI)	Cut-off value	P	Sen,%	Sepec,%
FGF21	0.716(0.611,0.820)	187.85	0.002**	73.1	65.0
Leptin	0.652(0.504,0.800)	0.31	0.037*	99.0	31.6
Resistin	0.630(0.523,0.737)	8.02	0.073	49.5	84.2
Adiponectin	0.685(0.571,0.798)	7.16	0.011*	55.6	79.0
TNF- α	0.657(0.509,0.804)	54.33	0.031*	67.7	68.4

Table 4: FGF-21, fibroblast growth factor 21; AUC, area under the curve; Sen, sensitivity; Spec, specificity; 95 % CI, 95% confidence intervals; TNF- α , tumor necrosis factor-alpha. *P<0.05,**P<0.01.

Discussion

Although FP was discovered many years ago, its pathophysiology is still unclear. Most of the existing studies focus on clinical morbidity and its related risk factors [18, 19]. Previous studies have shown that FP is closely related to metabolic diseases such as dyslipidemia, diabetes and fatty liver [20, 21, 22]. Increased age, central obesity, and fatty liver are independent risk factors for FP [5]. To date, there are no clinical molecular indicators for predicting or diagnosing FP.

FGF-21 is a recently discovered cytokine closely related to glycolipid metabolism and is the only protein in the fibroblast growth factor family that has no mitogenic activity [23]. The physiological function of FGF-21 is mainly involved in glycolipid metabolism and the metabolic regulation of insulin, body weight reduction and insulin resistance improvement [24, 25, 26]. High-fat-diet-fed FGF-21-deficient mice exhibited liver fat accumulation and obvious lipid metabolic disorders; in contrast, injection of FGF-21 protein into diet-induced diabetic mice reversed the steatosis of the liver and restored the normal structure of the liver [27, 28]. Additionally, serum FGF-21 levels in fatty liver or diabetic patients were higher than those in the participants in the NC group, with a negative correlation with serum HDL and a positive correlation with BMI and serum TG [8]. These results suggest that FGF-21 is closely related to metabolic diseases.

The levels of serum FGF-21 in patients with FP, as a common metabolic disease, have not been reported. Johnson et al. showed that FGF-21-deficient mice had fat deposition in pancreatic tissue, which suggests that FGF-21 may be involved in the development of FP [15]. In this study, serum FGF-21 levels in the FP group were significantly higher than those in healthy controls, which is consistent with the previously reported changes in serum FGF-21 levels observed in other metabolic diseases, such as fatty liver, obesity, and diabetes [8, 9, 10, 11]. However, this finding does not seem to match the animal experiment of Johnson et al. [15]. The exact reasons are not yet clear. We made possible speculations based on leptin. It

is well known that leptin deficiency in mice leads to obesity and insulin resistance [29]; however, the current discordant finding is that almost all obese subjects had increased serum leptin levels [30]. A relatively reasonable explanation is “leptin resistance”. It is not clear whether there is “FGF-21 resistance” in populations with metabolic diseases, which requires further study.

According to the current results, the ROC curve analysis showed that 187.85 pg/mL is the best critical value of FGF-21 for predicting FP, and the corresponding sensitivity and specificity are 73.1% and 65.0%, respectively. The results of this study can provide some help for the prediction of FP in the clinic.

There are several limitations of our study. First, it is difficult to find FP patients without common metabolic syndrome in the clinic. Therefore, the overall sample size of this study was small, and the results may be biased. Second, transabdominal ultrasonography can only be used to identify whether there is fat infiltration in the pancreas, but it cannot quantify the fat content. Therefore, the study of the correlation between serum FGF-21 and the degree of fat infiltration in the pancreas is hampered. Finally, all the serum samples in this study were frozen in a -80°C refrigerator. The results may deviate from the results obtained from fresh serum samples, but the results are still of reference value.

Conclusion

In summary, serum FGF-21 levels are closely related to FP. The detection of serum FGF-21 levels may help identify the population susceptible to FP.

Abbreviations

FGF-21: Fibroblast growth factor-21 FP: Fatty pancreas NC: Normal control ROC: Receiver operating characteristic AUC: Area under curve BMI: Body mass index ELISA: Enzyme linked immunosorbent FBG: Fasting blood glucose CHO: Cholesterol TG: Triglyceride HDL: High density lipoprotein LDL: Low density lipoprotein TNF- α : Tumor necrosis factor-alpha SD: Standard deviation UA: Uric acid

Declarations

Acknowledgments

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Authors' contributions

FH: Formal analysis, Writing-original draft preparation, Visualization. LY: Investigation, Data curation. XPY: Conceptualization, Investigation. RYX: Resources, Investigation. MXT: Validation, Supervision. XNL:

Validation. LZ: Data curation, Validation. LHH: Writing-review and editing, Investigation. WJG: Writing-review and editing. WMX: Project administration, Writing-review and editing. GTL: Methodology, Writing-review and editing. YBD: Conceptualization, Writing-review and editing, Funding acquisition. All authors read and approved the final manuscript.

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Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

The study was approved by Ethics Committee of Affiliated Hospital of Yangzhou University. All participants agreed to participate in the study, and written informed consent was obtained from each subject.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. van Herpen NA, Schrauwen-Hinderling VB. Lipid accumulation in non-adipose tissue and lipotoxicity. *Physiol Behav* 2008; 94(2): 231-41.
2. Della CC, Mosca A, Majo F, Lucidi V, Panera N, Giglioni E, et al. Nonalcoholic fatty pancreas disease and nonalcoholic fatty liver disease: more than ectopic fat. *Clin Endocrinol (Oxf)* 2015; 83(5): 656-62.
3. Ogilvie R. The islands of langerhans in 19 cases of obesity. *J Pathol* 1933; 37(3): 473-81.
4. Li S, Su L, Lv G, Zhao W, Chen J. Transabdominal ultrasonography of the pancreas is superior to that of the liver for detection of ectopic fat deposits resulting from metabolic syndrome. *Medicine (Baltimore)* 2017; 96(37): e8060.
5. Wang D, Yu XP, Xiao WM, Jiao XP, Wu J, Teng DL, et al. Prevalence and clinical characteristics of fatty pancreas in Yangzhou, China: A cross-sectional study. *Pancreatology* 2018; 18(3): 263-268.

6. Fisher FM, Maratos-Flier E. Understanding the physiology of FGF21. *Annu Rev Physiol* 2016; 78: 223-41.
7. Micanovic R, Raches DW, Dunbar JD, Driver DA, Bina HA, Dickinson CD, et al. Different roles of N- and C-termini in the functional activity of FGF21. *J Cell Physiol* 2009; 219(2): 227-34.
8. Li H, Wu G, Fang Q, Zhang M, Hui X, Sheng B, et al. Fibroblast growth factor 21 increases insulin sensitivity through specific expansion of subcutaneous fat. *Nat Commun* 2018; 9(1): 272.
9. Akour A, Kasabri V, Boulatova N, Bustanji Y, Naffa R, Hyasat D, et al. Levels of metabolic markers in drug-naive prediabetic and type 2 diabetic patients. *Acta Diabetol* 2017; 54(2): 163-170.
10. Li H, Fang Q, Gao F, Fan J, Zhou J, Wang X, et al. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. *J Hepatol* 2010; 53(5): 934-40.
11. Keuper M, Häring HU, Staiger H. Circulating FGF21 Levels in Human Health and Metabolic Disease. *Exp Clin Endocrinol Diabetes* 2019.
12. Fon TK, Bookout AL, Ding X, Kurosu H, John GB, Wang L, et al. Research resource: Comprehensive expression atlas of the fibroblast growth factor system in adult mouse. *Mol Endocrinol* 2010; 24(10): 2050-64.
13. Johnson CL, Mehmood R, Laing SW, Stepniak CV, Kharitononkov A, Pin CL. Silencing of the Fibroblast growth factor 21 gene is an underlying cause of acinar cell injury in mice lacking MIST1. *Am J Physiol Endocrinol Metab* 2014; 306(8): E916-28.
14. Luo Y, Yang Y, Liu M, Wang D, Wang F, Bi Y, et al. Oncogenic KRAS Reduces Expression of FGF21 in Acinar Cells to Promote Pancreatic Tumorigenesis in Mice on a High-Fat Diet. *Gastroenterology* 2019; 157(5): 1413-1428.
15. Johnson CL, Weston JY, Chadi SA, Fazio EN, Huff MW, Kharitononkov A, et al. Fibroblast growth factor 21 reduces the severity of cerulein-induced pancreatitis in mice. *Gastroenterology* 2009; 137(5): 1795-804.
16. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. *Am J Gastroenterol* 2007; 102(12): 2708-15.
17. Smereczynski A, Kołaczyk K. Is a fatty pancreas a banal lesion? *J Ultrason* 2016; 16(66) : 273-80.
18. Lesmana CR, Pakasi LS, Inggriani S, Aidawati ML, Lesmana LA. Prevalence of non-alcoholic fatty pancreas disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. *BMC Gastroenterol* 2015; 15: 174.
19. Pham YH, Bingham BA, Bell CS, Greenfield SA, John SD, Robinson LH, et al. Prevalence of pancreatic steatosis at a pediatric tertiary care center. *South Med J* 2016; 109(3): 196-8.
20. Wang CY, Ou HY, Chen MF, Chang TC, Chang CJ. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. *J Am Heart Assoc* 2014; 3(1): e000297.

21. Makino N, Shirahata N, Honda T, Ando Y, Matsuda A, Ikeda Y, et al. Pancreatic hyperechogenicity associated with hypoadiponectinemia and insulin resistance: A Japanese population study. *World J Hepatol* 2016; 8(33): 1452-1458.
22. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in us youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA* 2018; 319(16): 1723-1725.
23. Kharitonov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. *J Clin Invest* 2005; 115(6): 1627-35.
24. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes* 2008; 57(5): 1246-53.
25. Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, DeFronzo RA, Tripathy D. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. *Diabetes Care* 2009; 32(8): 1542-6.
26. Zhang J, Li Y. Fibroblast growth factor 21 analogs for treating metabolic disorders. *Front Endocrinol (Lausanne)* 2015; 6: 168.
27. Murata Y, Konishi M, Itoh N. FGF21 as an endocrine regulator in lipid metabolism: from molecular evolution to physiology and pathophysiology. *J Nutr Metab* 2011; (2011) 981315.
28. Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. *Diabetes* 2009; 58(1): 250-9.
29. Sjögren M, Soylu-Kucharz R, Dandunna U, Stan TL, Cavalera M, Sandelius Å, et al. Leptin deficiency reverses high metabolic state and weight loss without affecting central pathology in the R6/2 mouse model of Huntington's disease. *Neurobiol Dis* 2019; 132: 104560.
30. Zhao S, Zhu Y, Schultz RD, Li N, He Z, Zhang Z, et al. Partial Leptin Reduction as an Insulin Sensitization and Weight Loss Strategy. *Cell Metab* 2019; 30(4): 706-719.

Figures

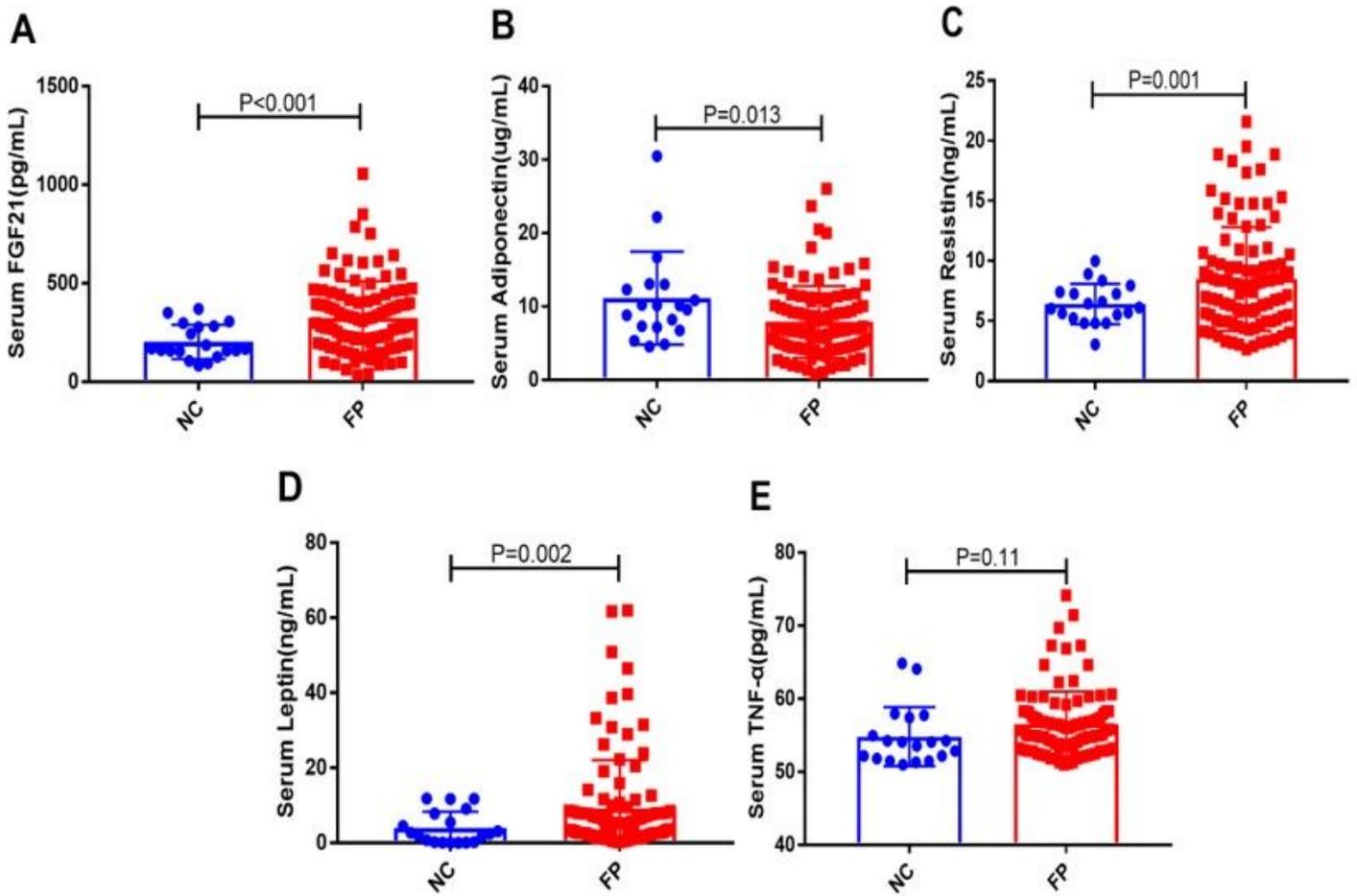


Figure 1

Comparisons of the levels of serum FGF-21 and adipocytokines (adiponectin, resistin, leptin and TNF- α) in NC and FP group. FGF-21, fibroblast growth factor-21; FP, fatty pancreas; NC, normal control; TNF- α , tumor necrosis factor-alpha.

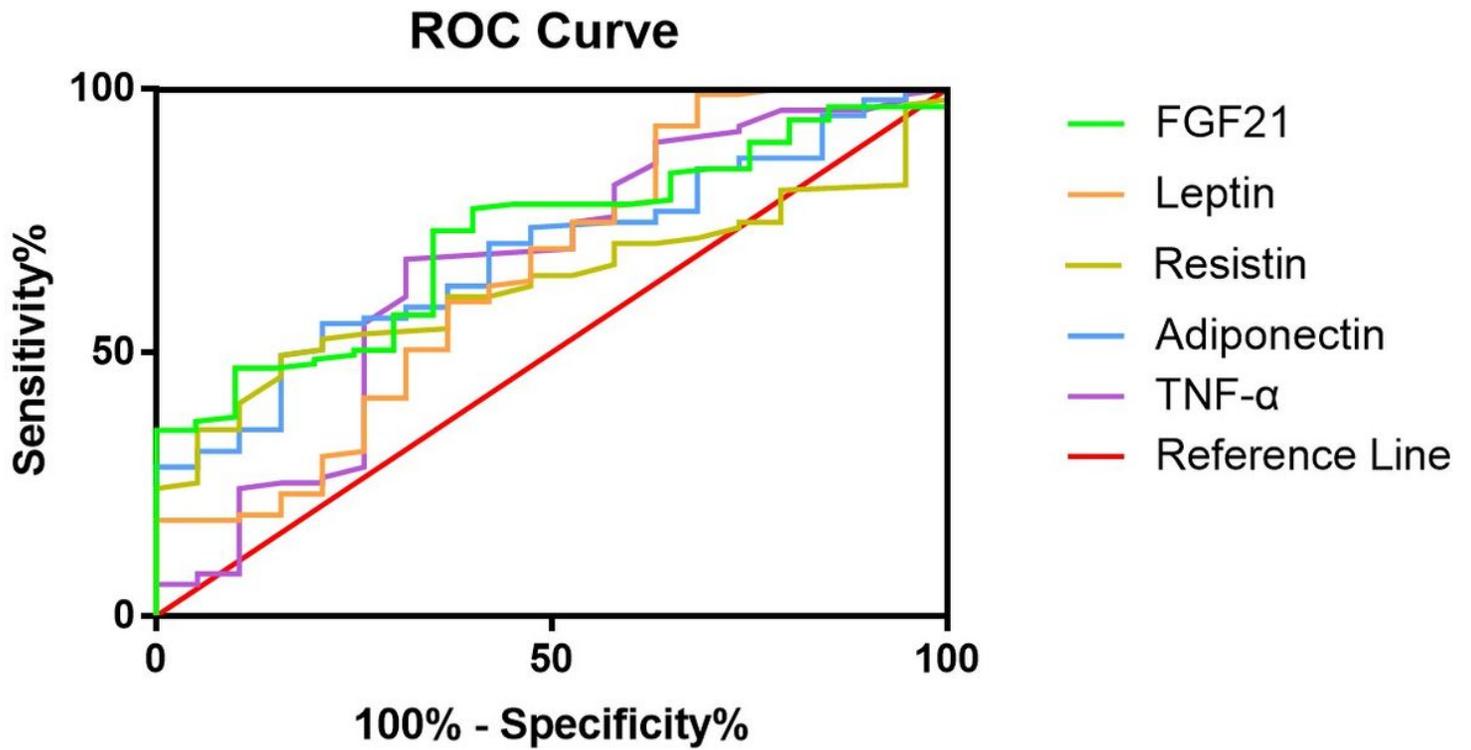


Figure 2

FGF-21 and adipocytokines (adiponectin, resistin, leptin and TNF- α) for prediction in patients with fatty pancreas: ROC analysis. FGF-21, fibroblast growth factor-21; TNF- α , tumor necrosis factor-alpha; ROC, receiver operating characteristic.