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Research Article

FGF-21 and GDF-15 Levels in Patients with Insulin Resistance and It's Relation with Other Biochemical Parameters

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Abstract

Objectives: Since it forms a basis to diabetes, IR, a part of metabolic syndrome, is the most important health problem of our age. Mitochondrial dysfunction and oxidative stress associated with obesity and IR is found in the pathogenesis of metabolic syndrome. This study was concluded in order to analyze whether biomarkers such as fibroblast growth factor 21(FGF-21) and growth differentiation factor 15(GDF-15) which are the indicators of mitochondrial disorder, increased in IR and at the same time in order to research the relation between these cytokines with other biochemical parameters in people with IR.

Methods: This cross-sectional prospective study was performed with 101 outpatients with the ages between 18 and 75 years, who applied to a private internal medicine clinic in Istanbul between November 2022 and May 2023. 54 people with IR were selected as the patient group and 47 people without IR were selected as the control group. We evaluated serum FGF-21 and GDF-15 concentrations by ELISA (enzyme-linked immunosorbent assay) in patients with and without IR. At the same time, the relation of these cytokines with other biochemical parameters in people with IR was researched.

Results: The mean of FGF-21 and GDF-15 in the IR (+) group were found statistically significantly higher than the IR (-) group (p=0.0001), (p=0.0001). Statistically significant positive correlation was observed between weight, waist circumference (WC), body mass index (BMI), hypertension, aspartate aminotransferase (AST) alanine aminotransferase (ALT), gammaglutamyl transferase (GGT). hemoglobin A1C (HbA1C), uric acid, triglyceride, high-density lipoprotein (HDL) values in the group in which both FGF-21 and GDF-15 values are IR (+). In IR (+) patients, HDL has statistically significant negative correlation with both FGF-21 and GDF-15. In addition, cut-off values for FGF-21 and GDF-15 were developed in this study. The possibility to have IR in a patient with FGF-21>328,76 is found as 22,15 times more likely than a patient with <328,76 FGF-21 with a sensitivity of 96.03% and specificity of 95.65% (p=0.004) (CI: 0,959-1,000). For GDF-15, the possibility to have IR in a patient with GDF-15>120,05 is 14,77 times more than a patient with <120,05 with a sensitivity of 96.03% and specificity of 93.48% (p=0.007) (CI: 0,954-0,997).

Conclusion: FGF-21and GDF-15 increases significantly in patients with IR. The determined cut-off values of these two markers have the importance for being used in early diagnosis in IR. At the same time, the analogues to be developed from these markers shall be weapons that can be used against the current IR, diabetes and obesity pandemics.

Keywords: FGF-21, GDF-15, Insulin Resistance

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Since it forms a basis to diabetes, IR, a part of metabolic syndrome, is the most important health problems of our age. Turkey is the European country with the highest incidence of diabetes with 11.1%. At the same time, Turkey is one of the European countries with the highest diabetes-related death rate. It is estimated that there shall be 10.4 million people with diabetes in Turkey by 2045 and that Turkey shall be one of the 10 countries where diabetes is most common in adults.[1] Increased body lipidosis (especially the enlargement of waist circumference) and decreased physical activity are the two most important factors related with IR which forms a basis to IR. Metabolic balance is impaired in IR. There are metabolic modulators such as serum FGF-21 and GDF-15 mediating mediate interorgan communication in order to maintain the metabolic balance between food intake and energy expenditure. These are known as hepatocytes and myokines, and the level of both cytokines in circulation increase during obesity and related metabolic complications.[2] The mechanisms in the increase of their levels are largely unknown. While GFD-15 stimulates the myelencephalon to suppress appetite, increased FGF-21 leads to energy and fat consumption of liver and adipose tissues.[3]

FGF-21 regulates glucose and lipid hemostasis.[4] It is released from the liver and functions by connecting to the FGF receptor on the cell surface.[4,5] It was first revealed in 2005 that FGF-21 is a metabolic regulator.[6] In 2011, it was accepted as a biomarker of mitochondrial dysfunction.[7] Since its initial definition, FGF-21 has attracted great attention of researchers. Salehi et al. have defined mitochondrial dysfunction diseases as a marker that can be used to distinguish them from other diseases.[8] Several studies have proven that FGF-21 stimulates the oxidation of fatty acids, the production of ketone bodies, and the inhibition of lipogenesis.[9] Therefore, FGF-21 was thought to regulate glucose-lipid metabolism and this situation makes it a promising therapeutic target for metabolic disease. However, some studies have shown that administration of FGF-21 prevents diet-related obesity and IR in mice and humans.[9,10] FGF 21 has a lowering effect on blood glucose levels by increasing glucose uptake by white and brown fat cells. It is also known that it increases energy expenditure by inducing the use of fatty acids in energy metabolism.[11]

GDF-15 is a cytokine showing increase in inflammatory conditions and tissue injury and is released from cardiomyocytes, macrophages, vascular smooth muscle cells and endothelial cells. Therefore, its level increases in all cases involving endothelial damage, for example; IR, diabetes, obesity, atherosclerosis, heart failure, smoking, surgery, exercise, cancer, non-alcoholic fatty liver disease (NAFLD), kidney diseases and in pathological or stress conditions such as mitochondrial disease.[12-15] In healthy individuals, it is expressed at low levels ranging from 0.1 to 1.2 ng/mL, mainly from the bladder, kidney, stomach, gallbladder, colon, pancreas, liver, lung, and endometrium.[12] GDF-15 concentrations were positively associated with obesity.[16, 17] It has been argued that desensitization of the receptors may occur, GDF-15 may contribute to diabetes and obesity by reducing the effect of GDF-15 on appetite suppression and insulin sensitivity.[18]

There is mitochondrial dysfunction and oxidative stress associated with obesity and IR in the pathogenesis of metabolic syndrome.[19,20] Biomarkers of this mitochondrial disorder may be increased in IR. This study was performed in order to analyze whether the presence of IR affects serum levels of FGF-21 and GDF-15, as well as the relationship of these cytokines with other biochemical parameters in people with IR.

Methods

This cross-sectional prospective study was performed with outpatients with IR applied to a private internal medicine clinic in Istanbul between November 2022 and May 2023. All participants were informed about the study and voluntarily written consent was obtained from all participants before starting the study.

Participants

101 people between 18 and 75 years old with IR were involved in the study. Healthy volunteers whose age and gender were compatible with the study group and who applied to the polyclinic for check-up, were involved as control group. The biochemical data of involved patients were obtained from the laboratory information system and their height, weight, and BMI were measured and recorded. Individuals with IR who are overweight and obese (BMI>25) with metabolic syndrome parameters were involved in the study group.

HbA1C below 6 and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) greater than 2.7 was considered sufficient for the patient to be diagnosed with IR.[21] Patients without diabetes and IR were involved in the control group. Age, body weight (kg), Height (cm), BMI (kg/m^2), WC (cm), overnight fasting blood glucose, hemoglobin A1c (HbA1c), HOMA-IR, liver tests; AST, ALT, GGT BUN (Blood Urea nitrogen), creatinine, GFR (Glomerular filtration rate), uric acid, total cholesterol, HDL cholesterol, LDL(low density lipoprotein) cholesterol, triglyceride, vitamin D3 were

tested for in patients with and without IR in accredited laboratories. Tanita F1BC-601PRO weighing device was used in all patients.

Venous blood samples were collected in tubes from the antecubital vein, followed by an overnight fasting. The tubes were centrifuged at 1500 g (10 min) to remove the serum. The serum samples were kept at –80 °C until analysis of FGF-21 and GDF-15. Serum FGF-21 and GDF-15 levels were assessed by enzyme-linked immunosorbent assay (ELISA) technique using Human FGF-21 and GDF-15 Immunoassay Quantikine®ELISA (Catalog Number DF2100) purchased from R&D Systems following the manufacturer's instructions. Serum levels were expressed as pg/ml. U The intra- and interassay coefficient of variations (CV) were <5%, and <8% respectively.

Statistical Analysis

Statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program in this study. In addition to descriptive statistical methods (mean, standard deviation, median, interquartile range) in the evaluation of the data, the distribution of the variables was examined with the Shapiro–Wilk normality test, the independent t-test for the comparison of the paired groups of the variables with normal distribution, the Mann Whitney U test for the comparison of the pairwise groups of the non-normally distributed variables, Chi-square test was used to compare the qualitative data, and Pearson correlation test was used to determine the relations of the variables with each other. Logistic Regression analysis was performed to determine the factors affecting IR. Analysis for the area under ROC Curve was performed to determine the place of FGF-21 and GDF-15 variables in the differential diagnosis of IR. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, LR (+) (Likelihood Ratio) values have been calculated in order to determine the cut-off points. The results were evaluated at the significance level of $p<0.05$.

Results

This study was conducted with 101 individuals, 54 (54%) with IR and 46 (46%) without IR. Age, gender, WC (cm), BMI (kg/m^2), hypertension, AST(IU/ml), ALT (IU/ml), GGT (IU/ml), HbA1C (%), BUN, Creatinine (mg/dl), uric acid (mg/dl), GFR(ml/min), Total Cholesterol (mg/dL), LDL Cholesterol (mg/dL), HDL Cholesterol (mg/dL), Triglyceride (mg/dL), 25-OH vit D3 (ng/mL), FGF-21, GDF-15 values of individuals with and without IR are given in Table 1 (Fig. 1).

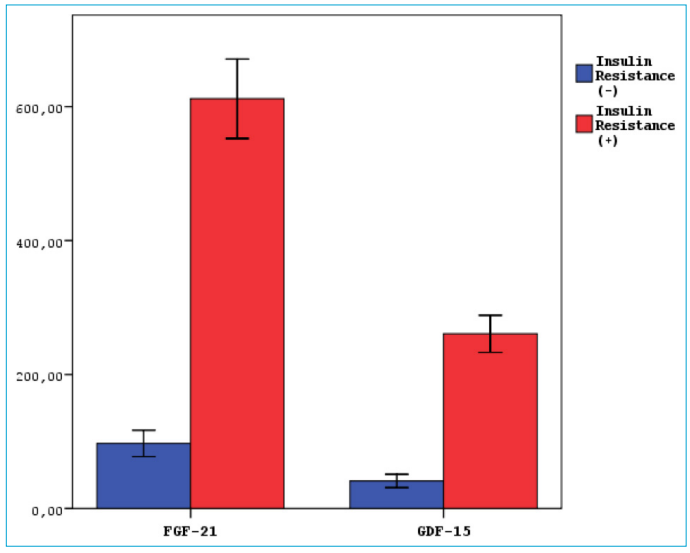

Figure 1. FGF-21 and GDF-15 values in individuals with and without IR.

The areas under the ROC curve were calculated to determine the location of FGF-21 and GDF-15 in the differential diagnosis of IR. For FGF-21, the area under ROC Curve was found as 0,998 (0,959-1,000),for GDF-15, the area under ROC Curve was found as 0,995 (0,954–0,997). It is above the desired 0.700 limit value in both areas (Table 2).

For FGF-21 in >328,76 cut-off point Sensitivity was found as 96,30, Specificity 95,65, Positive Predictive Value 96,30, Negative Predictive Value 95,70, LR (+) value was found as 22,15. (In other words >the possibility of having IR in a patient with 328,76 FGF-21 is 22,15 times more than a patient with <328,76 FGF-21).

For GDF-15 in >120,05 cut-off point Sensitivity was found as 96,30, Specificity 93,48, Positive Predictive Value 94,50, Negative Predictive Value 95,60, LR (+) value was found as 14,77.(In other words >the possibility of having IR in a patient with 120,05 GDF-15 is 14,77 times more than a patient with <120,05 GDF-15) (Table 3) (Fig. 2).

Logistic Regression analysis was performed with WC (cm), BMI (kg/m^2), Hypertension, AST (U/L), ALT (U/L), GGT (IU/mL), HbA1C, Creatinine (mg/dl), Uric acid (mg/dl), HDL Cholesterol (mg/dL), Triglyceride (mg/dL), FGF-21 and GDF-15 variables in order to determine the factors affective in the positivity of IR.WC (cm) (p=0,186), BMI (kg/m^2) (p=0,420), Hypertension (p=0,065), AST (U/L) (p=0,956), ALT (U/L) (p=0,825), HbA1C (p=0,483), Creatinine (mg/dl) (p=0,089), Uric acid (mg/dl) (p=0,163), HDL Cholesterol (mg/dL) (p=0,271) variables were found statistically insignificant, GGT (IU/mL) height (p=0,028), triglyceride (mg/dL) height (p=0,046), FGF-21 height (p=0,0001) and GDF-15 height (p=0,0001) was found statistically significant and determined as effective factors (Table 4).

Table 1. Patient characteristics

	Insulin Resistance (-)		Insulin Resistance (+)		P
Age					
Mean±SD	40.35±12.58		43.09±11.1		0.249*
Gender					
Male	16	34.78%	28	51.85%	0.087+
Female	30	65.22%	26	48.15%	
WC (cm)					
Mean±SD	79.28±13.37		99.13±15.88		0.0001*
BMI (kg/m^2)					
Mean±SD	27.67±6.91		32.93±5.65		0.0001*
Hypertension					
(-)	42	91.30%	25	46.30%	0.0001+
(+)	4	8.70%	29	53.70%	
AST (U/L)					
Mean±SD	15.97±3.63		23.1±12.41		0.0001†
Median (IQR)	15.2 (14-18.1)		19.5 (15.75-26)		
ALT (U/L)					
Mean±SD	15.68±6.08		33.97±32.47		0.0001†
Median (IQR)	16 (11.75-19.85)		23.15 (15-40.25)		
GGT (IU/mL)					
Mean±SD	14.6±8.42		35.32±18.14		0.0001†
Median (IQR)	13 (9.75-16.68)		35 (21.08-45)		
HbA1C					
Mean±SD	5.26±0.37		5.49±0.39		0.003*
BUN					
Mean±SD	12.45±3.99		13.32±4.10		0.289*
Creatinine (mg/dl)					
Mean±SD	0.73±0.17		0.82±0.21		0.019†
Median (IQR)	0.7 (0.6-0.85)		0.78 (0.69-0.91)		
Uric acid (mg/dl)					
Mean±SD	4.41±1.18		6.05±1.50		0.0001*
GFR (ml/min)					
Mean±SD	108.31±19.50		103.84±22.30		0.293*
Total Cholesterol (mg/dL)					
Mean±SD	196.98±34.75		206.24±45.34		0.261*
LDL Cholesterol (mg/dL)					
Mean±SD	120.46±34.37		129.91±41.05		0.220*
HDL Cholesterol (mg/dL)					
Mean±SD	61.77±17.28		49.73±16.96		0.001*
Triglyceride (mg/dL)					
Mean±SD	82.63±39.64		173.16±110.11		0.0001†
Median (IQR)	78 (54.75-97)		135 (96.55-217.75)		
Vitamin D (25-OH vit D3) (ng/mL)					
Mean±SD	28.72±13.51		32.65±15.28		0.213†
Median (IQR)	27 (18.85-35.5)		29.68 (20.98-39.25)		
FGF-21					
Mean±SD	97.07±65.98		611.71±217.31		0.0001†
Median (IQR)	81.06 (65.2-104.97)		554.24 (418.57-753.87)		
GDF-15					
Mean±SD	41.03±33.29		260.75±101.35		0.0001†
Median (IQR)	25.57 (20.69-48.37)		234.69 (174.27-331.63)		

*Independent t test,†Mann Whitney U test +chi-square test. WC (Waist circumference-cm), BMI (body mass index), HbA1c (hemoglobin A1c), AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (γ-glutamyltransferase), HDL (high-density lipoprotein), LDL(low-density lipoprotein), FGF-21 (fibroblast growth factor), GDF-15 (growth differentiation factor 15).

Table 2. Area under ROC Curve

	AUC	SE	95% CI
FGF-21	0.998	0.004	0.959 - 1.000
GDF-15	0.995	0.007	0.954 - 0.997

AUC: Area under the ROC curve; SE: Standart Error.

Table 3. Cut Off values of FGF-21 and GDF-15

	Cut Off	Sensitivity	Specificity	PPV	NPV	LR (+)
FGF-21	>328,76	96.30	95.65	96.30	95.70	22.15
GDF-15	>120,05	96.30	93.48	94.50	95.60	14.77

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR: Likelihood Ratio.

The relations of FGF-21 and GDF-15 values with other biochemical parameters other than IR were also examined: A statistically significant positive correlation was observed between FGF-21 values and GDF-15 values (r=0.824 p=0.0001).

No statistically significant correlation was observed between FGF-21 and GDF-15 values and age values, respectively (r=0.145 p=0.151) (r=0.037 p=0.717).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and weight values, respectively (r=0.507 p=0.0001) (r=0.647 p=0.0001).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and Waist circumference (cm) values, respectively (r=0.596 p=0.0001) (r=0.694 p=0.0001).

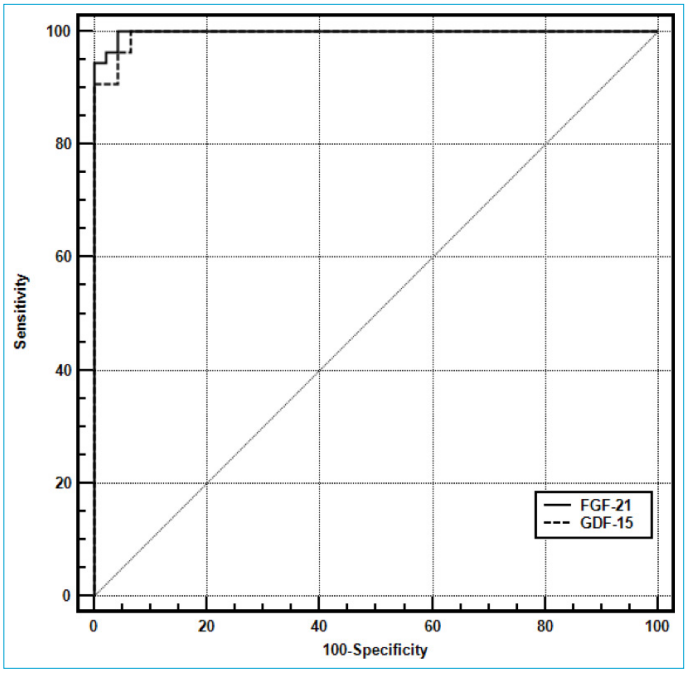

Figure 2. Sensitivity and specificity of FGF-21 and GDF-15.

Table 4. Logistic Regression Analysis

	OR	OR (95,0% C.I)	p
WC (cm)	1.08	0.96-1.21	0.186
BMI (kg/m^2)	0.91	0.73-1.14	0.420
Hypertension	0.18	0.03-1.11	0.065
AST (U/L)	1.00	0.83-1.21	0.956
ALT (U/L)	1.01	0.90-1.13	0.825
GGT (IU/mL)	1.09	1.01-1.18	0.028
HbA1C	0.46	0.07-1.06	0.483
Creatinin (mg/dl)	0.80	0.07-1.89	0.089
Uric acid (mg/dl)	1.58	0.83-2.28	0.163
HDL Cholesterol (mg/dL)	0.97	0.93-1.02	0.271
Trigliseride (mg/dL)	1.02	1.00-1.38	0.046
FGF-21	3.41	1.03-7.11	0.0001
GDF-15	6.26	1.85-9.08	0.0001

WC: Waist circumference-cm; BMI: body mass index; HbA1c: hemoglobin A1c; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; HDL: high-density lipoprotein; FGF-21: fibroblast growth factor; GDF-15: growth differentiation factor 15.

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and BMI (kg/m^2) values, respectively (r=0.454 p=0.0001) (r=0.537 p=0.0001).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and AST (U/L) values, respectively (r=0.537 p=0.0001) (r=0.504 p=0.0001).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and ALT (U/L) values, respectively (r=0.505 p=0.0001) (r=0.500 p=0.0001).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and GGT (IU/mL) values, respectively (r=0.637 p=0.0001) (r=0.683 p=0.0001).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and HbA1C values, respectively (r=0.364 p=0.0001) (r=0.278 p=0.005).

No statistically significant correlation was observed between FGF-21 and GDF-15 values and BUN values, respectively (r=0.182 p=0.07) (r=0.067 p=0.505).

A statistically significant positive correlation was observed between FGF-21 values and creatinine (mg/dl) values (r=0.255 p=0.011). No statistically significant correlation was observed between GDF-15 values and creatinine (mg/dl) values (r=0.193 p=0.054).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and Uric acid (mg/dl) values, respectively (r=0.519 p=0.0001) (r=0.526 p=0.0001).

No statistically significant correlation was observed between FGF-21 and GDF-15 values and GFR (ml/min) values, respectively (r=-0.165 p=0.102) (r=0.034 p=0.739)

No statistically significant correlation was observed between FGF-21 and GDF-15 values and Total Cholesterol (mg/dL) values, respectively (r=0.128 p=0.205) (r=0.035 p=0.728).

No statistically significant correlation was observed between FGF-21 and GDF-15 values and LDL Cholesterol (mg/dL) values, respectively (r=0.109 p=0.281) (r=0.038 p=0.704).

A statistically significant negative correlation was observed between FGF-21 and GDF-15 values and HDL Cholesterol (mg/dL) values, respectively (r=-0.305 p=0.0001) (r=-0.373 p=0.0001).

A statistically significant positive correlation was observed between FGF-21 and GDF-15 values and Triglyceride (mg/dL) values, respectively (r=0.500 p=0.0001) (r=0.553 p=0.0001).

No statistically significant correlation was observed between FGF-21 and GDF-15 values and Vitamin D (25-OH vit D3) (ng/mL) values, respectively (r=0.149 p=0.138) (r=0.023 p=0.824).

Discussion

This is the first comprehensive clinical study conducted in Turkey with the combination of both FGF-21 and GDF-15 in individuals with IR. In our study, it was shown that FGF-21 and GDF-15 were significantly increased in people with IR, and a cut-off value for FGF-21 and GDF-15, which was shown with >90% specificity and sensitivity rates, could also be determined for the development of IR in these patients. It was determined that these markers showed positive correlations with BMI, WC, AST, ALT, GGT elevation, cholesterol levels, TG, uric acid, which are other parameters related to IR. All these findings strongly suggest that these two markers are associated with pre-diabetes and obesity.

Previously, studies on GDF-15 or FGF-21 alone were carried out abroad. In a study showing the relationship between GDF-15 as a cardiovascular marker and IR in obese patients, Vila G et al. found a correlation between GDF-15 and IR.[22] Similarly, it was thought that FGF-21 might be an early predictive biomarker in the development of IR in animal studies.[23]

There are studies showing that GDF-15 is a powerful biomarker for coronary heart disease and heart failure, even in apparently healthy women.[24-26] In the study conducted by Chavez AO et al., clinical conditions such as abdominal adiposity, hepatic steatosis, insulin resistance, hypertriglyceridemia and type 2 diabetes mellitus (T2DM) were found to be associated with increased serum FGF-21 levels.[27] In our study, a significant correlation was found between FGF-21 as well as GDF-15 and the above-mentioned parameters.

FGF-21 may play a role in the pathogenesis of T2DM. Interestingly, in the study of Angelin et al, it was found that high FGF-21 levels in patients with impaired glucose tolerance or T2DM were found to be significantly higher than the control group 10 years before the diagnosis.[28] In our study, we obtained a cut-off value of >328,76 for FGF-21 in people with IR. In other words , we can say with this study that the possibility of having IR in a patient with>328,76 FGF-21 is 22,15 times more than a patient with <328,76 FGF-21. Likewise, a cutoff value was obtained with GDF-15 in this study. The possibility of having IR in a patient with GDF-15 >120,05 is found 14,77 times more than a patient with <120,05 GDF-15. IR may develop in the future, but the detection of high FGF-21 and GDF-15 levels in healthy individuals shall be a useful parameter for early diagnosis.

In fact, since it is positively correlated with HT, it may be useful to investigate heart diseases in patients with high levels of these biomarkers. There are some studies showing experimentally that these biomarkers are used in the treatment of diseases such as IR, T2DM, obesity, coronary heart disease and heart failure.[29] For example, although many drugs are used in current treatment for T2DM, it is observed that sufficient success has not been achieved in the treatment of this disease. Recent findings show that pharmacological modulation of stress-induced GDF-15 promise hope for the treatment of T2DM.[30] GDF-15 suppresses appetite, reduces inflammation, increases lipid catabolism, and improves IR and hepatic adiposity.[30] In addition, it is reported that GDF-15 levels in circulation increase in response to many antidiabetic drugs, including metformin, and GDF-15 mediates some of their effects.[29]

Similar results were found in animal experiments.[31, 32] Findings obtained from both mice and humans have shown that metformin and exercise increase GDF-15 levels in circulation.[33] These unique and different mechanisms for suppressing food intake and inflammation have made GDF-15 an attractive candidate for treating many metabolic diseases, including obesity, T2DM, cardiovascular disease and cancer cachexia.

Conclusion

As the result, this study shows that FGF-21 and GDF-15 are significantly increased in people with IR and it has been observed that these biomarkers are guiding in risk assessment in terms of IR development. In line with the information we obtained from our study, these two markers were thought

to be of importance to be used in the early diagnosis of IR. At the same time, it is predicted that analogues to be developed from these markers may be important agents that can be used in the treatment of current IR, T2DM and obesity pandemics.

Limitation

Despite obtaining valuable data in our study, it is important to acknowledge the limitations and areas for improvement. The smaller number of people and being single-centered are the limitations of the study. It is recommended to conduct studies in patient populations with wider participation.

Disclosures

Ethics Committee Approval: The study was performed in accordance with the Declaration of Helsinki, and was approved by the Bakırkoy Dr. Sadi Konuk Hospital Clinical Research Ethics Committee (Date: 14.12.2022, Decision No: 2022-428).

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Conflict of Interest: None declared.

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