Serum Fibroblast Growth Factor 19 Level Correlate with Metabolic Syndrome in Egyptian People

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Abstract

Background: Metabolic syndrome (MetS) refers to the concurrence of several cardiovascular risk factors including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. Fibroblast Growth Factor 19 (FGF-19) was introduced as a novel metabolic regulator reversing diabetes mellitus, hepatic steatosis, hyperlipidemia, and adiposity. In view of these data, we assume that serum FGF-19 levels could be associated with all parameters of MetS. **Aim:** The main objective of this case-control study was to evaluate the level of FGF-19 in subjects with MetS, diagnosed according to the 2005 International Diabetes Federation (IDF) criteria, and to clarify the correlation, if any, with all its parameters. **Subjects and methods:** One hundred and sixty subjects aged from 25 to 50 years were subdivided into 2 groups. Group A includes 80 subjects with MetS. Group B includes 80 normal subjects. Detailed clinical history was taken and FGF-19 was measured. **Results:** FGF-19 level was statistically significantly lower among the MetS group than in the control group ($p<0.001$). A cutoff value of ≤ 137 pg/ml can discriminate between those with MetS vs. control group with a sensitivity, specificity, PPV, and NPV of 75%, 93.7%, 92.3%, and 78.9%, respectively, and the AUC for FGF-19 was 0.907 (excellent performance). **Conclusion:** FGF-19 may be considered as a reliable biomarker for the early detection of risky subjects with MetS.

Keywords: Metabolic syndrome (MetS); Fibroblast Growth Factor 19 (FGF-19; International Diabetes Federation (IDF).

Introduction:

The fibroblast growth factor (FGF) family comprises 20 members with diverse functions, such as embryonic development, cell growth, and differentiation [1]. Members of this family, include FGF15/19 (which are the mouse and human orthologs, respectively), FGF-21, and FGF-23, are endocrine factors involved in hormone-like metabolic effects through activation of FGF receptors [2].

FGF-19 is mainly produced by the enterocytes in the distal part of the small intestine and is implicated in regulating bile acid homeostasis [3]. FGF-19 is released into the portal circulation that supplies nutrient-rich blood to the liver and functions as an enterohepatic signal to regulate bile acid homeostasis. After consumption of a meal, FGF-19 expression is induced by bile acid–mediated activation of the farnesoid X receptor (FXR) [4].

The metabolic syndrome (MetS) refers to the concurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension [5]. These risk factors have been shown to act synergistically via mechanisms poorly defined and are associated with high cardiovascular morbidity and mortality [6]. MetS affects approximately 22% of the adult population in industrialized countries and over 40% of those aged 50 years and older [7].

The term metabolic syndrome has been replaced by global cardiometabolic risk, which implies cardiovascular risk factors beyond the MetS [8]. There are multiple definitions for the MetS, with the most recent being the consensus from the IDF [9].

Although FGFs are widely appreciated as differentiation factors, it has become apparent that the biology of FGFs is more complex and participates in the maintenance of physiological homeostasis [3]. FGF-19, a peptide with 216 amino acids, including a signal peptide of 22 amino acids, was introduced as a novel metabolic regulator reversing diabetes mellitus, hepatic steatosis, hyperlipidemia, and adiposity [10].

In the view of these data, we assume that serum FGF-19 levels could be associated with all parameters of MetS.

Subjects and methods:

Subjects:

This case-control study includes 160 participants, 80 subjects with MetS, and 80

normal subjects aged from 25 to 50 years. All cases and controls, both men and women were recruited from subjects attending diabetes and endocrinology outpatient clinic at Mansoura specialized medical hospital, Mansoura University, Egypt. The study was carried out over the period from June 2019 to June 2020. Agreement to participate in the study by informed written consent was approved by the local ethical committee at the Mansoura faculty of medicine. This research was approved by Institutional Review Board (IRB) Mansoura Faculty of Medicine, Mansoura University.

The following are excluded:

1) Subjects with organ failure as liver cell failure, kidney failure, and heart failure.
2) Subjects with acute infection and malignancy.
3) Subjects with other endocrinal disorders and pregnant women.
4) Subjects with active inflammatory conditions and GIT disorders such as malabsorption syndrome & inflammatory bowel diseases.
5) Subjects refuse to participate in the study.

Grouping of the patients:

The 160 participants classified into 2 groups:

- **Group A:** 80 subjects with MetS (12 men, 68 women).
- **Group B:** 80 normal subjects (16 men, 64 women).

Clinical and Anthropometric Measurements:

All participants were subjected to full medical history with stress on associated chronic diseases (diabetes mellitus, hypertension, ischemic heart diseases, liver diseases, endocrinal diseases, cardio-obstructive pulmonary disease, and psychiatric disorders), anthropometric measurements as weight, height, body mass index (BMI), Waist circumference (WC), Hip circumference (HC), and waist-to-hip ratio (WHR) and complete clinical examination with specific reference to any vascular complications.

In our current study, anthropometric measurements were performed when all subjects wore light clothing with no shoes. Bodyweight, fat mass, lean muscle mass, and body fat rate were measured by using a bioelectric-impedance analyzer (BC-420, Tanita, Tokyo, Japan). WC measured by

using a cloth measuring tape at the midpoint between the iliac crest and the lowest margin of the ribs. HC measured by wrapping a cloth measuring tape around the maximum circumference of the hips. BMI, WHR and fat-to-muscle ratio were calculated as weight (kg)/height (m2), WC (cm)/HC (cm), and fat mass (kg)/lean muscle mass (kg), respectively [11].

Blood Sampling and Biochemical Measurements:

After overnight fasting (12h), venous blood samples (5 ml) were withdrawn from each subject via proper venipuncture technique under complete aseptic condition. All blood samples were divided into two aliquots: the first part was collected in a vacutainer tube containing Na2-EDTA for the assay of HbA_{1c}; the second was collected in a plain vacutainer tube and centrifuged (3000 rpm) for serum preparation. Serum was used to measure total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, creatinine, and liver enzymes. The serum for FGF-19 measurement was stored at −80°C, until the measurement was performed.

HbA_{1c} was measured by ion-exchange chromatography method (Biosystem co, Spain). Plasma glucose was measured by the glucose oxidase method (Cobas Integra 400 plus, Germany). TC, TG, HDL-C levels were measured by spectrophotometric method (Human, Germany). LDL-C levels were calculated using the Friedewald equation LDL = TC – HDL – (TG/5), provided that TG level was not above 400 mg/dl [12].

FGF-19 measurement:

The human FGF-19 was measured in duplicate by sandwich enzyme-linked immunosorbent assay (Biovendor, Human and Diagnostic Products, Cat no: RD191107200R, Czech Republic). The manufacturer declared the within-run and between-run coefficient of variations as 7.0% and 8.5 %, respectively with a sensitivity of 4.8 pg/mL and linearity 800 pg/mL. Organon Teknika Microwell system, Reader 230s (Germany) ELISA reader was used [13].

Statistical analysis:

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) Qualitative

data were expressed as frequency (N) and percentage (%). Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if, p>0.050. The presence of significant outliers (extreme values) was tested for by inspecting the boxplots. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if not. IQR = 75th percentile minus 25th percentile. Qualitative data were compared by the Chi-Square test. Quantitative data in two groups were compared by Independent-Samples t-Test (for normally distributed data in both groups) or its non-parametric equivalent; Mann-Whitney U test if data were not normally distributed in one or both groups and/or significant outliers.

Point Biserial correlation was used to assess the association between one dichotomous variable and one continuous variable. Spearman's correlation was used to assess the strength and direction of the association/relationship between two continuous variables. The Receiver Operating Characteristic (ROC) curve analysis was used to find a cutoff value of a continuous variable that can discriminate between two conditions. For any of the used tests, results were considered as statistically significant if p-value ≤ 0.050. Appropriate charts were used to graphically present the results whenever needed. F1 score and Matthews correlation coefficient (MCC) were computed manually [14].

Results:

Demographic data of subjects:

Our 160 participants were classified into two groups: Group A (MetS) included 80 (12 men, 68 women) subjects with metabolic syndrome and Group B (control) included 80 age and sex-matched healthy subjects (16 men and 64 women).

The medians of age were (39.9 ± 5.2 years and 40.4 ± 4.7 years) in the MetS and the control group respectively. Also, the BMIs of the two groups were (43.7 (39.1-47.9), and 27.7 (26-31.2), in order.

The differences between the two groups:

Table (1) shows a statistically significantly higher proportions of low activity, FH of DM, anemia, and FGF-19 ≤ 137 in MetS group. It also shows a statistically significantly higher BMI, FBG, PPBG, HbA1c, serum creatinine, AST, ALT, TC, TG, and LDL-C in MetS group. There was a statistically significantly lower hemoglobin level in MetS group. There was no

statistically significant difference in age, sex, marital status, and HDL-C. As 4 male subjects (14.3%) and 89 female subjects (67.4%) have anemia defined as hemoglobin level <13 g/dl in male, and <12 g/dl in female (WHO criteria).

So, HbA1c was corrected according to the proposal that stated HbA1c will be falsely decreased by 0.053% in the male gender and 0.047% in the female gender for each 1 g/dL decrement of hemoglobin level [15].

Analysis of FGF-19 in the two study groups:

There was a statistically significantly lower FGF-19 level among MetS group as shown in **Table (1)** than in the control group ($p<0.001$). **Figure (1)** shows an AUC for FGF-19 of 0.907 (excellent performance) and a cutoff value of ≤ 137 pg/ml can discriminate between those with MetS vs. control group with a sensitivity, specificity, PPV, and NPV of 75%, 93.7%, 92.3%, and 78.9%, respectively. Also, **Table (2)** shows the diagnostic performance of FGF-19 in MetS.

Correlation between FGF19 level and clinico-laboratory parameters:

Table (3) shows a statistically significantly negative correlation between FGF-19 and body weight, BMI, WC, HC, FBG, PPBG, HbA1c, serum creatinine, TC, TG, and LDL-C. There was no statistically significant correlation between FGF-19 and physical activity, sex, height, WHR, hemoglobin level, AST, ALT, and HDL-C.

Table (1): The differences between the two groups.

Parameter	Control group	MetS group	Statistic	P value
N	80	80		
Categorical			χ^2	**P value**
Sex			0.693	0.405
Male	16 (20%)	12 (15%)		
Female	64 (80%)	68 (85%)		
Marital status			2.133	0.144
Single	24 (30%)	16 (20%)		
Married	56 (70%)	64 (80%)		
Physical activity			4.279	0.039
Low	38 (47.5%)	51 (63.7%)		
Moderate to high	42 (52.5%)	29 (36.3%)		
Family history of DM	32 (40%)	56 (70%)	14.545	<0.001
Anemia	40 (50%)	53 (66.3%)	4.340	0.037
FGF-19 category			78.381	<0.001
≤ 137	5 (6.3%)	60 (75%)		
> 137	75 (93.8%)	20 (25%)		
Quantitative			**t / Z**	**P value**
Age (years)	40.4 ± 4.7	39.9 ± 5.2	t = 0.665	0.507
BMI (kg / m^2)	27.7 (26-31.2)	43.7 (39.1-47.9)	Z = -9.921	<0.001
FGF-19 level	293.5 (250.8-313.8)	126 (117.8-179)	Z = -8.893	<0.001
Hemoglobin level (g/dl)	12.3 (11 – 14.5)	11.3 (10.6 – 12.2)	Z = -3.648	<0.001
FBG	78 (71.3 – 80)	112.5 (108 - 140)	Z = -10.964	<0.001
PPBG	112.5 (110 - 120)	220 (200 - 280)	Z = -11.019	<0.001
HbA1c	5 (4.6 – 5)	6.8 (6.1 – 7.3)	Z = -5.607	<0.001
Corrected HbA1c	5 (4.7 – 5.02)	6.9 (6.1 – 7.31)	Z = -10.943	<0.001
Serum creatinine	0.8 (0.7 – 0.8)	0.9 (0.8 – 1.0)	Z = -3.024	0.002
AST	18.5 (18 – 20)	20.5 (18 – 28.8)	Z = -2.474	0.013
ALT	20 (18.3 – 23)	22.5 (18 - 30)	Z = -10.034	<0.001
TC	161 (143.3 – 179.5)	189 (164.3 – 215.8)	Z = -4.158	<0.001
TG	113 (89.3 – 164.8)	145.5 (106.3 – 218.3)	Z = -3.646	<0.001
HDL-C	39 (35.3 - 44)	40 (33.3 - 46)	Z = -0.451	0.652
LDL-C	103.9 (79.3 - 114)	111 (96.3 – 144.5)	Z = -2.369	0.018

Data expression [test of significance]: N (%) [Chi-square test] for categorical variables. Mean ± SD [Independent-Samples t-test] for age. Median (25^{th} – 75^{th} percentiles) [Mann-Whitney U-test] for other quantitative variables.

Table (2): Diagnostic performance of FGF-19 in MetS.

TP	TN	FP	FN	Accuracy	F1 score	MCC
60	75	5	20	0.844	0.828	0.6999

TP=true positive, TN=true negative, FP=false positive, FN=false negative. MCC=Matthews correlation coefficient.

Table (3): Correlation between FGF-19 level and clinico-laboratory parameters.

Parameter	Correlation coefficient	P value
***Physical activity**	0.058	0.465
***Sex**	0.147	0065
Weight	-0.674	**<0.001**
Height	0.048	0.546
BMI	-0.618	**<0.001**
WC	-0.637	**<0.001**
HC	-0.656	**<0.001**
WHR	-0.131	0.100
Hemoglobin level	-0.002	0.976
FBG	-0.701	**<0.001**
PPBG	-0.646	**<0.001**
HbA1c	-0.753	**<0.001**
Corrected HbA1c	-0.732	**<0.001**
Serum creatinine	-0.310	**<0.001**
AST	-0.094	0.238
ALT	-0.074	0.355
TC	-0.320	**<0.001**
TG	-0.191	**0.015**
HDL-C	0.030	0.704
LDL-C	-0.223	**0.005**

Test of significance: Spearman's correlation and *Point biserial correlation.

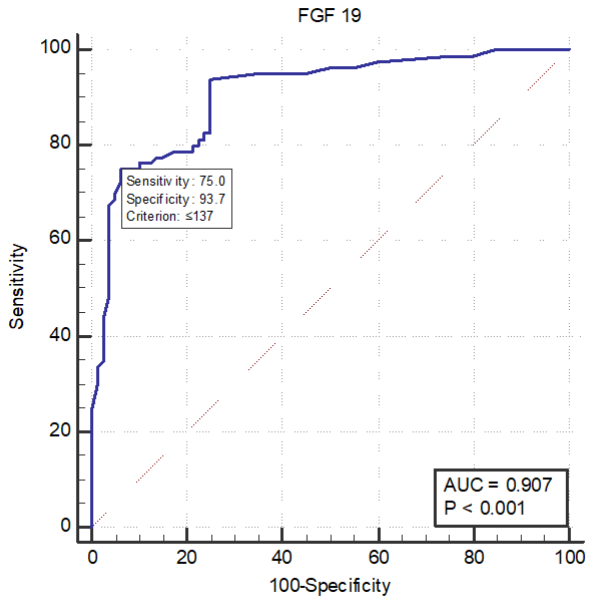

Figure (1): ROC curve for FGF-19 in discriminating MetS from control.

Discussion:

The MetS defined as the presence of several cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. Individuals with MetS have an increased burden of cardiovascular disease (CVD) [16]. In addition to their effect on cardiovascular morbidity and mortality, the components of MetS have been associated with diabetes [17].

MetS and insulin resistance are associated with certain lipid disturbances, including high fasting and postprandial levels of TG as well as instability in HDL-C concentrations and non-HDL cholesterol levels [18].

For a person to be defined as having MetS according to the 2005 IDF definition, they must have central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women, with ethnicity-specific values for other groups), plus any two of the following four factors [19]:

1) Raised TG level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
2) Reduced HDL cholesterol: < 40 mg/dL (1.0 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females, or specific treatment for this lipid abnormality
3) Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
4) Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

Fibroblast growth factors FGF-19, a peptide with 216 amino acids, including a signal peptide of 22 amino acids, was introduced as a novel metabolic regulator reversing diabetes mellitus, hepatic steatosis, hyperlipidemia, and adiposity [10].

In our current study, FBG, PPBG, and HbA1c levels were statistically significantly higher among the subjects with MetS as compared to the control group ($p<0.001$).

Also, there was a statistically significantly lower hemoglobin level in the MetS group, which may relate to an unhealthy lifestyle. So, HbA1c was corrected according to the proposal that stated HbA1c will be falsely decreased by 0.053% in the male gender and 0.047% in the female gender for each 1 g/dL decrement of hemoglobin level [15].

Our results are supported by another study as they reported the mean HbA1c value in the MetS group was 8.7% that was statistically significantly higher as compared to the control group [20].

In our current study, TC, TG, and LDL-C levels were statistically significantly higher among the MetS group as compared to the control group ($p<0.001$,<0.001, and 0.018 respectively), While HDL-C levels were higher among the control group as compared to the MetS group but weren't statistically significant ($p=0.652$).

Such results agreed with another study that found higher TG levels and lower HDL-C levels among the MetS group than the control group [21].

In the same context, a study reported that TC, TG, LDL-C, and VLDL levels, were found to be statistically significantly higher ($p<0.001$) among the MetS group than controls. Also stated that serum HDL-C was significantly lower ($p<0.001$) among MetS subjects (41.28 ± 8.81) as compared to controls (54.00 ± 6.31) [22].

A study done showed a significant difference in the cholesterol levels between the MetS group and the controls [20]. Also, another one found a significantly higher proportion of TC and LDL-C levels among subjects with MetS [23].

However LDL-C and TC levels have been widely used to assess lipid atherogenesis, but its utility for insulin resistance isn't well known, in contrast to TG and HDL-C [24].

In our current study, the median level of FGF-19 in the MetS group was 126 (117.8-179) pg/mL, which was statistically significant lower than the level in the control group ($p<0.001$).

This result came in agreement with a study that showed FGF-19 levels were lower in subjects with type 2 diabetes exclusively on lifestyle intervention [170.05 (89.01–244.70) pg/mL] and even lower in the diabetic group [142.25 (55.55–187.58) pg/mL] than in normal control group [245.03 (126.23–317.43) pg/mL] regardless of the degree of insulin resistance [13].

A similar result was reported by a study that showed FGF-19 levels in subjects with IFG (210 pg/mL [142–327]) and subjects with type 2 diabetes (196 pg/mL [137– 280]) were significantly lower than NGT subjects (289 pg/mL [224–393]) ($P<0.001$) and inversely associated with FBG levels [25]. Also, another study done showed that FGF-19 levels were low in T2DM subjects with MetS, and the median FGF-19 levels in T2DM subjects with MetS and healthy controls were 122.90 (108.63-237.60) pg/ml

and 293.45 (153.64-370.31) pg/ml, respectively (P=0.003) [26].

Another study done observed reduced FGF-19 levels in subjects with type 2 diabetes [27]. Also, a study reported that FGF-19 levels were significantly lower in subjects with gestational diabetes compared with healthy pregnant females [28]. In contrast, a study reported that fasting and postprandial FGF-19 levels didn't differ between controls and diabetic subjects [29].

A clinical study showed that FGF-19 levels were significantly lower among obese subjects compared with healthy control subjects [30]. Similarly, another study reported that serum FGF-19 levels were lower in obese adolescents with NAFLD, compared with healthy control subjects, and are inversely correlated with the probability of nonalcoholic steatohepatitis and fibrosis in children with NAFLD [31].

The negative correlation between FGF-19 and obesity was further confirmed in experimental studies involving animal models. Administration of human recombinant FGF-19 to high-fat diet-induced obese mice results in a significant dose-dependent decrease in body mass and blood glucose levels, which were associated with a decrease in the TG levels, as well as increased fatty acid oxidation, brown tissue mass, and insulin sensitivity [32].

FGF-19 could mediate its function via activating the FGFR4-β-Klotho complex. FGF-19 combined with the FGFR4-β-Klotho complex to activate an insulin-independent endocrine pathway and mediate different metabolic effects [33].

In our current study, there was a statistically significantly negative correlation between FGF19 and body weight, BMI, WC, HC, FBG, PPBG, HbA1c, serum creatinine, TC, TG, and LDL-C. There was no statistically significant correlation between FGF19 and physical activity, sex, height, WHR, hemoglobin level, AST, ALT, and HDL-C.

A study done demonstrated a negative association of FGF-19 levels with age and FBG and after adjustment for age, a significant negative association of FGF-19 levels with FBG was still found [25]. Also, another one demonstrated a negative correlation between FGF-19 levels and FBG, HDL-C, and TG levels, but they found no significant correlation between FGF-19 and BMI [34].

A study done showed significant negative correlations were found between FGF-19 and BMI, triglyceride, log (TG/HDL-c), hsCRP, and HbA1c [26].

In another study, FGF-19 levels were positively correlated with insulin levels. They suggested that FGF-19 was independently correlated with insulin secretion and sensitivity and that increased FGF-19 may improve the function of islet beta cells [13].

A study done reported that FGF-19 levels are positively associated with glucose effectiveness and negatively associated with hepatic glucose production (HGP). The increase in HGP in humans is partially due to the insulin-independent decrease in FGF-19 [35].

An animal study reported that when FGF-19 was administered to diabetic mice, plasma glucose levels were reduced, and glucose homeostasis was maintained [36].

So in our current study, the negative correlation between FGF-19 and FBG, PPBG, and HbA1c, supports the relationship between FGF-19 and glucose homeostasis.

We also found that a cutoff value of ≤ 137 pg/ml can discriminate between those with MetS vs. control group with a sensitivity, specificity, PPV, and NPV of 75%, 93.7%, 92.3%, and 78.9%, respectively, and the AUC for FGF-19 was 0.907 (excellent performance).

Conclusion:

FGF-19 level was statistically significantly lower among the MetS group than in the control group. A cutoff value of ≤ 137 pg/ml can discriminate between those with MetS vs. control group with a sensitivity, specificity, PPV, and NPV of 75%, 93.7%, 92.3%, and 78.9%, respectively, and the AUC for FGF-19 was 0.907 (excellent performance). So, our study proposes that FGF-19 may be considered as a reliable biomarker for the early detection of risky subjects with MetS.

Abbreviations:

MetS: Metabolic syndrome; **FGF-19:** Fibroblast Growth Factor 19**; IDF**: International Diabetes Federation; **CVD:** cardiovascular disease; **BMI**: Body mass index; **WC:** Waist circumference; **HC:** Hip circumference; **WHR:** waist-to-hip ratio**; FBG**: fasting blood glucose; **PPBG**: postprandial blood glucose; **HbA1c**: glycosylated hemoglobin; **TC**: total cholesterol; **TG**: triglyceride; **HDL-C:** high-density lipoprotein cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **AUC**: area under curve; **NPV:** negative predictive value; **PPV:** positive predictive value.

References:

1) Itoh N. Hormone-like (endocrine) Fgfs: their evolutionary history and roles in development, metabolism, and disease. Cell Tissue Res. 2010 Oct;342(1):1-11.

2) Fukumoto S. Actions and mode of actions of FGF19 subfamily members. Endocr J. 2008 Mar;55(1):23-31.

3) Xie MH, Holcomb I, Deuel B, Dowd P, Huang A, Vagts A, et al. FGF-19, a novel fibroblast growth factor with unique specificity for FGFR4. Cytokine. 1999 Oct;11(10):729-35.

4) Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab. 2005 Oct;2(4):217-25.

5) Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004 Jan 27;109(3):433-8.

6) Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation. 2004 Jan 6;109(1):42-6.

7) Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA. 2002 Dec 4;288(21):2709-16.

8) Nádas J, Jermendy G. From the metabolic syndrome to the concept of global cardiometabolic risk. Orv Hetil. 2009 May 3;150(18):821-9. Hungarian.

9) Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006 May;23(5):469-80.

10) Degirolamo C, Sabbà C, Moschetta A. Therapeutic potential of the endocrine fibroblast growth factors FGF19, FGF21 and FGF23. Nat Rev Drug Discov. 2016 Jan;15(1):51-69.

11) WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. (2000) 894:i–xii; 1– 253.

12) Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem; 1972: 18:499–502.

13) Tang MJ, Su JB, Xu TL, Wang XQ, Zhang DM, Wang XH. Serum fibroblast growth factor 19 and endogenous islet beta cell function in type 2 diabetic patients. Diabetol Metab Syndr. 2019 Sep 24;11:79.

14) Chicco D, Jurman G. The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation. BMC Genomics. 2020 Jan 2;21(1):6.

15) Villacreses MC, Karnchanasorn R, Ou HY, Feng W, Samoa R, Chuang LM, et al. OR26-05 The Correction Factor for A1C in Anemic Patients, J. Endocr. Soc. 2020 May;4(1):OR26–05.

16) Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res. 2017 May;183:57-70.

17) Tracy BM, Wilson JM, Staley C, Frias B, Schenker ML, Gelbard RB. Metabolic Syndrome: Major Risk Factor for Morbidity and Mortality in Severely Injured Trauma Patients. J Am Coll Surg. 2020; 230: 145-150.

18) Koren D, Dumin M, Gozal D. Role of sleep quality in the metabolic syndrome. Diabetes Metab Syndr Obes. 2016 Aug 25;9:281-310.

19) Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005 Sep 24-30;366(9491):1059-62.

20) Sutkovic J and Abdić-Nekić V. Study Of HbA1c As A Reliable Indicator For Metabolic Syndrome In Non Diabetic Patients. Southeast Europe Journal of Soft Computing. 2013 Mar;2(1):27.

21) Worawongprapa O. Glycemic control in diabetes with metabolic syndrome in community hospital. J Med Assoc Thai. 2008 May;91(5):641-7.

22) Gutch M, Rungta S, Kumar S, Agarwal A, Bhattacharya A, Razi SM. Thyroid functions and serum lipid profile in metabolic syndrome. Biomed J. 2017 Jun;40(3):147-153.

23) Ogbera AO. Prevalence and gender distribution of the metabolic syndrome. Diabetol Metab Syndr. 2010 Jan 12;2:1.

24) Nimmanapalli H, Ambika D, Prabath k, & Vani N. "Lipid ratios, atherogenic coefficient, and atherogenic index of plasma as parameters in assessing cardiovascular risk in type 2 diabetes mellitus." *International Journal of Research in Medical Sciences* [Online], 4.7 (2016): 2863-2869.

25) Fang, Q., Li, H., Song, Q., Yang, W., Hou, X., Ma, X., et al. "Serum fibroblast growth factor 19 levels are decreased in Chinese subjects with impaired fasting glucose and inversely associated with fasting plasma glucose levels." Diabetes care. 2013 Sep;36(9): 2810-2814.

26) Barutcuoglu B, Basol G, Cakir Y, Cetinkalp S, Parildar Z, Kabaroglu C, et al. Fibroblast growth factor-19 levels in type 2 diabetic patients with metabolic syndrome. Ann Clin Lab Sci. 2011 Fall;41(4):390-396.

27) Schaap FG. Role of fibroblast growth factor 19 in the control of glucose homeostasis. Current Opinion in Clinical Nutrition and Metabolic Care. 2012 Jul;15(4):386-391.

28) Wang D, Zhu W, Li J, An C, Wang Z. Serum concentrations of fibroblast growth factors 19 and 21 in women with gestational diabetes mellitus: association with insulin resistance, adiponectin, and polycystic ovary syndrome history. PLoS One. 2013 Nov 19;8(11):e81190.

29) Brufau G, Stellaard F, Prado K, Bloks VW, Jonkers E, Boverhof R, Kuipers F, et al. Improved glycemic control with colesevelam treatment in patients with type 2 diabetes is not directly associated with changes in bile acid metabolism. Hepatology 2010; 52: 1455-64.

30) Gallego-Escuredo JM, Gómez-Ambrosi J, Catalan V, Domingo P, Giralt M, Frühbeck G, et al. Opposite alterations in FGF21 and FGF19 levels and disturbed expression of the receptor machinery for endocrine FGFs in obese patients. Int J Obes (Lond). 2015 Jan;39(1):121-9.

31) Wojcik M, Janus D, Dolezal-Oltarzewska K, Kalicka-Kasperczyk A, Poplawska K, Drozdz

D, et al. A decrease in fasting FGF19 levels is associated with the development of non-alcoholic fatty liver disease in obese adolescents. J Pediatr Endocrinol Metab. 2012;25(11-12):1089-93.

32) Fu L, John LM, Adams SH, Yu XX, Tomlinson E, Renz M, et al. Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. Endocrinology. 2004 Jun;145(6):2594-603.

33) Izaguirre M, Gil MJ, Monreal I, Montecucco F, Frühbeck G, Catalán V. The Role and Potential Therapeutic Implications of the Fibroblast Growth Factors in Energy Balance and Type 2 Diabetes. Curr Diab Rep. 2017 Jun;17(6):43.

34) Stejskal D, Karpísek M, Hanulová Z, Stejskal P. Fibroblast growth factor-19: development, analytical characterization and clinical evaluation of a new ELISA test. Scand J Clin Lab Invest. 2008;68(6):501-7.

35) Zhang J, Li H, Bai N, Xu Y, Song Q, Zhang L, et al. Decrease of FGF19 contributes to the increase of fasting glucose in human in an insulin-independent manner. J Endocrinol Invest. 2019;42:1019–27.

36) Hansen AMK, Vienberg SG, Lykkegaard K, Zhao X, Tingqing G, Han D, et al. Differential receptor selectivity of the FGF15/FGF19 orthologues determines distinct metabolic activities in db/db mice. Biochem J. 2018;475(18):2985–96.

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