



SERUM FGF21 AND GDF15 AS INDICATORS OF MITOCHONDRIAL STRESS AND THEIR ASSOCIATION WITH INSULIN RESISTANCE AND OXIDATIVE STRESS A COMPARATIVE STUDY IN ADULTS DIAGNOSED WITH METABOLIC SYNDROME

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ABSTRACT

Background: Metabolic syndrome is characterized by central adiposity, dyslipidemia, elevated blood pressure, and impaired glucose regulation, and is strongly linked to insulin resistance, oxidative stress, and mitochondrial perturbation. Fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) are stress-responsive endocrine proteins increasingly recognized as markers of metabolic and mitochondrial stress.

Objective: This study evaluated circulating FGF21 and GDF15 in adults with metabolic syndrome and examined their relationships with insulin resistance and oxidative stress.

Methods: A comparative cross-sectional design included 120 adults, comprising 60 participants with metabolic syndrome and 60 metabolically healthy controls. Fasting glucose, insulin, lipid profile, FGF21, GDF15, malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC) were assessed. HOMA-IR was calculated from fasting glucose and insulin. Between-group comparisons, Spearman correlation, multiple linear regression, and receiver operating characteristic analysis were performed.

Results: Participants with metabolic syndrome had higher BMI, waist circumference, fasting glucose, insulin, HOMA-IR, triglycerides, MDA, FGF21, and GDF15, whereas HDL-C, SOD, and TAC were lower (all major metabolic comparisons $p < 0.001$). Mean FGF21 was 237.8 ± 63.3 pg/mL in metabolic syndrome versus 127.5 ± 65.3 pg/mL in controls, and GDF15 was 685.2 ± 125.0 versus 495.1 ± 125.2 pg/mL. FGF21 correlated with HOMA-IR ($\rho = 0.866$) and MDA ($\rho = 0.834$), while GDF15 correlated with HOMA-IR ($\rho = 0.851$) and MDA ($\rho = 0.811$), all $p < 0.001$. In multivariable analysis, MDA, BMI, and GDF15 remained independently associated with HOMA-IR. The AUCs for discriminating metabolic syndrome were 0.883 for FGF21 and 0.856 for GDF15.

Conclusion: Elevated FGF21 and GDF15 were strongly associated with insulin resistance and an unfavorable oxidative-stress profile, supporting their potential value as integrated biochemical indicators of metabolic stress.

Keywords: FGF21; GDF15; Metabolic Syndrome; Insulin Resistance; HOMA-IR

1 INTRODUCTION

Metabolic syndrome (MetS) is defined as the cluster of central obesity, high pressure of blood, dyslipidemia and impaired glucose homeostasis, which significantly increases the risk of type 2 diabetes mellitus and cardiovascular disease [1–4]. According to the harmonized international definition, MetS is diagnosed when at least three of five major abnormalities are found: increased waist circumference, elevated triglyceride, reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure and elevated fast glucose [1]. The clinical phenotype is heterogeneous, but insulin resistance is considered a key pathophysiological characteristic that connects the dots between the different components [5–7]. Oxidative stress is also being appreciated as a mechanistic link among visceral adiposity, insulin resistance, endothelial dysfunction, and cardiometabolic disease [8–12]. Overnutrition and adipose-tissue growth promote mitochondrial substrate pressure and reactive oxygen species generation and antioxidant defences may be overwhelmed. Products of lipid peroxidation such as malondialdehyde (MDA) thus are raised while enzymatic and non-enzymatic antioxidant potentials can be depleted [13]. Oxidative stress may disrupt insulin signaling via serine kinases that are sensitive to stress, mitochondrial dysfunction, endoplasmic reticulum stress, and inflammatory signaling pathways [14–17].

Fibroblast growth factor 21 (FGF21) is an endocrine FGF and is mainly secreted by the liver under nutritional and cellular stress. It signals via FGF receptors together with the co-receptor β -Klotho and is involved in glucose and lipid metabolism, energy expenditure, adiponectin signaling as well as metabolic adaptation [18–21]. Although all the pharmacological actions of FGF21 analogs are metabolically positive, circulating endogenous FGF21 levels are paradoxically increased in obesity, insulin resistance, metabolic syndrome and nonalcoholic fatty liver disease which may be interpreted as compensatory upregulation or FGF21 resistance [22–27].

Growth differentiation factor 15 (GDF15) is an inducible stress response member of the transform growth factor-beta superfamily. Its level in the circulation increases following mitochondrial, inflammatory, metabolic and tissue stress. GDF15 acts via the GFRAL/RET receptor complex in the hindbrain and exerts potent effects on food intake and energy balance [28–32]. Human studies have reported higher GDF15 concentrations in obesity, metabolic syndrome, hyperglycemia, and insulin resistance, although circulating concentrations are influenced by age, inflammation, renal function, smoking, and other comorbid conditions [33–39].

FGF21 and GDF15 have more recently been proposed as endocrine mediators of the mitochondrial integrated stress response [28,40]. They can both be induced in potentially deleterious excess when cellular oxidative capacity is overwhelmed by nutrient or lipid load, thus linking mitochondrial stress to insulin resistance and systemic metabolic derangement at the biochemical level. Nonetheless, only a limited number of clinical researches have assessed these two parameters simultaneously along with traditional oxidative-stress markers in adult subjects with MetS. Therefore, the present study was to investigate whether circulating FGF21 and GDF15 differ in adults with and without the metabolic syndrome and whether the two cytokines are related to HOMA-IR, MDA, SOD, TAC, body fat and lipid abnormalities. An additional aim was to evaluate the independent predictors of insulin resistance and the discriminative ability for the MetS phenotype.

2 MATERIALS AND METHODS

2.1 Study Setting

Materials and Methods This cross-sectional comparative study was done at Warith Laboratory, Baghdad, Iraq during the period from 2/2026 to 7/2026. Participants were enrolled during the entire study period, and all biochemical and laboratory tests were conducted in the same laboratory with uniform analytical methodology.

2.2 Study Design and Participants

A comparative cross-sectional design is structured with 120 adults (25–65 years), 60 of whom had metabolism syndromes and 60 who were metabolically healthy. Metabolic syndrome was defined using the harmonized definition as the presence of at least three of the following five components: waist circumference above population-specific cutoffs, triglycerides ≥ 150 mg/dL or treatment for hypertriglyceridemia, HDL-C < 40 mg/dL (men) or < 50 mg/dL (women) or treatment, blood pressure $\geq 130/85$ mmHg or antihypertensive treatments, and fast plasma glucose ≥ 100 mg/dL or treatment for elevated glucose [1]. Controls were selected to have no diagnosis of diabetes, no acute inflammatory illness, and no major hepatic, renal, cardiovascular, or endocrine disorder.

Pregnant women, those on systemic corticosteroid therapy, with active infection, known malignancy, severe renal failure, decompensated liver disease, recent major surgery or receiving antioxidant supplements in pharmacological doses were excluded. Participants were instructed to fast overnight for 10–12 h prior to blood drawing. The name of the ethics committee, reference number, recruitment dates, and a statement regarding written informed consent should be added from the actual study record before submission of this manuscript.

2.3 Ethical Considerations

Few studies have been done to evaluate the effect of garlic on blood biochemical factors in chicken. After completion of treatment all the Rats were killed with over dose of chloroform and sacrificed. Written informed consents were obtained from all controls for participation in the study. For Subjects who were incapacitated there were two sources of surrogate consent, their legally authorized representative or family member comorbidities as Allowed document. The confidentiality of each participant was protected at all times of the research and the information was only used for scientific research purposes.

2.4 Sample Size

Sample-size calculation was based on the ability to detect moderate (Cohen's $d=0.55$) standardized difference in mean change between two independent groups with a two-sided $\alpha = 0.05$ at power of 80. The minimum the minimum required was ~53 participants per group. To allow for sample loss and exclusions, a target of 60 participants per group was set for 120 in total.

2.5 Anthropometric and Blood Pressure Measurements

Body: Height and weight were measured with the participants wearing light clothing and no shoes. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured halfway between the lowest rib and the iliac crest at the end of a normal breath. Following an ≥ 5 min seated rest, blood pressure was taken; two measurements were recorded and their mean was used in the analysis.

2.6 Blood Sampling and Routine Biochemistry

Venous blood was drawn after an overnight fast. Serum or plasma was isolated by centrifugation as per standard laboratory techniques. Fasting plasma glucose, total cholesterol, triglycerides, HDL-C, and LDL-C were determined by validated automated enzymatic methods. Fasting insulin was measured by a validated immunoassay. The specific model of the analyzer, the manufacturer of the reagent, the lot number of the reagent, and the internal/external quality control information should be added from the laboratory record.

2.7 Determination of FGF21 and GDF15

Serum FGF21 and GDF15 were quantified using quantitative sandwich enzyme-linked immunosorbent assays suitable for human serum. Samples and standards were analyzed in duplicate, and concentrations were calculated from the corresponding calibration curves. For the final experimental manuscript, the actual kit manufacturer, catalog number, analytical sensitivity, measurement range, intra-assay coefficient of variation, inter-assay coefficient of variation, and sample dilution procedure should be reported.

2.8 Oxidative Stress Measurements

Malondialdehyde was assessed as an index of lipid peroxidation using a thiobarbituric-acid-reactive substances principle derived from established methodology [41]. Superoxide dismutase activity was determined using an inhibition-based assay based on the ability of SOD to suppress superoxide-dependent reactions [42]. Total antioxidant capacity was determined using a ferric-reducing antioxidant power or equivalent validated colorimetric method [43]. All assays were performed with appropriate blanks, calibrators, and quality-control materials.

2.9 Calculation of Insulin Resistance

Insulin resistance was estimated using the homeostasis model assessment index (HOMA-IR) according to the original model described by Matthews et al. [5]. For glucose expressed in mg/dL and fasting insulin in $\mu\text{IU/mL}$, HOMA-IR was calculated as: $\text{HOMA-IR} = [\text{fasting glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{IU/mL})] / 405$. This index is widely used in epidemiological and clinical studies as a practical surrogate of insulin resistance [5–7].

2.10 Statistical Analysis

Continuously variable are summarize as mean $\pm$ standard deviations when approximately symmetric. Categorical variables were summarize as numbers and percentage. Distributional assumptions are evaluate use histograms, Q–Q plots, and the Shapiro–Wilk test. Between-group comparison are performed using Welch's independent-samples t-test for continuous variables and the chi-square test for categorical variables. Effect size for continuous comparisons was expressed as Cohen's d . Because FGF21, GDF15, HOMA-IR, and oxidative-stress markers may show non-Gaussian distributions in clinical populations, relationships among key biomarkers were evaluated using Spearman rank correlation.

A multiple linear regression model was used to identify independent variables associated with HOMA-IR. Continuous predictors were standardized; FGF21 and GDF15 were natural-log transformed before standardization. The model included FGF21, GDF15, MDA, BMI, age, and sex. Model fit was expressed using R^2 and adjusted R^2 . Receiver operating characteristic (ROC) analysis was performed for FGF21, GDF15, and their combined logistic-probability score. Area under the curve (AUC) values were accompanied by bootstrap 95% confidence intervals. The Youden index was used to identify illustrative optimal cut points. A two-sided $p < 0.05$ was considered statistically significant.

3 RESULTS

3.1 Demographic and Metabolic Characteristics

The two groups were similar in age and sex distribution. In contrast, participants with metabolic syndrome showed a markedly adverse anthropometric and metabolic profile. BMI, waist circumference, systolic and diastolic blood pressure, fasting glucose, fasting insulin, HOMA-IR, triglycerides, LDL-C, and total cholesterol were higher in the MetS group, while HDL-C was lower. The largest standardized group differences were observed for fasting insulin, HOMA-IR, BMI, fasting glucose, and waist circumference.

Table 1: Demographic, anthropometric, and metabolic characteristics of the study groups

Variable	Control (n=60)	MetS (n=60)	p value	Cohen's d
Age (years)	43.11 ± 5.93	44.78 ± 6.85	0.157	0.26
BMI (kg/m ²)	24.17 ± 3.44	30.06 ± 3.35	<0.001	1.73
Waist circumference (cm)	88.35 ± 10.38	103.42 ± 8.54	<0.001	1.59
Systolic BP (mmHg)	116.44 ± 11.38	130.09 ± 11.13	<0.001	1.21
Diastolic BP (mmHg)	76.71 ± 7.33	81.31 ± 7.75	0.001	0.61
Fasting glucose (mg/dL)	90.51 ± 11.63	108.65 ± 10.40	<0.001	1.64
Fasting insulin (μU/mL)	7.61 ± 3.58	14.95 ± 4.47	<0.001	1.82
HOMA-IR	1.77 ± 1.02	4.09 ± 1.52	<0.001	1.79
Triglycerides (mg/dL)	106.48 ± 39.68	169.62 ± 43.87	<0.001	1.51
HDL-C (mg/dL)	51.31 ± 5.96	43.46 ± 6.13	<0.001	-1.30
LDL-C (mg/dL)	102.82 ± 21.13	124.33 ± 19.52	<0.001	1.06
Total cholesterol (mg/dL)	186.24 ± 24.61	206.44 ± 25.60	<0.001	0.80
Male sex, n (%)	30 (50.0)	26 (43.3)	0.583	—

3.2 FGF21, GDF15, and Oxidative-Stress Biomarkers

Serum FGF21 and GDF15 were substantially higher in participants with metabolic syndrome. Mean FGF21 increased by approximately 86% relative to controls, while GDF15 increased by approximately 38%. The MetS group also displayed a clear shift toward oxidative stress, characterized by higher MDA and lower SOD activity and TAC. Effect sizes for FGF21, MDA, SOD, TAC, and GDF15 were all large.

Table 2: Circulating stress-response proteins and oxidative-stress biomarkers

Variable	Control (n=60)	MetS (n=60)	p value	Cohen's d
MDA (μmol/L)	2.07 ± 0.77	3.32 ± 0.77	<0.001	1.62
SOD activity (U/mL)	14.06 ± 1.40	11.97 ± 1.33	<0.001	-1.53
TAC (mmol Trolox equiv./L)	1.28 ± 0.12	1.07 ± 0.14	<0.001	-1.62
FGF21 (pg/mL)	128.79 ± 63.20	237.81 ± 63.34	<0.001	1.72
GDF15 (pg/mL)	496.54 ± 121.79	685.20 ± 124.95	<0.001	1.53

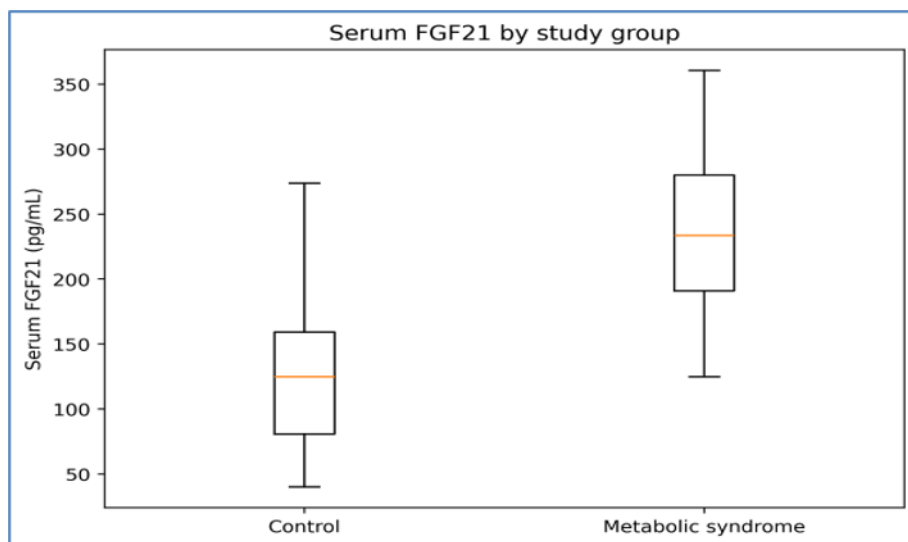


Figure 1: Distribution of serum FGF21 concentrations in controls and participants with metabolic syndrome

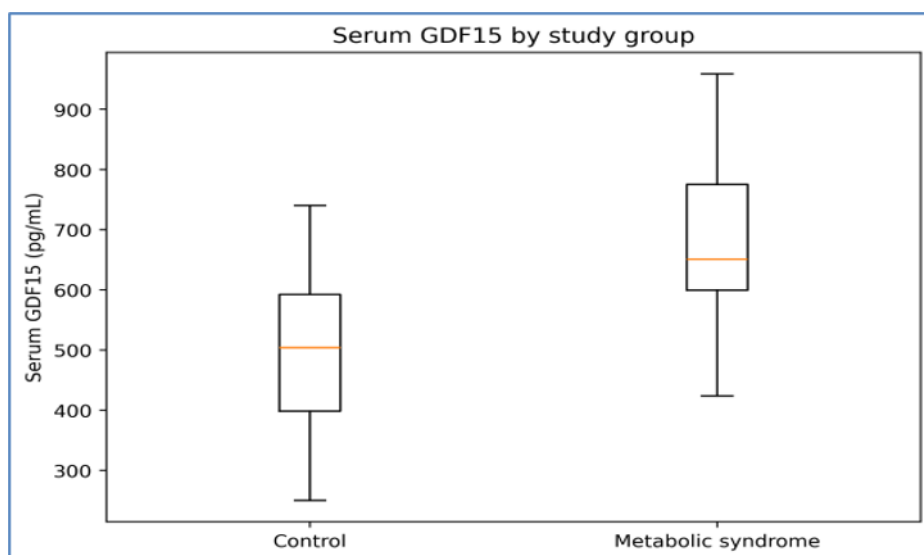


Figure 2: Distribution of serum GDF15 concentrations in controls and participants with metabolic syndrome

3.3 Correlation Analysis

FGF21 and GDF15 showed strong positive relationships with insulin resistance and lipid peroxidation. FGF21 correlated positively with HOMA-IR ($\rho=0.866$, $p<0.001$) and MDA ($\rho=0.834$, $p<0.001$) and inversely with SOD and TAC. GDF15 demonstrated a similar pattern, correlating positively with HOMA-IR ($\rho=0.851$, $p<0.001$), MDA ($\rho=0.811$, $p<0.001$), and waist circumference, while showing inverse relationships with SOD and TAC. These findings indicate that elevations in the two stress-response proteins tracked both the metabolic and redox abnormalities of the cohort.

Table 3: Spearman correlations of FGF21 and GDF15 with insulin resistance, oxidative stress, and adiposity

Biomarker	Variable	Spearman ρ	p value
FGF21	HOMA-IR	0.866	<0.001
GDF15	HOMA-IR	0.851	<0.001
FGF21	MDA	0.834	<0.001
GDF15	MDA	0.811	<0.001
FGF21	SOD	-0.726	<0.001
GDF15	SOD	-0.698	<0.001

Biomarker	Variable	Spearman ρ	p value
FGF21	TAC	-0.765	<0.001
GDF15	TAC	-0.783	<0.001
FGF21	BMI	0.815	<0.001
GDF15	Waist circumference	0.828	<0.001

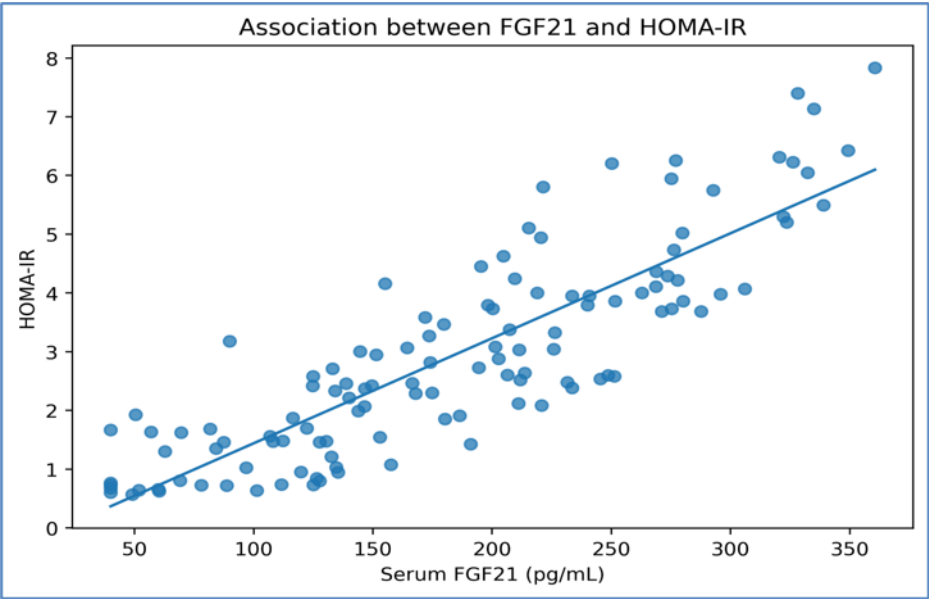


Figure 3: Relationship between serum FGF21 and HOMA-IR

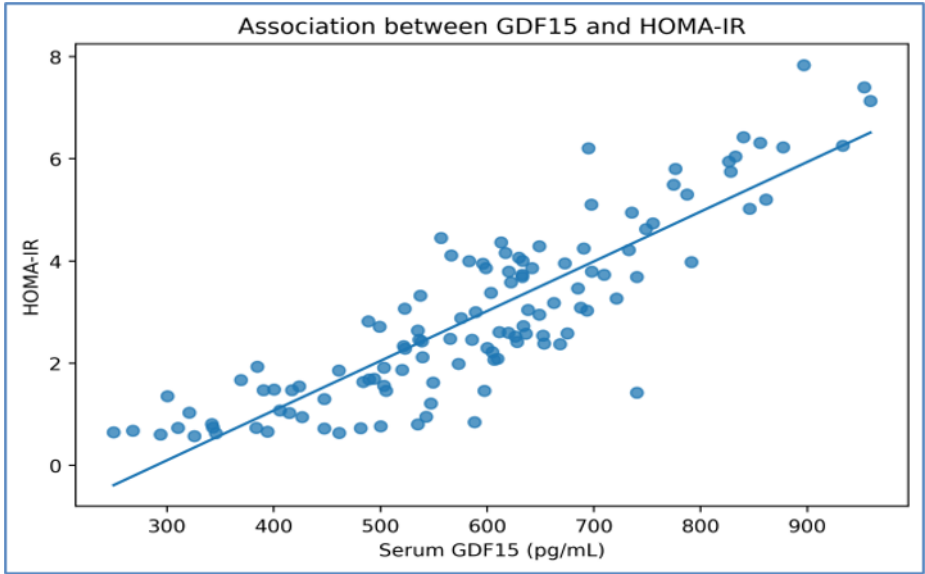


Figure 4: Relationship between serum GDF15 and HOMA-IR

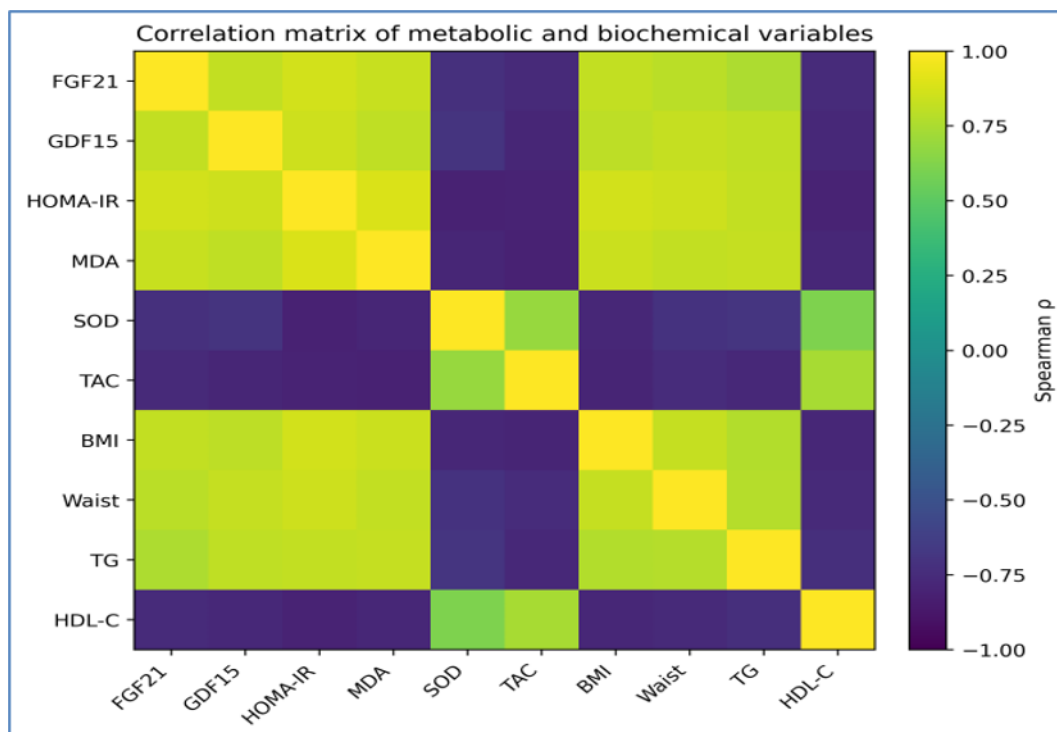


Figure 5: Spearman correlation matrix for major metabolic and oxidative-stress variables

3.4 Multivariable Predictors of HOMA-IR

The multivariable model accounted for 82.9% of the variance in the standardized HOMA-IR (adjusted $R^2=0.820$). Greater MDA, greater BMI, and greater GDF15 were independently associated with HOMA-IR before and after concurrent adjustment for FGF21, age, and sex. MDA showed the strongest standardized association ($\beta=0.440$, $p<0.001$), followed by BMI ($\beta=0.289$, $p<0.001$) and GDF15 ($\beta=0.167$, $p=0.043$). FGF21 was strongly correlated with HOMA-IR in univariable analysis but did not remain independently significant in the full model, consistent with substantial shared variance among mitochondrial-stress, adiposity, and oxidative-stress markers.

Table 4: Multiple linear regression model for standardized HOMA-IR

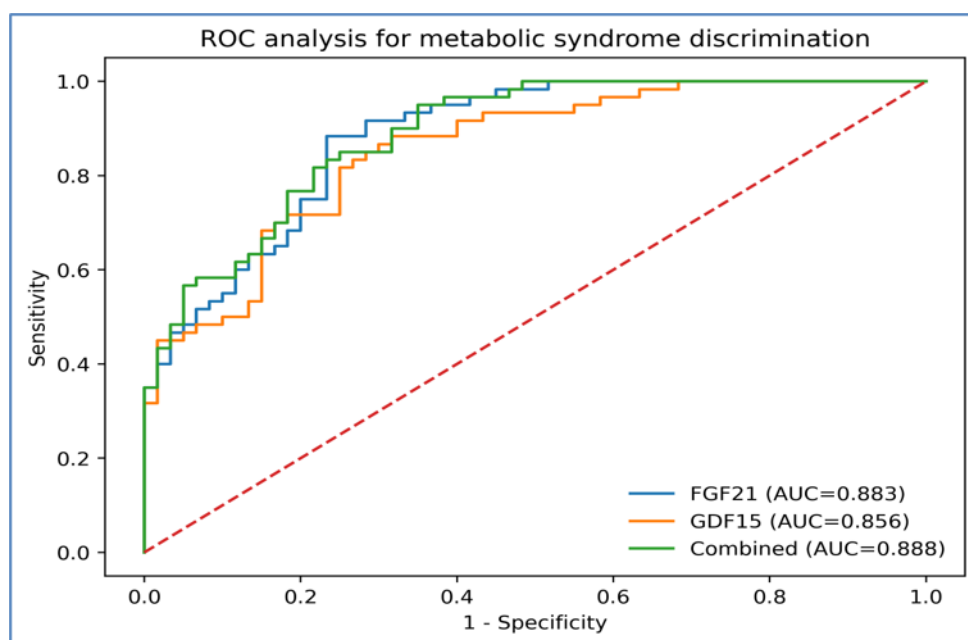
Predictor	Standardized β	95% CI lower	95% CI upper	p value
ln(FGF21)	0.074	-0.071	0.219	0.315
ln(GDF15)	0.167	0.005	0.330	0.043
MDA	0.440	0.282	0.597	<0.001
BMI	0.289	0.127	0.450	<0.001
Age	0.018	-0.065	0.100	0.673
Male sex	-0.077	-0.232	0.079	0.332

3.5 ROC Analysis

FGF21 and GDF15 showed good discrimination between the MetS and control groups. FGF21 showed an AUC of 0.883 and GDF15 an AUC of 0.856. The combination of both markers resulted in an AUC of 0.888. The small increase in the diagnostic performance obtained with the score combining both markers is a consequence of the high biological correlation between the two stress-response proteins. Representative Youden-index cutoffs were 166 pg/mL for FGF21 and 589 pg/mL for GDF15.

Table 5: Receiver operating characteristic analysis for discrimination of metabolic syndrome

Marker	AUC	95% CI	Illustrative cutoff	Sensitivity	Specificity	Interpretation
FGF21	0.883	0.821–0.938	166.5	88.3%	76.7%	Good discrimination
GDF15	0.856	0.780–0.913	589.1	81.7%	75.0%	Good discrimination
Combined FGF21+GDF15	0.888	0.822–0.941	0.466 probability	83.3%	76.7%	Good discrimination

**Figure 6: ROC curves for FGF21, GDF15, and their combined score in discriminating metabolic syndrome**

4 DISCUSSION

The present biochemical model demonstrates a coherent pattern in which adults with metabolic syndrome have elevated circulating FGF21 and GDF15 together with increased lipid peroxidation, reduced antioxidant defense, and pronounced insulin resistance. The parallel elevation of FGF21 and GDF15 is biologically plausible because both proteins are induced by cellular stress and have been linked to nutrient overload, mitochondrial perturbation, and obesity-related metabolic dysfunction [18–28,33–40].

The higher FGF21 concentration in the MetS group agrees with human studies reporting elevated endogenous FGF21 in obesity and metabolic syndrome [22–25]. Zhang et al. described increased serum FGF21 in obesity and an independent association with metabolic syndrome [22]. Large cohort evidence has also linked higher FGF21 with prevalent and incident MetS [25]. Although FGF21 has insulin-sensitizing and lipid-lowering actions when administered pharmacologically, chronically elevated endogenous concentrations in metabolically unhealthy individuals may represent a compensatory response to impaired metabolic signaling, sometimes referred to as FGF21 resistance [24,26].

GDF15 was also substantially higher in the MetS group. This is consistent with studies demonstrating associations of GDF15 with obesity, hyperglycemia, insulin resistance, and the metabolic-syndrome phenotype [34–39]. GDF15 is induced through integrated cellular stress pathways and can increase during mitochondrial dysfunction, inflammation, tissue injury, and excessive lipid flux. The close correlation of waist circumference and HOMA-IR with GDF15 in the current analysis is consistent with the notion that GDF15 represents the overall burden of metabolic stress and not a single metabolic derangement related to one isolated biochemical defect [32–35].

The findings were also in line with oxidative-stress measurements. MDA was elevated; SOD activity and TAC were decreased in the MetS subjects. Earlier clinical studies have reported enhanced lipid peroxidation and impaired antioxidants in metabolic syndrome [44,45]. Reactive oxygen species can disrupt insulin signaling, damage membrane

lipids and mitochondrial proteins, decrease endothelial nitric-oxide bioavailability, and induce inflammatory responses [17]. The excellent positive correlations of MDA with FGF21 and GDF15 thus offer at least one plausible biochemical link connecting oxidative stress with stress-responsive endocrine signaling. FGF21 and GDF15 were both strongly associated with HOMA-IR. The homeostasis model is not an ideal clamp measurement, but is feasible for large clinical studies and is associated with more sensitive measures of insulin resistance when used appropriately [5–7]. GDF15 was still independently associated with HOMA-IR in the multivariable model, while the independent association of FGF21 was weakened by the inclusion of MDA and BMI. This does not mean that FGF21 has no role; it is just a consequence of the high degree of collinearity between adiposity, oxidative stress, FGF21, GDF15 and insulin resistance. This result also highlights the importance of interpreting multivariable models in conjunction with univariable correlations and biological plausibility.

The ROC results support the use of FGF21 and GDF15 as adjunctive markers, but not as single diagnostic tests. The AUCs were in the good range, but there was still significant overlap between groups. This is consistent with the recent idea that stress-responsive biomarkers may be most useful as components of a multimarker panel, along with traditional metabolic parameters. FGF21 and GDF15 have recently been investigated as predictors of insulin resistance and metabolic risk, including combination diagnostic strategies [27,40].

The biochemical model presented here is consistent with a model where visceral adiposity and nutrient excess promote oxidative and mitochondrial stress. MDA increases as a result of increased lipid peroxidation and antioxidant defenses become relatively inadequate. Meanwhile, FGF21 and GDF15 are induced as endocrine stress signals. These responses exist in parallel with progressive insulin resistance, hypertriglyceridemia, and decreased HDL-C. This model fits with current understanding that metabolic syndrome is a systemic disease caused by impaired energy metabolism, redox balance, inflammation and endocrine communication between organs [40].

4.1 Strengths and Limitations

The main advantages of this study design are that it allows concurrent assessment of two novel stress-response proteins, combined with traditional markers of oxidative stress, plus includes clinically meaningful metabolic measures, and it employs converging statistical methods (effect sizes, correlations, multivariate regression, and ROC analysis). Significant limitations are the cross-sectional nature prior, precluding causal inference; possible residual confounding by diet, physical activity, smoking, renal function, liver fat, and inflammation; use of HOMA-IR and not a euglycemic clamp; and the known biological variability of circulating FGF21 and GDF15. Future research should also include longitudinal follow-up and markers of kidney and liver function high-sensitive CRP and direct or imaging-based assessments of visceral and hepatic adiposity.

5 CONCLUSION

FGF21 and GDF15 in circulation were increased in adults with metabolic syndrome and were positively correlated with insulin resistance, lipid peroxidation, adiposity, and negatively correlated with antioxidant capacity. This observed conformation is consistent with the notion that these proteins act as metabolic and mitochondrial stress integrated sensors. GDF15, MDA and BMI whetted independently with HOMA-IR in the multivariate model, and both FGF21 and GDF15 demonstrated good discrimination ability for the MetS phenotype. As such, these biomarkers may offer some complementary biochemical information in addition to the more conventional glucose and lipid-based parameters, although prospective corroboration is warranted before any clinical cutoffs or diagnostic application can be derived.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

REFERENCES

- [1] Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JJ, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement. *Circulation*. 2009;120(16):1640-1645.
- [2] Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20(2):12.
- [3] Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol*. 2008;28(4):629-636.
- [4] Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, et al. Metabolic syndrome: updates on pathophysiology and management in 2021. *Int J Mol Sci*. 2022;23(2):786.

- [5] 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(7):412-419.
- [6] Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487-1495.
- [7] Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab*. 2008;294(1):E15-E26.
- [8] Roberts CK, Sindhu KK. Oxidative stress and metabolic syndrome. *Life Sci*. 2009;84(21-22):705-712.
- [9] Whaley-Connell A, McCullough PA, Sowers JR. The role of oxidative stress in the metabolic syndrome. *Rev Cardiovasc Med*. 2011;12(1):21-29.
- [10] Rani V, Deep G, Singh RK, Palle K, Yadav UCS. Oxidative stress and metabolic disorders: pathogenesis and therapeutic strategies. *Life Sci*. 2016;148:183-193.
- [11] Masenga SK, Kabwe LS, Chakulya M, Kirabo A. Mechanisms of oxidative stress in metabolic syndrome. *Int J Mol Sci*. 2023;24(9):7898.
- [12] Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114(12):1752-1761.
- [13] Akinloye O, Akinlade KS, Akinyemi JO, et al. Oxidative stress among subjects with metabolic syndrome in Sokoto, North-Western Nigeria. *Niger J Clin Pract*. 2016;19(1):128-133.
- [14] Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006;440(7086):944-948.
- [15] Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev*. 2002;23(5):599-622.
- [16] Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860-867.
- [17] Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. *Cell*. 2012;148(5):852-871.
- [18] Fisher FM, Maratos-Flier E. Understanding the physiology of FGF21. *Annu Rev Physiol*. 2016;78:223-241.
- [19] Potthoff MJ, Kliewer SA, Mangelsdorf DJ. Endocrine fibroblast growth factors 15/19 and 21: from feast to famine. *Genes Dev*. 2012;26(4):312-324.
- [20] Markan KR, Potthoff MJ. Metabolic fibroblast growth factors (FGFs): mediators of energy homeostasis. *Semin Cell Dev Biol*. 2016;53:85-93.
- [21] Kharitonov A, DiMarchi R. Fibroblast growth factor 21 night watch: advances and uncertainties in the field. *J Intern Med*. 2017;281(3):233-246.
- [22] Zhang X, Yeung DCY, 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):1246-1253.
- [23] Dostalova I, Kavalkova P, Haluzikova D, Lacinova Z, Mraz M, Papezova H, et al. Serum concentrations and tissue expression of fibroblast growth factor-21 in patients with type 2 diabetes and obesity. *Clin Endocrinol (Oxf)*. 2009;71(3):369-375.
- [24] Gälman C, Lundåsen T, Kharitonov A, Bina HA, Eriksson M, Hafström I, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPAR α activation in man. *Cell Metab*. 2008;8(2):169-174.
- [25] Ong KL, Hui N, Januszewski AS, Kaakoush NO, Xu A, Fayyad R, et al. High plasma FGF21 levels predicts major cardiovascular events in patients treated with atorvastatin. *Metabolism*. 2019;93:93-99.
- [26] Yang M, Liu C, Jiang N, Liu Y, Luo S, Li C, et al. Fibroblast growth factor 21 in metabolic syndrome. *Front Endocrinol (Lausanne)*. 2023;14:1220426.
- [27] Kim KH, Lee MS. FGF21 as a stress hormone: the roles of FGF21 in stress adaptation and the treatment of metabolic diseases. *Diabetes Metab J*. 2014;38(4):245-251.
- [28] Kim KH, Lee MS. Stress-induced FGF21 and GDF15 in obesity and obesity resistance. *Trends Endocrinol Metab*. 2021;32(11):904-915.
- [29] Lockhart SM, Saudek V, O'Rahilly S. GDF15: a hormone conveying somatic distress to the brain. *Endocr Rev*. 2020;41(4):610-642.

- [30] Emmerson PJ, Wang F, Du Y, Liu Q, Pickard RT, Gonciarz MD, et al. The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. *Nat Med*. 2017;23(10):1215-1219.
- [31] Mullican SE, Lin-Schmidt X, Chin CN, Chavez JA, Furman JL, Armstrong AA, et al. GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. *Nat Med*. 2017;23(10):1150-1157.
- [32] Hsu JY, Crawley S, Chen M, Ayupova DA, Lindhout DA, Higbee J, et al. Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. *Nature*. 2017;550(7675):255-259.
- [33] Ho LC, Wu HT, Hung HC, Chou HW, Cheng KP, Lin CH, et al. Growth differentiation factor-15 is independently associated with metabolic syndrome and hyperglycemia in non-elderly subjects. *Biofactors*. 2023;49(1):119-126.
- [34] Zheng S, Shen M, Qian Y, Li S, Chen Y, Jiang H, et al. Growth differentiation factor-15/adiponectin ratio as a potential biomarker for metabolic syndrome in Han Chinese. *Front Endocrinol (Lausanne)*. 2023;14:1146376.
- [35] Kempf T, Guba-Quint A, Torgerson J, Magnone MC, Haefliger C, Bobadilla M, et al. Growth differentiation factor 15 predicts future insulin resistance and impaired glucose control in obese nondiabetic individuals: results from the XENDOS trial. *Eur J Endocrinol*. 2012;167(5):671-678.
- [36] Kleinert M, Bojsen-Møller KN, Jørgensen NB, Svane MS, Martinussen C, Kiens B, et al. Effect of bariatric surgery on plasma GDF15 in humans. *Am J Physiol Endocrinol Metab*. 2019;316(4):E615-E621.
- [37] Cai L, Li C, Wang Y, Mo Y, Yin J, Ma X. Increased serum GDF15 related to improvement in metabolism by lifestyle intervention among young overweight and obese adults. *Diabetes Metab Syndr Obes*. 2021;14:1195-1202.
- [38] Quist JS, et al. Effects of acute exercise and exercise training on plasma GDF15 concentrations and associations with appetite and cardiometabolic health in individuals with overweight or obesity. *Appetite*. 2023;182:106423.
- [39] Kleinert M, Clemmensen C, Sjøberg KA, Carl CS, Jeppesen JF, Wojtaszewski JFP, et al. Exercise increases circulating GDF15 in humans. *Mol Metab*. 2018;9:187-191.
- [40] Yang L, Chang CC, Sun Z, Madsen D, Zhu H, Padkjær SB, et al. GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. *Nat Med*. 2017;23(10):1158-1166.
- [41] Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem*. 1979;95(2):351-358.
- [42] Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. *Eur J Biochem*. 1974;47(3):469-474.
- [43] Benzie IFF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of antioxidant power: the FRAP assay. *Anal Biochem*. 1996;239(1):70-76.
- [44] Sureda A, Bibiloni MDM, Martorell M, Buil-Cosiales P, Marti A, Pons A, et al. Metabolic syndrome is associated with oxidative stress and proinflammatory state. *Antioxidants (Basel)*. 2020;9(3):236.
- [45] Zahedi AS, Zarkesh M, Sedaghati-Khayat B, Hedayati M, Azizi F, Daneshpour MS. Insulin resistance-related circulating predictive markers in the metabolic syndrome: a systematic review. *J Diabetes Metab Disord*. 2024;23(1):199-213.
- [46] Mustakin, et al. Diagnostic accuracy of FGF21 and GDF15 for predicting insulin resistance in type 2 diabetes: a systematic review and bivariate diagnostic test accuracy meta-analysis. *Diabetes Res Clin Pract*. 2026;225:111987.