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Serum GDF15 as a supportive biomarker in female fibromyalgia patients based on a prospective case-control study

Ertugrul Yigit[1], Osman Cure[2]✉, Merve Huner Yigit[3] & Hakki Uzun[4]

This study aimed to evaluate serum growth differentiation factor 15 (GDF15) as a potential supportive biomarker for fibromyalgia (FM) and investigate its association with disease severity. This prospective case-control study evaluated serum GDF15 levels in female fibromyalgia patients and healthy controls. Participants were recruited from the Rheumatology Outpatient Clinic of Recep Tayyip Erdoğan University Hospital between May and September 2024. GDF15 concentrations were quantified by ELISA. Disease severity was assessed using the Revised Fibromyalgia Impact Questionnaire (FIQR), Widespread Pain Index (WPI), and Symptom Severity Score (SSS). Diagnostic accuracy was evaluated via ROC curve analysis. We analyzed 120 women (FM $n = 60$; controls $n = 60$). Serum GDF15 levels were significantly higher in FM patients (median: 1022.33 pg/mL) than in healthy controls (473.08 pg/mL, $p < 0.001$). There were no significant differences in age or BMI between the FM and control groups ($p > 0.05$). ROC analysis showed high diagnostic sensitivity (96.7%) and low specificity (53.3%) for GDF15 at a cutoff of 478.31 pg/mL (AUC = 0.922, 95% CI: 0.875–0.969, $p < 0.001$). Although GDF15 was markedly elevated in FM, no significant correlation was found between GDF15 levels and WPI, SSS, and FIQR scores ($p > 0.05$). Serum GDF15 may serve as a supportive biomarker for FM; however, its limited specificity suggests it should complement—rather than replace—clinical assessment. Future studies should confirm its clinical utility and validate its role within multi-marker diagnostic panels.

Keywords Fibromyalgia, Pain measurement, Biomarkers, Female, GDF15

Fibromyalgia (FM) is a chronic disorder characterized by widespread musculoskeletal pain, fatigue, cognitive dysfunction, and sleep disturbances, disproportionately affecting women[1–4]. Despite its high prevalence, the diagnosis of FM remains challenging due to the lack of objective biomarkers and reliance on subjective clinical criteria such as the Widespread Pain Index (WPI) and Symptom Severity Score (SSS)[5–7]. Moreover, FM is increasingly recognized as a biopsychosocial condition, frequently accompanied by psychiatric comorbidities including anxiety, depression, and somatization, which further complicate its clinical profile[8,9].

Emerging evidence suggests that FM involves a complex interplay of central sensitization, neuroimmune dysregulation, and low-grade inflammation[10,11]. Growth differentiation factor 15 (GDF15)—a stress-responsive cytokine elevated in metabolic, inflammatory, and mitochondrial disorders—has gained attention as a potential biomarker[12–14]. Elevated serum GDF15 levels have been documented in chronic inflammatory and autoimmune conditions such as RA and SLE[15–17]. Although FM is not classified as an autoimmune disorder, it frequently coexists with these diseases, and shares overlapping clinical features such as fatigue and widespread pain[18,19]. Furthermore, GDF15 has been implicated in disorders associated with central sensitization, highlighting its relevance to FM pathophysiology[11].

This study aimed to investigate serum GDF15 concentrations in women diagnosed with FM and evaluate their relationship with symptom severity using the Revised Fibromyalgia Impact Questionnaire (FIQR). Although GDF15 has been studied in various chronic and metabolic disorders, its specific diagnostic or clinical relevance in fibromyalgia remains largely unexplored. To our knowledge, this is one of the first prospective case-

[1]Department of Medical Biochemistry, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey. [2]Department of Rheumatology, Faculty of Medicine, Recep Tayyip Erdogan University, Rize 53000, Turkey. [3]Department of Medical Biochemistry, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Turkey. [4]Department of Urology, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Turkey. ✉email: osman.cure@erdogan.edu.tr

control studies focusing exclusively on female FM patients. Given the pressing need for objective indicators in FM, GDF15 may serve as a promising candidate biomarker, offering both diagnostic and prognostic utility and contributing to a deeper understanding of FM as a multifactorial disorder.

Materials and methods

Study design and participants

This single-center, prospective, case-control study was conducted between May 1, 2024, and September 1, 2024, at the Rheumatology Outpatient Clinic of Recep Tayyip Erdoğan University Training and Research Hospital. Although data collection occurred at a single time point, patient recruitment and sample collection were prospectively conducted based on a pre-specified study protocol. Patients with fibromyalgia were diagnosed according to the American College of Rheumatology (ACR) criteria[6]. An a priori sample size calculation was performed using G*Power software (version 3.1, University of Kiel, Germany), based on an anticipated large effect size (Cohen's d = 0.80), α = 0.05, and 80% power, resulting in a minimum of 48 participants per group.

Ethical approval

The study protocol was approved by the Recep Tayyip Erdoğan University Clinical Research Ethics Committee (Approval No: 2024/39). All participants provided written informed consent prior to enrollment. The study was conducted following the Declaration of Helsinki[20].

Inclusion and exclusion criteria

Participants were selected according to predetermined inclusion and exclusion criteria to ensure the study groups' homogeneity and the findings' validity.

Inclusion Criteria: Women participants aged 18–65 years were included. The diagnosis of FM was established based on the ACR 2016 criteria. According to these criteria, a WPI score of ≥ 7 with a SSS score of ≥ 5, or a WPI score of 3–6 with an SSS score of ≥ 9, confirms the presence of FM[6]. The WPI assesses the number of painful body areas experienced over the past week (score range: 0–19), while the SSS evaluates symptom intensity, including fatigue, non-restorative sleep, and cognitive complaints (score range: 0–12). Exclusion Criteria: Presence of autoimmune, endocrine, or autoimmune inflammatory rheumatic diseases. History of malignancy or ongoing immunosuppressive therapy. Severe hepatic, renal, or cardiovascular dysfunction. Pregnancy or lactation. Use of anti-inflammatory or immunomodulatory drugs within the last three months.

Questionnaires

The FIQR was administered to FM patients to assess disease severity and functional impact. The FIQR includes 21 items covering three domains: function, overall impact, and symptom severity, with total scores ranging from 0 to 100[21]. All participants underwent a comprehensive clinical evaluation, and demographic data such as age, height, weight, BMI, and medication use were recorded.

Sample collection and laboratory analyses

Blood sample collection

Venous blood samples were collected from all participants after an overnight fast in the morning to minimize potential diurnal variations in biochemical parameters. Blood was drawn from the antecubital vein under sterile conditions using vacutainer tubes. The collected samples were processed as follows: Serum separation: Blood samples were centrifuged at 2000 x g for 10 min to separate serum. Plasma separation: EDTA-containing tubes were used for plasma separation under the same centrifugation conditions. Storage: Serum aliquots were immediately stored at -80 °C until further analysis.

Biochemical and inflammatory marker analyses

The following biochemical and inflammatory parameters were measured using an automated clinical chemistry analyzer (Beckman Coulter AU5800, Brea, CA, USA): metabolic and renal function markers: glucose, blood urea nitrogen (BUN), creatinine, eGFR, and uric acid. Lipid profile: Total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), non-HDL, very low-density lipoprotein (VLDL). Liver function tests: alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH). Minerals: Calcium, magnesium, phosphorus. Inflammatory markers: C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR). All biochemical measurements were conducted following the manufacturer's standard protocols.

Hematological analysis

Hematological parameters were analyzed using a hematology analyzer (Mindray BC-6000, Shenzhen, P.R. China). The following parameters were assessed: White blood cell parameters, white blood cell count (WBC), lymphocytes (LY), monocytes (MO), neutrophils (NE), eosinophils (EO), and basophils (BA). Red blood cell parameters: Red blood cell count (RBC), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW-SD, RDW-CV). platelet indices: platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), platelet large cell ratio (PLCR), platelet large cell concentration (PLCC).

Measurement of serum GDF15 levels

Serum GDF15 levels were measured using a commercially available ELISA kit (Quantikine ELISA, R&D Systems, Minneapolis, MN, USA; Catalog No: DGD150) in accordance with the manufacturer's instructions. Serum samples stored at − 80 °C were thawed at room temperature and diluted as recommended. Following incubation

and washing steps, detection was performed using a conjugated antibody and substrate solution. Optical density was measured at 450 nm with correction at 540–570 nm, and GDF15 concentrations were calculated using a four-parameter logistic (4-PL) standard curve.Each sample was analyzed in duplicate due to limited serum volume and based on the manufacturer's standard protocol. The assay showed a typical intra-assay CV of < 5% and inter-assay CV of < 10%, ensuring acceptable reproducibility.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test, which indicated that the variables did not follow a normal distribution. Therefore, non-parametric statistical methods were applied. Comparisons between the FM and control groups were conducted using the Mann-Whitney U test for continuous variables, as the data were not normally distributed. The correlation between GDF15 levels and clinical, biochemical, and hematological parameters was assessed using Spearman's correlation test. The diagnostic accuracy of GDF15 in distinguishing FM patients from healthy controls was evaluated using the Receiver Operating Characteristic (ROC) curve analysis. The optimal cut-off value of GDF15 was determined using the Youden Index[22], calculated as follows:

$$\text{Youdens Index} = \text{Sensitivity} + \text{Specificity} - 1.$$

Continuous variables were expressed as median (Q1–Q3) due to their non-normal distribution, while categorical variables were presented as frequencies and percentages. A p-value of < 0.05 was considered statistically significant. Tables were created using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and figures were generated using OriginPro 24 (OriginLab Corp., Northampton, MA, USA) and IBM SPSS.

Results

Demographic and clinical characteristics

The demographic characteristics of the study groups are summarized in Table 1. The FM and control groups were exclusively female participants (100%). There were no statistically significant differences between the groups in terms of median age ($p = 0.684$), height ($p = 0.660$), weight ($p = 0.223$), or BMI ($p = 0.652$), indicating successful age and BMI matching. As expected, clinical symptom scores such as FIQR, WPI, and SSS were only assessed in the FM group.

Biochemical and inflammatory markers

Biochemical and inflammatory marker levels for both groups are presented in Table 2. Among the parameters measured, VLDL and calcium levels were statistically higher in the FM group than in controls ($p = 0.038$ and $p = 0.037$, respectively). Other metabolic markers, including glucose, renal function indices (BUN, creatinine, eGFR, uric acid), and lipid profile components (total cholesterol, triglycerides, HDL, LDL, non-HDL), as well as inflammatory markers (CRP, RF, ESR), showed no statistically significant differences between the groups (all $p > 0.05$).

Hematological parameters and blood cell indices

The hematological findings are summarized in Table 3. No significant differences were found in WBC, LY, MO, NE, EO, BA, Hb, and platelet indices. However, there were significant differences in red blood cell indices: MCV was higher in the FM group ($p = 0.039$). RDW-SD was significantly elevated in FM patients ($p = 0.005$). RDW-CV was also significantly increased ($p = 0.043$). These findings suggest potential red blood cell morphology alterations in FM patients, which may indicate underlying metabolic or inflammatory changes.

Serum GDF15 levels

Serum GDF15 levels were significantly elevated in FM patients compared to healthy controls (Fig. 1). The median GDF15 concentration in the FM group was 1022.33 pg/mL, while it was 473.08 pg/mL in the control group. This difference was statistically significant ($p < 0.001$), indicating a marked increase in circulating GDF15 levels in FM.

Parameters	Control ($n = 60$) Median (Q1–Q3)	Fibromyalgia ($n = 60$) Median (Q1–Q3)	Mann-Whitney U/p
Age (years)	44.5 (36.25–54.25)	43.5 (39.25-49)	$p = 0.684$
Height (cm)	162.5 (160–168)	161.5 (158–165)	$p = 0.66$
Weight (kg)	76 (69-80.75)	73 (66-79.75)	$p = 0.223$
BMI (kg/m^2)	27.98 (25.71–29.71)	27.79 (25.8–29.4)	$p = 0.652$
FIQR (scale)	–	67.5 (55–77.75)	–
WPI (scale)	–	9.5 (8–12.75)	–
SSS (scale)	–	9 (7–10)	–

Table 1. Demographic characteristics and fibromyalgia index results of the study groups.

Parameters	Control ($n=60$) Median (Q1–Q3)	Fibromyalgia ($n=60$) Median (Q1–Q3)	Mann–Whitney U p
Glucose (mg/dL)	92 (86–98.75)	88.5 (85–94.75)	$p=0.058$
BUN (mg/dL)	25 (22–31)	23.65 (20.25–29)	$p=0.471$
Creatinine (mg/dL)	0.7 (0.63–0.76)	0.7 (0.6–0.8)	$p=0.933$
eGFR (mL/min/1.73 m^2)	101.5 (92.25–114)	103.9 (96.25–112)	$p=0.674$
Uric acid (mg/dL)	4.2 (3.42–5)	4.5 (3.62–5.1)	$p=0.351$
Total protein (g/L)	74.95 (73.2–78.4)	74.7 (72.5–76.8)	$p=0.271$
Albumin (g/L)	46.05 (44.5–48)	44.8 (42.8–46.6)	$p=0.08$
Cholesterol (mg/dL)	216 (193–249)	223 (199–238)	$p=0.741$
Triglyceride (mg/dL)	110 (74–148)	129 (107–144)	$p=0.058$
HDL (mg/dL)	58.3 (50.95–70.1)	54.8 (51.4–61)	$p=0.133$
Non-HDL (mg/dL)	160.5 (126.5–195.25)	169.7 (150.8–182.6)	$p=0.249$
LDL (mg/dL)	136.5 (107.25–164.5)	143.5 (127.4–154.5)	$p=0.337$
VLDL (mg/dL)	22.1 (14.9–29.6)	25.9 (21.4–28.9)	$p=0.038$
ALP (U/L)	68.5 (53.25–86)	67 (57.7–73.7)	$p=0.385$
ALT (U/L)	15.5 (12.25–21)	15.2 (13–20)	$p=0.971$
AST (U/L)	17 (14.25–20.75)	17 (16–19)	$p=0.521$
GGT (U/L)	19 (13.25–25.25)	16 (13–22)	$p=0.190$
LDH (U/L)	178.5 (157.5–197)	173 (152.7–189.5)	$P=0.469$
Calcium (mg/dL)	9.9 (9.6–10.3)	9.75 (9.5–9.9)	$p=0.037$
Magnesium (mg/dL)	1.98 (1.89–2.09)	2 (1.9–2.1)	$p=0.451$
Phosphorus (mg/dL)	3.49 (3.17–3.88)	3.4 (3.12–3.6)	$p=0.165$
CRP (mg/L)	1.67 (0.86–4.08)	1.69 (0.76–5.03)	$p=0.921$
RF (IU/mL)	14.2 (12.02–19.32)	15 (13.2–20.7)	$p=0.203$
ESR (one hour) (mm/1 h)	10.4 (5–15.5)	9 (5–16)	$p=0.781$

Table 2. Biochemical and inflammatory markers of the study groups.

Parameters	Control ($n=60$) Median (Q1–Q3)	Fibromyalgia ($n=60$) Median (Q1–Q3)	Mann Whitney U p
WBC (10^3/μL)	6.57 (5.25–7.31)	6.7 (5.59–7.94)	$p=0.259$
LY (10^3/μL)	2.01 (1.7–2.41)	2.18 (178 – 2.58)	$p=0.312$
MO (10^3/μL)	0.38 (0.31–0.44)	0.39 (0.33–0.47)	$p=0.383$
NE (10^3/μL)	3.72 (2.93–4.47)	3.89 (3.1–4.66)	$p=0.451$
EO (10^3/μL)	0.11 (0.07–0.2)	0.12 (0.08–0.18)	$p=0.912$
BA (10^3/μL)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	$p=0.547$
RBC (10^6/μL)	4.56 (4.35–4.75)	4.49 (4.25–4.76)	$p=0.213$
Hb (g/dL)	13.6 (12.8–14.1)	13.4 (12.52–14.1)	$p=0.399$
HCT (%)	40.15 (37.95–41.95)	39.8 (37.9–42.1)	$p=0.657$
MCV (fL)	87.85 (85.25–89.6)	90 (86.3–91.8)	$p=0.039$
MCH (pg)	29.5 (28.8-30.75)	30.1 (29-30.9)	$p=0.349$
MCHC (g/dL)	33.65 (33.2–34)	33.4 (32.9–33.9)	$p=0.127$
PLT (10^3/μL)	269.5 (224-307.75)	281.5 (235.5-317.5)	$p=0.407$
MPV (fL)	10.5 (9.72–11.3)	10.4 (9.65–11.5)	$p=0.896$
PCT (%)	0.27 (0.24–0.32)	0.28 (0.23–0.32)	$p=0.676$
PDW (fL)	16 (15.8–16.3)	15.9 (15.8–16.1)	$p=0.321$
RDW-SD (fL)	45.05 (43.47–45.97)	46.2 (44-48.8)	$p=0.005$
RDW-CV (%)	13.1 (12.7–13.8)	13.35 (12.9–14.1)	$p=0.043$
PLCC (10^3/μL)	77 (61.25–92.5)	79.5 (62-99.5)	$p=0.745$
PLCR (%)	29.8 (23.4–35.9)	29.4 (24-36.8)	$p=0.844$
NLR	1.85 (1.44–2.31)	1.85 (156 – 2.22)	$p=0.823$

Table 3. Hematological parameters and blood cell indices of the study groups.

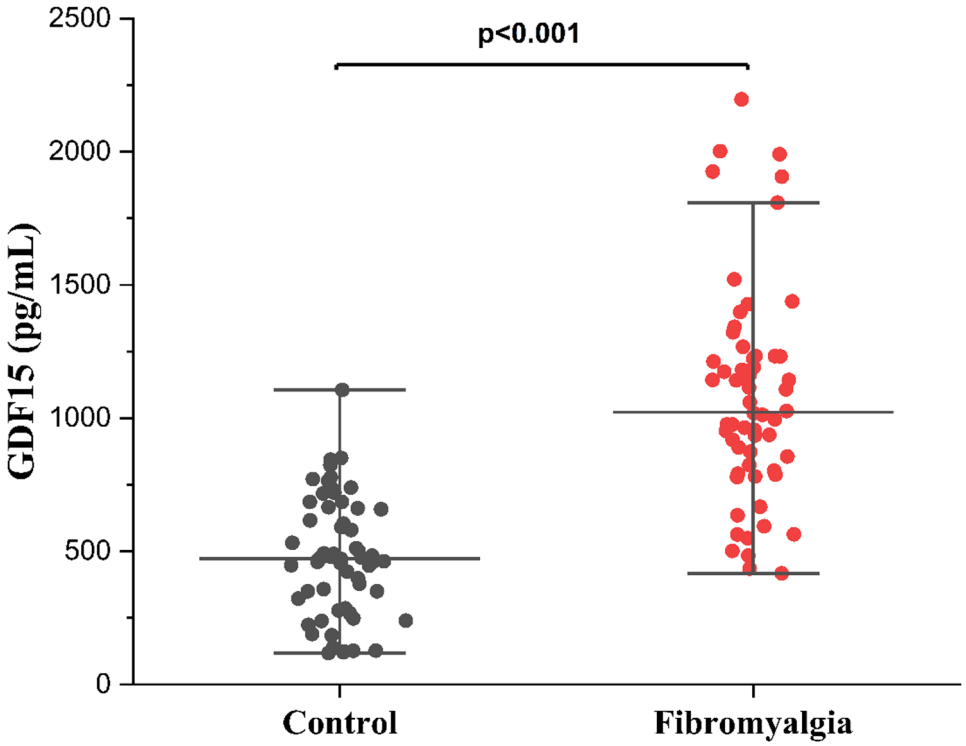


Fig. 1. Serum GDF15 levels.

Correlation analysis

A Spearman's correlation analysis was conducted to examine associations between serum GDF15 levels and selected hematological, biochemical, and clinical parameters in FM patients (Fig. 2). No statistically significant correlation was found between GDF15 levels and FIQR scores ($r = 0.164$, $p = 0.211$), nor with RDW-SD ($r = 0.161$, $p = 0.220$) or calcium ($r = 0.144$, $p = 0.273$). Although GDF15 levels tended to be slightly higher in patients with greater disease burden, the observed correlations were weak and did not reach statistical significance.

ROC curve analysis and cut-off value determination

ROC curve analysis was performed to evaluate the diagnostic performance of serum GDF15 in distinguishing FM patients from healthy controls (Fig. 3). The analysis yielded an area under the curve (AUC) of 0.922 (95% CI: 0.875–0.969; $p < 0.001$), indicating excellent discriminatory ability. An optimal cut-off value of 478.31 pg/mL, determined using the maximum Youden Index, provided a sensitivity of 96.7% and a specificity of 53.3%. While the high sensitivity suggests that GDF15 may be helpful for screening purposes, the relatively low specificity limits its potential as a standalone diagnostic biomarker.

Discussion

The current diagnosis of FM primarily actually, solely relies on clinical criteria, as there are no established objective biomarkers readily confirmable through laboratory or imaging methods[23]. In our study, serum GDF15 levels were significantly elevated in FM patients compared to healthy controls, suggesting its potential as a complementary biomarker for FM diagnosis and severity assessment. However, despite this significant elevation, GDF15 showed no statistically significant correlation with clinical severity measured by FIQR scores. Thus, while GDF15 appears promising, its role as a sole predictor of wolFM severity remains uncertain and requires further investigation.

The pathophysiology of FM involves central sensitization, low-grade inflammation, and peripheral metabolic disturbances[24]. GDF15, a stress-responsive cytokine elevated during inflammation, oxidative stress, and mitochondrial dysfunction, might reflect these underlying mechanisms in FM[25]. Muscle metabolic abnormalities and oxidative stress markers previously observed in FM patients further support this association[24]. Consequently, elevated GDF15 levels in FM patients might reflect a state of chronic cellular stress rather than a specific inflammatory condition unique to FM.

Furthermore, experimental evidence has shown that GDF15 may influence pain modulation by reducing nociceptive neuron excitability through peripheral mechanisms involving Nav1.8 sodium channel suppression and modulation of protein kinase A (PKA) and extracellular signal-regulated kinase (ERK) signaling pathways[26–29]. This peripheral analgesic potential might imply that increased GDF15 levels in FM serve as a compensatory or protective biological response to chronic pain. GDF15 also acts centrally via the glial cell-derived neurotrophic factor family receptor alpha-like (GFRAL), potentially contributing to symptoms like

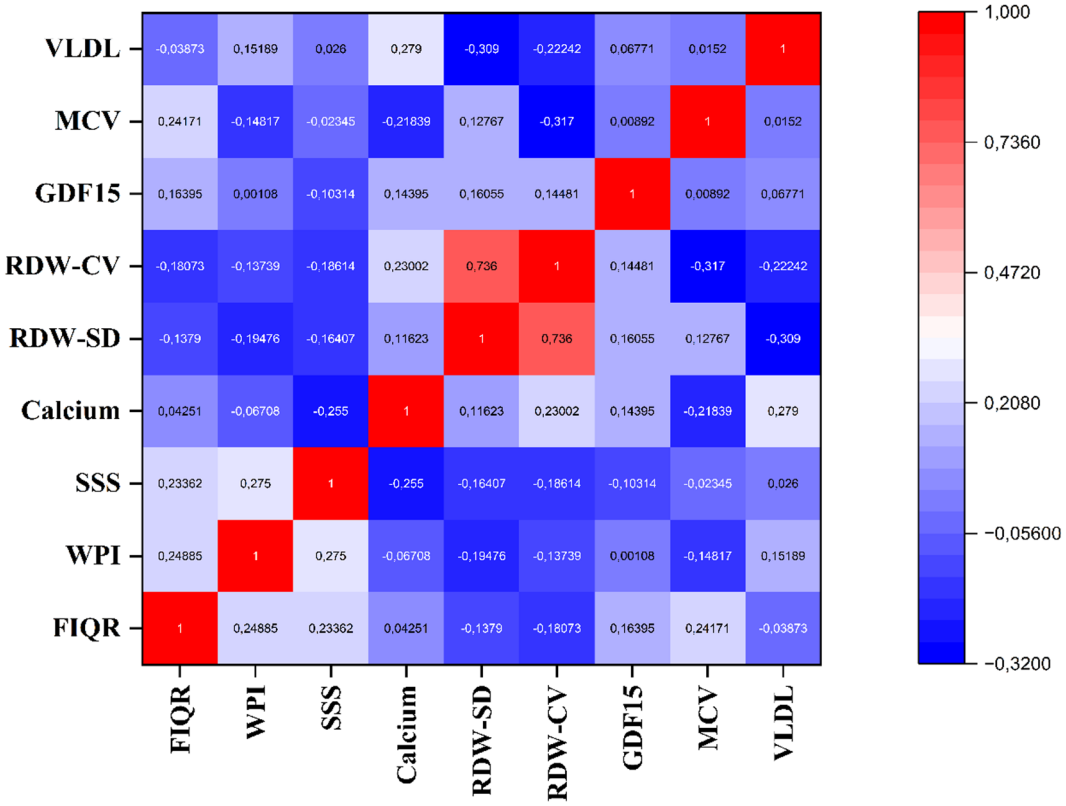


Fig. 2. Correlation analysis of hematological and biochemical parameters in FM patients.

fatigue, nausea, and stress in FM[30–34]. These central effects of GDF15 could partially explain common FM-associated symptoms such as fatigue, appetite dysregulation, and heightened stress sensitivity.

Given FM's diagnostic and monitoring challenges, identifying reliable and stable biomarkers is crucial. GDF15 levels have previously been stable over extended periods in chronic disorders, including chronic fatigue syndrome (ME/CFS), suggesting potential as a monitoring biomarker[35]. Consequently, longitudinal evaluation of GDF15 could allow clinicians to objectively assess disease activity and treatment response in FM.

Nonetheless, GDF15 elevation is not specific to FM, as significantly increased levels have been reported in various chronic inflammatory and metabolic diseases, including RA, SLE, metastatic cancers, and cardiovascular diseases[17,36]. However, this nonspecificity does not preclude its elevation in FM, nor does it diminish its potential relevance as a biomarker within this context. FM is not a diagnosis of exclusion, but rather based on established clinical criteria, and elevated GDF15 should be interpreted as complementary information rather than contradictory evidence. In the present study, GDF15 levels did not correlate significantly with clinical indices of disease severity, including FIQR, WPI, or SSS scores. This finding suggests that while GDF15 may help distinguish FM patients from healthy individuals, its utility as a monitoring biomarker or as an indicator of symptom progression is limited. The lack of correlation may be attributed to the relatively homogeneous severity profile of our FM cohort, which might have constrained the variability needed to detect meaningful associations. Future studies with larger, stratified patient groups and broader symptom distributions are warranted to explore this potential more comprehensively.

An important limitation in our study was the relatively low specificity (53.3%) of GDF15 at the determined cut-off value (473.085 pg/mL). This limitation underscores that GDF15, despite its high sensitivity (96.7%), should not be used alone as a definitive diagnostic marker for FM. Instead, combining GDF15 with other biomarkers such as interleukin-6 (IL-6), interleukin-8 (IL-8), and possibly neurotransmitters such as substance P and glutamate may enhance diagnostic accuracy[37–40]. Elevated IL-6 and IL-8 have previously been associated with FM severity, indicating that multi-marker panels rather than single biomarkers might provide a more robust diagnostic approach. Our study contributes to the existing literature by identifying GDF15 as an additional biochemical marker potentially helpful in this context, although further research in diverse clinical settings is necessary. Moreover, the current analysis did not include comparative ROC curves or Net Reclassification Improvement (NRI) statistics with existing clinical or laboratory tools, limiting our ability to fully determine the added diagnostic value of GDF15. Future studies should incorporate such comparative approaches to better evaluate its clinical utility. This finding is consistent with previous reports of elevated GDF15 in a variety of inflammatory and metabolic conditions, thereby limits its disease-specific diagnostic power. Therefore, the current data support its use as a supportive, rather than standalone, biomarker—best applied as part of a multi-marker panel in clinically challenging cases.

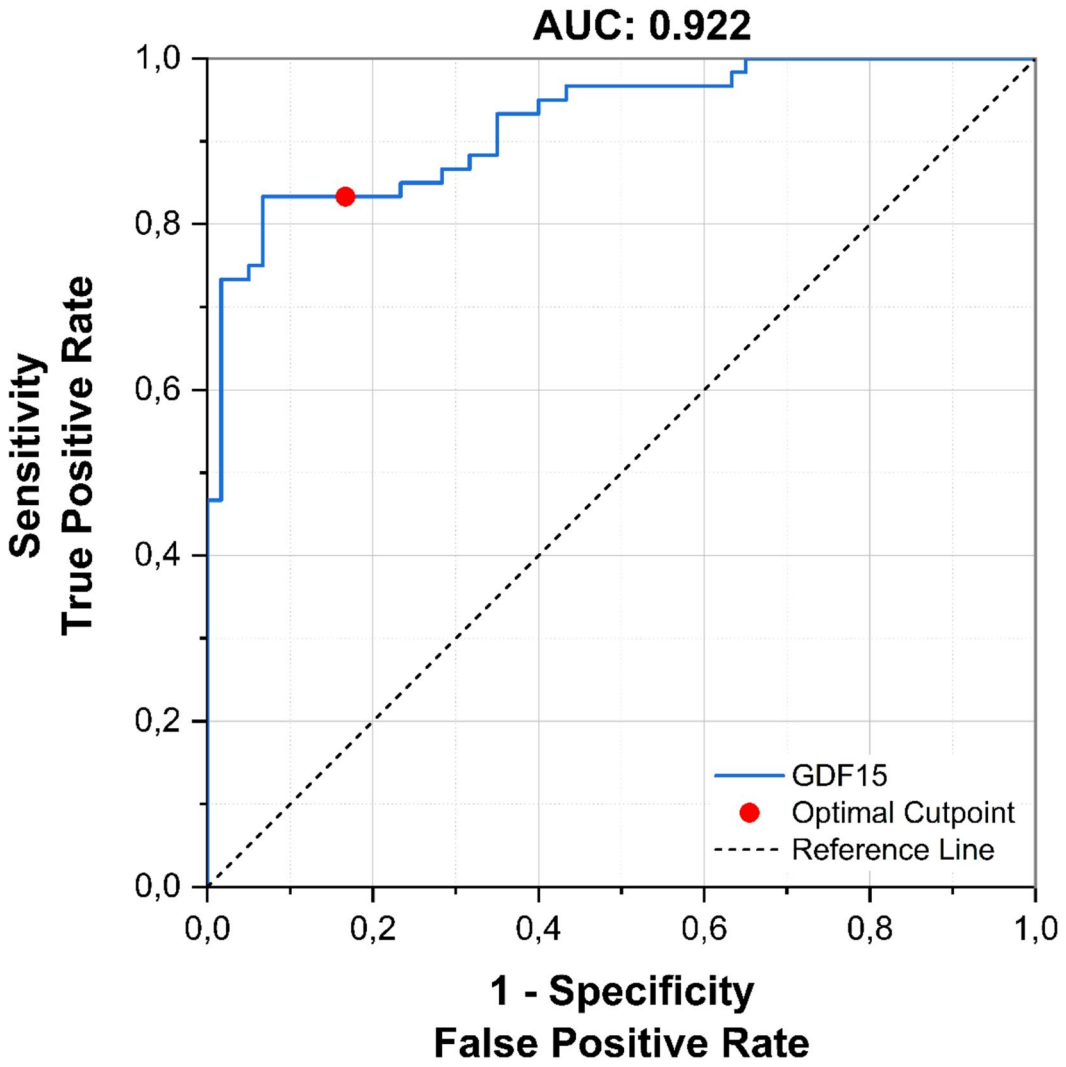


Fig. 3. ROC curve for GDF15, the optimal cut-off value calculated using the highest Youden index is 478.31.

Consistent with our results, recent literature also identifies elevated GDF15 levels in various chronic pain conditions beyond FM, including chronic low back pain and migraines. This suggests a shared stress or inflammatory response across these conditions, possibly mediated through the hypothalamic-pituitary-adrenal (HPA) axis or other stress-related pathways. The typical elevation of GDF15 and related stress-response biomarkers such as Fibroblast Growth Factor 21 (FGF21) highlights the contribute of sustained inflammatory stress and metabolic alterations across different chronic pain syndromes[41,42]. In this broader context, GDF15 elevation might represent a compensatory or protective response to mitigate chronic inflammatory or nociceptive stress.

Welsh et al. reported that among 18,507 participants with no history of hospitalization due to heart disease or stroke and who were known not to be pregnant, the median GDF15 level was 816 pg/mL in women and 793 pg/mL in men. They also noted that GDF15 levels could rise to approximately 19,000 pg/mL during pregnancy[43]. The GDF15 concentrations observed in the control group of our study are consistent with these findings. GDF15 levels are known to exhibit physiological variability influenced by several factors, including age, hormonal status, and metabolic stress[44]. In designing our study sample, pregnancy was among the exclusion criteria; however, menopausal status was not recorded. It is well established that levels of inflammatory cytokines increase following menopause[45]. Nevertheless, to our knowledge, there are no studies in the current literature that have directly compared premenopausal and postmenopausal GDF15 levels. Importantly, in our study, there was no statistically significant difference in age between the FM and control groups, which helps to reduce potential hormonal confounding related to menopausal status.

While this study possesses several strengths—including its prospective design, strict inclusion criteria, and well-matched control group—it is also subject to certain limitations that should be considered when interpreting the results. First, its cross-sectional design precludes any inference of causality between GDF15 elevation and FM symptoms. Second, although participant age was statistically comparable between the fibromyalgia and control groups and was deliberately selected to minimize menopausal variability, specific information on

menopausal status, menstrual cycle phase, physical activity, and dietary habits was not collected. These variables are known to influence GDF15 concentrations and may have introduced uncontrolled variability. Additionally, the study included only female participants, which, while reducing biological and hormonal variability, limits the generalizability of the findings to male fibromyalgia patients. Furthermore, the exclusion of individuals with autoimmune, endocrine, malignant, or severe systemic diseases, as well as those on immunomodulatory or anti-inflammatory therapies, was necessary to avoid confounding GDF15 levels; however, this approach limits the applicability of the findings to broader clinical populations with comorbid conditions. Finally, the study was conducted at a single center with a relatively homogeneous sample, limiting the generalizability of the results to other populations.

Conclusion

In conclusion, this study demonstrates that serum GDF15 levels are significantly elevated in female patients with fibromyalgia compared to healthy controls. These findings highlight the potential of GDF15 as a supportive biomarker within a multi-marker panel for the diagnosis and monitoring of FM. However, its limited specificity and lack of correlation with clinical severity suggest that GDF15 should not be used in isolation. This aligns with existing evidence showing that GDF15 is elevated in various inflammatory and metabolic disorders, reinforcing its role as a supportive—but non-specific—biomarker best interpreted within a broader clinical context. Future multicenter and longitudinal studies are needed to elucidate its clinical relevance in fibromyalgia further.

Data availability

The original contributions presented in this study are included in the article; further inquiries can be directed to the corresponding author.

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Author contributions
E.Y. and M.H.Y. designed the study and conducted the investigation. E.Y. and H.U. performed the formal analysis and contributed to the methodology. E.Y. prepared the software and curated the data. H.U. validated the results. M.H.Y. prepared the visualizations. O.C. supervised the project and administered its execution. E.Y. wrote the original draft. M.H.Y., O.C., and H.U. reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
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Informed consent statement
Informed consent was obtained from all the subjects involved in this study, and written informed consent was obtained from the patients to publish this paper.

Additional information
Correspondence and requests for materials should be addressed to O.C.

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