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# Elevated Circulating Fibroblast Growth Factor 21 in Lean Type 2 Diabetes: Evidence of Metabolic Dysregulation in the Absence of Adiposity

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## ABSTRACT

**Introduction.** Lean type 2 diabetes mellitus (T2DM) is a form of diabetes that develops in persons with normal Body Mass Index (BMI) and considerable metabolic impairment. High levels of Fibroblast Growth Factor-21 (FGF21) can indicate disrupted metabolic signaling in this group. The study aimed to assess circulating FGF21 levels in lean T2DM and to examine their association with insulin resistance and hepatic steatosis, both biomarkers of metabolic dysregulation.

**Methods:** This cross-sectional study included 425 lean adults (body mass index 18.5–22.9 kg/m$^2$), comprising 200 lean T2DM patients and 225 non-diabetic controls. An enzyme-linked immunosorbent assay (ELISA) was used to measure serum FGF21 levels. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and ultrasonography was used to evaluate hepatic steatosis.

**Results:** Lean T2DM patients had significantly higher levels of glycated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), fasting glucose, fasting insulin, low-density lipoprotein (LDL) cholesterol, aspartate aminotransferase (AST), and total cholesterol, while high-density lipoprotein (HDL) cholesterol was lower than non-diabetic controls (all $p < 0.001$). In multivariable analyses of the lean T2DM cohort, serum FGF21 was independently associated with HOMA-IR ($\beta = 0.775$, $p < 0.001$) and hepatic steatosis (OR, 1.02; 95% CI, 1.01-1.03).

**Conclusions:** Circulating FGF21 levels are elevated in lean T2DM and may reflect compensatory upregulation or altered FGF21 signaling rather than confirmed tissue-level resistance. FGF21 was an independent predictor of insulin resistance and hepatic steatosis, suggesting its potential as a biomarker of metabolic dysfunction in the normal-BMI group.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) has traditionally been associated with obesity and metabolic syndrome; however, a substantial proportion of individuals with T2DM have a lean body phenotype.[1] These individuals often are described as having lean T2DM and may exhibit distinct metabolic characteristics, including insulin resistance, altered lipid metabolism, and increased susceptibility to hepatic steatosis compared with individuals with obesity-related T2DM.[2,3] The pathophysiology of lean T2DM remains incompletely understood, and conventional risk factors such as body mass index (BMI) do not fully explain disease development in this population.[4]

Fibroblast growth factor 21 (FGF21) is an endocrine hormone primarily secreted by the liver that plays important roles in glucose and lipid metabolism, insulin sensitivity, and energy homeostasis.[5] Experimental and clinical studies suggest that FGF21 has protective metabolic effects, including improving insulin sensitivity and reducing hepatic steatosis, making it a potential therapeutic target for metabolic diseases.[6,7] Paradoxically, elevated circulating FGF21 levels are observed in metabolic disorders such as obesity, Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), and T2DM, suggesting the presence of impaired FGF21 signaling or a state of FGF21 resistance, in which target tissues become less responsive to the hormone despite increased circulating concentrations.[7,8]

Although FGF21 resistance has been extensively studied in obesity-related metabolic disorders, its role in lean T2DM remains poorly understood.[9,10] Recent studies have demonstrated elevated circulating FGF21 levels in individuals with T2DM and have associated higher FGF21 concentrations with metabolic dysfunction and diabetes-related vascular and microvascular complications, suggesting an important role for FGF21 in the pathophysiology of T2DM.[8,11] However, evidence linking elevated FGF21 levels to insulin resistance and hepatic abnormalities specifically in lean individuals with T2DM remains limited.[12]

Understanding the mechanisms underlying metabolic dysfunction in lean T2DM is clinically important, as these individuals may develop significant metabolic complications despite the absence of obesity. Therefore, we evaluated circulating FGF21 levels in individuals with lean T2DM and examined their associations with insulin resistance and hepatic steatosis, providing insight into metabolic dysregulation that occurs independently of excess adiposity.

## METHODS

### Study Design and Setting

This cross-sectional study assessed circulating FGF21 levels and their associations with insulin resistance and hepatic steatosis among lean individuals with T2DM. Participants were recruited from three cardiometabolic and endocrinology clinics at tertiary care centers in the United Kingdom. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13]

### Study Population

A convenience sample of 425 adults aged 18-45 years was enrolled, including 200 individuals with lean T2DM and 225 non-diabetic controls. The age range intentionally was restricted to younger adults to minimize the potential confounding effects of age-related metabolic changes, multimorbidity, and prolonged diabetes duration, thereby enabling a more homogeneous evaluation of the association between circulating FGF21 levels, insulin resistance, and hepatic steatosis in lean T2DM. Lean T2DM was defined as physician-diagnosed T2DM in individuals with a BMI of 18.5-22.9 kg/m$^2$, based on the Asian BMI classification proposed by the WHO Expert Consultation and consistent with published definitions of lean T2DM.[14] Controls had normal fasting glucose levels and no history of diabetes.

Individuals with chronic liver disease, alcohol use disorder, pregnancy, incomplete laboratory data, or use of medications known to significantly affect liver function were excluded. Participants receiving oral glucose-lowering therapy were eligible, whereas insulin users were excluded. The participant selection process is shown in Figure 1.

### Data Collection

***Demographic and Clinical Data.*** Age, sex, BMI, duration of diabetes (among participants with T2DM), family history of diabetes, hypertension, smoking status, physical activity, and dietary patterns were collected using a structured questionnaire.

***Laboratory Assessment.*** Venous blood samples were collected after an ≥8-hour overnight fast. Fasting blood glucose (mg/dL) was measured using an automated clinical chemistry analyzer (Cobas c702; Roche Diagnostics,

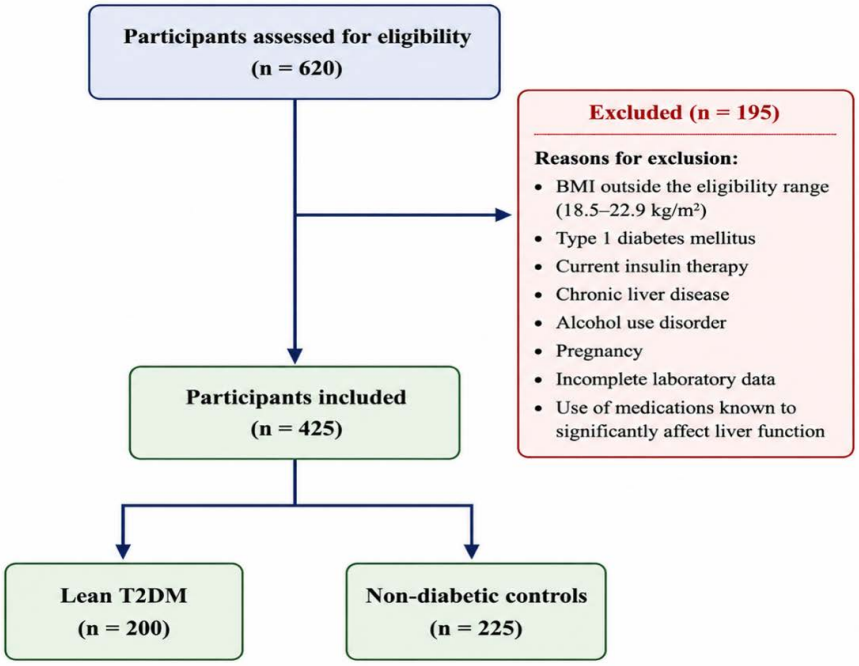


**Figure 1.** Participant flow diagram of study recruitment and selection.

Mannheim, Germany), and fasting serum insulin (μIU/mL) was measured using an electrochemiluminescence immunoassay analyzer (Cobas e801; Roche Diagnostics, Mannheim, Germany). Serum FGF21 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Insulin resistance was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) as follows:

HOMA-IR = [Fasting insulin (μIU/mL) × Fasting glucose (mg/dL)] / 405

***Assessment of Hepatic Steatosis.*** Hepatic ultrasonography was performed by an experienced radiologist who was blinded to participants' clinical and biochemical data. Hepatic steatosis was graded on a scale of 0 to 3 based on hepatic echogenicity.

### Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26. Group comparisons were performed using the Mann–Whitney *U* test, chi-square test, or Fisher's exact test, as appropriate. Covariates were selected *a priori* based on their clinical relevance and biological plausibility for insulin resistance and hepatic steatosis. Multiple linear regression was used to identify factors independently associated with HOMA-IR, and binary logistic regression was used to identify factors independently associated with hepatic steatosis. For the binary logistic regression analysis, hepatic steatosis was dichotomized as absent (grade 0) and present (grades 1–3). Statistical significance was defined as a two-sided $p < 0.05$.

### Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of Lincoln County Hospital (LCH/REC/2026-0147). Written informed consent was obtained from all participants before enrollment, and all study procedures were conducted in accordance with the Declaration of Helsinki.

## RESULTS

### Participant Characteristics

The study included 425 participants, comprising 200 individuals with lean T2DM and 225 non-diabetic controls. Males and females were similarly distributed between the two groups, and most participants were 26-45 years of age. Among individuals with lean T2DM, the majority had a diabetes duration of 1-6 years. Additional demographic and clinical characteristics are summarized in Table 1.

**Table 1.** Comparison of baseline characteristics between lean T2DM and non-diabetic controls.

| Variable | Lean T2DM (n = 200) | Non-diabetic Controls (n = 225) | *P*-value |
|---|---|---|---|
| **Gender: Male, n (%)** | 107 (53.5) | 112 (49.8) | 0.496 |
| Age Group, n (%) | | | |
| 18–25 years | 51 (25.5) | 54 (24.0) | |
| 26–35 years | 75 (37.5) | 80 (35.6) | |
| 36–45 years | 74 (37.0) | 91 (40.4) | 0.767 |
| **Duration of Diabetes (T2DM only, n = 200)** | | | |
| <1 year | 31 (15.5) | — | |
| 1–3 years | 71 (35.5) | — | |
| 4–6 years | 61 (30.5) | — | |
| >6 years | 37 (18.5) | — | N/A |
| Family History of Diabetes Mellitus: Yes, n (%) | 129 (64.5) | 66 (29.3) | **<0.001** |
| History of Hypertension: Yes, n (%) | 83 (41.5) | 32 (14.2) | **<0.001** |
| **Smoking Status, n (%)** | | | |
| Current Smoker | 51 (25.5) | 24 (10.7) | |
| Former Smoker | 27 (13.5) | 31 (13.8) | |
| Never Smoked | 122 (61.0) | 170 (75.6) | **<0.001** |
| **Physical Activity Level, n (%)** | | | |
| Sedentary | 111 (55.5) | 36 (16.0) | |
| Moderate | 63 (31.5) | 81 (36.0) | |
| Active (4–5 days/week) | 26 (13.0) | 108 (48.0) | **<0.001** |
| **Dietary Pattern, n (%)** | | | |
| Mostly Carbohydrates | 110 (55.0) | 49 (21.8) | |
| Balanced Diet | 62 (31.0) | 121 (53.8) | |
| High-Protein / Low-Carb | 28 (14.0) | 55 (24.4) | **<0.001** |

***Note.*** Data are presented as n (%) unless otherwise indicated. Group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Duration of diabetes was assessed only in the Lean T2DM group.
T2DM, Type 2 Diabetes Mellitus; BMI, Body Mass Index; HbA1c, Glycated Hemoglobin.

**Comparison of Metabolic Parameters Between Lean T2DM and Non-diabetic Controls**

As presented in Table 2, individuals with lean T2DM had significantly higher serum FGF21 concentrations than non-diabetic controls (median [IQR], 412.50 [315.00–560.00] pg/mL vs. 185.40 [140.00–250.00] pg/mL; p <0.001). They also had significantly higher levels of glycated hemoglobin (HbA1c), fasting glucose, fasting insulin, HOMA-IR, LDL cholesterol, total cholesterol, and aspartate aminotransferase (AST), and significantly lower HDL cholesterol levels than non-diabetic controls (all p <0.001). No significant differences were observed in age or body mass index (BMI), indicating that the groups were well matched for these characteristics.

**Predictors of Insulin Resistance and Hepatic Steatosis**

The multivariable regression analyses are presented in Table 3. In the multiple linear regression model, serum FGF21 was independently associated with HOMA-IR (β = 0.775, B = 0.03; 95% CI, 0.034-0.037, p <0.001). HbA1c was also independently associated with HOMA-IR (β = 0.19, B = 0.99; 95% CI, 0.56-1.43, p <0.001), whereas male sex was associated with lower HOMA-IR than female sex (β = –0.09, B = –0.45; 95% CI, –0.88 to –0.03, p = 0.04). In the binary logistic regression analysis, serum FGF21 (OR, 1.02; 95% CI 1.01-1.03, p = 0.003) and HOMA-IR (OR, 1.35; 95% CI, 1.06-1.72, p =

**Table 2.** Comparison of metabolic parameters between lean T2DM and non-diabetic controls (N = 425).

| Variable | Lean T2DM Median (IQR) (n = 200) | Non-diabetic Controls Median (IQR) (n = 225) | *P*-value |
|---|---|---|---|
| **Serum FGF21 (pg/mL)** | **412.50 (315.00–560.00)** | **185.40 (140.00–250.00)** | **<0.001** |
| HbA1c (%) | 6.50 (6.50–6.90) | 5.20 (5.00–5.40) | **<0.001** |
| HOMA-IR | 8.06 (6.62–10.30) | 1.50 (1.14–1.82) | **<0.001** |
| Fasting Glucose (mg/dL) | 159.25 (141.38–176.50) | 85.60 (80.70–90.50) | **<0.001** |
| Fasting Insulin (μIU/mL) | 21.38 (17.71–24.88) | 7.05 (5.45–8.42) | **<0.001** |
| HDL Cholesterol (mg/dL) | 36.35 (31.65–40.12) | 54.50 (48.90–60.00) | **<0.001** |
| LDL Cholesterol (mg/dL) | 124.85 (107.07–140.10) | 95.60 (84.90–106.70) | **<0.001** |
| AST (U/L) | 37.80 (27.58–47.02) | 20.50 (16.40–24.30) | **<0.001** |
| Total Cholesterol (mg/dL) | 203.75 (188.22–222.80) | 178.10 (162.60–190.90) | **<0.001** |
| BMI (kg/m²) | 21.20 (20.50–21.73) | 20.93 (20.28–21.67) | 0.067 |
| Age (years) | 31.00 (24.00–38.00) | 32.00 (26.00–39.00) | 0.398 |

***Note.*** Values are presented as median (IQR) and compared using the Mann–Whitney *U* test. BMI and Age are shown to demonstrate comparable baseline characteristics between groups.
HbA1c, Glycated Hemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; AST, Aspartate Aminotransferase; BMI, Body Mass Index.

**Table 3.** Multiple regression analysis: full model of predictors of HOMA-IR (linear) and hepatic steatosis (logistic) in lean T2DM (N = 200).

| **Model A: Linear Regression: Predictors of HOMA-IR \| $R^2$ = 0.695, Adjusted $R^2$ = 0.687, $F(5, 194)$ = 88.381, p <0.001 \| N = 200** | | | | | | |
|---|---|---|---|---|---|---|
| **Predictor** | **B** | **SE** | **β / Wald** | ***t* / OR** | ***P*-value** | **95% CI** |
| Serum FGF21 (pg/mL) | 0.034 | 0.002 | 0.775 | 17.894 | **<0.001** | (0.030, 0.037) |
| HbA1c (%) | 0.992 | 0.221 | 0.188 | 4.481 | **<0.001** | (0.556, 1.429) |
| Gender (Male vs Female) | –0.454 | 0.216 | –0.087 | –2.102 | **0.037** | (–0.881, -0.028) |
| BMI (kg/m²) | 0.021 | 0.107 | 0.008 | 0.197 | 0.844 | (–0.191, 0.233) |
| Triglycerides (mg/dL) | –0.003 | 0.002 | –0.048 | –1.201 | 0.231 | (–0.007, 0.002) |
| **Model B: Binary Logistic Regression: Predictors of Hepatic Steatosis \| Nagelkerke $R^2$ = 0.432, H-L p = 0.085, Accuracy = 78.5% \| N = 200** | | | | | | |
| **Predictor** | **B** | **SE** | **β / Wald** | ***t* / OR** | ***P*-value** | **95% CI** |
| Serum FGF21 (pg/mL) | 0.017 | 0.006 | 9.028 | 1.017 | **0.003** | (1.006, 1.028) |
| HOMA-IR | 0.303 | 0.123 | 6.097 | 1.353 | **0.014** | (1.064, 1.721) |
| ALT (U/L) | –0.026 | 0.013 | 3.833 | 0.975 | 0.050 | (0.950, 1.000) |
| BMI (kg/m²) | –0.147 | 0.187 | 0.618 | 0.863 | 0.432 | (0.598, 1.246) |
| HbA1c (%) | –0.127 | 0.382 | 0.111 | 0.881 | 0.739 | (0.416, 1.862) |
| Gender (Male vs Female) | 0.039 | 0.367 | 0.012 | 1.040 | 0.915 | (0.507, 2.136) |

***Note.*** All variables entered into the regression models are presented regardless of statistical significance. B, unstandardized coefficient; β, standardized coefficient; Wald, Wald chi-square statistic; t, t-statistic; OR, odds ratio (Exp(B)); SE, standard error; CI, confidence interval.

0.014) were independently associated with hepatic steatosis. Complete multivariable regression models, including variables that were not statistically significant, are presented in Table 3 to provide the full set of covariates evaluated.

As shown in Table 4, hepatic steatosis was significantly more prevalent among individuals with lean T2DM than among non-diabetic controls (p <0.001). Only 31.0% of participants with lean T2DM had no evidence of hepatic steatosis

**Table 4.** Distribution of hepatic steatosis grades between lean T2DM and non-diabetic controls.

| Hepatic steatosis grade | Lean T2DM n (%) | Controls n (%) | *P*-value |
|---|---|---|---|
| No steatosis (Grade 0) | 62 (31.0) | 155 (68.9) | |
| Mild steatosis (Grade 1) | 84 (42.0) | 55 (24.4) | |
| Moderate steatosis (Grade 2) | 42 (21.0) | 14 (6.2) | |
| Severe steatosis (Grade 3) | 12 (6.0) | 1 (0.4) | |
| **Total** | 200 (100.0) | 225 (100.0) | **<0.001** |

***Note.*** Values are presented as n (%). Hepatic steatosis was graded (Grades 0–3) using ultrasonography. Group comparisons were performed using the chi-square test.

(Grade 0), compared with 68.9% of controls. Mild steatosis (Grade 1) was the most common grade among individuals with lean T2DM (42.0% vs. 24.4%), while moderate (21.0% vs. 6.2%) and severe steatosis (6.0% vs. 0.4%) were also considerably more frequent in the lean T2DM group than in controls, indicating a substantially greater burden of hepatic steatosis despite normal BMI.

## DISCUSSION

The present study examined circulating FGF21 concentrations in lean individuals with T2DM and their associations with insulin resistance and hepatic steatosis. Serum FGF21 levels were significantly higher in individuals with lean T2DM than in non-diabetic controls, consistent with previous studies reporting elevated circulating FGF21 levels in T2DM and their association with metabolic and vascular complications.[11]

In addition, aspartate aminotransferase (AST) levels were significantly higher in the lean T2DM group, consistent with previous evidence showing that elevated AST and other liver enzymes are independently associated with diabetes and reflect underlying metabolic abnormalities.[15]

Unlike many previous studies that focused primarily on obesity-related T2DM, our study specifically evaluated metabolic abnormalities in lean individuals with T2DM. Although comparisons with overweight or obese individuals with T2DM may provide additional clinical insight, our primary objective was to characterize metabolic dysfunction associated with lean T2DM while minimizing the confounding effects of excess adiposity. Future studies directly comparing lean and overweight or obese individuals with T2DM are warranted to further define the distinct metabolic characteristics of these populations.

Individuals with lean T2DM also exhibited significantly higher fasting insulin levels and HOMA-IR, indicating substantial insulin resistance despite having a normal BMI. Abnormalities in lipid profiles and liver enzymes further support the presence of metabolic and hepatic dysfunction in this population, consistent with previous reports.[16-18] Collectively, these findings suggest that lean T2DM is characterized by metabolic disturbances that extend beyond hyperglycemia alone.

In the multivariable analyses, serum FGF21 was independently associated with HOMA-IR, whereas HbA1c and sex were also independently associated with insulin resistance. These findings are consistent with a previous study linking elevated FGF21 levels to insulin resistance and poor glycemic control.[19] The independent association between sex and HOMA-IR also is consistent with evidence suggesting that sex-related differences in insulin resistance may be influenced by variations in body fat distribution and sex hormones.[20] Furthermore, both FGF21 and HOMA-IR were independently associated with hepatic steatosis. Similar associations have been reported in individuals with MASLD.[21,22] However, because of the cross-sectional study design, these findings should be interpreted as associations rather than evidence of causal relationships.

Overall, lean T2DM was characterized by elevated circulating FGF21 levels, insulin resistance, and hepatic abnormalities despite normal BMI. Elevated FGF21 may represent a compensatory response to metabolic stress or impaired FGF21 signaling; however, circulating FGF21 concentrations alone cannot confirm tissue-level FGF21 resistance. Together, these findings suggest that FGF21 may serve as a biomarker of metabolic dysfunction in lean T2DM and highlight the need for further investigation into its role in disease pathophysiology.

### Limitations

This study has several limitations. First, its cross-sectional design precludes causal inference and does not establish the temporal relationship between elevated FGF21 levels and metabolic dysfunction. Second, hepatic steatosis was assessed using ultrasonography rather than histologic confirmation, and tissue-level FGF21 signaling was not

evaluated. Although all ultrasonographic examinations were performed by a single experienced radiologist who was blinded to participants' clinical and biochemical data, inter- and intra-observer reliability were not formally assessed, which may have introduced measurement variability. Third, participants were recruited through convenience sampling from three tertiary care centers, which may limit the representativeness of the study population and the generalizability of the findings. In addition, restricting enrollment to adults aged 18-45 years may further limit the applicability of the findings to older individuals with lean T2DM. Additionally, information regarding the specific classes of oral glucose-lowering medications used by participants with T2DM was not collected or analyzed. Because several glucose-lowering agents may directly influence circulating FGF21 concentrations, the potential confounding effects of medication use could not be assessed. Finally, the multivariable regression models were not externally validated. Prospective, multicenter studies incorporating direct measures of FGF21 signaling, broader and more representative populations, and external validation of predictive models are needed to confirm and extend these findings.

## CONCLUSIONS

Lean T2DM was associated with elevated circulating FGF21 levels, insulin resistance, and hepatic dysfunction despite normal BMI. These findings suggest that FGF21 may serve as a biomarker of metabolic dysfunction in lean T2DM. Longitudinal and mechanistic studies are needed to determine whether elevated FGF21 contributes to disease progression or primarily reflects underlying metabolic stress.

## ARTICLE INFORMATION

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***Keywords:*** *Type 2 diabetes mellitus; fibroblast growth factor 21; insulin resistance; hepatic steatosis; body mass index*