Original Article

Beyond Human Chorionic Gonadotropin: The Role of Growth Differentiation Factor-15 and Insulin-like Growth Factor-binding Protein-7 in the Pathogenesis of Hyperemesis Gravidarum

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ABSTRACT

Objective: To evaluate the levels of serum growth differentiation factor 15 and insulin-like growth factor binding protein-7 in pregnant women with hyperemesis gravidarum and healthy matched pregnant controls, and their independent and combined discriminatory value

Study Design: Prospective case-control study

Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynecology, Alzahraa Teaching Hospital, Najaf city, Iraq from May 2026 to July 2026.

Methodology: The study included 60 women who had hyperemesis gravidarum and 60 healthy pregnant controls of similar gestational age (6-16 weeks). To diagnose hyperemesis gravidarum, the patient had to have weight loss ≥5%, ketonuria ≥2+, dehydration and a PUQE-24 score ≥8. Serum growth differentiation factor 15 and insulin-like growth factor binding protein-7 were quantified by sandwich enzyme-linked immunosorbent assay. Diagnostic performance was measured using Receiver Operating Characteristic curve analysis and logistic regression adjusted for gestational age, maternal age, parity and body mass index.

Results: The median value of growth differentiation factor 15 was significantly greater in hyperemesis gravidarum (4,277 pg/mL) than controls (1,785 pg/mL; p<0.001). Median insulin-like growth factor binding protein-7 was also elevated (124.0 vs. 67.5 ng/mL; p<0.001). Growth differentiation factor 15 was positively correlated with the PUQE-24 score (Spearman r=0.58; p<0.001). The combined growth differentiation factor 15 + insulin-like growth factor binding protein-7 adjusted model achieved AUC=0.949 (95% CI: 0.897-0.987). There was no significant difference between groups (p=0.34) for serum human chorionic gonadotropin.

Conclusion: The levels of growth differentiation factor 15 and insulin-like growth factor binding protein-7 are significantly higher in HG and show good combined diagnostic accuracy. The absence of a difference in serum human chorionic gonadotropin between groups corroborates the finding that growth differentiation factor 15, instead of human chorionic gonadotropin, is the more important hormone involved in hyperemesis gravidarum.

Key Words: H yperemesis gravidarum, Biomarker, First trimester**,** Human chorionic gonadotropin.

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INTRODUCTION

Hyperemesis gravidarum (HG) represents the most life-threatening manifestation of nausea and vomiting in pregnancy, affecting 0.3-2% of all pregnancies, and is the most common indication for early hospital admission in high-income countries[1]. The 2021 FIGO consensus definition of HG includes severe nausea and/or vomiting starting before 16 weeks of gestation with inability to consume normal food and/or fluids, leading to marked restriction in daily functioning[2]. HG is characterized by intractable vomiting, loss of 5% or more of body weight[3], dehydration, and electrolyte disturbances, and is accompanied by maternal complications such as Wernicke's encephalopathy, central pontine myelinolysis and mental illness[4], as well

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as fetal complications including low birth weight, small-for-gestational-age, premature delivery, and increased neonatal intensive care admission[5]. It shows well-known familial clustering, with a 55% recurrence risk in subsequent pregnancies, suggesting high heritability[6].

Diagnosis of HG is clinical, based on excluding other causes of first-trimester vomiting such as urinary tract infection, thyroid disease, gastroenteritis and cholecystitis[1]. PUQE-24 is a validated scoring system that quantifies nausea, vomiting and retching over a 24-hour period; a score above 7 defines moderate-to-severe NVP[7]. Treatment includes antihistamines (H1 receptor antagonists), phenothiazines, and in refractory cases the serotonin (5-HT3) antagonist ondansetron[8]. Poor responders require intravenous rehydration, electrolyte correction, and thiamine supplementation to prevent Wernicke's encephalopathy[9,10].

For many years the pathophysiology of HG remained poorly understood; older hypotheses centered on elevated hCG or psychosomatic causes failed to explain the disease's severity and variability[11]. A major paradigm shift occurred when a landmark 2018 genome-wide association study by Fejzo and colleagues[12] identified two independent genetic risk loci specifically linked to HG susceptibility: GDF15, located on chromosome 19p13.11, and IGFBP7, located on chromosome 4q12.

This GWAS was performed in a large 23andMe cohort, and the GDF15 association ($p=2.47\times10^{-47}$) was confirmed by meta-analysis and replicated in a Norwegian cohort[12]. Whole-exome sequencing of 926 HG cases subsequently identified a common GDF15 coding variant (H6D substitution, rs1058587), correlated with higher serum GDF15 and lower body weight and BMI, as the only variant found to be significant across the entire exome ($p=9.98\times10^{-11}$)[13]. The largest GWAS meta-analysis to date (8,960 cases with HG; 369,843 controls) confirmed GDF15 as the leading risk locus in the pathway, while also identifying GFRAL as a linked gene ($p=8.85\times10^{-9}$)[12]).

GDF15 itself is a stress-inducible, homodimeric (25 kDa) cytokine, a distantly related member of the TGF superfamily, with normal serum levels of 150-1,200 pg/mL that increase significantly during pregnancy, with high expression in placental trophoblasts[14]. GFRAL, the specific high-affinity receptor for GDF15, is almost exclusively expressed in neurons of the area postrema and nucleus tractus solitarius (NTS) of the hindbrain, which form the chemoreceptor trigger zone of emesis. To create a functional signaling complex, GFRAL must engage the co-receptor RET tyrosine kinase to activate PI3K/AKT, MEK/ERK and PLC/PKC signaling, mediating nausea, vomiting, decreased appetite and aversive conditioned responses[15].

A pivotal 2024 study by Fejzo et al[16] showed that the vast majority of circulating GDF15 in early pregnancy is produced in the feto-placental unit, and that pre-pregnancy GDF15 levels dictate receptor sensitisation: women with lower pre-pregnancy GDF15 show the greatest receptor sensitisation and highest HG susceptibility. In contrast, patients with chronically high pre-pregnancy GDF15 concentrations, such as those with beta-thalassemia, exhibit receptor desensitization and are largely protected against severe HG.

IGFBP7 encodes a protein of the IGFBP superfamily with low affinity for insulin-like growth factors but high affinity for insulin; it is highly induced after embryo implantation, where it regulates uterine receptivity and influences trophoblast invasion by modulating Th1/Th2 cytokines[17]. Serum IGFBP7 correlates with placental functional activity[18], and its concurrent up-regulation with GDF15 in early pregnancy and in HG patients indicates that both are transcriptionally controlled in the placenta. The precise mechanism by which IGFBP7 contributes to emesis, whether through IGF axis dysregulation, IGF-independent appetite-suppressive effects, or synergistic potentiation of GDF15-GFRAL signaling, remains to be fully elucidated[16].

Fejzo et al. compared sera from clinically diagnosed HG women with two control groups (NVP and no NVP) at 12 and 24 weeks' gestation; both GDF15 and IGFBP7, but not hCG, were significantly higher in the HG group at 12 weeks, with differences no longer apparent once symptoms resolved at 24 weeks[16]. Petry et al[19] conducted a nested case-control study within the Cambridge Baby Growth Study (n=791), showing that GDF15 at week 15 was associated with increased risk of vomiting during the second trimester, increased anti-emetic use, and lower pre-pregnancy BMI, consistent with the desensitisation model.

Despite growing evidence for the role of both proteins in HG pathogenesis in Western cohorts, data are limited regarding their effect in Middle Eastern populations, where genetic, metabolic and environmental factors differ; this study was conducted to address this research gap.

METHODOLOGY

This prospective case-control study was conducted at the Department of Obstetrics and Gynecology, Alzahraa Teaching Hospital, Najaf city, Iraq, from May 2026 to July 2026. The inpatient cohort (n=60) comprised women admitted with HG at the sixth to sixteenth week (singleton pregnancy, ultrasound confirmed); diagnosis required weight loss ≥5% of pre-pregnancy body weight, ketonuria ≥2+ on urine dipstick, clinical dehydration (or need for IV fluid therapy), and a PUQE-24 score ≥8. The control group (n=60) comprised healthy pregnant women randomly selected from the antenatal clinic, ±1 gestational week from the corresponding case, with no vomiting or mild

nausea (PUQE-24 ≤6) and no weight loss from pre-pregnancy baseline.

For both groups, exclusion criteria were multiple gestation, gestational trophoblastic disease, pre-existing thyroid or gastrointestinal disorder, urinary tract infection, use of anti-emetics before blood sampling, and refusal of informed consent.

Ten mL of venous blood was drawn from each participant, centrifuged for 10 minutes at 3000 rpm, and serum was frozen at -80°C until batch analysis. Serum GDF15 and IGFBP7 were quantified in duplicate using validated sandwich ELISA kits, acceptable coefficients of variation were <8% (intra-assay) and <10% (inter-assay). All laboratory operators were blinded to clinical status. Contemporaneous results for serum hCG, electrolytes, thyroid function and urinalysis were also recorded.

Data were analyzed statistically using SPSS-26. The Shapiro-Wilk test assessed normality. Normally distributed variables are presented as mean±SD and compared using Student's t-test; non-normally distributed data are presented as median (IQR) and compared using the Mann-Whitney U test. Chi-square or Fisher's exact test was used for categorical variables, and Spearman's rank correlation for relationships between biomarkers. AUCs were compared using the ROC curve with DeLong's method. Independent predictors of HG were identified by logistic regression controlling for gestational age, maternal age, parity and BMI. A p value <0.05 was considered statistically significant.

RESULTS

Overall, the two groups were comparable in gestational age, maternal age and BMI. However, the proportion of primiparous women was greater among cases than controls (60.0% vs. 38.3%, p=0.028); 36.7% of cases, compared with none of the controls, had a prior history of HG (p<0.001). Mean PUQE-24 scores were markedly higher in cases (13.4±2.1 vs. 3.2±1.8; p<0.001); hypokalemia was present in 68.3% of patients, and clinical ketonuria was documented in all 60 cases (100%) [Table 1].

Expression of both GDF15 and IGFBP7 was significantly higher in HG cases than in controls (Table 2, Fig. 1). Median GDF15 was 4,277 pg/mL in cases versus 1,785 pg/mL in controls (p<0.001), a 2.4-fold increase; median IGFBP7 was 124.0 ng/mL versus 67.5 ng/mL (p<0.001). Median serum hCG did not differ significantly between groups (68,240 vs. 61,850 mIU/mL, p=0.34).

The area under the ROC curve and diagnostic accuracy for each biomarker and the combined model are shown in Tables 3-4 and Figure 2; strong diagnostic performance was seen for each biomarker, and the combined model was superior. GDF15 alone achieved AUC=0.913 (95% CI: 0.848-0.967; optimal cut-off 3,576 pg/mL, sensitivity 85.0%, specificity 91.7%). IGFBP7 alone achieved AUC=0.852 (95% CI: 0.774-0.927; optimal cut-off 74 ng/mL, sensitivity 86.7%, specificity 83.3%). After adjustment for gestational age, maternal age, parity and BMI, adjusted AUCs rose to 0.933 (95% CI: 0.875-0.978) for GDF15 and 0.892 (95% CI: 0.827-0.951) for IGFBP7. By DeLong's test, the combined model showed a numerically higher AUC than the adjusted GDF15 model, though not statistically significant (p=0.191), but performed significantly better than the adjusted IGFBP7 model (p=0.012).

Significant positive correlations were found between GDF15 and PUQE-24 scores (r=0.58; p<0.001) and between GDF15 and IGFBP7 (r=0.61; p<0.001); GDF15 correlated negatively with gestational weight change (r=-0.47; p<0.001). Neither GDF15 nor IGFBP7 correlated significantly with serum hCG (Table 5, Figs. 3-4).

Table No. 1: Baseline demographic and clinical characteristics of HG cases and controls

Variable	HG Cases (n=60)	Controls (n=60)	p-value
Gestational age (weeks)	10.2±2.1	10.4±2.0	0.61
Maternal age (years)	27.3±4.8	26.9±4.5	0.63
Pre-pregnancy BMI (kg/m²)	23.8 ± 3.9	24.2 ± 4.1	0.57
Primiparity	36 (60.0%)	23 (38.3%)	0.03
Prior HG history	22 (36.7%)	-	<0.001
PUQE-24 score	13.4±2.1	3.2±1.8	<0.001
Weight loss from pre-pregnancy (%)	7.4±2.3	-	N/A
Serum hCG (mIU/mL), median (IQR)	68,240 (51,200-88,400)	61,850 (47,600-79,300)	0.34
Hypokalemia (K^+ <3.5 mmol/L)	41 (68.3%)	-	<0.001
Ketonuria ≥2+,	60 (100%)	-	<0.001

Table No. 2: Comparison of serum GDF15, IGFBP7 and hCG between HG cases and controls

Variable	HG Cases (n=60)	Controls (n=60)	p-value
GDF15 - Median (IQR), pg/mL	4,277 (3,783-4,562)	1,785 (1,451-1,984)	<0.001
GDF15 - Mean±SD, pg/mL	4,195±891	1,791±498	<0.001
IGFBP7 - Median (IQR), ng/mL	124.0 (95.0-134.3)	67.5 (63.8-71.3)	<0.001
IGFBP7 - Mean±SD, ng/mL	119.8±28.4	67.2±9.6	<0.001
hCG - Median (IQR), mIU/mL	68,240 (51,200-88,400)	61,850 (47,600-79,300)	0.34

Table No. 3: ROC curve analysis: diagnostic performance of GDF15, IGFBP7 and combined model for HG

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Optimal Cut-off
GDF15 alone	0.913 (0.848–0.967)	85.0	91.7	3,576 pg/mL
IGFBP7 alone	0.852 (0.774–0.927)	86.7	81.7	74 ng/mL
Combined model†	0.949 (0.897–0.987)	88.3	85.0	Prob ≥0.65

†Combined model: logistic regression including GDF15 + IGFBP7, adjusted for gestational age, maternal age, parity, and BMI

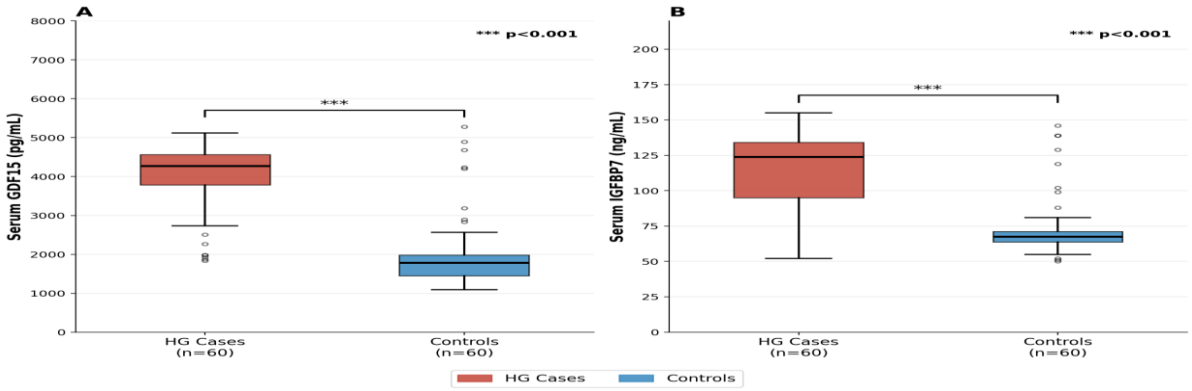


Figure No. 1: Box plots comparing serum GDF15 (A) and IGFBP7 (B) concentrations in HG cases (red) versus healthy pregnant controls (blue). The central line represents the median; box limits represent the 25th–75th percentiles; whiskers extend to 1.5× IQR. *** p<0.001 (Mann-Whitney U test).

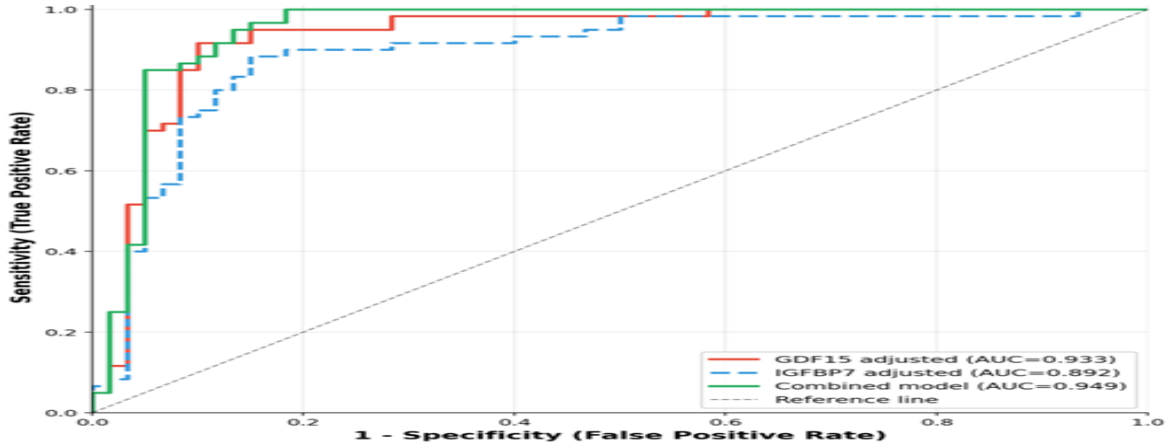


Figure No. 2: Receiver operating characteristic curves for serum GDF15 alone, IGFBP7 alone, and the combined GDF15+IGFBP7 logistic regression model in discriminating HG cases from healthy pregnant controls. AUC values with 95% confidence intervals are shown in the legend.

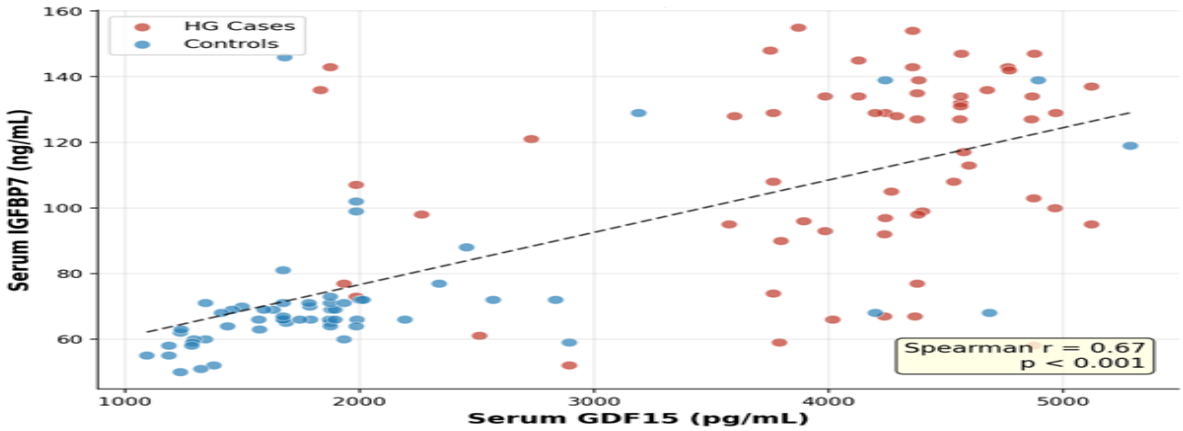


Figure No. 3: Positive correlation between serum GDF15 and PUQE-24 score across all study participants (HG cases: red circles; controls: blue circles). Spearman's r = 0.58, p<0.001

Table No. 4: Multivariable logistic regression: independent predictors of hyperemesis gravidarum

Variable pair	Spearman r	95% CI	p-value
GDF15 vs. PUQE-24 score	0.58	0.43–0.70	<0.001
IGFBP7 vs. PUQE-24 score	0.49	0.33–0.63	<0.001
GDF15 vs. IGFBP7	0.61	0.47–0.73	<0.001
GDF15 vs. gestational weight change	-0.47	-0.61 to -0.31	<0.001
GDF15 vs. serum hCG	0.12	-0.06 to 0.30	0.18
IGFBP7 vs. serum hCG	0.09	-0.09 to 0.27	0.32

All correlations assessed by Spearman's rank correlation coefficient. r = Spearman's rho

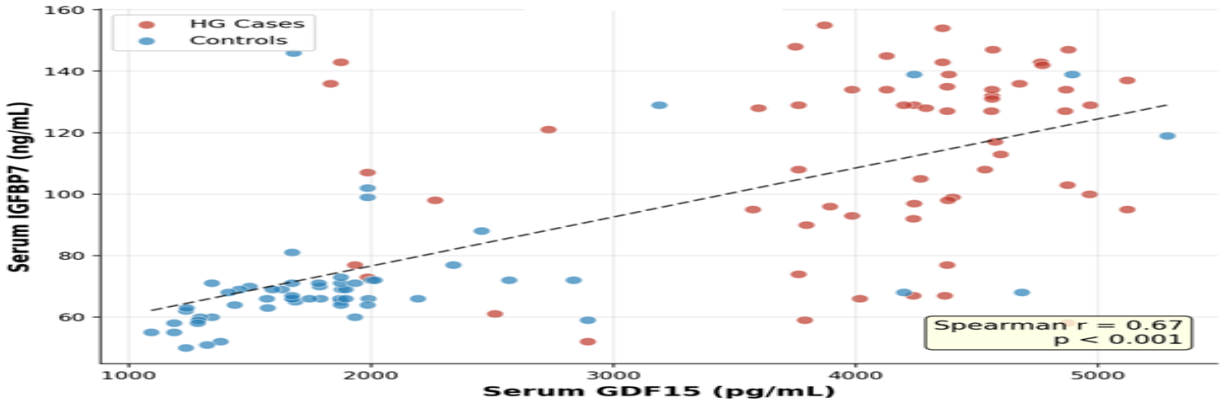


Figure No. 4: Positive correlation between serum GDF15 and IGFBP7 concentrations across all study participants (HG cases: red circles; controls: blue circles). Spearman's r = 0.61, p<0.001

DISCUSSION

This study demonstrates a substantial increase in both serum GDF15 and IGFBP7 during the first trimester in women with HG, consistent with prior clinical findings[16]. The progressive rise in serum GDF15 in early pregnancy was about 2.4-fold higher than controls, with an AUC of 0.913 for GDF15 and 0.852 for IGFBP7, demonstrating clinically useful diagnostic accuracy.

A significant difference in parity was observed between groups, with primiparous women more common among HG cases than controls (60.0% vs. 38.3%, p=0.028). Because parity may influence HG risk[14], it was included as a covariate in the multivariable logistic regression models together with maternal age, gestational age, and BMI. The association between GDF15, IGFBP7, and HG remained significant after adjustment, suggesting the biomarker effects were independent of parity differences.

GDF15 level correlated with PUQE-24 score[20], providing dose-response evidence linking GDF15-GFRAL signaling intensity to clinical symptom severity. This is supported by evidence that increased plasma GDF15 activates area postrema and NTS neurons via the GFRAL-RET pathway[12], and is consistent with the 2024 Nature study linking elevated maternal GDF15 to increased vomiting frequency[1]. GDF15 may therefore serve as both a diagnostic and prognostic marker, guiding treatment intensity, though longitudinal studies are needed to confirm this.

The mechanism by which IGFBP7 causes HG symptoms remains poorly understood and warrants further research. The null finding for serum hCG (p=0.34) directly confirms Fejzo et al[16] and represents an important negative finding that overturns the traditionally accepted hCG hypothesis of HG pathogenesis. Together with the landmark 2024 Nature study[15] and large genetic evidence[12], this favors GDF15, rather than hCG, as the main hormonal driver of HG, with direct implications for clinical care and the development of new therapeutic strategies.

The GDF15-GFRAL axis represents several potential targets for therapeutic intervention. Growing pre-clinical and early clinical evidence shows that antibodies blocking GFRAL can reduce GDF15-induced emesis[2]. The desensitisation hypothesis, whereby low pre-pregnancy GDF15 mimics allergen desensitisation, is supported mechanistically by the observation that women with beta-thalassemia, who have long-term elevated GDF15, experience significantly less NVP[15].

CONCLUSION

A significant increase in serum GDF15 and IGFBP7, positively correlated with clinical severity (PUQE-24 scores), was observed in women with hyperemesis gravidarum during the first trimester. Used together, the two biomarkers achieved greater diagnostic accuracy (AUC=0.949) than either marker alone. The absence of a significant difference in serum hCG levels suggests GDF15 may play a more important role than hCG in HG pathogenesis. These results offer a robust basis for

incorporating GDF15 and IGFBP7 into the clinical evaluation of HG and support development of therapeutic interventions targeting the GDF15-GFRAL axis.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Aseel Abdulameer Mohammed, Amal Muner Mubarak
Drafting or Revising Critically:	Aseel Abdulameer Mohammed, Rusul Jabbar Tuama
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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