The changes of serum fibrinogen-like protein 1 levels associated with improved liver function and uric acid after laparoscopic sleeve gastrectomy

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Research Article

Keywords: fibrinogen-like protein 1, obesity, laparoscopic sleeve gastrectomy

Posted Date: February 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1311106/v1

Abstract

Background: Fibrinogen-like protein (FGL)-1 is a novel hepatokine that plays an important role in the development of hepatic steatosis and insulin resistance. The purpose of this study is to analyze serum FGL-1 levels in patients with obesity before and after laparoscopic sleeve gastrectomy (LSG).

Methods: Ninety-two individuals (32 people with normal weight and 60 patients with obesity) were included in this study. All patients with obesity finished follow-up visits at 6 months after LSG. Clinical data, anthropometric parameters and biochemical variables were collected. Serum FGL-1 levels were assessed by enzyme-linked immunosorbent assay (ELISA).

Results: FGL-1 levels in patients with obesity (44.66 ± 20.03 ng/mL) were higher than individuals with normal weight (20.73 ± 9.73 ng/mL, $P < 0.001$). At baseline, FGL-1 levels were positively correlated with body mass index (BMI), blood pressure, hepatic enzyme levels, glucose metabolism, lipid metabolism and uric acid (UA). After LSG, FGL-1 levels were significantly decreased (27.53 ± 11.45 ng/mL, $P < 0.001$). Besides, BMI, hepatic enzyme levels, glucose metabolism, lipid metabolism and UA were significantly improved. After adjusting possible confounders, changes in FGL-1 levels at 6 months after surgery were positively correlated with changes in ALT, AST and UA levels.

Conclusions: FGL-1 levels were closely correlated with various metabolic factors and decrease following LSG in patients with obesity. Furthermore, FGL-1 levels were more closely related to liver function and uric acid metabolism, but not body weight and glucolipid metabolism.

Trial registration: This study protocol was approved by the Ethical Committee of Shanghai Tenth People's Hospital. The Clinical Registration Number is ChiCTR-OCS-12002381. Date: 23 July 2012.

Background

With the global incidence of obesity rising dramatically over the past 40 years, obesity has been a growing crucial concern [1]. Obesity increases the risk of type 2 diabetes mellitus (T2DM), cardiovascular disease, hepatobiliary disease and kidney disease [2]. All these conditions can be ameliorated by losing weight [3]. Long-term follow-up studies have shown that bariatric surgery is a safe and effective method of assisting patients to lose weight [4]. Laparoscopic sleeve gastrectomy (LSG) is one of the most common bariatric procedures used currently [5]. Researches have indicated that LSG reduced insulin resistance, which involved mechanism via reduction of adipose tissue and obesity-associated inflammation, as well as changes in gastrointestinal hormones and adipokines [6]. In addition to altering adipokines, bariatric surgery also regulates myokines and hepatokines [7]. Previous studies have found that many hepatokines can be significantly altered after bariatric surgery, such as fibroblast growth factor 21 (FGF-21), angiopoietin-like protein 6 (ANGPTL-6), fetuin-A and selenoprotein P (SeP) [8-10].

Fibrinogen-like protein (FGL)-1 is a hepatokines secreted by the liver, also known as hepatocyte-derived fibrinogen related protein 1 or hepassocin [11]. FGL-1 has similar structure with angiopoietin like factors

(ANGPTLs) which regulate lipid metabolism and energy utilization [12]. Also, FGL-1 participates in the regulation of hepatocyte proliferation and liver regeneration, and involved in regulating lipid metabolism and the progression of several cancer types [13, 14]. Previous cross-sectional studies demonstrated serum FGL-1 levels elevated in patients with non-alcoholic fatty liver (NAFLD), pre-diabetes, T2DM, gestational diabetes mellitus (GDM) and obesity [15-18]. FGL-1 leads to hepatic lipogenesis, insulin resistance and adipogenesis by increasing the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) [15, 18]. FGL-1 has also been implicated in skeletal muscle insulin resistance through EGFR/JNK-mediated pathway [19]. Taken together, these reports suggest that FGL-1 may be a useful biomarker for obesity and metabolic dysregulation.

However, literature on FGL-1 modulation following bariatric surgery is limited. The present study was designed to determine the serum FGL-1 levels in bariatric patients and the changes in FGL-1 levels after LSG, and further confirm whether these changes are associated with changes in metabolic parameters.

Materials And Methods

Study population

Ninety-two individuals (32 individuals with normal weight and 60 patients with obesity that underwent LSG) from the Department of Endocrinology and Metabolism, Shanghai Tenth People's Hospital were enrolled in this retrospective study between July 2018 and April 2021. The inclusion criteria of bariatric patients were BMI ≥ 32.5 kg/m^2, or BMI ≥ 27.5 kg/m^2 with two or more obesity-related comorbidities, such as T2DM, hypertriglyceridemia, hypertension, or NAFLD [20]. The exclusion criteria of bariatric patients were: (1) severe cardiac, hepatic, or renal dysfunction; (2) severe systemic or organic diseases; (3) presence of endocrine diseases causing obesity; (4) use of medications that affect body weight. During the same period, thirty-two age-matched healthy adults of normal weight (BMI range 18.5 to 24) were recruited from the medical examination center. The exclusion criteria of normal weight individuals were: (1) severe heart, liver, and kidney dysfunction; (2) presence of severe systemic diseases (malignant tumors or autoimmune diseases); (3) clinical or laboratory data missing. All individuals of this study signed written informed consent.

Measurements

Anthropometric and biochemical measurements

All patients with obesity were hospitalized for a comprehensive examination before surgery and followed up at 6 months post-surgery. Patients' weight was measured without shoes and with light clothes by a professional staff. Body mass index (BMI) was calculated by weight (kg)/(height^2) (m^2). Blood pressure was measured twice after the individual sat silently for 10 minutes and the average value was

used for analysis. Fasting blood samples was obtained after overnight fasting. The following biochemical parameters were measured: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γGT), fasting plasma glucose (FPG), fasting insulin (FINS), glycosylated hemoglobin A1 (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), uric acid (UA), creatinine (Cr), urea nitrogen (BUN). Homeostasis model assessment of insulin resistance (HOMA-IR) calculated by the conventional formula [21]: FPG (mmol/L) × FINS (mU/L) / 22.5. The serum FGL-1 levels were measured by enzyme-linked immunosorbent assay (ELISA, Cusabio, Wuhan, China) according to the instruction manual.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (SPSS, Chicago, USA). All continuous variables were expressed as means ± standard deviation (SD), and categorical variables are expressed as percentages. Differences between continuous variables of normally distributed variables were analyzed by Student's t-test, while differences between categorical variables expressed as percentages were evaluated by chi-square test. Pearson's correlation analysis was used to investigate the correlation between two indices. Paired-sample t-test was used to compare the data before and after surgery. Multiple linear regression was used to analyze the relationship between the changes in FGL-1 and changes in other indices. $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of the individuals

Basic anthropometric examination data and biochemical indices are summarized in Table 1. The mean age and gender distribution were comparable between the obesity and normal-weight groups. The BMI in the normal weight group was 20.75 ± 1.73 kg/m^2 and that in the obesity group was 39.84 ± 6.10 kg/m^2. Compared to individuals with normal weight, patients with obesity had significantly higher FPG, FINS, HOMA-IR, SBP, DBP, ALT, AST, γGT, TG, UA levels and lower HDL levels (for all, $P < 0.05$). FGL-1 levels in the obesity group were much higher than in the normal group (44.66 ± 20.03 vs. 20.73 ± 9.73 ng/mL, $P < 0.001$).

Correlation between FGL-1 and Metabolic Factors at baseline

Pearson's correlation analysis were used to analyze the relationships of FGL-1 and metabolic factors at baseline (Figure. 1). FGL-1 levels were positively correlated with BMI ($r = 0.530$, $P < 0.001$), FPG ($r = 0.277$, $P = 0.008$), FINS ($r = 0.408$, $P < 0.001$), HOMA-IR ($r = 0.423$, $P < 0.001$), UA ($r = 0.406$, $P < 0.001$), ALT ($r = 0.341$, $P = 0.001$), AST ($r = 0.338$, $P = 0.001$), γGT ($r = 0.316$, $P = 0.002$), TG ($r = 0.290$, $P =$

0.005), SBP (r = 0.302, P = 0.004), DBP (r = 0.336, P = 0.001), and were negatively correlated with HDL (r = -0.288, P = 0.005). Whereas, FGL-1 levels were not related to age, gender, TC, LDL, Cr, BUN (for all, $P > 0.05$).

Changes in serum FGL-1 levels and Metabolic Factors at 6 months after LSG

At 6 months postoperatively, significant improvements in BMI, liver function and UA were observed. As shown in Figure. 2 and Table 2, BMI declined significantly from 39.84 ± 6.10 kg/m^2 to 28.42 ± 5.01 kg/m^2, ALT decreased significantly from 67.27 ± 60.71 U/L to 13.62 ± 8.92 U/L, AST reduced significantly from 40.51 ± 33.47 U/L to 14.47 ± 3.74 U/L and UA changed significantly from 416.14 ± 95.81 μmol/L to 362.91 ± 89.55 μmol/L. Besides, γGT, TC, TG, LDL, FPG, FINS, HOMA-IR, HbA1c levels decreased and HDL levels increased significantly at 6 months after LSG (for all, $P < 0.05$). For patient with obesity (Figure. 2), FGL-1 levels decreased after LSG (from 44.66 ± 20.03 ng/mL to 27.53 ± 11.45 ng/mL, $P < 0.001$).

Associations between change in FGL-1 level and changes in metabolic markers after LSG

To further explore the association between decreased FGL-1 level and metabolic factors, linear regression analysis was performed after adjusting for possible confounders (gender, BMI, TG, HbA1c and SBP). As shown in Table 3, decreased FGL-1 levels were significantly associated with change in ALT (P = 0.037), AST (P = 0.047) and UA (P = 0.047) at 6 months after LSG. Otherwise, changes of FGL-1 levels had no correlation with changes of BMI, HbA1c, HOMA-IR, FPG, FINS, γGT, TC, TG, HDL and LDL (for all, $P > 0.05$).

Discussion

The global prevalence of NAFLD has been increasing over the past two decades, parallel to the rising prevalence of obesity [22]. Previous studies have shown liver regulates energy homeostasis through hepatokine secretion [23]. Moreover, hepatokine secretion is generally improved after bariatric surgery, which might drive the long-term metabolic improvements following bariatric surgery [24]. Recently, studies found that plasma FGL-1 levels are associated with obesity [25]. However, the role of FGL-1 in patients with obesity who undergo LSG remains obscure, and purpose of the present study is to investigate the changes of FGL-1 after LSG, and whether it is correlated with other metabolic indices.

In the present study, patients with obesity have higher levels of FGL-1 than individuals with normal weight. In addition, linear regression analysis showed that FGL-1 levels were positively correlated with BMI, SBP, DBP, ALT, AST, γGT, TG, FPG, FINS, HOMA-IR, UA, and were negatively correlated with HDL. These results are consistent with previous cross-sectional studies that FGL-1 is associated with body weight, blood pressure, lipid metabolism, insulin resistance and uric acid [25, 26]. One of the

mechanisms behind this may be that FGL-1 induces hepatic lipid accumulation by activating ERK1/2 pathway [15]. Moreover, FGL-1 promotes adipogenesis through an ERK1/2-C/EBPβ-dependent pathway [18]. In addition, increased FGL-1 expression induces insulin resistance through an EGFR/JNK mediated pathway [19]. Since FGL-1 is not only associated with obesity, but also with other obesity-related indicators. Thus, it is interesting to explore the changes of FGL-1 after LSG and the clinical indicators related to the changes.

With the decrease in body weight, FGL-1 levels significantly decreased at 6 months after LSG. Our study is the first to show a significant reduction in elevated levels of FGL-1 after weight loss, which suggested LSG can reduce FGL-1 levels. In previous studies, Wu *et al.* indicated that deletion of FGL-1 decreased oleic acid-induced lipid accumulation in HepG2 cells and knockdown of FGL-1 in adipose tissue of mice decreased adipose hypertrophy [15, 18], which suggested reduced FGL-1 after LSG may be related to the reduction of lipid accumulation and adipose hypertrophy. However, the changes in FGL-1 were not associated with the changes in BMI (r = -0.035, p = 0.791, data not shown). The same result as ours, Lim *et al.* found bariatric surgery might alter hepatokines levels independent of weight loss [9].

After adjusting for possible confounders, the changes in FGL-1 are associated with the improvement of ALT and AST levels, which was supported by the previous clinical studies showing that changes in hepatokines levels were related to improvement of hepatic metabolism after bariatric surgery [9]. Moreover, in previous experiments with rats, compared with the SHAM surgery group, the expression of FGF-21 mRNA in the liver of the bariatric surgery group was lower, suggesting that the expression of the hepatokine in the liver was changed and the liver metabolic functions were improved after bariatric surgery [27]. To our knowledge, FGL-1 is known to regulate hepatocyte proliferation and is expressed mainly in the liver [28, 29]. Meanwhile, it has been reported that plasma FGL-1 concentrations increased significantly in hyperglycemic crisis patients and decreased significantly after treatment with improved liver function [30]. Since circulating ALT and AST can be associated with the progression of chronic liver disease [31], postoperative improvement of FGL-1 levels is closely related to liver function. Besides, many studies have shown that NAFLD can be improved after bariatric surgery, but there was no correlation could be detected between the improvement of NAFLD and weight loss [32]. There seems to be some mechanism for improving liver function independent of weight loss that needs to be explored in future studies.

Meanwhile, the changes in FGL-1 are associated with the improvement of UA levels after adjusting for possible confounders. Additionally, another study found that with increasing FGL-1 tertiles, patients had higher UA levels [26]. UA is produced in the liver, adipose tissue and muscle [33]. After excessive consumption of fructose and sucrose, the liver will decrease the peripheral availability of anabolic factors such as hormones and amino acids, and produce catabolic effectors such as hepatokines and UA [34]. On the other hand, Xie et al. found UA induces hepatic fat accumulation via the ROS/JNK/AP-1 pathway [35]. Therefore, UA is closely related to liver metabolism which may explain the association between UA and FGL-1. However, the causal relationship between UA and FGL-1 needs to be further verified by experiments.

Our study is the first study to follow up on the change in FGL-1 levels before and after bariatric surgery, and our results showed losing weight can significantly reduce FGL-1 levels. Besides, these results demonstrated LSG can reduce FGL-1 levels which may be involved in the mechanism of improving liver function and uric acid metabolism, but not body weight and glucolipid metabolism. However, this study has several limitations. Firstly, our study lacked the results of detecting NAFLD. Secondly, this was a single-center retrospective study only included Chinese individuals and has a relatively small sample size. Finally, there was a short follow-up duration of this study. Therefore, future research is needed to use a larger sample size and longer follow-up duration to verify the results of this study.

Conclusion

In this study, serum FGL-1 levels were higher in patients with obesity. Moreover, FGL-1 levels significantly decreased at 6 months after LSG, and correlated with the changes of ALT, AST and UA levels. Therefore, postoperative improvement of FGL-1 levels might relate to the improvement of liver function and uric acid metabolism.

Abbreviations

BMI: body mass index; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; HbA1c: glycosylated hemoglobin A1; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; γGT: γ-glutamyl transpeptidase; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; UA: uric acid; Cr: creatinine; BUN: blood urea nitrogen; FGL-1: fibrinogen-like Protein 1.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants. This study was approved by the Ethical Committee of the Shanghai Tenth People's Hospital (Registration number: ChiCTR-OCS-12002381).

Consent for publication

Not applicable.

Availability of data and material

The datasets of the current study are available from the author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

This study was supported by the National Key R&D Program of China (2018YFC1314100), Clinical Research Plan of SHDC (No. SHDC2020CR1017B), the Natural Science Foundation of China (81970677), and the Shanghai Committee of Science and Technology, China (18411951803, 17AZ1910603).

Authors' contributions

Conceived and designed of the study: SQ and MZ. Acquisition, statistical analysis, or interpretation of the data: DD, MC, and YZ. Evaluation and implementation of LSG surgery: LD, DZ, and JZ. Follow-up of surgical patients: LS and XH. Checking and interpretation of the data, drafting of the manuscript, and approved the submitted version of the manuscript: all authors.

Acknowledgements

We appreciate all participants in this study.

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Tables

Table 1

Baseline characteristics of the study

Items	Normal weight (n = 32)	Obesity (n = 60)	*P* value
Age (years)	31.31 ± 5.05	32.18 ± 12.42	0.636
Gender (male %)	31.25%	26.67%	0.642
BMI (kg/m^2)	20.75 ± 1.73	39.84 ± 6.10	<0.001
FPG (mmol/L)	4.73 ± 0.53	6.61 ± 2.25	<0.001
FINS (mU/L)	4.58 ± 2.50	30.12 ± 14.70	<0.001
HOMA-IR	1.00 ± 0.61	8.56 ± 4.11	<0.001
SBP (mmHg)	112.66 ± 11.68	137.31 ± 18.62	<0.001
DBP (mmHg)	70.91 ± 8.23	82.83 ± 11.30	<0.001
ALT (U/L)	18.16 ± 9.83	67.27 ± 60.71	<0.001
AST (U/L)	16.38 ± 3.27	40.51 ± 33.47	<0.001
γGT (U/L)	22.74 ± 8.98	44.29 ± 32.91	<0.001
TC (mmol/L)	4.34 ± 0.55	4.60 ± 0.79	0.073
TG (mmol/L)	0.83 ± 0.30	1.86 ± 1.20	<0.001
HDL (mmol/L)	1.61 ± 0.32	1.09 ± 0.40	<0.001
LDL (mmol/L)	2.56 ± 0.55	2.78 ± 0.76	0.152
UA (μmol/L)	305.53 ± 67.13	416.14 ± 95.81	<0.001
Cr (μmol/L)	63.72 ± 7.71	61.29 ± 10.63	0.219
BUN (mmol/L)	4.61 ± 1.16	4.78 ± 1.34	0.546
FGL-1 (ng/mL)	20.73 ± 9.73	44.66 ± 20.03	<0.001

Data are presented as mean ± SD or number (percentage).

BMI: body mass index, FPG: fasting plasma glucose, FINS: fasting insulin, HOMA-IR: homeostasis model assessment of insulin resistance, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: alanine aminotransferase, AST: aspartate aminotransferase, γGT: γ-glutamyl transpeptidase, TC: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, UA: uric acid, Cr: creatinine, BUN: blood urea nitrogen, FGL-1: fibrinogen-like Protein 1.

Table 2

Changes in metabolic markers after LSG

	Pre-surgery	Post-surgery	*P*
	(n = 60)	(n = 60)	
BMI (kg/m^2)	39.84 ± 6.10	28.42 ± 5.01	<0.001
ALT (U/L)	67.27 ± 60.71	13.62 ± 8.92	<0.001
AST (U/L)	40.51 ± 33.47	14.47 ± 3.74	<0.001
γGT (U/L)	44.29 ± 32.91	13.19 ± 9.04	<0.001
TC (mmol/L)	4.60 ± 0.79	4.17 ± 0.80	0.001
TG (mmol/L)	1.86 ± 1.20	0.96 ± 0.48	<0.001
HDL (mmol/L)	1.09 ± 0.40	1.20 ± 0.32	<0.001
LDL (mmol/L)	2.78 ± 0.76	2.46 ± 0.71	0.006
FPG (mmol/L)	6.61 ± 2.25	4.67 ± 0.78	<0.001
FINS (mU/L)	30.12 ± 14.70	8.33 ± 3.93	<0.001
HOMA-IR	8.56 ± 4.11	1.75 ± 0.89	<0.001
HbA1c (%)	6.66 ± 1.89	5.46 ± 0.55	<0.001
UA (μmol/L)	416.14 ± 95.81	362.91 ± 89.55	<0.001
Cr (μmol/L)	61.29 ± 10.63	61.45 ± 9.38	0.660
BUN (mmol/L)	4.78 ± 1.34	4.79 ± 1.24	0.738
FGL-1 (ng/mL)	44.66 ± 20.03	27.53 ± 11.45	<0.001

Data are presented as mean ± SD.

BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, γGT: γ-glutamyl transpeptidase, TC: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, FPG: fasting plasma glucose, FINS: fasting insulin, HOMA-IR: homeostasis model assessment of insulin resistance, HbA1c: glycosylated hemoglobin A1, UA: uric acid, Cr: creatinine, BUN: blood urea nitrogen, FGL-1: fibrinogen-like Protein 1.

Table 3

Associations between change in FGL-1 level and changes in metabolic markers after LSG, after adjusting for possible confounders (gender, BMI, TG, HbA1c and SBP)

	ΔFGL-1		
	β	R^2	*P* value
ΔBMI	-0.038	0.021	0.836
ΔALT	0.324	0.105	0.037
ΔAST	0.323	0.106	0.047
ΔγGT	0.005	0.035	0.977
ΔTC	-0.037	0.022	0.821
ΔTG	0.072	0.021	0.849
ΔHDL	-0.013	0.021	0.933
ΔLDL	-0.177	0.045	0.273
ΔFPB	-0.031	0.021	0.857
ΔFINS	0.017	0.014	0.916
ΔHOMA-IR	0.019	0.014	0.899
ΔHbA1c (%)	0.017	0.013	0.972
ΔUA	0.287	0.097	0.047
ΔCr	0.241	0.065	0.123
ΔBUN	-0.049	0.018	0.750

FGL-1: fibrinogen-like Protein 1, BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, γGT: γ-glutamyl transpeptidase, TC: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, FPG: fasting plasma glucose, FINS: fasting insulin, HOMA-IR: homeostasis model assessment of insulin resistance, HbA1c: glycosylated hemoglobin A1, UA: uric acid, Cr: creatinine, BUN: blood urea nitrogen.

Figures

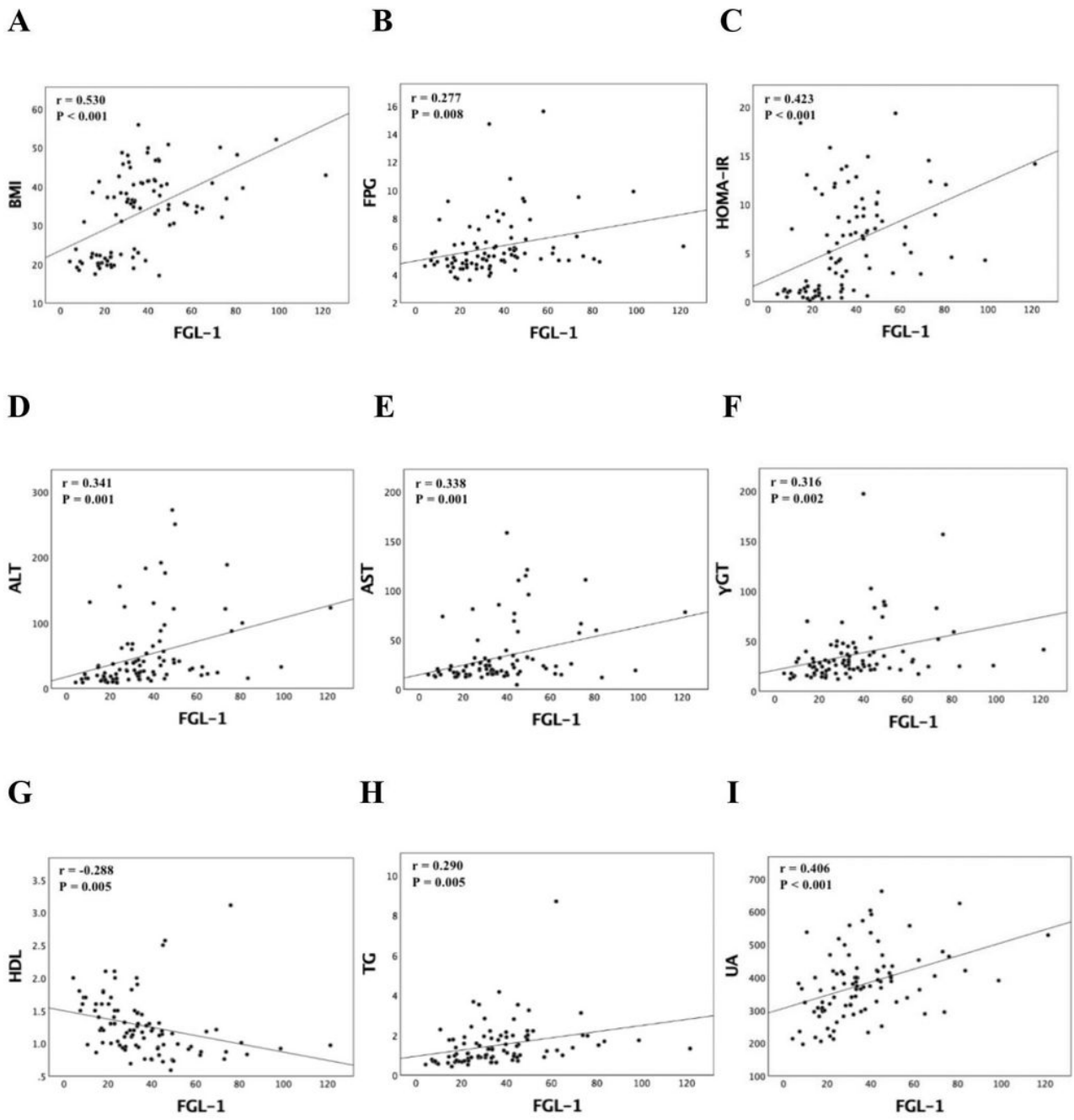

Figure 1

Correlation between FGL-1 and metabolic factors. Changes in FGL-1 were positively associated with changes in BMI (A), FPG (B), HOMA-IR (C), ALT (D), AST (E), γGT (F), TG (H) and UA (I); It was also negatively correlated with HDL (G).

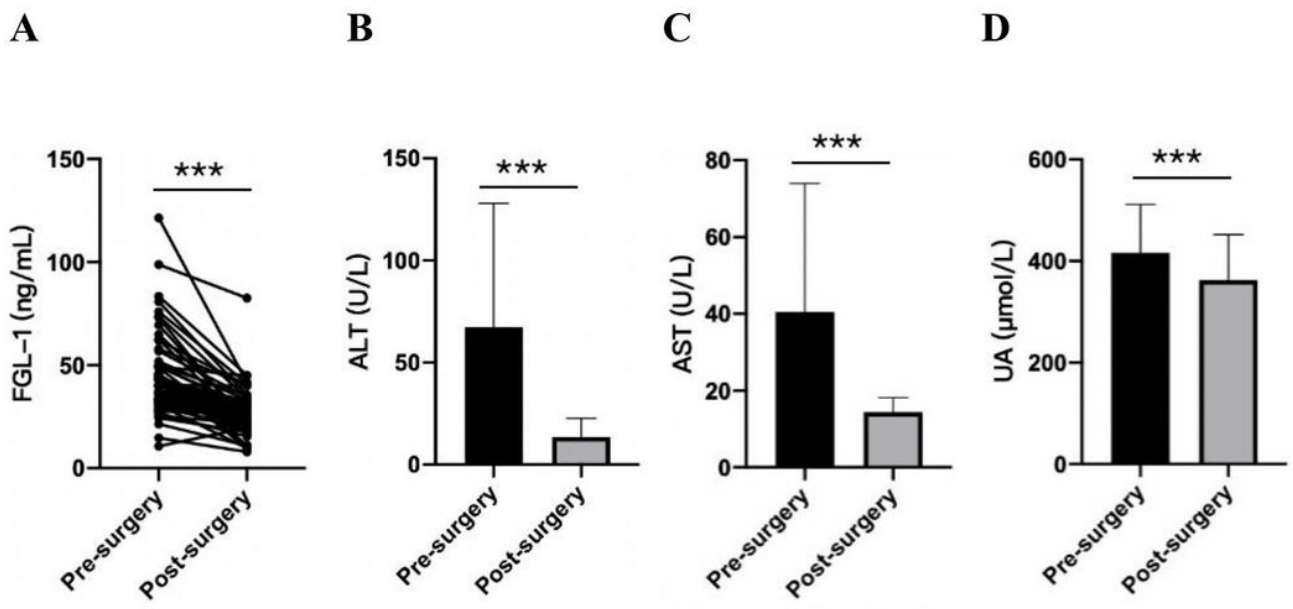

Figure 2

Change in FGL-1 (A), ALT (B), AST (C) and UA (D) levels at 6 months after LSG. Data are presented as mean. Error bars are SD. ***P < 0.001