Decreased Serum Growth Differentiation Factor 15 Levels After Lifestyle Intervention in Patients With Newly Diagnosed Type 2 Diabetes Mellitus

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Research

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Abstract

Background: Recent studies noted that circulating growth differentiation factor 15 (GDF15) were closely related to metabolic states. The study aimed to explore the changes of GDF15 levels and their influencing factors after 4 weeks of lifestyle intervention (LI) or LI combined with breakfast meal replacement (LI+MR) in newly diagnosed type 2 diabetes patients.

Methods: A total of 84 patients with available serum samples at both baseline and Week 4 were enrolled in this biomarker substudy. All subjects underwent a 2-hour 75g oral glucose tolerance test at baseline and Week 4. Serum GDF15 levels were determined by a sandwich enzyme-linked immunosorbent assay.

Results: After 4-weeks of LI, GDF15 levels overall significantly decreased compared with baseline ($P<0.05$). ΔGDF15 levels were significantly and negatively associated with baseline GDF15 levels ($r=-0.450$, $P<0.001$). The optimal cut-off point of baseline GDF15 levels for predicting a GDF15 decrease after 4-weeks of LI was 904.57 pg/ml, with an area under curve of 0.699. Based on the cut-off point of 900 pg/ml, patients with baseline GDF15 ≥900 pg/ml had significantly decreased GDF15 levels after LI, while those <900 pg/ml had no significant changes. Regression models showed that baseline GDF15 level was an independent positive factor for the improvement of fasting plasma glucose and homeostasis model assessment for insulin resistance only in patients with baseline GDF15 levels ≥900 pg/ml.

Conclusions: LI led to significantly decreased GDF15 levels among patients with newly diagnosed type 2 diabetes and its effect was more significant among patients with baseline GDF15 levels ≥900 pg/ml.

Trial registration: ClinicalTrials.gov, NCT02248714. Registered 25 September 2014 - Retrospectively registered, https://www.clinicaltrials.gov/ct2/show/NCT02248714?term=NCT02248714&draw=2&rank=1

Background

Growth differentiation factor 15 (GDF15), an inflammatory and stress responsive cytokine and also a member of the transforming growth factor-β cytokine superfamily [1], is considered as a promising new cardiovascular biomarker [2–6]. Recent studies revealed that circulating GDF15 levels increased markedly in the obese state, and further elevated when combined with type 2 diabetes mellitus (T2DM) [7, 8]. Cross-sectional studies showed that circulating GDF15 levels were significantly and positively correlated to insulin resistance [9, 10]. However, circulating GDF15 levels further increased when insulin resistance was significantly improved in the prospective studies of obese/T2DM patients after bariatric surgeries [8, 11, 12]. It is not clear whether high GDF15 levels indicate metabolic disorder or metabolic improvement.

Insulin resistance and β-cell dysfunction are the main pathophysiological mechanisms for the incidence and development of T2DM [13]. As the most basic part of diabetes treatment, lifestyle intervention (LI) is employed throughout the whole process of diabetes management [14]. Previous studies have shown that LI can help improve insulin resistance, increase the sensitivity of tissues to insulin, and prevent or delay the progression of β-cell dysfunction, that is, the progression of T2DM [15–17]. However, there are few

studies focusing on the effect of LI on circulating GDF15 levels in T2DM patients. Therefore, the present study aimed to explore the changes of serum GDF15 levels and their influencing factors after 4 weeks of LI or LI combined with breakfast meal replacement (LI + MR) in patients with newly diagnosed T2DM.

Methods

Study population

The present study is a substudy of a previously published randomized clinical trial [18]. Briefly, subjects were recruited from the outpatient clinic at the Department of Endocrinology of Shanghai Jiao Tong University Affiliated Sixth People's Hospital from March 2011 to March 2018. All subjects had never been diagnosed with diabetes, without diet control or drug intervention that affected glucose metabolism. The inclusion criteria were patients with newly diagnosed and untreated T2DM, body mass index (BMI) ≥ 18.5 kg/m^2, and glycated haemoglobin A_{1c} (HbA_{1c}) ≥ 6.5%. The exclusion criteria were described previously [18]. Subjects were randomly divided into a LI group or a LI+MR group in a 1:1 ratio according to the random number table, and had a followed up for 4 weeks. Both groups received lifestyle education delivered by an experienced nutritionist. Participants in the LI + MR group were instructed to an additional replace breakfast with Glucerna SR (Abbot Nutrition). The composition of Glucerna SR powder was described in our previous study [18]. There was no difference in nutritional content and energy between the two groups at lunch and dinner. All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and complied with the principles of the Helsinki Declaration. This study was registered at ClinicalTrials.gov, number NCT02248714.

In this biomarker substudy, we included 84 patients (42 in the LI group and 42 in the LI+MR group) who had available serum samples for GDF15 measurements at both baseline and Week 4.

Anthropometric and biochemical assessments

As described previously [18], all subjects underwent anthropometric and biochemical assessments at baseline and Week 4 after LI. Anthropometric measurements included height, weight, and blood pressure. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Fat mass (FM) and fat free mass (FFM) were determined by an automatic bioelectrical impedance analyzer (BC-420; Tanita Corp., Tokyo, Japan).

All subjects underwent a 2-hour 75g oral glucose tolerance test (OGTT) at baseline and at Week 4. Fasting venous blood samples were collected in the morning after an overnight fasting, and 2-hour venous blood samples were collected approximately 2 h after OGTT. Fasting plasma glucose (FPG), fasting insulin (FINS), HbA_{1c}, serum lipid profiles [including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c)], 2-hour postload plasma glucose (2hPG), 2-hour postload insulin (2hINS) were assessed as previously described [18]. The assessments of basal insulin sensitivity and β-cell dysfunction were the same as in the previous study

[18]: homeostasis model assessment for insulin resistance (HOMA-IR) = FINS (in mU/L) · FPG (in mmol/L)/22.5, and homeostasis model assessment for β-cell dysfunction (HOMA-β) = 20 · FINS [in mU/L]/(FPG [in mmol/L] – 3.5).

A sandwich enzyme-linked immunosorbent assay was used to measure serum GDF15 levels (R & D Systems, Inc. Minneapolis, USA), with inter and intra- assay coefficients of variation of 5.77–9.24% and 0.46–4.08%, respectively.

Statistical analysis

The determination of sample size was performed, as described previously [18]. Data analyses were performed by SPSS version 22.0. All variables were tested for normality. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with the interquartile range. The differences of clinical parameters between baseline and the study end were indicated by Δ. Unpaired Student's t test and Wilcoxon rank sum test were used to compare differences in normally and non-normally distributed variables. Paired Student's t test and Wilcoxon rank sum test were used to compare differences before (baseline) and after (Week 4) intervention. Spearman correlation was used to analyze the correlation between baseline GDF15 levels and other clinical variables. The receiver operating characteristic (ROC) curve was generated to analyze the optimal cut-off point of baseline GDF15 levels for predicting whether GDF15 would decrease after 4 weeks of LI. The multiple linear regressions were conducted to explore the association between baseline GDF15 levels and the changes of clinical parameters. All *P* values were tested bilaterally, and $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study participants

A total of 84 patients including 42 in the LI group and 42 in the LI+MR group were included in this study, with a median age of 59 (50–64) years and an average BMI of 24.99 ± 3.08 kg/m^2. The values of body weight, BMI, systolic pressure (SBP), diastolic pressure (DBP), FPG, 2hPG, HbA_{1c}, FINS, FM, fat%, TC, TG, and HOMA-IR were significantly decreased from baseline to the end of study (Week 4) in the total population (Table 1). There were no significant differences in all baseline clinical variables between the LI group and the LI+MR group (all $P>0.05$). Moreover, all changes of clinical variables had no significant differences between the LI group and the LI+MR group.

The changes of serum GDF15 levels and their relationship with baseline GDF15 levels

GDF15 levels at both baseline and Week 4 had no significant differences between the LI group and the LI+MR group (both $P>0.05$). After intervention, both LI group and LI+MR group had significantly decreased in GDF15 levels (both $P<0.05$), however, the changes of GDF15 levels had no significant differences between two groups ($P>0.05$). Therefore, we carried out the analysis in the total population.

In total population, serum GDF15 levels had significant decreased from baseline to Week 4 (P<0.001), which was 937.12 ± 334.25 pg/ml at baseline and 797.25 ± 293.21 pg/ml at the end of the study, respectively.

Correlation analysis showed that ΔGDF15 levels were significantly and inversely associated with the baseline GDF15 levels (r=−0.450, P<0.001) (Fig. 2). We further made an ROC curve and found that the optimal cut-off point of baseline GDF15 levels for predicting a GDF15 decrease after 4 weeks of LI was 904.57 pg/ml, with sensitivity of 62.26%, specificity of 74.19%, and area under curve of 0.699 (Fig. 3).

Based on this cut-off point of 900 pg/ml, we divided the total population into two groups: patients with baseline GDF15 levels <900 pg/ml, and those with baseline GDF15 levels ≥900 pg/ml. The results showed that there was no significant change in GDF15 levels after intervention in patients with baseline GDF15 levels <900 pg/ml (P=0.252), while those with baseline GDF15 levels ≥900 pg/ml had a significant decrease in GDF15 levels after intervention (P<0.001) (Fig. 4-A). The distributions of ΔGDF15 levels of the two groups were shown in Fig. 4-B. The proportions of patients who had a significant decrease in GDF15 levels after 4-week LI were significantly higher in the baseline GDF15 levels ≥900 pg/ml group than in the baseline GDF15 levels <900 pg/ml group (P=0.017).

Associations of the changes of clinical parameters with baseline GDF15 levels

To further explore whether the changes of clinical parameters were also associated with baseline GDF15 levels, we compared the changes of clinical parameters between the baseline GDF15 levels <900 pg/ml group and ≥900 pg/ml group. Results showed no significant difference in the changes of clinical parameters between the two groups (all P>0.05). A multivariate linear regression analysis was conducted in patients with baseline GDF15 levels <900 pg/ml and ≥900 pg/ml, with the changes of clinical parameters as dependent variables, respectively. After adjusting for age, gender, and BMI, the regression analysis showed that the baseline GDF15 level was an independent negative factor for ΔFPG (standardized =−0.346, P=0.026) and ΔHOMA-IR (standardized =−0.304, P=0.044) among those with baseline GDF15 levels ≥900 pg/ml only.

Discussion

The present study firstly discussed the effect of LI on changes in serum GDF15 levels among patients with newly diagnosed type 2 diabetes patients. After 4 weeks of LI, most metabolic parameters including body weight, blood glucose, and HOMA-IR were significantly improved, and serum GDF15 levels significantly decreased compared with baseline levels. We also found that the decrease in GDF15 levels after the 4-week LI was related to baseline GDF15 levels. Patients with baseline GDF15 levels ≥ 900 pg/ml had a significant decrease in GDF15 levels after the 4-week LI, while those with baseline GDF15 levels < 900 pg/ml had no significant changes in GDF15 levels after LI. Only in patients with baseline GDF15 levels ≥ 900 pg/ml, a high baseline GDF15 level was an independent positive factor for the improvement of FPG and HOMA-IR.

In recent years, a number of studies have noted that circulating GDF15 was a regulator of energy homeostasis, and was closely related to metabolic states [19–21]. LI has been recommended as one major part of diabetes management. However, very few studies have assessed the effect of LI on changes in circulating GDF15 levels among patients with diabetes. Previous studies have explored the changes of circulating GDF15 levels in T2DM patients with diet intervention, drug intervention or bariatric surgeries, however, the sample sizes were relatively small and the results were not consistent. Several studies [8, 11, 12] found that the GDF15 levels of obese/T2DM patients ($n < 50$) significantly increased after the bariatric surgery compared with levels before the bariatric surgery (< 500 pg/ml). Two studies [22, 23] indicated that a 2-week very low calorie diet ($n = 14$) or a 6-week high-protein diet ($n = 37$) did not change the GDF15 levels (> 1000 pg/ml) among patients with T2DM patients. Another study in 41 T2DM patients with an additional gliptin therapy if HbA_{1c} goals were not reached under metformin monotherapy, demonstrated that GDF15 levels significantly decreased from baseline (1630 ± 180.52 pg/ml) to Month 6 [24]. In the present study with 84 newly diagnosed T2DM patients, serum levels of GDF15 overall decreased after 4 weeks of LI. However, only patients with baseline GDF15 levels ≥ 900 pg/ml but not those with baseline GDF15 levels < 900 pg/ml had a significant decrease in GDF15 levels after a 4-week LI. The results indicated that decreased GDF15 levels after LI might relate to the baseline GDF15 levels.

To further analyze the consistence of the studies, we compared the results of the present study with the results of previous intervention studies. Interestingly, in some previous studies patients with baseline GDF15 levels below 900 pg/ml had their GDF15 levels significantly increased after intervention [8, 11, 12], while in other studies patients with baseline GDF15 levels above 900 pg/ml had their GDF15 levels remained unchanged or significantly decreased after intervention [22–24]. Based on our and previous research results, we preliminarily speculated that in the process of metabolic improvement, the GDF15 levels either increased or remained unchanged when baseline GDF15 levels were < 900 pg/ml, and either decreased or remained unchanged when baseline GDF15 levels were ≥ 900 pg/ml.

In addition, the present study found similar metabolic changes between patients with baseline GDF15 levels < 900 pg/ml and ≥ 900 pg/ml after 4 weeks of LI. There were no significant difference in the changes of all clinical metabolic parameters between the two groups. The subgroup analysis only showed a positive correlation between baseline GDF15 levels and metabolic improvement in patients with baseline GDF15 levels ≥ 900 pg/ml. The baseline GDF15 level was an independent positive factor for the improvement of FPG and HOMA-IR only in patients with baseline GDF15 levels ≥ 900 pg/ml.

To our knowledge, this study was the first to report that decreased serum GDF15 levels after 4 weeks of LI were related to baseline GDF15 levels in newly diagnosed T2DM patients. We also firstly investigated the relationship between the improvement of clinical metabolic parameters and baseline GDF15 levels, and found that in patients with baseline GDF15 levels ≥ 900 pg/ml, better metabolic improvement could be obtained under the a 4-week LI. However, in the process of metabolic improvement, different change trends of circulating GDF15 levels were reported in different studies [8, 11, 12, 22–24]. At present, the

causal relationship and mechanisms between the change of GDF15 levels and the improvement of metabolism are still unclear, which need to be further explored.

There are some limitations in this study. First, the study is of short intervention duration, results may be confounded by factors not accounted for in the analysis. Second, the sample size of this study was relatively small, and the effect of LI on serum GDF15 levels and the influencing factors of changes in serum GDF15 levels still need to be verified in further prospective studies including long-duration T2DM patients and non-diabetic population.

Conclusions

The effect of LI on the decrease of GDF15 levels was associated with the baseline GDF15 levels among patients with newly diagnosed T2DM. In newly diagnosed T2DM patients with baseline GDF15 levels ≥ 900 pg/ml, serum GDF15 levels and other metabolic factors were improved after a 4-week LI.

Abbreviations

2hINS, 2-hour postload insulin; 2hPG, 2-hour postload plasma glucose; BMI, body mass index; DBP, diastolic pressure; FFM, fat free mass; FINS, fasting insulin; FM, fat mass; FPG, fasting plasma glucose; GDF15, growth differentiation factor 15; HbA_{1c}, glycated haemoglobin A_{1c}; HDL-c, high-density lipoprotein cholesterol; HOMA-β, homeostasis model assessment for β-cell dysfunction; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-c, low-density lipoprotein cholesterol; LI, lifestyle intervention; MR, meal replacement; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; SBP, systolic pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

Declarations

Ethics approval and consent to participate

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XM and JZ designed the study. XH, JS, and JL collected the data. XH and JS performed the statistical analysis and wrote the manuscript. YW performed serum GDF15 measurements. XM, JZ, GH, JY and YB revised the manuscript and contributed to the discussion. XH and JS contributed equally to this manuscript.

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Authors' information

Not applicable.

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Tables

Table 1 Characteristics of study participants at baseline and study end

Variables	Baseline		Study end		*P*
	Mean	SD	Mean	SD	
Gender (men/women)	44/40		/		
Age (y)	57	9	/		
Weight (kg)	68.96	10.83	67.64	10.84	< 0.001
BMI (kg/m^2)	24.99	3.08	24.51	3.06	< 0.001
SBP (mmHg)	132	14	125	14	< 0.001
DBP (mmHg)	80	10	78	10	0.022
FPG (mmol/L)	7.36	1.01	6.72	0.97	< 0.001
2hPG (mmol/L)	15.11	2.63	12.74	3.02	< 0.001
HbA_{1c} (%)	7.1	0.5	6.7	0.5	< 0.001
FINS (mU/L)	12.47	6.75	10.46	5.88	< 0.001
2hINS (mU/L)	86.36	43.29	79.20	42.25	0.119
FM (kg)	19.50	6.44	18.15	6.22	< 0.001
FFM (kg)	49.34	9.40	49.41	9.69	0.636
Fat %	28.30	7.67	26.91	7.90	< 0.001
TC (mmol/L)	5.16	0.87	4.98	0.87	0.018
TG (mmol/L)	1.68	0.89	1.40	0.61	< 0.001
HDL-c (mmol/L)	1.17	0.25	1.18	0.26	0.602
LDL-c (mmol/L)	3.24	0.73	3.12	0.77	0.056
HOMA-IR	4.18	2.59	3.29	2.36	< 0.001
HOMA-β	67.20	37.87	67.15	36.88	0.986

Data are expressed as mean ± SD or median (interquartile range);

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2hPG, 2-hour postload plasma glucose after 75g oral glucose tolerance test; HbA_{1c}, glycated hemoglobin A_{1c}; FINS, fasting insulin; 2hINS, 2-hour insulin after 75g oral glucose tolerance test; FM, fat mass; FFM, fat free mass; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-β, homeostasis model assessment for β cell function.

Figures

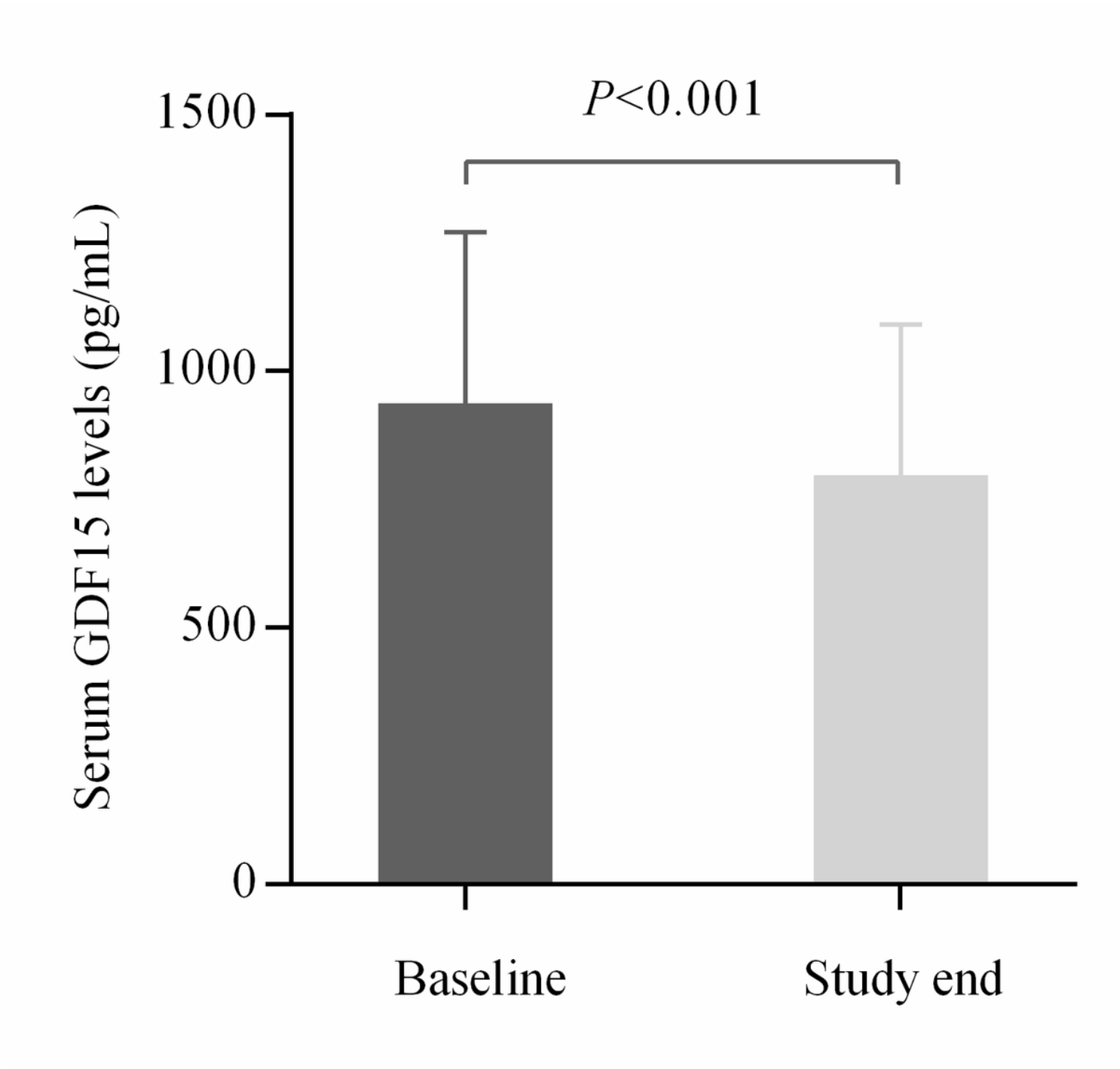

Figure 1

Comparisons of serum GDF15 levels at baseline and the study end in total population Abbreviation: GDF15, growth differentiation factor 15

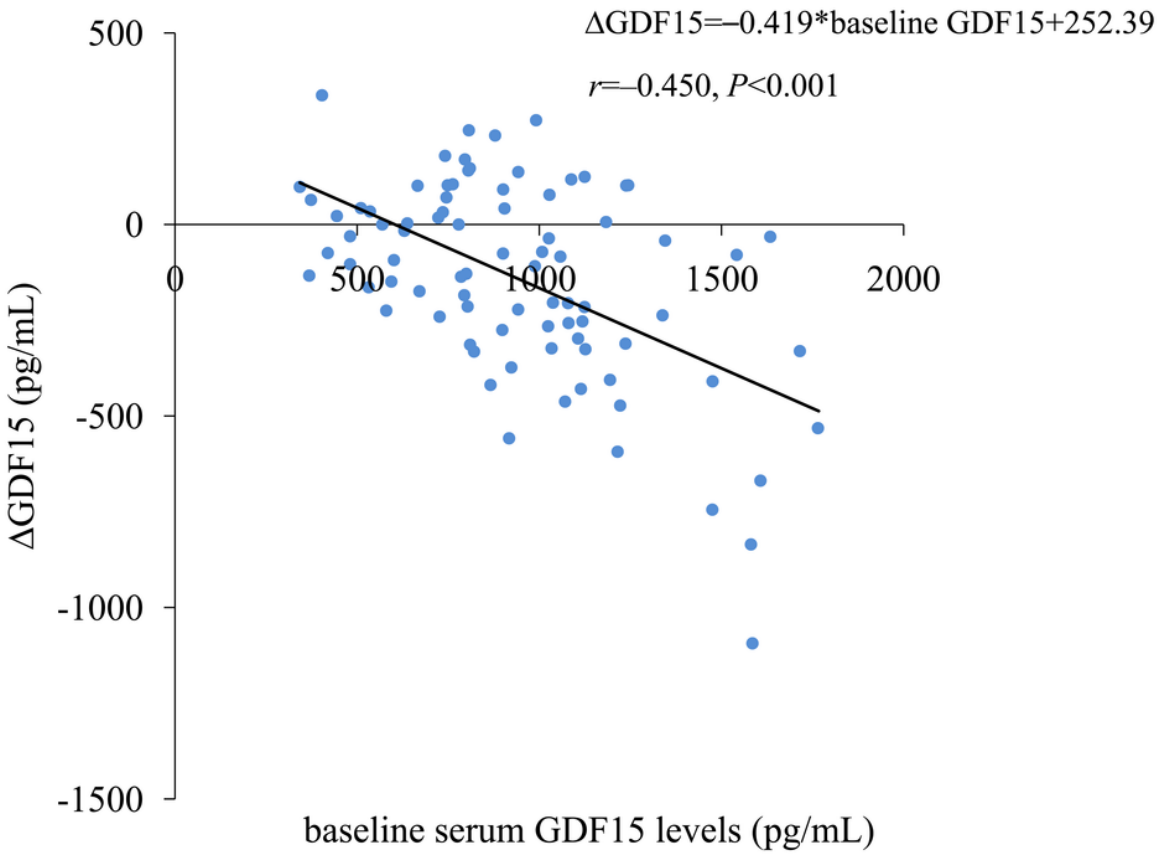

Figure 2

Correlation between the change of GDF15 (ΔGDF15, the differences at the study end and baseline) levels with baseline GDF15 levels Abbreviation: GDF15, growth differentiation factor 15; Δ, the differences between baseline and the study end

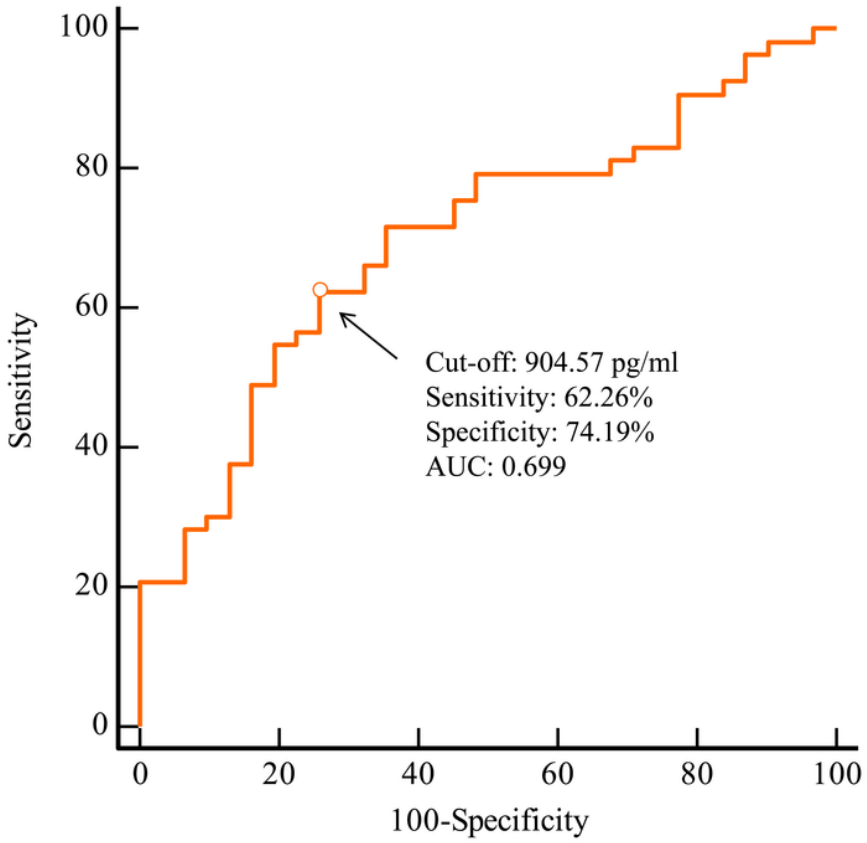

Figure 3

Receiver operating characteristic curve for baseline GDF15 levels to predict whether GDF15 would decrease after 4 weeks of LI Abbreviation: GDF15, growth differentiation factor 15; LI, lifestyle intervention

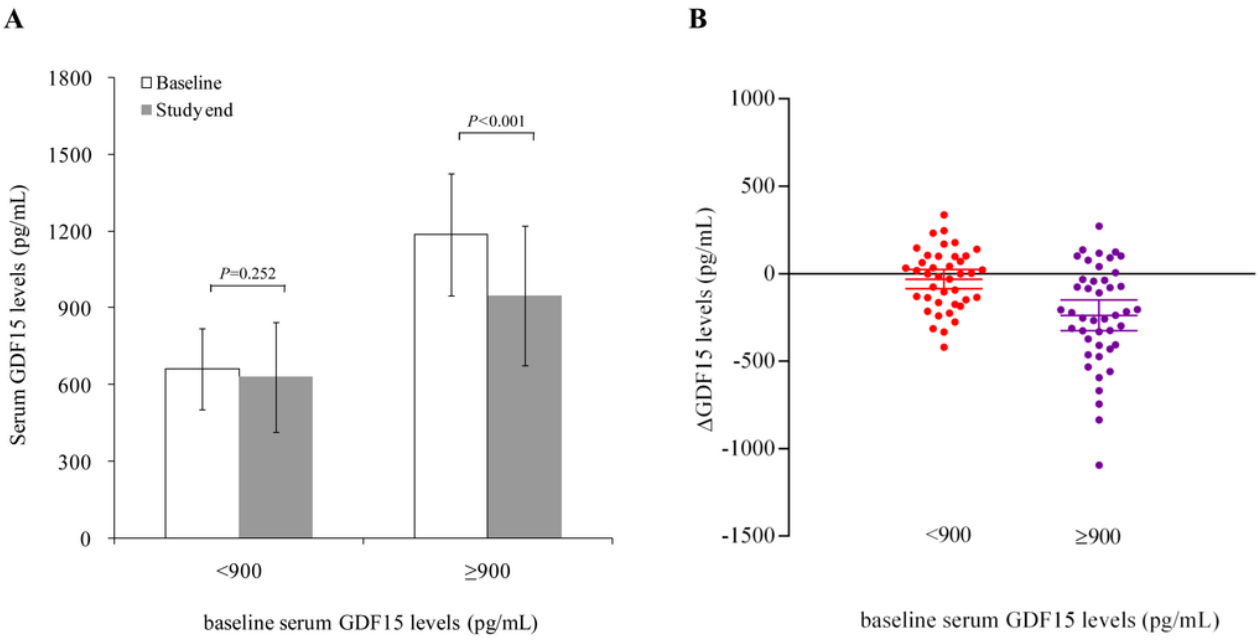

Figure 4

(A) Comparisons of serum GDF15 levels at baseline and the study end in patients with baseline GDF15 levels <900 pg/ml and ≥900 pg/ml; (B) The distribution of the change of GDF15 (ΔGDF15, the differences at the study end and baseline) levels in patients with baseline GDF15 levels <900 pg/ml and ≥900 pg/ml Abbreviation: GDF15, growth differentiation factor 15; Δ, the differences between baseline and the study end