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Effect of sleeve gastrectomy on plasma growth differentiation factor-15 (GDF15) in human

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ABSTRACT

Background: Sleeve gastrostomy (SG) induces significant weight loss primarily as a result of increased satiety and reduced food intake. Growth differentiation factor-15 (GDF15) is a satiety hormone which induces a dramatic reduction of food intake and body weight.
Objective: To assess the effect of sleeve gastrectomy on plasma GDF 15 level and the association with the weight loss and diabetes control after SG.
Method: We assessed plasma GDF15 level in 21 patients (15 with obesity and 6 with obesity and diabetes) before and then at 1, 3 and 12 months after SG.
Results: GDF15 was significantly increased at 1 month after SG compared to before surgery level *(301.9 ± 135.2 pg/ml vs 215.1 ± 119.9 pg/ml, respectively p<0.05)* and increased even further at 3 months *(338.86 ± 131.14 pg/ml, p<0.01)* and remain elevated at 12 months *(329.39 ± 152.1 pg/ml p<0.05)* after SG. At 3 months after surgery, the increased GDF15 level was correlated with the magnitude of BMI loss *($r^2 = 0.204$, p<0.05)*.
Conclusion: SG induces a significant increase in GDF15 level which is correlated with the magnitude of BMI loss.

Introduction

The continual increase in the global burden of obesity remains a problem of significant magnitude. Recently, bariatric surgery has proven to be a potent and safe option for achieving sustained weight loss and resolution of comorbidities in people with obesity.[1] Sleeve gastrectomy, one of the most commonly performed bariatric procedures, induces significant weight loss and diabetes remission.[2] Compared to Roux-en Y gastric bypass, the mechanism of sleeve gastrectomy remains relatively poorly understood. However, it is generally accepted that weight loss after SG is primarily a result of reduced food intake. Central to the reduced food intake after sleeve gastrostomy is the mechanical restriction caused by the resection of most of the stomach along the greater curvature. But, more evidence suggests that factors other than the mechanical restriction such as increased satiety are key to the reduced food intake leading to the decrease bodyweight after SG. A decreased ghrelin (an orexigenic hormone) and an increase in GIP and GLP-1 (anorexigenic hormones) after SG have also been indicated.[3]

Recently, Growth differentiation factor-15 (GDF15) a circulating protein also referred to as macrophage inhibitory cytokine-1 (Mic-1) which is a divergent member of the TGF-beta superfamily; implicated in multiple biological processes, including energy homeostasis, body weight regulation, and cachexia driven by cancer and chronic disease has been identified as a novel satiety hormone.[4,5]

A study by Johnen H. et al.[6] found that GDF15 significantly reduces food intake in rats. Subsequent studies showed GDF15 to be an anti-obesity and appetite suppressor.[7,8]

The overexpression of GDF15 in two independent transgenic models from birth exhibited lower body weight, fat mass, as well as enhanced glucose tolerance.[6,9] The overexpression of GDF15 also protected mice against obesity, hepatic steatosis, and impaired glucose tolerance.[10,11]

A receptor for GDF15 has been identified in the area postrema in

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Table 1
Study participants. Data are presented as means ± SD.

	NGT	T2D
Sex (F/M)	*6/9*	*2/4*
Age (Yr)	*29.3 ± 8.5*	*42.3 ± 10.3*
Weight (kg)	*129.7 ± 30.0*	*122.6 ± 36.9*
BMI (kg/m^2)	*43.9 ± 7.2*	*42.6 ± 7.5*
HbA1c (%)	*5.8 ± 0.47*	*9.1 ± 2.7*
Fasting Plasma Glucose (mmol/l)	*5.5 ± 0.9*	*11.3 ± 3.3*
Fasting Insulin (pmol/L)	*232.4 ± 111.1*	*196.2 ± 123.7*
No. on Metformin	*0*	*4*
No. on Insulin	*0*	*2*

NGT: Normal Glucose Tolerance. T2D: Type 2 Diabetes.

the hind brain which mediates the metabolic action with respect to bodyweight and food intake.[7,8,12]

Unlike the animal experiments, data from human studies remains inconclusive. On one hand, some studies have found increased level of GDF15 in patient with obesity and diabetes[13,14] while on the other hand, other studies have found increased level in patients with anorexia nervosa as well as patients with cancer experiencing cachexia-driven weight loss.[6,15]

A recent study by Frikke-S H. et al.[16] reported that the deletion of Gdf15 (GDF15-null mice) did not alter the food intake or bodyweight after sleeve gastrostomy in mice. The author therefore concluded that GDF15 was not necessary for the weight loss induced by bariatric surgery.

Interestingly, In contrast to the animal study, recent human studies suggested that GDF15 may be necessary for the weight loss induced by bariatric surgery.[17,18]

In this study we aim to assess the effect of sleeve gastrostomy on plasma GDF 15 level in patients with obesity and obesity plus diabetes, before and then at 1, 3 and 12 months after sleeve gastrostomy. We also sought to understand the relationship between the changes in GDF15 level and the weight-loss and diabetes outcomes after SG.

Method and material

This study was approved by the Ethics Committee of Xuzhou Medical University in accordance with the Helsinki-II declaration. Written informed consent was obtained from all participants.

A total of 21 patients with obesity (13 males: 61.9% and 8 female: 38.1%) including 6 (28.57%) with T2D, all ethnic Chinese undergoing laparoscopy SG between November 2017 to July 2018 in the department of gastrointestinal surgery at the affiliated hospital of Xuzhou medical university were recruited.

Inclusion and exclusion criteria of the studies

Adult (men and women), age 18–65; undergoing LSG between November 2017 to July 2018 in the department of gastrointestinal surgery at the affiliated hospital of Xuzhou medical university and willing and able to take part in a study requiring multiple visits and telephone interviews were enrolled prior to surgery.

Any condition that would exclude a patient from bariatric

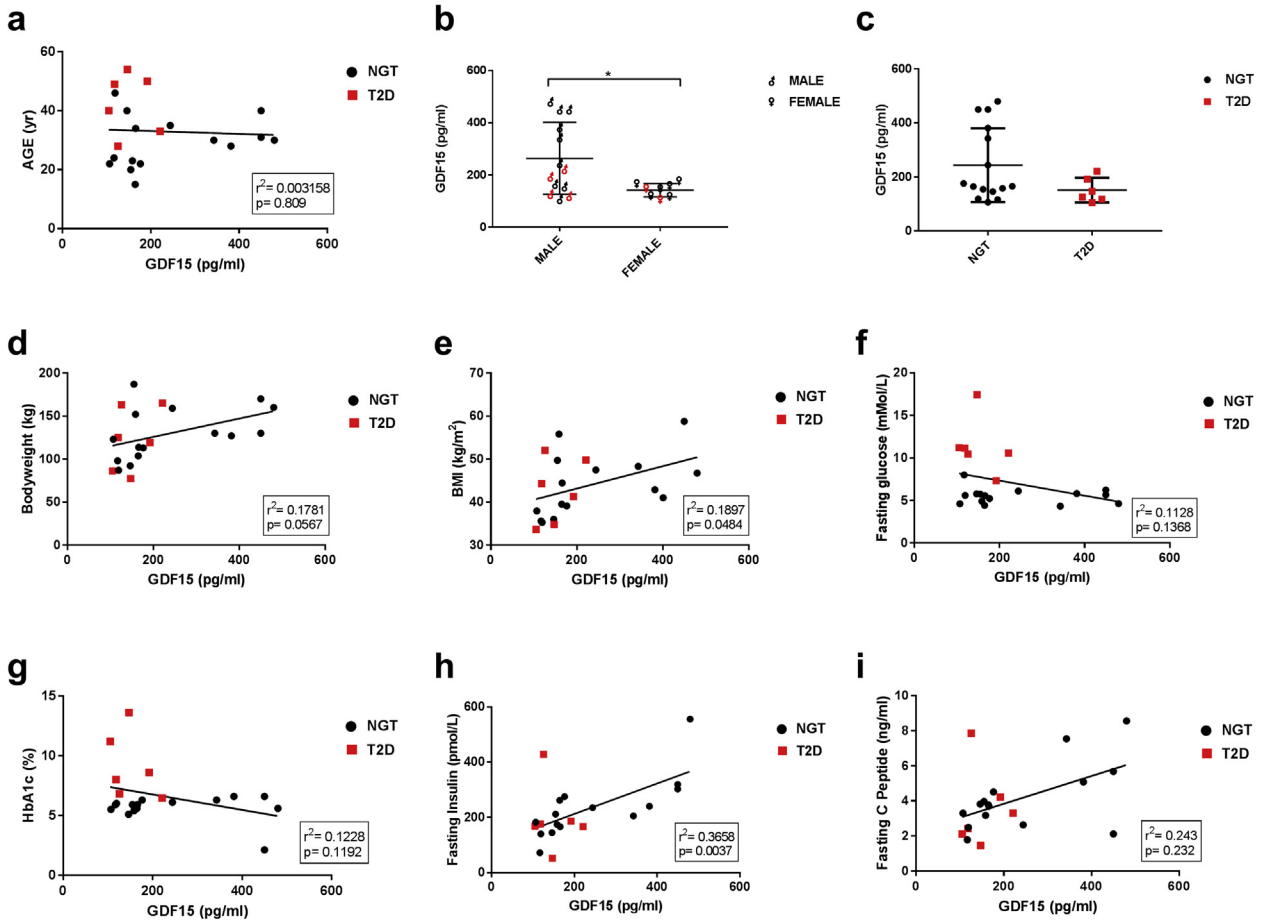

Fig. 1. ***Before surgery,*** Correlation of GDF15 with **a)** Age; **b)** sex; **c)** Glucose tolerance; **d)** Bodyweight; **e)** Body Mass Index (BMI); **f)** Fasting glucose; **g)** HbA1c; **h)** Fasting Insulin; **i)** Fasting C peptide. NGT: Normal glucose tolerance, T2D: Type 2 diabetes; *Significant ($p < 0.05$).

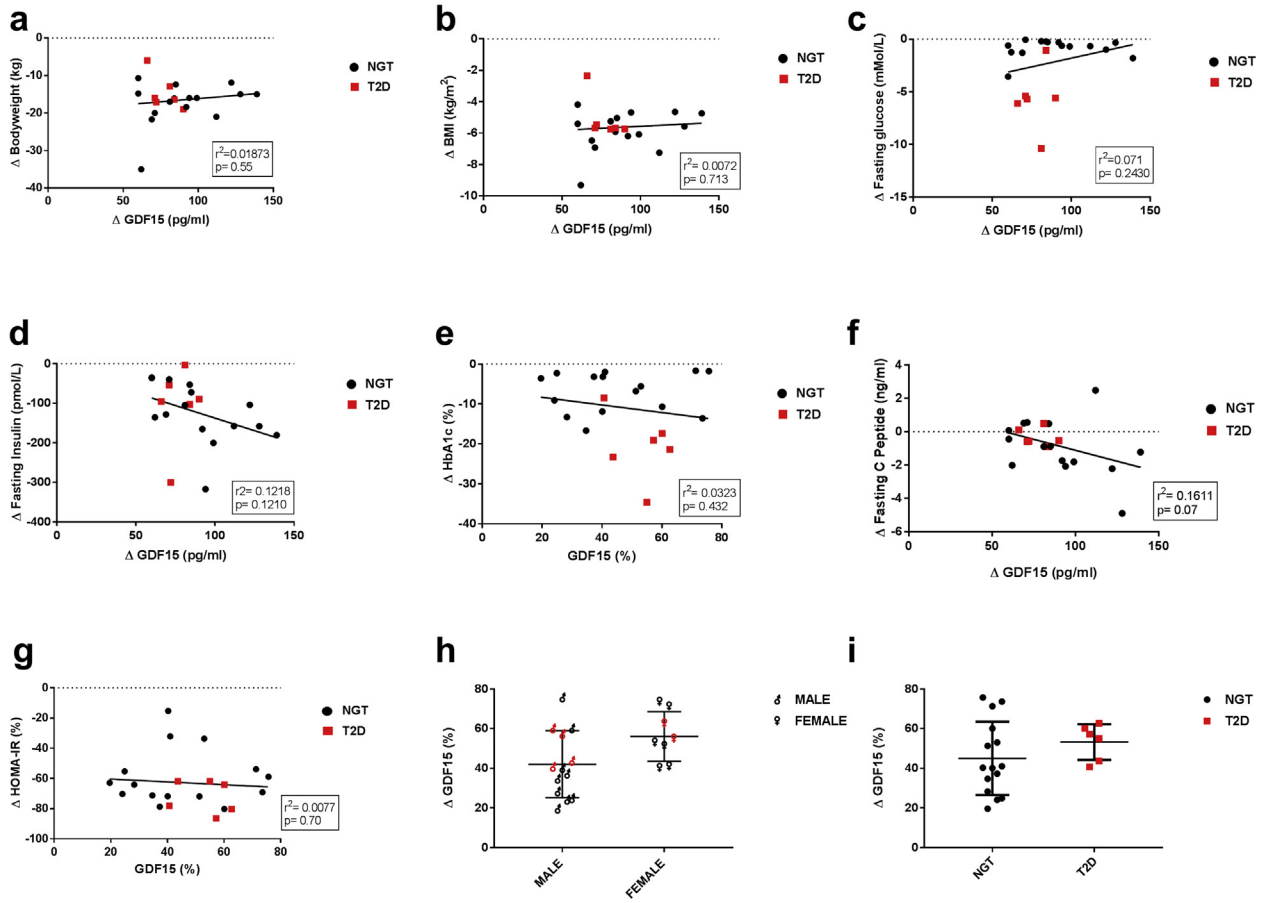

Fig. 2. ***One month after surgery***, Correlation of change in GDF15 with **a)** change in bodyweight; **b)** change in Body Mass Index (BMI); **c)** change in fasting glucose; **d)** change in fasting Insulin; **e)** change in HbA1c; **f)** change in fasting c peptide; **g)** change in HOMA-IR; **h)** Sex; **i)** glucose tolerance. **Δ**: change; NGT: Normal Glucose Tolerance, T2D: Type 2 diabetes.

surgery such as untreated major depression or psychosis, binge eating disorders, current drug and alcohol abuse, severe cardiac disease, severe coagulopathy, inability to comply with nutritional requirements, pregnancy, and unwillingness or unable to take part in a study requiring multiple visits and telephone interviews as well as any condition which in the opinion of the investigators makes the candidate unsuitable for participation in this study were the exclusion criteria. The mean Age, Bodyweight, and BMI were 33 ± 10.7 years, 127.7 ± 31.3 kg, and 43.5 ± 7.1 kg/m^2 respectively.

Study participants data are presented in Table 1.

Laparoscopic sleeve gastrectomy procedure

The standard technique for laparoscopic SG was used for all 21 patients. Briefly; the surgery was performed through 4 trocar-port (12 mm, 10 mm, 5 mm, 5 mm). Following the insertion of the trocars, the procedure began with the division of greater omentum from the stomach using a Ligasure. Then the first linear stapler (Ethicon Echelon Flex Powered Endopath 60 mm) was fired beginning 4 cm from the gastro-duodenal junction. A 36-Fr boggie gastric calibration tube was then inserted into the stomach. The remaining staplers were fired consecutively until the gastric sleeve was complete. A total of 5 stapler (green, yellow, yellow, blue and blue respectively) firings were needed to complete the gastric resection. Finally the entire staple line was reinforced with seromuscular suturing (burying the staple line) using Covidien 3-0 V-Loc suture. All procedures were successful. There were no intraoperative adverse events. The mean operative time was 105 ± 28 min. All the 21 cases of sleeve gastrectomy were performed by a single surgeon. The mean postoperative hospital stay was 3.1 ± 0.7 days. There were no early postoperative complications.

GDF 15 assay

Fasting blood for GDF 15 assay was collected in chilled -ethylenediamine tetraacetic acid (EDTA) tubes. After an immediate centrifuge at 3000 rpm for 10 min, serum was collected and stored at −80° Celsius awaiting hormone analysis. GDF 15 assay was performed using an enzyme-linked immunosorbent assay (ELISA) kit according the to manufacturer's instruction (Cloud-Clone Corp, 1304 Langham Creek Dr, Suite 226, Houston, TX 77084 USA). The homeostasis of Insulin Resistance (HOMA-IR) index [(Fasting Glucose×Fasting Insulin)/22.5] was used to calculated insulin resistance.

Statistical analysis

All data are presented as mean ± standard deviation (SD). Student's t-test was used to compare means. Spearman correlation coefficients of changes in GDF15 with change in BMI, HbA1c, C-peptide, insulin and fasting blood glucose at one, three, and twelve months after operation was assessed. All test were two-tailed (statistically significant with $p < 0.05$). Statistics were performed

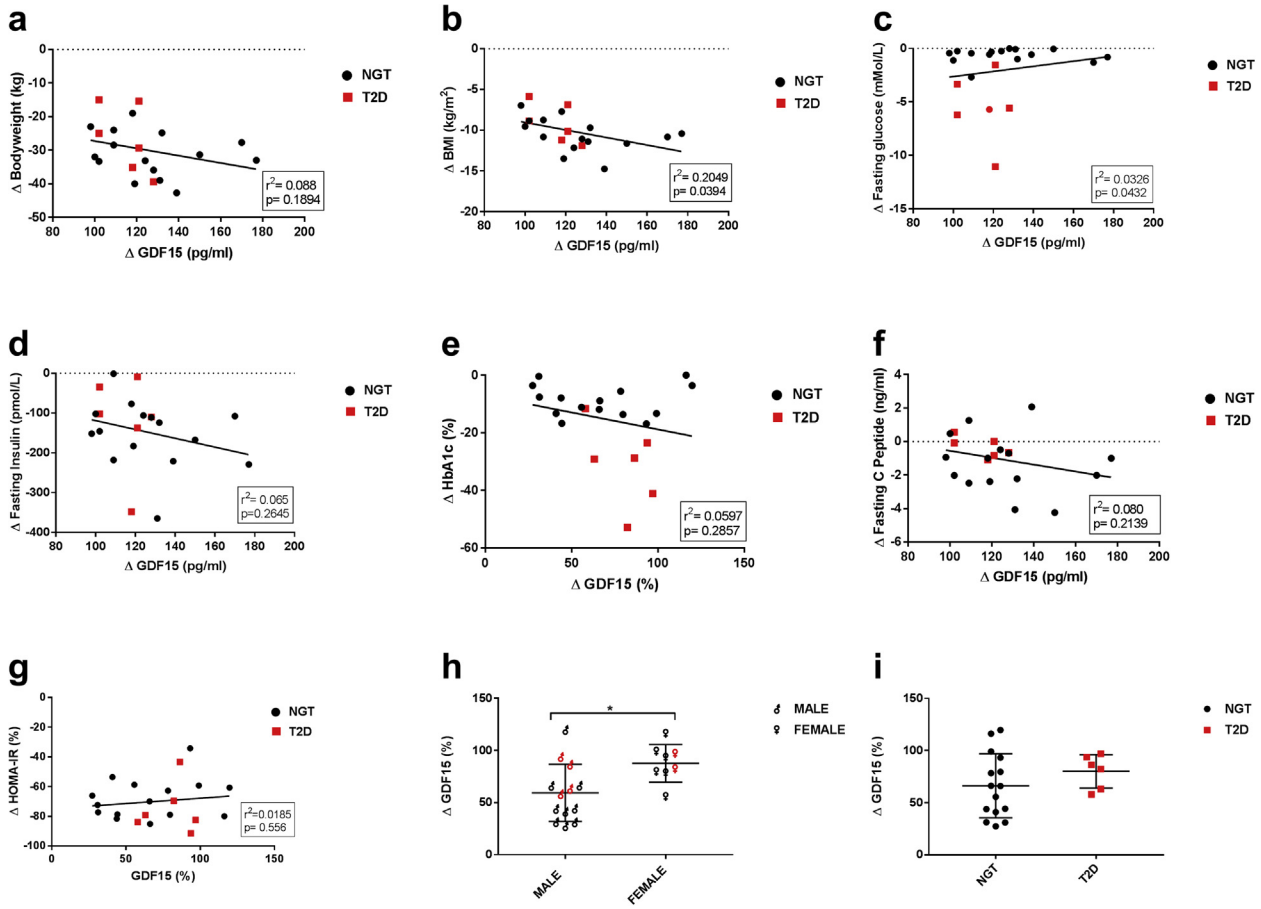

Fig. 3. ***Three month after surgery***, Correlation of change in GDF15 with **a)** change in bodyweight; **b)** change in Body Mass Index (BMI); **c)** change in fasting glucose; **d)** change in fasting Insulin; **e)** change in HbA1c; **f)** change in fasting c peptide; **g)** change in HOMA-IR; **h)** Sex; **i)** glucose tolerance. **Δ**: change; NGT: Normal Glucose Tolerance, T2D: Type 2 diabetes; *Significant ($p < 0.05$).

using Graphpad Prism 7.0 (GraphPad Software, La Jolla, CA, 107 USA).

Results

Weight loss and T2D remission outcomes

The mean percentage of total body weight loss (%TWL) at 1, 3 and 12 months after surgery were 13.0 ± 2.8%, 25.5 ± 3.8%, and 32.2 ± 6.0% respectively. The amount of weight loss did not differ between the T2D and NGT patients.

In patients with T2D, Fasting glucose, and HbA1c decreased by 47.4 ± 16.5% and 20.7 ± 8.5% at 1 month, 46.2 ± 16.7% and 31.2 ± 14.3% at 3 months and 51.5 ± 11.6% and 35.5 ± 15.4% at 12 months respectively. Twelve months after surgery, 5 out of 6 patients (83.33%) with T2D achieved HbA1c level of <6.0. The remaining 1 patient (16.66%) reached HbA1c level of 6.1. All the T2D patients (100%) reached fasting glucose level of <7.0 at 12 months after surgery. No patient required oral hypoglycemic medication or insulin injection at 12 months after surgery. HbA1c and fasting glucose level changes in the NGT patients was not significant. Preoperative Fasting insulin decrease significantly ($p < 0.05$) at all time points after surgery in all patients. The decreased fasting insulin did not differ between the T2D and NGT patients.

GDF 15 outcomes

Before surgery, GDF15 level correlated with BMI ($r^2 = 0.1897$, $p < 0.05$) and fasting Insulin level ($r^2 = 0.3658$, $p < 0.01$). GDF 15 level was also significantly higher in male subjects compared to female subjects (264 ± 38.38 pg/ml, n = 13 vs 141.9 ± 9.023 pg/ml, n = 8; $p < 0.05$ respectively). These correlations disappeared after Sleeve gastrectomy. There were no correlation between GDF15 level and fasting glucose, HbA1c, C-peptide, T2D and Age preoperatively. The correlation with bodyweight did not reach statistical significance ($r^2 = 0.1781$, $p = 0.056$). GDF15 level was slightly lower in T2D patients. ***GDF 15 Correlations Before surgery are shown in*** Fig. 1.

After Sleeve gastrectomy: Mean Fasting plasma GDF15 levels recorded before surgery (215.1 ± 119.9 pg/ml) was increased significantly at 1 month (301.9 ± 135.2 pg/ml $p < 0.05$) after surgery and increased even further at 3 months (338.86 ± 131.14 pg/ml, $p < 0.01$) and remain elevated at 12 months (329.39 ± 152.1 pg/ml $p < 0.05$) after surgery(Fig. S1). The amount of increased plasma GDF15 level in female was greater compared to male subjects after surgery and reached statistical significance 3 months after surgery (87.63 ± 6.366% vs 59.31 ± 7.635%, respectively $p < 0.05$).

The Lower preoperative level of GDF15 in T2D patients recovered remarkably after surgery such that the amount of increase was greater than the amount of increase in the NGT subjects (**1-month**: 53.2 ± 3.6% vs 45 ± 4.7%; **3-month**: 80 ± 6.5% vs 66.1 ± 7.9; **12-month**: 86 ± 26.7 vs 59.7 ± 12.1% respectively).

GDF 15 Correlations after Surgery: The increased GDF15 level at 3 months postoperatively was significantly correlated with the decrease in BMI ($r^2 = 0.204$, $p < 0.05$). Changes in GDF15 level did not correlate with the changes in fasting glucose, and HOMA-IR.

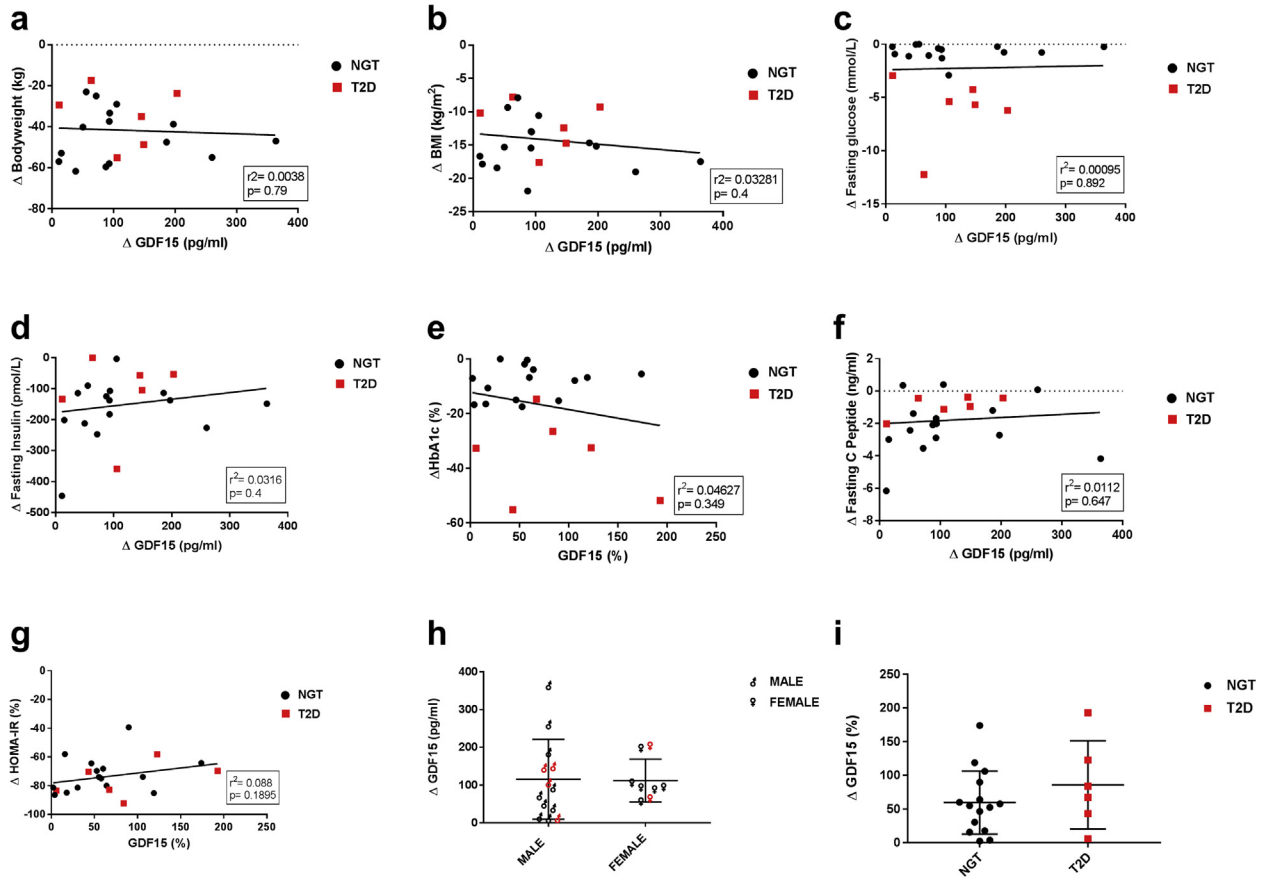

Fig. 4. ***Twelve month after surgery***, Correlation of change in GDF15 with **a)** change in bodyweight; **b)** change in Body Mass Index (BMI); **c)** change in fasting glucose; **d)** change in fasting Insulin; **e)** change in HbA1c; **f)** change in fasting c peptide; **g)** change in HOMA-IR; **h)** Sex; **i)** glucose tolerance. **Δ**: change; NGT: Normal Glucose Tolerance, T2D: Type 2 diabetes; *Significant ($p < 0.05$).

The increase in GDF15 level was slightly associated with the decreased in HbA1c, Fasting Insulin, and fasting c-peptide at 1 and 3 months after surgery but only HbA1c at 12 months after surgery. ***GDF 15 Correlations at 1, 3 and* 12 months *after Surgery are shown in*** Fig. 2, Fig. 3 and Fig. 4 ***respectively***.

Discussion

Our study provides the first assessment on the effect of sleeve gastrectomy on circulating plasma GDF15 level in patient with obesity, and obesity plus T2D. We found a significantly increased plasma GDF15 level at 1 month (47.4 ± 16.5%), 3 months (70.1 ± 27.7%) and 12 months (67.2 ± 52.5%) after sleeve gastrectomy. The increased GDF15 level was associated with the degree of BMI loss.

Recently, it was reported that GDF-15 may be one mechanism of the reduced food intake and weight loss after bariatric surgery.

In the study by Vila G. et al.,[18] they reported a significantly increased GDF15 level 1 year after RYGB surgery which was correlated with the magnitude of weight loss.

In our current study, GDF15 level was increased significantly at 1 month after surgery and continue to increase at 3 months, at which time the increased level correlated with the amount of decrease in BMI, and the level remained elevated at 1 year after surgery. Our finding is consistent with the study by Vila G. et al.[18]

A more recent study by Kleinert M et al.[17] even found an increased GDF15 level up to 2.5–4years after RYGB. Consistent with our findings in the current study, the studies by Vila G. et al.,[18] and Kleinert M et al.[17] found that the increased GDF15 level after surgery was associated with the magnitude of weight loss.

Taken together, these findings (including ours) support the extensive literature on the role of GDF15 in bodyweight regulation and further suggest that GDF15 may play a role in the weight loss after bariatric surgery.

Interestingly, unlike the studies by Vila G. et al.,[18] and Kleinert M et al.[17] (conducted in RYGB), the amount of increase in GDF 15 level after surgery in our study (conducted in Sleeve gastrectomy) was significantly greater. Could this means that the effect of sleeve gastrectomy on plasma GDF15 level is more profound than RYGB?

We also noted that the preoperative level of GDF15 in the above studies were significantly greater than those in our study which may also be one reason for the varying degree of increase in GDF-15 level.

Data and knowledge on the effect of bariatric surgery on GDF15 are only now emerging. Most of our knowledge on GDF15 comes from preclinical work which has shown the satiety effect of GDF15 in rodents and other primates. It has been shown that GDF15 mediates bodyweight regulation by binding and activating the receptor GDNF family receptor alpha-like (GFRAL) in the brainstem.[7] This has been illustrated in rodent with genetically deleted gfral or following the use of monoclonal antibody to block the interaction between GDF15 and GFRAL.[12] In those (gfral knockout, or blocked) rodents, the GDF15 mediated decrease in food intake and bodyweight were abolished.

In humans, elevated GDF15 level has also been shown to correlate with weight loss,[15] but others have also found increased circulating GDF15 in people with obesity.[13,14,19]

This contradiction has led to suggestion that perhaps in obesity,

GDF15 could be part of a compensatory mechanism that limits energy intake during periods of excess nutrient.[5]

Similar paradox has also been noted before with higher circulating Fibroblast growth factor 21 (FGF21) in people with obesity[20] which also significantly increases further following bariatric surgery.[21,22] FGF21 was then found to be an important metabolic regulator of glycemic level and adiposity.[23]

The increased GDF15 level post bariatric surgery (associated with resolution of the metabolic complications) also argues against GDF15 as a prognostic biomarker for mortality, since in fact bariatric surgery dramatically lead to a resolution of the comorbidities and decrease mortality.

Studies have also associated GDF15 level with trauma and tissue injury.[24] Thus the increased GDF15 level immediate after surgery may seem predictable, but certainly not after 12 months or even 4 years[17] after surgery. This suggests that bariatric surgery inherently increases GDF15 level through currently unknown mechanisms.

GDF15 is expressed in most tissues including the liver, muscles and adipose.[25–27] Perhaps the recalibration of energy metabolism in these tissues after bariatric surgery may be of essence. The increased physical activity in obese people after bariatric surgery may also be a factor contributing to the increased GDF 15 level.

But at the moment, whether the increase in GDF15 level after bariatric surgery plays a role in the weight loss or whether it is merely an accidental bystander remains to be elucidated. Nevertheless, given that the Pharmacological treatment with GDF15 analogues results in dramatic reductions of food intake and body weight, the increased GDF15 level after Bariatric surgery may be a putative factor in the reduced food intake and weight loss after the surgery.

Well-conducted human or animal studies are urgently needed to understand the mechanism of GFD15 in the weight loss and the resolution of metabolic complications post bariatric surgery.

Our study is limited by the small sample size and only 1 year of follow-up. The lack of a proper control group is also a limitation to our study.

Conclusion

Sleeve gastrectomy induces a significant increase in GDF15 level which is correlated with the magnitude of weight loss. Therefore increased GDF15 after SG may be part of the mechanism of decreased food intake and weight loss after surgery.

Statement of informed consent

This study was approved by the Ethics Committee of Xuzhou Medical University in accordance with the Helsinki-II declaration. Written informed consent was obtained from all participants.

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Declaration of competing interest

All authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2020.01.041.

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