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RAPID REPORT

Effect of bariatric surgery on plasma GDF15 in humans

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Kleinert M, Bojsen-Møller KN, Jørgensen NB, Svane MS, Martinussen C, Kiens B, Wojtaszewski JF, Madsbad S, Richter EA, Clemmensen C. Effect of bariatric surgery on plasma GDF15 in humans. *Am J Physiol Endocrinol Metab* 316: E615–E621, 2019. First published February 5, 2019; doi:10.1152/ajpendo.00010.2019.—Bariatric surgery results in marked body weight loss and improves type 2 diabetes in most patients with obesity. The growth differentiation factor 15 (GDF15) has recently emerged as a novel satiety factor. To begin to understand whether GDF15 is involved in mediating the effects of bariatric surgery on body weight and glycemia in humans, we measured plasma GDF15 in patients with obesity ($n = 25$) and in patients with obesity and diabetes ($n = 22$) before and after Roux-en-Y gastric bypass (RYGB) surgery. GDF15 was increased 1 wk after RYGB compared with before surgery (689 ± 45 vs. 487 ± 28 pg/ml, $P < 0.001$) and GDF15 remained elevated at 3 mo (554 ± 37 pg/ml, $P < 0.05$), at 1 yr (566 ± 37 pg/ml, $P < 0.05$), and at 2.5–4 yr (630 ± 50 pg/ml, $P < 0.001$) after RYGB surgery. Both age and insulin sensitivity correlated with GDF15 before the surgery ($r = 0.46$, $P < 0.0001$ and $r = 0.34$, $P < 0.001$, respectively). These correlations disappeared at 2.5–4 yr following the surgery. Conversely, weight loss magnitude correlated with GDF15, measured 2.5–4 yr postsurgery ($r = 0.21$, $P < 0.0055$). In summary, circulating GDF15 increases and correlates with body weight loss following RYGB surgery.

bariatric surgery; diabetes; GDF15; obesity; Roux-en-Y gastric bypass

INTRODUCTION

Given the current obesity pandemic with its many fatal comorbidities, potent and safe options to achieve meaningful weight loss are urgently needed. Gastric bypass surgery produces sustained weight loss of 25–40% and improves a series of metabolic comorbidities (21), but the financial cost and medical risk make these irreversible surgeries an untenable large-scale intervention. Nonetheless, their robust efficacy demonstrates what is possible in terms of weight loss. Importantly, the metabolic benefits are not solely a result of physical restriction of the gastrointestinal system but are largely due to alterations in intricate neuroendocrine signaling patterns that alter defended body weight (5). Deciphering the biological adaptions following bariatric surgery may accelerate the progression of novel pharmacological interventions with improved efficacy over the currently available obesity drugs.

The growth differentiation factor 15 (GDF15) has recently emerged as a potential anti-obesity therapeutic. It is part of the transforming growth factor- β (TGF-β) superfamily, and it circulates as a 25-kDa homodimer. First identified in 1997 as a factor that blocks macrophage activation (4), a role for GDF15 in the regulation of energy balance was established in 2007, when it was shown that GDF15 reduces food intake in rodents (14). In follow-up reports, pharmacological and genetic studies established that GDF15 administration reduces body weight, predominantly by suppressing appetite (9, 13, 17, 19, 23). Recently, the glial cell-derived neurotrophic factor (GDNF) family receptor α-like (GFRAL), exclusively located in the hindbrain, was identified as the receptor that mediates the anorexic effect of GDF15 (9, 13, 19, 23).

In contrast to these preclinical findings, data on GDF15 in human energy metabolism are still scarce and inconsistent. For example, increased plasma GDF15 levels have been reported in subjects with obesity and diabetes (8, 12), but also in patients with anorexia nervosa and in response to diet-induced weight loss (7, 8) and metformin treatment (11). One study observed an increase in circulating GDF15 1 yr following Roux-en-Y gastric bypass (RYGB) surgery in subjects with obesity (~90% female) (22). Together, these findings suggest that GDF15 levels are impacted by multiple factors, including stress, surgery, pharmacology, aging, and glycemia, making it imperative to not look at GDF15 in isolation but to follow GDF15 over time and carefully characterize the study subjects to get a better handle on human GDF15 biology.

Therefore, we measured plasma GDF15 in cross-sectional cohorts (64% female) of subjects with obesity and normal glucose tolerance (NGT) and subjects with obesity and type 2 diabetes (T2D) and carefully gauged confounding factors such as age, sex, adiposity, and glycemic control. The fact that we had postoperative samples ranging from 1 wk following RYGB and out until 4 yr postsurgery enabled us to illuminate the acute and chronic effect of bariatric surgery on circulating GDF15.

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MATERIALS AND METHODS

Written informed consent was obtained from all participants, and the studies were approved by the Municipal Ethical Committee of Copenhagen in accordance with the Helsinki-II Declaration and by the Danish Data Protection Agency and registered with https:/clinicaltrials.gov/ (ID nos.: NCT00810823, NCT01993511, NCT01202526, and NCT03046147).

For this descriptive study, subjects from three different previously studied patient cohorts were included in this investigation. The 30-mo (2.5 yr) follow-up was performed in a cohort of patients from two previous studies (15, 18). The majority of patients [12 normal glucose tolerant (NGT)/11 type 2 diabetic (T2D)] are described by Jorgensen et al., but an additional five subjects from the Martinussen study (4 NGT/1 T2D) were included in the 2.5-yr follow-up. The 4-yr follow-up was an extension study of 16 (7 NGT/9 T2D) patients from a previous study by Bojsen-Møller et al. (3). Of note, patients were on a liquid diet of ~1,200 kcal/day until 14 days postoperatively, when the diet gradually changed toward solid foods.

In all studies, blood was drawn into prechilled tubes, spun, aliquoted, and frozen at −80 ºC. GDF15 was measured in plasma using the Quantikine ELISA Human GDF-15 Immunoassay (ELISA, R&D systems, Minneapolis, MN; catalog no. DGD150).

Statistical analyses were performed using Graphpad Prism 7.0 (GraphPad Software, La Jolla, CA), except for Fig. 2*A* for which SigmaPlot 13.0 (Systat Software, San Jose, CA) was used. The type of statistical test performed is described in the figure legends. A P value < 0.05 was considered significant. Differences in variance were assessed. Data are presented as means ± SE.

RESULTS

Fasting plasma GDF15 levels were measured before and after RYGB surgery in patients from three previously described study cohorts. Table 1 shows pooled subject characteristics.

Before the surgery. Plasma GDF15 levels were similar in men and women (Fig. 1*A*). Circulating GDF15 was 26% higher ($P < 0.05$) in subjects with type 2 diabetes (T2D) compared with subjects with normal glucose tolerance (NGT) (Fig. 1*B*). The T2D group, however, was on average 7.5 yr older than the NGT patients ($P < 0.05$) (Table 1), and age significantly correlated with GDF15 levels (Fig. 1*C*). Body weight and body mass index (BMI) did not correlate with circulating GDF15 before the surgery (Fig. 1, *D* and *E*). In contrast, fasting C-peptide and homeostatic model assessment 2 of insulin resistance (HOMA2IR) significantly correlated with GDF15 plasma levels (Fig. 1, *F* and *G*). However, GDF15 did not correlate with the percentage of glycated hemoglobin (%HbA1c), fasting insulin, fasting glucose, or the ratio of fasting C-peptide and fasting insulin (CI ratio), a surrogate measure for hepatic insulin clearance (2) (Fig. 1, *H–K*).

After the surgery. Fasting plasma GDF15 levels were increased by 41% 1 wk after the surgery ($P < 0.001$). The surgery-induced increase in GDF15 was maintained, albeit at lower absolute levels, at 3 mo after the surgery (14% increase, $P < 0.05$) and at 1 yr after the surgery (16%, $P < 0.05$). At 2.5–4 yr after the surgery, GDF15 levels were 27% higher than preoperative plasma levels ($P < 0.001$) (Fig. 2*A*). The changes in GDF15 (ΔGDF15) levels from preoperative to 2.5–4 yr were not different between men and women, or between subjects with NGT or T2D (Fig. 2, *B* and *C*). In contrast to before the surgery, the correlation between age and circulating GDF15 was lost 2.5–4 yr after surgery (Fig. 2*D*). ΔGDF15 after 2.5–4 yr correlated with absolute body weight loss magnitude (Fig. 2*E*) and changes in BMI (Fig. 2*F*). Patients that lost more than 30% body weight by 2.5–4 yr after the surgery exhibited greater ΔGDF15 levels than patients that lost less than 10% body weight (Fig. 2*G*).

Table 1. *Study participants*

	NGT	T2D
Sex, Women/Men	18/7	12/10
Age, yr	42.3 ± 2.3	49.8 ± 2.0
Weight, kg	122.7 ± 3.4	126.8 ± 4.7
BMI, kg/m^2	41.2 ± 0.8	41.7 ± 1.2
HbA1c, %	5.5 ± 0.1	6.8 ± 0.2
Fasting plasma glucose, mM	5.3 ± 0.1	8.8 ± 0.4
Fasting plasma insulin, pM	87.1 ± 6.1	121.0 ± 12.1
No. of subjects on metformin	1	19
No. of subjects on sulfonylurea	0	4

Data are presented as means ± SE. NGT, normal glucose tolerance; T2D, type 2 diabetes; BMI, body mass index; HbA1c, glycated hemoglobin.

In contrast, changes (i.e., Δ) in indexes of glycemia, comprising fasting C-peptide levels, HOMA2IR, %HbA1c, fasting insulin, fasting glucose, and the CI ratio, did not correlate to changes in GDF15 2.5–4 yr after surgery (Fig. 3, *A–F*).

Furthermore, 2.5–4 yr after surgery, absolute plasma GDF15 levels still significantly correlated with fasting C-peptide and HOMA2IR, but seemingly to a weaker extent compared with the association detected before the surgery. There was no correlation between circulating GDF15 and %HbA1c, fasting insulin, fasting glucose, and the CI ratio at 2.5–4 yr after surgery (Fig. 3, *G–L*).

DISCUSSION

We here provide the first comprehensive long-term assessment of circulating GDF15 in subjects with obesity and either NGT or T2D that underwent RYGB surgery. Plasma GDF15 significantly increased postoperatively, which correlated with the amount of body weight lost due to the surgery. This warrants investigations into the causality between GDF15 and reversal of obesity following bariatric surgery. We also observed that GDF15 levels were substantially increased already 1 wk after RYGB surgery, where no significant weight loss was reported.

Our data are consistent with an increase in circulating GDF15 previously noted in subjects with obesity after RYGB surgery (22), but in that study GDF15 levels were determined at only a single time point, 1 yr after the surgery, and 25 of the 28 subjects assessed were female, whereas our cohort was more balanced for sex. Interestingly, in that study GDF15 correlated with age before but also 1 yr after the surgery. We now found that the correlation between age and circulating GDF15 was lost 2.5–4 yr after surgery, possibly indicating that the increase in GDF15 following RYGB surgery is not merely a function of aging per se.

A recent study reported that GDF15 is dispensable for the benefits of vertical sleeve gastrectomy (VSG) on body weight in mice (10). However, the animals in this study were relatively lean when the surgeries were performed. Thus it remains to be seen if GDF15 contributes to the metabolic benefits of VSG in more metabolically compromised, highly obese rodents. In addition, it is unknown whether VSG and/or RYGB actually increases circulating GDF15 in rodents.

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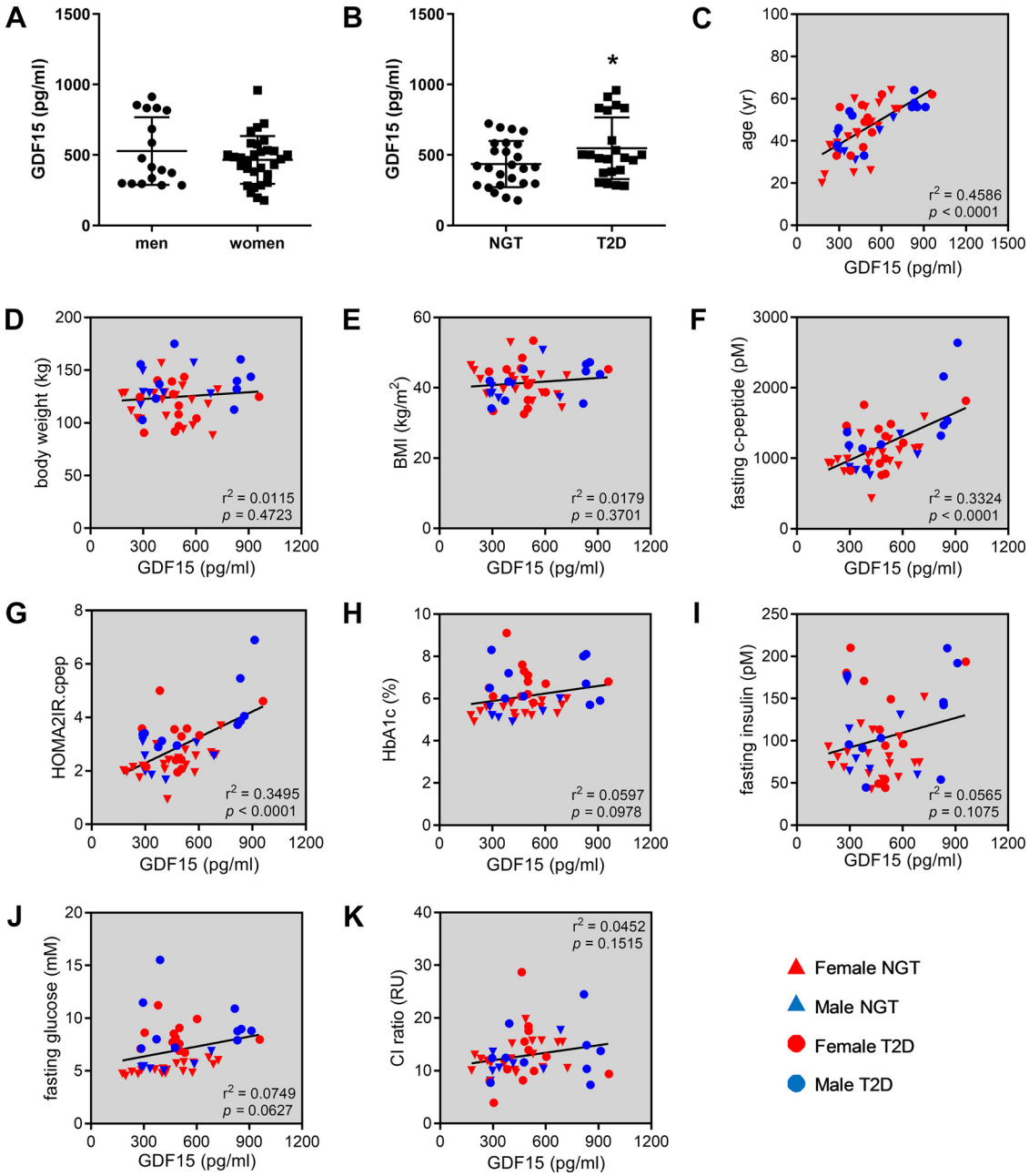

Fig. 1. Before Roux-en-Y gastric bypass (RYGB) surgery growth differentiation factor 15 (GDF15) correlates with markers of glycemia, but not with body weight in subjects with obesity and either normal glucose tolerance (NGT) or type 2 diabetes (T2D). *A* and *B*: fasting plasma GDF15 in men and women with obesity and either NGT or T2D. *C–K*: relationship among plasma GDF15 and the parameters indicated on the *y*-axes. BMI, body mass index; HOMA2IR, homeostatic model assessment 2 of insulin resistance; HbA1c, glycated hemoglobin; CI ratio, ratio of fasting C-peptide and fasting insulin. Data are means ± SE. A 2-tailed Student's *t*-test was used to compare means in *A* and *B*. $*P < 0.05$ between NGT and T2D. For *C–K*, linear regression analyses were performed.

Most of our current knowledge on GDF15 comes from elegant preclinical work, demonstrating that GDF15 pharmacology signals satiety in rodents and nonhuman primates by binding and activating the receptor GFRAL discretely located in the brain stem (9, 13, 19, 23). However, our knowledge of the GDF15-GFRAL pathway, especially in humans, is rudimentary and at times seems counterintuitive. For example, circulating GDF15 levels are higher in diseases like certain cancers (1), but also following exercise (16), which generally is beneficial to health. Therefore, careful analysis and interpretation of well-conducted studies in humans are crucial to understand the regulation and role of GFD15 in physiology vs. pathophysiology. In context, a recent study using human subjects found that circulating GDF15 increases in response to starvation, but not overfeeding (20). Our data suggest that GDF15 is increased in subjects with obesity and diabetes, and that GDF15 increases further in response to RYGB and thus in conjunction with the resolution of the metabolic complications. Such paradoxical regulation is analogous to how other endocrine stress signals, such as FGF21, are regulated with obesity and in response to bariatric surgery (6, 24). However, whether

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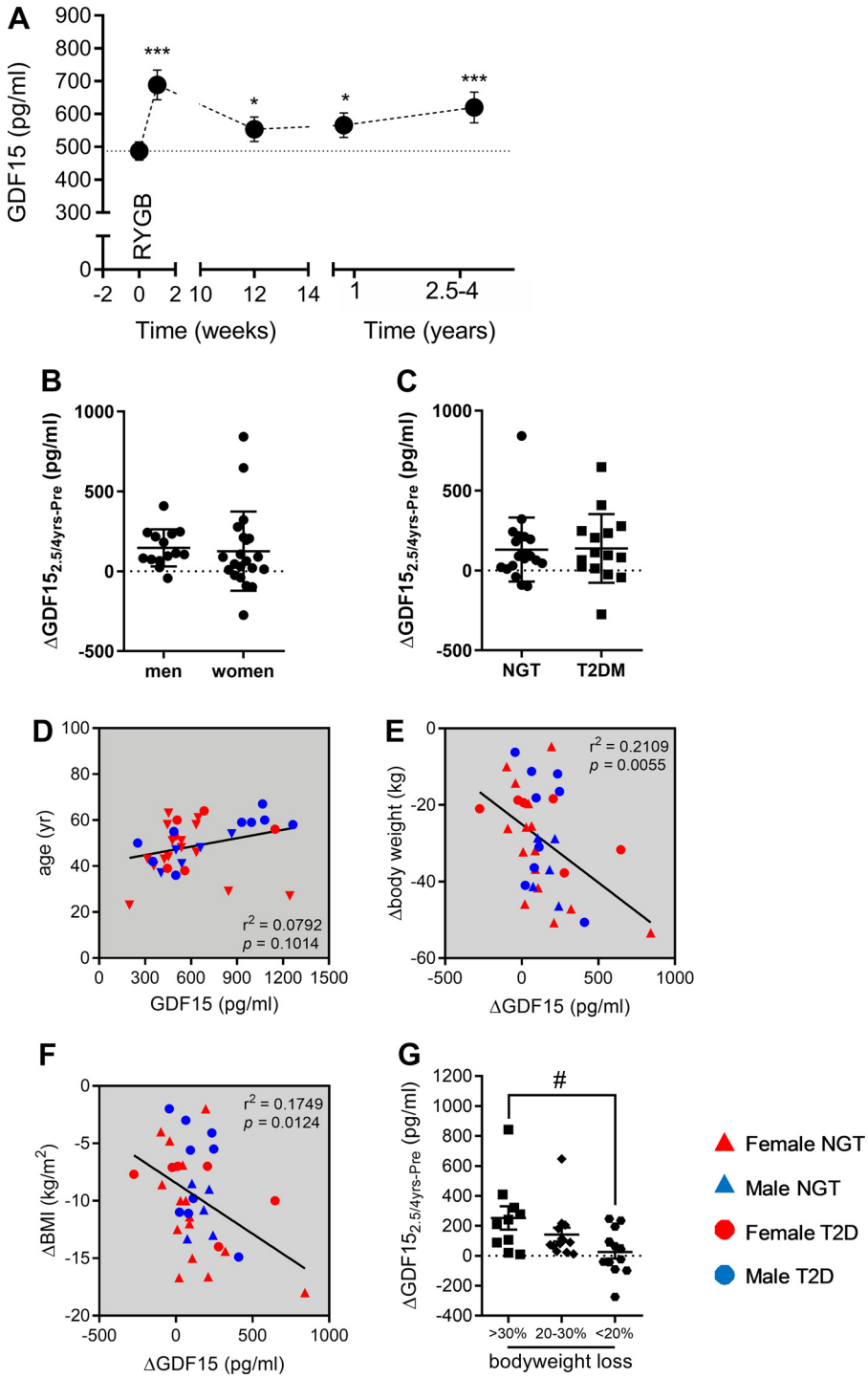

Fig. 2. After Roux-en-Y gastric bypass (RYGB) surgery circulating growth differentiation factor 15 (GDF15) is increased and correlates with body weight loss. *A*: fasting plasma GDF15 before RYGB and at indicated time points after surgery are shown. *B* and *C*: the differences (Δ) of GDF15 levels at 2.5–4 yr after surgery and before surgery in men and women with obesity and either NGT or T2D were calculated. In *D*, the relationship between age of the subject and fasting plasma GDF15 levels at 2.5–4 yr after the surgery is tested. *E* and *F*: the relationship between ΔGDF15 levels and corresponding changes (Δ) in body weight (*E*) and body mass index (BMI) (*F*). *G*: ΔGDF15 in patients divided into the indicated groups defined by the % magnitude of weight loss at 2.5–4 yr after the surgery. Data are means ± SE. For *A*, the data are analyzed for a time effect with a 1-way repeated-measures analysis of variance. Differences in means in *B* and *C* were assessed with 2-tailed Student's *t*-tests. For *D*–*F*, linear regression analyses were performed. In *G*, differences among the 3 groups were assessed with a 1-way analysis of variance. $***P < 0.001$ and $*P < 0.05$ are differences between indicated postoperative time point and pre-surgery level (i.e., time point 0). $\#P < 0.05$ between indicated groups. For *C*, a significant difference in variance was detected.

the physiological induction in GDF15 observed following RYGB impacts appetite and/or aversion in order to regulate body weight, or whether this is an accidental "bystander" remains to be determined.

A limitation of this interventional study is the lack of a proper control group, but this is difficult to achieve, since sham surgery is not an ethical option in humans and the magnitude of weight loss due to bariatric surgery is not reliably obtained using lifestyle or pharmacological interventions. Furthermore, it should be noted that our sample size is rather modest, and we encourage the research community to follow-up on this work. The herein presented data are limited to the RYGB surgery. Whether GDF15 changes in response to other gastrointestinal surgeries in humans, e.g., VSG, remains to be investigated. This seems relevant to study, given that rodent models suggest that GDF15 is dispensable for the weight-lowering benefits of VSG (10). Finally, the patients included in our investigation suffer from a multitude of comorbidities, and many subjects were medicated before the surgical intervention. Metformin has

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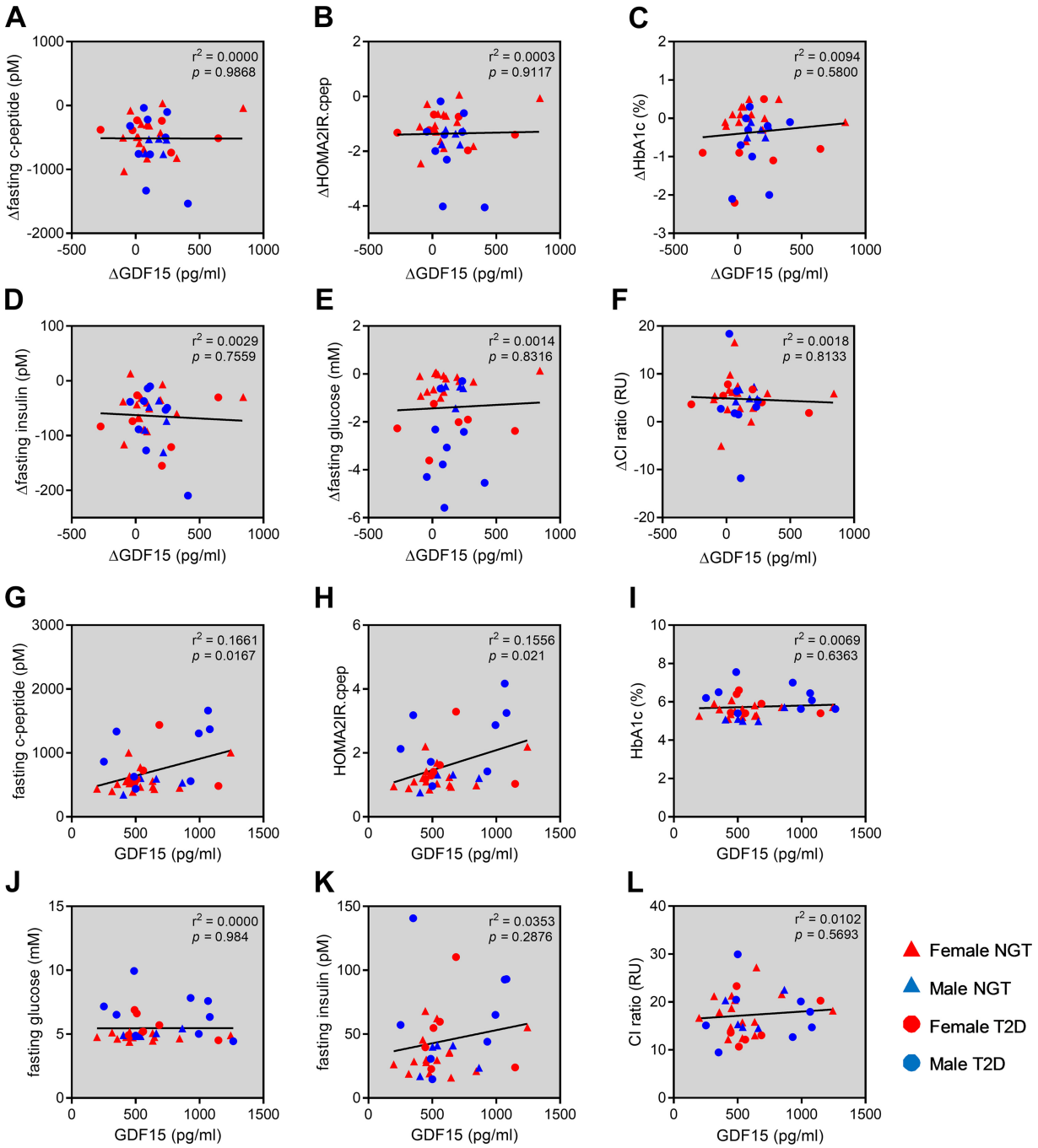

Fig. 3. The relationship between growth differentiation factor 15 (GDF15) and glycemic parameters after Roux-en-Y gastric bypass (RYGB) surgery. *A–F*: the relationship among Δ plasma GDF15 levels and corresponding Δ changes in the parameters indicated on the *y*-axes at 2.5–4 yr after the surgery. *G–L*: relationship among absolute GDF15 levels and absolute parameters indicated on the *y*-axes. Linear regression analyses were performed in each panel. NGT, normal glucose tolerance; T2D, type 2 diabetes; HOMA2IR, homeostatic model assessment 2 of insulin resistance; HbA1c, glycated hemoglobin; CI ratio, ratio of fasting C-peptide and fasting insulin.

been reported to impact GDF15 levels (11), and it cannot be ruled out that the presurgery increased circulating GDF15 levels in the T2D group is confounded by the use of antidiabetic medication.

The mechanisms underpinning the acute and long-term increase in circulating GDF15 are unknown. We speculate that the acute, robust increase in GDF15 detected just 1 wk after the RYGB procedure is caused by surgery-related stress and the concomitant postoperative caloric restriction. The potential reasons for the moderate long-term increase in GDF15 is even more speculative, but factors like altered protein absorption, increased physical activity, or other endocrine changes might play a role, although clearly this research area requires more work.

In conclusion, circulating GDF15 increases and correlates with body weight loss following RYGB surgery. Future studies

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are needed to test the hypothesis that GDF15 might contribute to the robust surgery-induced body weight loss.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.N.B.-M., N.B.J., M.S.S., B.K., S.M., E.A.R., and C.C. conceived and designed research; K.N.B.-M., N.B.J., M.S.S., C.M., B.K., S.M., and C.C. performed experiments; M.K., K.N.B.-M., M.S.S., B.K., S.M., and C.C. analyzed data; M.K., K.N.B.-M., N.B.J., M.S.S., B.K., J.F.W., S.M., E.A.R., and C.C. interpreted results of experiments; M.K., K.N.B.-M., M.S.S., B.K., S.M., and C.C. prepared figures; M.K., K.N.B.-M., M.S.S., B.K., S.M., E.A.R., and C.C. drafted manuscript; M.K., K.N.B.-M., N.B.J., M.S.S., B.K., J.F.W., S.M., E.A.R., and C.C. edited and revised manuscript; M.K., K.N.B.-M., N.B.J., M.S.S., C.M., B.K., J.F.W., S.M., E.A.R., and C.C. approved final version of manuscript.

C.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analyses.

REFERENCES

1. **Bauskin AR, Brown DA, Kuffner T, Johnen H, Luo XW, Hunter M, Breit SN.** Role of macrophage inhibitory cytokine-1 in tumorigenesis and diagnosis of cancer. *Cancer Res* 66: 4983–4986, 2006. doi:10.1158/0008-5472.CAN-05-4067.
2. **Bojsen-Møller KN, Dirksen C, Jørgensen NB, Jacobsen SH, Hansen DL, Worm D, Naver L, Kristiansen VB, Holst JJ, Madsbad S.** Increased hepatic insulin clearance after Roux-en-Y gastric bypass. *J Clin Endocrinol Metab* 98: E1066–E1071, 2013. doi:10.1210/jc.2013-1286.
3. **Bojsen-Møller KN, Dirksen C, Jørgensen NB, Jacobsen SH, Serup AK, Albers PH, Hansen DL, Worm D, Naver L, Kristiansen VB, Wojtaszewski JF, Kiens B, Holst JJ, Richter EA, Madsbad S.** Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. *Diabetes* 63: 1725–1737, 2014. doi:10.2337/db13-1307.
4. **Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, Zhang HP, Donnellan M, Mahler S, Pryor K, Walsh BJ, Nicholson RC, Fairlie WD, Por SB, Robbins JM, Breit SN.** MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. *Proc Natl Acad Sci USA* 94: 11514–11519, 1997. doi:10.1073/pnas.94.21.11514.
5. **Clemmensen C, Müller TD, Woods SC, Berthoud HR, Seeley RJ, Tschöp MH.** Gut-brain cross-talk in metabolic control. *Cell* 168: 758–774, 2017. doi:10.1016/j.cell.2017.01.025.
6. **Crujeiras AB, Gomez-Arbelaez D, Zulet MA, Carreira MC, Sajoux I, de Luis D, Castro AI, Baltar J, Baamonde I, Sueiro A, Macias-Gonzalez M, Bellido D, Tinahones FJ, Martinez JA, Casanueva FF.** Plasma FGF21 levels in obese patients undergoing energy-restricted diets or bariatric surgery: a marker of metabolic stress? *Int J Obes* 41: 1570–1578, 2017. doi:10.1038/ijo.2017.138.
7. **Dostálová I, Kaválková P, Papežová H, Domluvilová D, Zikán V, Haluzík M.** Association of macrophage inhibitory cytokine-1 with nutritional status, body composition and bone mineral density in patients with anorexia nervosa: the influence of partial realimentation. *Nutr Metab (Lond)* 7: 34, 2010. doi:10.1186/1743-7075-7-34.
8. **Dostálová I, Roubícek T, Bártlová M, Mráz M, Lacinová Z, Haluzíková D, Kaválková P, Matoulek M, Kasalicky M, Haluzík M.** Increased serum concentrations of macrophage inhibitory cytokine-1 in patients with obesity and type 2 diabetes mellitus: the influence of very low calorie diet. *Eur J Endocrinol* 161: 397–404, 2009. doi:10.1530/EJE-09-0417.
9. **Emmerson PJ, Wang F, Du Y, Liu Q, Pickard RT, Gonciarz MD, Coskun T, Hamang MJ, Sindelar DK, Ballman KK, Foltz LA, Muppidi A, Alsina-Fernandez J, Barnard GC, Tang JX, Liu X, Mao X, Siegel R, Sloan JH, Mitchell PJ, Zhang BB, Gimeno RE, Shan B, Wu X.** The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. *Nat Med* 23: 1215–1219, 2017. doi:10.1038/nm.4393.
10. **Frikke-Schmidt H, Hultman K, Galaske JW, Jørgensen SB, Myers MG Jr, Seeley RJ.** GDF15 acts synergistically with liraglutide but is not necessary for the weight loss induced by bariatric surgery in mice. *Mol Metab* S2212-8778(18)31143-8, 2019. doi:10.1016/j.molmet.2019.01.003.
11. **Gerstein HC, Pare G, Hess S, Ford RJ, Sjaarda J, Raman K, McQueen M, Lee S, Haenel H, Steinberg GR; ORIGIN Investigators.** Growth Differentiation Factor 15 as a novel biomarker for metformin. *Diabetes Care* 40: 280–283, 2017. doi:10.2337/dc16-1682.
12. **Hong JH, Chung HK, Park HY, Joung KH, Lee JH, Jung JG, Kim KS, Kim HJ, Ku BJ, Shong M.** GDF15 is a novel biomarker for impaired fasting glucose. *Diabetes Metab J* 38: 472–479, 2014. doi:10.4093/dmj.2014.38.6.472.
13. **Hsu JY, Crawley S, Chen M, Ayupova DA, Lindhout DA, Higbee J, Kutach A, Joo W, Gao Z, Fu D, To C, Mondal K, Li B, Kekatpure A, Wang M, Laird T, Horner G, Chan J, McEntee M, Lopez M, Lakshminarasimhan D, White A, Wang SP, Yao J, Yie J, Matern H, Solloway M, Haldankar R, Parsons T, Tang J, Shen WD, Alice Chen Y, Tian H, Allan BB.** Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. *Nature* 550: 255–259, 2017. doi:10.1038/nature24042.
14. **Johnen H, Lin S, Kuffner T, Brown DA, Tsai VW, Bauskin AR, Wu L, Pankhurst G, Jiang L, Junankar S, Hunter M, Fairlie WD, Lee NJ, Enriquez RF, Baldock PA, Corey E, Apple FS, Murakami MM, Lin EJ, Wang C, During MJ, Sainsbury A, Herzog H, Breit SN.** Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1. *Nat Med* 13: 1333–1340, 2007. doi:10.1038/nm1677.
15. **Jørgensen NB, Jacobsen SH, Dirksen C, Bojsen-Møller KN, Naver L, Hvolris L, Clausen TR, Wulff BS, Worm D, Lindqvist Hansen D, Madsbad S, Holst JJ.** Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab* 303: E122–E131, 2012. doi:10.1152/ajpendo.00073.2012.
16. **Kleinert M, Clemmensen C, Sjøberg KA, Carl CS, Jeppesen JF, Wojtaszewski JFP, Kiens B, Richter EA.** Exercise increases circulating GDF15 in humans. *Mol Metab* 9: 187–191, 2018. doi:10.1016/j.molmet.2017.12.016.
17. **Macia L, Tsai VW, Nguyen AD, Johnen H, Kuffner T, Shi YC, Lin S, Herzog H, Brown DA, Breit SN, Sainsbury A.** Macrophage inhibitory cytokine 1 (MIC-1/GDF15) decreases food intake, body weight and improves glucose tolerance in mice on normal & obesogenic diets. *PLoS One* 7: e34868, 2012. doi:10.1371/journal.pone.0034868.
18. **Martinussen C, Bojsen-Møller KN, Dirksen C, Jacobsen SH, Jørgensen NB, Kristiansen VB, Holst JJ, Madsbad S.** Immediate enhancement of first-phase insulin secretion and unchanged glucose effectiveness in patients with type 2 diabetes after Roux-en-Y gastric bypass. *Am J Physiol Endocrinol Metab* 308: E535–E544, 2015. doi:10.1152/ajpendo.00506.2014.
19. **Mullican SE, Lin-Schmidt X, Chin CN, Chavez JA, Furman JL, Armstrong AA, Beck SC, South VJ, Dinh TQ, Cash-Mason TD, Cavanaugh CR, Nelson S, Huang C, Hunter MJ, Rangwala SM.** GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. *Nat Med* 23: 1150–1157, 2017. doi:10.1038/nm.4392.
20. **Patel S, Alvarez-Guaita A, Melvin A, Rimmington D, Dattilo A, Miedzybrodzka EL, Cimino I, Maurin AC, Roberts GP, Meek CL, Virtue S, Sparks LM, Parsons SA, Redman LM, Bray GA, Liou AP, Woods RM, Parry SA, Jeppesen PB, Kolnes AJ, Harding HP, Ron D, Vidal-Puig A, Reimann F, Gribble FM, Hulston CJ, Farooqi IS, Fafournoux P, Smith SR, Jensen J, Breen D, Wu Z, Zhang BB, Coll AP, Savage DB, O'Rahilly S.** GDF15 provides an endocrine

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signal of nutritional stress in mice and humans. *Cell Metab* S1550-4131(18)30753-8, 2019. doi:10.1016/j.cmet.2018.12.016.

21. **Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ES, Nissen SE, Kashyap SR; STAMPEDE Investigators.** Bariatric surgery versus intensive medical therapy for diabetes–3–year outcomes. *N Engl J Med* 370: 2002–2013, 2014. doi:10.1056/NEJMoa1401329.
22. **Vila G, Riedl M, Anderwald C, Resl M, Handisurya A, Clodi M, Prager G, Ludvik B, Krebs M, Luger A.** The relationship between insulin resistance and the cardiovascular biomarker growth differentiation factor-15 in obese patients. *Clin Chem* 57: 309–316, 2011. doi:10.1373/clinchem.2010.153726.
23. **Yang L, Chang CC, Sun Z, Madsen D, Zhu H, Padkjær SB, Wu X, Huang T, Hultman K, Paulsen SJ, Wang J, Bugge A, Frantzen JB, Nørgaard P, Jeppesen JF, Yang Z, Secher A, Chen H, Li X, John LM, Shan B, He Z, Gao X, Su J, Hansen KT, Yang W, Jørgensen SB.** GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. *Nat Med* 23: 1158–1166, 2017. doi:10.1038/nm.4394.
24. **Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, Wong RL, Chow WS, Tso AW, Lam KS, Xu A.** Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes* 57: 1246–1253, 2008 [Erratum in *Diabetes* 68: 235, 2019]. doi:10.2337/db07-1476.

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