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Adults with long-duration type 2 diabetes have blunted glycemic and β-cell function improvements after bariatric surgery

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Abstract

Objective—This study investigated the effect of type 2 diabetes duration on glucose regulation 24 months post-bariatric surgery.

Methods—Twenty-seven adults with short (<5 years) and long-duration (≥10 years) type 2 diabetes received a mixed-meal tolerance test at baseline and 24 months (m) post-surgery. Body

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AUTHOR CONTRIBUTIONS

All authors contributed to data collection and organization. VK and SKM wrote the manuscript and all authors provided edits. SKM, JB, and SRK share responsibility for the integrity of analysis. SRK is the guarantor of this work. RW performed C-peptide deconvolution measures of ISR.

Conflict of Interest: Authors report none for this analysis

weight, insulin sensitivity, 1st and 2nd phase meal-stimulated insulin secretion, disposition index (i.e. DI or pancreatic β-cell function), and incretin responses were examined.

Results—Adults with short-duration type 2 diabetes had better HbA_{1c}, greater insulin secretory capacity, and greater DI compared with adults with long-duration type 2 diabetes, despite similar weight loss and incretin responses. Diabetes duration correlated with smaller improvements in HbA_{1c} and DI, but not weight loss.

Conclusions—Enhanced β-cell function characterizes the effect of bariatric surgery in adults with diabetes for <5 years, independent of weight loss or incretins. Additional therapy post-surgery may be required to improve glycemia for people with long-standing type 2 diabetes.

Keywords

Bariatric surgery; type 2 diabetes; beta cells; glycemic control

INTRODUCTION

Not all individuals with type 2 diabetes meet remission criteria following bariatric surgery (1) and diabetes duration has emerged as an important clinical factor in predicting disease resolution. In fact, recent work suggests that individuals with short- vs. long-duration diabetes improve glycemic control up to 3 months post-op through improvements in insulin sensitivity (2). However, differences in pre-existing HbA_{1c} and adiposity between groups (2) limit our understanding of the interaction between diabetes duration *per se* and bariatric surgery. High fasting C-peptide levels pre-surgery have also been reported to predict diabetes remission 1-5 years post-surgery (3), and we recently demonstrated that bariatric surgery lowered blood glucose by predominantly augmenting pancreatic function via gastrointestinal hormone-related mechanisms (4, 5). Given that individuals with long-duration diabetes typically exhibit severe β-cell dysfunction, we hypothesized that bariatric surgery would promote greater glycemic benefit 24 months post-surgery in individuals with short- vs. long-duration diabetes matched on glycemic control and BMI, and that this would relate to accentuated β-cell function.

RESEARCH DESIGN & METHODS

This prospective study was performed as part of the STAMPEDE trial, of which the methods have been reported and approved by our Institutional Review Board (1). Metabolic studies on diabetes duration were performed before and 24 months following bariatric surgery (i.e. Roux-en Y Gastric Bypass (RYGB) or Sleeve Gastrectomy (SG)). Our sample consisted of 27 adults (***Table 1***) with short (n=14; <5y; 2y [2, 3], 46% SG) and long-duration (n=13; ≥10y, 11y [10, 13] 53% SG) diabetes. Type 2 diabetes duration was identified using electronic medical records and confirmed by a health history questionnaire. Diabetes remission was defined as HbA_{1c} < 6.5% and fasting glucose levels < 126 mg/dl. DiaRem scores were also calculated to characterize factors involved in diabetes remission (6). Subjects abstained from diabetes medication 24-hours prior to testing. After an overnight fast, subjects were given a mixed meal tolerance test (MMTT: Boost; 350 kcal) and blood samples were obtained for HbA_{1C}, glucose, insulin, and C-peptide at 0, 30, 60, 90

and 120 min of the MMTT to determine glycemic control, insulin sensitivity (IS) and β-cell function. GIP (gastric inhibitory polypeptide) and GLP-1 (glucagon-like polypeptide-1) were also measured at 0 and 60 minutes to determine incremental incretin responses. IS was estimated using the Matsuda Index (7) and insulin secretion rates (ISR) during the MMTT were calculated using C-peptide deconvolution techniques (4). Meal-stimulated insulin secretion (MSIS) was calculated as incremental area under the curve (iAUC) of C-peptide ISR divided by glucose during the first 30 and last 60 minutes of the MMTT (i.e. $C\text{-}pep_{0\text{-}30}/Glc_{0\text{-}30}$ and $C\text{-}pep_{60\text{-}120}/Glc_{60\text{-}120}$). Pancreatic β-cell function was estimated using the disposition index (DI; MSIS x IS). Plasma insulin was assayed by a radioimmunoassay (Linco Research), C-peptide by a chemiliuminescence immunoassay (Linco Research), and total GIP and GLP-1 were measured using an ELISA (ALPCO Diagnostics). Data were analyzed using R (Vienna, Austria). Group differences were evaluated using Wilcoxon rank sum tests, while categorical baseline factors were tested with Fisher's exact test. Spearman's correlation was used to examine associations. Significance was accepted as $p \leq 0.05$.

RESULTS

Before surgery, BMI, HbA_{1c}, DiaRem, MSIS and DI, as well as incretin levels, were comparable between patients with short and long-duration diabetes (all $p>0.05$, ***Table 1***). Subjects with long-duration diabetes, compared to those with short-duration diabetes, had similar use of incretin mimetics (92.3 vs. 57.1%; p=0.07), metformin (92.9 vs. 100%; p=0.99), and insulin (53.8 vs. 28.5%; p=0.25). However, long-duration subjects with diabetes required more overall oral medications when compared to short-duration diabetes (***Table 1***), and this was specifically reflected by the difference in thiazolidinediones usage (100 vs. 50%; p=0.006). Lastly, patients with long-duration diabetes had lower fasting C-peptide levels (p=0.003, ***Table 1***) compared to short-duration subjects.

At 24 m post-surgery, improvements in BMI, insulin sensitivity, and incretin responses were similar between groups (all $p>0.05$, ***Table 1***). However, short-duration subjects had significantly better HbA_{1c}, higher 2^{nd} phase MSIS, and greater 1^{st} and 2^{nd} DI responses compared with long-duration subjects (all $p<0.05$, ***Table 1 and Figure 1)***. In fact, 42.9% of short-duration diabetics were in remission compared to only 7.7% in the long duration diabetes group. Moreover, short-duration diabetes subjects had lower total medication intake than subjects with long duration diabetes (***Table 1***), which was primarly the result of decreased metformin use (21.4 vs. 84.6%, p=0.002). Use of other medications was not statistically different at 24 m, including thiazolidinediones (0 vs. 7.7%, p=0.48), incretin mimetics (21.4 vs. 23.1, p=0.99), insulin use (0 vs. 23.1, p=0.09) or secretagogues (0 v. 23.1%, p=0.09) in patients with short- vs. long-duration diabetes. Baseline diabetes duration correlated with smaller improvements in HbA_{1c} ($r=0.39$, $p<0.04$) as well as 1^{st} ($r=-0.50$, p=0.002) and 2^{nd} ($r=-0.40$, p=0.03) phase DI (***Figure 2***). Pre-operative 1^{st} phase MSIS and DI were inversely linked to changes in 1^{st} phase MSIS and DI, respectively ($r=-0.79$, $p<0.001$ and $r=-0.58$, p=0.002). However, pre-operative 2^{nd} phase MSIS, or DI were not statistically associated with changes in 2^{nd} phase MSIS or DI ($r=-0.18$, p=0.37 and $r=-0.30$, p=0.13).

DISCUSSION

Consistent with prior work following lifestyle intervention in hyperglycemic adults (8, 9), our novel findings suggest that bariatric surgery promotes better glycemic control in individuals with short- vs. long-duration diabetes 2 years after bariatric surgery. Unlike prior short-term data following bariatric surgery (2), our data indicate that β-cell function, not insulin sensitivity, is the key determinant of post-operative glycemic control. There are several reasons for this apparent difference between studies. Weight loss has been directly linked to both improved insulin sensitivity and secretion through anti-inflammatory mediated mechanisms following bariatric surgery (10). However, both groups in the current study lost similar amounts of weight, suggesting that caloric restriction *per se* and/or inflammatory changes are unlikely to explain the 2 year differences in glycemic benefit between individuals with short- vs. long-duration diabetes (11). Moreover, the intravenous glucose tolerance test was previously used to determine insulin sensitivity and β-cell function independent of incretin effects (2). However, a strength of the current study is that using the MMTT increases the clinical application and physiologic insight of our findings. In this context, Dutia and colleagues recently observed that incretins are a major determinant of pancreatic function following bariatric surgery (5, 12, 13). In fact, GLP-1 is a leading candidate for not only increasing β-cell mass in rodents, but also augmenting β-cell function in humans following bariatric surgery (14, 15). Despite significant parallel increases in meal-stimulated GLP-1 and GIP with enhanced DI at 24 m post-surgery in short-duration diabetes, adults with long-duration diabetes had similar rises in circulating incretins. Although blood incretins do not necessarily reflect GLP-1 or GIP action and total circulating levels were determined, our data are in line with recent work by Jimenez and colleagues suggesting that subjects with long-duration diabetes are either less responsive to these endogenous incretins and/or due to a pre-operative inability to secrete insulin (16). In either case, the blunted rise in insulin secretion in those with long duration diabetes suggests that using gut-mediated treatments for pancreatic function remains a feasible approach for glycemic control. It is also worth noting that pre-operative use of GLP-1 agonists may be effective at enhancing diabetes remission rates following gastric bypass (17). While there were no differences in baseline incretin mimetics in our study, suggesting that pre-operative GLP-1 treatment was unlikely to have impacted glycemic responses in long-duration diabetes following our intervention, our study was not powered to test such a hypothesis. Further work is required pre- and post-operation to clarify the optimal therapy behind bariatric surgery-induced diabetes remission.

The progression from normal glucose tolerance to diabetes is characterized by reductions in β-cell mass that, in turn, lead to impaired β-cell function (18). The exact mechanism(s) for this exhausted β-cell mass is unclear, but glucotoxicity is known to promote apoptosis and cause proliferative defects in β-cells (19). As such, it is reasonable to expect that extended periods of time or ambient hyperglycemia, as reflected by the blunted reduction in $HbA_{1c,}$ induce β-cell apoptosis and dysfunction (19). While fasting C-peptides were lower in subjects with long-duration diabetes both before and after the intervention, baseline DI was similar between short-and long-duration subjects in our study, suggesting that the functionality of pre-existing β-cells may have impacted the responsiveness to bariatric

surgery. Indeed, those individuals with lower pre-operative MSIS or β-cell function were observed to have larger increases in insulin secretion following bariatric surgery, which is consistent with pancreatic responses to lifestyle modification in adults with prediabetes (20). Our findings do not exclude the benefit of enhanced insulin sensitivity, as individuals with short-duration diabetes had greater improvements, although not statistically (p=0.17), than long-duration subjects. However, there was no relationship between insulin sensitivity and glycemic control. Whether "resting the β-cell" or accentuating pancreatic endocrine function improves glycemic control in long-duration subjects with lifestyle modification or pharmacology awaits further investigation. Therefore, our data call attention to inadequate β-cell function as a key factor characterizing the attenuated glycemic responses to bariatric surgery in people with long-duration diabetes.

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What is already known about this subject?

- Bariatric surgery induces type 2 diabetes remission
- Not all individuals meet diabetes remission criteria following bariatric surgery
- Diabetes duration may be a clinical factor that predicts disease resolution

What this study adds:

- Bariatric surgery promotes better glycemic control in individuals with short- vs. long-duration diabetes 2 years after bariatric surgery
- Inadequate β-cell function is a key factor characterizing the attenuated glycemic responses to bariatric surgery in people with long-duration diabetes

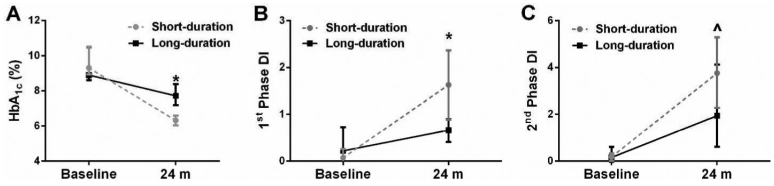

Figure 1.

Effect of bariatric surgery on Hb_{A1c} and DI in subjects with short vs. long-duration type 2 diabetes. Change in Hb_{A1c} (A), 1st phase DI (B), and 2nd phase DI (C) from baseline to 24 months post-surgery. Compared with baseline, **p*=0.04 and ^*p=0.01*. DI = disposition index (meal-stimulated insulin secretion rate [iAUC C-peptide/iAUC Glucose] multiplied by insulin sensitivity).

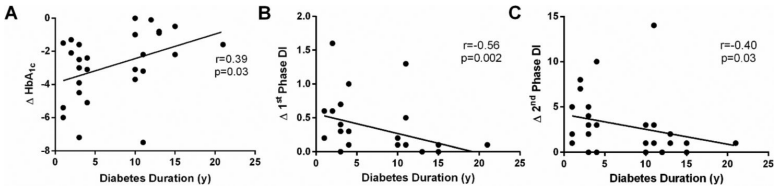

Figure 2.

Correlations between diabetes duration and 1st phase DI (A), 2nd phase DI (B), and Hb_{A1c} (C). DI = disposition index (meal-stimulated insulin secretion rate [iAUC C-peptide/iAUC Glucose] multiplied by insulin sensitivity). Hb_{A1c} reflects absolute difference between Post-Pre.

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Table 1

Comparison between short- and long-duration diabetes subjects following bariatric surgery at baseline and 24 months.

	Short-Duration		**Long-Duration**		***P-value***	
	Pre	**Δ**	***Pre***	**Δ**	***Pre vs. Pre***	**Δ *vs.* Δ**
n (M,F)	14 (11F, 3M)	-	13 (7F, 6M)	-	0.24	-
n (RYGB, SG)	14 (7, 7)	-	13 (5, 8)	-	0.70	-
Age (years)	50.4 [38.2, 55.5]	-	52.0 [42.5, 59.1]	-	0.39	-
DiaRem	10.5 [9.25, 17]	−8 [−12.75, −6]	18 [10, 19]	−2 [−10, 0]	0.39	0.12
Medication Sum	4 [2, 4.7]	−2.5 [−4, −2]	5 [4, 5]	−3 [−4, −2]	**0.02**	0.69
Weight (kg)	99.3 [93.8, 111.5]	−22.6 [−29.0, −17.8]	105.8 [91.2, 112.5]	−19.7 [−23.5, −16.8]	0.83	0.17
BMI (kg/m^2)	36.76 [34.77, 37.99]	−8.2 [−10.1, −6.8]	35.3 [34.1, 37.8]	−6.81 [−8.6, −5.5]	0.83	0.12
HbA_{1c} (%)	9.3 [8.9, 10.5]	−3.0 [−4.9, −2.1]	8.9 [8.6, 10.5]	−1.6 [−3.1, −0.8]	0.61	**0.04**
HbA_{1c} (mmol/mol)	74 [70, 91]	−33.6 [−54.2, −23.7]	78 [74.2, 84.2]	−18 [−34, −9]	0.61	**0.04**
FPG (mg/dl)	204.5 [144, 238]	−95.5 [−141.7, −60.7]	171 [112, 209]	−72 [−104, −8]	0.45	0.42
FPI (μU/ml)	26.35 [15.1, 40.8]	−14.7 [−30.0, −7.1]	11.5 [5.7, 22.8]	−1 [−5.7, 3.4]	**0.009**	**0.003**
FPCpep (ng/ml)	3.8 [2.4, 4.6]	−1.8 [−2.5, −0.5]	1.4 [0.5, 2.6]	−0.2 [−0.8, 0.3]	**0.003**	**0.01**
PG $AUC_{0\text{-}30}$	7.1 [4.3, 12.5]	12 [3.5, 23.6]	6.5 [3.5, 8.2]	20.2 [13.5, 27]	0.42	0.22
PI $AUC_{0\text{-}30}$	3.2 [1.2, 5.9]	24.0 [18.7, 31.9]	2.0 [0.7, 2.5]	9.7 [6.2, 17.9]	0.28	**0.01**
ISR/PG ($iAUC_{0\text{-}30}$)	0 [−0.02, 0.02]	0.04 [0, 0.07]	0.01 [0, 0.02]	0 [0, 0.02]	0.49	0.15
PG $AUC_{60\text{-}120}$	90.2 [57.5, 99.6]	−52.3 [−67.8, −40.0]	80.2 [75.7, 82.2]	−12.2 [−42.2, 21]	0.45	**0.003**
PI $iAUC_{60\text{-}120}$	20.2 [5.3, 34.3]	12.9 [−13.4, 18.9]	8.9 [7.7, 17.7]	6.2 [−0.9, 20.2]	0.28	0.87
ISR/PG ($iAUC_{60\text{-}120}$)	0.01 [0, 0.02]	0.07 [0.04, 0.1]	0.01 [0, 0.01]	0.01 [0, 0.03]	0.65	**<0.001**
Insulin Sensitivity	1.3 [1.1,2.7]	2.3[1.6,3.2]	3.9 [2.7,6.2]	0.89 [0, 3.0]	**0.008**	0.17
DI (1st phase)	0.07 [−0.2, 0.2]	0.9 [0.7, 2.2]	0.2 [−0.04, 0.7]	0.2 [−0.3, 0.7]	0.30	**0.04**
DI (2nd phase)	0.1 [0.01, 0.3]	2.8 [1.8, 4.5]	0.1 [−0.04, 0.6]	0.4 [0.1, 1.3]	0.62	**0.01**
fGLP-1	1.1 [0.8, 2]	0 [−0.3, 1.0]	1.2 [0.6, 2.3]	0 [−0.2, 0.2]	>0.99	>0.99
ΔGLP-1 (60 min)	3.0 [2.5, 3.8]	4.6 [3.1, 9.6]	1.9 [0.9, 3.1]	8.5 [5.9, 30.3]	0.09	0.21
fGIP	5 [1.8, 8.7]	−1.2 [−4.2, 0.5]	3.7 [2, 4.9]	−0.2 [−2.1, 1.9]	0.92	0.26

Data are reported as median [25%, 75%]. BMI = body mass index. FPG = fasting plasma glucose. FPI = fasting plasma insulin. FPCpep = fasting plasma C-peptide. iAUC = incremental area under the curve. ISR = meal-stimulated insulin secretion rate (iAUC C-peptide divided by iAUC Glucose). RYGB = Roux-en-Y Gastric Bypass. SG = Sleeve Gastrectomy. Bold type denotes statistical significance.