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Six and 12 Weeks of Caloric Restriction Increases β Cell Function and Lowers Fasting and Postprandial Glucose Concentrations in People with Type 2 Diabetes[1–3]

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Abstract

Background: Caloric restriction alone has been shown to improve insulin action and fasting glucose metabolism; however, the mechanism by which this occurs remains uncertain.

Objective: We sought to quantify the effect of caloric restriction on β cell function and glucose metabolism in people with type 2 diabetes.

Methods: Nine subjects (2 men, 7 women) with type 2 diabetes [BMI (in kg/m^2): 40.6 ± 1.4; age: 58 ± 3 y; glycated hemoglobin: 6.9% ± 0.2%] were studied using a triple-tracer mixed meal after withdrawal of oral diabetes therapy. The oral minimal model was used to measure β cell function. Caloric restriction limited subjects to a pureed diet (<900 kcal/d) for the 12 wk of study. The studies were repeated after 6 and 12 wk of caloric restriction.

Results: Fasting glucose concentrations decreased significantly from baseline after 6 wk of caloric restriction with no further reduction after a further 6 wk of caloric restriction (9.8 ± 1.3, 5.9 ± 0.2, and 6.2 ± 0.3 mmol/L at baseline and after 6 and 12 wk of caloric restriction, respectively; $P = 0.01$) because of decreased fasting endogenous glucose production (EGP: 20.4 ± 1.1, 16.2 ± 0.8, and 17.4 ± 1.1 μmol · kg^{-1} · min^{-1} at baseline and after 6 and 12 wk of caloric restriction, respectively; $P = 0.03$). These changes were accompanied by an improvement in β cell function measured by the disposition index (189 ± 51, 436 ± 68, and 449 ± 67 10^{-14} dL · kg^{-1} · min^{-2} · pmol^{-1} at baseline and after 6 and 12 wk of caloric restriction, respectively; $P = 0.01$).

Conclusions: Six weeks of caloric restriction lowers fasting glucose and EGP with accompanying improvements in β cell function in people with type 2 diabetes. An additional 6 wk of caloric restriction maintained the improvement in glucose metabolism. This trial was registered at clinicaltrials.gov as NCT01094054. *J Nutr* 2015;145:2046–51.

Keywords: caloric restriction, endogenous glucose production, bariatric surgery, gastric emptying, insulin secretion, insulin action, disposition index

Introduction

Bariatric surgery ameliorates type 2 diabetes to a degree that depends in part on the nature of the procedure (1) and in part on underlying subject factors such as duration and severity of diabetes preceding surgery (2). Nevertheless, initial metabolic responses to intervention are quite dramatic and occur independently of weight loss (3). Because caloric restriction per se is shown to have salutary effects on glucose metabolism (4, 5), it is likely that this contributes substantially to the early amelioration of glucose metabolism after bariatric surgery. However, the response to a meal challenge after caloric restriction remains ill defined.

Glucose uptake during hyperinsulinemic, euglycemic conditions is reported to be increased after 7 d of caloric restriction (~800 kcal/d), despite minimal weight loss (5). More recently, a very-low-calorie diet (500 kcal/d) and Roux-en-Y gastric bypass (RYGB)[9] resulted

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[3] Supplemental Tables 1 and 2 and Supplemental Figure 1 are available in the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[8] These authors contributed equally to this work.
[9] Abbreviations used: DI, disposition index; EGP, endogenous glucose production; Meal Ra, Meal Rate of Appearance; Rd, glucose disappearance; RYGB, Roux-en-Y gastric bypass; S_I, insulin action; ϕ, β cell responsivity.
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TABLE 1 Anthropometric characteristics of subjects in the study at the time of their screening visit and then after 6 and 12 wk of caloric restriction[1]

Characteristic	Screening[2]	6 wk	12 wk
Sex, M/F	2/7	—	—
Age, y	58 ± 3	—	—
Glycated hemoglobin, %	6.9 ± 0.2[3]	NM	NM
Fasting glucose, mmol/L	7.0 ± 0.3[3]	5.9 ± 0.2	6.2 ± 0.3
Weight, kg	114 ± 6	105 ± 5	101 ± 6
BMI, kg/m^2	40.6 ± 1.4	37.3 ± 1.6	35.8 ± 1.8
Lean body mass, kg	56 ± 3	53 ± 2	53 ± 3
Weight lost, kg	NA	8.9 ± 1.0	14.8 ± 1.4
Weight lost, %	NA	−8 ± 1	−14 ± 1

[1] Values are means ± SEMs, n = 9 except at 12 wk, n = 8. NA, not applicable; NM, not measured.
[2] Medical therapy for type 2 diabetes included metformin (n = 6) and glimepiride (n = 2). One participant received no medication. Therapy was withdrawn 3 wk before baseline.
[3] On treatment at the time of screening.

in a comparable improvement in insulin action (S_i) and β cell function measured by an intravenous glucose tolerance test in patients with type 2 diabetes (6). In contrast, an 800-kcal/d diet produced less improvement in β cell function than a matched cohort of subjects after RYGB with equivalent weight reduction, implying an additive effect of RYGB (7). The lack of concordance between studies may in part be due to the use of differing, qualitative measures of S_i and secretion (8). More importantly, the effects of caloric restriction on fasting and postprandial glucose metabolism remain indeterminate (9).

To address these questions, we examined the effect of caloric restriction on glucose metabolism by using a labeled mixed meal (10) to simultaneously measure β cell function, S_i, and fasting and postprandial glucose metabolism (11). People with type 2 diabetes were studied before and after 6 and 12 wk of caloric restriction.

Methods

Subjects. After approval from the Mayo Institutional Review Board, we recruited 9 subjects (2 men, 7 women) with type 2 diabetes [BMI (in kg/m^2): 40.6 ± 1.4; age: 58 ± 3 y; glycated hemoglobin: 6.9% ± 0.2%] who gave written, informed consent to participate in the study. All subjects had no active microvascular or macrovascular complications of diabetes, were weight stable, and did not actively exercise. They were instructed to follow a weight maintenance diet (~55% carbohydrate, 30% fat, and 15% protein) in the run-up to the baseline study. All glucose-lowering medication was withdrawn for the 3 wk before the study, and this withdrawal was subsequently maintained for the duration of the study.

Subjects met with the study dietician on a weekly basis. They were instructed to consume a diet of 740 kcal daily by using meals derived from the Nutritional Guidelines after Bariatric Surgery (**Supplemental Table 1**). After 4 wk, subjects increased caloric consumption to 875 kcal daily. Compliance was monitored by weekly meetings with the dietician using an electronic record of food intake. Subjects also met with a behavioral psychologist every other week during the study period. The psychologist used motivational enhancement and behavior change techniques to promote compliance with the dietary guidelines. Body composition was measured with DXA (DPX scanner; Lunar) before each meal study.

Experimental design. Subjects were studied on 3 occasions: at baseline and then after 6 and 12 wk of caloric restriction. The study was registered at clinicaltrials.gov as NCT01094054. Subjects were admitted to the clinical research unit at 1700 on the evening before all meal studies. They consumed a standardized low-calorie meal (10 kcal/kg body weight: 40% carbohydrate, 30% fat, and 30% protein) and then fasted overnight. At 0630 the next morning (−180 min), an 18-gauge needle was inserted into a forearm vein to allow infusions to be performed. An 18-gauge cannula was inserted retrogradely into a vein on the dorsum of the contralateral hand. This hand was placed in a heated acrylic plastic box maintained at 55°C to allow sampling of arterialized venous blood. A primed (12 mg/kg) continuous (0.12 mg · kg^{-1} · min^{-1}) infusion of [6,6-$^2H_2$] glucose was initiated. At time 0 (0930), subjects consumed a meal (220 kcal, 56% carbohydrate, 25% fat, 19% protein) consisting of 1 scrambled egg, 55 g

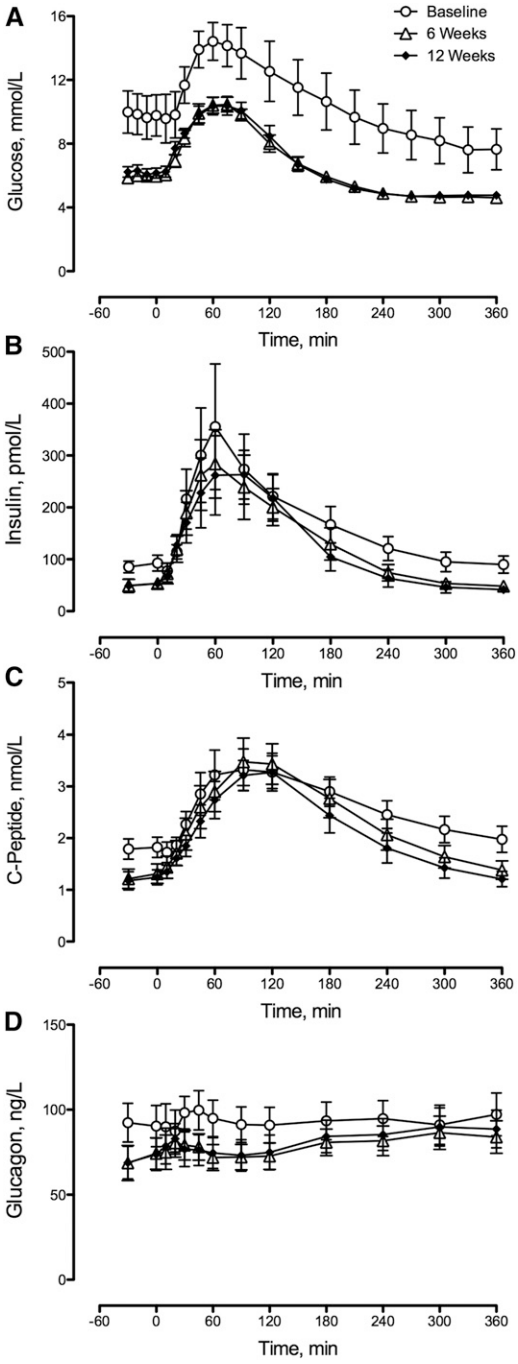

FIGURE 1 Plasma glucose (A), insulin (B), C-peptide (C), and glucagon (D) concentrations during meal studies at baseline and after 6 and 12 wk of caloric restriction for patients with type 2 diabetes. The changes in fasting concentrations of glucose, insulin, C-peptide, and glucagon and peak postprandial glucose concentrations after 6 and 12 wk of caloric restriction are detailed in Table 2. Values are means ± SEMs, n = 9 except at 12 wk, n = 8.

TABLE 2 Fasting and postprandial glucose and hormone concentrations during the baseline meal study and after 6 and 12 wk of caloric restriction for patients with type 2 diabetes[1]

Concentrations	Baseline study	6 wk study	12 wk study	P^2	Post hoc comparisons
Fasting glucose, mmol/L	9.8 ± 1.3	5.9 ± 0.2	6.2 ± 0.3	$<1 \times 10^{-4}$	BL > (6 wk = 12 wk)
Peak postprandial glucose, mmol/L	14.9 ± 1.4	11.0 ± 0.4	10.9 ± 0.5	$<1 \times 10^{-4}$	BL > (6 wk = 12 wk)
AAB glucose, mmol/L × 6 h	197 ± 101	186 ± 68	160 ± 38	0.28	NA
Fasting insulin, pmol/L	89 ± 13	51 ± 11	51 ± 11	$<1 \times 10^{-4}$	BL > (6wk = 12 wk)
Peak postprandial insulin, pmol/L	369 ± 120	325 ± 66	310 ± 74	0.97	NA
AAB insulin, nmol/L × 6 h	29.5 ± 8.9	29.5 ± 6.2	23.8 ± 5.4	0.69	NA
Fasting C-peptide, nmol/L	1.8 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	$<1 \times 10^{-4}$	BL > (6 wk = 12 wk)
Peak postprandial C-peptide, nmol/L	3.5 ± 0.5	3.7 ± 0.5	3.5 ± 0.3	0.40	NA
AAB C-peptide, nmol/L × 6 h	296 ± 20	402 ± 48	339 ± 32	0.19	NA
Fasting glucagon, ng/L	91 ± 12	71 ± 10	71 ± 9	0.02	BL > (6 wk = 12 wk)
Peak postprandial glucagon, ng/L	107 ± 12	95 ± 9	96 ± 10	0.19	NA
AAB glucagon, μg/L × 6 h	0.7 ± 1.0	2.9 ± 0.9	3.8 ± 0.6	0.006	BL < (6 wk = 12 wk)

[1] Values are means ± SEMs, $n = 9$ except at 12 wk, $n = 8$. AAB, area above basal; BL, baseline; NA, not applicable.
[2] Determined by repeated-measures ANOVA.

Canadian bacon, 100 mL water, and gelatin that contained 35 g glucose labeled with [1-^{13}C] glucose (4% enrichment). To enable measurement of solid-phase gastric emptying, the egg was labeled with 0.1 mCi ^{111}In-DTPA. An infusion of [6-^{3}H] glucose was started at time 0. The infusion rates for the tracers were varied to minimize changes in specific activity as previously described (12). At the end of the meal subjects drank 30 mL water. The meal was consumed in the sitting position. For 1 subject intravenous access was lost during the third meal study (after 12 wk of caloric restriction), and data from that study were not used.

Analytical techniques. Plasma samples were placed on ice, centrifuged at 4°C, separated, and stored at −20°C until assayed. Glucose concentrations were measured with a glucose oxidase method (Yellow Springs Instruments). Plasma insulin was measured with a chemiluminescence assay (Access Assay; Beckman). Plasma glucagon and C-peptide were measured by radioimmunoassay (Linco Research). Plasma [6,6-$^{2}H_2$] glucose and [1-^{13}C] glucose enrichments were measured with gas chromatographic mass spectrometry (Thermoquest) to simultaneously monitor the C-1 and C-2 and C-3 to C-6 fragments, as described by Beylot et al. (13). In addition, [6-^{3}H] glucose-specific activity was measured by liquid scintillation counting after deproteinization and passage over anion and cation exchange columns (12).

Gastric emptying was measured by anterior and posterior gamma camera images obtained in the supine position immediately after meal ingestion, and then every 15 min for the first 2 h, then every 30 min for the next 2 h (total 4 h after the meal). A region of interest analysis with counts corrected for radionuclide decay and tissue attenuation was used as previously described (14).

Calculations. The systemic Meal Rate of Appearance (Meal Ra), endogenous glucose production (EGP), and glucose disappearance (Rd) were calculated with Steele's model (15). Meal Ra was calculated by multiplying rate of appearance of [1-^{13}C] glucose (obtained from the infusion rate of [6-^{3}H] glucose and the clamped plasma ratio of [6-^{3}H] glucose and [1-^{13}C] glucose) by the meal enrichment. EGP was calculated from the infusion rate of [6,6-$^{2}H_2$] glucose and the ratio of [6,6-$^{2}H_2$] glucose to endogenous glucose production. Rd was calculated by subtracting the change in glucose mass from the overall rate of glucose appearance (i.e., Meal Ra + EGP). Values from −30 to 0 min were averaged and considered as basal. Incremental, integrated excursions were calculated with the trapezoidal rule.

Net S_i was measured with the oral minimal model (16). β Cell responsivity (ϕ) (11) was estimated with the oral C-peptide minimal model (17), incorporating age-associated changes in C-peptide kinetics (18). Disposition indexes (DIs) were subsequently calculated as $\phi \times S_i$.

Statistical analysis. Data in the text are presented as (observed) means ± SEMs. Differences between the baseline and 6- and 12-wk studies were assessed with a repeated-measures ANOVA and assumed the absence of a Gaussian distribution (Friedman test). Subsequently, in the presence of significant between time point differences, a post hoc Student's paired t test was used to examine differences between the 3 study days (baseline vs. 6 wk, baseline vs. 12 wk, and 6 wk vs. 12 wk). A Dunn test was used if values were not normally distributed. The statistical analysis was undertaken in Primer 5 (GraphPad Software). $P < 0.05$ was considered statistically significant.

Results

Volunteer characteristics. Subject characteristics are summarized in **Table 1**.

Plasma glucose, insulin, C-peptide, and glucagon concentrations before and after 6 and 12 wk of caloric restriction. Fasting glucose decreased after 6 wk of caloric restriction (**Figure 1**A). No further decrease in fasting glucose was observed after 6 additional weeks of caloric restriction (**Table 2**). Peak postprandial glucose concentrations also decreased after 6 wk with no further decrease observed at 12 wk (Table 2). Of note, caloric restriction did not alter area above basal postprandial glucose concentrations (Table 2).

Fasting insulin concentrations decreased after 6 wk of caloric restriction, with no further decrease thereafter (Figure 1B, Table 2). Caloric restriction did not alter peak or area above basal postprandial insulin concentrations.

Fasting C-peptide concentrations decreased after caloric restriction with no difference between 6- and 12-wk values (Figure 1C, Table 2). Neither peak nor area above basal postprandial C-peptide concentrations was altered by 6 or 12 wk of caloric restriction (Table 2).

Fasting glucagon concentrations were decreased by caloric restriction with no difference between 6- and 12-wk values (Figure 1D, Table 2). Peak postprandial glucagon concentrations were unchanged by caloric restriction (Table 2). However, the postprandial area above basal glucagon concentrations was increased by caloric restriction (Table 2), with no difference between 6- and 12-wk values. However, area under the curve for postprandial glucagon concentrations was unchanged by caloric restriction.

EGP, Meal Ra, and Rd before and after 6 and 12 wk of caloric restriction. Six weeks of caloric restriction decreased fasting EGP with no difference between 6- and 12-wk values (**Figure 2**A, **Table 3**).

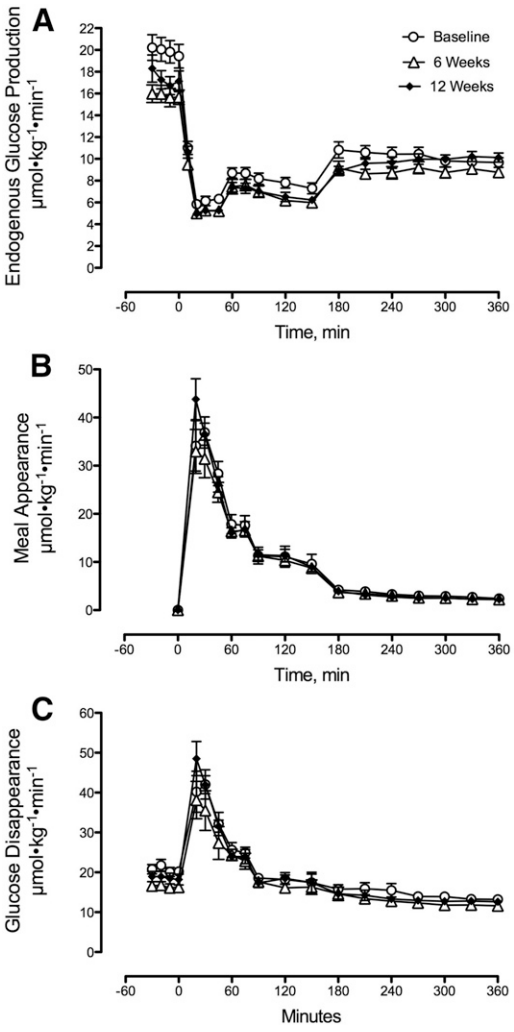

FIGURE 2 Rates of endogenous glucose production (A), meal appearance (B), and glucose disappearance (C) during meal studies at baseline and after 6 or 12 wk of caloric restriction for patients with type 2 diabetes. The changes in fasting endogenous glucose production after 6 and 12 wk of caloric restriction are detailed in Table 3. Values are means ± SEMs, n = 9 except at 12 wk, n = 8.

Nadir postprandial EGP was unchanged by caloric restriction (Table 3).

Caloric restriction did not alter either peak or area above basal postprandial Meal Ra (Figure 2B, Table 3).

Fasting Rd was decreased by caloric restriction with no difference between 6- and 12-wk values (Figure 2C, Table 3). Peak and integrated rates of postprandial glucose disposal were not altered by caloric restriction (Figure 2C, Table 3).

Gastric emptying before and after 6 and 12 wk of caloric restriction. Caloric restriction did not alter the rate of gastric emptying of radiolabeled solids (**Figure 3**).

S_i, ϕ, and DI before and after 6 and 12 wk of caloric restriction. S_i did not change significantly after caloric restriction (4.4 ± 1.0 vs. 6.2 ± 1.6 vs. $6.0 \pm 1.3\ 10^{-4}\ min^{-1} \cdot nU^{-1} \cdot mL^{-1}$ at baseline and 6 and 12 wk, respectively; $P = 0.19$) (**Figure 4**A).

However, caloric restriction increased ϕ (25 ± 8 vs. 36 ± 5 vs. $37 \pm 6\ 10^{-9}$ min at baseline and 6 and 12 wk, respectively; $P < 0.01$; Figure 4B), primarily because of an increase in the static component of ϕ (data not shown) with no difference between the 6- and 12-wk values.

When the ϕ was considered in light of the prevailing degree of S_i by calculating the DI, ϕ increased after caloric restriction (189 ± 51 vs. 436 ± 68 vs. $449 \pm 67\ 10^{-14}\ dL \cdot kg^{-1} \cdot min^{-2} \cdot pmol^{-1}$ at baseline and 6 and 12 wk, respectively; $P < 0.01$; Figure 4C), with no difference between the 6 and 12 wk values. The 95% CIs are shown in **Supplemental Figure 1**.

Discussion

Six weeks of caloric restriction in people with type 2 diabetes lowered fasting and postprandial glucose concentrations to values that approached those typically observed in people who do not have diabetes (19, 20). The decrease in fasting glucose was attributable to a decrease in fasting EGP. However, caloric restriction did not alter either postprandial Meal Ra or stimulation of postprandial Meal Ra, accounting for the lack of change in postprandial glycemic excursion as measured by the area above basal. The improvement in glycemic control was accompanied by an increase in insulin secretion and a trend toward improved postprandial S_i. Despite ongoing caloric restriction and additional weight loss, no further improvement was found in insulin secretion or S_i and fasting EGP and on the pattern of postprandial glucose metabolism. Adherence to the caloric restriction is confirmed by the average 8% and 14% weight loss at 6 and 12 wk, respectively.

The decrease in fasting glucose and EGP observed in the present study are consistent with prior studies in which people with type 2 diabetes lost ~15 kg after consuming a very-low-calorie

TABLE 3 Fasting and postprandial variables of glucose metabolism during the baseline meal study and after 6 and 12 wk of caloric restriction for patients with type 2 diabetes[1]

Variables	Baseline study	6 wk study	12 wk study	P^2	Post hoc comparisons
Fasting EGP, μmol · kg^{-1} · min^{-1}	20.4 ± 1.2	16.2 ± 0.8	17.4 ± 1.1	0.003	BL > (6 wk = 12 wk)
Nadir EGP, μmol · kg^{-1} · min^{-1}	5.9 ± 0.4	4.8 ± 0.2	5.1 ± 0.3	0.07	NA
Peak Meal Ra, μmol · kg^{-1} · min^{-1}	40.1 ± 3.0	32.1 ± 3.4	38.1 ± 3.7	0.33	NA
AAB Meal Ra, mmol/kg × 6 h	3.2 ± 0.3	3.0 ± 0.1	3.0 ± 0.3	0.82	NA
Fasting Rd, μmol · kg^{-1} · min^{-1}	20.7 ± 1.1	16.4 ± 0.8	18.6 ± 1.3	$<1 \times 10^{-4}$	BL > (6 wk = 12 wk)
Peak Rd, μmol · kg^{-1} · min^{-1}	45.0 ± 3.3	38.7 ± 2.9	44.9 ± 2.6	0.33	NA
AAB Rd, mmol/kg × 6 h	6.4 ± 0.2	6.2 ± 0.4	6.1 ± 0.3	0.15	NA

[1] Values are means ± SEMs, n = 9 except at 12 wk, n = 8. AAB, area above basal; BL, baseline; EGP, endogenous glucose production; NA, not applicable; Meal Ra, rate of meal appearance; Rd, rate of disappearance.
[2] Determined by repeated-measures ANOVA.

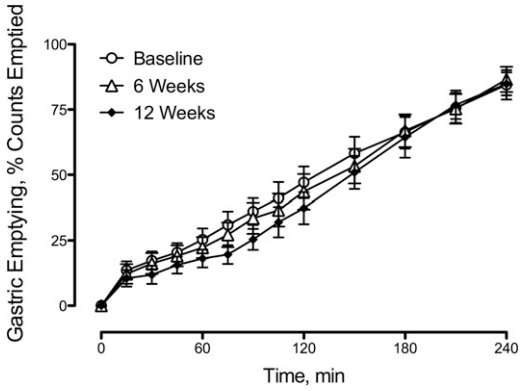

FIGURE 3 Gastric emptying after meal ingestion at baseline and after 6 and 12 wk of caloric restriction for patients with type 2 diabetes. The rate of gastric emptying was unchanged by caloric restriction. Values are means ± SEMs, $n = 9$ except at 12 wk, $n = 8$.

diet (330 kcal/d) over 40 d. As in the present study, the effects on fasting glucose were rapid with most of the effect seen within the first 10 d of caloric restriction (4). Similarly, despite minimal weight loss, subjects fed 800 kcal/d for 1 wk had a decrease in fasting glucose and EGP equal in magnitude to about one-half of the change observed after weight loss of ~12 kg with greater caloric restriction (400 kcal/d) for 8 wk (5). In the present experiment, the decrease in fasting glucose was accompanied by an improvement in insulin secretion with a trend toward improvement in S_i. The improvement in insulin secretion was primarily because of an increase in the static response to glucose which is believed to represent the provision of new insulin to the releasable pool (17). Previously, β cell function measured with a hyperglycemic clamp was shown to improve after caloric restriction of 400 kcal/d for 7 d (21) or caloric restriction of ~1100 kcal/d (22).

Improvements in β cell secretion are typically accompanied by decreased α-cell secretion (12). In addition, ingestion of a mixed meal that contained fat and protein is typically accompanied by an increase in postprandial glucagon concentrations (23). During the present experiment, postprandial peak glucagon concentrations were unchanged from baseline by caloric restriction. The increase in incremental glucagon concentrations we observed after caloric restriction is explained not by increased peak postprandial glucagon concentrations but by the greater change from (the lower) fasting concentrations observed after caloric restriction. The effect of caloric restriction on glucagon was previously examined by Kelley et al. (5) who reported a decrease in fasting glucagon concentrations. Vetter et al. (9) reported a similar decrease in fasting glucagon after caloric restriction similar to that undertaken in this experiment. However, peak and incremental postprandial glucagon concentrations were also decreased by caloric restriction. Whether that reflects differences in the composition of the meal ingested and rate of its emptying (liquid vs. solid meal) remains to be ascertained (24).

The lack of improvement in S_i contrasts with reports that used a greater degree (400–500 kcal/d) of caloric restriction (5, 6, 21) but is in concordance with other studies that used less (~1100 kcal/d) caloric restriction (22). Notably, however, both fasting glucose and insulin decreased after caloric restriction and were accompanied by a decrease in fasting EGP, suggesting an improvement in hepatic insulin sensitivity. However, the systemic Meal Ra that represented the net balance of gastric emptying, intestinal absorption, and hepatic extraction of absorbed glucose was unchanged. Given that gastric emptying was unchanged by caloric restriction, this would suggest that hepatic extraction of ingested glucose is also unaltered.

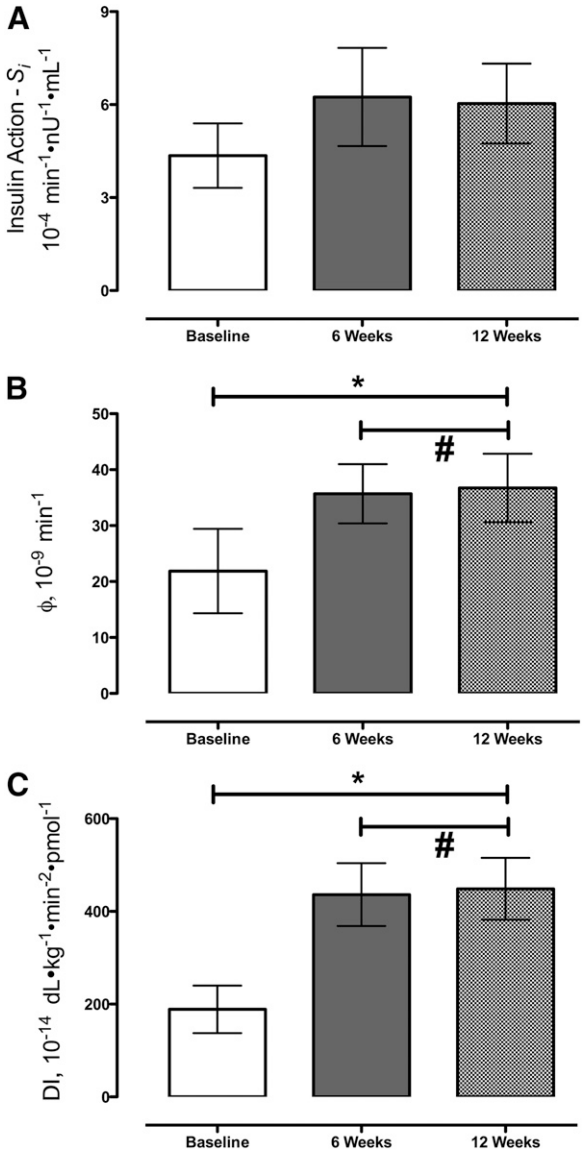

FIGURE 4 S_i (A), ϕ (B), and DI (C) during meal studies at baseline and after 6 and 12 wk of caloric restriction for patients with type 2 diabetes. S_i was unchanged by caloric restriction. Values are means ± SEMs, $n = 9$ except at 12 wk, $n = 8$.*Different from baseline, $P < 0.05$ (ANOVA). $^{\#}P > 0.05$ (post hoc t test). DI, disposition index; S_i, insulin action; ϕ, β cell responsivity.

As in the present experiment, Isbell et al. (8) noted a significant effect of caloric restriction alone on glucose metabolism, an effect that did not differ from that of RYGB. Two other studies demonstrated similar (7) or equivalent (6) effects of caloric restriction on glucose metabolism compared with bariatric surgery. Taken together these data strongly suggest that caloric restriction can account for many of the early effects of bariatric surgery (9, 25).

The study had certain limitations. The sample size of 9 subjects certainly allowed detection of the large changes in fasting glucose metabolism observed after 6 wk of caloric restriction (**Supplemental Table 2**). However, the study may have been underpowered to detect small(-er) changes in other variables or differences between the 6- and 12-wk studies. We have provided a power estimate in Supplemental Table 1. Nevertheless, our observations are congruent with those observed by Vetter et al. (9) in 10 subjects. We measured net S_i rather than

the individual contributions of insulin-induced suppression of glucose production and insulin-induced stimulation of glucose uptake. Although it is possible that caloric restriction resulted in offsetting effects on hepatic and extrahepatic S_i, this seems to be an unlikely explanation for the lack of a significant change in S_i after caloric restriction. We only studied the effect of restricting caloric intake to ~800 kcal/d. We chose this degree of caloric restriction because it mimics that which patients undergoing bariatric surgery consume in the first postoperative weeks.

In conclusion, 6 wk of caloric restriction lowered EGP and fasting glucose. Six weeks of caloric restriction also increased insulin secretion and tended to improve postprandial S_i. However, caloric restriction did not alter the pattern and degree of postprandial suppression of EGP, the postprandial stimulation of glucose uptake, or the systemic Meal Ra. Although 6 additional weeks of caloric restriction resulted in further weight loss, it had no additional effects on fasting glucose concentrations, EGP, insulin secretion, or S_i. Because caloric restriction per se lowers fasting EGP and fasting glucose and increases insulin secretion, these effects need to be considered in experiments that attempt to determine the mechanisms by which other interventions that also cause caloric restriction (e.g., bariatric surgery) ameliorate type 2 diabetes. These data suggest that caloric restriction or other therapeutic approaches that lower EGP will result in substantial improvement in glycemic control in people with type 2 diabetes.

Acknowledgments

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