Effect of Pioglitazone on Energy Intake and Ghrelin in Diabetic Patients

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OBJECTIVE — To measure ghrelin and energy intake in the laboratory after pioglitazone treatment.

RESEARCH DESIGN AND METHODS — This was a parallel, three-arm study with 51 obese diabetic subjects randomized to either *1*) pioglitazone plus a portion-controlled diet (Pio+PC), *2*) pioglitazone plus American Diabetes Association (ADA) dietary advice (Pio+ADA), or *3*) metformin plus ADA advice (Met+ADA). Energy intake and the suppressive response of a meal on ghrelin were measured at weeks 0 and 16. Mixed models tested if changes from week 0 to 16 differed by group.

RESULTS — The Pio+ADA group had a significantly larger increase ($P < 0.05$) in energy intake ([adjusted means ± SE] 207 ± 53 kcal) compared with the Pio+PC (50 ± 46 kcal) and Met+ADA (52 ± 49 kcal) groups. Change in restraint and disinhibition (variables associated with eating behavior) mediated weight change. Ghrelin suppression increased in the Pio+ADA group, which gained weight.

CONCLUSIONS — A portion-controlled diet attenuated the increase in energy intake after pioglitazone. Ghrelin responded to weight change not pioglitazone exposure.

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Thiazolidinediones (TZDs) improve insulin sensitivity (1) and shift visceral fat to subcutaneous fat (2). TZDs are associated with weight gain (3,4), which can negatively affect treatment acceptability. It is unclear if increased energy intake is responsible for TZD-associated weight gain. The effect of TZDs on ghrelin in the absence of weight gain is also unclear.

This study tested the effect of pioglitazone treatment on *1*) energy intake, measured in the laboratory; *2*) ghrelin; *3*) appetite; *4*) dietary restraint and disinhibition; and *5*) food cravings. Potential mediators of energy intake and weight change were also examined.

RESEARCH DESIGN AND METHODS

— Participants (51 obese men and women) aged 35–75 years who were diagnosed with type 2 diabetes were enrolled. The study was approved by the institutional review board, and participants provided written informed consent. Complete descriptions of the study are described elsewhere (5). Participants had not been previously treated with TZDs and were not using drugs that affect metabolism or body weight (e.g., sibutramine).

Treatment arms

Participants were randomly assigned to one of three treatment groups for the 16-week study: *1*) pioglitazone plus standard dietary advice from the American Diabetes Association (ADA) (Pio+ADA); *2*) pioglitazone plus a portion-controlled diet (Pio+PC); and *3*) an active control group, metformin plus ADA advice (Met+ADA). These treatments have been previously described (5). Briefly, all participants were prescribed a diet that was 500 kcal/day less than their energy requirements. The Pio+PC group drank one Glucerna (290 kcal) for breakfast and one for lunch, with a planned evening meal.

Outcome variables

Change from baseline to week 16 (week 16 minus week 0) on the following variables was quantified.

Four hours after a 371-kcal breakfast, energy intake was measured objectively at lunch in the laboratory using methods that produce repeatable/reliable energy intake measurements (6). Serum ghrelin levels were measured before and 2 h after the start of lunch to quantify ghrelin response to a meal (postmeal minus premeal). Ratings of hunger, desire to eat, fullness, and prospective food consumption were measured with visual analog scales (VASs) (7) before and after lunch. The eating inventory quantified dietary restraint (the intent to restrict energy intake) and disinhibition (the tendency to overeat) (8). The food-craving inventory (FCI) measured general cravings (total score) and cravings for the following specific types of foods: sweets, high fats, carbohydrates/starches, fruits/vegetables, and fast-food fats (9).

Data analyses

Analyses were conducted with $\alpha = 0.05$ using SAS version 9.0 (Cary, NC). Mixed models tested if change on the outcome variables differed by group (baseline values were covariates). Posthocs tested for differences among the three groups.

Regression methods (10) were used to test for mediators of differential body weight change between the Pio+PC and Pio+ADA groups. The following possible mediators were tested: ghrelin, energy intake, dietary restraint, and disinhibition. Pearson correlation coefficients were calculated to determine the amount of variance in body weight (and energy intake) change that was accounted for by change in restraint and disinhibition.

RESULTS — Forty-eight of 51 participants completed the trial (2 subjects dropped out from the Pio+ADA and 1 from the Met+ADA group). As previously reported (5), Pio+ADA gained (means ± SD) 2.15 ± 1.09 kg, Met+ADA lost 3.21 ± 0.7 kg, and Pio+PC lost

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2.59 ± 1.25 kg. The Pio+ADA group had a smaller decrease in visceral fat compared with Pio+PC group but a larger increase in deep subcutaneous fat compared with the Met+ADA group (5).

Baseline characteristics and change in outcome variables are provided in Table 1. Energy intake increased significantly in the Pio+ADA ($P < 0.001$) but not the Met+ADA ($P = 0.30$) or Pio+PC ($P = 0.28$) groups. Increased energy intake in the Pio+ADA group was significantly larger than the Met+ADA and Pio+PC groups ($P < 0.05$). The difference in least squares (LS) means ± SE between the Pio+ADA and Met+ADA and Pio+ADA and Pio+PC groups was 155 ± 73 and 157 ± 70 kcal, respectively.

The Pio+ADA group had a significantly larger meal-induced suppression of ghrelin at week 16 compared with week 0, which was significantly larger than the nonsignificant changes in the Met+ADA and Pio+PC groups. The within-run assay coefficient of variation was 10%. Change in appetite ratings did not differ significantly among the groups (data not shown) ($P > 0.25$). The Pio+PC group had a significant increase in dietary restraint and a decrease in disinhibition and hunger. Change in these end points differed significantly between the Pio+PC and Pio+ADA groups ($P < 0.01$). The difference in LS means ± SE between the Pio+PC and Pio+ADA groups on restraint and disinhibition was 4.8 ± 1.4 and 2.5 ± 0.9, respectively. The Met+ADA group experienced a significant decrease in general cravings and cravings for high-fat foods. Change in cravings did not differ among groups ($P > 0.06$).

Change in restraint and disinhibition mediated differential weight change between the Pio+PC and Pio+ADA groups. Mediators of energy intake change were nonsignificant. Change in restraint and disinhibition were negatively ($r = -0.53$, $P < 0.001$) and positively ($r = 0.39$, $P < 0.01$) associated with change in body weight, accounting for 28.4 and 15.2% of body weight change variance, respectively. Change in restraint and disinhibition were negatively ($r = -0.44$, $P < 0.01$) and positively ($r = 0.31$, $P < 0.05$) associated with change in energy intake, accounting for 19 and 9.3% of energy intake change variance, respectively.

Table 1—*Baseline (week 0) participant characteristics and change on outcome variables from week 0 to 16*

	Met+ADA	Pio+ADA	Pio+PC
n	16	14	18
Sex (male/female)	6/10	4/10	6/12
Race (percent white)	62.5	78.5	50
Age (years)	56.9 ± 2.0	59.2 ± 2.5	55.7 ± 2.4
Weight (kg)	97.8 ± 3.8	98.5 ± 3.4	95.3 ± 4.5
BMI (kg/m^2)	36.4 ± 1.7	35.7 ± 1.7	34.3 ± 1.4
Waist circumference (cm)			
Men	103 ± 5	109 ± 6	110 ± 7
Women	114 ± 5	113 ± 3	102 ± 4
A1C (percent)	6.0 ± 0.2	6.2 ± 0.2	6.4 ± 0.2
Glucose (mg/dl)	129 ± 6	140 ± 8	135 ± 5
Insulin (μU/ml)	18.8 ± 2.0	19.4 ± 1.8	18.8 ± 2.2
Homeostasis model assessment of insulin resistance	2.73 ± 0.29	2.66 ± 0.22	2.72 ± 0.48
Total energy intake (kcal)	559 ± 80	462 ± 49	509 ± 50
Change from week 0 to week 16	52 ± 49[a]	207 ± 53*[b]	50 ± 46[a]
Ghrelin change after a meal (pg/ml), week 0	−54.2 ± 126.8	−102.9 ± 124.6	−18.1 ± 91.6
Ghrelin change after a meal (pg/ml), week 16†	−43.7 ± 93.7	−172.4 ± 107.2	−46.5 ± 112.2
Change from week 0 to week 16	11.4 ± 25.1[a]	−103.3 ± 27.6*[b]	−1.9 ± 24.9[a]
Eating inventory			
Hunger	6.2 ± 1.0	5.9 ± 1.0	6.6 ± 0.8
Change from week 0 to week 16	−0.6 ± 0.6[a]	0.1 ± 0.64[a]	−1.4 ± 0.58*[a]
Restraint	10.3 ± 0.9	9.0 ± 1.3	9.7 ± 1.2
Change from week 0 to week 16	1.8 ± 0.95[ab]	−0.8 ± 1.02[a]	4.0 ± 0.92*[b]
Disinhibition	7.6 ± 1.0	8.4 ± 1.0	8.9 ± 0.9
Change from week 0 to week 16	−0.3 ± 0.64[a]	0.9 ± 0.68[b]	−1.5 ± 0.62*[ab]
Food-craving inventory			
High fats	2.60 ± 0.18	2.10 ± 0.16	2.50 ± 0.12
Change from week 0 to week 16	−0.25 ± 0.11*[a]	−0.19 ± 0.12[a]	0.01 ± 0.1[a]
Sweets	2.70 ± 0.20	2.30 ± 0.21	2.50 ± 0.17
Change from week 0 to week 16	−0.20 ± 0.16[a]	−0.24 ± 0.17[a]	−0.25 ± 0.15[a]
Carbohydrates/starches	2.60 ± 0.23	2.20 ± 0.16	2.40 ± 0.12
Change from week 0 to week 16	−0.17 ± 0.12[a]	−0.07 ± 0.12[a]	−0.13 ± 0.11[a]
Fast-food fats	2.80 ± 0.23	2.30 ± 0.13	2.40 ± 0.19
Change from week 0 to week 16	−0.26 ± 0.14[a]	−0.22 ± 0.15[a]	−0.08 ± 0.13[a]
Fruits and vegetables	2.80 ± 0.25	2.20 ± 0.24	2.60 ± 0.15
Change from week 0 to week 16	−0.20 ± 0.14[a]	−0.08 ± 0.15[a]	0.16 ± 0.13[a]
Total score	2.70 ± 0.18	2.20 ± 0.16	2.50 ± 0.10
Change from week 0 to week 16	−0.21 ± 0.1*[a]	−0.15 ± 0.11[a]	−0.07 ± 0.1[a]

Data are means ± SE. LS means ± SE, which are adjusted for baseline values, depict change on the outcome variables from week 0 to 16 and are included below the week 0 values. *Change score differed significantly from 0 ($P < 0.05$). Lettered superscripts that differ indicate that those groups' change scores differed significantly from each other ($P < 0.05$). †The suppression of ghrelin after a meal at week 0 and week 16 is included in the table.

CONCLUSIONS — This is the first study to demonstrate that pairing pioglitazone treatment with a portion-controlled diet (Pio+PC) attenuates pioglitazone-associated increases in energy intake. Suppression of ghrelin in response to a meal increased only in the group who gained weight (Pio+ADA), indicating that ghrelin suppression is dependent on body weight change and not pioglitazone treatment. The results indicate that pioglitazone-associated weight gain is secondary to increased energy intake. Larger increases in restraint and decreases in disinhibition were observed in the Pio+PC group, with restraint accounting for 28.4% of the variance in body weight change. Change in restraint and disinhibition mediated weight change.

Strengths of the study include the objective measurement of energy intake in a controlled study design. Limitations include measuring energy intake during

only one meal before and after short-term treatment. Further research is warranted to examine the long-term effect of pioglitazone treatment on energy and macronutrient intake.

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