Nutrient infusion bypassing duodenum-jejunum improves insulin sensitivity in glucose-tolerant and diabetic obese subjects

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Salinari S, Carr RD, Guidone C, Bertuzzi A, Cercone S, Riccioni ME, Manto A, Ghirlanda G, Mingrone G. Nutrient infusion bypassing duodenum-jejunum improves insulin sensitivity in glucose-tolerant and diabetic obese subjects. Am J Physiol Endocrinol Metab 305: E59–E66, 2013. First published May 7, 2013; doi:10.1152/ajpendo.00559.2012.—The mechanisms of type 2 diabetes remission after bariatric surgery is still not fully elucidated. In the present study, we tried to simulate the Roux-en-Y gastric bypass with a canonical or longer biliary limb by infusing a liquid formula diet into different intestinal sections. Nutrients (NutriSport Energy) were infused into mid- or proximal jejunum and duodenum during three successive days in 10 diabetic and 10 normal glucose-tolerant subjects. Plasma glucose, insulin, C-peptide, glucagon, incretins, and nonesterified fatty acids (NEFA) were measured before and up to 360 min following. Glucose rate of appearance (Ra) and insulin sensitivity (SI), secretion rate (ISR), and clearance were assessed by mathematical models. SI increased when nutrients were delivered in mid-jejunum vs. duodenum (SI0.22, 0.05, in diabetic subjects), whereas glucose Ra was not affected. In controls, Sensitivity of NEFA production was doubled in mid-jejunum vs. duodenum (2.80 ± 1.36 vs. 1.13 ± 0.78 × 10⁶, P < 0.005) and insulin clearance increased in mid-jejunum vs. duodenum (2.05 ± 1.05 vs. 1.09 ± 0.38 l/min, P < 0.03). Bypass of duodenum and proximal jejunum by nutrients enhances insulin sensitivity, inhibits lipolysis, and increases insulin clearance. These results may further our knowledge of the effects of bariatric surgery on both insulin resistance and diabetes.

bariatric surgery; intestinal glucose infusion; insulin sensitivity

ANATOMIC CHANGES of the gastrointestinal tract induced by bariatric surgery and which include the bypass of different portions of the small intestine are followed by a net improvement in insulin sensitivity (15, 24, 25). The mechanisms underlying these changes in the peripheral tissues and/or liver have not yet been fully elucidated. The association of type 2 diabetes mellitus with obesity and the observation that diabetes undergoes remission after bariatric surgery (20) make further investigation most relevant. In this respect, it is not coincidental that surgical treatment of obesity is one of the most rapidly growing areas of surgical practice today (5).

It is generally agreed (2) that the severity of diabetes is markedly improved following bariatric surgery, with 85.4% of patients experiencing complete resolution or substantial improvement. However, the degree of improvement differs depending on the surgical technique used, ranging from 98.9% for biliopancreatic diversion (BPD) or duodenal switch, to 83.7% for Roux-en-Y gastric bypass (RYGB), to 71.6% for gastrogastroplasty, and to 47.9% for gastric banding. These types of bariatric surgery not only differ in their effects on food intake, being subclassified into two major categories, restrictive and malabsorptive surgical procedures (with a variety of intermediate forms, where food restriction or malabsorption are alternatively prominent), but also, most importantly, these different types of surgery differ in relation to the particular portion of intestine that is bypassed by food, which, in our opinion, is particularly intriguing.

We (15) have recently demonstrated that both BPD and gastric bypass determine a prompt reversibility of type 2 diabetes by improving peripheral insulin sensitivity and enhancing β-cell sensitivity to glucose (24–26); these changes occur within a few days after these procedures, largely before changes in body weight occur (15, 25).

The response of pancreatic β-cells to glucose is reduced in type 2 diabetic subjects (9). In addition to this specific β-cell dysfunction, the inability to sense the fall or rise of plasma glucose concentration to provide adequate insulin secretion is another peculiar defect of β-cells (8).

Different methods for glucose administration, including hyperglycemic clamp, intravenous glucose tolerance test, oscillatory glucose infusion, and graded glucose infusion, are used to assess β-cell responsiveness to glucose. A characteristic feature and advantage of the graded glucose infusion protocol over the other glucose infusion techniques is its ability to describe the transient response of insulin secretion to a changing glucose stimulus and, therefore, the dose-response relationship between glucose and secretion rate during a physiological challenge. Although graded infusion of glucose is used largely in human studies (12, 32), its application during intestinal infusion of glucose or glucose plus other nutrients is lacking.

The aim of the present study was to investigate insulin secretion and β-cell response, as well as insulin sensitivity and incretin secretion, during a graded mixed infusion of a liquid formula diet (carbohydrates, proteins, and fat) in the duodenum or the proximal or mid-jejunum. The infusion of nutrients into the proximal jejunum was aimed at simulating gastric bypass where gastroenteroanastomosis is performed immediately after the Treitz ligament, while the mid-jejunum infusion might mimic a modified gastric bypass with a longer than canonical biliary limb.

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**RESEARCH DESIGN AND METHODS**

**Subjects.** Studies were carried out in 20 obese subjects of both sexes, 10 with type 2 diabetes and 10 with normal glucose tolerance (Table 1), recruited from the outpatient clinics of the Catholic University.

Inclusion criteria were men and women 30–60 yr old, BMI between 30 and 40 kg/m², Hb A_1c_ between 6.5 and 8.5% (for diabetic patients). Normal-glucose-tolerant subjects (hereafter defined as control subjects) were recruited on the basis of absence of diabetes or impaired glucose tolerance after a standard oral glucose tolerance test. All diabetic subjects were drug naive. Women of reproductive age engaged themselves in avoiding pregnancy during the study protocol. Before the start of each experimental session, a pregnancy test was performed, and pregnant women were excluded from the investigation. All women were studied in the follicular phase of their menstrual cycle.

Exclusion criteria were past or active medical history of major endocrinological, renal, cardiac, respiratory, liver, or gastrointestinal diseases.

The protocol was approved by the Catholic University in Rome (Italy) School of Medicine Ethics Committee. All of the subjects signed written informed consent.

**Intestinal infusion of liquid formula diet.** Subjects underwent three studies, single-blind, during which intraintestinal infusions of a liquid formula diet were administered. The intestine was cannulated by means of a 10 French tube 240 cm long (Cook Medical, Bloomington, IN). The tube was connected to a balloon which was used to occlude the intestinal lumen proximal to the site of infusion.

The three studies were performed on three successive days after a 12-h fast at 8:00 AM. On the first day, the tube was positioned during endoscopy in the mid-jejunum (120 cm from the nose). The second day, the tube was retracted by 30 cm (proximal jejunum, 90 cm distant from the nose), and on the third day it was retracted to the duodenum (60 cm distant from the nose). The position of the tube’s terminus was confirmed by fluoroscopy. In no case did the fluoroscopy show that the tube was in the stomach. The subjects kept the nasogastric tube for the whole 3 days, and they were able to eat and drink normally between the study sessions. Therefore, no changes in nutritional and hydration status occurred.

The lipid-glucose-protein test meal was a mixture of Nutrison Energy (Nutricia) diluted with 1/6 water to avoid abdominal discomfort. One hundred milliliters of Nutrison Energy (total caloric value 524 kcal) contains 18.5 g (49% of energy) carbohydrates, 6.0 g (16% of energy) fat, and 5.8 g (35% of energy) protein. A graded perfusion of energy (fat, and 5.8 g (35% of energy) protein. A graded perfusion of energy (Nutricia) diluted with 1/6 water to avoid abdominal discomfort. The following parameters were estimated for each subject: the rate of appearance of enteral nutrient infusion to provide the time courses of glucose and GLP-1 coupled with the minimal model of glucose kinetics (4), was validated related to glucose transit into gut lumen. The absorption model, coupled with the minimal model of glucose kinetics (4), was validated related to glucose transit into gut lumen. The absorption model, coupled with the minimal model of glucose kinetics (4), was validated related to glucose transit into gut lumen. The absorption model, coupled with the minimal model of glucose kinetics (4), was validated related to glucose transit into gut lumen. The absorption model, coupled with the minimal model of glucose kinetics (4), was validated related to glucose transit into gut lumen.

In the present study, the model utilizes the known rates of enteral nutrient infusion to provide the time courses of glucose and GLP-1 concentrations. The model-predicted time courses were fitted to the measured concentrations to estimate the values of model parameters. The following parameters were estimated for each subject: the rate coefficient γ of intestinal absorption, the velocity u of the luminal glucose bolus, glucose effectiveness S_G, insulin sensitivity S_I, the rate constant p of insulin action, the basal value of plasma GLP-1 concentration GLP*_b, and the coefficient of GLP-1 release b_GLPI. The glucose distribution volume was computed for each subject by a formula that accounts for sex, age, total body fat, and basal glucose concentration (6). We note that glucose effectiveness is defined as the

### Table 1. Anthropometric and clinical parameters of the subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Fat-Free Mass, kg</th>
<th>Fat Mass, kg</th>
<th>BMI, kg/m²</th>
<th>Hb A_1c_, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-tolerant subjects</td>
<td>7M 3F</td>
<td>45.9 ± 9.1</td>
<td>113.0 ± 11.9</td>
<td>169.7 ± 8.5</td>
<td>56.2 ± 8.0</td>
<td>56.8 ± 6.6</td>
<td>39.1 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Diabetic subjects</td>
<td>6M 4F</td>
<td>47.4 ± 7.7</td>
<td>111.2 ± 17.3</td>
<td>168.3 ± 12.3</td>
<td>56.1 ± 8.6</td>
<td>55.1 ± 9.7</td>
<td>39.0 ± 0.9</td>
<td>7.6 ± 0.7</td>
</tr>
</tbody>
</table>

*Values are means ± SE.*

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rate constant of glucose uptake independent of insulin. The central nervous system is the major utilizer of glucose without insulin regulation; therefore, $S_G$ has a relevant clinical importance.

The means and standard deviations of model parameters were estimated by the NONMEM method (29). Minimization was performed using a constrained Levenberg-Marquardt minimization routine of the MATLAB library. The coefficients of variation of the estimates were found to be smaller than 20%.

Determination of C-peptide plasma concentrations allowed us to measure the rate of insulin secretion, ISR, by means of a deconvolution procedure, using the two-compartment model of C-peptide kinetics (7) with the standard values of C-peptide kinetic parameters computed for each subject (35). A rough estimate of the insulin clearance of each individual subject was obtained as the ratio between the area under the curve (AUC) of the ISR, as assessed by deconvolution, and the AUC of the insulin concentration measurements. The AUC values were computed by the trapezoidal rule.

From NEFA concentration data, the initial decrease of NEFA concentration that accompanies glucose infusion was computed, for each subject, as $\Delta$NEFA = NEFA$_{b} -$ NEFA$_{min}$, where subscript “b” denotes basal value and “min” the minimal NEFA concentration attained. Similarly, from insulin concentration data, the initial increase
of insulin concentration (I) was computed as $\Delta I = I_{\text{max}} - I_b$, with $I_{\text{max}}$ the maximal insulin concentration. The ratio $\Delta \text{NEFA}/\Delta I$ gave an index of the sensitivity to insulin of the NEFA production.

**Statistics.** All of the data were expressed as means ± SD unless otherwise specified. In the figures, in particular, means ± SE are reported. Two-factor ANOVA followed by Tukey’s test was used for intergroup comparisons and one-factor ANOVA followed by Tukey’s test for intragroup comparisons. $P < 0.05$ was considered significant.

**RESULTS**

The control and diabetic subjects were well matched by sex (7 W and 3 M in control vs. 6 W and 4 M in diabetic subjects), age (45.9 ± 9.1 yr in control vs. 47.4 ± 7.7 yr in diabetic subjects), and BMI (39.1 ± 0.7 kg/m² in control vs. 39.0 ± 0.9 kg/m² in diabetic subjects) (Table 1). The average Hb A₁c was 7.62%, meaning that the subjects were in a moderate decompensated diabetic state.
The time courses of the concentrations of glucose, insulin, NEFA, C-peptide, GIP, and GLP-1 after the test meal are reported in Figs. 1 and 2 for control and diabetic subjects, respectively. Glucagon concentration time courses are reported in Fig. 3. For control subjects, glucagon concentrations during infusion were larger in mid- and proximal jejunum vs. duodenum ($P < 0.0001$), whereas they were larger in mid-jejunum vs. duodenum ($P < 0.0001$) in diabetic subjects. As expected, plasma glucose concentration both while fasting and during the nutrient infusion was significantly higher in diabetic subjects compared with diabetic subjects without reaching statistical significance due to the large interindividual variability.

The sensitivity of NEFA production to insulin ($\Delta$NEFA/AI) was doubled in mid-jejunum compared with duodenum in control subjects ($2.80 \pm 1.36 \times 10^6$ in mid-jejunum vs. $1.56 \pm 0.65 \times 10^6$ in proximal jejunum vs. $1.13 \pm 0.78 \times 10^6$ in duodenum, $P < 0.005$ mid-jejunum vs. duodenum and $P < 0.05$ mid-jejunum vs. proximal jejunum). The sensitivity values were not significantly different in diabetic subjects ($2.35 \pm 2.60 \times 10^6$ in mid-jejunum vs. $1.72 \pm 0.92 \times 10^6$ in proximal jejunum vs. $1.87 \pm 1.72 \times 10^6$ in duodenum).

The most prominent feature in the data was a progressive reduction of plasma insulin concentration from duodenal to proximal and mid-jejunal infusion in control subjects as seen in Fig. 1B. Accordingly, the insulin concentration incremental AUC was significantly different ($P < 0.05$) between duodenum and mid-jejunum $6.36 \pm 1.72$ vs. $4.20 \pm 1.03 \times 10^4$ pM-min. A similar trend, although less pronounced, was found for the C-peptide time course. In diabetic subjects, by contrast, no significant difference was found among duodenal and proximal and mid-jejunal infusion.

The values of total ISR, estimated by the C-peptide deconvolution, tended to be lower, without reaching significance, in diabetic subjects than in controls with no significant difference among infusion sites ($57.52 \pm 35.1$ vs. $61.98 \pm 18.9$ pmol in duodenum; $58.38 \pm 31.3$ vs. $65.18 \pm 13.7$ pmol in proximal jejunum; $52.32 \pm 36.1$ vs. $70.30 \pm 11.3$ pmol in mid-jejunum). The insulin clearance, computed as the ratio between the AUC of the insulin secretion rate and the AUC of insulin concentration, was significantly increased in control subjects only when mid-jejunum was compared with duodenum ($2.05 \pm 1.05$ vs. $1.09 \pm 0.38$ l/min, $P < 0.03$). No significant changes were observed, however, in diabetic subjects.

Figure 4 illustrates the model fitting of glucose and GLP-1 data (duodenal vs. proximal vs. mid-jejunal infusion from top to bottom) in control subjects and, respectively, diabetic patients. The AUC of the $R_g$ in plasma of infused glucose was not statistically different among the infusion sites in both groups (between 85 and 90% of the amount administered).

The estimates of model parameters are reported in Table 2 for control and diabetic subjects. The coefficient of the rate of glucose intestinal absorption ($\gamma$) increased significantly from duodenum to mid-jejunum ($P < 0.0001$ for all comparisons in controls, and $P < 0.001$ mid-jejunum vs. duodenum and proximal jejunum in diabetic subjects). As expected, diabetic subjects were more insulin resistant than control subjects independently of the intestinal tract where the nutrients were delivered. In both groups of subjects, insulin sensitivity progressively increased from duodenum to proximal jejunum to mid-jejunum. In the control subjects, the insulin sensitivity was significantly higher ($P < 0.015$) when nutrients were infused in mid-jejunum vs. duodenum, reaching values observed in lean subjects (27). Also in diabetic subjects insulin sensitivity was improved ($P < 0.05$) without reaching normal values. The NEFA sensitivity to insulin was linearly correlated with the glucose insulin sensitivity independently of the intestinal tract.
of nutrient infusion in control subjects (duodenum $r = 0.69$, $P < 0.05$, proximal jejunum $r = 0.66$, $P < 0.05$, mid-jejunum $r = 0.70$, $P < 0.025$, with overall values of $r = 0.58$, $P < 0.001$). The parameter $b_{GLP}$ of GLP-1 release doubled from duodenum to mid-jejunum in controls ($P < 0.05$) while remaining statistically nonsignificant in diabetic subjects.

**DISCUSSION**

The major findings of the present study are the following. 1) Insulin sensitivity was significantly increased in both control and diabetic subjects when nutrients were infused in the mid-jejunum compared with duodenum. 2) The improvement in insulin sensitivity translated into a larger inhibitory effect of insulin on lipolysis, as shown by the significantly larger sensitivity of NEFA production to insulin in control subjects. 3) The glucose absorption rate coefficient, derived from the simultaneous fitting of glucose and GLP-1 concentration, progressively increased from duodenum to proximal and mid-jejunum in both control and diabetic subjects. 4) The insulin clearance was significantly increased in control subjects from...
in the initial position (and ileal length at 150–160 cm. Therefore, when the tube was length is estimated at book of Surgery (33) reports the following values: duodenal effect is not fully comparable with the chronic adaptation bypassed (23). Although we tried to simulate some metabolic operations in which duodenum or a portion of jejunum is possible variant of gastric bypass with a longer biliary limb. The nutrient infusion into the proximal jejunum might simulate an RYGB, which is the most performed bariatric surgery. We note that the Sabiston Text- book of Surgery (33) reports the following values: duodenal length is estimated at ~20 cm, jejunal length at 100–110 cm, and ileal length at 150–160 cm. Therefore, when the tube was in the initial position (~60 cm distal to the pylorus) its terminus was in the mid-jejunum; when the tube was retracted by 30 cm, its terminus was positioned in the proximal jejunum; and when retracted by additional 30 cm it was in the duode- num. The nutrient infusion into the proximal jejunum might simulate an RYGB, which is the most performed bariatric operation. Moreover, the mid-jejunum infusion might mimic a possible variant of gastric bypass with a longer biliary limb.

Although other types of bariatric operations, such as BPD (15, 24, 26) where the whole jejunum and the first portion of the ileum are bypassed, allow the complete normalization of insulin sensitivity, the present study shows that the longer the jejunum bypass, the better is the insulin sensitivity improve- ment. Indeed, delivery of nutrients inside the mid-jejunum normalizes insulin sensitivity in normal-glucose-tolerant subjects and improves it in diabetic subjects. It is possible that this effect derives from the lack of stimulation of insulin resistance factor/s produced in the duodenum or proximal jejunum (28). In any case, these responses do not appear to be mediated via the incretin hormones, since no significant changes in either GIP or GLP-1 were observed. We acknowl- edge that ours is an acute study, and therefore we cannot fully extrapolate these results to the RYGB outcome, although the increase in the GLP-1 was observed very early after gastric bypass, before time for any adaptive response.

Table 2. Estimates of mathematical model parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Duodenum</th>
<th>Proximal Jejunum</th>
<th>Mid-Jejunum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma$ (min$^{-1}$)</td>
<td>14.08 ± 3.07</td>
<td>18.01 ± 2.20</td>
<td>25.13 ± 3.26*</td>
</tr>
<tr>
<td>$a$ (cm·min$^{-1}$)</td>
<td>2.47 ± 0.42</td>
<td>2.34 ± 0.39</td>
<td>2.58 ± 0.24</td>
</tr>
<tr>
<td>$s_d \times 10^5$ (min$^{-1}$)</td>
<td>3.12 ± 1.48</td>
<td>3.68 ± 1.00</td>
<td>3.22 ± 1.02</td>
</tr>
<tr>
<td>$s_j \times 10^4$ (min$^{-1}$)</td>
<td>0.62 ± 0.22</td>
<td>0.73 ± 0.33</td>
<td>1.11 ± 0.44†</td>
</tr>
<tr>
<td>$p \times 10^6$ (min$^{-1}$)</td>
<td>1.18 ± 0.77</td>
<td>0.97 ± 0.46</td>
<td>0.84 ± 0.28</td>
</tr>
<tr>
<td>GLPs (pM)</td>
<td>1.96 ± 0.93</td>
<td>2.10 ± 0.94</td>
<td>1.99 ± 1.06</td>
</tr>
<tr>
<td>$b_{GLP} \times 10^9$ (l/min)</td>
<td>0.21 ± 0.14</td>
<td>0.36 ± 0.20</td>
<td>0.45 ± 0.09§</td>
</tr>
<tr>
<td>Diabetic subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma$ (min$^{-1}$)</td>
<td>14.30 ± 3.97</td>
<td>17.01 ± 0.84</td>
<td>25.12 ± 4.09‡</td>
</tr>
<tr>
<td>$a$ (cm·min$^{-1}$)</td>
<td>2.51 ± 0.42</td>
<td>2.33 ± 0.06</td>
<td>2.49 ± 0.67</td>
</tr>
<tr>
<td>$s_d \times 10^5$ (min$^{-1}$)</td>
<td>2.51 ± 1.68</td>
<td>3.42 ± 1.46</td>
<td>2.17 ± 2.49</td>
</tr>
<tr>
<td>$s_j \times 10^4$ (min$^{-1}$)</td>
<td>0.40 ± 0.20</td>
<td>0.60 ± 0.35</td>
<td>0.79 ± 0.34†</td>
</tr>
<tr>
<td>$p \times 10^6$ (min$^{-1}$)</td>
<td>1.05 ± 0.73</td>
<td>0.86 ± 0.32</td>
<td>0.55 ± 0.13</td>
</tr>
<tr>
<td>GLPs (pM)</td>
<td>1.47 ± 0.41</td>
<td>1.90 ± 0.73</td>
<td>1.31 ± 0.79</td>
</tr>
<tr>
<td>$b_{GLP} \times 10^9$ (l/min)</td>
<td>0.28 ± 0.33</td>
<td>0.30 ± 0.35</td>
<td>0.32 ± 0.19</td>
</tr>
</tbody>
</table>

Values are means ± SD. See text for definitions. Significance: *$P < 0.0001$ mid- vs. proximal jejunum and duodenum, †$P < 0.015$ mid-jejunum vs. duodenum, §$P < 0.05$ mid-jejunum vs. duodenum, ‡$P < 0.001$ mid-jejunum vs. duodenum.

The NEFA insulin sensitivity and glucose insulin sensitivity were well correlated, suggesting that a significant improvement in insulin sensitivity during nutrient administration translated into a larger antilipolytic effect of insulin, as shown by the larger decrease of plasma NEFA concentration per unit increase of insulin concentration in control subjects. In this regard, it has been ascertained that impaired insulin suppression of NEFA reflects NEFA flux from the adipose tissue rather than impaired NEFA uptake (13, 14). Therefore, the improve- ment of NEFA insulin sensitivity observed in our study should reflect the improvement of insulin action.

As shown by the increase in the glucose absorption rate coefficient, glucose absorption was enhanced in mid-jejunum compared with both duodenum and proximal jejunum, possibly as a compensatory effect. In fact, the model parameter $b_{GLP}$, which represents the efficiency of GLP-1 secretion in response to glucose absorption, increased significantly from duodenum to mid-jejunum in normal-glucose-tolerant subjects (Table 2). After a 50% proximal enterectomy in dogs, the net absorptive fluxes of water, electrolytes, or simple nutrients were in fact unmodified even early after the operation, suggesting that ileum vicariates the absorptive function of duodenum and jejunum (34). On the other hand, we have shown that in BPD glucose is efficiently absorbed and metabolized (31).

Although it is well ascertained that insulin secretion is the major determinant of the hyperinsulinemia observed in obesity, a reduction in the metabolic clearance rate of insulin contributes to maintaining elevated circulating levels of this hormone (1, 22). In the present study, insulin clearance was increased when nutrients were infused into the mid-jejunum. However, our measurement of the insulin clearance did not allow us to determine whether this change occurs at hepatic or nonhepatic sites, although it is clearly ascertained that ~80% of endog- enously secreted insulin is cleared by the liver (10). Impaired insulin clearance is a typical feature of insulin resistance (17). Insulin clearance is decreased in obesity (19, 30), in particular in abdominal obesity (21) and in type 2 diabetes (16). Insulin clearance is inversely related to liver fat content (11). Kotonen et al. (16) have shown that impaired insulin clearance exacerb- ates hyperinsulinemia, leading to underestimation of insulin resistance in type 2 diabetes. Weight loss in obesity enhances hepatic insulin sensitivity and clearance (36). Therefore, we hypothesize that the improved insulin clearance observed in this study might be a consequence of an improved hepatic insulin sensitivity.

The rapid rise of incretins, with an early peak about 30 min after the beginning of nutrient intestinal infusion observed in our series, might reflect the effect of proteins, whereas the late peak at a time between 180 and 240 min might depend on fat stimulation, as shown by Lindgren et al. (18).

In conclusion, bypass of duodenum and proximal jejunum by nutrients enhances insulin sensitivity, inhibits lipolysis, and increases insulin clearance. These results might help our compre- hension of the effect of bariatric surgery on insulin resis- tance and diabetes.

GRANTS

Clinical Trials NIH no. NCT00994435.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
GUT NUTRIENT INFUSION AND INSULIN RESISTANCE

AUTHOR CONTRIBUTIONS

REFERENCES

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