First-Phase Insulin Secretion Restoration And Differential Response To Glucose Load Depending On The Route Of Administration In Type 2 Diabetic Subjects After Bariatric Surgery

Serenella Salinari, DSC, Alessandro Bertuzzi¹, DSC, Simone Asnaghi, MSC, Caterina Guidone², MD, Melania Manco³, MD, Geltrude Mingrone², MD, PHD

Department of Systems Analysis and Informatics, University of Rome “La Sapienza”, Rome, Italy
¹Institute of Systems Analysis and Computer Science – CNR, Rome, Italy
²Institute of Internal Medicine, Catholic University, School of Medicine, Rome, Italy
³Liver Unit, Bambino Gesù Hospital and Research Institute, Rome, Italy

Corresponding author:
Serenella Salinari
E-mail: salinari@dis.uniroma1.it

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Objective: To elucidate the mechanisms of diabetes reversibility after malabsorptive bariatric surgery.

Research design and methods: Peripheral insulin sensitivity and beta-cell function after either intravenous (IVGTT) or oral glucose (OGTT) tests and minimal model analysis were assessed in 9 obese, type 2 diabetic subjects before and 1 month after bilio-pancreatic diversion (BPD) as compared with 6 normal-weight controls. Insulin-dependent whole-body glucose disposal was also measured by the euglycemic clamp. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) were measured.

Results: The first phase of insulin secretion after the IVGTT was fully normalized following the operation. The disposition index (DI), from OGTT data, was increased about tenfold and became similar to the values found in controls, while the DI, from IVGTT data, increased about 3.5 fold similarly to what happened after the euglycemic clamp. The AUC_{GIP} decreased about 4 times (from 3,000±816 to 577±155 pM·min $P<0.05$). On the contrary, the AUC_{GLP1} was almost triplicate (from 150.4±24.4 to 424.4±64.3 pM·min $P<0.001$). No significant correlation was found between GIP or GLP1 % changes and modification of the sensitivity indexes independently of the route of glucose administration.

Conclusions: The restoration of the first-phase insulin secretion as well as the normalization of insulin sensitivity in type 2 diabetic subjects after malabsorptive bariatric surgery seem to be related to the reduction of the effect of some intestinal factor/s due to intestinal bypass.
In 1987, Pories et al. (1) published a stunning observation, that 99% of morbidly obese patients with frank type 2 diabetes mellitus or impaired glucose tolerance undergone Roux-en-Y gastric bypass (RYGB) became and remained euglycemic since surgery. But, most interestingly, these Authors reported that the patients were converted to euglycemia within 10 days, even if they required large doses of insulin.

Successively, we (2, 3) and other Authors (4) have found that either restrictive or malabsorptive bariatric surgery is effective in improving/resolving type 2 diabetes. In particular, using the euglycemic hyperinsulinemic clamp we have demonstrated that insulin sensitivity was normalized after malabsorptive bariatric surgery in both obese type 2 diabetic (2) and obese normo-tolerant subjects.

We conceived that the normalization of insulin sensitivity, that occurs very early after biliopancreatic diversion (BPD) before a significant weight loss can intervene (2), might be dependent on the hormonal changes related to the nutrient diversion from the duodenum, the entire jejunum, and the proximal portion of the ileum. In fact, the enteroendocrine cells are largely represented in these tracts of the small intestine.

Two main hypotheses have been advanced until now to explain which part of the small intestine is implicated in the reversibility of diabetes. The first, known as the hindgut hypothesis (5), holds that diabetes control results from the accelerated delivery of nutrients in the distal small intestine. The second, the so-called foregut hypothesis, states that the exclusion of duodenum and jejunum from nutrient transit might prevent the secretion of a putative signal, that promotes insulin resistance (2, 6). The balance between the stimulatory action on insulin secretion exerted by incretins and the anti-incretin effect might allow a finer control of the glucose disposal.

In the hypothesis that an imbalance in the release of intestinal hormone/s can determine insulin resistance and that after BPD its/their secretion is reduced – allowing normalization of insulin sensitivity with subsequent beta-cell glucose sensitivity improvement – we have assessed the peripheral insulin sensitivity and the beta-cell function after either intravenous or oral glucose test in 9 obese, type 2 diabetic subjects as compared with 6 normal weight age and sex matched controls. To further support our results, the insulin dependent whole body glucose disposal was also measured by the euglycemic clamp.

MATERIALS AND METHODS

Subjects. Nine (five women and four men) morbidly obese [body mass index (BMI) = 51.7±8.1 kg/m², age 41±9 years (mean±SD)], type 2 diabetic patients and six normo-tolerant [according to the American Diabetes Association (ADA) criteria (7)] sex and age-matched volunteers (three women and three men, BMI = 24.6±1.3 kg/m², 39±7 years) were studied. The patients were all characterized as having type 2 diabetes according to the ADA criteria. Glycosylated haemoglobin [HbA (1c)] ranged from 7.5 to 9.5%.

Study protocol. At the time of the baseline study, all subjects were on a diet with the following average composition: 60% carbohydrate, 30% fat, and 10% protein (≈1 g/kg body wt). This dietary regimen was maintained for 1 wk before the study. In all the patients, an oral glucose tolerance test (OGTT), an intravenous glucose tolerance test (IVGTT), and a euglycemic hyperinsulinemic clamp (EHC) were randomly performed within 1 month before surgery and 1 month after surgery. Also the healthy volunteers underwent the same tests. All patients
received the same parenteral nutrition regimen (ca. 7,100 kJ/day) during the first 6 days after surgery, then they were on free diet.

The study protocol was approved by the Institutional Ethics Committee of the Catholic University of Rome. The nature and purpose of the study were carefully explained to all subjects before they provided their written consent to participate.

**Body composition.** On a separate day, total body water (TBW) was determined using 0.19 MBq $^3$H$_2$O in 5 ml of saline administered as an intravenous bolus injection. Blood samples were drawn before and 3 h after the injection. Radioactivity was determined in duplicate on 0.5 ml of plasma in a beta-scintillation counter (Model 1600TR; Canberra-Packard, Meriden, CT). Corrections were made for nonaqueous hydrogen exchange. Water density at body temperature was assumed to be 0.99371 kg/l. TBW (kg) was computed as $^3$H$_2$O dilution space (liters) $\times$ 0.95 $\times$ 0.99371. Fat-free mass (FFM) was obtained by dividing TBW by 0.732 (8).

**OGTT.** After an overnight fasting, a standard 75-g OGTT was performed in each patient at baseline and within 1 month after surgery as well as in each volunteer, with blood sampling at 0, 30, 60, 90, 120, 150, 180 and 240 min. Samples were placed in chilled tubes, and plasma was separated within 20 min and stored at –70°C.

**IVGTT.** An IVGTT was carried out preoperatively and within 1 months postoperatively. At 8:00–9:00 A.M, after a 12-h overnight fast, an intravenous catheter was placed in one antecubital vein and an intravenous bolus of 0.33 g glucose/kg bw as 50% water solution was injected in the contralateral antecubital vein. Blood samples were obtained at –15, –5, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180, and 240 min relative to the start of dextrose injection. Samples were placed in chilled tubes, and plasma was separated within 20 min and stored at –70°C.

**Euglycemic-hyperinsulinemic clamp.** Peripheral insulin sensitivity was evaluated by the EHC (9) at baseline and within 4 weeks after surgery. After inserting a cannula in a dorsal hand vein for sampling arterialized venous blood and another in the antecubital fossa of the contralateral arm for infusions, the subjects rested in the supine position for at least 1 h. They were placed with one hand warmed in a heated-air box set at 60°C to obtain arterialized blood samples. Insulin sensitivity, as the total insulin-mediated glucose uptake, was determined during a primed constant infusion of insulin at the rate of 6 pmol min$^{-1}$ kg$^{-1}$. To maintain the glycemia in a normal range, rapid insulin and potassium phosphate in saline were infused overnight before BPD. The plasma glucose concentration was clamped at 5.1±0.5 mM before and at 3.9±0.4 mM (mean±SD) after BPD respectively, throughout the insulin infusion by means of a variable glucose infusion and blood glucose determinations every 5 min. Insulin sensitivity was determined during the last 40 min of the clamp by computing the whole-body glucose uptake ($\mu$mol min$^{-1}$ kg$_{FFM}$$^{-1}$) or the clearance rate (ml min$^{-1}$ kg$_{FFM}$$^{-1}$) during steady-state euglycemic hyperinsulinemia.

**BPD.** This malabsorptive surgical procedure (2) consists of an approximately 60% distal gastric resection with stapled closure of the duodenal stump. The residual volume of the stomach is about 300 ml. The small bowel is transected at 2.5 m from the ileo-caecal valve, and its distal end is anastomosed to the remaining stomach. The proximal end of the ileum, comprising the remaining small bowel (involved in carrying bilio-pancreatic juice but excluded from food transit), is anastomosed in an end-to-side fashion to the bowel, 50 cm proximal to the ileo-caecal valve. Consequently, the total length of absorbing bowel is reduced to
250 cm, the final 50 cm of which, the so-called common channel, represents the site where ingested food and biliary-pancreatic juices mix.

**Analytical procedures.** Plasma glucose was measured by the glucose oxidase technique on a Beckman Glucose Analyzer (Beckman, Fullerton, CA). Plasma insulin was assayed by microparticle enzyme immunoassay (MEIA, Abbott, Pasadena, CA) with sensitivity of 1 µU/ml and intra-assay coefficient of variation (CV) of 6.6%. C-peptide was assayed by radioimmunoassay (MYRIA; Technogenetics, Milan, Italy); this assay has a minimal detectable concentration of 17 pmol/l and intra-assay and inter-assay CVs of 3.3–5.7 and 4.6–5.3 %, respectively.

Total glucose-dependent insulinotropic polypeptide (GIP) was measured by ELISA (Linco). The assay is 100% specific for GIP 1–42 and GIP 3–42 and does not cross-react with GLP-1, GLP-2, oxyntomodulin, or glucagon. The intra-assay and inter-assay CVs were 3.0–8.8 and 1.8–6.1%, respectively. Active glucagon-like peptide-1 (GLP-1), an indicator of potential action, was measured by ELISA (Linco). The assay is 100% specific for GLP-1(7–36) and GLP-1(7–37) and does not react with GLP-1(9–36), glucagon, or GLP-2.

**Mathematical Model.** The OGTT and IVGTT minimal models (10) were used to compute the insulin sensitivity (SI). The indexes of beta–cell sensitivity to glucose for the IVGTT (the first phase beta-cell sensitivity, \( \Phi_1 \), and the second phase sensitivity, \( \Phi_2 \)) and for the OGTT (the dynamic beta–cell sensitivity, \( \Phi_d \), the static sensitivity, \( \Phi_s \), and the total sensitivity, \( \Phi \)) were computed by the C-peptide minimal model as proposed by Toffolo et al. (11) and Breda et al. (12) . The disposition index (DI) was computed as \( \Phi \times SI \). The model parameters were estimated by minimization of a weighted least-square index using a constrained Levenberg-Marquardt minimization routine of the MAT LAB library. The standard errors of the estimates of individual parameters were evaluated by the Jackknife method (3), and the coefficients of variation were found to be smaller than 20%.

**Statistics.** All of the data were expressed as mean±SE unless otherwise specified. The Wilcoxon paired-sample test and the ANOVA test for repeated measurements, followed by Tukey test, were used for intragroup and intergroup comparisons, respectively. Two-sided \( P < 0.05 \) was considered significant. Non-parametric Spearman correlations (SPSS for Windows version 10) were used to assess linear relationships between single variables.

**RESULTS**

A small, but significant, weight loss (from 153.1 ± 34.2 to 143.5 ± 32.8 kg, mean±SD, \( P<0.01 \)) was observed 1 month after BPD.

The OGTT glucose incremental area under the curve (\( \Delta AUC \)) significantly (\( P<0.02 \)) decreased after BPD from 0.74±0.08 to 0.22±0.04 × 10^{-3} \text{mM·min} becoming not statistically different from that of controls. Insulin \( \Delta AUC \) decreased from 3.83±0.99 to 1.01±0.28 × 10^{4} \text{pM·min} (\( P<0.02 \)) reaching a value comparable to that of healthy controls (\( P=NS \)). Finally, the C-peptide \( \Delta AUC \) declined from 2.48±0.35 to 1.10±0.34 × 10^{2} \text{nM·min} (\( P<0.02 \)); its value in controls was 1.71±0.36 × 10^{2} \text{nM·min} (\( P=NS \)).

Also in the IVGTT, the \( \Delta AUC \) of glucose significantly decreased from 0.63±0.08 to 0.51±0.06 × 10^{3} \text{mM·min} (\( P<0.05 \)) (controls: 0.31±0.02 × 10^{3} \text{mM·min}, \( P=NS \)). Similarly, insulin \( \Delta AUC \) decreased from 3.66±0.65 to 1.90±0.27 × 10^{4} \text{pM·min} (\( P<0.02 \)) (controls: 0.50±0.06 × 10^{4} \text{pM·min}). C-peptide \( \Delta AUC \) did not change significantly (from 1.63±0.28 to 1.54±0.50 × 10^{2} \text{nM·min}, \( P=NS \)); however, the latter was not
Differential response to glucose load after BPD

The estimates of the indexes computed by the oral and intravenous mathematical models are reported in Table 1. The first phase of insulin secretion was fully normalized after BPD, as shown in Table 1 by the marked increase of the $\Phi_1$ index. Figure 1 shows the recovery of the first phase of the insulin secretion rate (ISR) in the IVGTT. The dynamic sensitivity index also showed a tendency to increase after BPD.

Before BPD, the insulin sensitivity determined by the OGTT was significantly smaller than that found by the IVGTT or the euglycemic clamp (Table 1), with the M value increasing from 27.7±6.4 to 77.9±20.0 µmol·kg$^{\text{FFM}}$·min$^{-1}$ after BPD ($P<0.0001$). However, 1 month after BPD, insulin sensitivity reached values comparable to those found in control subjects, independently of the glucose administration route. In particular, a threefold increase in the insulin sensitivity estimated by either the IVGTT minimal model and the EHC was observed, while the same index computed by the OGTT minimal model raised six times ($P<0.05$). The disposition index, calculated by the OGTT, was increased about tenfold and became similar to the values found in controls, while the DI calculated by the IVGTT increased about 3.5 times.

The time courses of GIP and GLP-1 during the OGTT are reported in Figure 2. GIP peaked earlier after than before BPD, i.e. 30 min compared to 60 min. The $\Delta$AUC$_\text{GIP}$ (mean±SE) decreased about 4 times, from 3,000±816 pM·min preoperatively to 577±155 pM·min postoperatively ($P<0.05$). The contrary, the $\Delta$AUC$_\text{GLP1}$ was almost triplicated, from 150±24 pM·min to 424±64 pM·min ($P<0.001$). The $\Delta$AUC of both GLP1 and GIP in controls (392±11 pM·min and 983±77 pM·min, respectively) were not statistically different from the values observed in diabetic patients after BPD.

No significant correlation was found between the percent change in the AUC of GIP and GLP-1 and the modification of the oral sensitivity index.

**DISCUSSION**

The principal findings of our study are that:

1. The first-phase insulin secretion was restored 1 month after BPD ($\Phi_1$)
2. The beta-cell glucose sensitivity was fully normalized
3. The disposition index was normalized thanks to the normalization of insulin sensitivity and the consequent reduced requirement of insulin secretion.
4. The increase in the insulin sensitivity estimated by the OGTT minimal model was larger than that estimated by the IVGTT minimal model.

The association of $\beta$-cell dysfunction with insulin resistance represents the main pathophysiological defect responsible for the development of type 2 diabetes. The $\beta$-cell function in type 2 diabetes is characterized by a progressive decline, from a net reduction to the disappearance of the first phase of glucose-induced insulin secretion to the impairment of the second-phase insulin secretion. The early insulin response disappears, even in the early stages of the disease, when fasting glucose concentrations are only slightly higher than normal. This defect is important because first-phase insulin secretion seems to have the greatest impact on postprandial plasma glucose excursions (13), determining post-meal hyperglycemia.

Actually, the causes of this $\beta$-cell dysfunction are not completely recognized. Autopsy studies have shown that less than 20 to 50% of the $\beta$-cells may have been lost after many years of disease (14). However, there is experimental evidence that a 65% partial pancreatectomy in dogs reduces the...
maximum secretive pancreatic insulin response, but that the residual pancreatic β-cells become more sensitive to glucose thus providing a partial compensation (15). Therefore, Porte and Kahn (16) noticed that “the loss of β-cell function is disproportionately more important than the degree of β-cell loss”. Furthermore, there is more recent evidence from the autopsy of type 2 diabetic patients that the β-cell mass is not significantly diminished in most patients and that β-cells maintain active insulin gene transcription and translation even in amyloid-containing islets. This suggests that the main defect resides in an abnormal coupling of insulin secretion to glycemia (17).

It is interesting to note that in the present investigation the first-phase insulin secretion impairment was reversible after BPD, when the body weight was reduced only in the order of about 6%. Briatore et al. (18) have recently reported that the acute insulin response (AIR) after IVGTT was significantly increased after BPD in morbidly obese, type 2 diabetic subjects. However, being based on insulin concentration, AIR does not correspond directly to the first phase of insulin secretion, since it also reflects the hepatic insulin extraction. Since the hepatic extraction differs depending on the pattern and amount of insulin release, AIR does not provide an independent assessment of insulin secretion. Furthermore, insulin clearance appeared to be significantly reduced before BPD, according to recently published findings (19).

Recently, Henquin et al. (20) have clearly shown that the first-phase insulin secretion, which was absent in vivo in mice with a double knockout for islet antigen 2 (IA-2) and 2β (IA-2β) (21), was fully restored in the islets of the same animals studied in vitro. Thus, these Authors (20) suggested the existence of factors, extrinsic to the islets, which can inhibit the in vivo insulin response to an intra-peritoneal glucose challenge. In analogy with the Henquin’s (20) hypothesis, we suggest that a “factor” inhibiting insulin secretion can be produced in the small intestine and that the intestinal bypass, as it occurs in BPD, can reduce/suppress its synthesis and/or delivery into the circulatory stream allowing the restoration of the first-phase insulin secretion.

It has been shown that a 3 hour synthetic GLP-1 infusion in type 2 diabetic individuals was able to increase the AIR after IVGTT from 197 ± 97 to 1,141 ± 409 pM min, which, however, was still 7 times lower than the levels reached in healthy controls (22). The corresponding circulating levels of GLP1 were in the order of 40–50 pM. In our series, the first-phase insulin secretion was normalized while the circulating GLP1 reached levels of about 35 pM, suggesting that other mechanisms, such as the presence of still unrecognized intestinal factor/s can play a role in normalizing insulin secretion.

This very “factor”, or even another “factor” secreted by the small intestine, might determine also the insulin resistance. In fact, insulin sensitivity was fully normalized after BPD when a small but significant weight loss was achieved. In support of this hypothesis, we have found that the insulin-mediated glucose uptake was significantly higher after BPD when the glucose load was administered orally instead of intravenously. Dalla Man et al. (23) have shown that insulin action on glucose disposal estimated by the oral minimal model [S_{1*}] was almost identical to that measured by a euglycemic hyperinsulinemic clamp, [S_{1*}^{clamp}], suggesting that the glucose disposal component of the oral glucose minimal model was well described. Therefore, at least in healthy controls, the OGTT minimal model of glucose kinetics provides equivalent estimates of insulin action than the euglycemic clamp. This observation reinforces our findings that after BPD insulin sensitivity increases much more after an oral than an intravenous glucose
challenge. Furthermore, the insulin resistance before bariatric surgery was much higher after an oral than after an intravenous glucose load. Therefore, the anatomical changes induced by the operation led to a complete inversion of the insulin sensitivity response depending on the route of glucose administration.

To our knowledge, very few data in the literature report the insulin sensitivity after RYGB, mostly measured by empirical methods and thus uneasily comparable with the present results. We previously reported (24) that insulin mediated glucose uptake, measured by the EHC, did not change significantly after RYGB, while it was dramatically increased after BPD in normo-tolerant, morbidly obese patients becoming even higher than that reported in healthy subjects. Burnstein et al (25) observed a significant increase in the glucose metabolic clearance rate, from a mean baseline value of 3.0 ± 1.6 to 6.7 ± 3.9 ml·kg⁻¹·min⁻¹ at post RYGB ($P<0.02$), that however, as noted by the authors, was not completely reversed to normality.

We note that GLP-1 plasma concentration was increased about threefold at post-BPD; however, neither the changes in GLP-1 plasma levels nor those in GIP did explain the normalization of insulin sensitivity. This fact might suggest the existence of other intestinal factors implicated in the control of insulin action in peripheral tissues, whose secretion is inhibited by surgery-induced nutrient diversion.

In conclusion, the restoration of the first-phase insulin secretion as well as the normalization of the insulin sensitivity in type 2 diabetic subjects after malabsorptive bariatric surgery seems to be related to the reduction of the effect of some intestinal factor/s as a consequence of intestinal bypass.

**FIGURE LEGENDS**

**Figure 1.** IVGTT data (mean±SE). Top: glucose (left) and insulin (right) plasma concentrations before (dotted line) and after (solid line) BPD. Bottom: ISR (left) and C-peptide data points with the fitting curves superimposed (right). Pre-BPD data: dotted lines and filled squares; post-BPD data: solid lines and filled triangles. Due to the overlapping of SE bars, only mean values of C-peptide data are reported.

**Figure 2.** Glucose-dependent insulinogetic polypeptide (GIP) and plasma glucagon-like peptide-1 (GLP-1) concentrations during OGTT in diabetic patients before (squares) and after (triangles) BPD.
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Table 1 - Estimates of the indexes computed by the oral and the intravenous mathematical models (Mean±SD).

| Indexes OGTT | Controls | Diabetic Subjects preBPD | Diabetic Subjects post BPD |
|--------------|----------|--------------------------|---------------------------|
| $SI \times 10^2$ (ml·min$^{-1}$·kgFFM$^{-1}$·pM$^{-1}$) | 2.70±0.98 | 0.64±0.19 | 3.60±0.97* |
| $SI_{post}/SI_{pre}$ | | | 6.3±3.1 |
| $\Phi_s \times 10^9$ | 500±140 | 203±144 | 480±365 |
| $\Phi_s \times 10^9$ (min$^{-1}$) | 39.2±20.8 | 23.0±10.0 | 32.0±16.0 |
| $\Phi_s \times 10^9$ (min$^{-1}$) | 47.7±24.3 | 25.9±11.2 | 37.7±12.0# |
| $AUC_{ISR}$ (nmoles m$^2$) | 33.4±12.8 | 62.3±28.4 | 37.2±13.3§ |
| $DI \times 10^{14}$ (dl·min$^{-2}$·kgFFM$^{-1}$·pM$^{-1}$) | 1,197±599 | 148±51 | 1,227±276§ |

| Indexes IVGTT | | | |
|--------------|----------|--------------------------|---------------------------|
| $SI \times 10^2$ (ml·min$^{-1}$·kgFFM$^{-1}$·pM$^{-1}$) | 2.10±0.80 | 1.04±0.28 | 2.70±0.60§ |
| $SI_{post}/SI_{pre}$ | | | 2.7±1.1 |
| $\Phi_s \times 10^9$ | 242±199 | 27.9±17.1 | 164±119§ |
| $\Phi_s \times 10^9$ (min$^{-1}$) | 10.2±2.9 | 10.0±4.8 | 12.5±8.5 |
| $\Phi_s \times 10^9$ (min$^{-1}$) | 16.6±5.3 | 10.8±5.2 | 16.5±9.5# |
| $AUC_{ISR}$ (nmoles m$^2$) | 23.9±3.7 | 43.9±22.8 | 41.9±21.7 |
| $DI \times 10^{14}$ (ml·min$^{-1}$·kgFFM$^{-1}$·pM$^{-1}$) | 341±124 | 118±78 | 453±318§ |

| Indexes EHC | | | |
|--------------|----------|--------------------------|---------------------------|
| $SI \times 10^2$ (ml·min$^{-1}$·kgFFM$^{-1}$·pM$^{-1}$) | | 1.4±0.7 | 4.5±1.5 |
| $SI_{post}/SI_{pre}$ | | | 3.5±1.2 |

OGTT (after/before): * $P<0.005$  # $P<0.05$  ¶ $P<0.02$; Diabetic subjects after BPD/Controls NS
IVGTT (after/before): § $P<0.01$  ¶ $P<0.05$; Diabetic subjects after BPD/Controls NS
EHC: SI before BPD is significantly different from SI (OGTT) ($P<0.001$).

SI (OGTT) and SI (IVGTT) before BPD are significantly different ($P<0.05$); SI (EHC), SI (OGTT) and SI (IVGTT) after BPD are not significantly different.
Figure 1.

Figure 2.