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A B S T R A C T

Background. After Roux-en-Y gastric bypass (RYGB), hypoglycemia can occur and be associated with adverse events such as intense malaise and impaired quality of life.

Objective. To compare insulin secretion, sensitivity, and clearance between two groups of patients, with or without hypoglycemia, after an oral glucose tolerance test (OGTT 75-g), and also to compare real-life glucose profiles within these two groups.

Setting. Bariatric surgery referral center.

Methods. This study involves a prospective cohort of 46 consecutive patients who complained of malaise compatible with hypoglycemia after RYGB, in whom an OGTT 75-g was performed. A plasma glucose value of lower than 2.8 mmol/L (50 mg/dl) between 90 and 120 min after the load was considered to be a significant hypoglycemia. The main outcome measures were insulin sensitivity, beta-cell function, and glycemic profiles during the test. Glucose parameters were also evaluated by continuous glucose monitoring (CGM) in a real-life setting in 43 patients.

Results. Twenty-five patients had plasma glucose that was lower than 2.8 mmol/L between 90 and 120 from the load (HYPO group). Twenty-one had plasma glucose that was higher than 2.8 mmol/L (NONHYPO group). The HYPO patients were younger, had lost more weight after RYGB, were less frequently diabetic before surgery, and displayed higher early insulin secretion rates compared with the NONHYPO patients after the 75-g OGTT, and they had lower late insulin secretion rates. The HYPO patients had lower interstitial glucose values in real life, which suggests that a continuum exists between observations with an oral glucose load and real-life interstitial glucose concentrations.

Abbreviations: RYGB, Roux-en-Y gastric bypass; OGTT, oral glucose tolerance test; CGM, continuous glucose monitoring; HYPO, hypoglycemia; HAS, Haute Autorité de Santé; GLP-1, glucagon-like-peptide-1; IG, interstitial glucose; EWL, excess weight loss; BMI, body mass index; HOMA, Homeostasis Model Assessment; AUC, area under curve; S_I, insulin sensitivity; SI h, hepatic insulin sensitivity; ISR, insulin secretion rate.

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Conclusions. This study suggests that HYPO patients after RYGB display an early increased insulin secretion rate when tested with an OGTT. CGM shows that HYPO patients spend more time below 3.3 mmol/L when compared with NONHYPO patients. This phenotype of patients should be monitored carefully after RYGB.

1. Introduction

Obesity surgery, especially Roux-en-Y gastric bypass (RYGB), is recognized as the most efficient long-term weight loss strategy. Bariatric surgery induces a decrease in mortality, cardiovascular events, and cancer prevalence [1,2], and it also improves metabolic obesity-related co-morbidities [3–5].

A major concern after RYGB is hypoglycemia (HYPO), which can be associated with adverse events such as intense malaise and impaired quality of life. Moreover, although rare, severe episodes can lead to car accidents, seizure, coma, and hospitalization [6,7]. The prevalence of severe episodes is less than 0.5% in the operated patients [7,8], but the prevalence of low glucose values after a glucose challenge can be higher than 10% at 12 months after RYGB [9]. The Endocrine Society consensus has recommended that the Whipple triad is necessary for defining HYPO [10], which has also been made clear after bariatric surgery [11,12].

The inappropriate insulin secretion found in severe hypoglycemic episodes [13,14] is not always retrieved in less severe cases [15–17]. Clinically severe episodes of HYPO are associated with an inadequately increased plasma insulin concentration after a glucose load [13,14]. Salehi et al. have elegantly demonstrated that GLP-1 mediates the hypersecretion of insulin [14]. The literature is less clear about an increased insulin secretion in subjects who have low glucose values after an oral glucose load [9,16].

The modeling of insulin secretion after an oral carbohydrate load yields interesting aspects of insulin secretion. The observation and computation of peripheral C-peptide concentrations provides a direct estimate of beta-cell function. The comparison of peripheral C-peptide and insulin kinetics estimates the insulin clearance. The insulin sensitivity of the whole body can be calculated in the post-prandial phase and is a measurement of glucose disposal [18]. These models bring more information than the mere comparison of plasma concentrations.

Continuous glucose monitoring is commonly used for the diagnosis of hypoglycemia in diabetic patients [19] and is also useful for that diagnosis in non-diabetic individuals [20] and after bariatric surgery [21]. It is a useful tool to confirm whether the findings of standardized tests or in-hospital observations translate into real life.

Therefore, the primary aim of this study was to compare insulin secretion, sensitivity, and clearance after an oral glucose tolerance test (OGTT 75-g) in patients who were separated into one group with confirmed hypoglycemia after OGTT (Whipple triad positive) and another group without hypoglycemia. CGM was performed to address the correspondence between the observations made during the OGTT and the glucose profiles in real life.

2. Methods

2.1. Study Design

We analyzed insulin sensitivity, β-cell function and glycemic profiles of 46 consecutive patients after an RYGB. All of the patients had symptoms that were compatible with HYPO under real-life circumstances (autonomic symptoms and neuroglucopenia).

2.2. Patients

Inclusion criteria were age between 18 and 65 years, an indication for bariatric surgery based on the HAS (Haute Autorité de Santé) [22], which are similar to the National Institute of Health Consensus Statement criteria [23], and the presence of symptoms that are compatible with HYPO during post-surgery follow-up.

The evaluation involved an OGTT, with a full assessment of insulin secretion (see below). Continuous glucose monitoring was performed in 43 patients.

2.3. OGTT

All of the patients received 75-g of liquid glucose in the fasting state. Plasma samples were taken at T0 and, then, at 15, 30, 45, 60, 90, and 120 min later. Plasma glucose was measured with glucose oxidase, plasma insulin with an immunoreactive assay, and C peptide with the ELISA kit. A plasma glucose value that was lower than 2.8 mmol/L (50 mg/dl) between 90 and 120 min after the carbohydrate load was considered to be significant hypoglycemia [11,12], and the patients were classified as HYPO or NONHYPO based on this criterion. A subset (N = 27; 13 HYPO, 14 NONHYPO) had measurements of GLP-1 before and, then, 30, 60, and 120 min later, as tested with an Elisa kit (Glucagon-Like-Peptide-1 active ELISA kit, Millipore, France).

2.4. CGM

Glucose profiles were evaluated by continuous glucose monitoring (CGM; CGMS gold or i-pro2, Medtronic, Northridge, CA) in a real-life setting in 43 patients. The interstitial glucose (IG) mean, standard deviation of the IG mean, maximum and minimum IG and the percentage of time spent under 3.3 and above 7.7 mmol/L were recorded. Hyperglycemia was defined by the presence of at least three consecutives measures above 7.7 mmol/L, and hypoglycemia was defined by the presence of at least three consecutive measures below 3.3 mmol/L.

2.5. *Ethical Permission*

The local ethics committee of CHU de Toulouse approved the study protocol (No. 34-1210), and each patient signed a written consent form.

2.6. *Statistics and Calculations*

2.6.1. *Calculations*

2.6.1.1. Excess weight loss (EWL). Excess weight is the weight above the value that corresponds to an individual Body Mass Index (BMI) of 25. The excess weight loss is the ratio of the weight lost after surgery to the initial excess weight [24].

2.6.1.2. Insulin Sensitivity. The Homeostasis Model Assessment (HOMA) estimates steady-state beta-cell function (%B) and insulin sensitivity (%S) as a percentage of a normal reference population. In the fasting state, HOMA-IR is the product plasma fasting glucose-fasting plasma insulin/22.5.

Insulin sensitivity S_I was measured with the oral minimal model according to Caumo [18]. This well-validated procedure extends Bergman's minimal model computation to the analysis of an oral glucose challenge and provides an evaluation of S_I from glucose and insulin data.

2.6.2. *Hepatic Insulin Sensitivity*

Hepatic insulin sensitivity was calculated as the product of the total area under the curve (AUC) for plasma glucose and insulin during the first 30 min of the challenge (AUC glucose (0–30) × AUC insulin (0–30)), according to Abdul-Ghani [25]. This index was strongly correlated with the hepatic insulin resistance index given by the glucose clamp. This index was converted into units of minimal model S_I ($min^{-1}/(\mu U/ml) \times 10^{-4}$) on the basis of a validation study performed in our unit, as follows:

$$\text{SI h} = 1.34/(\text{AUC glucose}(0\text{-}30) \times \text{AUC insulin}(0\text{-}30)) \times 1000000$$

2.6.3. *Calculations of Insulin Secretion*

The insulin secretion rate (ISR) was quantified from C-peptide kinetics as described by the two-compartment model originally proposed by Eaton et al. [26] and further improved by van Cauter et al. [27], in which the model parameters were individually adjusted to the subject's anthropometric data.

The β-cell response that was obtained with this classical calculation was then quantified with several parameters that are defined by the two most widely accepted models available in the literature [28,29]. The maximal insulin secretion (pmol min^{-1} m^{-2}), i.e., the highest value of ISR during the test, and the total insulin release over 120 min (pmol/m^2), which is calculated as the area under the curve, were estimated.

Φ is a measurement of the total insulin secretion and was calculated according to Breda [28].

2.6.3.1. Second phase insulin secretion. β-cell sensitivity to glucose [29] measures the effect of glucose on β-cell secretion at steady state. It is calculated as the slope (pmol min^{-1} $mmol^{-1}$ m^{-2}) of the relationship between ISR and the glucose concentration.

2.6.3.2. First Phase Insulin Secretion. Two indexes were measured. The derivative component, also called the "rate sensitivity" or k1 (pmol m^{-2} $mmol^{-1}$), according to Mari [29], is the dynamic dependence of insulin secretion on the rate of change of the glucose concentration. The dynamic sensitivity index Φ_D is a measure of the stimulatory effect of the rate at which glucose increases upon the secretion of stored insulin [28].

2.6.3.3. Disposition Index. The disposition index was calculated as the insulin secretion multiplied by the insulin sensitivity, in analogy with Bergman et al. [30]. Three different disposition indices can be calculated after mixed-meal ingestion, by multiplying S_I by either the value of k1 or the β-cell sensitivity to glucose or the total insulin secretion Φ.

2.6.3.4. Insulin Clearance. The individual parameters of the insulin kinetics were calculated from insulin and C peptide data using Tura's model [31].

3. Statistical Analysis

Statistical analysis was performed with Stata statistical software, release 11.2 (STATA Corporation, College station, TX, USA). We described the patients' characteristics using the number and frequency for the qualitative data and the mean (±SD) for the quantitative data or the median for non-parametric data. In bivariate analysis, qualitative variables were compared between groups (with hypoglycemia versus without hypoglycemia) using the χ^2-test (or Fisher's exact test in the case of small expected numbers). Student's *t* test was used to compare the distribution of the quantitative data (or Mann–Whitney *U* test when the distribution departed from normality or when homoscedasticity was rejected). The model that evaluates the occurrence of hypoglycemia included the independent variables from a bivariate analysis (with a $P < 0.20$). Then, a backward stepwise procedure was applied to assess the variables that were significantly and independently associated with the occurrence of hypoglycemia ($P < 0.05$). Interactions between independent covariates were tested in final regression models, and none were significant. The homoscedasticity and normality of the model residuals were verified. The goodness of fit of the models was assessed using the adjusted R^2. All of the reported *P* values were two-sided, and the significance threshold was <0.05.

4. Results

4.1. *OGTT*

Between 90 and 120 min from the load, 25 patients had a plasma glucose that was lower than 2.8 mmol/L (the HYPO group), and 21 had a plasma glucose that was higher than 2.8 mmol/L (the NONHYPO group). The patients who were in the HYPO group were younger, had lost more weight at the

time of the exploration, and had diabetes that was less prevalent before surgery (Table 1). All of the patients had symptoms that were compatible with hypoglycemia. The Sigstat score did not differ between the groups (13.2 ± 5.1 vs. 13.2 ± 6.0; $P = 0.803$).

4.2. *Plasma Profiles*

The plasma profiles of glucose, insulin, GLP-1 and C peptide and the ISR profiles are shown in Fig. 1. The fasting glycemia differed between the two groups (4.2 ± 0.4 mmol/L in the HYPO group vs. 4.6 ± 0.6 mmol/L in the NONHYPO group, $P = 0.0102$), whereas the fasting plasma insulin did not (5.8 ± 3.8 mIU/L in the HYPO group vs. 7.4 ± 3.8 mIU/L in the NONHYPO group, $P = 0.0729$). Post-challenge glycemia concentrations were similar at 15, 30 and 60 min but not at 90 and 120 min, where it was lower in the HYPO group (at 120 min, 2.6 ± 0.6 vs. 4.4 ± 1.2 mmol/L, $P < 0.0001$). The plasma insulin concentrations were higher in the HYPO patients compared with the NONHYPO patients, from times 15–30 min ($P < 0.05$), and they did not differ afterward. The plasma C peptide concentrations were lower at 90 and 120 min after the oral load in the HYPO group. Furthermore, in the HYPO group and at 120 min, the mean insulin concentrations were higher than 3 mIU/L, and the C peptide values were higher than 0.6 pg/ml, the threshold for an excessively high value for the corresponding glycemia (lower than 2.8 mmol/L) [10]. The plasma GLP-1 concentrations did not differ between the groups (Fig. 1).

4.3. *Insulin Secretion*

In HYPO vs. NONHYPO patients, the insulin secretion rate (ISR) calculated from C Peptide kinetics was significantly higher 15 min after the oral load and lower at 90 and 120 min (Fig. 1). The cumulated insulin secretion rate of the two groups did not differ. However, the slope of ISR with a time between 30 and 90 min was steeper in HYPO patients (−13.3 ± 7.5 vs. −7.1 ± 10.0, $P = .006$), which shows that ISR reduced more over time in HYPO compared with NONHYPO patients.

When corrected for either glycemia or for changes in the plasma glucose, indicators of insulin secretion (either first- or second-phase indicators) did not differ between HYPO and NONHYPO patients (Table 2). Neither whole body insulin clearance nor post-challenge insulin sensitivity differed between the groups (Table 2).

In the multivariate analysis (Table 3), the determinants independently and significantly associated with a hypoglycemia after OGTT were EWL (OR 1.07, 95% CI 1.02–1.13, $P = 0.008$) and Phi (Breda and Cobelli) (OR 1.02, 95% CI 1.002–1.03, $P = .025$). The existence of diabetes before surgery was negatively associated with HYPO, although the association had marginal significance (OR 0.08, 95% CI 0.004–1.05, $P = 0.054$).

The ROC curve analysis of the EWL as a determinant of HYPO showed that the AUC was 0.754 and that for an EWL of 71.7%, the sensitivity was 88%, the specificity was 55%, and 73.3% of the patients were correctly classified.

4.4. *CGM*

Continuous glucose monitoring (CGM) measures were recorded for an average of 4.97 (±1.2) days for the HYPO patients and 4.34 (±1.1) for the NONHYPO patients (P = NS). The CGM showed that the HYPO patients had a lower mean interstitial glucose and a lower minimum interstitial glucose value compared with the NONHYPO patients (Table 4). More HYPO patients (N = 13/22) had an interstitial glucose value <3.3 mmol/L during the CGM than NONHYPO patients (N = 5/21, $P = 0.02$).

5. Discussion

The results of this study indicate that patients with hypoglycemia after OGTT (HYPO patients) are younger, have lost more weight after RYGB, are less frequently diabetic before surgery, and display different insulin secretion concentrations 15 min after the 75-g OGTT, compared with NONHYPO patients. Interestingly, the HYPO patients have lower interstitial glucose values in real life, which suggests that a continuum exist between observations with an oral glucose load and real life interstitial glucose concentrations.

The early insulin secretion rate after the glucose load is higher in HYPO patients. However, the sensitivity of β-cell to glucose, whole body insulin clearance, and insulin sensitivity do not differ between HYPO and NONHYPO patients. It is only in the multivariate model that glucose-adjusted insulin secretion was identified as a determinant of the HYPO phenotype. Furthermore, GLP-1 concentrations did not differ between the two groups.

Is there an inappropriate insulin secretion?

Table 1 – Physical characteristics of the patients.

Mean ± SD	Patients with hypoglycemia (N = 25)	Patients without hypoglycemia (N = 21)	P (Mann–Whitney)
Age (years)	39.6 ± 10.4	46.8 ± 8.8	0.018
Time of appearance of malaise after surgery (months)	13.4 ± 13.0	13.4 ± 9.1	0.999
Weight before surgery (kg)	114.4 ± 21.0	116.1 ± 16.0	0.450
BMI before surgery (kg/m^2)	42.3 ± 6.6	43.2 ± 6.4	0.681
Diabetes before surgery (n, %)	1 (4%)	5 (24%)	0.079[1]
Weight after surgery (kg)	72.3 ± 14.7	83.0 ± 13.0	0.003
BMI after surgery (kg/m^2)	26.6 ± 4.0	31.0 ± 5.0	0.003
EWL (%)	93.9 ± 25.9	68.8 ± 24.4	0.003

[1] Fisher exact test.

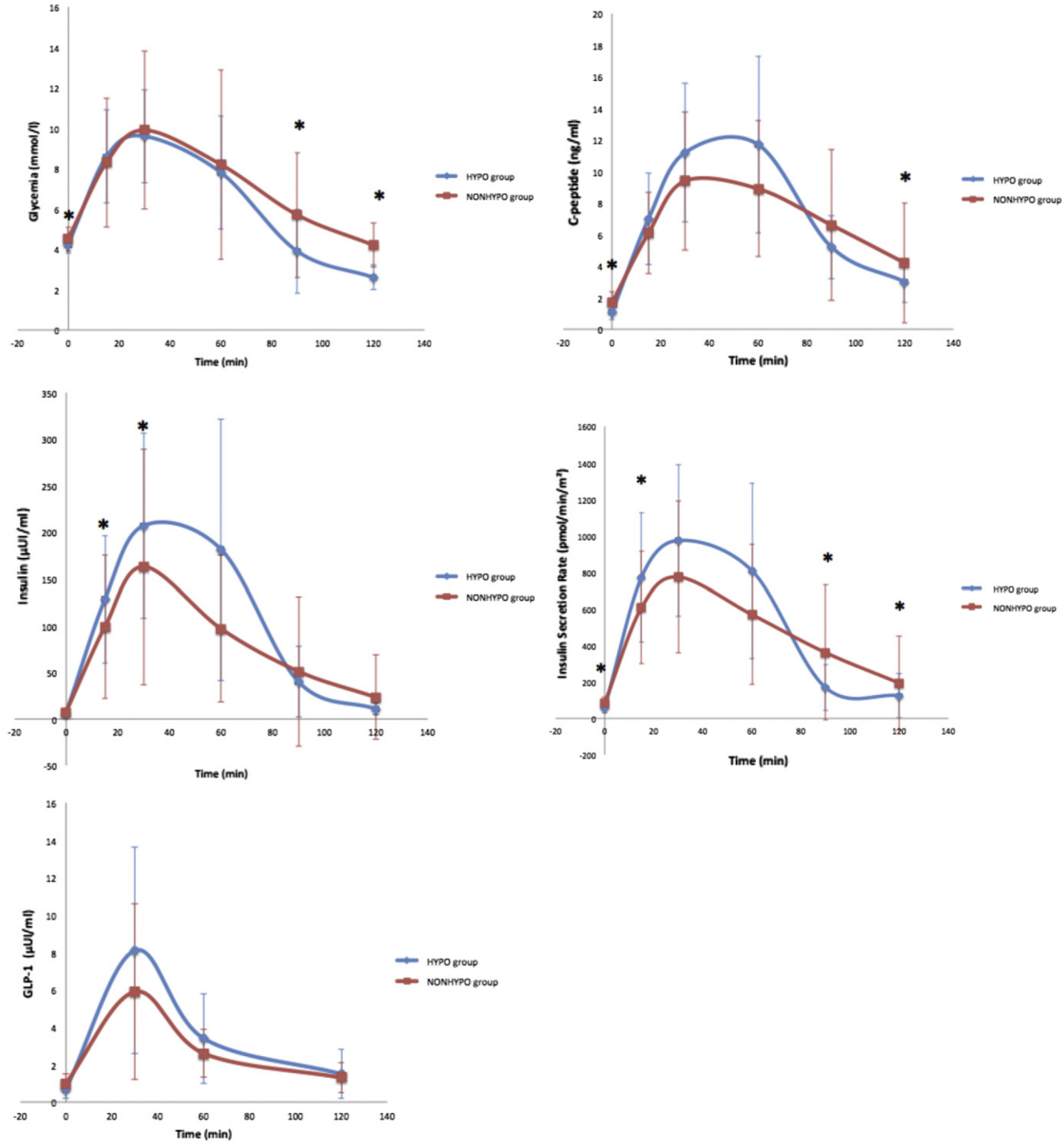

Fig. 1 – Plasma profiles of glycemia, insulin, C-peptide, GLP-1, and Insulin Secretion Rate profile.* indicates significant difference.

This study shows that patients with HYPO at the OGTT have both an increased insulin response to the OGTT and a preserved capacity to slow the insulin secretion down.

In severe episodes of hypoglycemia, Goldfine et al. has shown that after an RYGB, there is an inappropriate insulin secretion compared with both non-operated and asymptomatic patients [13]. Salehi et al. further suggested that only the patients with neuroglucopenic symptoms might display a higher insulin secretion rate and a lower insulin clearance [15]. Salehi et al. [14] elegantly showed that GLP-1 is responsible for most of the hyperinsulinemic response. Indeed, an antagonist of the GLP-1 receptor (Exendin 9) could reduce insulin concentrations to the level of asymptomatic patients and erase biological hypoglycemia and its symptoms after a meal test. Rumilla [32] et al. analyzed the histology of the pancreas (when tail-pancreatectomy is performed) and demonstrated that in

Table 2 – Insulin secretion and insulin sensitivity.

Mean ± SD	Patients with hypoglycemia (N = 25)	Patients without hypoglycemia (N = 21)	P (Mann–Whitney)
Insulin Secretion			
ISR 15 min (pmol min^{-1} m^{-2})	793 ± 363	588 ± 323	0.046
ISR Slope 30–90 min	−13.3 ± 7.5	−7.1 ± 10.0	0.006
AUC ISR (pmol/m^2)	64639 ± 24919	64586 ± 30354	0.782
Second phase			
Beta cell sensitivity (pmol min^{-1} $mmol^{-1}$ m^{-2})	217 ± 173	162 ± 105	0.182
ϕ Breda and Cobelli × 10^{-9}	92 ± 48	74 ± 54	0.083
First phase			
Rate sensitivity (k_1) (pmol m^{-2} $mmol^{-1}$)	870 ± 764	611 ± 524	0.197
ϕ_D (Breda and Cobelli) (pmol $mmol^{-1}$) × 10^{-9}	389 ± 237	333 ± 374	0.225
Disposition index			
$S_I^*\phi$ [1]	543 ± 173	599 ± 545	0.275
S_I^* k_1	5188 ± 7691	4943 ± 7078	0.305
$S_I^*\phi_D$	2177 ± 1658	2063 ± 2252	0.360
Insulin clearance			
n (min^{-1})	0.5 ± 0.4	0.5 ± 0.3	0.163
Insulin sensitivity			
Oral minimal model insulin sensitivity [1] (min^{-1}/(μU/ml) × 10^{-4})	5.9 ± 3.6	8.1 ± 10.1	0.903
S_Ih (min^{-1}/(μU/ml) × 10^{-4})	2.2 ± 1.6	4.9 ± 5.6	0.114
OGIS	654 ± 80	741 ± 285	0.596
HOMA 2			
HOMA %B	109.8 ± 43.6	108.4 ± 43.5	0.877
HOMA %S	176 ± 80	130 ± 54	0.056
HOMA-IR	0.74 ± 0.4	0.92 ± 0.5	0.053

Abbreviations: AUC ISR: area under the curve of the insulin secretion rate; ϕ Breda and Cobelli: global index of insulin secretion in response to glucose; n: parameter of Tura's model for measuring insulin peripheral clearance; ϕ_D (Breda and Cobelli): component of insulin secretion triggered by the rapid change in blood glucose; HOMA IR: homeostasis-model assessment index of insulin resistance; S_Ih: hepatic insulin sensitivity calculated according to Abdul-Ghani and deFronzo and expressed in minimal model units.
[1] Caumo and Cobelli.

more than 75% of the cases, anomalies similar to nesidioblastosis could be evidenced.

The picture is less clear in patients who do not show severe clinical presentation. Salehi et al. have shown that cumulated ISR was not increased in HYPO vs. NONHYPO patients and that all of the parameters of insulin secretion were similar between the groups, only for the patients with neuroglucopenic signs that displayed an inappropriate insulin secretion [14]. Pigeyre et al. [9] suggested that early insulin concentrations after an OGTT were higher in HYPO than in NONHYPO patients [9]. Itariu et al. [16] analyzed patients with biological HYPO (after a 100-g glucose load, with a 3.3-mmol/L threshold to define HYPO) and suggested that neither plasma insulin nor plasma C peptide concentrations differed from subjects without HYPO. Note that the prevalence of HYPO was 50% of the subjects studied by Itariu [16].

The present study suggests that there is some degree of inadequate insulin secretion in patients with HYPO after the OGTT. First, in the HYPO group, early plasma concentrations of insulin are significantly higher than in the NONHYPO group after the same challenge. Second, early ISR is increased. ISR is a robust estimate of β-cell insulin secretion before any splanchnic clearance because it is calculated from the C-peptide kinetics [27,28]. The present data also show that despite an attempt to put a break on ISR (as assessed from the slope of the 30–120 min ISR), low glucose values could not be avoided. The increased ISR occurs despite similar plasma glucose concentrations at 15 min of the OGTT. We used two well-validated models to investigate the β-cell response to glucose. Data from both models were in good agreement and only showed a tendency for a higher insulin response (Phi Cobelli, β-cell sensitivity) in the HYPO group. This finding suggests that some stimulus other than glucose plays a role in the exaggerated insulin secretion. Salehi et al. have shown that in severe HYPO, GLP-1 can be one such stimulus [14]. We could not show a relationship between GLP-1 and ISR because there were too few subjects with GLP-1 measurements.

What are the determinants of post-bypass HYPO?

Being diabetic before surgery had a borderline significant protective effect (OR 0.04), which suggests that patients in the HYPO group were also more likely to be NGT before surgery. This trend was previously suggested in Pigeyre et al. [9]. We have no explanation for the trend and can speculate that patients without diabetes or pre-diabetes before surgery could have a powerful β-cell function to counteract the insulin resistance related to massive obesity and that could predispose them to an inappropriate response to an oral glucose load after surgery.

The higher the glucose-induced insulin secretion is, the more likely that the patients would develop HYPO at the OGTT (Phi Breda and Cobelli had a positive effect, OR 1.02). We do not know whether the patients already had this phenotype before because they were not measured before surgery. However, some of the responses could be acquired after surgery and might result from the direct delivery of glucose to the jejunum. Indeed, Breitman et al. have shown that jejunal

Table 3 – Final model of the determinants that are significantly and independently associated with hypoglycemia after OGTT.

N = 46	OR [95% CI]	P
Phi (Breda and Cobelli)	1.02 [1.002–1.03]	0.025
EWL (%)	1.07 [1.02–1.13]	0.008
Diabetes before surgery	0.08 [0.004–1.05]	0.054

R^2 = 0.308; goodness-of-fit test: P = 0.570; area under ROC curve = 0.836.

delivery increased insulin and GLP-1 secretion and lowered the 120-min glucose values in non-operated obese patients given a 50-g glucose challenge in the jejunum compared with a similar load given orally [33].

Weight loss was the third determinant. Similarly to what we found in a review of all severe cases [34] and in Lee et al. [35], the HYPO patients in the present study lost much more weight than the NONHYPO patients. We have no explanation for this phenotype. We can speculate that the greater the weight loss is, the more intense the calorie restriction [36–38]. An intense calorie restriction could also impair the contribution of the splanchnic bed to glucose disposal, through the shortening of neogluconeogenetic substrates [36,37]. In obese non-operated patients, Breitman et al. has shown that when glucose is delivered to the jejunum, the splanchnic contribution is doubled compared with an oral load [33]. Failure to promote this splanchnic contribution because of the shortage of neoglucogenesis substrates and/or because of a failure in the counter-regulatory hormones [36,34] could impede the counter-regulatory response.

The translational potential of the message is the following: To summarize, HYPO patients show an inappropriate insulin secretion. This finding reveals an insulin stimulatory pathway that is independent of glucose. Despite an attempt of the β-cell to slow the insulin secretion down (the slope of the ISR over time), hypoglycemia occurs probably as a result of the inability of the body to counter-regulate the hypoglycemia. Whether this circumstance results from a failure of the neoglucogenesis/glycogenolysis pathway (because of the intense weight loss) or from its regulation (by catecholamine or glucagon, which we have not addressed) is not known.

The clinical relevance of this study is that the biological phenotype elicited by the 75-g load is coherent with the CGM reading over ca. five days under real-life circumstances. Patients with HYPO had a lower mean interstitial glucose, and there were many more who reached values of below 3.3 mmol/L. This relationship suggests that although 75-g glucose is difficult to consume after a gastric bypass unless it is in a liquid form, it is a meaningful challenge. Kefhurt et al. [39] used CGM to address the question of the different prevalences of hypoglycemia in everyday life (CGM) and in laboratory circumstances (mixed meal test), and found that the prevalence was higher with CGM. Therefore, these two datasets are complementary. Furthermore, in a recent study by Abrahamsson et al. [40], CGM showed that patients who underwent RYGB (n = 15) spent 2.9% of the time in hypoglycemia (<3.3 mmol/l), mainly in the postprandial state.

This study has strengths. The oral challenge is more appropriate than clamp or IVGTT studies because the OGTT tests the integrated response to a glucose load. We chose the OGTT, which is a standardized test that can be used for both studying glucose metabolism and defining NGT, IFG and IGT patients. The models used for the computation of insulin secretion, insulin sensitivity and insulin clearance are robust and have been used with RYGB patients [41,42] and provide information beyond the simple plasma concentrations. This study is the first to show a correspondence between biological findings and real life, using continuous glucose monitoring after obesity surgery.

This study has weaknesses. First, it is based on a small sample of subjects. Second, we cannot say whether the patients displayed this profile before the surgery because they did not have oral challenges before surgery. Meal tests would be more physiological but are not standardized.

6. Conclusions

Patients with HYPO (positive Whipple triad) display some degree of inappropriate insulin secretion after a 75-g glucose challenge, which appears to be mediated by stimuli other than glucose. These patients also have distinct characteristics, having lost more weight, being younger and less often diabetic before surgery, and displaying different CGM characteristics (lower mean and minimum capillary glucose, spending more time below the 3.3 mmol/L threshold). We do not know the health hazards that are related to this inappropriate insulin secretion. These patients may or may not develop

Table 4 – CGM characteristics.

	HYPO group n = 22	NONHYPO group n = 21	P (Mann–Whitney)
Mean interstitial glucose (IG) (mg/dl)	92.8 (±12.4)	100.1 (±12.3)	0.044
SD (mg/dl)	22.9 (±7.6)	28.9 (±9.5)	0.030
Minimum IG (mg/dl)	49.8 (10.5)	54.7 (±8.3)	0.051
Maximum IG (mg/dl)	199.3 (±53.4)	235.1 (±62.2)	0.060
Time >140 mg/dl (%)	5.0 (±6.3)	9.1 (±7.0)	0.024
Time <60 mg/dl (%)	3.9 (±4.5)	1.7 (±2.6)	0.084

This table displays the mean (SD) values for the CGM characteristics. For example, the "minimum IG" is the average of the minimum interstitial glucose values in the patients of the group.

severe episodes of HYPO. We recommend that the 75-g OGTT and CGM be performed in the patients who are referred for clinical presentation of HYPO, to better characterize the patients. Further studies are necessary to understand inappropriate insulin secretion.

Author Contribution

P Ritz and H Hanaire designed the study of the patients referred for malaise. Y Anduze and M Chalret du Rieu operated on and referred the patients. R Burcelin performed the GLP-1 measurements.

C Vaurs and JF Brun performed the dynamic insulin secretion calculations. C Vaurs conducted the statistical calculations.

C Vaurs, H Hanaire, and P Ritz wrote the manuscript, which was read and approved by all of the other authors.

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