Glucose Metabolism Parameters and Post-Prandial GLP-1 and GLP-2 Release Largely Vary in Several Distinct Situations: a Controlled Comparison Among Individuals with Crohn's Disease…

Article *in* Obesity Surgery · August 2017

DOI: 10.1007/s11695-017-2851-y

CITATION
1

READS
106

9 authors, including:

Daniela Magro
University of Campinas
59 PUBLICATIONS **523** CITATIONS
SEE PROFILE

Everton Cazzo
University of Campinas
121 PUBLICATIONS **262** CITATIONS
SEE PROFILE

Paulo Gustavo Kotze
Pontifícia Universidade Católica do Paraná (PUC-PR)
175 PUBLICATIONS **332** CITATIONS
SEE PROFILE

Ana Carolina Junqueira Vasques
University of Campinas
68 PUBLICATIONS **697** CITATIONS
SEE PROFILE

OBES SURG
DOI 10.1007/s11695-017-2851-y

ORIGINAL CONTRIBUTIONS

Glucose Metabolism Parameters and Post-Prandial GLP-1 and GLP-2 Release Largely Vary in Several Distinct Situations: a Controlled Comparison Among Individuals with Crohn's Disease and Individuals with Obesity Before and After Bariatric Surgery

Daniéla Oliveira Magro[1] · Everton Cazzo[1] · Paulo Gustavo Kotze[2] · Ana Carolina Junqueira Vasques[3] · Carlos Augusto Real Martinez[1] · Elinton Adami Chaim[1] · Bruno Geloneze[3] · José Carlos Pareja[1] · Cláudio Saddy Rodrigues Coy[1]

Abstract

Background This study aims to compare the post-prandial curves of glucose, insulin, GLP-1, and GLP-2 among individuals with Crohn's disease (CD), obese individuals before and after bariatric surgery, and healthy controls.

Methods This an exploratory cross-sectional study that involved five groups of patients (two groups of individuals with CD—active and inactive), bariatric patients (pre- and post-surgery, who were their own controls), and a distinct separated control group of healthy volunteers. C-reactive protein (CRP) levels and the post-prandial curves of glucose, insulin, GLP-1, and GLP-2 curves were assessed and compared.

Results The pre-RYGB group presented significantly higher levels of CRP than the post-RYGB ($p = 0.001$) and the control group ($p = 0.001$). The inactive CD group presented a higher post-prandial GLP-1 area under the curve (AUC) than the pre-RYGB group ($p = 0.009$). The post-RYGB group presented significantly higher AUCs of GLP-2 than the pre-RYGB group ($p < 0.0001$), both inactive and active CD groups ($p < 0.0001$ in both situations), and the control group ($p = 0.002$). The pre-RYGB group presented a significantly higher AUC of glucose than the post-RYGB ($p = 0.02$) and both active and inactive CD groups ($p = 0.019$ and $p = 0.046$, respectively). The pre-RYGB group presented a significantly higher AUC of insulin than the control ($p = 0.005$) and both CD groups ($p < 0.0001$).

Conclusions Obesity is associated with an inflammatory state comparable to the one observed in CD; inflammation may also be enrolled in the blockade of GLP-2. CD individuals present a more incretin-driven pattern of glucose metabolism, as a way to prevent hypoglycemia and compensate the carbohydrate malabsorption and GLP-2 blockade.

Keywords Obesity · Bariatric surgery · Crohn's disease · Glucagon-like peptide 1 · Glucagon-like peptide 2

Introduction

Obesity has reached epidemic proportions worldwide over the last decades. According to the World Health Organization, there were 600 million adult obese individuals in 2014 [1]. Although not nearly as frequent, the prevalence of inflammatory bowel diseases (IBDs) also presented a significant rise over the same period. A systematic review enrolling 260 population-based studies observed an estimated annual incidence of IBD that ranged from 10 to 30 cases per 100,000 persons in the Western world. Moreover, approximately 0.5%

✉ Everton Cazzo
notrevezzo@yahoo.com.br

[1] Department of Surgery, Faculty of Medical Sciences, State University of Campinas (UNICAMP), R. Alexander Fleming, s/n, 13083-887, Campinas, São Paulo, Brazil

[2] Colorectal Surgery Unit, Cajuru University Hospital, Catholic University of Paraná, Curitiba, Paraná, Brazil

[3] Research Laboratory of Metabolism and Diabetes (LIMED), Gastrocentro, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

Published online: 03 August 2017

of adults in the West suffer from IBD [2]. A potentially understated factor might be obesity, which has been associated with an increase in the risk of several autoimmune diseases such as rheumatoid arthritis, psoriasis, and psoriatic arthritis. Contrary to conventional belief, 15–40% of the individuals with IBD also present obesity, and it is uncertain whether it might contribute to the development and evolution of IBD [3].

The interplay between obesity and IBD is complex and poorly understood. Several factors have been enrolled in the potentially common pathophysiological pathways which might link both conditions. The disproportionate accumulation of visceral fat and impaired release of adipokines, such as adiponectin, disturbances in the gut microbiome, and chronic inflammation, have been enrolled as possible interconnecting links [4]. Furthermore, a connection between bariatric surgery and IBD has been reported over recent years. Several case reports and case series have reported the emergence of de novo IBD after bariatric surgery, with the onset of symptoms ranging from 2 months to 10 years after the procedure [5–8]. Shoar et al., in a systematic review, observed that among obese individuals with IBD, there is a trend towards remission and improvement of IBD (52.4%); however, there is also a significant proportion of individuals (16.7%) who present exacerbation of disease after surgery [9].

Glucose metabolism disturbances have also been reported to some extent in both diseases, as well as the release of gut hormones enrolled in the glucose homeostasis and gut physiology, such as the glucagon-like peptides 1 and 2 (GLP-1 and GLP-2) [10–12]. GLP-1 and GLP-2 are secreted in the L cells of the ileum and colon in response to the passage of nutrients; GLP-1 is an incretin that predominantly stimulates beta cell production and release of insulin, whereas GLP-2 plays trophic effects on the gut mucosa, such as stimulating nutrient absorption and maintenance of intestinal permeability, among other functions [13–15]. Several modalities of bariatric surgery, mainly the ones that encompass some degree of intestinal bypasses, such as the Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversions, lead to critical increases in the secretion of both hormones [15–20]. These changes are likely to be related to the passage of greater amounts of nutrients by the ileum, as well as the exclusion of the duodenum from the food transit [21–23]. There are reports of significant impairment of both GLP-1 and GLP-2 secretion in individuals with CD [24, 25]. Since the levels of these gut-derived hormones are significantly influenced by both the surgical procedures and IBD, it is likely to hypothesize that these changes could be enrolled in the pathophysiological process of post-bariatric de novo CD to some extent.

This study aimed to compare the post-prandial curves of glucose, insulin, GLP-1, and GLP-2 among different populations comprised of individuals with Crohn's disease, individuals with obesity before and after bariatric surgery, and healthy controls.

Methods

Patient Population

This is an exploratory cross-sectional study performed in patients with a previously confirmed diagnosis of CD, morbidly obese individuals who underwent bariatric surgery (RYGB) evaluated before and after surgery, and healthy controls.

The bariatric surgery group enrolled morbidly obese individuals aged 18–65 years old who underwent RYGB between January 2011 and December 2012. The CD groups comprised individuals aged 18–65 years old attended at the Inflammatory Bowel Diseases (IBD) Clinics of our institution from August 2014 through March 2015. The individuals were, respectively, recruited in the Bariatric Surgery outpatient service in the pre-operative phase of the following and in the IBD Clinics of our institution by means of a clinical interview personally conducted by the research team in which they were evaluated in regards to the inclusion and exclusion criteria, as well as their accordance to take part in the study protocol. Exclusion criteria were endocrine disorders (Cushing's disease, type 1 and 2 diabetes mellitus, Addison's disease), users of dipeptidil-peptidase-4 (DPP-IV) inhibitors, and antecedent of total colon resection and/or ileal resection. The diagnosis of CD was certified by means of clinical, endoscopic, and histological standard criteria. During routine visits to our clinics, patients who were in accordance with the study signed up to the informed consent form. The patients' blood samples were collected, and disease activity in CD patients was assessed by using the Crohn's disease activity index (CDAI) [26]. Scores above 150 points defined the presence of an active disease, whereas a CDAI index below 150 meant the presence of inactive disease (remission). The Montreal classification [27] was also employed among CD patients. Bariatric surgery was indicated based on the National Institutes of Health Consensus Statement criteria [28]. The individuals in the bariatric surgery group were evaluated immediately before and 12 months after surgery. These individuals were considered independent groups according to the period evaluated (pre- or post-operative). All the bariatric procedures were performed by the same surgical team and with the same technique. Blood samples were also collected from seven healthy controls, which were volunteering women who worked or studied at the university. The study underwent evaluation and was approved by the local Institutional Ethics Review Board under the references UNICAMP 801/2008 and 245/2010.

Bariatric Surgery Technique

The main features of the RYGB were a 30-mL gastric pouch, a 100-cm biliopancreatic limb, a 150-cm alimentary limb, and a

common limb consisting of the remainder of the small intestine.

Reagents and Serum Analysis

C-reactive protein (CRP) levels were determined using ELISA Kit (R&D Systems Inc., Minneapolis, MN). For glucose, insulin, GLP-1, and GLP-2 analysis, blood samples were collected in tubes with EDTA3 plus Sigma diprotin. Serum samples were stored in a freezer at −80 °C for later analysis of GLP-1 and GLP-2 with specific ELISA kits (ELISA, Millipore Billerica, MA).

Standard Meal Tolerance Test

After an overnight fasting (12 h), subjects underwent the standard meal tolerance test (MTT), based in a mixed meal containing 515 kcal (41.8% fat, 40.7% carbohydrates, and 17.5% protein). This test contained a protein bar and a liquid nutrition supplement. Blood samples were drawn for glucose, insulin, GLP-1, and GLP-2 at 0, 15, 30, 45, 60, 90, 120, 150, and 180 min.

Statistical Analysis

The results were expressed as means ± standard deviation (mean ± SD).The areas under the curve (AUC) of glucose, insulin, GLP-1, and GLP-2 were calculated by the trapezoidal rule after MTT. For the comparison of the results obtained between two groups, Mann-Whitney test was used. For five groups' comparison, ANOVA analysis was used for parametric variables and Kruskal-Wallis test was used for nonparametric variables. The significance level adopted was 5% for all statistical tests (p value <0.05). Considering the small number of individuals in each group and the unavailability of resources to analyze more subjects, a post hoc sample power analysis was performed considering a 20% alpha error. The software SSPS v.16.0 (Chicago, IL, USA) was used for the analysis.

Results

Patients' Demographics

There were 48 individuals enrolled in this study. They were divided into four groups: active CD (10 individuals), inactive CD (10), pre-bariatric surgery (11 individuals), post-bariatric surgery (10 individuals), and control (7). The bariatric surgery group was divided into two sub-groups independently enrolled in the analysis according to the period evaluated: pre-RYGB (11 individuals) and post-RYGB (10 individuals). Figure 1 presents a flow diagram of the groups' definition.

Characteristics of the CD Groups

The active CD group consisted of six women and four men, with a mean age of 35.1 ± 9.3 years and mean BMI of 20.2 ± 3.5 kg/m^2; 60% had a duration of disease of more than 5 years and mean CDAI 238 ± 71.8. Age at diagnosis between 17 and 40 years (A2) was 70%, and 40% had a location of CD colonic (L2); 60% presented non-penetrating CD phenotype (B1) and perianal disease was present in 60%. Of those, 6/10 patients had been treated with TNF-α antibody therapy or a thiopurine derivate (4 out of 10 patients). The inactive CD group consisted of one woman and nine men, with a mean age of 45.6 ± 13.6 years and mean BMI of 23.5 ± 3.3 kg/m^2; 90% had a duration of disease of more than 5 years and mean CDAI 59.4 ± 37.5. Age at diagnosis between 17 and 40 years (A2) was present in 80%, and 50% had CD located in the terminal ileum (L1); 50% presented a stricturing CD phenotype (B2), and perianal disease was present in 80%. Of this group, 4/10 patients had been treated with TNF-α antibody therapy (4 of 10 patients) or a thiopurine derivate (5 of 10 patients).

Characteristics of the Bariatric Surgery Group

The bariatric surgery group was comprised of 11 individuals who underwent RYGB and were followed up for 12 months, of which six (54.5%) were female. Before RYGB, mean age was 36.7 ± 8.2 years old, mean pre-operative weight was 123.5 ± 13.1 kg, and mean pre-operative BMI was 46.3 ± 3.1 kg/m^2. None of the individuals were diabetic, 36.4% presented impaired glucose tolerance, 45.4% presented hypertension, and 54.5% were dyslipidemic. In regards to chronic drug usage, 45.5% used anti-hypertensive agents and 36.4% used lipid-lowering drugs.

Weight Loss Results of the Bariatric Surgery Group

One year after RYGB, mean weight was 85.3 ± 16.1 kg and mean BMI was 32.1 ± 6.0; the mean weight loss was 38.2 ± 15.2 kg, and mean percentage of excess weight loss was 66.7 ± 12.2%.

Characteristics of the Control Group

The control group encompassed seven healthy women with a mean age of 48.42 ± 12.6 years, a mean BMI of 25.2 ± 2.9, and no comorbidities.

CRP Levels

The pre-RYGB group presented significantly higher levels of CRP than the post-RYGB (p = 0.001) and the control group (p = 0.001); the CRP levels of the pre-RYGB group were not

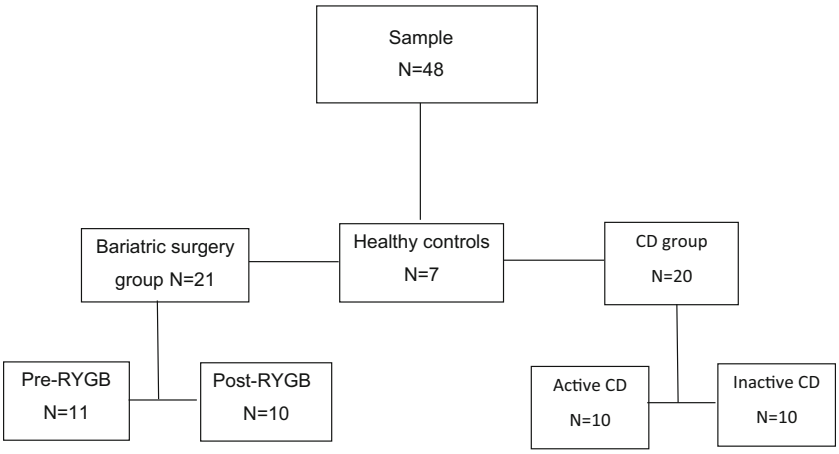

Fig. 1 Flow diagram of group definition

significantly different than both CD groups. Table 1 details the overall characteristics of the studied individuals, as well as the characteristics of each group.

Post-MTT Curves of GLP-1

Comparing the post-MTT curves of GLP-1, we observed that the inactive CD group presented a higher AUC than the pre-RYGB group ($p = 0.009$). Table 2 presents the complete comparison of the GLP-1 curves after MTT among the five groups. Evaluating the values from 0 to 180 min, it was observed that the pre-RYGB did not present a significant response, generating a flat curve, whereas the post-RYGB presented an intense increase until 60 min; the active CD presented a late increase after 150 min, whereas the inactive CD presented an increase after 120 min, followed by an abrupt decrease. The controls presented a slight and sustained increase. A graphic representation of the GLP-1 curves in the five groups is shown in Fig. 2a.

Post-MTT Curves of GLP-2

In regard to GLP-2 curves following MTT, it was observed that the post-RYGB group presented significantly higher

Table 1 Characteristics of the individuals of the five groups studied

Variables	Pre-RYGB (I)	Post-RYGB (II)	Active CD (III)	Inactive CD (IV)	Control (V)	Values of *p*
Gender (female/male)	6/5	6/5	6/4	1/9	7/0	I vs. IV 0.001 I vs. V <0.0001 II vs. IV 0.003 II vs. V <0.0001 III vs. IV 0.003 IV vs. V <0.0001 Remaining NS
Age (years)	36.7 ± 8.2	37.8 ± 8.7	35.1 ± 9.3	45.6 ± 13.6	48.42 ± 12.6	All NS
Weight (kg)	123.5 ± 13.1	85.3 ± 16.1	57.2 ± 10.2	67.7 ± 13.1	62.8 ± 9.01	I vs. II <0.0001 I vs. III <0.0001I vs. IV <0.0001 I vs. V <0.0001 Remaining NS
BMI (kg/m^2)	46.3 ± 3.1	32.1 ± 6.0	20.2 ± 3.5	23.5 ± 3.3	25.2 ± 2.9	I vs. II <0.0001 I vs. III <0.0001I vs. IV <0.0001 I vs. V <0.0001 Remaining NS
CRP (mg/L)	6.6 ± 4.7	0.7 ± 0.9	4.3 ± 0.5	4.4 ± 0.7	1.3 ± 0.2	I vs. II 0.001 I vs. V 0.001 IV vs. V 0.05 Remaining NS
HOMA-IR	4.4 ± 4	1.2 ± 0.7	2.2 ± 3.8	1.7 ± 2.1	1.3 ± 0.8	All NS

RYGB Roux-en-Y gastric bypass, *BMI* body mass index, *CRP* C-reactive protein, *HOMA-IR* homeostasis model assessment–insulin resistance, *NS* non-significant

Table 2 Comparison of the GLP-1 AUCs following MTT in the five groups evaluated [expressed in means ± SD (value of *p*)]

	Pre-RYGB	Post-RYGB	Inactive CD	Active CD	Control
Pre-RYGB	NA	705.8 ± 343.4 vs. 954.2 ± 725.9 (p = 0.945)	*705.8 ± 343.4 vs. 1885.9 ± 147.4 (p = 0.009)*	705.8 ± 343.4 vs. 1226.8 ± 809.5 (>p = 0.533)	705.8 ± 343.4 vs. 1080.2 ± 514.5 (p = 0.849)
Post-RYGB	954.2 ± 725.9 vs. 705.8 ± 343.4 (p = 0.945)	NA	954.2 ± 725.9 vs. 1885.9 ± 1147.4 (p = 0.068)	954.2 ± 725.9 vs. 1226.8 ± 809.5 (p = 0.931)	954.2 ± 725.9 vs. 1080.2 ± 514.5 (p = 0.997)
Inactive CD	*1885.9 ± 1147.4 vs. 705.8 ± 343.4 (p = 0.009)*	1885.9 ± 147.4 vs. 954.2 ± 725.9 (p = 0.068)	NA	1885.9 ± 1147.4 vs. 1226.8 ± 809.5 (p = 0.321)	1885.9 ± 1147.4 vs. 1080.2 ± 514.5 (p = 0.225)
Active CD	1226.8 ± 809.5 vs. 705.8 ± 343.4 (p = 0.533)	1226.8 ± 809.5 vs. 954.2 ± 725.9 (p = 0.931)	1226.8 ± 809.5 vs. 1885.9 ± 1147.4 (p = 0.321)	NA	1226.8 ± 809.5 vs. 1080.2 ± 514.5 (p = 0.995)
Control	1080.2 ± 514.5 vs. 705.8 ± 343.4 (p = 0.849)	1080.2 ± 514.5 vs. 954.2 ± 725.9 (p = 0.997)	1080.2 ± 514.5 vs. 1885.9 ± 147.4 (p = 0.225)	1080.2 ± 514.5 vs. 1226.8 ± 809.5 (p = 0.995)	NA

Values of p in italic indicate statistical significance

Post hoc power = 50%

RYGB Roux-en-Y gastric bypass, *GLP-1* glucagon-like peptide 1, *AUC* area under the curve, *SD* standard deviation, *MTT* meal tolerance test

AUCs than the pre-RYGB group ($p < 0.0001$), both inactive and active CD groups ($p < 0.0001$ in both situations), and the control group ($p = 0.002$). Table 3 details the complete comparisons of the GLP-2 curves following MTT. Analyzing the values from 0 to 180 min, it was observed that there was no significant post-prandial response in the pre-RYGB group, whereas the post-RYGB group presented a rapid and sustained response during the whole curve. In both the CD groups, there was no significant response after the MTT, whereas the controls presented a rapid increase

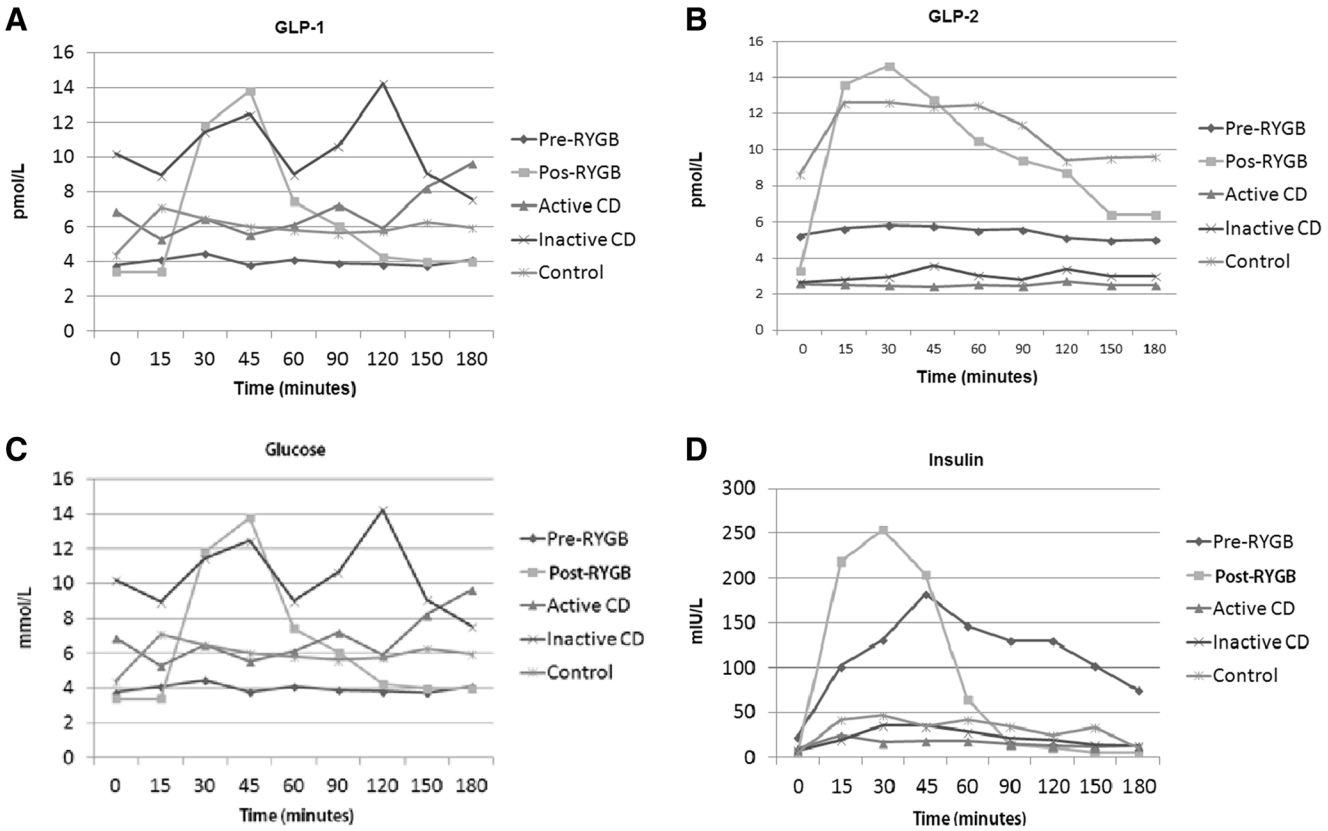

Fig. 2 Graphic representations of the post-prandial curves evaluated. **a** GLP-1. **b** GLP-2. **c** Glucose. **d** Insulin

Table 3 Comparison of the GLP-2 AUCs following MTT in the five groups evaluated [expressed in means ± SD (value of *p*)]

	Pre-RYGB	Post-RYGB	Inactive CD	Active CD	Control
Pre-RYGB	NA	974.6 ± 610 vs. 1751.9 ± 598.3 *(p = 0.028)*	974.6 ± 610 vs. 611 ± 157.5 (p = 0.606)	974.6 ± 610 vs. 469.2 ± 170.1 (p = 0.283)	974.6 ± 610 vs. 1978.3 ± 1075.2 *(p = 0.007)*
Post-RYGB	1751.9 ± 598.3 vs. 974.6 ± 610 *(p = 0.028)*	NA	1751.9 ± 598.3 vs. 611 ± 157.5 *(p = 0.001)*	1751.9 ± 598.3 vs. 469.2 ± 170.1 *(p < 0.0001)*	1751.9 ± 598.3 vs. 1978.3 ± 1075.2 (p = 0.931)
Inactive CD	611 ± 157.5 vs. 974.6 ± 610 (p = 0.60)	611 ± 157.5 vs. 1751.9 ± 598.3 *(p = 0.001)*	NA	611 ± 157.5 vs. 469.2 ± 170.1 (p = 0.982)	611 ± 157.5 vs. 1978.3 ± 1075.2 *(p < 0.0001)*
Active CD	469.2 ± 170.1 vs. 974.6 ± 610 (p = 0.283)	469.2 ± 170.1 vs. 1751.9 ± 598.3 *(p < 0.0001)*	469.2 ± 170.1 vs. 611 ± 157.5 (p = 0.982)	NA	469.2 ± 170.1 vs. 1978.3 ± 1075.2 *(p < 0.0001)*
Control	1978.3 ± 1075.2 vs. 974.6 ± 610 *(p = 0.007)*	1978.3 ± 1075.2 vs. 1751.9 ± 598.3 (p = 0.931)	1978.3 ± 1075.2 vs. 611 ± 157.5 *(p < 0.0001)*	1978.3 ± 1075.2 vs. 469.2 ± 170.1 *(p < 0.0001)*	NA

Values of *p* in italic indicate statistical significance

Post hoc power = 100%

RYGB Roux-en-Y gastric bypass, *GLP-2* glucagon-like peptide 2, *AUC* area under the curve, *SD* standard deviation, *MTT* meal tolerance test, *NA* not applicable

until 90 min. A graphic representation of the GLP-1 curves in the five groups is shown in Fig. 2b.

Post-MTT Curves of Glucose

In regard to the post-prandial glucose curves, it was observed that the pre-RYGB group presented a significantly higher AUC than the post-RYGB ($p = 0.02$) and both active and inactive CD groups ($p = 0.019$ and $p = 0.046$, respectively). Table 4 presents the complete comparison of the glucose curves following MTT among the five groups. Analyzing the values of glucose from 0 to 180 min, it was observed that the pre-RYGB group presented hyperglycemia during the whole test; the post-RYGB group presented normalization of the glucose curve after 45 min, quicker than the control group, where the normalization was observed after 150 min; in the active CD group, it was observed

Table 4 Comparison of the glucose AUCs following MTT in the five groups evaluated [expressed in means ± SD (value of *p*)]

	Pre-RYGB	Post-RYGB	Inactive CD	Active CD	Control
Pre-RYGB	NA	23,321.9 ± 5,893 vs. 16,949.3 ± 3,932.4 *(p = 0.020)*	23,321.9 ± 5,893 vs. 17,438.4 ± 5,322.5 *(p = 0.046)*	23,321.9 ± 5,893 vs. 16,915.6 ± 3,673.6 *(p = 0.019)*	23,321.9 ± 5,893 vs. 18,982.6 ± 2,312.5 (p = 0.295)
Post-RYGB	16,949.3 ± 3,932.4 vs. 23,321.9 ± 5,893 *(p = 0.020)*	NA	16,949.3 ± 3,932.4 vs. 17,438.4 ± 5,322.5 (p = 0.999)	16,949.3 ± 3,932.4 vs. 16,915.6 ± 3,673.6 (p = 1.000)	16,949.3 ± 3,932.4 vs. 18,982.6 ± 2,312.5 (p = 0.892)
Inactive CD	17,438.4 ± 5,322.5 vs. 23,321.9 ± 5,893 *(p = 0.046)*	17,438.4 ± 5,322.5 vs. 16,949.3 ± 3,932.4 (p = 0.999)	NA	17,438.4 ± 5,322.5 vs. 16,915.6 ± 3,673.6 (p = 0.999)	17,438.4 ± 5,322.5 vs. 18,982.6 ± 2,312.5 (p = 0.961)
Active CD	16,915.6 ± 3,673.6 vs. 23,321.9 ± 5,893 *(p = 0.019)*	16,915.6 ± 3,673.6 vs. 16,949.3 ± 3,932.4 (p = 1.000)	16,915.4 ± 3,673.6 vs. 17,438.4 ± 5,322.5 (p = 0.999)	NA	16,915.6 ± 3,673.6 vs. 18,982.6 ± 2,312.5 (p = 0.886)
Control	18,982.6 ± 2,312.5 vs. 23,321.9 ± 5,893 (p = 0.295)	18,982.6 ± 2,312.5 vs. 16,949.3 ± 3,932.4 (p = 0.892)	18,982.6 ± 2,312.5 vs. 17,438.4 ± 5,322.5 (p = 0.886)	18,982.6 ± 2,312.5 vs. 16,915.6 ± 3,673.6 (p = 0.961)	NA

Values of *p* in italic indicate statistical significance

Post hoc power = 85%

RYGB Roux-en-Y gastric bypass, *AUC* area under the curve, *SD* standard deviation, *MTT* meal tolerance test, *NA* not applicable

rather constant levels of glucose during the test, whereas the inactive CD group presented a normalization of glucose levels after 90 min. A graphic representation of the glucose curves in the five curves is shown in Fig. 2c.

Post-MTT Curves of Insulin

Regarding the insulin curves following MTT, the pre-RYGB group presented a significantly higher AUC than the control ($p = 0.005$) and both the active and inactive CD groups ($p < 0.0001$ in both comparisons). In Table 5, the complete comparisons of the post-MTT insulin AUCs are shown. Analyzing the values of insulin from 0 to 180 min, it was observed that the pre-RYGB group presented a rapid and sustained increase, maintaining such higher levels even until 180 min; the post-RYGB group presented a rapid and intense increase followed by an abrupt decrease right after 60 min; and the active CD group presented a slight increase followed by the restoration of nearly basal levels after 150 min, whereas the inactive CD group presented a slightly attenuated curve similar to the presented by the control group, characterized by a rapid and sustained increase until 120–150 min. A graphic representation of the insulin curves in the five groups is shown in Fig. 2d.

Discussion

Obesity has been proven to be strongly linked with insulin sensitivity abnormalities. Several factors are associated with these abnormalities, and the complex interplay among them is not completely known. Chronic inflammation and impairment on the release of the gut hormones collectively called incretins are known to play significant roles in this regard. The strong impact of bariatric surgery on IR-related abnormalities has also been clearly demonstrated over the years [29–36]. RYGB, the second most performed bariatric surgical technique worldwide [37], leads to high rates of resolution of IR-related diseases [29–36]. RYGB is associated with significant increases in the secretion of both GLP-1 and GLP-2, comparable to the findings of this study [38–41]. Glucose metabolism in individuals with IBD is yet to be completely understood. Despite the high frequency of low body weight among these individuals, insulin resistance and adiposopathy have been previously reported as features commonly observed in this group [42, 43]. Several features observed in IBD seem to be associated with abnormalities in the glucose metabolism: (1) rapid intestinal transit, which has been previously associated with glucose malabsorption [44, 45]; (2) isolated disaccharide intolerance (mainly lactose and saccharose) [46]; (3) gut barrier defects, mainly the insufficient expression of claudin-15, which leads to sodium and glucose malabsorption [47, 48]; (4) small bowel bacterial overgrowth, associated with the production of lipopolysaccharides (LPSs) and chronic endotoxemia [49]; (5) chronic inflammatory activity, which leads to pathophysiologic responses that impair regular glucose metabolism [50, 51]; (6) and GLP-2 blockade that leads to impairment of the overall gut absorption capacity [52–54]. Chronic inflammation seems to be a considerable part of the link between obesity and IBD, and since both IBD and bariatric

Table 5 Comparison of the insulin AUCs following MTT in the five groups evaluated [expressed in means ± SD (value of *p*)]

	Pre-RYGB	Post-RYGB	Inactive CD	Active CD	Control
Pre-RYGB	NA	24,128.7 ± 17,588.9 vs. 15,730.2 ± 10,193.2 *(p = 0.40)*	24,128.7 ± 17,588.9 vs. 4,198.4 ± 2,266.5 *(p < 0.0001)*	24,128.7 ± 17,588.9 vs. 2,897 ± 2,011.8 *(p < 0.0001)*	24,128.7 ± 17,588.9 vs. 6,306.9 ± 2,687.9 *(p = 0.005)*
Post-RYGB	15,730.2 ± 10,193.2 vs. 24,128.7 ± 17,588.9 (p = 0.40)	NA	15,730.2 ± 10,193.2 vs. 4,198.4 ± 2,266.5 (p = 0.14)	15,730.2 ± 10,193.2 vs. 2,897 ± 2,011.8 (p = 0.79)	15,730.2 ± 10,193.2 vs. 6,306.9 ± 2,687.9 (p = 0.38)
Inactive CD	4,198.4 ± 2,266.5 vs. 24,128.7 ± 17,588.9 *(p < 0.0001)*	4,198.4 ± 2,266.5 vs. 15,730.2 ± 10,193.2 (p = 0.14)	NA	4,198.4 ± 2,266.5 vs. 2,897 ± 2,011.8 (p = 0.99)	4,198.4 ± 2,266.5 vs. 6,306.9 ± 2,687.9 (p = 0.99)
Active CD	2,897 ± 2,011.8 vs. 24,128.7 ± 17,588.9 *(p < 0.0001)*	2,897 ± 2,011.8 vs. 15,730.2 ± 10,193.2 (p = 0.079)	2,897 ± 2,011.8 vs. 4,198.4 ± 2,266.5 (p = 0.998)	NA	2,897 ± 2,011.8 vs. 6,306.9 ± 2,687.9 (p = 0.95)
Control	6,306.9 ± 2,687.9 vs. 24,128.7 ± 17,588.9 *(p = 0.005)*	6,306.9 ± 2,687.9 vs. 15,730.2 ± 10,193.2 (p = 0.386)	6,306.9 ± 2,687.9 vs. 4,198.4 ± 2,266.5 (p = 0.954)	6,306.9 ± 2,687.9 vs. 2,897 ± 2,011.8 (p = 0.992)	NA

Values of *p* in italic indicate statistical significance

Post hoc power = 99%

RYGB Roux-en-Y gastric bypass, *AUC* area under the curve, *SD* standard deviation, *MTT* meal tolerance test, *NA* not applicable

surgery are associated with different degrees of changes in the intestinal food transit, it is likely that the release and function of gut-derived hormones and its physiological functions would be significantly different among these distinct conditions.

Thus, in this study, we evaluated five groups of individuals with somewhat different situations in regards to the gut functional and anatomical domains: (1) the pre-RYGB group, which presented functional and anatomical integrities associated with a chronic inflammatory condition; (2) the post-RYGB group, which presented surgically induced changes in both anatomical and functional domains, associated with an intense attenuation of the chronic inflammation; (3) the active CD group, which presented anatomical integrity of the distal bowel associated with a severe chronic inflammatory state and functional impairment mainly due to the increase in the food transit; (4) the inactive CD group, which presented anatomical integrity of the distal small bowel associated with an attenuated chronic inflammation and a mildly impaired functional domain; and (5) the control group, which presented both anatomical and functional integrities with no chronic inflammation.

In regard to chronic inflammation, a relevant finding was the intensity of the inflammatory state assessed by means of the CRP in the pre-RYGB group; it did not statistically differ from the values observed in both the active and inactive CD groups. Although obesity has been previously proven to be associated with a pro-inflammatory state [55–57], the inflammation in IBD is usually characterized as much more intense than the one observed in obesity, even despite the usage of TNF-α antibody therapy or thiopurine derivates among the CD individuals.

There were several differences in regards to the glucose, insulin, and gut hormone-related metabolisms observed among CD individuals when compared to pre- and post-RYGB groups and the healthy controls in this study. Both the active and inactive CD groups and the pre-RYGB group presented significantly lower levels of GLP-2 than the controls and the pre-RYGB group, and the inactive CD and post-RYGB groups presented significantly higher levels of GLP-1 than the active CD, pre-RYGB, and control groups. Both the active and inactive CD groups presented significantly lower post-prandial levels of insulin than the controls, whereas the pre-RYGB tended to present an almost continuous hyperinsulinemia following the food stimulus and the post-RYGB presented a normalization of this pattern, characterized by a quick peak followed by an abrupt decrease. The post-prandial glucose levels were strongly higher in the pre-RYGB group, a finding that may be easily explained by the IR state of these individuals. The complete meaning of these findings is yet to be determined, but it seems that the post-prandial glucose metabolism in CD individuals follows a different pattern to maintain stable levels of circulating glucose. Since individuals with CD tend to present a rapid food transit, as well as the post-RYGB individuals whose small bowel is significantly bypassed, the secretion of proglucagon-derived peptides provoked by the passage of higher amounts of nutrients through the distal small bowel [58] may receive more stimuli than in the healthy individuals; this could be explained by the higher levels of GLP-1. The rapid transit and inflammatory changes in the gut mucosa of the individuals with CD also associate with varying degrees of carbohydrate malabsorption [44–46]; this abnormality could impair the usual secretion of insulin mediated by the absorption of carbohydrates in the proximal small bowel and the passage of the glucose-rich blood flow through the pancreas (glucose-dependent insulin secretion). Hence, the insulin release in the individuals with CD would be more controlled by the uncertain release than by the direct absorption of carbohydrates observed in regular situations. Since GLP-1 is quickly degraded by DPP-IV, the stimulus for insulin release in the pancreas would be self-limited and last for less time than the usual, preventing the occurrence of hypoglycemia, especially in these individuals with carbohydrate malabsorption. GLP-1 potentiates glucose-stimulated insulin secretion and has little or no activity on insulin secretion in the absence of elevated blood glucose concentrations [59]. This insulinotropic effect is also glucose-dependent; when the extracellular levels of glucose are in the normal fasting range (lower than 4 mmol/L), the GLP-1 secretion does not stimulate insulin release [60, 61]. The flat post-prandial insulin curve observed in the individuals with active CD points out a limitation in the insulin effects on the liver especially the inhibition of gluconeogenesis. Among the post-RYGB group, nonetheless, the increase in the GLP-1 and GLP-2 releases are seemingly accompanied by the expected proportional increases in the secretion of insulin and absorption of glucose. Eriksson [55] observed that, among individuals with IBD, despite the carbohydrate and protein malabsorption, there was a normal net splanchnic glucose output, associated with accelerated hepatic gluconeogenesis. Although GLP-1 may inhibit hepatic gluconeogenesis [62], it presents short-time effects, and its net effects may be not enough to suppress this feature.

Since GLP-1 and GLP-2 are both produced by cleavage of proglucagon after secretion by the L cells of the ileum, the post-prandial circulating levels of both should present the same behavior. However, both the active and inactive CD groups, as well as the pre-RYGB groups, presented significantly lower post-prandial levels than the post-RYGB group. G-protein-coupled receptor (GPR) 40 and GPR120 are probably involved in GLP-2 production, and the mechanisms by which they intrinsically affect the GLP-2 release remain unclear [63]. Tsukuhara et al. [26] observed that the GPR120-dependent signaling inhibited the stimulatory effects of G-protein-coupled receptor 40 on GLP-2 expression and tumor necrosis factor-α (TNF-α) treatment decreased GLP-2

expression by upregulating GPR120 expression in L cells, concluding that the TNF-α decreases GLP-2 expression by upregulating G-protein-coupled receptor 120 in CD. Since individuals with CD, especially in active disease, tend to present higher levels of TNF-α [64], this could explain the discrepancy between the levels of GLP-1 and GLP-2 in CD individuals. The active inflammatory state observed in the obese individuals' group may also be enrolled as a possible cause for the lack of post-prandial response in the GLP-2 secretion. There is previous evidence of elevated levels of TNF-α among obese individuals [65, 66].

Considering the abnormal basal enteroendocrine function observed in the CD population, the possible effect of bariatric surgeries that enroll some degree of intestinal bypasses on obese individuals which also present CD would be somewhat unpredictable. In regard to the effect of surgery on disease activity, there are sparse reports, but the occurrence of newly diagnosed or reactivated disease after RYGB is more than merely circumstantial [6–9]. Since weight loss is associated with a decrease in the inflammatory activity, a surgical technique without an intestinal bypass, such as the sleeve gastrectomy, seems to be more appropriate in this setting.

This study has some limitations that should be taken into account. Firstly, it was performed in a small patient population; this occurs primarily due to the high costs of the assays utilized in this study. Secondly, the populations of the five groups are not perfectly matched by gender; it happened due to the usually observed predominance of females among the bariatric population, in contrast to the male predominance observed among individuals with CD. Moreover, to measure the inflammatory status during continuous therapy (mainly biological agents) for CD may have biased the results of some of the molecules that were measured. However, it would be difficult to select patients before treatment and unethical to suspend ongoing treatment regimens for research purposes. There is previous evidence showing mixed results in regards to the possibility of anti-TNF-α therapy to promote direct interference in glucose metabolism [67–71]. The glucose homeostasis in this specific group remains to be completely elucidated, and further investigation is required, but this study provided a novel insight in regards to the metabolic pathways enrolled in such complex topic.

In summary, this study has shown that CD individuals present a different pattern of glucose metabolism when compared to healthy controls and pre- and post-RYGB individuals. This specific pattern appears to be more dependent on the release of GLP-1 than to nutrient absorption, and it may be assumed that it presents a compensatory/adaptive mechanism to prevent the occurrence of hypoglycemia in a potentially high-risk group, such as the active CD patients, which present GLP-2 blockade, chronic diarrhea, and nutrient malabsorption. On the other hand, the secretion of GLP-2 was also suppressed in the obese individuals evaluated, which is likely to be associated with the chronic inflammation observed in this group, that was comparable to the one observed in the CD groups.

Conclusions

Obesity is associated with a chronic inflammatory state comparable to the one observed in CD; this state may also be enrolled in the blockade of the post-prandial release of GLP-2. RYGB attenuates the chronic inflammation and leads to normalization in the post-prandial glucose and insulin curves, as well as increases the post-prandial GLP-1 and GLP-2 responses. CD individuals present a different pattern of glucose metabolism, apparently more incretin-driven, as a way to prevent hypoglycemia and compensate the carbohydrate malabsorption and the GLP-2 blockade.

Compliance with Ethical Standards

Conflict of Interest Paulo Gustavo Kotze is a speaker and consultant for Abbvie, Ferring, Janssen, and Takeda.

Other authors declare that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

Statement of Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding This study was supported by grants from *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP), protocols 2009/50430-6 and 2014/06164-8.

References

1. World Health Organization. Global status report on noncommunicable diseases 2014. WHO: Geneva; 2014. p. 1–298.
2. Singh S, Dulai PS, Zarrinpar A, et al. Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nat Rev Gastroenterol Hepatol. 2017 Feb;14(2):110–21.
3. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.e42. quiz e30
4. Nic Suibhne T, Raftery TC, McMahon O, et al. High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. J Crohns Colitis. 2013;7(7):e241–8.
5. Bernstein GR, Pickett-Blakely O. De novo inflammatory bowel disease after bariatric surgery: a case series and literature review. Dig Dis Sci. 2016; https://doi.org/10.1007/s10620-016-4412-y.
6. Janczewska I, Nekzada Q, Kapraali M. Crohn's disease after gastric bypass surgery. BMJ Case Rep. 2011; https://doi.org/10.1136/bcr.07.2010.3168.

7. Ahn LB, Huang CS, Forse RA, et al. Crohn's disease after gastric bypass surgery for morbid obesity: is there an association? Inflamm Bowel Dis. 2005;11(6):622–4.
8. Kotze PG, Bremer-Nones R, Kotze LM. Is there any relation between gastric bypass for morbid obesity and the development of Crohn's disease? J Crohns Colitis. 2014;8(7):712–3.
9. Shoar S, Shahabuddin Hoseini S, Naderan M, et al. Bariatric surgery in morbidly obese patients with inflammatory bowel disease: a systematic review. Surg Obes Relat Dis. 2017;13(4):652–9.
10. Harper JW, Zisman TL. Interaction of obesity and inflammatory bowel disease. World J Gastroenterol. 2016;22(35):7868–81.
11. Bregenzer N, Hartmann A, Strauch U, et al. Increased insulin resistance and beta cell activity in patients with Crohn's disease. Inflamm Bowel Dis. 2006;12(1):53–6.
12. Nagahori M, Hyun SB, Totsuka T, et al. Prevalence of metabolic syndrome is comparable between inflammatory bowel disease patients and the general population. J Gastroenterol. 2010;45(10):1008–13.
13. Karrasch T, Obermeier F, Straub RH. Systemic metabolic signaling in acute and chronic gastrointestinal inflammation of inflammatory bowel diseases. Horm Metab Res. 2014;46(6):445–51.
14. Meek CL, Lewis HB, Reimann F, et al. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. Peptides. 2016;77:28–37.
15. Lee J, Koehler J, Yusta B, et al. Enteroendocrine-derived glucagon-like peptide-2 controls intestinal amino acid transport. Mol Metab. 2017; https://doi.org/10.1016/j.molmet.2017.01.005.
16. Cazzo E, Pareja JC, Chaim EA. Weight loss surgery and the surrogate insulin resistance markers HOMA, TyG, and TG/HDL-c in relation to metabolic syndrome. In: Preedy VR, Rajendram R, Martin CR. Metabolism and pathophysiology of bariatric surgery: nutrition, procedures, outcomes and adverse effects. London: Academic Press; 2017. p. 325–31. https://doi.org/10.1016/B978-0-12-804011-9.00055-8.
17. Jacobsen SH, Olesen SC, Dirksen C, et al. Changes in gastrointestinal hormone responses, insulin sensitivity, and beta-cell function within 2 weeks after gastric bypass in non-diabetic subjects. Obes Surg. 2012;22(7):1084–96.
18. Cazzo E, Gestic MA, Utrini MP, et al. GLP-2: a poorly understood mediator enrolled in various bariatric/metabolic surgery-related pathophysiologic mechanisms. Arq Bras Cir Dig. 2016;29(4):272–5.
19. LeRoux CW, Borg C, Wallis K, et al. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. Ann Surg. 2010;252(1):50–6.
20. Taqi E, Wallace LE, de Heuvel E, et al. The influence of nutrients, biliary-pancreatic secretions, and systemic trophic hormones on intestinal adaptation in a Roux-en-Y bypass model. J Pediatr Surg. 2010;45(5):987–95.
21. Cazzo E, Pareja JC, Geloneze B, et al. Postprandial GLP-2 levels are increased after biliopancreatic diversion in diabetic individuals with class I obesity: a prospective study. Obes Surg. 2017; https://doi.org/10.1007/s11695-017-2554-4.
22. Suzuki S, Ramos EJ, Gonçalves CG, et al. Changes in GI hormones and their effect on gastric emptying and transit times after Roux-en-Y gastric bypass in rat model. Surgery. 2005;138(2):283–90.
23. Huda MS, Wilding JP, Pinkney JH. Gut peptides and the regulation of appetite. Obes Rev. 2006;7(2):163–82.
24. Vahl T, D'Alessio D. Enteroinsular signaling: perspectives on the role of the gastrointestinal hormones glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide in normal and abnormal glucose metabolism. Curr Opin Clin Nutr Metab Care. 2003;6(4):461–8.
25. Bendet N, Scapa E, Cohen O, et al. Enhanced glucose-dependent glucagon-like peptide-1 and insulin secretion in Crohn patients with terminal ileum disease is unrelated to disease activity or ileal resection. Scand J Gastroenterol. 2004;39(7):650–6.
26. Tsukahara T, Watanabe K, Watanabe T, et al. Tumor necrosis factor α decreases glucagon-like peptide-2 expression by up-regulating G-protein-coupled receptor 120 in Crohn disease. Am J Pathol. 2015;185:185–96.
27. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439–44.
28. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55:749–53.
29. National Institutes of Health. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. Am J Clin Nutr 1992;55(2 Suppl):615S–619S.
30. Lee WJ, Huang MT, Wang W, et al. Effects of obesity surgery on the metabolic syndrome. Arch Surg. 2004;139(10):1088–92.
31. Dorman RB, Serrot FJ, Miller CJ, et al. Case-matched outcomes in bariatric surgery for treatment of type 2 diabetes in the morbidly obese patient. Ann Surg. 2012;255(2):287–93.
32. Mumme DE, Mathiason MA, Kallies KJ, et al. Effect of laparoscopic Roux-en-Y gastric bypass surgery on hemoglobin A1c levels in diabetic patients: a matched-cohort analysis. Surg Obes Relat Dis. 2009;5(1):4–10.
33. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
34. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357(8):753–61.
35. Batsis JA, Romero-Corral A, Collazo-Clavell ML, et al. Effect of bariatric surgery on the metabolic syndrome: a population-based, long-term controlled study. Mayo Clin Proc. 2008;83(8):897–907.
36. Inabnet 3rd WB, Winegar DA, Sherif B, et al. Early outcomes of bariatric surgery in patients with metabolic syndrome: an analysis of the bariatric outcomes longitudinal database. J Am Coll Surg. 2012;214(4):550–6.
37. Cazzo E, Gestic MA, Utrini MP, et al. Influence of insulin resistance status on the development of gallstones following Roux-en-Y gastric bypass: a prospective cohort study. Obes Surg. 2016;26(4):769–75.
38. Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery and endoluminal procedures: IFSO worldwide survey 2014. Obes Surg. 2017; https://doi.org/10.1007/s11695-017-2666-x.
39. de Hollanda A, Jiménez A, Corcelles R, et al. Gastrointestinal hormones and weight loss response after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2014;10(5):814–9.
40. le Roux CW, Borg C, Wallis K, et al. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. Ann Surg. 2010;252(1):50–6.
41. Romero F, Nicolau J, Flores L, et al. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-en-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. Surg Endosc. 2012;26(8):2231–9.
42. Cazzo E, Pareja JC, Chaim EA, et al. GLP-1 and GLP-2 levels are correlated with satiety regulation after Roux-en-Y gastric bypass: results of an exploratory prospective study. Obes Surg. 2016; https://doi.org/10.1007/s11695-016-2345-3.
43. Tigas S, Tsatsoulis A. Endocrine and metabolic manifestations in inflammatory bowel disease. Ann Gastroenterol. 2012;25(1):37–44.
44. Gonçalves P, Magro F, Martel F. Metabolic inflammation in inflammatory bowel disease: crosstalk between adipose tissue and bowel. Inflamm Bowel Dis. 2015;21(2):453–67.
45. Sellin JH, Hart R. Glucose malabsorption associated with rapid intestinal transit. Am J Gastroenterol. 1992;87(5):584–9.

46. Bjørneklett A, Fausa O, Midtvedt T. Bacterial overgrowth in jejunal and ileal disease. Scand J Gastroenterol. 1983;18(2):289–98.
47. Raithel M, Weidenhiller M, Hagel AF, et al. The malabsorption of commonly occurring mono and disaccharides: levels of investigation and differential diagnoses. Dtsch Arztebl Int. 2013;110(46): 775–82.
48. Hering NA, Fromm M, Schulzke JD. Determinants of colonic barrier function in inflammatory bowel disease and potential therapeutics. J Physiol. 2012;590(5):1035–44.
49. Tamura A, Hayashi H, Imasato M, et al. Loss of claudin-15, but not claudin-2, causes Na^+ deficiency and glucose malabsorption in mouse small intestine. Gastroenterology. 2011;140(3):913–23.
50. Caradonna L, Amati L, Magrone T, et al. Enteric bacteria, lipopolysaccharides and related cytokines in inflammatory bowel disease: biological and clinical significance. J Endotoxin Res. 2000;6(3): 205–14.
51. Herlitz-Cifuentes HS, Garces PC, Fernandez LI, et al. Effect of systemic inflammation on the function of insulin and glucose metabolism in rheumatoid arthritis. Curr Diabetes Rev. 2015;12(2): 156–62.
52. Guerrero-Romero F, Simental-Mendía LE, Rodríguez-Morán M. Association of C-reactive protein levels with fasting and postload glucose levels according to glucose tolerance status. Arch Med Res. 2014;45(1):70–5.
53. Schmidt PT, Ljung T, Hartmann B, et al. Tissue levels and postprandial secretion of the intestinal growth factor, glucagon-like peptide-2, in controls and inflammatory bowel disease: comparison with peptide YY. Eur J Gastroenterol Hepatol. 2005;17:207–12.
54. Sigalet DL, Kravarusic D, Butzner D, et al. A pilot study examining the relationship among Crohn disease activity, glucagon-like peptide-2 signalling and intestinal function in pediatric patients. Can J Gastroenterol. 2013;27:587–92.
55. Coy CSR, Calixto A, Vasques AC, et al. Evaluation of GLP-2 levels in Crohn's disease. Inflamm Bowel Dis. 2016;22(Suppl 1):S58.
56. Divella R, De Luca R, Abbate I, et al. Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. J Cancer. 2016;7(15):2346–59.
57. Cooke AA, Connaughton RM, Lyons CL, et al. Fatty acids and chronic low grade inflammation associated with obesity and the metabolic syndrome. Eur J Pharmacol. 2016;785:207–14.
58. Tarantino G. Gut microbiome, obesity-related comorbidities, and low-grade chronic inflammation. J Clin Endocrinol Metab. 2014;99(7):2343–6.
59. van Avesaat M, Troost FJ, Ripken D, et al. Ileal brake activation: macronutrient-specific effects on eating behavior? Int J Obes. 2015;39(2):235–43.
60. Meloni AR, DeYoung MB, Lowe C, et al. GLP-1 receptor activated insulin secretion from pancreatic β-cells: mechanism and glucose dependence. Diabetes Obes Metab. 2013;15(1):15–27.
61. Ahren B. Islet G protein-coupled receptors as potential targets for treatment of type 2 diabetes. Nat Rev Drug Discov. 2009;8(5):369–85.
62. Eriksson LS. Splanchnic exchange of glucose, amino acids and free fatty acids in patients with chronic inflammatory bowel disease. Gut. 1983;24(12):1161–8.
63. Lee YS, Shin S, Shigihara T, et al. Glucagon-like peptide-1 gene therapy in obese diabetic mice results in long-term cure of diabetes by improving insulin sensitivity and reducing hepatic gluconeogenesis. Diabetes. 2007;56(6):1671–9.
64. Zietek T, Daniel H. Intestinal nutrient sensing and blood glucose control. Curr Opin Clin Nutr Metab Care. 2015;18(4):381–8.
65. Magro D, Kotze P, Camargo M, et al. Serum levels of lipopolysaccharides and CD26 in patients with Crohn's disease. Inflamm Bowel Dis. 2017;23(Suppl 1):S90.
66. Olszanecka-Glinianowicz M, Zahorska-Markiewicz B, Janowska J, et al. Serum concentrations of nitric oxide, tumor necrosis factor (TNF)-alpha and TNF soluble receptors in women with overweight and obesity. Metabolism. 2004;53(10):1268–73.
67. Cartier A, Lemieux I, Alméras N, et al. Visceral obesity and plasma glucose-insulin homeostasis: contributions of interleukin-6 and tumor necrosis factor-alpha in men. J Clin Endocrinol Metab. 2008;93(5):1931–8.
68. Gentile S, Guarino G, Bizzarro A, et al. Infliximab does not interfere with insulin secretion, insulin resistance and production of GAD and islet cell antibodies in patients with Crohn's disease. Diabetes Obes Metab. 2002;4(4):276–7.
69. Rosenvinge A, Krogh-Madsen R, Baslund B, et al. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha therapy. Scand J Rheumatol. 2007;36(2):91–6.
70. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes. Curr Diabetes Rev. 2013;9(1):25–53.
71. Pina T, Armesto S, Lopez-Mejias R, et al. Anti-TNF-α therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. J Eur Acad Dermatol Venereol. 2015;29(7):1325–30.