Surgery for Obesity and Related Diseases 19 (2023) 727–734

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Plasma short-chain fatty acid changes after bariatric surgery in patients with severe obesity

María A. Martínez-Sánchez, M.Sc.[a], Andrés Balaguer-Román, M.Sc.[a,b], Virginia E. Fernández-Ruiz, Ph.D.[a,c], Sonia Almansa-Saura, Ph.D.[b], Victoria García-Zafra, Ph.D.[a,c], Mercedes Ferrer-Gómez, Ph.D.[a,c], María D. Frutos, Ph.D.[b], María I. Queipo-Ortuño, Ph.D.[d,e], Antonio J. Ruiz-Alcaraz, Ph.D.[f], María Á. Núñez-Sánchez, Ph.D.[a,*], Bruno Ramos-Molina, Ph.D.[a]

[a]*Obesity and Metabolism Research Laboratory, Biomedical Research Institute of Murcia (IMIB), Murcia, Spain*
[b]*Department of General and Digestive System Surgery, Virgen de la Arrixaca University Hospital, Murcia, Spain*
[c]*Department of Endocrinology and Nutrition, Virgen de la Arrixaca University Hospital, Murcia, Spain*
[d]*Department of Medical Oncology, Virgen de la Victoria and Regional University Hospitals-IBIMA, UMA-CIMES, Málaga, Spain*
[e]*Department of Surgical Specialties, Biochemistry and Immunology, Faculty of Medicine, University of Málaga, Málaga, Spain*
[f]*Department of Biochemistry, Molecular Biology B and Immunology, Faculty of Medicine, University of Murcia, Murcia, Spain*

Received 1 September 2022; accepted 1 December 2022

Abstract

Background: Obesity has reached epidemic dimensions in recent decades. Bariatric surgery (BS) is one of the most effective interventions for weight loss and metabolic improvement in patients with obesity. Short-chain fatty acids (SCFA) are gut microbiota-derived metabolites with a key role in body weight control and insulin sensitivity. Although BS is known to induce significant changes in the gut microbiota composition, its impact on the circulating levels of certain metabolites produced by the gut microbiota such as SCFA remains poorly understood.

Objective: To determine the impact of BS on the circulating SCFA levels in patients with severe obesity.

Setting: University hospital.

Methods: An observational, prospective study was performed on 51 patients undergoing Roux-en-Y gastric bypass. Plasma samples were collected at baseline (1 day before surgery) and at 6 and 12 months after BS. Plasma SCFA levels were determined by liquid chromatography–mass spectrometry.

Results: The results revealed significant changes in the circulating levels of SCFA after BS. A marked increase in propionate, butyrate, isobutyrate, and isovalerate levels and a decrease in acetate, valerate, hexanoate, and heptanoate levels were observed 12 months after BS. Furthermore, the changes in the levels of propionate, butyrate, and isobutyrate negatively correlated with changes in body mass index, while those of isobutyrate correlated negatively with changes in the homeostatic model assessment for insulin resistance index.

Conclusion: These results suggest that propionate, butyrate, and isobutyrate levels could be related to weight loss and improved insulin sensitivity in patients with severe obesity after BS. (Surg Obes Relat Dis 2023;19:727–734.)

Keywords: Obesity; Bariatric surgery; Weight loss; Insulin resistance; Short-chain fatty acids

María A. Martínez-Sánchez and Andrés Balaguer-Román contributed equally to this work and share first authorship.

*Correspondence: María Ángeles Núñez-Sánchez, Ph.D., Obesity and Metabolism Research Laboratory, Biomedical Research Institute of Murcia (IMIB), 30120 Murcia, Spain.

E-mail address: mariaa.nunez@imib.es (M.Á. Núñez-Sánchez).

https://doi.org/10.1016/j.soard.2022.12.041

Obesity has achieved epidemic dimensions with more than 1.9 billion adults affected worldwide and represents one of the major public health concerns [1]. Although the prevalence of obesity has been growing over decades, little advance has been made in terms of treatment. In this regard, bariatric surgery (BS) remains the gold-standard intervention for weight loss, metabolic improvement, and overall survival in patients with severe obesity (body mass index [BMI] $\geq$40 or BMI $\geq$35 with associated health conditions) [2]. Indeed, BS has demonstrated to be associated with the resolution of obesity co-morbidities such as dyslipidemia, hypertension, and glycemic control, and remission of type 2 diabetes (T2D) [3].

The gut microbiota has been recognized as a key player in the pathophysiology of obesity and related disorders [4,5]. Previous studies have shown that the gut microbiota of patients with obesity greatly differs from their lean counterparts and is characterized by a reduced diversity with an enrichment of specific bacteria such as *Lactobacillus reuteri* or *Escherichia coli* [6]. In addition, perturbations in gut microbiota have also been linked to the development of T2D, mainly through the increased inflammatory response due to an increased gut barrier permeability [7]. Some of the processes involved in the effects of gut microbiota on the development of obesity and related disorders include energy harvesting, modulation of the immune system, regulation of gut endocrine function, and altered production of metabolites [8].

Several clinical studies have demonstrated that BS greatly affects the composition of gut microbiota [9,10]. After BS, microbial richness increases, which has been related to changes in metabolism and glucose homeostasis, decreased levels of circulating biomarkers of inflammation, and reduced fat mass deposition [11]. Moreover, such changes have been associated with weight loss and amelioration of insulin sensitivity, although the exact mechanisms remain unclear.

BS has not only an effect on gut microbiota composition but also on the microbial-derived metabolites. Among these, short-chain fatty acids (SCFA), the main end-products of microbial fermentation, are the most studied in relation to weight loss interventions. They can be divided into straight SCFA (sSCFA) which come from the saccharolytic fermentation by certain bacteria such as *Faecalibacterium prausnitzii*, and branched SCFA (bSCFA) coming from the catabolism of branched amino acids (valine, leucine, and isoleucine) [12]. Moreover, they are known to be involved in several physiologic functions such as maintenance of the mucosa integrity, energy expenditure, or regulation of the inflammatory response [13]. Thus, it could be expected that imbalances in SCFA levels might be related to the appearance and progression of a wide range of disorders such as obesity and T2D [14]. However, although BS is known to induce important changes in circulating levels of certain metabolites related to the gut microbiota [15,16], its impact on the plasma levels of SCFA and their significance to such metabolic improvements remain poorly understood.

In this study, we aimed to evaluate the changes in circulating levels of SCFA in patients with severe obesity undergoing BS. Furthermore, we studied the potential associations between those changes in SCFA levels and different markers of metabolic health at different time points after BS.

Methods

Study design and participants

A total of 51 patients with severe obesity with scheduled for Roux-en-Y gastric bypass were consecutively enrolled at the Virgen de la Arrixaca University Hospital (Murcia, Spain) between January 2020 and December 2020. Inclusion criteria were patients with severe obesity eligible for BS according to the National Institutes of Health Consensus Statement [17], that is, history of severe obesity for at least 5 years, and aged between 18 and 65 years. Exclusion criteria were cardiovascular disease, arthritis, acute inflammatory disease, and infectious diseases. All participants gave their written consent. The study was performed in agreement with the Declaration of Helsinki according to local and national laws and approved by the Ethics and Clinical Research Committees of the Virgen de la Arrixaca University Hospital (#2020-2-4-HCUVA).

Anthropometric and biochemical evaluation

Blood pressure (BP) was measured at baseline and at 6 and 12 months after the BS by trained personnel. The nutritional status of the participants was characterized by anthropometric measurements of weight, height, and waist circumference. The BMI of the individual, total weight loss (TWL), percentage of TWL (%TWL), and the percentage of excess weight loss (EWL) were calculated as outlined in Supplementary methods.

For the biochemical evaluation, blood samples were collected from study patients after an overnight fast (12 hours) at 3 different time points: the day before surgery (baseline) and at 6 and 12 months after BS. Plasma was separated by centrifugation for 10 minutes at 4000 rpm and frozen at –80 oC until analysis. The levels of HbA1C were measured with the glycohemoglobin analyzer HLC-723G8 (Tosoh Bioscience). The determination of fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) levels was carried out using the Cobas Analyzer c702 (Roche) while insulin levels were measured using the Cobas Analyzer e801 (Roche). Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as insulin (μU/ml) $\times$ glucose (nmol/L)/22.5.

Analysis of SCFA in plasma by liquid chromatography–mass spectrometry

Eight SCFA were analyzed by liquid chromatography–mass spectrometry (LC-MS). Acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid (tert-butyl-valeric acid), and caproic acid were purchased from Sigma Aldrich Co. (St. Louis, MO). The stock solutions were adjusted by using methanol. The ultra-performance liquid chromatography (UPLC) system was a UHPLC Infinity II (Agilent Technologies, Santa Clara, CA). A reverse phase analysis was performed via a Poroshell C18 EC 100 mm × 2.1 mm × 3 μm (Agilent Technologies) at 35°C. The injection volume was 4 μL. The mobile phase consisting of solvent A (.2% formic acid in water) and solvent B (.2% formic acid in methanol) was delivered at a flow rate of .4 mL/min. The gradient elution was as follows: B% = 15, 15, 70, and 98 (0, 3, 8, and 15 min). An Agilent Technologies 6470 triple quadrupole mass spectrometer was operated with an electrospray ionization (ESI) source in the positive mode. The ionization source conditions were as follows: capillary voltage, 3.00 kV; source temperature and flow, 200°C and 10 L/min, respectively; nebulizer pressure, 20 psi; sheath gas temperature and flow, 250 oC and 10 L/min, respectively; collision energy, 5–30 eV. The MRM conditions were optimized by injecting 1 ppm of each SCFAs at different collision energy (CE). The selected mass–mass transitions were the MRM optimum from point of view of sensitivity and selectivity for each SCFA.

Plasma samples were treated as previously described [18]. Briefly, 100 μL of plasma was precipitated by adding 100 μL of methanol and the resulting mixture was shaken for 1 minute and centrifuged at 14,000 rpm for 10 minutes at 4°C. Then, 100 μL of supernatant was mixed with water and was incubated with 30 μL of .1M O-Benzylhydroxylamine hydrochloride (BHA) in MeOH and 30 μL of .25M N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) in MeOH at 25°C for 1 hour. After the incubation, the sample was extracted with dichloromethane. The dichloromethane was then removed, and the remaining residue was reconstituted in 250 μL of methanol:water. This solution was injected into LC-MS. The quantification was made by the addition of a volume of standard mix with all SCFAs (Volatile Free Acid Mix #46975-U, Sigma Aldrich) to plasma samples to obtain 5 concentrations for calibration (.25, .5, 1, 5, and 10 μM). Thus, calibration mode allowed to evaluate the matrix effect and the recovery directly in the analytical method.

Statistical analysis

Data were analyzed using the SPSS 28.0.1.1 software (IBM, Armonk, NY). All variables were checked for normality using the Kolmogorov-Smirnov test. Comparison between parameters was performed using the repeated measures one-way analysis of variance followed by Bonferroni post hoc for those with normal distribution and the Friedman test followed by Dunn's post hoc analysis for those without normal distribution. The fold changes in circulating levels of SCFA, BMI, fasting insulin, and the homeostatic model assessment for insulin resistance (HOMA-IR) were used to determine relationships between variables based on the Spearman correlation test. All values are given as mean ± standard deviation (SD). A P value $<.05$ was considered statistically significant. Principal component analysis and heat map construction were performed using the MetaboAnalyst 5.0 Web application (https://www.metaboanalyst.ca) [19].

Results

Characteristics of the study population

Clinical, anthropometric, and biochemical characteristics before and after the surgery of the participants included in this study are shown in Table 1. Data from 51 patients with severe obesity who underwent BS were analyzed at baseline and 6 and 12 months after the surgery. There was a statistically significant reduction in body weight and BMI after 6 and 12 months of the surgery. Waist and hip circumference significantly decreased 12 months after the surgery. Plasma levels of HbA1C, fasting insulin, and the HOMA-IR were also significantly reduced after 6 and 12 months after BS (Table 1).

Plasma SCFA profile after BS

The absolute and relative amounts of all the SCFA at baseline and 6 and 12 months after the BS are shown in Fig. 1A. Results showed a significant decrease in total SCFA levels after the surgery independently of the time measured. The concentration of absolute levels of sSCFA (i.e., the addition of acetate, propionate, butyrate, valerate, hexanoate, and heptanoate) measured was reduced while the levels of bSCFA (i.e., the addition of isobutyrate and isovalerate) increased after 12 months.

At individual level, the sSCFA acetate, valerate, and hexanoate were significantly reduced between baseline and the postoperative time points measured. Acetate exhibited a broad decrease in circulating levels with a mean reduction of 82.02% and 77.75% at 6 and 12 months after BS, respectively, while plasma levels of propionate and butyrate were increased at 6 and 12 months after BS. There was a modest, but significant, decrease in plasma concentrations of heptanoate at 12 months after BS. The increase in the levels of all these sSCFA continued over time showing statistically significant differences between 6 and 12 months. Regarding bSCFA, both isobutyrate and isovalerate were increased after the surgical treatment. The increase in the levels of these bSCFA continued over time showing statistically significant differences between 6 and 12 months.

Table 1
Characteristics of the study population

	T_1		T_2		T_3		T_1 versus T_2	T_1 versus T_3	T_2 *versus* T_3
	Mean	SD	Mean	SD	Mean	SD	*P* value	*P* value	*P* value
Sex (F/M)	41/10	-	-	-	-	-	-	-	-
Age, yr	48.33	11.19	-	-	-	-	-	-	-
Weight, kg	115.39	16.43	84.35	13.64	76.40	13.63	**<.001**	**<.001**	**<.001**
BMI, kg/m^2	43.60	5.16	31.89	4.46	28.76	4.61	**<.001**	**<.001**	**<.001**
WC, cm	125.80	11.23	101.29	9.88	92.84	11.95	**<.001**	**<.001**	**<.001**
HC, cm	137.09	13.13	114.62	10.71	107.98	11.24	**<.001**	**<.001**	**<.001**
TWL, kg	-	-	31.04	8.19	38.98	11.43	-	-	-
% TWL	-	-	26.86	5.79	33.66	8.12	-	-	-
% EWL	-	-	60.54	15.87	75.84	21.36	-	-	-
Change BMI, kg/m^2	-	-	11.71	2.95	14.84	4.15	-	-	-
SBP, mm Hg	140.12	17.55	125.86	16.09	124.16	18.13	**<.001**	**<.001**	.881
DBP, mm Hg	84.08	9.89	76.04	8.85	72.06	10.29	**<.001**	**<.001**	.110
Glucose, mg/dL	105.08	32.43	92.16	19.52	88.02	17.43	**<.001**	**<.001**	**.038**
HbA1*C*, %	5.94	1.00	5.53	0.80	5.57	1.03	**<.001**	**<.001**	.166
Insulin, μIU/mL	16.94	11.78	10.10	4.80	8.96	6.24	.080	**<.001**	.606
HOMA-IR	4.53	3.49	2.33	1.37	2.02	1.61	.030	**<.001**	**.012**
Cholesterol, mg/dL	166.22	33.12	162.00	27.33	160.31	28.96	.413	.544	>.999
LDL-c, mg/dL	90.51	29.77	90.82	24.28	84.43	24.81	.643	.063	.164
HDL-c, mg/dL	42.42	8.28	50.59	7.87	58.16	9.69	**<.001**	**<.001**	**<.001**
Triglycerides, mg/dL	187.40	93.68	103.06	45.66	88.75	34.64	**<.001**	**<.001**	.072

T_1 = baseline; T_2 = 6 months after the surgery; T_3 = 12 months after the surgery; F = female; M = male; BMI = body mass index; WC = waist circumference; HC = hip circumference; TWL = total weight loss; EWL = excess weight loss; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA1C = glycated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol.

P values were calculated using repeated measures one-way analysis of variance followed by Bonferroni's post hoc analysis for those with normal distribution (weight, WC, HC, and HDL-c) and the Friedman test followed by Dunn's post hoc analysis for those without normal distribution (BMI, SBP, DBP, glucose, HbA1c, insulin, HOMA-IR, cholesterol, LDL-c, and triglycerides) considering $P < .05$ significant (values in boldface).

Principal component analysis showed good separation of SCFA for pre- versus post-BS, especially after 12 months, with 2 components explaining 41.7% and 31.9% of the variance respectively (Fig. 1B). Such separation was also observed in the heat map construction with hierarchical cluster analysis of SCFA (Fig. 1C).

Correlations between SCFA and anthropometric/ biochemical parameters

Correlations between plasma SCFA levels and clinical variables at baseline and at either 6 or 12 months after BS are shown in Table S1 and Table 2, respectively. At 12 months, a negative correlation was observed between BMI reduction and changes in different SCFA measured including total SCFA, bSCFA, propionate, butyrate, valerate, heptanoate, and isobutyrate. Similarly, isobutyrate and isovalerate showed negative correlations with insulin resistance markers, including fasting insulin levels and HOMA-IR. Negative correlations between total SCFA, sSCFA, bSCFA, acetate, isobutyrate, and isovalerate, and fasting glucose levels were observed (Table 2). No significant associations were found between changes in plasma SCFA levels at 6 months and the anthropometric and biochemical parameters analyzed except for isobutyrate, which showed a significant correlation with BMI and fasting insulin levels (Table S1).

Discussion

In this study, we evaluated the circulating levels of SCFA of patients with severe obesity undergoing BS at baseline (1 d before surgery) and 6 and 12 months after the surgical intervention. Our results showed that plasma levels of SCFA were significantly modified after the BS together with an improvement in BMI and other markers related to insulin resistance. Except for isobutyrate, no correlations were found 6 months after surgery. However, we observed a strong negative correlation between the changes in most of the SCFA quantified and the decrease in BMI 12 months after the BS. Furthermore, we also observed strong associations between the changes in bSCFA and the reduction in fasting glucose, insulin levels, and HOMA-IR.

Our detailed analysis of the plasma SCFA profile showed that the absolute amounts of sSCFA (acetate, propionate, butyrate, valerate, hexanoate, and heptanoate) were reduced, and the absolute levels of bSCFA were significantly increased after the BS suggesting an increase of the microbial proteolytic fermentation versus the saccharolytic one. These results partially agree with those after weight loss conservative and surgical treatments described by other authors [14,20,21]. However, while these studies reported that the decrease in individual sSCFA occurred independently of the SCFA type analyzed, our analysis at individual level showed that

A

	T_1	T_2	T_3
SCFA	Mean± SD	Mean ± SD	Mean ± SD
TSCFA	52.19 ± 77.80^{a}	15.30 ± 6.16^{b}	20.12 ± 12.41^{b}
SSCFA	51.77 ± 77.78^{a}	14.52 ± 5.81^{b}	18.62 ± 12.35^{c}
Acetate	43.75 ± 77.10^{a}	7.87 ± 4.86^{b}	9.74 ± 12.32^{b}
Propionate	1.40 ± 0.58^{a}	2.57 ± 2.19^{b}	4.70 ± 2.70^{c}
Butyrate	0.71 ± 0.32^{a}	0.92 ± 0.45^{a}	1.57 ± 0.96^{b}
Valerate	0.47 ± 0.26^{a}	0.37 ± 0.21^{b}	$0.45 \pm 0.23^{a,b}$
Hexanoate	4.39 ± 3.26^{a}	1.98 ± 1.50^{b}	1.34 ± 1.41^{c}
Heptanoate	1.05 ± 0.53^{a}	0.81 ± 0.48^{b}	$0.82 \pm 0.31^{a,b}$
BSCFA	0.43 ± 0.24^{a}	0.78 ± 0.74^{b}	1.51 ± 0.80^{b}
Isobutyrate	0.21 ± 0.12^{a}	0.27 ± 0.17^{b}	0.41 ± 0.23^{c}
Isovalerate	0.22 ± 0.17^{a}	0.51 ± 0.61^{b}	1.10 ± 0.63^{c}

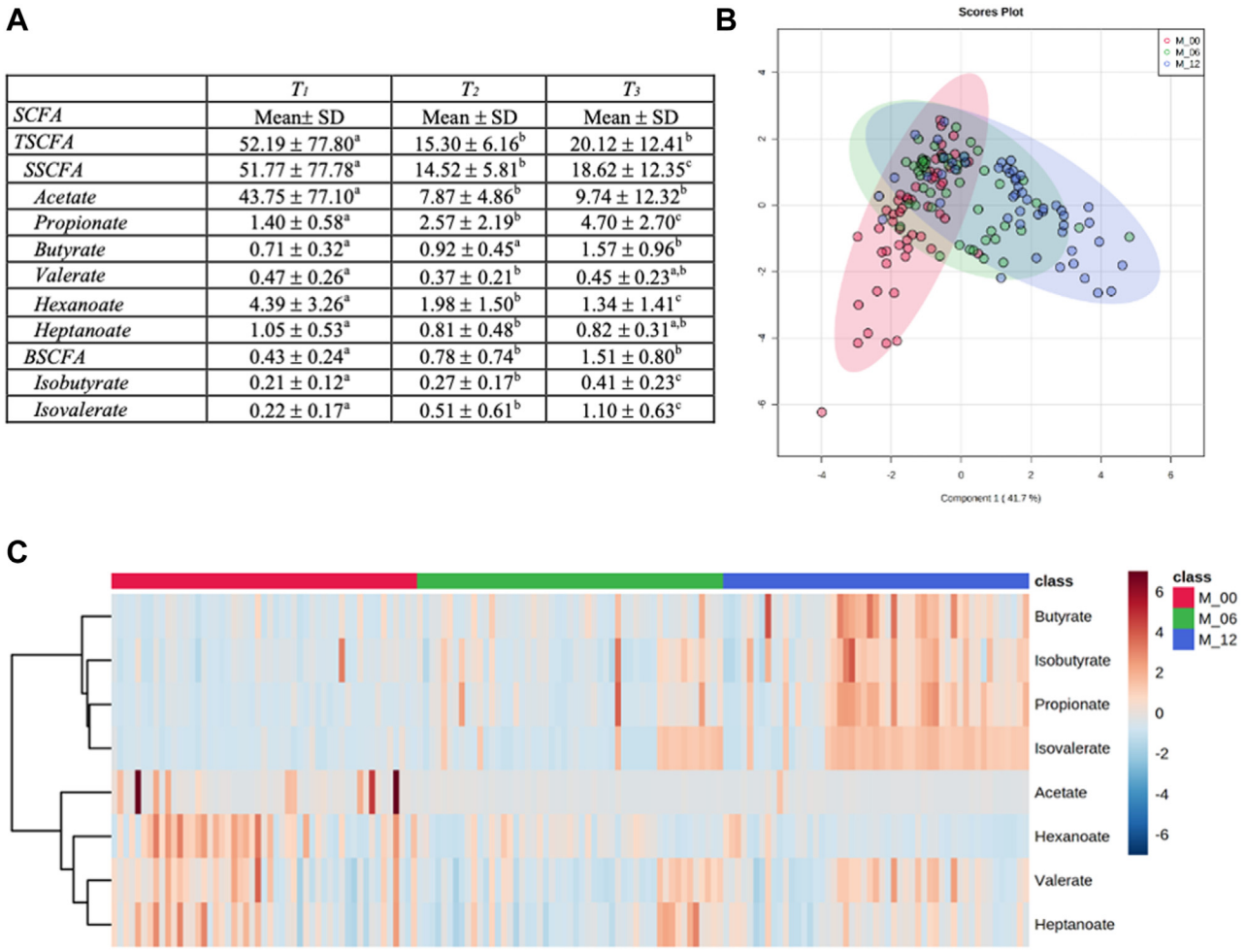

Fig. 1. Effect of BS on SCFA profile of patients with severe obesity. (A) Concentrations of SCFA before and after BS. Values are expressed as micromolesper liter (mean ± standard deviation [SD]). *P* values were calculated using the Friedman test followed by Dunn's post hoc analysis considering $P < .05$ significant. (B) Partial least-squares discriminant analysis of plasma SCFA before (M_00) and 6 (M_06) and 12 (M_12) months after BS. (C) Heatmap showing normalized abundance of SCFA before and after BS. Color indicates higher (red) to lower (blue) abundance. BS = bariatric surgery; SCFA = short-chain fatty acids; T_1 = baseline; T_2 = 6 months after the surgery; T_3 = 12 months after the surgery; tSCFA = total short-chain fatty acids calculated as the sum of all the SCFA quantified; sSCFA = straight short-chain fatty acids calculated as the sum of acetate, propionate, butyrate, valerate, hexanoate, and heptanoate; bSCFA = branched short-chain fatty acids calculated as the sum of isobutyrate and isovalerate.

the drastic reduction in sSCFA was mainly caused by the decrease in acetate, and hexanoate since circulating levels of propionate and butyrate were significantly increased in our study. Such discrepancy might be explained by the fact that unlike studies carried out by others, we explored the changes in plasma samples rather than fecal samples. This is remarkable because fecal concentrations of SCFA do not necessarily reflect the concentrations in plasma samples as the majority of SCFA produced by gut microbiota are absorbed by the colon [22,23]. A recent study in patients with obesity showed that, while circulating levels of acetate directly correlate with those detected in feces, levels of butyrate and propionate did not relate to the fecal concentrations [24]. Furthermore, in this study the authors showed that the circulating levels of butyrate and propionate were inversely associated with BMI, indicating that circulating but not fecal SCFA could be responsible for the effects on peripheral tissues and metabolic status [24]. These results agree with those observed in our study where increased levels of propionate and butyrate after the BS were inversely correlated with changes in BMI. In addition, we also found a strong correlation between changes in isobutyrate and weight loss. Increased levels of bSCFA and other SCFA including butyrate and propionate have been related to a higher release of the appetite-reducing hormone peptide YY and glucagon-like peptide-1, which are known to protect against obesity [25]. Therefore, although our results might suggest that SCFA could have a role in weight loss after surgery, further research is warranted to confirm this hypothesis.

Table 2
Correlations between plasma SCFA levels and anthropometric/biochemical parameters between baseline and 12 months after BS

	BMI	Insulin	HOMA-IR	HbA1*C*	Glucose
tSCFA	**–.278***	–.099	–.183	.099	**–.446**†
sSCFA	–.255	–.074	–.161	.096	**–.436**†
Acetate	–.135	–.043	–.137	–.109	**–.375**†
Propionate	**–.314***	–.147	–.172	.114	–.229
Butyrate	**–.330***	–.261	–.257	.134	–.230
Valerate	**–.369**†	–.017	–.018	–.067	–.094
Hexanoate	–.232	.025	.006	.045	–.135
Heptanoate	**–.448**†	–.033	–.068	.001	–.142
bSCFA	**–.388**†	**–.418**†	**–.439**†	.200	**–.474**†
Isobutyrate	**–.363**†	**–.320***	**–.368**†	.190	**–.449**†
Isovalerate	–.242	**–.380**†	**–.392**†	.229	**–.415**†

SCFA = short-chain fatty acids; BMI = body mass index; HOMA-IR = homeostatic model assessment of insulin resistance; HbA1C = glycated hemoglobin; tSCFA = total short-chain fatty acids; sSCFA = straight short-chain fatty acids; bSCFA = branched short-chain fatty acids.

Values are presented as Spearman correlation coefficients.

* $P < .05$.

† $P < .01$.

BS is known to have several health-related outcomes in patients with severe obesity such as rapid weight loss, reduced adiposity, improved glucose homeostasis and insulin sensitivity, and reduction of systemic inflammation and gut permeability [26–29]. Indeed, besides the effectiveness in the treatment of severe obesity, BS has recently emerged as a serious alternative for the treatment of T2D [30] and nonalcoholic fatty liver disease [31,32]. BS has been shown to be very effective for the resolution of insulin resistance, which has been described to occur shortly after the intervention and it has been described to be independent of weight loss [33,34]. Thus, other factors rather than weight loss are involved in insulin resistance resolution after BS. Remarkably, certain gut microbiome-related metabolites such as secondary bile acids and SCFA have been suggested to be involved in increased insulin sensitivity after BS [16,24,30,35]. However, the contribution of circulating SCFA in the resolution of insulin resistance after BS remains elusive [36]. Previous works have shown that circulating levels of butyrate are inversely associated with fasting glucose levels [37,38]. However, although we observed a significant increase in levels of butyrate after BS, these changes did not correlate with changes in glucose levels. On the other hand, changes in bSCFA were associated with the reduction of glucose levels at 12 months, with isobutyrate showing the strongest correlation. In this regard, bSCFA have been previously described to affect adipocyte lipid and glucose metabolism in vitro by inhibiting cAMP-mediated lipolysis and insulin-stimulated glucose uptake [12]. However, to the best of our knowledge, this is the first study showing the correlation between circulating levels of isobutyrate and reduction in fasting glucose after BS.

We acknowledge some limitations for the present study but also some strengths. First, this is an observational cohort study, so there is a lack of a control group and there might be confounders that cannot be controlled, making it challenging to stablish a causal effect of BS on SCFA status. Also, the small sample size may not be enough for detecting short-term differences. In addition, the first follow-up visit was established at 6 months after a substantial weight loss. Thus, there is a lack of information about the immediate effects of BS on circulating SCFA. On the other hand, the strengths of our study rely on the careful design and the determination of circulating levels of SCFA by LC-MS.

Conclusion

In this study we have shown for the first time that changes in circulating levels of total SCFA and bSCFA are associated with a decrease in weight loss 12 months after BS in patients with severe obesity. At individual level, changes in all SCFA types analyzed, except for acetate, hexanoate, and isovalerate, were associated with the decrease in BMI. In addition, the decrease in glucose levels was also related to changes in isobutyrate and isovalerate. Furthermore, we have shown that the increase in levels of isobutyrate is significantly correlated with the improvement in HOMA-IR. Therefore, we could postulate that the increase of plasma isobutyrate might have a role in the improvement of glucose control and insulin resistance resolution after BS, albeit further research is needed to confirm this hypothesis.

Acknowledgments

We are particularly grateful for the generous contribution of the patients and the collaboration of the Biobank Network of the Region of Murcia (BIOBANC-MUR), registered in the Registro Nacional de Biobancos (no. B.0000859). BIOBANC-MUR was supported by the Instituto de Salud Carlos III (no. PT20/00109), Instituto Murciano de Investigación Biosanitaria (IMIB), and Consejería de Salud de la Comunidad Autónoma de la Región de Murcia. We are also grateful to Dr. Antonio Silva for his support analytical services of the Facility of Innovation and Analysis in Animal Source Foodstuffs (SiPA) of SAIUEx of the University of Extremadura.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

This work was funded by the Carlos III Health Institute (ISCIII) and was cofunded by the Fondo Europeo de Desarrollo Regional (FEDER; grant no.PI20/00505). M.A. Martínez-Sánchez was supported by a PFIS predoctoral

fellowship from ISCIII (FI21/0003, ISCIII, Spain; cofunded by FEDER). B. Ramos-Molina was supported by the Miguel Servet Type I program (CP19/00098, ISCIII, Spain; cofunded by FEDER). M.I. Queipo-Ortuño was supported by the Miguel Servet Type II program (CPI13/00003, ISCIII, Spain; cofunded by FEDER) and belongs to the regional Nicolas Monardes research program of the Consejería de Salud (C-0030-2018, Junta de Andalucía, Spain). The funding organization played no role in the design of the study, review and interpretation of the data, or final approval of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2022.12.041.

References

[1] World Health Organization. Obesity and overweight. 2021. [cited 2022 Aug 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

[2] O'Brien PE, Hindle A, Brennan L, et al. Long-term outcomes after bariatric surgery: a systematic review and meta-analysis of weight loss at 10 or more years for all bariatric procedures and a single-centre review of 20-year outcomes after adjustable gastric banding. Obes Surg 2019;29(1):3–14.

[3] Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults: a review. JAMA 2020;324(9):879–87.

[4] Agus A, Clement K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut 2021;70(6):1174–82.

[5] Gomes AC, Hoffmann C, Mota JF. The human gut microbiota: metabolism and perspective in obesity. Gut Microbes 2018;9(4):308–25.

[6] Million M, Lagier JC, Yahav D, Paul M. Gut bacterial microbiota and obesity. Clin Microbiol Infect 2013;19(4):305–13.

[7] Iatcu CO, Steen A, Covasa M. Gut microbiota and complications of type-2 diabetes. Nutrients 2021;14(1):166.

[8] Aron-Wisnewsky J, Warmbrunn MV, Nieuwdorp M, Clément K. Metabolism and metabolic disorders and the microbiome: the intestinal microbiota associated with obesity, lipid metabolism, and metabolic health-pathophysiology and therapeutic strategies. Gastroenterology 2021;160(2):573–99.

[9] Guo Y, Huang ZP, Liu CQ, Qi L, Sheng Y, Zou DJ. Modulation of the gut microbiome: a systematic review of the effect of bariatric surgery. Eur J Endocrinol 2018;178(1):43–56.

[10] Yu D, Shu XO, Howard EF, Long J, English WJ, Flynn CR. Fecal metagenomics and metabolomics reveal gut microbial changes after bariatric surgery. Surg Obes Relat Dis 2020;16(11):1772–82.

[11] Aron-Wisnewsky J, Prifti E, Belda E, et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. Gut 2019;68(1):70–82.

[12] Heimann E, Nyman M, Palbrink AK, Lindkvist-Petersson K, Degerman E. Branched short-chain fatty acids modulate glucose and lipid metabolism in primary adipocytes. Adipocyte 2016;5(4):359–68.

[13] Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes 2016;7(3):189–200.

[14] Farup PG, Valeur J. Changes in faecal short-chain fatty acids after weight-loss interventions in subjects with morbid obesity. Nutrients 2020;12(3):802.

[15] Ocana-Wilhelmi L, Cardona F, Garrido-Sanchez L, Fernandez-Garcia D, Tinahones FJ, Ramos-Molina B. Change in serum polyamine metabolome pattern after bariatric surgery in obese patients with metabolic syndrome. Surg Obes Relat Dis 2020;16(2):306–11.

[16] Ahlin S, Cefalo C, Bondia-Pons I, et al. Bile acid changes after metabolic surgery are linked to improvement in insulin sensitivity. Br J Surg 2019;106(9):1178–86.

[17] Gastrointestinal surgery for severe obesity. Consens Statement 1991;9(1):1–20.

[18] Zeng M, Cao H. Fast quatification of short chain fatty acids and ketone bodies by liquid chromatography-tandem mass spectrometry after facile derivatization coupled with liquid-liquid extraction. J Chromatogr Analyt Technol Biomed Life Sci 2018;1083:137–45.

[19] Xia J, Wishart DS. Using MetaboAnalyst 3.0 for comprehensive metabolomics data analysis. Curr Protoc Bioinformatics 2016;55:14. 10.1–91.

[20] Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. Cell Metab 2015;22(2):228–38.

[21] Patrone V, Vajana E, Minuti A, et al. Postoperative changes in fecal bacterial communities and fermentation products in obese patients undergoing bilio-intestinal bypass. Front Microbiol 2016;7:200.

[22] Schwiertz A, Taras D, Schafer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring) 2010;18(1):190–5.

[23] Medawar E, Haange SB, Rolle-Kampczyk U, et al. Gut microbiota link dietary fiber intake and short-chain fatty acid metabolism with eating behavior. Transl Psychiatry 2021;11(1):500.

[24] Muller M, Hernandez MAG, Goossens GH, et al. Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans. Sci Rep 2019;9(1):12515.

[25] Ilhan ZE, DiBaise JK, Isern NG, et al. Distinctive microbiomes and metabolites linked with weight loss after gastric bypass, but not gastric banding. ISME J 2017;11(9):2047–58.

[26] Rubino F, Gagner M, Gentileschi P, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg 2004;240(2):236–42.

[27] Liou AP, Paziuk M, Luevano Jr JM, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med 2013;5(178):178ra41.

[28] Feng Y, Wang Y, Wang P, Huang Y, Wang F. Short-chain fatty acids manifest stimulative and protective effects on intestinal barrier function through the inhibition of NLRP3 inflammasome and autophagy. Cell Physiol Biochem 2018;49(1):190–205.

[29] Koutoukidis DA, Jebb SA, Zimmerman M, et al. The association of weight loss with changes in the gut microbiota diversity, composition, and intestinal permeability: a systematic review and meta-analysis. Gut Microbes 2022;14(1):2020068.

[30] Wang M, Li L, Chen Y, et al. Role of gut microbiome and microbial metabolites in alleviating insulin resistance after bariatric surgery. Obes Surg 2021;31(1):327–36.

[31] Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. Gastroenterology 2020;159(4):1290–12301 e5.

[32] Martinez-Montoro JI, Kuchay MS, Balaguer-Roman A, et al. Gut microbiota and related metabolites in the pathogenesis of nonalcoholic steatohepatitis and its resolution after bariatric surgery. Obes Rev 2022;23(2):e13367.

[33] Mika A, Wilczynski M, Pakiet A, et al. Short-term effect of one-anastomosis gastric bypass on essential fatty acids in the serum of obese patients. Nutrients 2020;12(1):187.

[34] Ferrannini E, Mingrone G. Impact of different bariatric surgical procedures on insulin action and beta-cell function in type 2 diabetes. Diabetes Care 2009;32(3):514–20.

[35] Shi Q, Wang Q, Zhong H, et al. Roux-en-Y gastric bypass improved insulin resistance via alteration of the human gut microbiome and alleviation of endotoxemia. Biomed Res Int 2021:5554991.

[36] Sowah SA, Riedl L, Damms-Machado A, et al. Effects of weight-loss interventions on short-chain fatty acid concentrations in blood and feces of adults: a systematic review. Adv Nutr 2019;10(4):673–84.

[37] de Groot P, Scheithauer T, Bakker GJ, et al. Donor metabolic characteristics drive effects of faecal microbiota transplantation on recipient insulin sensitivity, energy expenditure and intestinal transit time. Gut 2020;69(3):502–12.

[38] Mukorako P, Lemoine N, Biertho L, et al. Consistent gut bacterial and short-chain fatty acid signatures in hypoabsorptive bariatric surgeries correlate with metabolic benefits in rats. Int J Obes (Lond) 2022;46(2):297–306.