Liver Bacterial Colonization in Patients with Obesity and Gut Dysbiosis

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Abstract

Purpose Recently, the link between gut microbiota, liver inflammation, and obesity has become an interesting focus of research. The aim of this study is to show the possible relation between gut microbiota dysbiosis in patients with obesity and the presence of bacterial genomes in their liver biopsies.

Materials and Methods A prospective study on patients undergoing bariatric surgery was carried out. Anthropometric and metabolic data, comorbidities, stool samples, and hepatic biopsies were collected and analyzed at the time of surgery. The V3-16S rRNA region was sequenced using the Ion Torrent new-generation sequencing platform.

Results In each of the 23 patients enrolled, the bacterial population was analyzed both in the stools and liver. In eight patients (34.7%), *Prevotella* (62.5%), *Bacteroides* (50%), *Streptococcus* (12.5%), and *Dalister* (12.5%) were found in both samples, simultaneously; in 15 cases, the liver was free from colonization. The statistically significant difference between groups was a *Roseburia intestinalis* reduction in fecal samples of patients with liver biopsies colonized by bacteria (1% vs 3%; $p = 0.0339$).

Conclusion To the best of our knowledge, this is the first study reporting the presence of bacterial genome in a liver biopsy on bariatric patients, instead of the microbe-associated molecular patterns. Notably, in literature, the presence of *Roseburia intestinalis* in stool samples has been shown to prevent intestinal inflammation playing its role in the gut barrier integrity. In our population, the *Roseburia* reduction was associated with the presence of bacterial genome in the liver, probably related to a greater permeability of the gut and vascular barriers.

Keywords Obesity surgery · Microbiota · Bacterial translocation

Key Points
- *Roseburia intestinalis* reduction in the bowel microbiota was associated with the presence of bacterial genome in the liver.
- This finding may be related to a greater permeability of the gut and vascular barriers in those patients.
- No differences were found in terms of demographic and clinical data between the two studied groups.

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Introduction

The intestinal microbiota is the set of commensal microorganisms present within the intestine gastrointestinal tract [1], and its composition begins in the prenatal period with the transfer of bacteria from the mother to the fetus [2]. The colonization process continues after birth and is influenced by several factors such as the type of birth, breastfeeding method, antibiotic use, environment, and diet. In adult life, a symbiosis is established between the subject and his own microbiota [3], which plays a crucial role in maintaining health and can influence various aspects of the host organism [1]: it produces antimicrobial substances that protect against infections by pathogenic microorganisms [2]; promotes the proliferation and differentiation of intestinal epithelial cells enhancing the integrity of the mucosal surface [3]; contributes to the development of lymphoid tissue associated with the intestinal mucosa [4]; allows the initial degradation of plant polysaccharides into short-chain fatty acids (SCFAs) and gas, used as energy by bowel epithelial cell and helpful in maintaining colonic mucosa tropism and integrity;

and [5] contributes to the maintenance of the intestinal barrier and is believed to have a role in regulating mucosal permeability [1, 4]. *In vitro* studies have shown that the exposure of intestinal mucosal cells to both commensal and probiotic microorganisms determines an upregulation and increase in the strength of tight junctions [5]. Moreover, the composition of the intestinal microbiota is strongly influenced by the type of diet, and it seems to play a key role in obesity development. Studies on animal models have shown that germ-free mice have a lower body mass index (BMI) and body fat than wild-type mice, even when exposed to a diet rich in fats and sugars [6]. Transplantation of fecal microbiota from mice with obesity into germ-free mice exposed to a normocaloric diet determines a significant increase in fat mass [7]. Furthermore, the microbiome of a subject with obesity appears to be different from that of a normal-weight one because of a reduced quantity of genes (low gene count (LGC)) and a lower presence of bacterial species (low gene richness). LGC subjects show increased levels of leptin, reduced adiponectin, hyperinsulinemia and insulin resistance, elevated levels of triglycerides and free fatty acids, reduced high-density lipoprotein (HDL), and an increase in inflammatory markers [8] compared to high gene count (HGC) population. There is, therefore, a relationship between the microbiome and the development of the chronic inflammatory state typical of subjects with obesity and the resulting metabolic complications. In subjects with changes in microbiota composition, the permeability of the intestinal mucosa may be altered, allowing the passage of modest quantities of bacterial lipopolysaccharide (LPS) into the bloodstream or favoring bacterial translocation. A study in animal models demonstrated the presence of bacteria in the liver parenchyma in mice exposed to a high-fat diet [9]. In specific human conditions characterized by intestinal dysbiosis, such as obesity, research has shown that only microbe-associated molecular patterns (MAMPs), rather than whole bacterial species, can enter the portal circulation. This phenomenon is facilitated by increased intestinal permeability, both at the mucosal and endothelial levels, which allows for the LPS passage and bacterial metabolites into the portal circulation [10].

On this basis, the aims of the study are to assess bacterial colonization of the liver in individuals with obesity by examining the bacterial genome in liver biopsy samples rather than bacterial metabolites and to compare the bacterial genome found in the liver with that detected from fecal samples (gut–liver axis).

Methods

This is a prospective observational cohort study on consecutive patients with obesity undergoing bariatric surgery at a tertiary referral center for bariatric surgery between March and November 2016. Indication to surgery was given according to the contemporary International Guidelines.

Exclusion criteria were patients suffering from documented liver cirrhosis; alcohol consumption of more than 25 g/day; the presence of other liver diseases such as hepatitis B, hepatitis C, HIV, and neoplasms; the presence of chronic intestinal inflammatory diseases; and administration of antibiotic therapy up to 1 month before the enrollment. All the enrolled patients followed a 3-month hypocaloric and high-protein diet before the surgery time. The following data have been collected: demographic (weight, height, BMI, sex, history of arterial hypertension, and type 2 diabetes mellitus), preoperative alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin plasma level, total cholesterol, HDL, type of surgery, microbiota of stool samples and liver biopsy, liver steatohepatitis and fibrosis grade, length of hospitalization (LOS), postoperative complications at 30 days after surgery according to Clavien–Dindo classification [11], and the total weight loss percentage (%TWL). The day before surgery, for each patient, a stool sample was collected to analyze the bacterial population. During surgery, prior to the bariatric operation, a biopsy of the left lobe of the liver was performed. This allows to avoid liver sample contamination, possible during the anastomoses in gastric by-pass. The characterization of the microbiota was performed by sequencing the 16S rRNA gene with next-generation high-throughput sequencing using the Ion Torrent platform. DNA extraction was carried out using the NucliSENS® easyMAG® system (BioMèrieux, Gorman, NC, USA). Real-time PCR with EvaGreen® dye (Fisher Molecular Biology, Waltham, MA, USA) was performed with the degenerate primer 27FYM and subsequently with Bt338F in combination with the U534R primer. PCR targets the variable portion V3. The size of the amplicons was checked on 2% agarose gel. The amount of DNA after normalization was quantified with Qubit® 2.0 Fluorometer (Invitrogen, Carlsbad, CA, USA). Template preparation was performed with the Ion PGM Template OT2 200 kit on the Ion OneTouch™ 2 System (Thermo Fischer Scientific, Walthman, MA, USA) and then sequenced with the Ion PGM™ System, using the Ion PGM sequencing 200 KIT V2 (Thermo Fisher Scientific). QIIME 2.0 software was used to process the sequenced data.

To achieve accuracy in the analysis of the microbiota on both stool samples and liver biopsies, all possible bacteria due to contamination were excluded.

A histologic examination was performed on the liver biopsies to study steatohepatitis and liver fibrosis. The steatohepatitis was classified according to Brunt classification as mild (grade 1), moderate (grade 2), and severe (grade 3), considering the presence of hepatocellular steatosis, ballooning, and inflammation [12]. Liver fibrosis and lobular inflammation were defined in accordance with the Kleiner

classification [13] as follows: grade 0, absence of fibrosis; grade 1a, mild perisinusoidal or periportal fibrosis; grade 1b, moderate fibrosis in zone 3, perisinus; grade 1c, fibrosis localized only at the portal level; grade 2, perisinus and periportal fibrosis; grade 3, fibrosis with septa; and grade 4, cirrhosis.

The Kleiner classification was also utilized to determine the grade of lobular inflammation (ranging from 0 to 3), which was based on the number of inflammatory foci observed per field at 200× magnification [13]. The success of bariatric surgery was assessed by the total weight loss percentage (%TWL). This is calculated as follows:

$$\%\text{TWL} = \frac{\text{kilograms lost}}{\text{initial weight}} \times 100$$

Statistical Analysis

Nominal variables are expressed as numbers and percentages, non-normal quantitative variables as median and range, and normal variables as median ± standard deviation (SD). The Shapiro–Wilk test has been used to assess variables' normal distribution. Chi-squared and Fisher's exact tests were used to compare nominal variables, whereas the Mann–Whitney *U* test was used for non-normal quantitative variables and Student *t*-test for normal variables. Microbiota data were analyzed with the Kruskal–Wallis test with false discovery rate (FDR) correction. *P* values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSSv23.0 (IBM Corp, Armonk, NY).

Ethical Issues

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. Informed consent was obtained from all individual participants included in the study. The study was approved by protocol N. 22979 Local Ethical Committee.

Results

Twenty-three patients were enrolled in the study. For each of them, bacterial RNA extraction was carried out on both the stool sample and the liver biopsy. Of this cohort, in eight patients (34.7%), *Prevotella* (62.5%), *Bacteroides* (50%), *Streptococcus* (12.5%), and *Dalister* (12.5%) bacterial RNA were found in both samples, simultaneously; in 15 cases, the liver was free from bacterial colonization. Therefore, according to this finding, the population has been divided into two groups: group 1, where the liver biopsy was positive for bacterial RNA, and group 2, where the liver biopsy was negative for bacterial RNA. No differences were found in terms of demographic and preoperative data (Table 1).

The gut microbiota composition was analyzed for both groups to evaluate whether there were any differences in terms of dysbiosis that could explain the bacterial migration to the liver (Table 2). The two groups differ in the expression of *Roseburia intestinalis* (1% vs 3%; $p = 0.034$), statistically lower for group 1. Mainly liver and fecal microbiota composition for group 1 was represented by *Prevotella* (62.5%), *Bacteroides* (50%), *Streptococcus* (12.5%), and *Dalister* (12.5%) (Graph 1). No statistically significant differences were found in terms of steatohepatitis and liver fibrosis (Table 3). Median LOS was 7 days (range 5–8); in particular, median LOS for group 1 was 7 days (range 5–8) and 6 (range 5–7) for group 2, without any statistically significant difference. No postoperative complications were recorded at the 30-day follow-up. One-year median %TWL was 71.97% (range 60.68–88.46), for group 1, 71.97% (range 63.03–86.24), and for group 2, 71.45% (60.68–88.46); $p = 0.897$.

Conclusion

Recently, the link between gut microbiota, liver inflammation, and obesity has become an interesting focus of research. Alterations of the intestinal microbiota were reported in patients with obesity, associated with increased intestinal permeability, and endotoxemia, contributing to maintaining a chronic inflammation state [4]. In inflammatory disease, the translocation of microbial and danger-associated molecular patterns (MAMPs and DAMPs) from the gut to the liver has been demonstrated, due to the intestinal epithelial cell barrier permeability. The main hypothesis could be a modification of the intestinal barrier leading to a reduction of tight junctions' activity enabling the passage of proinflammatory metabolites. In fact, increased intestinal permeability allows the passage of MAMPs and LPS, into the circulation, as well as live bacteria [14]. This phenomenon, called bacterial translocation, has already been identified in several pathologies such as Alzheimer's disease, hemorrhagic shock, sepsis, acute pancreatitis, and cirrhosis [15]. Nevertheless, there is a lack of studies demonstrating the presence of a bacterial genome in the liver, particularly in subjects suffering from morbid obesity and consequently chronic systemic inflammatory status. The cohort analyzed in the present study showed that a group of patients with obesity had an intestinal bacterial colonization of the liver. However, no differences were found concerning demographic and biochemical data,

Table 1 Demographic and preoperative data of the population studied

	All population ($N = 23$)	Group 1 ($N = 8$)	Group 2 ($N = 15$)	p-value
Age	45.4±8.2	45.3±7.6	45.4±0.7	0.968
Sex				0.589
M	4 (17.0)	2 (25.0)	2 (13.0)	
F	19 (83.0)	6 (75.0)	13 (87.0)	
BMI (kg/m^2)	44.7±5.3	45.9±5.0	44.1±5.5	0.437
Comorbidities				
AH	10 (43.0)	2 (25.0)	8 (53.0)	0.195
DM2	3 (13.0)	1 (13.0)	2 (13.0)	0.731
Preoperative laboratory test				
AST (U/l)	20.3±4.7	21.0±3.9	20.0±5.2	0.641
ALT (U/l)	21.0 (13.0–53.0)	25.5 (19.0–34.0)	20.0 (13.0–53.0)	0.145
ALP (U/l)	74 (47.0–134.0)	74.5 (49.0–111.0)	74 (47.0–134.0)	0.458
GGT (U/l)	29.0 (16.0–84.0)	22.0 (18.0–51.0)	30.0 (16.0–84.0)	0.164
TB (mg/dl)	0.5±0.1	0.5±0.2	0.5±0.1	0.711
Albumin	4.4±0.3	4.3±0.4	4.4±0.2	0.468
TC (mg/dl)	212.4±28.8	206.4±27.6	215.6±29.9	0.477
HDL (mg/dl)	49.2±12.6	47.0±9.6	50.4±14.1	0.549
Type of surgery				0.510
SG	13 (56.5)	5 (62.0)	8 (53.0)	
GBP	10 (43.5)	3 (38.0)	7 (47.0)	

Nominal variables are expressed as numbers and percentages; non-normal quantitative variables as median (range); normal variables as mean ± standard deviation. Legend: *N* numbers; *M* male; *F* female; *BMI* body mass index; *AH* arterial hypertension; *DM2* type 2 diabetes mellitus; *AST* alanine transaminase; *AST* aspartate transaminase; *GGT* gamma-glutamyl transpeptidase; *ALP* alkaline phosphatase; *TB* total bilirubin; *TC* total cholesterol; *HDL* high-density lipoproteins; *SG* sleeve gastrectomy; *GBP* gastric by-pass

nor different grades of steatohepatitis, fibrosis, and lobular inflammation compared to the group without liver colonization. Moreover, the two groups were similar in terms of type of surgery, postoperative complications, and %TWL. The only difference was found in the intestinal microbiota analysis, where a statistically significant reduction of *Roseburia intestinalis* was found in the group with liver colonization.

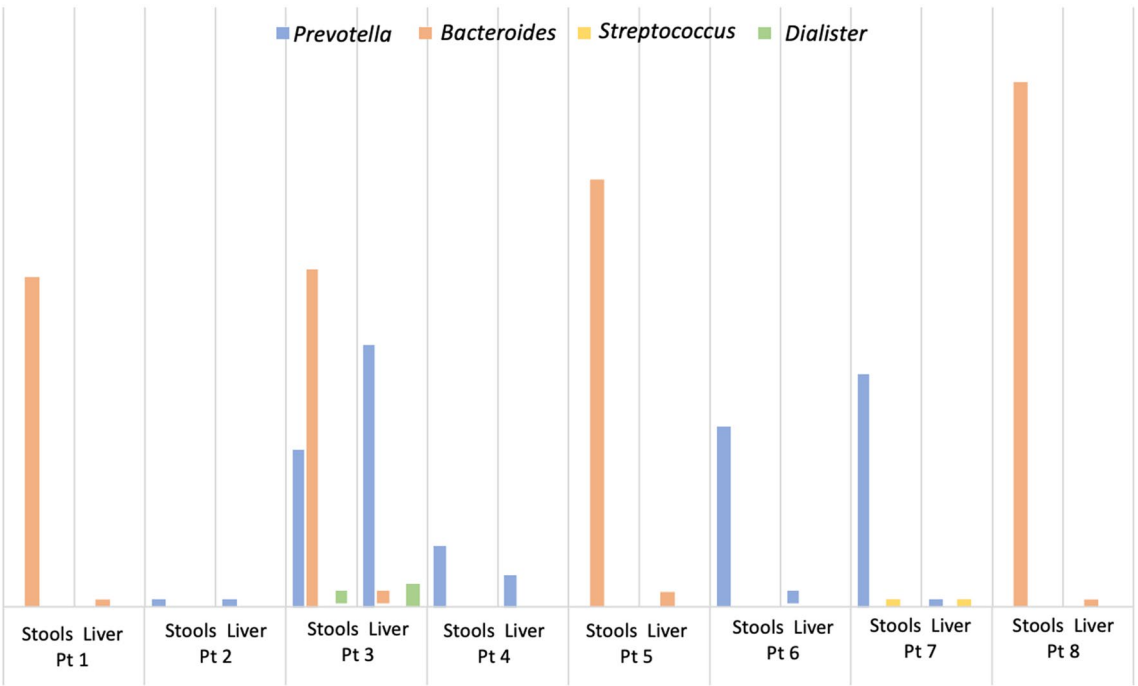
Roseburia intestinalis is an anaerobic, Gram-positive bacterium belonging to the *Firmicutes* group that produces butyrate in the colon [16]. There are five different species of *Roseburia*, which represent the most present species in the intestinal microbiota among butyrate-producing bacteria [17]. Butyrate is an SCFA used as an energy substrate by enterocytes and is responsible for maintaining the integrity of the intestinal mucosa [18]. *In vitro* and animal studies have shown that butyrate increases tight junction integrity and functioning [5, 19, 20]. In addition, *Roseburia intestinalis* flagellin, a spherical protein found in its flagellum, enhances the expression of tight junction proteins and modulates the inflammatory response through Toll-like receptor 5 [21]. Additionally, butyrate fosters the expansion of anti-inflammatory Treg lymphocytes, which produce interleukin 10 (IL-10), TGF-β, and interferon-gamma [16]. *Roseburia intestinalis* has demonstrated the ability to suppress the secretion of interleukin 17, a proinflammatory cytokine, in both *in vivo* studies using mice with induced colitis and *in vitro* experiments with human colonic epithelial cells [22]. It is indeed a beneficial microorganism exerting a protective effect on the intestinal mucosa and decreasing inflammation status. Its primary contribution lies in the production of butyrate, which serves a dual purpose: it exerts an anti-inflammatory influence, modulating immune responses, and plays a crucial role in regulating the permeability and integrity of the intestinal mucosa. Different studies have evaluated the relationship between *Roseburia intestinalis* and several inflammatory-based pathologies, highlighting a dysbiosis of this bacterium in patients with Crohn's disease, ulcerative colitis [23–25], irritable bowel syndrome, and constipation [16]. Moreover, it has been shown a lower concentration of *Roseburia intestinalis* in patients with obesity and with nonalcoholic steatohepatitis, compared with the healthy population [26]. Hence, a lower presence of *Roseburia intestinalis* in the intestines could elucidate the phenomenon of bacterial translocation into the liver via the portal system. The main hypothesis would be a modification of the intestinal barrier permeability, due to lower levels of butyrate, responsible for a reduction of tight junction activity Although the results obtained are promising, the limit of the study is due to its small sample size.

Table 2 Differences in microbiota population of the two Groups

	Group 1 ($N = 8$) Median expression % (range)	Group 2 ($N = 15$) Median expression % (range)	p-value
Bacteroides coprocola	0.1 (0–3.8)	0	0.810
Bacteroides dorei	0.3 (0.2–0.8)	1.2 (0.2–4.8)	0.070
Bacteroides faecis	0.3 (0–0.8)	0.6 (0–1.6)	0.441
Bacteroides massiliensis	1 (0–3.6)	0 (0–0.8)	0.246
Bacteroides stercoris	0.1 (0–0.8)	0 (0–2.5)	0.696
Bacteroides thetaiotaomicron	0 (0–0.4)	0.4 (0–0.8)	0.515
Bacteroides uniformis	6.1 (1.4–13.6)	2.1 (0.9–9.7)	0.582
Bacteroides vulgatus	1.0 (0.4–8.3)	6.4 (0.1–9)	0.496
Barnesiella intestinihominis	0.7 (0.2–2.1)	0.3 (0–2.1)	0.718
Blautia wexlerae	0.5 (0.2–1.5)	0.7 (0.2–1.5)	0.794
Clostridium bartlettii	1.4 (0.3–2.2)	0.2 (0–1.3)	0.347
Clostridium glycyrrhizinilyticum	0	0	0.818
Clostridium symbiosum	1 (0.7–1.4)	1.7 (1.1–2.8)	0.218
Faecalibacterium prausnitzii	2.6 (1.3–4.2)	2.9 (1.8–8.9)	0.496
Fusicatenibacter saccharivorans	1.1 (0.2–2.5)	0.5 (0.1–1.3)	0.496
Gemmiger formicilis	0.7 (0.4–1)	0.3 (0.2–0.8)	0.258
Parabacteroides distasonis	0.4 (0.3–0.7)	0.6 (0.1–1.1)	0.631
Parabacteroides merdae	1.2 (0.4–1.7)	1.2 (0.3–2.5)	0.794
Roseburia intestinalis	1.1 (1.0–1.8)	2.9 (1.7–4.7)	**0.034***
Sutterella wadsworthensis	0.3 (0–0.8)	0 (0–0.3)	0.896

Bacterial expression in intestinal microbiota is expressed in percentages. Data are reported as median (range)

*There is a statistically significant difference between the two groups ($p<0.05$)



Graph 1 Distribution of microbiota bacteria in the stool sample and in the liver biopsy in the group with intestinal bacterial colonization in the liver

Table 3 Steatohepatitis and liver fibrosis in the two groups

	Group 1 ($N = 8$)	Group 2 ($N = 15$)	p-value
Steatohepatitis according to brunt classification			
0	2 (25)	0	0.210
1	3 (38)	6 (40)	
2	3 (38)	6 (40)	
3	0	3 (20)	
Liver fibrosis according to Kleiner classification			0.402
0	2 (25)	2 (13)	
1a	0	2 (13)	
1b	2 (25)	1 (7)	
1c	2 (25)	8 (53)	
2	2 (25)	2 (13)	
Lobular inflammation according to Kleiner classification			0.320
0	4 (50)	4 (27)	
1	3 (38)	10 (67)	
2	1 (12)	1 (6)	

Data are expressed as numbers and percentages. Legend: *N* numbers

In conclusion, little is known in the current literature about the presence of bacterial genome in liver samples in patients with obesity. Therefore, our study could offer an additional contribution to this topic. In particular, this study reports the presence of bacterial genome (instead of MAMPS or DAMPS) in the liver biopsy of patients with obesity eligible for bariatric surgery. In these patients, the same bacterial genome was found in stool and liver samples, suggesting bacterial translocation from the gut to the liver. In addition, our data showed that intestinal dysbiosis was characterized by a lower presence of *Roseburia intestinalis* in the intestinal microbiota of patients with obesity with liver bacterial colonization: this finding could be related to a reduction of butyrate production, leading to tight junction misfunctioning and, consequently, a greater intestinal barrier permeability. Intestinal dysbiosis and the presence of liver colonization may be responsible for the chronic inflammatory status associated with obesity. Further studies with a larger sample size are needed to confirm our data and, possibly, to explore the clinical or pathological meaning and the therapeutic implications of these results in clinical practice.

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

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