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Metabolomic signatures after bariatric surgery – a systematic review

Sara Matilde Branco Vaz

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Metabolomic signatures after bariatric surgery – a systematic review

Sara Matilde Branco Vaz

sarambvaz@gmail.com

Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Orientadora

Professora Doutora Mariana P. Monteiro

Professora Associada

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Coorientadora

Professora Doutora Sofia S. Pereira

Professora Auxiliar

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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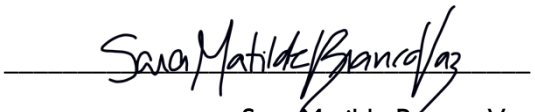

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Resumo

Introdução: A metabolómica tem vindo a surgir como uma ferramenta poderosa, ao possibilitar a compreensão das respostas do organismo a diferentes intervenções terapêuticas. A cirurgia bariátrica é o tratamento mais eficaz para a obesidade e respetivas comorbilidades.

Objetivo: O nosso propósito foi a elaboração de uma revisão sistemática tendo por base os dados disponíveis relativamente aos perfis metabolómicos que caracterizam os pacientes submetidos a diferentes tipos de cirurgia bariátrica. Como objetivo adicional foram revistos os perfis metabolómicos com utilidade na previsão da remissão da diabetes tipo 2 e das diferenças na perda de peso após a cirurgia.

Metodologia: Foram seguidas as guidelines PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses - para a execução da revisão sistemática. Quarenta e seis estudos satisfizeram os critérios de elegibilidade. Foram compilados e resumidos os dados de artigos originais, cujo conteúdo se focava nos perfis metabolómicos induzidos pela cirurgia bariátrica.

Resultados: Os metabolitos mais frequentemente influenciados pela cirurgia bariátrica são os aminoácidos, lípidos, metabolitos relacionados com o metabolismo energético e metabolitos associados à microbiota intestinal. Dentro destes, os padrões pré-operatórios e pós-operatórios imediatos dos aminoácidos de cadeia ramificada, aminoácidos aromáticos, metabolitos do ciclo do ácido tricarboxílico, fosfolípidos, ácidos gordos de cadeia longa e ácidos biliares foram aqueles que tiveram uma associação mais significativa com as diferenças nas respostas induzidas após a cirurgia.

Conclusões: O perfil metabolómico pode vir a destacar-se como um forte auxiliar para a previsão de respostas a longo prazo, consequentes dos diferentes tipos de cirurgia bariátrica. Deste modo, poderá possibilitar uma maior personalização nos tratamentos, levando a uma otimização na alocação dos recursos para a saúde.

Palavras-chave: Metabolómica · Cirurgia Bariátrica · Resultados terapêuticos · Perda de peso · Diabetes tipo 2

Abstract

Introduction: Metabolomics emerged as an important tool to gain insights on how the body responds to therapeutic interventions. Bariatric surgery is the most effective treatment for severe obesity and obesity-related co-morbidities.

Purpose: Our aim was to conduct a systematic review of the available data on metabolomics profiles that characterize patients' submitted to different bariatric surgery procedures, which could be useful to predict type 2 diabetes remission and weight loss and outcomes.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses - PRISMA guidelines were followed. Forty-six studies successfully met the eligibility criteria. Data from original study reports addressing metabolomics profiles induced by bariatric surgery were compiled and summarized.

Results: Amino acids, lipids, energy metabolism-related metabolites and gut microbiota-related metabolites were the metabolite classes that were most frequently influenced by bariatric surgery. Among these, branched chain amino acids, aromatic amino acids, tricarboxylic acid cycle metabolites, phospholipids, long-chain fatty acids and bile acids were the ones which pre-operative or early post-operative pattern, seems to better correlate with bariatric surgery outcome.

Conclusions: Metabolite profiling could become a useful tool to predict long term response to different bariatric surgery procedures, allowing more personalized interventions and improving healthcare resources allocation.

Keywords: Metabolomics · Bariatric Surgery · Clinical outcome · Weight loss · Type 2 Diabetes

Abbreviation List | Lista de abreviaturas

3-HAA	3-hydroxyanthranilic acid
5-HIAA	5-hydroxyindoleacetic acid
5-HTrp	5-hydroxytryptophan
AA	Amino Acid
AAA	Aromatic Amino Acid
AC	Acylcarnitine
BA	Bile Acid
BCAA	Branched Chain Amino Acid
BMI	Body Mass Index
BPD	Biliopancreatic Diversion
BPL	Biliopancreatic Limb
CDCA	Chenodeoxycholic Acid
DCA	Deoxycholic Acid
DJB	Duodenal Jejunal Bypass
DS	Duodenal Switch
FFA	Free Fatty Acid
FXR	Farnesoid X Receptor
G-	Glycine amidated sub-fraction
HbA1c	Glycated Hemoglobin
HCA	Hyocholic Acid
HDL	High-density Lipoprotein
HOMA-IR	Homeostasis Model Assessment–Insulin Resistance
L-DOPA	L-dihydroxyphenylalanine
LAGB	Laparoscopic Adjustable Gastric Band
LDL	Low-density Lipoprotein
LPC	Lysophosphatidylcholines
MCA	Muricholic Acid
MCSFA	Medium-Chain Saturated Fatty Acids
NEFA	Non-Esterified Fatty Acids
PC	Phosphatidylcholines
PE	Phosphatidylethanolamines
PL	Phospholipid
QUICKI	Quantitative Insulin Sensitivity Check Index
RYGB	Roux-en-Y Gastric Bypass
SADI-S	Single-anastomosis duodeno-ileal bypass with Sleeve Gastrectomy
SG	Sleeve Gastrectomy
SM	Sphingomyelin
T2D	Type 2 Diabetes Mellitus
TCA	Tricarboxylic Acid

TLR4	Toll-Like Receptor 4
TMAO	Trimethylamine N-Oxide
VLDL	Very-low-density Lipoprotein

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Introduction | Introdução

The increasing prevalence of obesity in modern society makes it one of the main public health concerns[1]. Obesity is a major risk factor for several other medical conditions and particularly for non-communicable diseases, which besides having a great negative impact on the individual's quality of life, are also responsible for the majority of deaths in western countries[2-4]. Bariatric surgery is the most effective treatment for severe obesity and its associated co-morbidities, since it has proven to successfully achieve a significant and sustained body mass index (BMI) decrease, besides improving several obesity related diseases, such as diabetes, hypertension, dyslipidemia and cardiovascular events risk[4]. Consequently, bariatric surgery not only improves the health status but also reduces overall mortality and increases the life expectancy of patients with obesity.

Metabolomics has arisen as a valuable tool to study the metabolome dynamic adaptations[3]. Metabolomics has been widely used across several scientific areas in the quest for molecular fingerprints that could act as diagnostic and prognostic biomarkers. Metabolomics analyses are usually performed by stand-alone hydrogen nuclear magnetic resonance technique or mass spectrometry technique, combined with different metabolite chromatographic separation methods, such as capillary electrophoresis, liquid or gas chromatography[5]. These metabolite detection methods allow the characterization of low molecular weight metabolites from several different classes in a qualitative and quantitative approach[5]. The use of metabolomics in the study of obesity has empowered, not only the understanding of the biochemical and metabolic disruptions underlying this disease condition, but also the acknowledgement of the metabolic and physiological impact of therapeutic interventions, such as bariatric surgery[6]. Metabolomics studies enable to evaluate to what extent does the anatomical modifications of the gastro-intestinal tract induced by bariatric surgery alter the individual's metabolomics profile[5]. Furthermore, these techniques also allow to understand how different bariatric surgery techniques that result in distinct anatomical rearrangements of the gut, impact on the individuals' metabolic profiles[7]. Some metabolomics signatures harbor the potential to provide a mechanistic explanation on the heterogeneity of patient outcomes elicited by bariatric surgical interventions[8, 9].

Thus, the aim of this review was to systematize the available data in order to describe the metabolic fingerprints that characterize patients' submitted to different bariatric surgery procedures. Our goal was also to identify a pre-operative or early postoperative metabolite

profile potentially useful to predict weight loss response and type 2 diabetes (T2D) remission after bariatric surgery.

Methods | Métodos

Protocol and registration

This project was submitted to PROSPERO (registration number CRD42021235341) and it is available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021235341. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10].

Information sources and search approach

Publications reporting original data on metabolomics profiles induced by bariatric surgery were searched in three different electronic bibliographic databases: PubMed, Scopus and Isi Web of Knowledge, in February 2021. The detailed search approaches for each database are described in the Supplementary File 1.

Study selection and inclusion criteria

The main domain of this review were metabolomics studies carried out in patients submitted to bariatric surgery for the primary treatment of obesity and obesity related-disorders. The inclusion criteria comprised studies conducted in adult individuals submitted to bariatric surgery, including Sleeve Gastrectomy (SG), Laparoscopic Adjustable Gastric Band (LAGB), Roux-en-Y Gastric Bypass (RYGB), Duodenal Jejunal Bypass (DJB), Biliopancreatic Diversion (BPD), Duodenal Switch (DS), Single Anastomosis with DS, and Single-anastomosis Duodeno-ileal Bypass with Sleeve Gastrectomy (SADI-S). The exclusion criteria were study data pertaining to children (under 18 years old) and pregnant women.

Pre-established restrictive conditions for article retrieval and eligibility were: type of experimental design (only original observational studies, including cohort and case control), species submitted to analysis (only human species), type of biological fluid used for metabolomics analysis (plasma or urine) and publication language (English). No publication date restrictions were applied.

Data extraction

Studies provided by the bibliographic databases were screened to eliminate duplicates. Afterwards, the publications were independently reviewed by two authors, based on title and abstracts, in order to assess the eligibility criteria of each study. Thereafter, full text examination was also required in case of doubt. A third author conducted an independent review of the discordant articles and solved disagreements by majority consensus.

The papers selected for inclusion were scored according to the Newcastle-Ottawa Scale, for cohort or cross-sectional studies as appropriate, to assess the quality and risk of bias. Only studies considered to be at least of moderate quality, i.e. with a score of 6 or higher, were included for data analysis. The corresponding scores for each final selected study are described in Table 1.

The selected studies were divided among authors for individual data extraction, and later reviewed by other author in a cross-over manner. Data was retrieved and summarized according to the following information: author(s), study name, reference, experimental design, number of subjects enrolled, most relevant patient features (age, gender proportion, BMI and presence of T2D), type of bariatric surgery procedure, type of biological fluid used for metabolomics analysis, time points of the sample collection, experimental approach, study outcomes when applicable and major findings.

The articles were also subdivided into four different groups: 1) studies considering pre-operative and post-operative metabolomic signatures; 2) studies that disclosure pre-operative and early post-operative metabolomic signatures associated with T2D; 3) studies that disclosure pre-operative and early post-operative metabolomic signatures associated with weight loss response; 4) studies comparing metabolomic profiles after different bariatric surgery interventions.

Results | Resultados

Our search identified 378 papers in Scopus, 227 in PubMed and 233 in Isi Web of Knowledge, resulting in a total of 838 papers. After elimination of duplicates (n=328), a total of 510 papers were submitted to an initial screen by reading papers' titles and abstracts by two independent researchers. From those, 461 were out of scope resulting in a total of 49 full-text papers to be evaluated for eligibility. After reading the full texts, 6 papers were eliminated due to the following reasons: repeated data (n=1), out of scope (n=3), no description of metabolites analyzed (n=1) and metabolomics studies conducted in biological fluids other than urine or blood (n=1). Additionally, 3 papers were identified from reading the full texts reference list, resulting in a total of 46 papers to be included in the systematic review (Figure 1). Among these, 45 studies included conducted metabolomic analysis on plasma or serum and only 1 study was conducted on urine.

1) Metabolomic profiles induced by bariatric surgery

Several studies focused on evaluating the changes in metabolomic profile induced by bariatric surgeries (Table II). Amino acids, lipids, energy metabolism-related metabolites and gut microbiota-related metabolites were the most frequently studied metabolite classes. For simplification purposes, only metabolites reported to be more consistently altered after bariatric surgery are presented in this section.

Amino acids are one of the metabolite classes that is most affected by bariatric interventions. Numerous studies demonstrated that circulating levels of valine[11-26], isoleucine[11-18, 20, 21, 23-28], leucine[11-18, 20, 21, 23-29], phenylalanine[11, 12, 14, 15, 17, 18, 20-23, 29], tyrosine[11-15, 17, 18, 21, 23, 24, 29], tryptophan[11, 15, 18, 23, 29, 30], alanine[11-15, 17, 22, 24, 31], proline[11-13, 15, 22, 31], methionine[12, 17, 24], aspartate[15], threonine[13, 15, 26], lysine[13] and ornitine[12, 15, 18, 24, 32] decrease after bariatric surgery. Contrarily, circulating levels of glycine[12-16, 18, 20, 21, 25, 28, 30, 33] and serine[12, 22, 25, 30] were reported to increase after bariatric procedures. While other AAs, such as glutamine, histidine, arginine and asparagine were inconsistently reported as being either increased [14, 18, 21, 28, 33, 34] or decreased [12, 13, 15, 17, 22, 24, 31] after bariatric surgery. No pattern, regarding the type of surgical procedures or the post-operative time, was recognized as potentially responsible for the differences in these specific AA profiles observed across the studies.

Among the lipid class, acylcarnitines (ACs), free fatty acids (FFAs), bile acids (BAs) and phospholipids (PLs) were the metabolites most frequently studied in patients submitted to bariatric surgery interventions.

Acylcarnitines are esters of L-carnitine and fatty acids. These molecules can be divided into three different subclasses: short-, medium and long-chain ACs. The short chain AC acetylcarnitine was reported to increase rapidly after interventions and to remain elevated for 6 to 12 months after bariatric surgery[11, 15, 22, 26, 29, 35]. Contrarily, the short chain acylcarnitines derived from the branched chain amino acids (BCAAs) catabolism, C3 and C5, were shown to decrease after bariatric surgery[11, 12, 22, 24, 35]. A transient increase in long-chain ACs levels was observed two-weeks after surgery [22, 36], while most studies report a decrease in medium- and long-chain ACs over the long-term in patients submitted to bariatric surgery[11, 12, 34, 35].

Analysis of circulating fatty acids profiles identified a decrease in unsaturated and long-chain saturated fatty acids and non-esterified fatty acids (NEFA) after bariatric surgery, despite some inconsistent results across different studies[11, 13, 16, 19, 26, 37]. The opposite pattern was observed for medium-chain saturated fatty acids (MCSFA), in particular for the decanoic acid, which was found to increase after surgery[14, 16, 19, 26, 29].

Fasting primary and secondary circulating BA levels were also found to increase significantly after bariatric surgery interventions with a malabsorption component, namely RYGB and BPD[36, 38, 39]. This effect was demonstrated to be even more pronounced in the post-prandial for total BA, glycine- and taurine-conjugated BA[40]. In contrast, studies conducted in patients submitted to restrictive procedures yielded inconsistent results, with some studies reporting no differences between pre- and post-operative BA levels and others reporting increased levels in fasting and post-prandial level of glycine conjugated- BA[39, 41].

Phospholipids are important molecules within the cell membrane structure, which include several subclasses such as sphingomyelins (SMs), lysophosphatidylcholines (LPCs), phosphatidylcholines (PCs) and phosphatidylethanolamines (Pes). SM is the dominant sphingolipid in mammalians cells membranes. After BPD, most saturated and unsaturated SMs were found to be decreased[39]. A decrease in saturated SMs levels[35, 42] and increase in unsaturated SMs levels[29, 35, 42] after RYGB was identified by the majority of studies, although results are not consistent across reports[11, 15, 19, 29, 35-37, 42].

LPC, PC and PE levels were also reported as being overall decreased after bariatric surgeries with a malabsorptive component, RYGB and BPD, by the majority of studies[11, 19, 29, 36, 37, 42], although post-operative increase in some species of PLC and PE was also reported [11, 13, 39]. Noticeably, most of the aforementioned PLs were found to increase after SG[39].

Likewise, an increase in ketone bodies (3-hydroxybutyrate and acetoacetate) levels was also identified after bariatric surgery[13, 21, 29, 30, 35, 43]. Although, carboxylic acids and ketone bodies levels were only observed or were more pronounced in short-term period after surgery[16, 21].

Most studies reported a decrease in pyruvate[21, 22, 27, 33] and lactate[13, 22, 26] levels after bariatric surgery. Contrarily, the Krebs cycle intermediates (citrate [13, 18, 21, 29], succinate [18, 30], fumarate [30, 33], malate [18, 33], oxalacetate [27]) were found to increase after surgery.

Gut microbiota metabolites related to AAs and carnitine metabolism were also found to increase after bariatric surgery. In particular, in the levels of p-cresol [11, 13, 26, 29], indole and indoxyl sulfate[14, 19, 23], trimethylamine N-oxide (TMAO)[14, 21], phenol sulfate [29], 3-indolelactic acid [29] and 4-hydroxy-L-proline[29].

2) Metabolomic signatures associated with post-bariatric T2D remission

Metabolomics profiles associated with glucose and insulin homeostasis after the bariatric surgery were analyzed in fourteen independent prospective cohort study studies. While seven papers focused on T2D remission after bariatric surgery, another six studies addressed the specific profile associated with T2D related parameters, namely glycated hemoglobin (HbA1c) levels, insulin secretion and insulin sensitivity, as inferred from insulinogenic index, homeostasis model assessment-insulin resistance (HOMA-IR)[44] and QUICKI.[23] The majority of studies included individuals submitted either to SG[23, 45, 46] or RYGB[11, 14, 19, 44, 47-50]. The remaining three articles were conducted in individuals submitted to different bariatric surgery procedures having RYGB as constant comparator[38, 51, 52]. (Table III) (Figure 2)

Circulating AAs was the most differentially altered metabolite class distinguishing patients that achieved T2D remission from those with persistent disease after bariatric surgical interventions[23, 45-47, 50, 51]. BCAAs decrease after SG and RYGB, being more pronounced in patients achieving T2D remission[23, 44, 46, 47, 50]. *Kwon Y et al* described, not only an early decline in BCAAS, but also aromatic amino acids (AAAs)[23] in patients depicting improved insulin resistance 3 months after SG. The same authors also documented higher pre-preoperative levels of kynurenine pathway metabolites, such as 3-HAA, xanthurenic acid, anthranilic acid and 3-hydroxykynurenine, in patients who later experienced a considerable decrease of these metabolites along with improved insulin secretion and resistance[23]. Another study highlighted that patients who achieved T2D remission at 1 year after SG and RYGB had higher baseline levels of L-dihydroxyphenylalanine (L-DOPA) and 3-hydroxyanthranilic acid (3-HAA)[51].

Higher pre-operative levels of tryptophan[11] and tricarboxylic acid (TCA) cycle metabolites (citric acid, fumarate and aconitate)[19] were reported in patients with better T2D outcomes. Tryptophan-derived gut microbial metabolites after surgery also differed, as decreased indole-3-propionic acid and increased indole-3-acetic acid were shown to correlate with improved insulin homeostasis 3 months after intervention[23].

Pre-operative lipid metabolite fingerprints of patients who achieve T2D remission as compared to those without disease remission was shown to be characterized by higher PEs, triglycerides and PLs with long-chain fatty acids[19]; while postoperative metabolite profile was characterized by lower VLDL, LDL, N-acetyl glycoproteins and unsaturated lipids, and increased HDL and PCs [11, 45, 47, 52]. *Zhao L et al* described that higher baseline ratios of stearic acid/palmitic acid and eicosadienoic acid/linoleic acid characterized patients undergoing T2D remission 1 year after RYGB. A substantial decrease in long chain fatty acids (FFA 16: 0, FFA 18: 3 and FFA 17: 2) levels at 6 months after RYGB was identified in patients experiencing T2D remission 1 year after surgery.[11] Other authors established that higher levels of 3-hydroxybutyrate 1 week after bariatric surgery (RYGB and DJB) was associated with greater HbA1c improvements 3 months later[52] and lower 2-hydroxybutyric acid at 6 months after RYGB was associated with HOMA-IR improvement[44]. *Arora T et al* studied the metabolic profile of patients submitted to RYGB who experienced T2D remission 2 years after surgery. Postoperative fasting plasma lipid profile was characterized by a significant reduction of most lipid species at 4 days and an increase of the same metabolites at 42 days after surgery.

The utility of bile acids levels as biomarkers of T2D improvement after bariatric surgery was explored in three independent studies[11, 48]. Two studies addressing T2D remission after RYGB identified higher total BA levels at baseline in the sub-groups of patients with better T2D outcomes[11, 38, 48]. *Yu H et al* even highlighted that Chenodeoxycholic Acid (CDCA) and the ratio of CDCA/total BA correlated with T2D remission 2 years after RYGB. *Ahlin et al* found that increased total BA levels at 185.3 (±72.9) days after RYGB and BPD were correlated insulin resistance improvement regardless the type of surgical procedure[38].

3) Metabolomic signatures associated with post-bariatric weight loss response

The analysis of pre- and post-operative metabolomics according to post-bariatric weight loss responses was assessed in 4 independent prospective studies, conducted in patients submitted to SG[41, 53] or RYGB[14, 54]. (Table III) (Figure 3)

AAs were the metabolic class that portrait more pronounced changes after bariatric surgeries[14, 53, 54]. Higher baseline BCAAs levels, in particular isoleucine, were correlated with greater weight

loss at 3 and 6 months after SG[53]. In the postoperative period, there was a significant decrease in creatine, ornithine, arginine and valine levels in the sub-group of patients with greater weight loss 1 year after RYGH[14].

Moreover, *Abidi W et al* compared metabolite pattern of patients with sustained weight loss with those of patients who experienced weight regain years after RYGB. The study unraveled lower levels of metabolites related to serine, glycine and threonine pathways, from phenylalanine alanine and glutamate metabolism and TCA cycle, as well as higher levels of other AAs, characterized the metabolomics profile of patients with poor long-term weight loss outcomes. While higher glycine levels were found in patients with sustained weight loss[54].

Serotonin, a molecule derived from the AA tryptophan, and its metabolites were also proposed as weight loss response molecular fingerprints. A pre-operative profile with lower serotonin levels and serotonin/5-HTrp ratio, and higher 5-HIAA levels and 5-HIAA/serotonin ratio was identified in patients with greater weight loss at 3 and 6 months after SG[53].

Patients with sustained weigh loss also presented upregulated lipolysis and consequently depletion of triacylglycerols, diaglycerols and cholesterol esters, in addition to higher levels of 3-hydroxybutyrate[54].

Increase in multiple BAs subtypes, more pronounced in postprandial rather than fasting period, was found to correlate with early (6 weeks) and short-term (12 weeks) weight loss response after SG and persistent. During fasting, HCA (total, unamidated and glycine amidated subtypes) was the only BA found to be increased, while the postprandial profile portrayed increased BAs (total and glycine amidated subtypes-), CDCA (total and glycine amidated), DCA (total and glycine amidated), MCA (total and glycine amidated), HCA (total, unamidated and glycine amidated). The authors highlighted the augmented post-prandial total and G-CDCA, as being significantly correlated to the 6 weeks BMI loss, as well as the increased post-prandial G-HCA, which was significantly correlated to a greater weight loss percentage at both 6 and 12 weeks [41].

4) Metabolomic profiles induced by different bariatric surgeries

Only reports comparing the metabolomic profiles induced by different types of bariatric surgery procedures from parallel arm studies were included in this review section. Nine prospective cohort studies and two cross-sectional studies compared the metabolomic profiles induced by different bariatric procedures [12, 21, 25, 29, 31, 38, 39, 46, 55] or its variants[21, 56]. (Table IV) From those, seven studies compared the effects of RYGB with two different restrictive bariatric surgeries: LAGB[12, 25, 42] and SG[21, 29, 31, 46], at several time points after surgery, ranging from 3 days to 1 year.

Metabolomic signatures associated with each type of bariatric surgery procedure were found. However, one study reported that metabolic signatures differences between RYGB and SG tend to be less prominent 12 months after surgery[29]. When comparing the two types of surgeries, changes in AAs and gut microbiota-related metabolites were the most differentially altered metabolite classes[21, 25, 29, 31, 46]. In addition, a rapid decrease in the majority of lipid classes was observed after both RYGB and LAGB surgeries in the short-term (1 month). However, some PC and SM species returned or tended to return to baseline values 3 months after LAGB, but not after RYGB[42].

One study that compared the effect of restrictive (SG) and malabsorptive (BPD) bariatric surgeries on metabolomics found that sphingolipids, PLs and BAs levels were differentially altered by the two bariatric surgery procedures. BPD induced an overall decline in sphingolipids and PLs and an increase in BAs levels. Contrarily, SG induced an increase in sphingolipids and PLs and no changes in BAs levels[39].

In contrast, in another study comparing RYGB and BPD, BAs levels were found to be similar after both surgeries[38].

Comparison of fasting and post-prandial metabolomics profile of patients submitted to two different malabsorptive surgeries (SADI-S and BPD-DS) was explored in a cross-sectional study. Higher post-prandial BCAAs levels after SADI-S, the least malabsorptive surgery, was the only difference observed[55].

The effects of two different RYGB variants on circulating metabolomics profiles was evaluated in a cross-sectional study and in another prospective study. However, the differences in RYGB limb lengths used in the two studies do not allow direct comparisons[56]. *Gralka et al* included patients submitted either to a proximal RYGB consisting of a biliopancreatic limb (BPL) of 60 cm and an alimentary limb of 150cm; or to a distal RYGB that had both BPL and common limb lengths of 60-100 cm[21, 56]. In contrast, the RYGB variants described by *Jarak et al* had different BPL length (short-BPL: 60-100cm vs long-BPL: 200cm) but the same alimentary limb length (120 cm)[56]. Despite the dissimilarities between RYGB variants and no differences on the post-operative AAs levels were noticed, both studies found diverse changes in gut microbiota-related metabolites, namely acetate and dimethyl sulfate, when comparing the two RYGB variants[21, 56].

Discussion| Discussão

High levels of circulating AAs is a well-known feature of patients with obesity[57]. BCAAs levels are particularly high and experience a rapid decrease after bariatric surgery[58 11-29]. The reduction in BCAA has been attributed to a combination of multiple factors including decreased protein intake; decreased in amino acids absorption; increased BCAA catabolism and decreased protein catabolism as a consequence of insulin sensitivity improvement and metabolic amelioration[3]. The upregulation of BCAAs catabolism is supported by the consistent postoperative decline of specific subproducts of BCAAs' mitochondrial oxidation, namely short chain acylcarnitine's C3 and C5.[11, 12, 22, 24, 35] Although BCAAs decrease after both restrictive and malabsorptive surgeries [11-29], parallel arm studies reported a greater effect of RYGB in BCAAs levels.[21, 25] Since the differences found in BCAA levels when comparing RYGB and the restrictive procedures seem to be independent of the weight loss, these were hypothesized to be related to impaired AAs absorption induced by the RYGB intestinal rearrangement[21, 25].

Similarly, AAAs were also found to be elevated in patients with obesity and decrease after bariatric surgery[21, 29]. This is consistent with the increase of AAAs derived gut microbiota metabolites (p-cresol, indoxyl sulfate, phenol sulfate and 3-indolelactic acid) after bariatric surgery[11, 13, 14, 23, 26, 29].

Circulating essential AAs levels were also associated with weight loss response after bariatric surgery, given that higher AAs levels were reported in patients experiencing weight regain[54]. On other hand, patients with significant weight loss presented lower pre-operative levels of serotonin, suggesting its potential use as prognostic biomarker to identify patients that are more likely to achieve greater weight loss after surgery[53]. Circulating serotonin interacts with multiple organs, preparing the body for energy storage by promoting insulin secretion and de novo lipogenesis in the liver and white adipose tissue, while reducing lipolysis[59].

Additionally, multiple studies reported that BCAAs and AAAs modifications induced by the bariatric procedures could play a relevant role predicting T2D remission[23, 45-47, 51]. Obesity associated hyperaminoacidemia is a consequence of insulin resistance, which positively affects protein synthesis and proteolysis[60]. BCAAs can also modulate insulin secretion and promote diabetes via hyperinsulinemia, considering its role as insulin secretagogues. Chronic hyperinsulinemia can further stimulate compensatory insulin resistance and potentially lead to pancreatic β-cell exhaustion[61, 62]. Contrariwise, improved insulin sensitivity and secretion after bariatric surgery are associated with decreased circulating AAs[20, 23, 47.] However, relevant pre-

operative metabolomic profiles are those that attract the greatest interest in order to identify patients that are more likely to benefit from bariatric treatment interventions. Hence, baseline levels of L-DOPA, 3-HAA, tryptophan and TCA cycle subproducts are the metabolites that demonstrated a potential prognostic value for T2D remission[11, 19, 51].

In opposition to most of AAs, the levels of the non-essential AA glycine and serine are known to be low in subjects with obesity and increase after bariatric surgery[12-16, 18, 20-22, 25, 28, 30, 33]. In healthy subjects, glycine is inter-convertible with serine. Glycine participates in multiple biological functions, such as the glutathione synthesis, purines and primary bile salts[63]. Previous studies described low fasting levels of glycine in individuals with impaired glucose tolerance and proposed glycine as an early marker for insulin resistance[64]. Increased levels of glycine after bariatric surgery suggests a reduction in insulin resistance and oxidative stress[16]. In addition, glycine and serine levels were noticeably significantly higher in patients with sustained weight loss, as compared to patients with weight regain[54]. In further support of the potential role of glycine in mediating weight loss, a recent animal model study also concluded that glycine supplementation to obese mice during calorie restriction accelerated fat loss and protected against muscle loss[65].

Gut microbiota plays an important role in various physiological processes, including metabolism of dietary components and some host-generated substances, with an impact on the use and storage of energy[66]. Gut microbiota of individuals with obesity is characterized by a reduced bacterial diversity and lower ratios of Bacteroidetes to Firmicutes[67]. After bariatric surgery, different gut microbiome related metabolites arise that differ depending on the type of bariatric procedure. In particular, p-cresol, a metabolite of phenylalanine and tyrosine fermentation by gut microbiota[68, 69], was reported to increase after SG[29]. *Bacteroides fragilis* is one of the bacteria responsible for phenylalanine and tyrosine fermentation. *Bacteroides* were previously demonstrated to increase after SG in individuals with prior T2D diagnosis[70]. So, the effect in tyrosine and phenylalanine levels found of patients with T2D after SG when compared to RYGB, may be related to increased fermentation by gut microbiota. Sulfate containing metabolites and TMAO, two other gut microbiome related metabolites were identified to increase after RYGB but not after SG[29]. The differences observed in sulfate containing metabolites results could easily be justified by the fact that the major group of sulfate-reducing bacteria is mainly present in the duodenum, which is trespassed in RYGB[71]. Contrary, the effects of RYGB in TMAO levels is not well understood and unexpected because high TMAO levels have been linked to cardiovascular diseases, whereas RYGB is known to reduce the cardiovascular risk and events[72, 73]. The increase in TMAO levels observed after RYGB, but not after SG, could be derived from the shortening of

the small bowel and a less anaerobic metabolism by the gut microbiota, in result of the increase in microbes, such as E. coli and Pseudomonas, responsible for raising TMAO levels[74]. Gut microbiota-related metabolites were also differentially altered by RYGBs with different absorptive limbs. *Gralka et al* found that RYGB with a shorter common limb led to a higher increase in dimethyl sulfate levels compared to a more absorptive RYGB[21]. A different study also found that post-prandial levels of acetate were higher in patients submitted to RYGB with a longer BPL[56]. Both metabolites (dimethyl sulfate and acetate) are produced in the colon by bacterial fermentation[75], which is enhanced by the higher quantity of undigested food that reaches the colon in the less absorptive RYGB.

The obesity associated energy metabolic disruption is characterized by decreased oxidation of ketone bodies and down-regulation of TCA cycle[76]. Metabolomic analysis suggests that after bariatric surgery a strong and early upregulation of catabolism and lipolytic activity occurs. Most of intermediate and end products of β-oxidation and ketogenesis increase after intervention, in particular in short-term period after surgery[13, 21, 22, 29, 30, 35, 36, 43]. These findings support a shift in energy metabolism from anabolic to catabolic status, possibly triggered by surgery and caloric restriction.

The increased levels of ketone bodies after bariatric surgery are consistent with the rapid decrease in ketogenic amino acids after bariatric surgery. The ketone body 3-hydroxybutyrate originates from fatty acids degradation for energy generation in the liver[77]. It has been previously reported that 3-hydroxybutyrate levels increase during the first week after bariatric surgery, as a consequence of the acute and adaptative fasting-like response[16]. Therefore, individuals with sustained long term weight loss after surgery maintain higher metabolic needs and fatty acid oxidation, responsible for the higher levels of 3-hydroxybutyrate observed[54]. The ketone body levels are also significantly higher in patients experiencing greater HbA1c improvement bariatric surgery[52]. Ketogenic diets are reported to have favorable effects on energy and glucose homeostasis regulation[78]. Intracerebroventricular injections of 3-hydroxybutyrate in diabetic rats resulted in improved serum glucose levels and peripheral insulin sensitivity due to a potentiated leptin and insulin signaling in the hypothalamus[78]. Thus, earlier increase of 3-hydroxybutyrate days after the bariatric surgery could hypothetically induce a similar central signaling in humans, contributing for a better glycemic control. This particular metabolite could enable the early identification of patients more likely to achieve T2D remission, although with the limitation of not being assessable prior to surgery.

Alanine, pyruvate and lactate decrease after bariatric surgery. This finding was reported to be possibly related to the reduction of gluconeogenic precursors after surgery[22]. An improved post-surgical mitochondrial function is also suggested, as most of glucogenic AAs that can be converted in Krebs cycle intermediates decrease, while most of Krebs cycle intermediates seems to increase after bariatric surgery. Fasting states or caloric restriction circumstances also generate substrates that upregulate reactions of TCA cycle[79]. Therefore, individuals that experience weight gain are characterized by lower TCA cycle metabolites.

Obesity is also characterized by a blunted post-prandial BAs response. Bariatric surgery, in particular RYGB and BPD normalizes that response, leading to an increase in postprandial BAs that can be justified by the accelerated delivery to the distal intestine where BAs are absorbed[38, 40, 48]. Since BPD lead to early delivery of food to the more distal gut, BPD would be expected to have a higher effect on BAs levels when compared to RYGB. However, BAs levels were found to be similar after both bariatric surgeries[38]. Accordingly, bile diversions to the mid-jejunum or mid-ileum led in rats led to the same BAs plasma level, suggesting that BAs absorption is not necessarily proportional to the length of the gut segment[80]. BAs are reported to have a key role on mediating the anti-diabetic effects of the bariatric surgery. Indeed, higher baseline levels of CDCA were correlated with better outcomes after RYGB[11, 48]. In addition, higher post-operative values of conjugated secondary BAs were associated with an increase of insulin sensitivity after both RYGB and BPD[38]. BAs metabolic effects are mainly mediated by the activation of two receptors: FXR and TGR5. TGR5 activation in the enteroendocrine cells increase the release of the incretin hormone, glucagon-like peptide-1, known for its anti-diabetic effects[81]. In addition, the receptor TGR5 is also expressed in the human muscle and brown adipose tissue, leading to an increase of muscle energy expenditure, via T4-T3 conversion than can further contribute to increase insulin sensitivity[82, 83].

Circulating levels of fatty acids, acylcarnitines, phospholipids, triglycerides, total cholesterol, and LDL are frequently elevated in individuals with obesity and particularly with obesity-related metabolic disorders[57]. Bariatric surgery induces an overall improvement in lipid profile with a marked decrease in most lipid classes. Apart from this trend stands the post-operative increase of MCSFA, known for suppressing fat deposition due to enhanced thermogenesis and fat oxidation in animals and humans[84]. Additionally, previous studies also proposed the pharmacological potential of MCSFA for preserving insulin sensitivity in T2D[85, 86].

A preoperative lipid profile with higher levels of PES, triglycerides and PLs with long-chain fatty acid could also be useful to assess the likelihood of T2D remission after surgery. Long-chain fatty

acid metabolism is known to be abnormal in diabetes, leading to impaired formation of labeled fatty acids dependent on delta-9, delta-6, and delta-5 desaturation, as well as on chain elongation[87]. Thereby, greater levels of triglycerides with higher carbon number are associated with a decreased diabetes risk[88]. Similar patterns were reported for other lipid classes, including PEs[89]. Palmitic Acid (FFA 16:0) is also strongly associated with T2D, since this main even-chain fatty acid is significantly decreased before[11] and after[49] RYGB in patients with better T2D outcomes. Palmitic acid was shown to activate TLR4 and, subsequently prompt inflammatory cytokines and lipotoxicity in pancreatic β cells, with consequent impaired insulin action[90].

Although the surgical rearrangements induced by RYGB are more disruptive of normal gastro-intestinal anatomy as compared to SG, the alterations induced by the two procedures on the overall lipidomic profile are not dissimilar[29]. Different findings were observed when the lipidomic profile of the malabsorptive surgery BPD was compared with the one induced by SG, as lipid signatures clearly differ depending on the type of bariatric surgery procedure[39]. Most sphingolipids and PLs decrease after BPD, which can be attributed to decreased lipid absorption after surgery. On the other hand, PLs levels increased after SG. Circulating levels of PLs are reduced in patients with obesity, which is associated with an increased oxidative status[91, 92]. SG seems to efficiently restore PLs levels to those found in subjects with normal weight by decreasing patients' oxidative profile. Sphingolipids levels also increase after SG. However, this observation is more difficult to understand since sphingolipids are associated to obesity-related disorders such as insulin resistance and cardiovascular diseases[93]. Notwithstanding, these lipids have been suggested to be partially associated with the weight regain observed after SG[39].

Nonetheless, the interpretation of the summarized data must be evaluated in the context of the limitations of the reported studies. There are some discrepant results across different analysis, raising the possibility of some bias, independent from the anatomical rearrangements of the surgery itself, such as patients' dietary habits, which could also have a significant impact on the metabolome. Additionally, it is important to mention that the time points of assessment before and after surgical interventions differed substantially across the studies, in some cases, the follow-up was not long enough for an adequate appreciation of patients' outcomes. Most of the studies reported the metabolomic profile induced by a single bariatric surgery procedure. Although comparison between studies can be made for understanding the metabolomic profile induced by different surgeries, it raises several constraints derived from the comparison of non-paired patients regarding pre- and post-operative characteristics and from the use of different methodological approaches.

Conclusions| Conclusões

This review summarizes the impact of bariatric surgery on the individuals' metabolomics profile and how different bariatric procedures result in distinct metabolomics signatures, which could contribute to explain the heterogeneity of surgical outcomes. A few pre-operative metabolomics fingerprints were identified as harboring the potential to be used as prognostic biomarkers for weight loss response and T2D remission. Moreover, these studies also highlighted many post-operative metabolic changes that contribute for understanding the molecular mechanisms inherent to dissimilar outcomes. By allowing the prediction of individuals' biological responses, metabolomics studies harbor the potential for identifying those individuals that are more likely to benefit from a given bariatric surgery intervention. Ultimately, this knowledge could positively influence patient care by avoiding unnecessary surgical risks in those that will not benefit from it, towards a more personalized medicine. Ultimately these advances could positively impact the optimization of healthcare resources allocation.

Appendix | Apêndice

Table I Summary of Newcastle-Ottawa Scale scores of the studies included for systematic review (cohort studies)

NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES									
FIRST AUTHOR AND YEAR	SELECTION				COMPARABILITY	OUTCOME			TOTAL SCORE
	1	2	3	4	1	1	2	3	(MAX 9)
Abidi W, 2020 [54]	0	1	1	1	2	1	1	1	8
Ahlin S, 2019 [38]	0	1	1	1	1	1	1	1	7
Ahmad NN, 2013 [40]	1	1	1	1	2	1	1	1	9
Arora T, 2015 [19]	0	1	1	1	2	1	1	1	8
Cabré N, 2020 [27]	1	1	1	1	2	1	1	1	9
Dadson P, 2020 [20]	1	1	1	1	1	1	1	1	8
Fiamoncini J, 2018 [26]	0	1	1	1	2	1	1	1	8
Friedrich N, 2012 [43]	1	1	1	1	2	1	1	0	8
Gralka E, 2015 [21]	1	1	1	1	2	1	1	1	9
Ha J, 2020 [51]	0	1	1	1	2	1	1	1	8
Herzog K, 2020 [35]	1	1	1	1	1	1	0	1	7
Hubal MJ, 2017 [28]	0	1	1	1	2	1	1	1	8
Jüllig M, 2014 [31]	0	1	1	1	2	1	1	1	8
Kayser BD, 2017 [42]	0	1	1	1	2	1	1	1	8
Khoo CM, 2014 [22]	0	1	1	1	2	1	1	1	8
Kindel TL, 2018 [41]	0	1	1	1	1	1	1	1	7
Kwon HN, 2014 [52]	0	1	1	1	2	1	0	1	7
Kwon Y, 2020 [53]	0	1	1	1	2	1	1	1	8
Kwon Y, 2021 [23]	0	1	1	1	1	1	0	1	6
Laferrère B, 2011 [24]	0	1	1	1	2	1	1	1	8
Li QR, 2018 [50]	0	1	1	1	2	1	1	1	8
Lips MA, 2014 [25]	1	1	1	1	2	1	0	1	8
Lopes T, 2015 [26]	0	1	1	1	2	1	1	1	8
Lopes T, 2016 [47]	0	1	1	1	1	1	1	1	7
Luo P, 2016 [11]	0	1	1	1	1	1	1	1	7
Magkos F, 2013 [12]	0	1	1	1	1	1	1	1	7
Mendonça Machado M, 2020 [30]	0	1	1	1	2	1	1	1	8
Mika A, 2017 [37]	0	1	1	1	2	1	1	1	8
Mutch DM, 2009 [13]	0	1	1	1	2	1	1	1	8
Narath SH, 2016 [14]	0	1	1	1	2	1	1	1	8
Oberbach A, 2011 [34]	1	1	1	1	2	1	1	1	9
Ocaña-Wilhelmi L, 2019 [32]	0	1	1	1	2	1	0	1	7
Palau-Rodriguez M, 2018 [15]	0	1	1	1	2	1	1	1	8

Table I Summary of Newcastle-Ottawa Scale scores of the studies included for systematic review (cohort studies) (cont.)

Ramos-Molina B, 2018 [39]	0	1	1	1	1	1	1	1	7
Samczuk P, 2018 [29]	0	1	1	1	2	1	1	1	8
Samczuk P, 2018 [45]	0	1	1	1	2	1	1	1	8
Sarosiek K, 2016 [33]	0	1	1	1	1	1	1	1	7
Shantavasinkul PC, 2018 [44]	0	0	1	1	1	1	1	1	6
Tan HC, 2016 [46]	1	0	1	1	2	1	1	1	8
Wijayatunga NN, 2018 [16]	0	1	1	1	2	1	1	0	7
Yao J, 2019 [17]	1	1	1	1	2	1	0	1	8
Yoshida N, 2020 [18]	0	1	1	1	2	1	1	1	8
Yu H 2015 [48]	0	1	1	1	2	1	1	1	8
Zhao L, 2017 [49]	0	1	1	1	2	1	1	1	8

Table II Summary of Newcastle-Ottawa Scale scores of the studies included for systematic review (cross-sectional studies)

NEWCASTLE-OTTAWA SCALE ADAPTED FOR CROSS-SECTIONAL STUDIES								
FIRST AUTHOR AND YEAR	SELECTION				COMPARABILITY	OUTCOME		TOTAL SCORE
	1	2	3	4	1	1	1	(MAX 10)
Jarak I, 2020 [56]	0	1	1	2	2	2	1	9
Pereira SS, 2020 [55]	0	1	1	2	2	2	1	9

Table III Summary of studies comparing the metabolomic profiles of patients after bariatric surgery

FIRST AUTHOR AND YEAR	EXPERIMENTAL DESIGN	SURGICAL PROCEDURE	SUBJECTS UNDER SURGERY	PRE-OPERATIVE BMI (KG/M^2)	AGE AT SURGERY (YEARS)	FEMALE: MALE	POST-OPERATIVE BMI (KG/M^2)	BIOLOGICAL SAMPLE	METABOLOMIC ANALYSIS	MAIN FINDINGS
Ahlin S, 2019[38]	Prospective cohort study	RYGB and BPD	N=15	51.6 ± 9.6 (SD)	44.3 ± 8.3 (SD)	1:2	37.7 ± 7.4	Fasting plasma samples	Targeted UPLC-MS	After a mean of 185.3 (72.9) days: increase in total BA concentrations after both RYGB and BPD.
Ahmad NN, 2013[40]	Prospective cohort study	RYGB	N=5	47.7 ± 7.4	44.8 ± 12.9	1:4	31.5 ± 5.0	Fasting and postprandial plasma samples	Targeted UPLC-MS	After 40 weeks: acceleration of the postprandial BA response, leading to an earlier rise and fall in glycine- and taurine-conjugated BAs after meal ingestion. RYGB normalizes the blunted postprandial circulating BA
Arora T, 2015[19]	Prospective cohort study	RYGB	N=16	48.9±1.3	47.4±1.9	11:5	Reduction of 31.3 ± 2.1%	Fasting plasma samples	GC-MS and UPLC-MS	After 4 days: reduction in most lipid species. After 42 days: higher levels of decanoic and octanoic acids; increase in most lipid species; lower levels SPMs (18:1/21:0 and 18:1/23:3)
Cabré N, 2020[27]	Prospective cohort study	NA	N=270	Median: 46.4 (42.4-51.6)	Median: 49 (41-58)	67:23	NA	Fasting plasma samples	Targeted GC-MS and UHPLC	After 12 months: decrease of leucine and isoleucine, α-ketoglutarate, 3- hydroxybutyrate, malate, malonil-CoA, glutamate and pyruvate. Increase of Sucinyl-CoA and oxaloacetate.
Dadson P, 2020[20]	Prospective cohort study	RYGB and SG	N=23	41.1 ± 4.2	42.8 ± 9.6	23:0	31.8 ± 13.5	Fasting serum samples	H NMR	After 6 months: decrease in ApoB/ApoA1, BCAA, AAA and GlycA; increase in glycine; lipid parameters remained unchanged.
Fiamoncini J, 2018[36]	Prospective cohort study	RYGB	N=26	44.1 ± 3.6	36.2 ± 7.8	18:8	35 ± 3.3	Fasting plasma and dried blood spots samples	Targeted LC-MS/MS (lipidomic)	After 90 days: transient increase in total ACs Sustained decrease in PCs and increase of SPMs and BAs.
Friedrich N, 2012[43]	Prospective cohort study	RYGB and SG	N=50	Median: 48.3 (42.9-52.5)	Range: 22 to 63	NA	NA	Urine	H NMR	After 3 to 9 days: increase in 3-HB, 2-HB, hippuric acid, trigonelline, and glycine.
Gralka E, 2015[21]	Prospective cohort study	SG, proximal RYGB and distal RYGB	N= 106	46.2 ± 7.8	43.6 ± 1.0	77:33	31.7 ± 4.1(SG) 29.4 ± 5.9 (proximal RYGB) 30.7 ± 4.9 (distal RYGB)	Fasting serum	Untargeted H-NMR	After 12 months: increase in arginine, glutamine and dimethyl sulfate; decrease in AAAs and BCAAs; normalization of pyruvate, methanol and isopropanol; temporary increase of citrate. TMAO increased 12 months after SG only.

Table III Summary of studies comparing the metabolomic profiles of patients after bariatric surgery (cont.)

Herzog K, 2020[35]	Prospective cohort study	RYGB	N=19	39.8 ± 3.3	43 ± 6.3	19:0	33.3 ± 3.1	Fasting and postprandial plasma	UPLC	After 1 day: reduction of medium-chain ACs and purines; increasing in short-chain AC 2:0, most aminoacids, carnitine and 3-HB; few lipids were altered. After 6 weeks: reduction in 6 out of the 20 detected ACs and 3-HB; few lipids were altered.
Hubal MJ, 2017[28]	Prospective cohort study	GB	N=6	51.2 ± 8.8	38.5 ± 6.8	6:0	32.6 ± 8.1	Plasma and serum samples	LC–MS	After 1 year: increased levels of apargine. citrulline, glutamine, glycineand histidine; lower levels of cysteinylglycine, glutamic acid, leucine/isoleucine, total BCAAs and Glu/Gln ratio.
Jüllig M, 2014[31]	Prospective cohort study	RYGB and SG	N=15	42.1 ± 4.0 (RYGB) 42.3 ± 5.9 (SG)	41.0 ± 3.1 (RYGB) 46.8 ± 2.9 (SG)	14:1	NA	Fasting plasma samples	Untargeted GC-MS	3 days after RYGB: decrease in histidine, proline, citrate and decanoic acid. 3 days after SG: increase in 2-HB and 3-methyl-2-oxo-pentanoic acid.
Kayser BD, 2017[42]	Prospective cohort study	RYGB and LAGB	N=59	46.5 ± 1.0 (RYGB) 43.6 ± 0.7 (LAGB)	37.3 ± 1.9 (RYGB) 34.5 ± 1.6 (LAGB)	59:0	38.0 ± 1.2 (RYGB) 38.3 ± 1.0 (LAGB)	Fasting serum samples	Targeted LC-MS/MS (lipidomic)	After 3 months, the majority of lipids decreased after both surgical procedures.
Khoo CM 2014[22]	Prospective cohort study	RYGB	N=20	45.6 ± 2.4	47.9 ± 5.0	7:3	Reduction of 6.5 ± 1.0%	Fasting and postprandial plasma	Targeted tandem MS	10 to 14 days after, in fasting analysis: - reduction in AA (proline, histidine, valine, phenylalanine, BCAA, AAA and total AA), alanine, and molar sum of C3 and C5 ACs; increasing in C2, long-chain (C14-C22), total AC, NEFA, ketones and 3-HB. 10 to 14 days after, in postprandial analysis: - reduction in multiple AA, molar sum of BCAA, aromatic and total AA; increasing in plasma C2, medium-chain, long-chain and total ACs
Kindel TL 2018[41]	Prospective cohort study	SG	N=28	45.0 ± 6.8	45.4 ± 12.9	41:9	38.9 ± 6.3	Fasting and postprandial serum samples	UPLC–MS	After 12 weeks, increase in multiple BA subtypes: fasting HCA (total, unamidated and G- sub-fractions), postprandial BAs (total and G-), CDCA (total and G-), DCA (total and G), postprandial MCA (total and G-) and postprandial HCA (total, unamidated and G-)
Kwon Y 2021[23]	Prospective cohort study	RYGB	N=23	38.9 ± 5.2	41.8 ± 13.1	17:6	31.4 ± 5.5	Fasting serum samples	Targeted LC–MS	After 3 months: decrease in KynP metabolites, BCAAs, AAAs and TDGMs.
Laferrère B, 2011[24]	Prospective cohort study	GB	N=21	44.9 ± 8.7 (SD)	43.3 ± 10.0 (SD)	NA	Decrease of 4.60 ± 2.13	Fasting plasma samples	Targeted tandem MS	After a BMI decrease of 4.60 ± 2.13 kg/m^2 in BMI, individuals had a significant decrease in AAs, in particular BCAAs and related metabolites.

Table III Summary of studies comparing the metabolomic profiles of patients after bariatric surgery (cont.)

Lips MA, 2014[25]	Prospective cohort study	RYGB and LAGB	N=27	43.1 ± 0.9 (LAGB) 44.2 ± 0.8 (RYGB and no T2D) 43.5± 1. 1 (RYGB and T2D)	46.3 ± 1.9 (LAGB) 48.6 ± 1.6 (RYGB and no T2D) 51.3 ± 1. 9 (RYGB and T2D)	27:0	39.0 ± 0.8 (LAGB) 36.63 ± 0.8 (RYGB and no T2D) 34.7 ± 0.8 (RYGB and T2D)	Fasting plasma samples	Targeted UPLC - tandem MS (AA analysis)	After 3 months: significant decrease in BCAAs in both procedures
Lopes TI, 2015[26]	Prospective cohort study	RYGB	N=10	32.38 ± 2.11	Range: 25 to 65	1:1	25.48 ± 1.85	Fasting and postprandial plasma samples	H NMR and CG-MS	After 12 months: decrease in lactate, BCAAs, very low-density lipoprotein, low-density lipoprotein, N-acetyl- glycoproteins, and unsaturated lipid; increase in PCs and HDL
Luo P, 2016[11]	Retrospective cohort study	RYGB	N=35[$]	30.8 ± 3.3	49.8± 9.9	19:16	24.3 ± 2.3	Fasting serum samples	Untargeted UPLC-MS	After 6 months:77 altered metabolites. After 12 months: 88 altered metabolites (64 common with 6 months). Alterations (mainly decrease) were observed in: AA and their derivates, FFAs, ACs, BAs, LPCs, PCs and SPMs.
Magkos F, 2013[12]	Prospective cohort study	RYGB and LAGB	N=20	45.6 ± 6.7 (RYGB) 46.5 ± 8.8 (LAGB)	43 ± 7 (RYGB) 47 ± 14 (LAGB)	17:3	36.4 ± 5.0 (RYGB) 37.6 ± 7.3 (LAGB)	Plasma samples	MS/MS (AAs and ACs analysis)	Post-operative decrease levels of BCCAs, C3 and C5 acyl-carnitine in both surgeries (22 ± 7 weeks after RYGB and 16 ± 2 weeks after LAGB)
Mendonça Machado N, 2020[30]	Prospective cohort study	RYGB	N=28	Weight: 112.8 ± 15.6 Kg	Range: 18–60	28:0	Weight: 91.8 ± 12.2 Kg	Plasma samples	Untargeted GC-MS	After 3 months: decrease levels of dicarboxylic acids (aminomalonate, fumaric acid, malic acid, oxalic acid); enriched metabolic pathways included arginine and proline metabolism, urea and TCA cycles, gluconeogenesis, malate-aspartate shuttle, and carnitine synthesis.
Mika A, 2017[37]	Prospective cohort study	RYGB, OLGB and SG	N=16	41 ± 1.1	44 ± 3.1	NA	31 ± 1.1	Serum samples	H-NMR	After 6 months: significant decrease in the levels of all analyzed lipids - TGs, PLs (PCs, Pes and SPMs), total, free and esterified cholesterol, total and specific fatty acids. The most evident decrease was in 7-lathosterol.
Mutch DM, 2009[13]	Prospective cohort study	RYGB	N=14	46.2 ± 1.7	45.4±3.6	14:0	35.1 ± 1.7	Serum samples	Untargeted GC-MS and LC-MS	After 6 months: decrease levels of BCAAs, ceramide, TGs and saturated fatty acids; increase levels of specific SPMs, unsaturated fatty acids and PLs.

Table III Summary of studies comparing the metabolomic profiles of patients after bariatric surgery (cont.)

Narath SH, 2016[14]	Prospective cohort study	RYGB	N=44	43.9 ± 5.4 (SD)	46.8 ± 11.3 (SD)	29:15	30.0 ± 4.4 (SD)	Serum samples	Untargeted LC–HRMS	After 1 year: increase levels of TMAO indoxyl-sulfate, glycine and PC C40:7; decrease levels of BCAAs, choline, tyrosine, alanine and phenylalanine. V pattern (only decrease at short time) observed for Creatine, LysoPC C16:1 and c18:2, Ornithine, PC C34:3, PC C36:5, PC C36:6, Sarcosine, Tryptophan and Uracil. ∧ pattern (only increase at short time) observed for Acetylglycine, Arginine, Carnitine, Hydroxyisobutyric acid, Leucine Proline, Pantothenic acid, PC C38:6, Pyroglutamic acid and Threonine.
Oberbach A, 2011[34]	Prospective cohort study	SG	N=14	54.00 ± 8.05	41.9 ± 13.29 (SD)	9:5	36.31 ± 7.25 (SD)	Fasting serum samples	Targeted MS/MS	After 6 months: increase in glutamine; decrease in phosphatidylcholine diacyl C42:0 and C18:2 carnitine.
Ocaña-Wilhelmi L, 2020[32]	Prospective cohort study	SG	N=32	50.4 ± 7.2 (SD)	44.6 ±7.6 (SD)	25:7	38.1 ± 5.9 (SD)	Fasting serum samples	Targeted UPLC-MS/MS	After 6 montths: increase levels of polyamide metabolome: putrescine, acetyl-spermidine (N8-acetyl-spermidine, and N1,N8-diacetyl-spermidine), and N1,N12-diacetyl-spermine.
Palau-Rodriguez M, 2018[15]	Prospective cohort study	SG and RYGB	N=39	50.52 ± 8.37	Range: 19 to 59	27:12	36.42 ± 6.14	Fasting serum samples	Untargeted LC-MS	After 1, 3 and 6 months: alteration in the indoles and derivates, AAs, glycerolipids, glycerophospholipids and fatty acids were observed.
Ramos-Molina B, 2018[39]	Prospective cohort study	SG and BPD	N=37	47.9 ± 6.1 (SG) 41.8 ± 6.9 (BPD)	47.0 ± 6.7 (SG) 44.4 ± 8.2 (BPD)	22:15	36.5 ± 4.5 (SG) 39.7 ± 4.4 (BPD)	Fasting plasma samples	UPLC-MS (lipidomics)	After 6 months: BPD induced an overall decline in sphingolipids and PLss and an increase in BAs levels; SG induced an increase of sphingolipids and PLs, and no changes in BAs levels
Samczuk P, 2018[29]	Prospective cohort study	SG and RYGB	N=54	50.92 ± 7.33 (SG) 45.79 ± 5.5 (RYGB)	49.3 ± 8.7 (SG) 50.1 ± 9.3 (RYGB)	29:25	37.33 ± 7.3 (SG) 32.61 ± 5.5 (RYGB)	Fasting serum samples	Untargeted GC-MS and LC-MS	6 months after both procedures: decrease in PCs, LPCs, Pes and LPEs; increase in SPMs and choline. After RYGB only: increased levels of sulfate containing metabolites. After SG only, increased p-cresol.

Table III Summary of studies comparing the metabolomic profiles of patients after bariatric surgery (cont.)

Sarosiek K, 2016[33]	Prospective cohort study	SG and RYGB	N=15	48.74 ± 8.2 (SG with T2D) 43.54 ± 4.13 (SG and no T2D) 47.56 ± 6.61 (RYGB)	46.0 ± 12.84 (SG and T2D) 45.2 ± 12.24 (SG and noT2D) 44.4 ± 17.57 (RYGB)	12:3	NA	Fasting serum samples	Untargeted UPLC-MS/MS and GC-MS	After 28 days: increased levels of histidine, trans-urocanate, cis-urocanate, pyroglutamylvaline, heme, glutathione, and its precursors, pentose phosphate pathway intermediates, derivate pentose sugars and 3-phosphoglycerate. Decrease in ascarbate, various tocopherols and pyruvate.
Wijayatunga NN, 2018[16]	Prospective cohort study	RYGB	N=20	46.83 ± 6.21	37.25 ± 11.68	15:5	34.34 ±6.44	Fasting serum samples	Untargeted GC-MS and NMR	After 6 months: decrease on BCAAs, 2-aminobutyrate, butyrate, 2-HB, 3-HB. acetone, 2-methylglutarate, and 2-oxoisocaproate; increase in alanine, glycine, pyruvate, taurine and fatty acids (C10:0, C13:0, C14:0, C15:0, and C18:0).
Yao J, 2019[17]	Prospective cohort study	SG	N=11	39.1 ± 1.4	36.8 ± 9.1	8:3	31.5 ± 1.1	Plasma samples during insulin clamp and fasting	NA	After 6 months: decrease in BCAAs, phenylalanine, glycine and tyrosine levels (during fasting and insulin clamp); decrease in methionine and glutamate/glutamine concentrations (during insulin clamp).
Yoshida N, 2021[18]	Prospective cohort study	SG	N=15	40.8 ± 6.6	52.2 ± 6.5	12:3	33.5 ± 6.1	Fasting plasma samples	Untargeted MS	After 3 months, decrease in BCAAs, tryptophan, phenylalanine, tyrosine, choline, creatine, ornithine, hypoxanthine, 2-oxoisovaleric acid, 2-HB, N,N-dimethylglycine and uridine. Increase in citric acid, succinic acid, malic acid, arginine and glycine.

$ - Asian cohort. Abbreviations: 2-HB - 2-hydroxybutyrate; 3-HB - 3-Hydroxybutyrate; AAA - Aromatic amino acid; AA - Amino acid; AC - Acylcarnitine; BA - Bile acid; BCAA - Branched chain amino acids; BMI- Body mass index; BPD – Biliopancreatic diversion; CDCA - Chenodeoxycholic acid; DCA - Deoxycholic acid; DJB - Duodenal-jejunal bypass; FFA - Free fatty acids; G- - glycine amidated; GB - Gastric bypass; GC - Gas chromatography; Glu/Gln - glutamic acid/glutamine; H-NMR - Proton nuclear magnetic resonance; HCA - Hyocholic acid; HRMS - High resolution mass spectrometry; IR - Insuline Resistance; KynP - Kynurenine pathway; LAGB - Laparoscopic adjustable gastric band; LC- Liquid chromatography; LPC - Lysophosphatidylcholines; LPE - Lysophosphatidylethanolamines; MCA - Beta-muricholic acid; MS - Mass Spectrometry; NGT- Normal glucose tolerance; OLGB - Omega-loop gastric bypass; PC- Phosphatidylcholines; PE - Phosphatidylethanolamines; PL - Phospholipid; RYGB - Roux-en-Y Gastric Bypass; SG – Sleeve gastrectomy; SPM - Sphingomyelin; T2D – Type 2 diabetes; TCA - tricarboxylic acid; TDGM - tryptophan-derived gut microbial metabolites; TG - Triglycerides; UPLC - Ultra-Performance Liquid Chromatography;

Table IV Summary of studies comparing the metabolomic profiles of patients with different outcomes (T2D and weight loss)

FIRST AUTHOR AND YEAR	EXPERIMENTAL DESIGN	SURGICAL PROCEDURE	SUBJECTS	PRE-OPERATIVE BMI (KG/M²)	AGE AT SURGERY (YEARS)	FEMALE: MALE	POST-OPERATIVE BMI (KG/M²)	BIOLOGICAL SAMPLE	METABOLOMIC ANALYSIS	OUTCOMES AND MAIN FINDINGS
Abidi W, 2020[54]	Prospective cohort study	RYGB	Control group - patients with obesity (N=11)	47.7 ± 8.6	42.0 ± 11.1	1:1	Nadir BMI: 28.2 ± 4.8 Current BMI: 29.4 ± 4.6	Serum fasting samples	LC–MS	Outcomes: Patients with sustained weight loss at 5.0 ± 3.7 years (N=14) and patients with weight regain at 8.9 ± 3.0 (N=21) <u>Patients with sustained weigh loss:</u> Depletion in metabolites of fatty acids metabolism, including TGs, DGs and CEs; increased levels of beta-hydroxybutyrate and glycine <u>Patients with weigh regain</u> Decreased levels of metabolites related to serine, glycine and threonine pathway, phenylalanine metabolism, TCA cycle, and alanine and glutamate metabolism; higher levels of other AAs.
			Patients with obesity undergoing RYGB (N=35)	49.9 ± 7.3	47.9 ± 10.7	20:1	Nadir BMI: 28.9 ± 2.9 Current BMI: 37.9 ± 5.7			
Ahlin S, 2019[38]	Prospective cohort study	RYGB + BPD	Patients with obesity (N= 15), in which 13,3% with T2D (N= 2)	51.6 ± 9.6 (SD)	44.3 ± 8.3 (SD)	1:2	37.7 ± 7.4	Fasting plasma	Targeted UPLC-MS	Outcome: Patients with obesity and improved IR after a mean of 185.3 (72.9) days Increase in total BAs concentrations after RYGB and BPD.
Arora T, 2015[19]	Prospective cohort study	RYGB	Patients with obesity (N= 16), in which 87.5% with T2D (N= 14)	51.0±2.3	48.1±2.3	3:4	Reduction of 30.5 ± 4.4 %	Fasting plasma	GC-MS and UPLC-MS	Outcomes: patients with (N=7) or without (N=7) T2D remission at 2 years <u>Patients with T2D remission:</u> Before surgery, higher levels of metabolites from TCA cycle and pentose phosphate pathways, TG and PLs with LCFAs, and PEs. After 4 days, higher levels of aconitate, indole acetic acid and ribitol; reduction in most lipid species. After 42 days, higher levels of decanoic and octanoic acids; increase in most lipid species.
				47.2±1.6	48.8±3.5	7:0	Reduction = 32.0 ± 2.3 %			
Ha J, 2020[51]	Prospective cohort study	RYGB + SG	Patients with obesity[$] and T2D (N= 24)	39.6 ± 7.9 (SD)	45.4 ± 10.2 (SD)	17:7	28.8 ± 6.6	Fasting serum samples	Targeted LC–MS	Outcomes: patients with (N=14) or without (N=10) T2D remission at 1 year <u>Patients with T2D remission:</u> Higher baseline levels of L-DOPA and 3-HAA (sustained up to 3 months after surgery). At 1 year, no differences in the levels of L-DOPA and 3-HAA between both outcomes. No distinction between both surgery procedures.
				33.9 ± 4.5 (SD)			28.9 ± 5.6			

Table IV Summary of studies comparing the metabolomic profiles of patients with different outcomes (T2D and weight loss) (cont.)

Luo P, 2016[11]	Retrospective cohort study	RYGB	Patients with obesity[$] and T2D (N=35)	30.8 ± 3.3	49.8± 9.9 (6months after surgery)	19:16	24.3 ± 2.4 24.2 ± 2.3	Serum samples	Untargeted UPLC-MS	Outcomes: Patients with (N=23) or without (N=!2) T2D remission at 1 year Significant metabolic alterations related to FFA, acylcarnitines, AAs, BAs, and lipids species in both outcomes. Patients with T2D remission: Higher baseline levels of glycoursodeoxycholate sulfate, bilirubin and tryptophan. 6 months after RYGB: significant decrease in FFA 16:0, FFA 18:3, FFA 17:2 and hippuric acid.
Narath SH, 2016[14]	Prospective cohort study	RYGB	Patients with obesity (N= 44), in which 54,5% with T2D (N= 24)	43.9 ± 5.4 (SD)	46.8 ± 11.3 (SD)	29:15	At 1-3 weeks: 40.8 ± 5.2 (SD) At 1 year: 30 ± 4.4 (SD)	Serum samples	Untargeted LC–HRMS	Outcomes: Patients with high or low WL at 1 year (above or below the median of the WL) After 1 year, significant decreased levels of creatine, ornithine, arginine and valine in patients with high WL.
Samczuk P, 2018[45]	Prospective cohort study	SG	Patients with obesity and T2D (N=20)	49 ± 4.5 51 ± 8.3	47 ± 10.3 51 ± 11.4	4:7 4:5	37 ± 3.6 43 ± 7.6	Fasting serum	Untargeted GC-MS and LC-MS	Outcomes: Patients with quicker (N=11) or slower (N=9) remission of T2D Quicker responders: Lower baseline levels of most LPC and LPE. Postoperative significantly changed metabolites can be classified mainly as PC, LPC, PE, LPE, AAs, organic acids, sugars and metabolites related to gutmicrobiota metabolism.
Shantav. PC, 2018[44]	Prospective cohort study	RYGB	Control group - patients with obesity in a WLMP (N=11) Patients with obesity and T2D undergoing RYGB (n=11)	38.2 ± 4.6 41.3 ± 3.0	56.5 ± 11.4 50.5 ± 7.8	4:7 8:3	Decrease of 7.5 ± 1.2 Decrease of 8.9 ± 1.9	Plasma samples	Non-targeted GC/MS and targeted MS	Outcomes: Patients with weight loss and improved HOMA-IR after RYGB (N=11) and patients with similar weight loss after WLMP (N=11) Patients undergoing RYGB: Higher pre-operative levels of 2-HB. After 6 months, greater decline of 2-HB, 3-HB, acetiacetic acid, CMPF, and hypoxanthine. After 6 months, greater decline of BCAAs and significant correlation between improved HOMA-IR and decline of valine and BCAAs.
Tan HC, 2016[46]	Prospective cohort study	SG	Control group - patients with normal weight (N=10) Patients with obesity and IR undergoing SG (N=8)	Median: 23.2 (22.1–23.7) Median: 38.5 (37.0–40.4)	Median: 30.3 (25.1–36.1) Median: 29.5 (26.8–41.8)	0:10 7:3	NA Median: 30.5 (29.1–32.6)	Fasting plasma samples	Targeted GC-MS and LC-tandem MS	Outcome: patient with weight loss and improved IR resistance at 6 months after SG (N=8) Patients undergoing SG: After 6 months, reduction in total BCAAs, acylcarnitines (C3 and C4) and leucine oxidation.

Table IV Summary of studies comparing the metabolomic profiles of patients with different outcomes (T2D and weight loss) (cont.)

Kindel T, 2018[41]	Prospective cohort study	SG	Patients with obesity (N= 28), in which 21% with T2D	45.0 ± 6.8	45.4 ± 12.9	41:9	At 6 weeks: 40.7 ± 6.1 At 12 weeks: 38.9 ± 6.3	Fasting/postprandial serum samples	UPLC–MS	Outcome: Patients with significant weight loss SG induced an early (6 weeks after) and persistent (12 weeks after) increase in multiple BAs subtypes: -fasting HCA (total, unamidated and G- sub-fractions). - post-prandial BAs (total and G-), CDCA (total and G-), DCA (total and G), MCA (total and G-), HCA (total, unamidated and G-). Increased post-prandial total and G-CDCA was significantly correlated to the 6 weeks BMI loss; increased post-prandial G-HCA was significantly correlated to increased weight loss at both 6 and 12 weeks.
Kwon H, 2014[52]	Prospective cohort study	RYGB + DJB	Patients with obesity and T2D (N= 22)	30.8 ± 5.6 24.6 ± 3.1	39.8 ± 9.2 49.8 ± 6.9	1:1 7:3	27.2 ± 3.0 21.7 ± 2.2	Plasma samples	GC-MS and H-NMR	Outcomes: Patients with (N=10) or without (N=12) HbA1c improvement at 3 months After 1 week, 3-HB is higher in the improved group, whereas glucose and lipids (LDL, VLDL) are higher in the non-improved group. No distinction between both surgery procedures.
Kwon Y, 2020[53]	Prospective cohort study	SG	Patients with obesity (N= 27), in which 74% with T2D (N=20)	38.7 ± 5.2	42.1 ± 12.9	17:10	At 3 months: 31.5 ± 5.1 At 6 months: 27.9 ± 4.6	Fasting serum samples	Targeted LC-MS	Outcome: Patients with significant weight loss Before SG, lower levels of serotonin and serotonin/5-HTrp ratio, and higher levels of 5-HIAA, 5-HIAA/serotonin ratio and BCAA (++isoleucine), were significantly associated with greater WL% at 3 and 6 months after SG.
Kwon Y, 2021[23]	Prospective cohort study	SG	Patients with obesity and T2D (N=23)	38.9 ± 5.2	41.8 ± 13.1	17:6	31.4 ± 5.5	Fasting serum	Targeted LC–MS	Outcome: Patients with obesity and T2D, but improved IR at 3 months KynP metabolites levels were higher before surgery and decrased after SG. BCAAs and AAAs levels decreased after surgery. TDGMs decreased after surgery.
Li QR, 2018[50]	Prospective cohort study	RYGB	Patients with obesity (N=19), in which 47% with T2D (N=9)	41.5 ± 4.8 (no T2D) 43.1 ± 5.1 (T2D)	43 ± 13 (no T2D) 52 ± 9 (T2D)	NA	31.0 ± 5.1 (no T2D) 33.9 ± 7.5 (T2D)	Fasting and postprandial plasma	LC-MS/MS	Outcome: Patients with obesity and no T2D (N=10) and patients with obesity and T2D, but improved IR at 12 months (N=9) After RYGB, significant decrease in fasting plasma BCAAs was associated with improved IR.
Lopes T, 2016[47]	Prospective cohort study	RYGB	Patients with obesity and T2D (N=10)	32.38 ± 2.11	25 to 65	1:1	25.48 ± 1.85	Plasma samples	H-NMR	Outcome: Patients with T2D remission at 1 year After RYGB: lower levels of BCAAs. After RYGB in postprandial analysis: decreased VLDL, LDL, N-acetyl glycoproteins and unsaturated lipids; increased HDL and PC.

Table IV Summary of studies comparing the metabolomic profiles of patients with different outcomes (T2D and weight loss) (cont.)

*Yu H, 2015[48]	Retrospective cohort study	RYGB	Patients with obesity[$] and T2D (N=38)	32.8 ± 3.9	43.7 ± 12.8	1:1	24.9 ± 2.9	Fasting serum samples	Targeted UPLC	Outcomes: Patients with (N=26) or without (N=12) T2D remission at 2 years Patients with TD2 remission: Higher baseline levels of CDCA relative to the total BAs. Patients with noTD2 remission: 1 year after RYGB, total BAs were significantly lower.
				31.0 ± 3.5		7:5	24.9 ± 2.5			
*Zhao L, 2017[49]	Prospective cohort study	RYGB	Patients with obesity[$] and T2D (N=38)	32.8 ± 3.9	43.7 ± 12.8	1:1	24.4 ± 2.8	Fasting serum samples	Targeted UPLC-QTOFMS (free fatty acids)	Outcomes: Patients with (N=26) or without (N=12) T2D remission at 2 years Patients with T2D remission: Higher baseline ratios of stearic/palmitic acid (C18:0/C16:0) and eicosadienoic/linoleic acid (C20:2 n6/C18:2 n6).
				31.0 ± 3.5		7:5	24.8 ± 2.4			

* - Both studies had the same participants; $ - Asian cohort. Abbreviations: 2-HB - 2-hydroxybutyrate; 3-HAA - 3-hydroxyanthranilic acid; 3-HB - 3-Hydroxybutyrate; 5-HIAA - 5-hydroxyindoleacetic acid; 5-HTrp - 5-hydroxytryptophan; AAA - Aromatic amino acid; AA - Amino acid; BA - Bile acid; BCAA - Branched chain amino acids; BMI- Body mass index; BPD – Biliopancreatic diversion; CDCA - Chenodeoxycholic acid; CE - Cholesterol ester; CMPF - 3- carboxy-4-methyl-5-propyl-2-furanpropionic acid; DCA - Deoxycholic acid; DG - Diglyceride; DJB - Duodenal-jejunal bypass; FFA - Free fatty acids; G- - Glycine amidated; GC - Gas chromatography; H-NMR - Proton nuclear magnetic resonance; HCA - Hyocholic acid; HRMS - High resolution mass spectrometry; IR - Insuline Resistance; KynP - Kynurenine pathway; L-DOPA - L-dihydroxyphenylalanine; LC- Liquid chromatography; LCFA - Long-chain fatty acid; LDL - Low density lipoprotein; LPC - Lysophosphatidylcholines; LPE - Lysophosphatidylethanolamines; MCA - Beta-muricholic acid; MS - Mass Spectrometry; NGT- Normal glucose tolerance; PC- Phosphatidylcholines; PE - Phosphatidylethanolamines; PL - Phospholipid; RYGB - Roux-en-Y Gastric Bypass; SG – Sleeve gastrectomy; T2D – Type 2 Diabetes; TCA - Tricarboxylic acid; TDGM - Tryptophan-derived gut microbial metabolites; TG - Triglyceride; UPLC - Ultra-Performance Liquid Chromatography; VLDL - Very low density lipoprotein; WL - Weight loss; WLMP - Weight Loss Maintenance Program

Table V Summary of studies comparing the metabolomic profiles induced by different bariatric surgery interventions

FIRST AUTHOR AND YEAR	EXPERIMENTAL DESIGN	PARTICIPANTS	SURGERY GROUPS	AGE AT SURGERY (YEARS)	FEMALE: MALE	PRE-OPERATIVE BMI (KG/M^2)	TIME AFTER SURGERY	POST-OPERATIVE BMI (KG/M^2)	SAMPLE TYPE	METABOLOMIC METHOD	MAIN FINDINGS
LAGB vs RYGB											
Magkos F, 2013[12]	Prospective cohort study	Patients with obesity and NGT (N=20)	LAGB (n=10)	47 ± 14	9:1	46.5 ± 8.8	22 ± 7 weeks	37.6 ± 7.3	Fasting plasma	Targeted MS/MS (AAs and acylcarnitine)	BCAAs and acylcarnitines decreased after both surgery in similar proportions
			RYGB (n=10)	43 ± 7	8:2	45.6 ± 6.7	16 ± 2 weeks	36.4 ± 5.0			
Lips M, 2014[25]	Prospective cohort study	Patients with obesity and NGT (N = 74: n= 27 submitted to bariatric surgeries)	LAGB (n=11)	46.3 ± 1.9	11:0	43.1 ± 0.9	3 weeks	41.10 ± 0.85	Fasting plasma	Targeted UPLC–tandem MS (AAs analysis)	BCAAs levels decreased after both surgeries. BCAAs levels decreased was higher in patients submitted to RYGB. Glycine and Serine levels only increased after RYGB. AAAs levels only decreased after RYGB.
							3 months	39.02 ± 0.82			
			RYGB (n=16)	48.6 ± 1.6	16:0	44.2 ± 0.8	3 weeks	40.48 ± 0.85			
							3 months	36.63 ± 0.82			
Kayser BD, 2017[42]	Prospective cohort study	Patients with obesity and at least one severe obesity-related comorbidity (N=59)	LAGB (n=22)	34.5 ± 1.6	22:0	43.6 ± 0.7	1 month	40.4 ± 1.0	Fasting serum	Targeted LC-MS/MS (lipidomic)	The majority of lipids decreased equivalently between both surgical groups. Some PC and SM species decreased 1 month after surgery and remained suppressed 3 months after RYGB, while they either returned or tended to return to baseline values 3 months after LAGB.
							3 months	38.3 ± 1.0			
			RYGB (n=37)	37.3 ± 1.9	37:0	46.5 ± 1.0	1 month	41.1 ± 1.1			
							3 months	38.0 ± 1.2			
SG vs RYGB											
Jüllig M, 2014[31]	Prospective cohort study	Patients with obesity and T2D (N=15)	SG (n=7)	46.8 ± 2.9	6:1	42.1 ± 4.0	3 days	NA	Fasting plasma	Untargeted GC-MS	Histidine, proline, citrate and decanoic acid only decreased after RYGB. 2-hydroxybutyrate and 3-methyl-2-oxo-pentanoic acid only increase after SG.
			RYGB (n=8)	41.0 ± 3.1	8:0	42.1 ± 4.0	3 days	NA			

Table V Summary of studies comparing the metabolomic profiles induced by different bariatric surgery interventions (cont.)

Samczuk P, 2018[45]	Prospective cohort study	Patients with obesity and T2D (N=54)	SG (n=34)	49.3 ± 8.7	14:20	50.92 ± 7.33	1 month	45.90 ± 6.9	Fasting serum	Untargeted GC-MS and LC-MS	AAAs levels decrease induced by SG was higher. p-cresol was only increased after SG. Increased levels of sulfate containing metabolites were only observed after RYGB group. PC, LPC, PE and LPE decreased after both surgeries. Sphingomyelins and choline increased after both surgeries.
							6 months	37.33 ± 7.3			
			RYGB (n=20)	50.1 ± 9.3	15:5	45.79 ± 5.5	1 month	40.97 ± 5.15			
							6 months	32.61 ± 5.5			
Tan G, 2016[46]	Prospective cohort study	Patients with obesity [9] (N=22, 13 with T2D)	SG (n=12)	36.3± 8	13:9	38.8± 1.3	12 months	NA	Fasting serum	Targeted LC/MS (AAs and acylcarnitine)	BCAAs decreased after both surgery in similar proportions. AAAs levels were only significantly reduced after SG.
			RYGB (n=10)	45.6 ± 9.1			12 months	NA			
Gralka E, 2015[21]	Prospective cohort study	Patients with obesity (N=106)	SG (n=19)	43.6 ± 1.0	73:33	53.6 ± 10.0	3 months	46.0 ± 10.1	Fasting serum	Untargeted ^{1}H-NMR	Metabolomic effect of RYGB are higher compared with SG. BCCAs and AAAs decreased after both bariatric surgeries. Valine levels reduction was weaker after SG. Carboxylic acids anions levels were modified similarly by the different bariatric surgeries. TMAO only increased after SG. Dimethyl sulfates increase after surgery was higher in the distal RYGB.
							6 months	38.3 ±10.0			
							9 months	33.3 ± 6.1			
							12 months	31.7 ± 4.1			
			Proximal RYGB (n=27)			43.0 ± 5.8	3 months	36.7 ± 5.5			
							6 months	32.6 ± 5.4			
							9 months	30.0 ± 5.5			
							12 months	29.4±5.9			
			Distal RYGB (n=60)			46.3 ± 6.5	3 months	39.1 ± 5.5			
							6 months	35.2 ± 5.4			
							9 months	32.4 ± 5.2			
							12 months	30.7 ± 4.9			

Table V Summary of studies comparing the metabolomic profiles induced by different bariatric surgery interventions (cont.)

RYGB with short BPL vs RYGB with long BPL											
Jarak I, 2020[56]	Cross-seccional study	Patients with obesity and NGT (N=20)	RYGB with short BPL (n=9)	38 ± 3	8:1	41.8 ± 1.1	1.6 ± 0.3 years	28.1 ± 2.3	Fasting and post-prandial plasma	Untargeted ^{1}H-NMR	Fasting similar global profiles between groups Post-prandial levels of acetate were higher in patients submitted to RYGB with long BPL
			RYGB with long BPL (n=11)	43 ± 2	10:1	40.6 ± 0.9	1.5 ± 0.3 years	26.2 ± 2.8			
SG vs BPD											
Ramos-Molina B, 2018[39]	Prospective cohort study	Patients with obesity and NGT (N=37)	SG (n=25)	47.0 ± 6.7	16:9	47.9 ± 6.1	6 months	36.5 ± 4.5	Fasting plasma	Targeted UPLC-MS (lipidomic)	Lipidomic profiles induced by the two surgeries are different. BPD induced an overall decline in sphingolipids and phospholipids and an increase in bile acids levels. SG induced an increase of sphingolipids and phospholipids, and no changes in bile acids levels.
			BPD (n=12)	44.4 ± 8.2	6:6	51.8 ± 6.9	6 months	39.7 ± 4.4			
BPD-DS vs RYGB											
Ahlin S, 2019[38]	Prospective cohort study	Patients with obesity and NGT (N=15)	BPD (n=9)	44.7 ± 8.1	5:4	55.8 ± 9.5	183.7 ± 61.8	39.1 ± 8.5	Fasting plasma	Targeted UPLC-MS (bile acids analysis)	No differences in fasting bile acid levels were observed between the RYGB and BPD groups.
			RYGB (n=6)	43. 7± 9.4	0:6	45.3 ± 5.7	187.8 ± 93.6	35.5 ± 5.5			
BPD-DS vs SADI-S											
Pereira SS, 2020[55]	Cross-seccional study	Patients with obesity and NGT (N= 18)	BPD-DS (n=9)	36 ± 12	6:3	51.9 ± 4.0	1.6 ± 0.3 years	29.7 ± 4.3	Fasting and post-prandial plasma	Untargeted ^{1}H-NMR	Fasting similar global profiles between groups Post-prandial levels of BCAAs were higher in SADI-S group
			SADI-S (n=9)	43 ± 7	7:2	52.0 ± 3.7	1.5 ± 0.3 years	30.0 ± 3.6			

$ - Asian cohort. Abbreviations: AA - Amino Acids; AAA - Aromatic amino acids; BCCA – Branched chain amino acids; BMI- Body mass index; BPD – Biliopancreatic diversion; BPD-DS – Biliopancreatic diversion with duodenal switch; BPL – Biliopancreatic limb; GC - Gas chromatography; ^{1}H-NMR - Proton nuclear magnetic resonance; LAGB – Laparoscopic adjustable gastric band; LC- Liquid chromatography; MS - Mass Spectrometry; NA - Not available; NGT- Normal glucose tolerance; PC- Phosphatidylcholines, LPC - lysophosphatidylcholines, PE - phosphatidylethanolamines, SG – Sleeve gastrectomy; RYGB - Roux-en-Y Gastric Bypass; SADI-S - Single Anastomosis with duodeno-ileal bypass with sleeve gastrectomy; T2D – Type 2 diabetes; TMAO - Trimethylamine N-oxide; UPLC - Ultra-Performance Liquid Chromatography

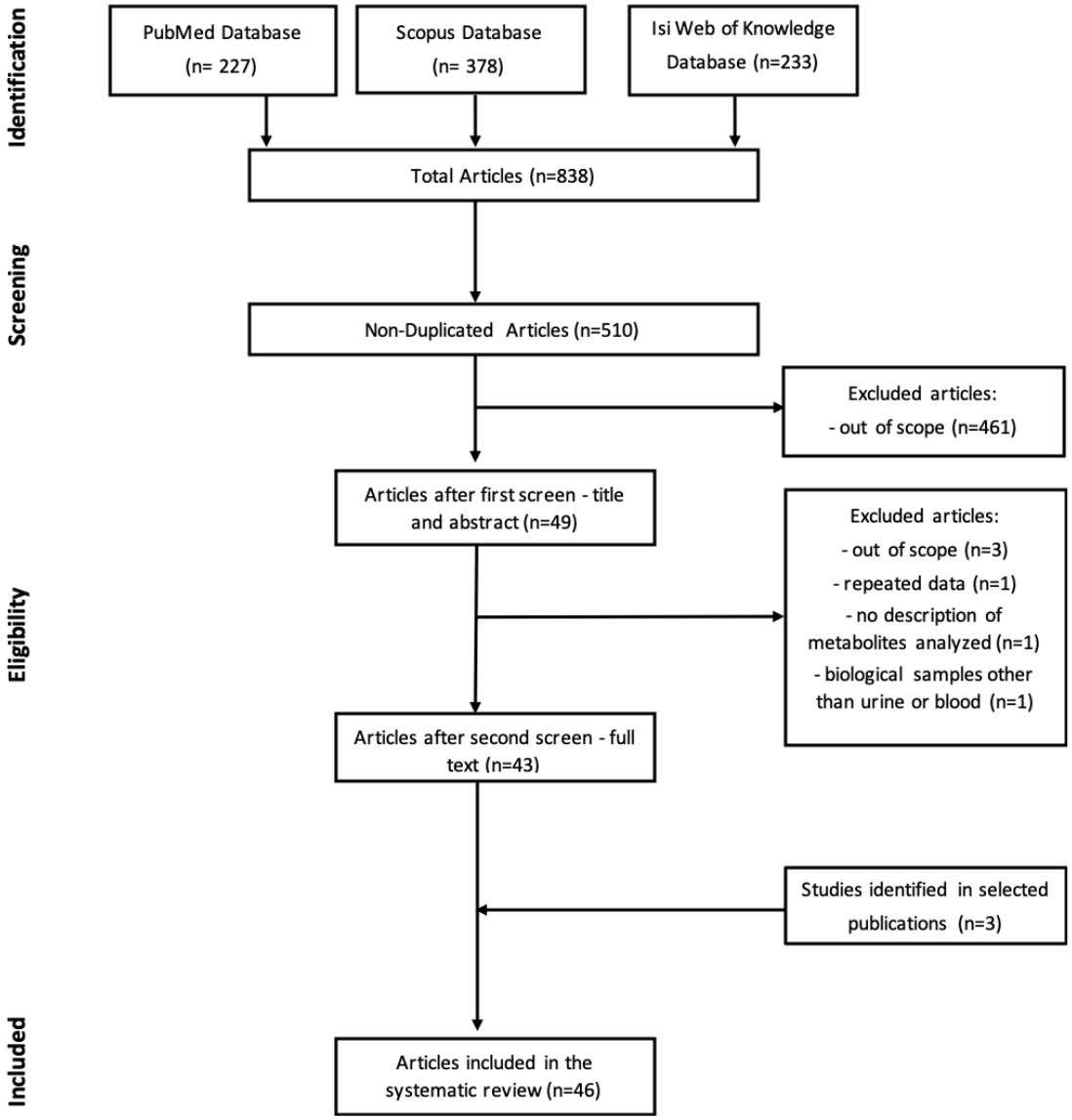
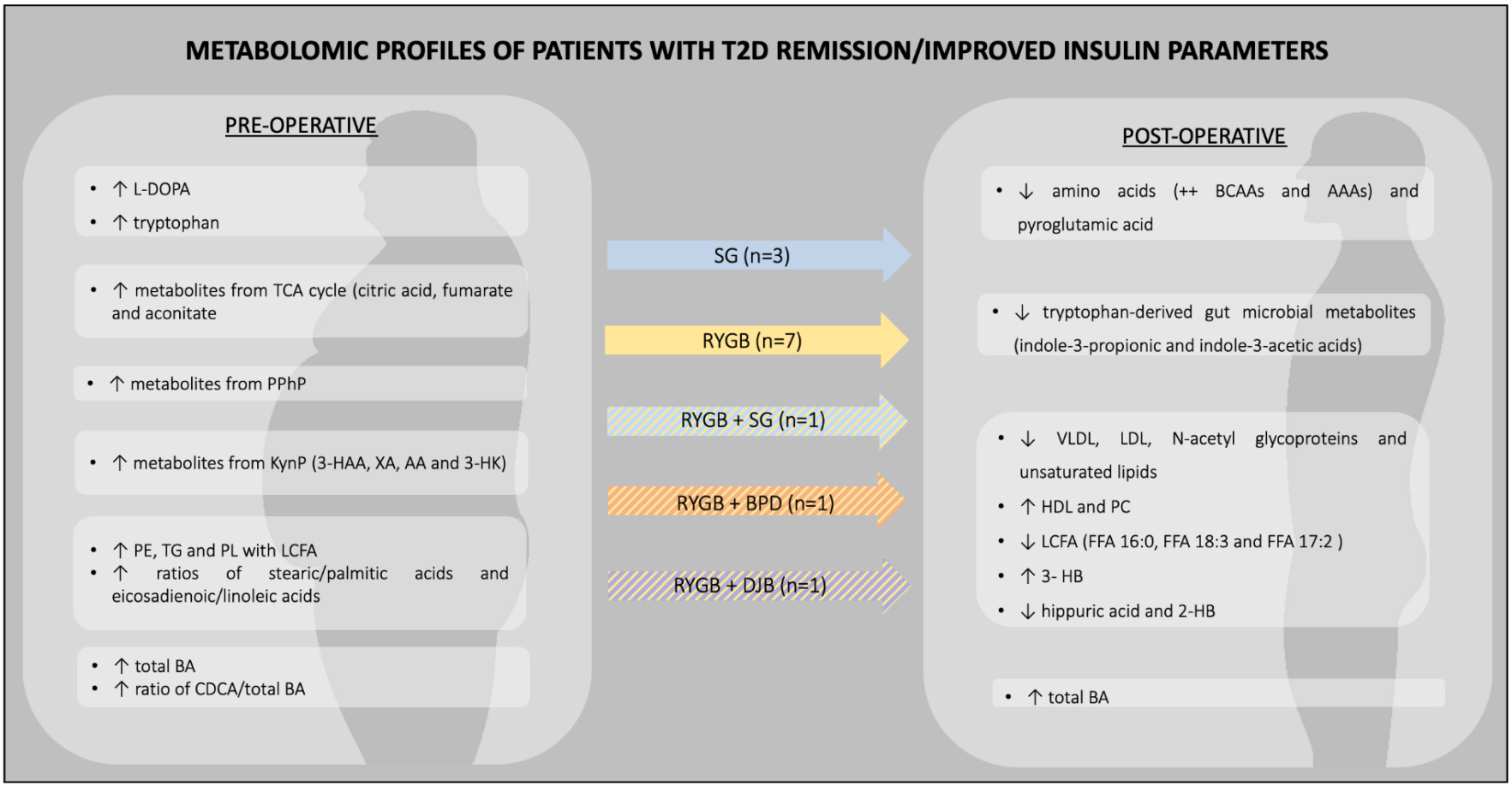
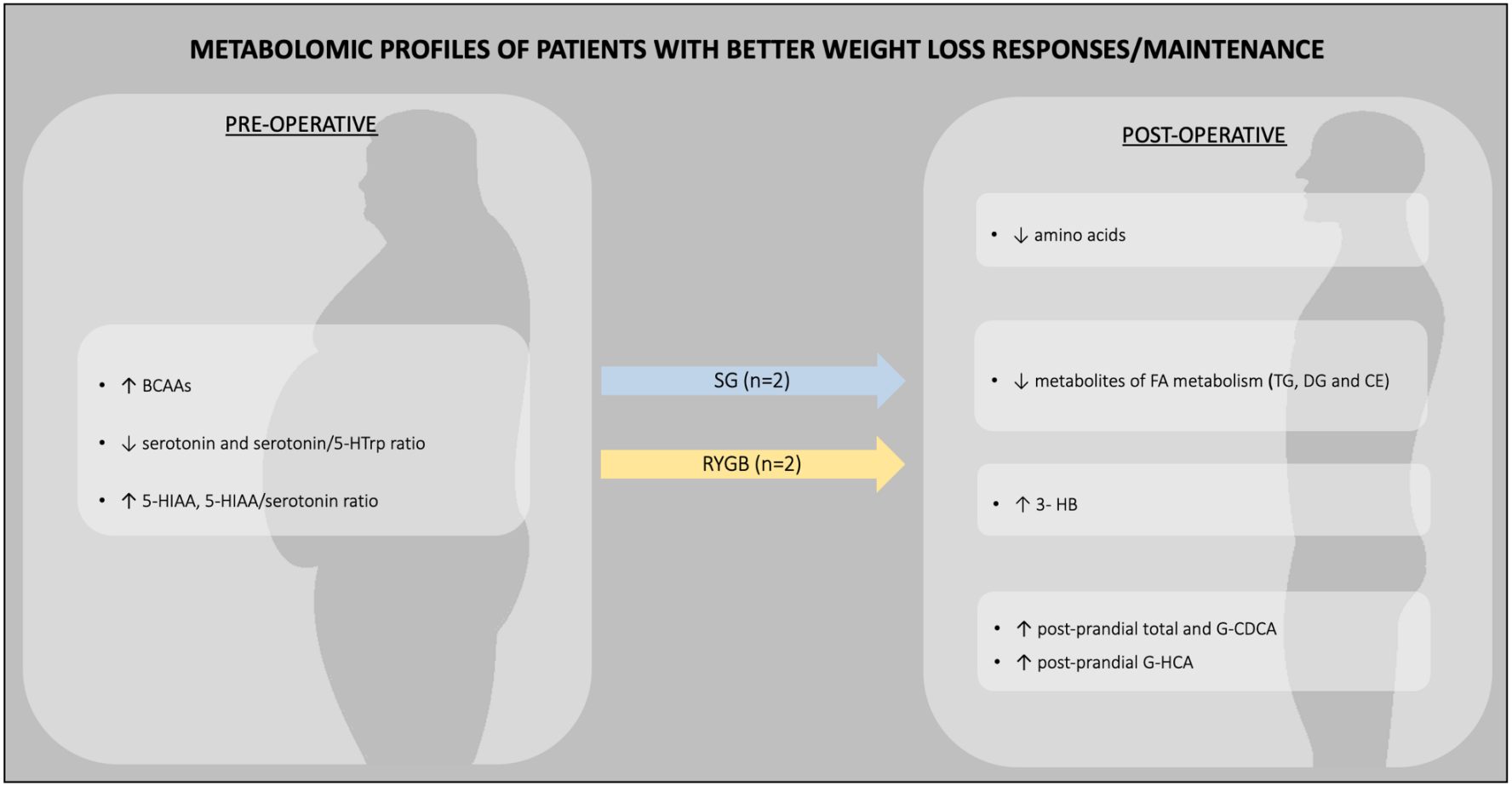


Figure 1 Flowchart of the search, eligibility criteria approaches and study inclusion for systematic review



Abbreviations: 2-HB - 2-hydroxybutyric; 3-HAA – 3-hydroxyanthranilic acid ; 3-HB - 3-hydroxybutyrate; 3-HK - 3-hydroxykynurenine; AA - anthranilic acid; AAA- Aromatic Amino Acid; BA - bile acids; BCAA – Branched Chain Amino Acid; ; BPD – Biliopancreatic diversion; CDCA - Chenodeoxycholic acid; DJB - Duodenal-jejunal bypass; FFA – Free Fatty Acid; HDL – High-density Lipoprotein; L-DOPA – L-dihydroxyphenylalanine; KynP – Kynurenine Pathway; LCFA - long-chain fatty acids; LDL – Low-density Lipoprotein; PC – Phosphatidylcholines; PE – Phosphatidylethanolamines; PL – phospholipids; PPh - pentose phosphate pathway; SG – Sleeve gastrectomy; RYGB - Roux-en-Y Gastric Bypass; T2D - Type 2 Diabetes Mellitus; TCA – Tricarboxylic Acid; TG – triglycerides; VLDL - Very-low-density Lipoprotein; XA - xanthurenic acid

Figure 2 Metabolomic profiles of patients with T2D remission/improved insulin parameters



Abbreviations: 3- HB - 3-hydroxybutyrate; 5-HIAA - 5-hydroxyindoleacetic acid; 5-HTrp - 5-hydroxytryptophan; BCAA – Branched Chain Amino Acid; CDCA – Chenodeoxycholic Acid; CE - cholesterol esters; DG - diaglycerols; F – fatty acids; G- - glycine amidated; HCA - hyocholic acid; SG – Sleeve gastrectomy; RYGB - Roux-en-Y Gastric Bypass; TG - triacylglycerols

Figure 3 Metabolomic profiles of patients with better weight loss responses/maintenance

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Supplementary File 1

DATABASE SEARCH

PUBMED

(“bariatric surger*” OR “bariatric intervention*” OR “obesity surger*” OR “bariatric procedur*”OR "gastric bypass" OR "biliopancreatic diversion" OR "RYGB" OR "sleeve gastrectomy" OR "BPD" OR "BPD-DS" OR "duodenal switch" OR “Single anastomosis duodeno–ileal bypass” OR “SADI-S” OR “SADI” OR “SIPS”) AND (metabolomic* OR metabonomic* OR metabolite* OR “metabolome”) NOT (“bronchopulmonary dysplasia” OR infant* OR child* OR “gestational” OR pregnanc* OR animal* OR “rat” OR “rats” OR “mice” OR “mouse”)

SCOPUS

TITLE-ABS-KEY (“bariatric surger*” OR “bariatric intervention*” OR “obesity surger*” OR “bariatric procedur*”OR "gastric bypass" OR "biliopancreatic diversion" OR "RYGB" OR "sleeve gastrectomy" OR "BPD" OR "BPD-DS" OR "duodenal switch" OR “Single anastomosis duodeno–ileal bypass” OR “SADI-S” OR “SADI” OR “SIPS”) AND TITLE-ABS-KEY (metabolomic* OR metabonomic* OR metabolite* OR “metabolome”) AND NOT TITLE-ABS-KEY (“bronchopulmonary dysplasia” OR “Borderline personality disorder” OR infant* OR child* OR “gestational” OR pregnanc* OR animal* OR “rat” OR “rats” OR “mice” OR “mouse”)

WEB OF SCIENCE

#1: ((TS=(“bariatric surger*” OR “bariatric intervention*” OR “obesity surger*” OR “bariatric procedur*”OR "gastric bypass" OR "biliopancreatic diversion" OR "RYGB" OR "sleeve gastrectomy" OR "BPD" OR "BPD-DS" OR "duodenal switch" OR “Single anastomosis duodeno–ileal bypass” OR “SADI-S” OR “SADI” OR “SIPS”)) NOT (TS=("bronchopulmonary dysplasia " OR “Borderline personality disorder” OR “infants” OR “pregnancy” OR “children” OR “animal” OR “gestational”))) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#2: ((TS=(metabolomic* OR metabonomic* OR metabolite* OR metabolome))) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#3 Final Search: #1 AND #2