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The impact of dietary, surgical, and pharmacological interventions on gut microbiota in individuals with diabetes mellitus: A systematic review

Patricia M. Bock [a,b,c,1,*], Andreza F. Martins [d,1], Rafaela Ramalho [d], Gabriela H. Telo [e], Gabriel Leivas [a], Clara K. Maraschin [a], Beatriz D. Schaan [a,c,f]

[a] Universidade Federal do Rio Grande do Sul, Faculty of Medicine, Department of Internal Medicine, Graduate Program in Medical Sciences: Endocrinology, Porto Alegre, Brazil
[b] Faculdades Integradas de Taquara, Taquara, Brazil
[c] National Institute of Science and Technology for Health Technology Assessment (IATS) – CNPq/Brazil, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
[d] Universidade Federal do Rio Grande do Sul, Department of Microbiology, Immunology, and Parasitology, Porto Alegre, Brazil
[e] Pontifícia Universidade Católica do Rio Grande do Sul, School of Medicine, Internal Medicine Division, Porto Alegre, Brazil
[f] Endocrine Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

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ABSTRACT

Aims: To conduct a systematic review assessing the association between dietary, surgical, and pharmacological interventions and changes in the gut microbiota of individuals with diabetes.
Methods: The MEDLINE, EMBASE, and Cochrane Library databases were searched focusing on the effects of dietary, bariatric surgery, and pharmacological interventions on gut microbiota in adults with diabetes. Studies were classified based on qualitative changes using a simple vote-counting method, evaluating reduction, no effect, or an increase in the gut microbiota outcomes.
Results: 6,004 studies were retained to review their titles and abstracts. A total of 149 full-text articles were reassessed, of which 49 were included in the final analysis. This review indicates that dietary, surgical, and pharmacological interventions increase or decrease bacterial populations from more than 60 families, genera, or species. In general, the interventions led to an increase in the bacterial population from phylum Firmicutes, mainly *Lactobacillus* species, compared to the gram-negative bacterial population from phylum Bacteroidetes.
Conclusions: The results of the included studies suggest that interventions aimed at reducing species related to uncontrolled diabetes and increasing species related to the healthy gut are potential adjuvants in treating diabetes; however, well-conducted interventional studies targeting gut microbiota are necessary.

1. Introduction

Human microbiota is a complex ecosystem of microorganisms that reside mainly in the gastrointestinal tract. It is typified by two dominant bacterial phyla, Bacteroidetes, composed mainly of gram-negative bacteria, and Firmicutes, composed mainly of gram-positive bacteria, which comprise approximately 90% of the gut microbiota and are responsible for metabolic and protective functions [1]. Modification of the gut microbiota profile (gut dysbiosis) has been implicated in the pathogenesis of diabetes [2] and prediabetes [3].

A comparison between the composition of fecal microbiota in adults with type 2 diabetes and that of adults without diabetes showed that the proportion of Firmicutes was higher in the adults without diabetes than in those with diabetes [4,5]. Interestingly, the ratio of Firmicutes to Bacteroidetes is not correlated with plasma glucose levels but is positively correlated with reduced glucose tolerance [6], indicating that the gut microbiome may be a new biomarker for the evaluation of diabetes mellitus progression and chronic low-grade inflammation associated with the disease [7].

Several researchers have aimed to change the composition of fecal microbiota in experimental diabetes. Among these interventions, sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB) surgery have been performed in rats with diabetes [8,9], in addition to the administration of drugs such as metformin, which induce a profound shift in the

* Corresponding author at: Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos, 2350. 90035-003 Porto Alegre, RS, Brazil.
E-mail addresses: patriciabock@faccat.br, pbock@hcpa.edu.br (P.M. Bock).
[1] Co-first authors: Patricia M. Bock and Andreza F. Martins (both authors contributed equally to the final version of this manuscript).

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composition of the gut microbiota [10,11]. Studies evaluating the manipulation of gut microbiota in human diabetes are difficult to design because the microbiota refers to an assemblage of living microorganisms, including many bacteria, whose composition can be affected by age, sex, host genetics, degree of glucose control, treatment (including medicines), diet, and other factors [12].

Recent systematic reviews of studies reporting the effect of dietary interventions on the gut microbiota in individuals with type 2 diabetes mellitus showed that changes in metabolic health were closely related to significant changes in gut microbiota composition [13], but dietary fiber was found to significantly improve the relative abundance of *Bifidobacterium* [14]. However, the included studies evaluated only dietary interventions and did not provide information on other types of interventions. Previous systematic reviews evaluating surgical or pharmacological interventions did not evaluate only individuals with diabetes, and although many studies have evaluated the effect of different interventions on the treatment of diabetes leading to changes in the gut microbiota, their results have not been summarized. Thus, this systematic review assessed the effectiveness of dietary, surgical, and pharmacological interventions in modulating gut microbiota in individuals with diabetes.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement was followed as a guideline for reporting this systematic review [15]. This systematic review was registered in the International Prospective Register for Systematic Review (PROSPERO) under the registration number CRD42017080071. Two questions were proposed:1) What is the impact of direct interventions in the gut microbiota on glycemic control in patients with diabetes? 2) What is the impact of glycemic control interventions on the gut microbiota in patients with diabetes? The first question was addressed in a published paper that evaluated glucose control and lipid profiles as outcomes [16]. The second question is the main objective of this study.

2.1. Eligibility criteria

The inclusion criteria were clinical trials or quasi-experiments focusing on the gut microbiota that evaluated glycemic control interventions, including dietary, bariatric surgery, and pharmacological agents, in adults with diabetes (≥18 years old). These interventions were selected because of their clinical importance in diabetes control.

We excluded studies based on the following criteria: (1) studies dealing with animals; (2) studies that did not evaluate gut microbiota; (3) studies in which patients did not have type 1 or type 2 diabetes; (4) studies with repeated reports; (5) studies in languages other than English, Spanish, or Portuguese; (6) conference abstracts; and (7) studies in which the gut microbiota was not evaluated using the 16S rRNA gene detection/sequencing technique.

2.2. Information sources and search strategy

In the article search process, we used the terms “diabetes mellitus” and “microbiota” in the selected databases. The MEDLINE, EMBASE, and Cochrane Library databases were searched using a combination of MeSH headings, keywords, and related entry terms to identify potentially relevant studies. The complete search strategy is presented in Electronic Supplementary Material (ESM) Text 1. The search process was completed in July 2020 and updated in September 2021. After combining the search results from the different databases, duplicates were removed. The records were managed using EndNote X7 (Clarivate Analytics, Philadelphia, PA, USA).

2.3. Study selection and data collection process

Two authors (PMB and RR) independently screened titles and abstracts to identify studies that met the inclusion criteria. Abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were retrieved for full-text evaluation by the same two authors. Any disagreements were resolved through consultation with a third author (GHT).

A standardized, pre-piloted form (Microsoft Excel) was used to extract data from the included studies for evidence preparation. The following information was extracted from the included studies: first author’s name, publication year, title, objective, intervention type, study design, sample size, follow-up duration, analysis method, and post-intervention microbiota outcomes. The primary outcome was a gut microbiota assessment (total bacterial abundance, richness, alpha and beta diversity, and bacterial taxonomic composition [phylum, genus, and species]). Relevant data were extracted by two authors (PMB and RR). Any disagreements were resolved through consultation with a third independent author (AFM).

2.4. Risk of bias

The risk of bias assessment was performed according to the revised Cochrane risk of bias tool (RoB2) (Cochrane, London, UK) [17]. Two authors (GL and CKM) independently assessed the RoB. Any disagreements were resolved by a third independent author (GHT).

2.5. Synthesis methods

Due to the diverse range of microorganisms analyzed and qualitative reports in original studies, a narrative synthesis is presented according to the “Synthesis without *meta*-analysis (SWiM) reporting guideline” [18].

The studies were grouped by intervention type as follows: (i) dietary (including prebiotics, probiotics, and synbiotics), (ii) surgical, and (iii) pharmacological.

We applied a simple vote-counting method to investigate whether different intervention types had any effect on the outcomes of interest. Studies were classified based on qualitative changes, whether they showed a reduction in the outcome measure, no effect, or an increase in the outcome measure following the interventions. The findings are summarized by microbiota effects in tables grouped by intervention type in the following structured format: evaluations of interventions *vs.* no intervention or evaluations of post-intervention *vs.* pre-intervention, when appropriate.

3. Results

3.1. Study selection

In an electronic search, we found 5,807 potentially relevant studies (2,890 from PubMed/MEDLINE, 150 from Cochrane, and 2,767 from Embase). In an updated search, 799 studies were identified. Following the elimination of duplicate and ineligible studies, 6,004 were retained to review their titles and abstracts. A total of 149 full-text articles retained at this stage were reassessed, of which 48 were included. A detailed flowchart illustrating the study selection process is presented in Fig. 1.

3.2. Study characteristics

The characteristics of the included studies are presented in Tables 1–3. Additional information about the study region, race, and sex of the participants is described in supplementary Table 1. All patients met the diagnostic criteria for type 2 diabetes, and no studies analyzing type 1 diabetes were found. Twenty-two studies evaluated dietary

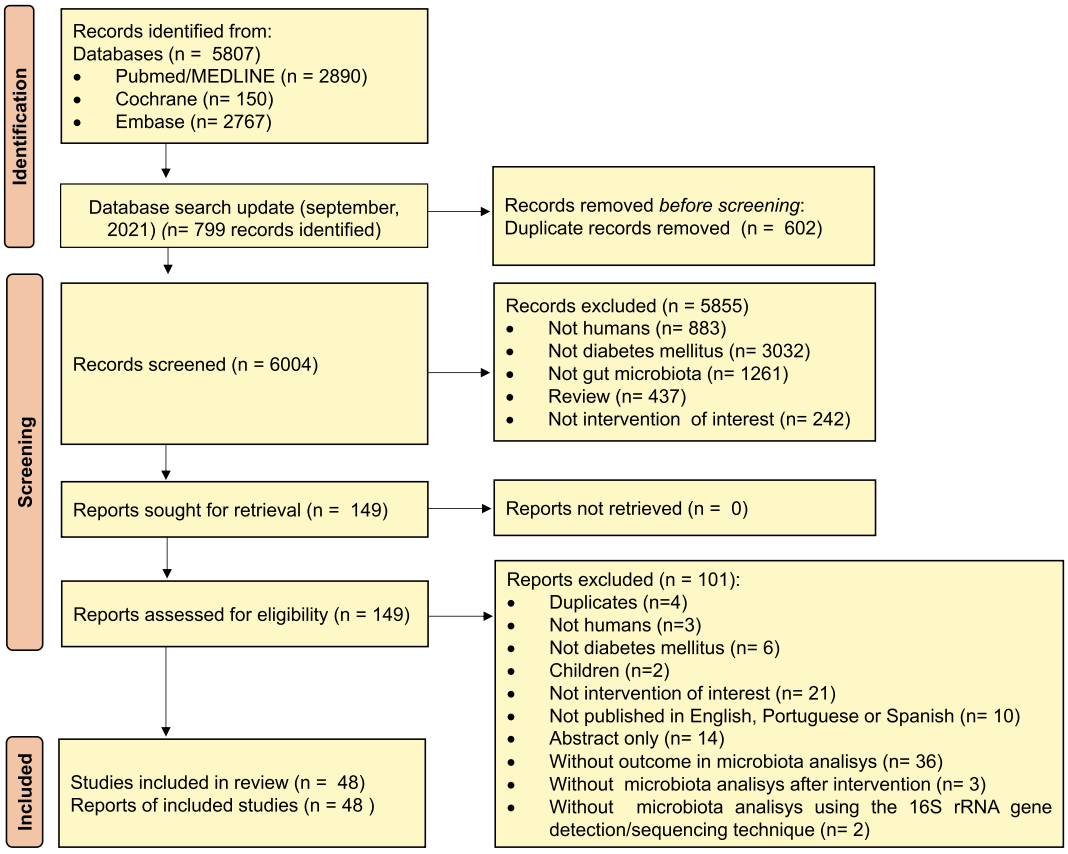

Fig. 1. Flowchart to illustrate how articles were identified and selected for inclusion in the systematic review.

interventions, 10 evaluated surgery, and 16 addressed pharmacological therapies. Distinct study designs were found, with randomized clinical trials (RCTs), non-RCTs, and quasi-experimental studies, and follow-up periods ranging from 3 weeks to 12 months.

Most studies have assessed fecal microbiota using the 16S rRNA gene detection/sequencing technique, targeting a different number of hypervariable regions (V1–V8). Different primers and techniques were used for DNA sequencing, including polymerase chain reaction (PCR), real-time quantitative PCR (RT-qPCR), pyrosequencing, and the Illumina sequencing MiSeq/HiSeq platform. Eight studies used metagenomic shotgun sequencing for microbiome analysis [19–21]. In one study, it was unclear whether the metagenomic or metataxonomic (16S rRNA amplicons) method was followed [22].

A total of 1,189 patients that involved trials with dietary interventions were included in the analysis (Table 1). One study used a sardine-enriched diet [23] and one used a macrobiotic diet [24]. Four studies used prebiotics [25–28], three used probiotics [29–31], one used probiotics plus berberine (a natural plant alkaloid extracted from *Berberis aristata* and *Coptis chinensis*) [32], and three used synbiotics [33–35]. One study involved the use of a strict vegetarian diet [36]; one, an Okinawan-based Nordic (O-BN) diet [37]; one, a Mediterranean diet [38]; one, a reduced-energy diet with a dietary portfolio comprising high-fiber, polyphenol-rich, and vegetable-protein functional foods [39]; one, a low-calorie formula diet [40]; one, a low-fat diet [41]; and one, a dietary fiber supplement (plantago seed and ispaghula husk) [42]; one, an almond-based low carbohydrate diet [43], and a dietary reduction of branched-chain amino acids [22].

In total, 170 patients involving surgical intervention trials were included in the analysis (Table 2). Four studies performed RYGB surgery [44–47], one performed duodenal–jejunal bypass with minimal gastric resection [48], one performed nonsurgical duodenal–jejunal bypass liner (DJBL) [49], three compared sleeve gastrectomy (SG) and RYGB surgery [19,50,51], and one compared laparoscopic adjustable gastric banding (AGB) and RYGB surgery [52]. The only study that evaluated exercise training [53] was excluded because the gut microbiota was not analyzed in stool samples using any method targeting the 16S rDNA gene.

Regarding pharmacological interventions, 861 patients were included in the analysis (Table 3). Four studies used metformin as a therapy [20,54–56], one used *Scutellaria baicalensis* (an Asian traditional herbal medicine) combined with metformin [57], two used glucagon-like peptide-1 (GLP-1) receptor agonists [58,59], two used transglucosidase [60,61], one compared acarbose and glipizide [21], one compared metformin and liraglutide [62], one compared traditional Chinese medicine and metformin [63], one compared dapagliflozin and gliclazide [64], one compared liraglutide and sitagliptin [65], and two evaluated acarbose [66,67].

3.3. Risk of bias assessment

The risk of bias in the included trials as per the RoB2 evaluation tool was overall low in 22.9% of the studies, indicating some concerns in 37.5% and high risk in 39.6% of the studies. Most studies had a low risk of bias due to deviations from intended interventions (81.2%), missing outcome data (87.5%), and measurement of the outcomes (85.4%). In the domain of bias arising from the randomization processes, 35.4% of the studies had some cause of concern. In the selection of the reported results, 6.2% of the studies were judged to have a high risk of bias, mostly because of an incomplete or no study protocol (ESM Fig. 1; ESM Fig. 2).

3.4. Results of syntheses of studies with dietary interventions

This review included 22 studies that evaluated the changes in the gut

Table 1
Characteristics of studies with dietary interventions.

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
Kim et al (2013) [36]	Quasi-experimental study	Intervention: Strict vegetarian diet	1 month	Intervention: 6	Taxonomic composition (relative abundance), α-diversity, β-diversity	Phylum: ↑ Bacteroidetes, ↓ Firmicutes	16S rRNA (V1-V2 region), 454 FLX pyrosequencing
Sheth et al (2015) [33]	Randomized control trial	Placebo: not informed Intervention: 1 gm of freeze dried synbiotic product (2 species of *Lactobacillus*, *Bifidobacterium* each, one species of *Streptococcus*, one species of yeast along with 300 mg Fructo oligosaccharide) daily to be taken along with meals	45 days	Placebo: 10 Intervention: 25	Abundance of *Bifidobacterium, Lactobacillus and Enterococcus*	Family/Genus/Specie: ↑ *Bifidobacterium, Lactobacillus*	16S rRNA (V6-V8 region), PCR
Xu et al (2015) [27]	Randomized, double-blinded, placebo-controlled clinical trial	Placebo: decoction of pregelatinized starch, caramel color, lemon yellow and 4.5% of the herbal decoction Intervention: Chinese herbal formula, a decoction of Gegen (Radix Puerariae), Huangqin (Radix Scutellariae), Huanglian (Rhizoma Coptidis) and Gancao (Honey-fried Licorice Root* 150 ml of the decoction two times daily)	12 weeks	Placebo: 41 Intervention: 44	Taxonomic composition (total and relative abundance) α-diversity, β-diversity Quantification: *F. prausnitzii*	↑ α-diversity, Diversity changed after intervention (β-diversity) Family/Genus/Specie: ↑ *Lachnospiraceae, Gemmiger, Bifidobacterium, Faecalibacterium,F. prausnitzii* ↓ *Alistipes, Parabacteroides, Pseudobutyrivibrio*	16S rRNA (V3 region) pyrosequencing (platform not mentioned).RT-qPCR
Balfegó et al (2016) [23]	Multicenter randomized, nutritional pilot trial	Placebo: standard diet Intervention: sardine-enriched diet (standard diet enriched with 100 g of sardines 5 days a week)	6 months	Placebo: 19 Intervention: 16	Abundance of Firmicutes (F), Bacteroidetes (B), *E. rectale-C.coccoides*, *Bacteroides-Prevotella*, *F. prausnitzii, E.coli*, F/B	↓ F/B Phylum: ↓ Firmicutes Family/Genus/Specie: ↑ *Escherichia coli*	16S rRNA, qPCR
Candela et al (2016) [24]	Controlled open-label trial	Placebo: control diet recommended by Italian professional societies for T2D treatment Intervention: fibre-rich macrobiotic diet(Ma-Pi 2)	21 days	Placebo: 19 Intervention: 21	Taxonomic composition (relative abundance), α-diversity, β-diversity	Diversity changed after intervention (β-diversity) Family/Genus/Specie: ↑ *Faecalibacterium, Bacteroides, Akkermansia* ↓ *Ruminococcus*	16S rRNA (V3-V4 region), Illumina Miseq
Pedersen et al (2016) [26]	Randomized, double-blind, placebo-controlled parallel study	Placebo: maltodextrin Intervention: galacto-oligosaccharide mixture* Both were supplied as dry white powders in sachets each containing 5·5 g and were readily mixed into beverages or food	12 weeks	Placebo: 15 Intervention: 14	Taxonomic composition (total and relative abundance), Abundance of *Bifidobacterium, C. coccoides, C.leptum, Enterobacteriaceae, Lactobacillus, Roseburia,* α-diversity, β-diversity	Not significant changes were reported	16S rRNA (V4-V5 region), 454 FLX pyrosequencing RT-qPCR
Gonai et al (2017) [25]	Double-blind, controlled trial	Placebo: 10 g/day of maltodextrin syrup Intervention: 10 g/day of galacto-oligosaccharide syrup	4 weeks	Placebo: 27 Intervention: 28	Taxonomic composition (total and relative abundance), α-diversity	↓ Total number OTUs, ↓ α-diversity Family/genus/Specie: ↑ *Bifidobacteriaceae* ↓ *Lachnospiraceae, Ruminococcaceae, Peptostreptococcaceae, Erysipelotrichaceae, Porphyromonadaceae*	16S rRNA (V1-V2 region), Illumina Miseq
Mobini et al (2017) [29]	Double-blind, randomized, placebo controlled trial	Placebo: powder with a mild sweet taste administered in a stick pack Intervention: stick pack with powder containing 10^8 or 10^{10} colony forming units of *L. reuteri* DSM 17,938* one dose per day in the morning before breakfast	12 weeks	Placebo: 15 Intervention: low dose 16, high dose 15	Taxonomic composition (relative abundance), α-diversity, β-diversity	Not significant changes were reported	16S rRNA (V4 region), Illumina Miseq
Sato et al (2017) [30]	Interventional randomized control study	Placebo: 80- ml bottle of non fermented milk at breakfast Intervention: 80-ml bottle of *L. casei* strain *Shirota* fermented milk at breakfast (4×10^{10} cells)	16 weeks	Placebo: 34 Intervention: 34	Abundance of *Bifidobacterium, Prevotella, Enterobacteriaceae, Enterococcus, Streptococcus, Staphylococcus, Pseudomonas, C. coccoides, C. leptum, B.*	Family/Genus/Specie:↑ *Enterococcus*, *Lactobacillus reuteri Lactobacillus gasseri*	16S rRNA, 23S rRNA, RT-qPCR

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Table 1 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
					fragilis, Atopobium cluster, Akkermansia muciniphila, C. difficile, C. perfringens, L. gasseri, L. brevis, L. casei, L. fermentum, L. fructiborans, L. plantarum, L. reuteri, L. ruminis, L. sakei, L.casei strain Shirota		
Huang et al (2018) [37]	Quasi-experimental study	Intervention: Okinawan-based Nordic diet (high proportion of vegetables and legumes, rich in omega-3 fats, moderate intake of fish products and alcohol, low consumption of dairy and meat products, glycaemic index and gluten content are low, salt intake is restricted)	12 weeks	Intervention: 28	*Enterobacteriaceae* (abundance and diversity)	No significant changes were reported	16S rRNA, RT-qPCR, T-RFLP
Frost et al (2019) [40]	Quasi-experimental study	Intervention: low-calorie formula diet (Sachets containing 96 g carbohydrates, 70 g proteins and 15 g fat per day, providing 800 kcal energy)	6 weeks	Intervention: 12	Taxonomic composition (relative abundance), α-diversity, β-diversity	Diversity changed after intervention (β-diversity) Family/genus/Specie:↑ *Pseudoflavonifractor, Odoribacter, Eggerthella* ↓ *Streptococcus, Collinsella, Roseburia, Lachnospiraceae incertae sedis, Veillonella*	16S rRNA (V1-V2 region), Illumina Miseq
Horvath et al (2019) [34]	Randomized, double-blind, placebo-controlled pilot study	Placebo: matrix without bacteriaIntervention: multispecies probiotic and prebiotic (approximately 1.5×10^{10} CFU in matrix) sachets to dissolve every morning in 250 ml of water and drank after 10 min of activation time	6 months	Placebo: 20 Intervention: 21	Taxonomic composition (relative abundance), α-diversity, β-diversity	No significant changes were reported	16S rRNA (V1-V2 region), Illumina Miseq
Karusheva et al (2019) [22]	Randomized, placebo-controlled, double-blinded, crossover trial	Placebo: in weeks 2 and 4 ~ 60% of the protein intake was covered by an amino acid powder containing all amino acids Intervention: Dietary reduction of branched-chain amino acids (in weeks 2 and 4 ~ 60% of the protein intake was covered by an amino acid powder lacking branched-chain amino acids). *During weeks 1 and 3, the protein intake was covered by commercially available regular foods.	4 weeks	Placebo: 12 Intervention: 12	Taxonomic composition (relative abundance)	Phylum:↑ Bacteroidetes, ↓ Firmicutes	Next-Generation sequencing (platform is not mentioned)
Lee SE et al 2019 [42]	Single center, open-label, single-arm pilot trial	Intervention: dietary fiber supplement (3.9 g of plantago seed and 0.13 g of ispaghula husk in one package, three packages per day)	4 weeks	Intervention: 10	Taxonomic composition (relative abundance)	Family/Genus/Specie: ↓ *Coriobacteriaceae, Blautia, Eubacterium, Blautia exlerae, Bifidobacterium longum, Enterobacter soli*	16S rRNA, pyrosequencing (platform is not mentioned).
Medina-Vera et al (2019) [39]	Placebo-controlled, randomized, double-blind study	Placebo: 8 g of calcium caseinate and 15 g of maltodextrin Intervention: dietary portfolio (14 g of dehydratednopal, 4 g of chia seeds, 30 g of soy protein and 4 g of inulin)* both were given in packets in dehydrated form ready to be dissolved in water.	3 months	Placebo: 25 Intervention: 28	Taxonomic composition (total and relative abundance), α-diversity	↑ α-diversity Family/Genus/ Specie: ↑ *Faecalibacterium prausnitzii, Akkermansia muciniphila, Bifidobacterium longum, Bacteroides fragilis* ↓ *Prevotella copri*	16S rRNA (V3-V4 region), Illumina Miseq
Birkeland et al (2020) [28]	Randomised, placebo controlled and double-blindcrossover trial	Placebo: maltodextrin Intervention: inulin-type fructans (a mixture of oligofructose and inulin, 16 g per day, powdered in	6 weeks	Placebo and Intervention: 25	Taxonomic composition (total and relative abundance), α-diversity	↑Total number OTUs Phylum: ↑ Bacteroidetes Family/Genus/ Specie:↑ *Faecalibacterium prausnitzii, Bacteroides ovatus, Bifidobacterium adolescentis* ↓	16S rRNA (V4 region), Illumina Miseq

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Table 1 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
		packages of 8 g, added to food or drinks)				*Ruminococcaceae, Lachnospiraceae, Erysipelotrichaceae, Ruminococcus*	
Liu et al (2020) [41]	Quasi-experimental study	Intervention: low fat diet based on the Mediterranean diet model, combined with local dietary habits, developed by the nutritional specialist and varied from person to person	6 months	Intervention: 16	Taxonomic composition (total abundance)	Family/Genus/Specie: ↑ *Butyricimonas*	16S rRNA (V3-V4 region), Illumina Miseq
Palacios et al (2020) [31]	Randomised, double blind, placebo-controlled clinical trial	Placebo: placebo capsules Intervention: multi-strain probiotic (*Lactobacillus plantarum,Lactobacillus bulgaricus, Lactobacillus gasseri, Bifidobacterium breve Bifidobacterium animalis sbsp. Lactis,Bifidobacterium bifidum, Streptococcus thermophilu, Saccharomyces boulardii*)	12 weeks	Placebo: 30 Intervention: 30	Taxonomic composition (total and relative abundance), β-diversity	Family/Genus/Specie: ↑ *Bifidobacterium breve, Bacteroides caccae, Bacteroidales bacterium*	Metagenomic shotgun, Illumina HiSeqX
Ren et al (2020) [43]	Randomized Controlled Trial	Intervention 1: low fat diet based on the diabetes dietary guideline Intervention 2: almond-based lowcarbohydrate diet (56 g/day almond which replacedfoods/meal rich in carbohydrate)	3 months	Intervention 1: 23 Intervention 2: 22	Taxonomic composition (total and relative abundance), α-diversity, β-diversity	Intervention 1 ↑α-diversity, Phylum: ↑Firmicutes Family/Genus/Specie: ↓*Roseburia, Ruminococcus* Intervention 2 ↑ α-diversity, Phylum: ↓Bacteroidetes Family/Genus/Specie: ↑*Roseburia, Eubacterium* ↓*Bacteroides*	16S rRNA (V3-V4 region), Illumina HiSeq2500
Zhang et al (2020) [32]	Randomized, double-blind, placebo controlled clinical trial	Participants were drug naive for glycaemic control, and were given an oral broad-spectrum antibiotic for 7 days during the run-in period. Placebo: placebo pills. Intervention 1: Berberin Intervention 2: Berberin plus probiotics Intervention 3: probiotics	12 weeks	Placebo: 96 Intervention 1: 85 Intervention 2: 102 Intervention 3: 98	Taxonomic composition (total and relative abundance), α-diversity	Intervention 1: ↑ α-diversity, Diversity changed after intervention (β-diversity) Family/Genus/Specie: ↑*Alistipes*, *Anaerostipes*, *caccae*, *Bacteroides clarus*, *Bacteroides coprocola*, *Bacteroides dorei*, *Bacteroides dorei/vulgatus*, *Bacteroides finegoldii*, *Bacteroides fluxus*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides salanitronis*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides xylanisolvens*, *Capnocytophaga* sp. *Citrobacter*, *Citrobacter koseri*, *Clostridiales bacterium*, *Clostridium*, *Clostridium bolteae*, *Clostridium difficile*, *Clostridium ramosum*, *Coprobacillus*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter hormaechei/cloacae*, *Erysipelotrichaceae bacterium*, *Escherichia coli*, *Eubacterium hallii*, *Fusobacterium ulcerans*, *Fusobacterium varium*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, Klebsiella *pneumoniae/ variicola group*, *Lachnospiraceae bacterium*, *Odoribacter splanchnicus*, *Parabacteroides distasonis*, *Paraprevotella xylaniphila*, *Parasutterella excrementihominis*, *Ruminococcus gnavus*,	Metagenomic shotgun, BIGESEQ-500

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Table 1 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
						Ruminococcus torques, *Solobacterium moorei*, *Streptococcus*, *Streptococcus mitis*, *Veillonella atypica* ↓*Alistipes shahii*, *Anaerotruncus colihominis*, *Bacteroides caccae*, *Bacteroides coprophilus*, *Bacteroides plebeius*, *Clostridium methylpentosum*, *Clostridium perfringens*, *Clostridium*, *Clostridium symbiosum*, *Dialister invisus*, *Eggerthella lenta*, *Eubacterium dolichum*,*Fusobacterium mortiferum*, *Haemophilus parainfluenzae*, *Holdemania filiformis*, *Oribacterium sinus*, *Prevotella bivia*, *Pseudoflavonifractor capillosus*, *Roseburia inulinivorans*, *Ruminococcaceae bacterium*, *Streptococcus anginosus*, *Streptococcus gordonii*, *Streptococcus infantis*, *Streptococcus parasanguinis*, *Streptococcus salivarius*, *Streptococcus*, *Streptococcus thermophilus*, *Streptococcus vestibularis*, *Veillonella*, *Veillonella dispar*, *Veillonella parvula* Intervention 2: ↑ α-diversity, Diversity changed after intervention (β-diversity) Family/Genus/ Specie: ↑ *Bacteroides fluxus Bacteroides salanitronis, Capnocytophaga,Clostridiales bacterium,Eubacterium hallii*, *Parabacteroides distasonis*, *Paraprevotella xylaniphila*, *Streptococcus*, *Veillonella atypica* ↓*Alistipes*, *Anaerostipes caccae*, *Bacteroides clarus*, *Bacteroides coprocola*, *Bacteroides dorei*, *Bacteroides dorei/vulgatus*, *Bacteroides finegoldii*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides xylanisolvens*, *Citrobacter*, *Citrobacter koseri*, *Clostridium*, *Clostridium bolteae*, *Clostridium difficile*, *Clostridium ramosum*, *Coprobacillus*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter hormaechei/cloacae*, *Erysipelotrichaceae bacterium*, *Escherichia coli*, *Fusobacterium ulcerans*, *Fusobacterium varium*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Klebsiella pneumoniae/ variicola group*, *Lachnospiraceae bacterium*, *Odoribacter splanchnicus*, *Parasutterella excrementihominis*,	

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Table 1 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
						Ruminococcus gnavus, *Ruminococcus torques*, *Solobacterium moorei*, *Streptococcus mitis* *Intervention 3: Family/ Genus/Specie: ↑Alistipes shahii, Alistipes, Anaerostipes caccae,Anaerotruncus colihominis, Bacteroides caccae, Bacteroides clarus, Bacteroides coprocola, Bacteroides coprophilus, Bacteroides dorei, Bacteroides dorei/vulgatus, Bacteroides finegoldii, Bacteroides fluxus, Bacteroides fragilis, Bacteroides ovatus, Bacteroides plebeius, Bacteroides salanitronis, Bacteroides stercoris, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides xylanisolvens, Capnocytophaga,Citrobacter koseri, Citrobacter, Clostridiales bacterium, Clostridium, Clostridium bolteae, Clostridium difficile, Clostridium methylpentosum, Clostridium perfringens, Clostridium ramosum, Clostridium symbiosum, Coprobacillus, Dialister invisus, Eggerthella lenta, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter hormaechei/ cloacae, Erysipelotrichaceae bacterium, Escherichia coli, Eubacterium dolichum, Eubacterium hallii, Fusobacterium mortiferum, Fusobacterium ulcerans, Fusobacterium varium, Haemophilus parainfluenzae, Holdemania filiformis, Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella pneumoniae/ variicola group, Lachnospiraceae bacterium, Odoribacter splanchnicus, Oribacterium sinus, Parabacteroides distasonis, Paraprevotella xylaniphila, Parasutterella excrementihominis, Prevotella bivia, Pseudoflavonifractor capillosus, Roseburia inulinivorans, Ruminococcaceae bacterium, Ruminococcus gnavus, Ruminococcus torques, Solobacterium moorei, Streptococcus anginosus, Streptococcus gordonii, Streptococcus infantis, Streptococcus mitis, Streptococcus parasanguinis, Streptococcus salivarius, Streptococcus, Streptococcus thermophilus, Streptococcus vestibularis, Veillonella atypica, Veillonella dispar, Veillonella parvula, Veillonella ↓Actinomyces*	

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Table 1 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
						viscosus, Akkermansia muciniphila, Alistipes putredinis, Bacteroides eggerthii, Bacteroides intestinalis, Bacteroides pectinophilus, Bifidobacterium adolescentis, Bifidobacterium catenulatum, Bifidobacterium longum, Bilophila wadsworthia, Blautia hansenii, Butyrivibrio crossotus, Clostridium, Clostridium bartlettii, Clostridium leptum, Clostridium saccharolyticum, Clostridium scindens, Collinsella aerofaciens, Coprococcus catus, Coprococcus comes, Coprococcus eutactus, Dorea formicigenerans, Dorea longicatena, Enterococcus faecium, Eubacterium biforme, Eubacterium eligens, Eubacterium rectale, Eubacterium siraeum, Eubacterium ventriosum, Faecalibacterium prausnitzii, Gemella sanguinis, Granulicatella adiacens, Lachnospiraceae bacterium, Megasphaera micronuciformis, Parabacteroides merdae, Prevotella copri, Roseburia hominis, Roseburia intestinalis, Ruminococcus, Ruminococcus bromii, Ruminococcus lactaris, Ruminococcus obeum, Streptococcus australis, Streptococcus pneumoniae, Streptococcus sanguinis, Subdoligranulum variabile	
Ismael et al (2021) [38]	Quasi-experimental study	Intervention: Mediterran diet based on the Portuguese Mediterranean Food Wheel	12 weeks	Intervention: 9	Taxonomic composition (total and relative abundance) α-diversity, β-diversity, P/B, F/B	↑Total Abundance ↑P/B ↓F/B	16S rRNA (V3-V4 region), Illumina MiSeq
Kanazawa et al (2021) [35]	Randomized Controlled Study	Placebo: placebo dry powder Intervention: Synbiotic (*Lacticasei bacillus paracasei* - strain *Shirota, Bifidobacterium breve*, Galacto-oligosaccharides	24 weeks	Placebo: 42 Intervention: 44	Taxonomic composition (total and relative abundance), α-diversity	Phylum: ↑Actinobacteria ↓Bacteroides, Fusobacteria	16S rRNA (V1-V2 region), Illumina MiSeq

↑: increased; ↓: decreased; F/B: Firmicutes/Bacteroidetes ratio; P/B: Prevotella/Bacteroides; rRNA: Ribosomal ribonucleic acid; qPCR: quantitative polymerase chain reaction; OTUs: operational taxonomic units.

microbiota population following dietary interventions for diabetes treatment.

Total abundance was reported in 10 trials, of which two showed an increase [28,38] and one showed a decrease in abundance [25]. Microbial α-diversity was also reported in 14 studies using different indices and methods, such as Shannon index, Simpson index, phylogenetic diversity, total observed species (richness), and Chao1. Four studies noted higher α-diversity [27,32,39,43], whereas one study reported lower diversity [25]. The other nine studies indicated no significant difference in this index after the intervention. β-diversity was evaluated in 11 studies, and in 4 of them, the authors detected changes in the bacterial community structure after the intervention [24,27,32,40].

Several differences were observed in the gut microbiota after the intervention in individuals with type 2 diabetes when comparing the relative abundance of individual bacterial phyla and order/family/genera/species. At the phylum level, Firmicutes and Bacteroidetes abundance was reported in only six studies, with an increased relative abundance of Bacteroidetes [22,28,36] and decreased Firmicutes abundance [22,23,36]. Only one trial reported a decreased Firmicutes/Bacteroidetes ratio [23], as well as Phylum Euryarchaeota [29] abundance.

At the family level, studies have reported a higher abundance of two families, Bifidobacteriaceae [25] and Methanobacteria [29], and a lower abundance of five families, Coriobacteriaceae [42], Erysipelotrichaceae [25,28], Peptostreptococcaceae [25], Porphyromonadaceae [25], and Ruminococcaceae [25,28]. The abundance of Lachnospiraceae [25,27,28,40] was reported in four studies, with contradictory results after the intervention.

Table 2
Characteristics of studies involving surgical interventions.

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
Graessler et al (2013) [45]	Quasi-experimental study	Intervention: RYGB	3 months	Intervention: 6	Taxonomic composition (relative abundance), F/B	↓ F/B Phylum: ↑ Proteobacteria, Verrucomicrobia, Fusobacteria ↓ Firmicutes, Bacteroidetes, Actinobacteria, Cyanobacteria Family/Genus/Specie:↑ *Enterobacter, Neurospora, Citrobacter, Veillonella, Salmonella, E. cancerogenus, Veillonella parvula, V. dispar, Shigella boydii, Salmonella enterica* ↓ *Faecalibacterium, Coprococcus, Helicobacter, Dictiostelium, Epidinium, Anaerostipes, Nakamurella, Eubacterium rectale, Dialister invisus, C. spiroforme, B. hyodysenteriae, L. reuteri, A. caccae, P. mendocina, F. periodondicum, T. roseum, L. interrogans, S. epidermidis, Nakamurella multipartita, L. acidophylus, A. johnsonii, F. succinogenes, Treponema pallidum, Mycobacterium kansasii, F. prausnitzii, C. comes*	Metagenomic shotgun (platform is not mentioned)
Chen et al (2017) [44]	Quasi-experimental study	Intervention: RYGB	180 days	Intervention: 24	Abundance of Phylum Firmicutes and Bacteroidetes, *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *E. coli*	Phylum: ↑ Bacteroidetes Family/ Genus/Specie: ↑ *Bifidobacterium*, ↓ *E. coli*	16S rRNA, RT-qPCR
Murphy et al (2017) [50]	Part of a double-blind (acessor and patient) clinical trial	Intervention 1: RYGB Intervention 2: SG	1 year	Intervention 1: 7 Intervention 2: 7	Taxonomic composition (relative abundance), α-diversity	Intervention 2 Phylum:↑ Bacteroidetes Family/Genus/ Specie:↑*Streptococcaceae, Lactobacillaceae, Streptococcus, Lactobacillus, Holdemania, Escherichia, Roseburia intestinalis, Lactobacillus salivarius, Streptococcus salivarius, Streptococcus parasanguinis* ↓*Roseburia inulinivorans, Lachnospiraceae bacterium* Intervention 1 ↑ α-diversity, Phylum:↑ Firmicutes, Actinobacteria ↓ Bacteroidetes Family/ Genus/Specie:↑ *Faecalibacterium, Klebsiella, Veillonella, Roseburia intestinalis, Streptococcus anginosus, Bifidubacterium dentium, Streptococcus thermophilus, Klebsiella pneumoniae, Veillonella dispar, Bifidubacterium longum, Ruminococcus bromi* ↓*Bacteroidaceae, Bacteroides, Coprobacillus, Ruminococcus torques, Clostridium bolteae, Coprobacillus bacterium*	Metagenomic shotgun, Illumina HiSeq
Cortez et al (2018) [48]	Randomized controlled trial	Control: standard medical care Intervention: Duodenal-jejunal bypass with minimal gastric resection	12 months	Control: 5 Intervention: 9	Taxonomic composition (relative abundance), α-diversity, β-diversity	↑ α-diversity, Diversity changed after intervention (β-diversity) Family/Genus/Specie: ↑ *Akkermansia muciniphila*	16S rRNA (V4 region), Illumina Miseq
De Jonge et al (2019) [49]	Quasi-experimental study	Intervention: DJBL	6 months	Intervention: 17	Abundance of 130 genus-level phylogenetic groups, α-diversity	↑ α-diversity Family/Genus/Specie: ↑ *Veillonella, Serratia, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Lactobacillus gasseri, Lactobacillus plantarum*	16S rRNA, HITChip probe level, RNA microarray
Lee CJ et al (2019) [52]	Randomized, controlled pilot trial	Intervention 1: RYGB Intervention 2: AGB	At a similar weight loss (~10%)	Intervention 1: 4 Intervention 2: 4	Taxonomic composition (relative abundance), α-diversity, β-diversity	Intervention 1:↓ α-diversity Phylum: ↑ Proteobacteria, Actinobacteria Family/Genus/ Specie: ↑ *Akkermansia, Faecalibacterium* — Intervention 2:↓ α-diversity Phylum:↑	16S rRNA (V3-V4 region), Illumina MiSeq

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Table 2 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota outcome measures	Microbiota effects	Analysis method
Wang FG et al (2019) [51]	Clinical trial (not randomized)	Intervention 1: RYGB Intervention 2: SG	3 months	Intervention 1: 3 Intervention 2: 8	Taxonomic composition (relative abundance), α-diversity, β-diversity	Proteobacteria Family/Genus/ Specie:↑ *Akkermansia*, ↓ *Roseburia* Intervention 1: β-diversity negatively changed after intervention Phylum: ↑ Bacteroidetes Family/Genus/ Specie: ↑ *Ruminococcaceae, Streptococcaceae*, *Streptococcus salivarius* subsp. *thermophilus* ↓ *Faecalibacterium Intervention 2 :* ↑ *α-diversity, Diversity changed after intervention (β-diversity)* Phylum: ↑ *Bacteroidetes* Family/Genus/Specie: ↑*Streptococcaceae, Rikenellaceae, Porphyromonadaceae, Alistipes,S treptococcus, Streptococcus salivarius subsp. thermophilus*	16S rRNA (V3 -V4 region), Ion S5TM XL
Al Assal et al (2020) [46]	Quasi-experimental study	Intervention: RYGB	12 months	Intervention: 14	Taxonomic composition (total and relative abundance), α-diversity, F/B	↑ α-diversity, ↓ F/B Family/Genus/ Specie: ↑*Veillonella, Streptococcus* ↓ *Flavonifractor, Butyricicoccus, Blautia*	16S rRNA (V4 region), Illumina MiSeq
Davies et al (2020) [19]	Double-blind (acessor and patient) randomised clinical trial	Intervention 1: RYGB Intervention 2: SG	12 months	Intervention 1: 22 Intervention 2: 22	Taxonomic composition (relative abundance), α-diversity	Intervention 1 Phylum:↑ Firmicutes, Proteobacteria Family/ Genus/Specie:↑*Veillonellaceae, Lactobacillales, Streptococcaceae, Pasteurelleales,Pasteurellaceae, Bacilli, Streptococcus, Veillonella, Haemophilus, Eubacterium rectale, H. parainfluenzae* ↓ *Clostridiaceae, Oscillospiraceae, Blautia, Oscilibacter, Clostridium, Ruminococcus torques, Bacteroides vulgatus* Intervention 2 Phylum: ↑ Proteobacteria, Bacteroidetes Family/Genus/Specie: ↑*Bacteroidia, Bacteroidales, Bacteroides stercoris, Barnesiella, ruminococcus, Barnesiella intestinihominis, Parabacteroides merdae, Ruminococcus bromii, Eubacterium rectale, Lactococcus lactis* ↓ *Enterobacteriaceae, Enterobacteriales, Escherichia, Parabacteroides, Clostridium, E. coli*	Metagenomic shotgun, Illumina HiSeq
Lau et al (2021) [47]	Open-label, randomised controlled clinical trial	Control: standard medical therapy Intervention: RYGB	12 months	Control: 10 Intervention: 8	Taxonomic composition (relative abundance), F/B, P/F, α-diversity, β-diversity	↑ P/F, ↑ α-diversity, Diversity changed after intervention (β-diversity) Phylum:↑ Proteobacteria Family/Genus/ Specie:↑ *Veillonellaceae, Klebsiella, Enterobacter* ↓ *Ruminococcus, Lachnospiraceae*, *Faecalibacterium*	16S rRNA (V3-V4 region), Illumina MiSeq

↑: increased; ↓: decreased; F/B: Firmicutes/Bacteroidetes ratio; P/F: Proteobacteria/Firmicutes ratio; AGB: adjustable gastric banding; DJBL: Nonsurgical duodenal–jejunal bypass liner; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; rRNA: Ribosomal ribonucleic acid; qPCR: quantitative polymerase chain reaction.

At the genera/species level, studies reported a higher abundance of eight genera; *Akkermansia* [24,39] *Bacteroides* [24,28] *Bifidobacterium* [27,28,33,39], *Eggerthella* [40], *Faecalibacterium* [24,27,28,39], *Lactobacillus* [29,30,33,34], *Pseudoflavonifractor* [40], and *Odoribacter* [40] eight species; *Akkermansia muciniphila* [39], *Bacteroides ovatus* [28], *Bacillus fragiles* [39], *Bifidobacterium adolescentis* [28], *Escherichia coli* [23], *Faecalibacterium prausnitzii* [28], *Lactobacillus gasseri* [30], and *Lactobacillus reuteri* [30]. Lower abundance was reported in 10 genera; including *Alistipes* [27], *Blautia* [42], *Collinsella* [40], *Eubacterium* [42], *Parabacteroides* [27], *Pseudobutyrivibrio* [27], *Roseburia* [40], *Ruminococcus* [24,28], *Streptococcus* [40], and *Veillonella* [40], and in four species; *Blautia exlerae* [42], *Enterobacter soli* [42], *Lachnospiraceae incertae sedis* [40], and *Prevotella copri* [39]. The abundance of *Bifidobacterium longum* [39,42] has been reported to have contradictory results after intervention.

3.5. Results of syntheses of studies with surgical interventions

This review included 10 studies that evaluated changes in the gut microbiota following surgical intervention for diabetes. Microbial α-diversity was reported in eight studies using different indices and methods. Six studies reported higher α-diversity [46–51], whereas one study reported lower diversity [52]. β-diversity was evaluated in four studies, and in three of them, the authors detected changes in the bacterial community structure after intervention [47,48,51].

Differences were observed in the gut microbiota after the intervention in individuals with type 2 diabetes when comparing the relative abundance of individual bacterial phyla and order/family/genera/species. At the phylum level, the proportion of organisms belonging to the four phyla, Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, showed contradictory results in their abundance when comparing the gut microbiota in individuals with diabetes before and after the intervention. Some studies have reported a higher abundance of the

Table 3
Characteristics of studies with pharmacological interventions.

Study	Design	Intervention	Follow-up	n	Microbiota Outcomes Measure	Microbiota Effects	Analysis method
Sasaki et al (2013) [60]	Randomized, double blind, placebo-controlled trial	Placebo: placebo capsule Intervention: TGD 300 mg and 900 mg	12 weeks	Placebo: 20 Intervention 1 300 mg: 20 Intervention 2 900 mg: 20	Abundance of 30 OTUs, F/B	Intervention 1:↓ F/B Intervention 2:↓ F/B	16S rDNA, T-RFLP
Napolitano et al (2014) [54]	Exploratory, unblinded study	Intervention: usual stable dose of metformin is stopped until blood glucose had increased by 25% from the average baseline and and then is re-introducted	Blood glucose returned to baseline levels after restarting the metformin	Intervention: 12	Taxonomic composition (relative abundance), α-diversity, β-diversity	Phylum: ↓ Firmicutes Family/ Genus/Species: ↑*Adlercreutzia*, ↓*Eubacterium*	16S rDNA (V1-V3 regions), 454 GS FLX pyrosequencing
Remely et al (2014) [58]	Quasi-experimental study	Intervention: GLP-1 agonists	4 months	Intervention: 24	Taxonomic composition (relative abundance), α-diversity	Not significant changes were observed	16S rDNA, 454 GS-FLX pyrosequencing, RT-qPCR
Su et al (2015) [66]	Randomized clinical trial	Placebo: similar antidiabetic treatment without acarbose Intervention: 50 mg of acarbose three times a day	4 weeks	Placebo: 36 Intervention: 59	Abundance of *Bifidobacterium longum*, *Enterococcus faecalis*	Family/Genus/Species: ↑ *Bifidobacterium longum*	16S rDNA, RT-qPCR
Remely et al (2016) [59]	Quasi-experimental study	Intervention: GLP-1 agonists	4 months	Intervention: 24	Taxonomic composition (relative abundance), F/B	Family/Genus/Species: ↑ *Alistipes, B. vulgatus, F. prausnitzii, A. muciniphila*	16S rDNA, 454 GS-FLX pyrosequencing, IS-region by RFLP
Gu et al (2017) [21]	Randomised, open-label, two-arm, multicentre clinical trial	Intervention 1: Acarbose Intervention 2: Glipizide	3 months	Intervention 1: 51 Intervention 2: 43	Taxonomic composition (total and relative abundance), α-diversity	Intervention 1: ↑ α-diversity Family/Genus/Species: ↑ *Lactobacillus gasseri*, *Bifidobacterium longum, Collinsella aerofaciens*, *Ruminococcus torques*, *Bifidobacterium longum*, *Bifidobacterium catenulatum*, *Streptococcus salivarius*, *Bifidobacterium adolescentis*, *Streptococcus thermophilus*, *Streptococcus vestibularis*, *Streptococcus* sp. *C150*, *Megasphaera elsdenii*, *Lactobacillus salivarius*, *Lactobacillus rhamnosus*, *Lactobacillus oris*, *Lactobacillus gasseri* ↓ *Bacteroides dorei/ vulgatus*, *Bacteroides uniformis*, *Alistipes putredinis*, *Ruminococcus 5_1_39BFAA*, *Bacteroides thetaiotaiomicron*, *Eubacterium eligens*, *Bilophila wadsworthia*, *Bacteroides stercoris*, *Bacteroides plebeius*, *Roseburia inulinivorans*, *Odoribacter splanchnicus*, *Eubacterium ventriosumRoseburia hominis*, *Bacteroides intestinalis*, *Clostridium bolteae*, *Ruminococcus lactaris*, *Eggerthella lenta*, *Holdemania filiformis*, *Clostridium leptumAlistipes* sp. *HGB5*, *Pseudoflavonifractor capillosus*, *Roseburia intestinalis*, *Lachnospiraceae bacterium*, *Clostridium*, *Clostridium scindens*, *Bacteroides finegoldiiAnaerotruncus colihominis* Intervention 2: Family/Genus/Species: ↑ *Bifidobacterium*, ↓ *Bacteroides*	Metagenomic shotgun, Illumina Hiseq

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Table 3 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota Outcomes Measure	Microbiota Effects	Analysis method
Shimozato et al (2017) [61]	Randomized double-blind, placebo-controlled study	Placebo: placebo capsule Intervention: TGD 300 mg and 900 mg	12 weeks	Placebo: 21 Intervention 1 TGD 300 mg: 23 Intervention 2 TGD 900 mg: 22	Abundance of 30 OTUs	Intervention 1: Family/Genus/Specie: ↑ *Clostridium* cluster XVIII, *Bifidobacterium* Intervention 2: Family/Genus/Specie: ↑ *Prevotella, Clostridium* subcluster XIVa, *Bacteroides*, ↓ *Bifidobacterium*	16S rDNA,T-RFLP
Wu et al (2017) [20]	Randomized, placebo-controlled, double-blind study	Placebo: placebo capsules Intervention: Metformin	4 months	Placebo: 18 Intervention: 22	Taxonomic composition (relative abundance)	Family/Genus/Species: ↑ *Bifidobacterium, Escherichia, Bacillus*, *Shewanella, Serratia, Pseudomonas*, *Helicobacter*, *Pectobacterium*, *Pantoea, Yersinia, Dickeya*, *Rheinheimera*, *Cronobacter*, *Dermacoccus*, *Citrobacter*, *Erwinia*, *Salmonella*, *Raphidiopsis*, *Enterobacter, Klebsiella*, *A. muciniphila*, *Ruminococcus* sp. *5_1*, *Bacteroides clarus*, *Rothia mucilaginosa*, *Lactobacillus brevis subsp. gravesensis*, *Lactobacillus fermentum*, *Staphylococcus epidermidis*, *Capnocytophaga gingivalis*, *Pseudomonas aeruginosa*, *Pantoea* sp. *At-9b*, *Lactobacillus ultunensis*, *Lactobacillus amylolyticus*, *Dickeya dadantii*, *Lactobacillus delbrueckii subsp. lactis DSM 20,072*, *Lactobacillus johnsonii*, *Dickeya zeae*, *Lactobacillus acidophilus*, *Weissella cibaria*, *Serratia* sp. *AS12*, *Bacillus coahuilensis*, *Enterobacter lignolyticus*, *Neisseria mucosa*, *Dickeya dadantii*, *Yersinia enterocolitica subsp. enterocolitica*, *Enterobacter cloacae*, *Rheinheimera* sp., *Enterococcus casseliflavus*, *Lactobacillus gasseri*, *Corynebacterium lipophiloflavum*, *Lactobacillus jensenii*, *Erwinia amylovora*, *Salmonella bongori*, *Citrobacter koseri*, *Staphylococcus aureus subsp. aureus*, *Enterobacter asburiae*, *Serratia odorifera*, *Corynebacterium striatum*, *Enterobacter aerogenes*, *Enterobacter cloacae subsp. cloacae*, *Cronobacter turicensis*, *Dermacoccus* sp. *Ellin185*, *Salmonella enterica* subsp. *arizonae*, *Neisseria elongata subsp. glycolytica*, *Raphidiopsis brookii*, *Erwinia tasmaniensis*, *Salmonella enterica subsp. enterica*, *Escherichia albertii*, *Citrobacter* sp. *30_2 Citrobacter rodentium*, *Erwinia billingiae*, *Escherichia coli*, *Enterobacter* sp. *638*, *Bacillus cereus*, *Klebsiella oxytoca*, *Pantoea ananatis*, *Citrobacter youngae*, *Klebsiella pneumoniae*, *Plautia stali symbiont*, *Enterobacter cancerogenus*, *Enterobacter cloacae subsp. cloacae*, *Helicobacter mustelae* ↓ *Dethiosulfovibrio*, *Bartonella, Deferribacter*, *Hippea, Pseudogulbenkiania*, *Acetivibrio, Subdoligranulum*,	Metagenomic Shotgun, Illumina NextSeq 500

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Table 3 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota Outcomes Measure	Microbiota Effects	Analysis method
						Pseudoflavonifractor, *Intestinibacter*, *Clostridium perfringens*, *Clostridium botulinum*, *Clostridium butyricum*, *Clostridium beijerinckii*, *Clostridium* sp. *7_2_43FAA*, *Deferribacter desulfuricans*, *Clostridium novyi NT*, *Clostridium bartlettii*, *Clostridium botulinum A3*, *Bifidobacterium adolescentis*, *Clostridium sticklandii*, *Pseudogulbenkiania* sp.*NH8*, *Hippea maritima*, *Alkaliphilus oremlandii*, *Ruminococcus flavefaciens*, *Subdoligranulum variabile*, *Pseudoflavonifractor capillosus*	
Tong et al (2018) [63]	Multicenter, randomized, positive-control, and open label clinical trial	Control: Metformin Intervention: Traditional Chinese medicine (*Rhizoma Anemarrhenae*, *Momordica charantia*, *Coptis chinensis*,*Salvia miltiorrhiza*, red yeast rice, *Aloe vera*, *Schisandra chinensis*, and dried ginger)	12 weeks	Control: 100 Intervention: 100	Taxonomic composition (relative abundance), α-diversity, β-diversity	Traditional Chinese medicine: ↓ α-diversity, Diversity changed after intervention (β-diversity) Family/Genus/Species:↑ *Roseburia, Gemmiger, Coprococcus, Megamonas, Blautia, F. prausnitzii* Metformin:↑ α-diversity, Diversity changed after intervention (β-diversity) Family/Genus/Species: ↑ *Blautia*, ↓ *Alistipes, Oscillibacter, Bacteroides, Akkermansia*	16S rRNA (V3-V4 region), Illumina MiSeq
Wang Z et al (2018) [62]	Clinical trial	Control: remained on metformin Intervention: switched from oral metformin to subcutaneous once daily injections of liraglutide	6 weeks	Control: 18 Intervention: 19	Taxonomic composition (relative abundance) α-diversity, β-diversity	Not significant changes were observed	16S rRNA (V4 region), Illumina MiSeq
Shin et al (2020) [57]	Double-blind, crossover, randomized clinical trial	Placebo: Placebo combined with metformin Intervention: *Scutellaria baicalensis* combined with metformin	8 weeks	Placebo and intervention: 17	Taxonomic composition (total and relative abundance) α-diversity, β-diversity	Family/Genus/Specie: ↑ *Mobilitalea, Acetivibrio*_g1, AB606281_g, AB606237_g, *Lactobacillus, Akkermansia* ↓ *Oscilibacter, Alloprevotella, Bifidobacterium, Clostridium*_g23	16S rRNA (V3-V4 region), Illumina MiSeq
Van Bommel et al (2020) [64]	Randomized double-blind, comparator-controlled, parallel-group trial	Intervention 1: dapagliflozin Intervention 2: gliclazide	12 weeks	Intervention 1: 24 Intervention 2: 20	Taxonomic composition (relative abundance) α-diversity, β-diversity	Not significant changes were observed	16S rRNA (V3-V4 region), Illumina MiSeq
Elbere et al (2020) [55]	Cohort	Intervention: Metformin	7 days	Intervention: 50	Taxonomic composition (relative abundance) α-diversity	Family/Genus/Species: ↑ *Clostridiaceae, Enterococcaceae, Oscillospiraceae, Enterococcus, Lactococcus, Clostridium, Oscillibacter, Bacteroides vulgatus, Enterococcus faecium, Lactococcus lactis, Parabacteroides distasonis* ↓ *Bifidobactericeae, Barnesiella, Bifidobacterium, Barnesiella intestinihominis, Bifidobacterium adolescentes, Clostridium bartlettii*	Metagenomic shotgun, Ion Proton
Nakajima et al (2020) [56]	Quasi-experimental study	Intervention: Metformin	4 weeks	Intervention: 31	Taxonomic composition (total and relative abundance) α-diversity, β-diversity	Not significant changes were observed	16S rDNA (V3-V4 region), Illumina MiSeq
Smits et al (2021) [65]	Randomized placebo-controlled, double-blind,	Placebo: Matching placebo (isotonic 0.9% saline or placebo capsules) Intervention	12 weeks	Placebo: 15 Intervention 1: 16 Intervention 2: 18	Taxonomic composition (relative abundance),	Not significant changes were observed	16S rDNA (V3-V4 region), Illumina MiSeq

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Table 3 (*continued*)

Study	Design	Intervention	Follow-up	n	Microbiota Outcomes Measure	Microbiota Effects	Analysis method
	parallel-group trial	1: liraglutide Intervention 2: sitagliptin			α-diversity, β-diversity		
Takewaki et al (2021) [67]	Quasi-experimental study	Intervention: acarbose	4 weeks	Intervention: 18	Taxonomic composition (relative abundance), α-diversity, β-diversity	Phylum: ↑Actinobacteria, ↓ Bacteroidetes Family/Genus/ Species: ↑*Bifidobacterium, Eubacterium, Lactobacillus, Megasphaera* ↓*Bacteroides, Blautia, Clostridium, Lachnoclostridium, Phascolarctobacterium, Prevotella*	16S rDNA (V3-V4 region), Illumina MiSeq

↑: increased; ↓: decreased; F/B: Firmicutes/Bacteroidetes ratio; OTU: operational taxonomic units; GLP-1: Glucagon-like peptide-1; GS FLX: Genome Sequencer FLX System; qPCR: quantitative polymerase chain reaction; TGD: Transglucosidase; T-RFLP: terminal-restriction fragment length polymorphism.

phylum Fusobacteria [45], while Verrucomicrobia [45,48] and Cyanobacteria [45] showed lower abundance. Two trials reported a decreased Firmicutes/Bacteroidetes ratio [45,46].

At the order/family level, Bacteroidales, Streptococcaceae [50,51], Lactobacillales [50], Rikenellaceae [51], Porphyromonadaceae [51], Pasteurelleales [19], Pasteurellaceae [19], Ruminococcaceae [51], Veillonelaceae [19,47,51], *Klebsiella*, and *Enterobacter* [47] were reported to be altered after intervention, showing higher abundance. Bacteroidaceae [50], Clostridiaceae [19], Enterobacteriales [19], Enterobacteriaceae [19], Oscillospiraceae [19], and Lachnospiraceae [47] showed lower abundance in only one study each. The most altered results reported were related to genera, including 12 in which the abundance increased and 14 in which it decreased (Table 2). The abundance of *Faecalibacterium* [45,47,51,52] was reported in four studies with contradictory results.

Regarding the species, the results showed increased *Klebsiella pneumoniae* [45,49,50], *Lactobacillus gasseri* [49], *Lactobacillus plantarum* [49], *Veillonella dispar* [45,50], and *Streptococcus salivarius* [50,51]. The other 15 species were reported to have decreased in proportion after the intervention, and most belonged to the Firmicutes phylum.

An altered abundance of *Escherichia coli* [44,45,49] and *Eubacterium rectale* [19,45] has been reported with contradictory results in some studies.

3.6. Results of syntheses of studies with pharmacological interventions

This review included 16 studies that evaluated the changes in the gut microbiota following pharmacological interventions for diabetes treatment.

Microbial α-diversity was reported in 11 studies using different indices and methods, and studies indicated a significant difference in this index after intervention with acarbose (increase) [21], metformin (increase) [63], and metformin plus traditional Chinese medicine (decrease) [63]. The bacterial community structure was evaluated in eight studies through β-diversity, and alterations were reported after intervening with metformin and metformin plus traditional Chinese medicine [63].

Differences were observed in the gut microbiota after intervention in individuals with type 2 diabetes when compared to the relative abundance of individual bacterial phyla and order/family/genera/species. At the phylum level, only one study has reported a significant reduction in the abundance of Firmicutes after the use of metformin [54]. In addition, only one study reported a decrease in Firmicutes/Bacteroidetes ratio after the intervention with transglucosidase, an enzyme that produces oligosaccharides from starch [60].

At the order/family/genera level, a higher abundance of *Bacteroides* [61], *Clostridium* cluster XVIII, subcluster XIVa [61], and *Prevotella* [61] was noted after intervention with transglucosidase and 21 genera after intervention with metformin (Table 3). Lower abundance of *Alistipes* [63], *Alloprevotella* [57], *Bacteroides* [63], *Clostridium* [55,57], *Eubacterium* [54], *Intestinibacter* [20] *Dethiosulfovibrio* [20], *Bartonella* [20], *Deferribacter* [20], *Hippea* [20], *Pseudogulbenkiania* [20], *Acetivibrio* [20], *Subdoligranulum* [20], *Pseudoflavonifractor* [20], and *Oscilibacter* [57,63] were reported after metformin intervention.

In one study, the use of metformin with *Scutellaria baicalensis* [57] led to an increase in the relative abundance of *Mobilitalea, Lactobacillus,* and *Akkermansia* and a decrease in *Oscilibacter, Alloprevotella,* and *Bifidobacterium*.

Contradictory results have been reported regarding the relative abundance of *Bifidobacterium* after the use of sulfonylureas [21,60] and metformin [20,57], *Bacteroides* after sulfonylurea intervention, and *Akkermansia* after metformin intervention [20,63].

At the species level, some studies have reported a higher abundance of 14 different species after acarbose intervention [21,66], as well as *Bacteroides vulgatus, F. prausnitzii, and Akkermansia muciniphila* [59], after GLP-1 receptor agonist intervention. After metformin intervention, one study reported an increase in the relative abundance of 61 different species/strains, including *A. muciniphila* [20]. A lower abundance of 27 species/strains was reported after acarbose intervention and 21 species/strains after metformin intervention, most of which belonged to the Firmicutes phylum [20].

4. Discussion

In individuals with type 2 diabetes mellitus, the use of probiotics, prebiotics, or synbiotics was associated with improvements in metabolic variables; reduced fasting plasma glucose, serum insulin, total cholesterol, and triacylglycerol levels; and increased high-density lipoprotein cholesterol levels [16], suggesting that interventions aimed at modulating gut microbiota composition could be used as adjuvant treatment for metabolic control in type 2 diabetes. This systematic review aimed to assess whether dietary, surgical, and pharmacological interventions can alter the gut microbiota of patients with diabetes. This review indicates that such interventions induced changes mainly in bacterial populations from phylum Firmicutes, in addition to increasing or decreasing the bacterial population from more than 60 families, genera, or species.

In general, the interventions led to an increase in the bacterial population belonging to the phylum Firmicutes, mainly *Lactobacillus* species, compared to the gram-negative bacterial population from phylum Bacteroidetes. In the meantime, there is a possibility that the large effect on lactobacilli, an intestinal bacterium that has attracted attention, was related to the risk of bias in the selection of the reported result, as approximately half of the studies were judged as having a high risk of bias or presented some concerns, primarily because of an

incomplete or no study protocol. A systematic review summarizing the findings on the differential composition of gut microbiota in type 2 diabetes found high levels of lactobacilli and the order Lactobacillales, a gram-positive bacterial population from the phylum Firmicutes, and suggested that the controversial effects of lactobacilli could be species- or strain-specific. Therefore, the role of lactobacilli remains unclear [68]. In the literature, the imbalance between Firmicutes and Bacteroidetes has frequently been considered an indicator of many diseases, including diabetes [69]. However, a large number of contradictory results have been reported in the literature, and many factors can affect microbiota composition and/or diversity, making it difficult to associate Firmicutes or Bacteroidetes with a specific health status and, more specifically, to consider it a hallmark of diabetes.

According to the hypothesis of metabolic endotoxemia, the interaction of lipopolysaccharide (LPS) produced by gram-negative bacterial cells with pattern recognition receptors may stimulate systemic inflammation by binding to receptors present on the surface of innate immune cells [12]. This binding results in an inflammatory response and cytokine production and plays a key role in insulin resistance [7,70], reducing glucose uptake in insulin-sensitive tissues, and increasing insulin requirement [71]. Therefore, an increase in the gram-positive bacterial population may be important in the treatment of diabetes.

As noted in this review, dietary interventions that were able to increase the number of organisms belonging to the *Lactobacillus* genus include the consumption of a diet rich in lactic acid bacteria and oligosaccharides [30,33]. Consistent with these findings, the intake of non-digestible carbohydrates increases the number of fermentative bacteria such as *Lactobacillus* [72], and the intake of probiotics enhances the growth of lactic acid bacteria [73]. However, changes in the Lachnospiraceae family and *Bifidobacterium* were not consistent among these studies. Since *Bifidobacterium* is more abundant in healthy people [74], interventions to increase the number of organisms belonging to this genus could induce a healthier metabolic profile. Additionally, an increase in *Faecalibacterium* was found in four studies [24,27,28,39], suggesting increased butyric acid production, which may ameliorate gut barrier function and reduce intestinal inflammation [75], leading to an increased insulin response after an oral glucose tolerance test [76]. It is important to mention that four studies (Table 1) used methodologies based on PCR to address microbiota composition, producing limited results.

With regard to surgical interventions, 10 small studies have examined the changes in gut microbiota after bariatric surgery in individuals with diabetes, with controversial results. Among microbial species that were affected by surgery, *Veillonella* proportion was increased in seven studies, which was unexpected, since this species was shown to be negatively associated with hemoglobin A1c [45]. In contrast, an increase in the abundance of the genus *Akkermansia* is related to improved insulin sensitivity and lower gut permeability [7,77]. Six studies reported an increase in microbiota diversity. Importantly, the diet of patients after this type of intervention changes completely, and it is expected that gut microbiome richness and diversity can be changed by the surgical procedure [78]. In addition, as the number of patients enrolled in most studies was less than 10 per group, statistical differences were difficult to detect.

These inconsistent results could also be related to the type of surgery, given that previous systematic reviews analyzing clinical trials that recruited subjects without diabetes observed a more pronounced microbial change in response to RYGB surgery than sleeve gastrectomy [79,80], suggesting that the beneficial effects of bariatric surgery are not solely explained by the restriction and malabsorption induced by the surgery itself. Some of the results of bariatric surgery can be related to an increase in the number of colonic bacteria that obtain energy in the large intestine from poorly absorbed nutrients [81]. In addition, an improvement in incretin hormone secretion was observed after RYGB surgery [82], and the use of an incretin agonist reduced the abundance of the Proteobacteria phylum and increased the abundance of *Akkermansia muciniphila* [83].

Regarding pharmacological interventions, drugs may induce metabolic benefits, in part, dependent upon their action in the gut, reshaping the gut microbiota and promoting a shift toward short-chain fatty acid-producing bacteria in individuals with diabetes [84]. Metformin is associated with an increased proportion of *Lactobacillus* [57] and *Akkermansia* [20,57]. These microbes can promote the inhibition of pro-inflammatory cytokines and chemokines such as IL-1β, IL-6, IL-8, IL-17, and tumor necrosis factor α, suggesting another pathway by which these microorganisms act to reduce low-grade inflammation [12]. In addition to the increase of *Escherichia coli*, it was also reported that metformin can be associated with an increase in acetate production and improved insulin sensitivity [85], despite *Escherichia* spp also being linked with LPS production [7].

Another anti-diabetic drug linked to microbiota is acarbose, an α-glucosidase inhibitor. Acarbose affects carbohydrate metabolism and has been hypothesized to affect microbiota composition. In patients with diabetes, acarbose treatment alters the gut microbiota, increasing α-diversity [21] and the content of *Bifidobacterium longum*, in addition to decreasing lipopolysaccharides and inflammatory cytokines [66]. This change in gut microbiota composition following acarbose treatment suggests that the therapeutic effect of this agent may be partially mediated through microbiota modification, although further clinical studies are needed. Moreover, transglucosidase reduced the Firmicutes/Bacteroidetes ratio [60]. Similar to what was reported for dietary interventions, five studies used methodologies other than next-generation sequencing to evaluate the microbiota, which was another problem in comparing the results.

In general, studies have reported an increase in species related to the Firmicutes and Proteobacteria in the gut. Although an increase in *Lactobacillus* species is associated with better gut conditions, increases in *Veillonella* and *Streptococcus* have also been reported. In addition, Proteobacteria, mainly Enterobacteriaceae, have been correlated with dysbiosis in inflammatory bowel disease and colorectal cancer initiation [86,87]. However, there have been no reports on their specific effects on diabetes. Furthermore, the decrease in *F. prausnitzii* (positively related to body mass index and glucose homeostasis) and the contradictory result for *Eubacterium rectale* (implicated in inflammatory bowel disease and colorectal cancer initiation) [88] must be considered.

Indeed, we have identified that the proportion of organisms belonging to the genus *Akkermansia* increased after specific diet and surgical interventions and showed contradictory results with metformin intervention [20,24,39,45,48,52,57]. On the other hand, the proportion of *Akkermansia muciniphila* increased with all types of interventions, reinforcing the idea that it can be an important marker for diabetes control. These species-derived extracellular vesicles, which are responsible for improving intestinal barrier integrity, are increased in the fecal samples of healthy controls compared to those of patients with type 2 diabetes [89]. Moreover, *Akkermansia* may contribute to restoring insulin sensitivity and improving glucose metabolism [90]; thus, reduced insulin resistance and adipose tissue inflammation could be promoted by these species.

The main limitation of this study is the wide diversity of the design, methodologies, and analytical and statistical approaches used in the studies, especially the species-level description, which is only possible based on specific methods or metagenomics and is different from most studies included in this review that are based on 16S rRNA amplicons. These limitations made it impossible to perform a meta-analysis; instead, we applied a vote-counting method to assess the effect of interventions on relevant outcomes. Moreover, we note that not all the data derived from these studies have been consistent, perhaps because study designs were suboptimal and too diverse for dedicated microbiome analyses and to allow comparisons between studies, making the link between intervention and gut microbiome blurred by too many confounders. Furthermore, the studies were small in terms of sample size, making their statistical power insufficient for detecting small

variations. This review supports the finding that analyzing the effect of interventions on gut microbial composition remains a challenge due to a multitude of factors, such as analysis methodologies, previous pharmacological status, and usual diet in studies, as this will likely influence the baseline gut microbiota composition to which changes will be compared. Overall, the methods used to analyze the composition of the gut microbiota (target genes, sequencing platform, measured parameters, and statistical approach) are suitable. However, the pre-processing steps and choice of tools and algorithms for downstream analysis are important and should be chosen carefully to avoid experimental errors and biases in the results [91].

5. Conclusions

Although the Firmicutes/Bacteroidetes ratio is decreased by diet and surgical interventions, we observed an increased abundance of genera/species related to Firmicutes when compared to those related to phylum Bacteroidetes, for all types of interventions. Moreover, genera related to *Lactobacillus* were more abundant, and *Rumminococcus* was less abundant. Similarly, an increased abundance of *Akkermansia muciniphila*, a new-generation probiotic species, has been reported. Some genera/species/strains may act as biomarkers in patients with diabetes better than Firmicutes/Bacteroidetes ratio or diversity index. Although the current review indicates that the effects may be related to these changes, the interpretation is tricky owing to differences in methodology. It is important to highlight that more adequately designed studies using next-generation sequencing approaches are needed to improve the data quality and knowledge about gut microbiota changes induced by diabetes treatments. However, these results suggest that interventions aimed at reducing species associated with uncontrolled diabetes and increasing species associated with a healthy gut to resemble the gut microbiota of an individual without diabetes are potential adjuvants to treat diabetes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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***Data** Availability*

Data are available on request from the authors.

Author Contributions

BDS had full access to all the data in the study, supervised the study, and took responsibility for the integrity of the data and the accuracy of data analysis. PMB, GHT, AFM, and BDS designed this study. PMB, RR, CKM, and GL acquired data. PMB and AFM analyzed the data. PMB, AFM, and BDS interpreted data. PMB drafted the manuscript. PMB, GHT, RR, CKM, GL, AFM, and BDS revised the manuscript for important intellectual content and approved the version to be published.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109944.

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