Diabetology & Metabolic Syndrome

REVIEW

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Assessing the impact of bariatric surgery on cardiovascular risk in type 2 diabetes: a systematic review and meta-analysis using OMICs data

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Abstract

Type 2 diabetes (T2D) is a complex, multifactorial metabolic disorder, and while bariatric surgery has emerged as a promising intervention for obesity-related T2D with significant metabolic benefits, its long-term durability and potential for remission vary among patients. This systematic review and meta-analysis explore how omics modalities—such as genomics, epigenomics, transcriptomics, metabolomics, proteomics, and gut microbiome—can reveal potential biomarkers linked to cardiovascular disease (CVD) of T2D patients who undergo bariatric surgery. Following PRISMA 2020 guidelines, a systematic search in PubMed identified 49 eligible studies. The meta-analysis of eight proteomic biomarkers, showed significant post-surgery improvements in total cholesterol (mean difference (MD) 0.44 (95% CI: 0.06–0.82), $p=0.02$), triglycerides (MD 1.00 (0.77–1.24), $p<0.00001$), LDL cholesterol (MD 0.27 (0.02, 0.52), $p=0.03$), HDL cholesterol (MD -0.22 (-0.30, -0.15), $p<0.00001$), hsCRP (MD 0.64 (0.44, 0.84), $p<0.00001$), C peptide levels (MD 1.29 (0.96, 1.61), $p<0.0001$), and IL-6 (MD 1.84 (0.85, 2.84), $p=0.0003$). These findings highlight the value of integrated omics in developing personalized diagnostics, predicting disease risks, and designing targeted therapies. The present study is the first systematic review presenting the omics disciplines that offer a comprehensive view of the effectiveness of bariatric surgery in managing T2D, subsequently reducing the risk of CVD.

Keywords Type 2 diabetes, Bariatric surgery, Omics, Cardiovascular disease, Precision medicine, Risk predictor

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Introduction

Type 2 diabetes (T2D) is a chronic, metabolic disorder that is characterized by a complex set of genetic, metabolic, and environmental factors. The International Diabetes Federation (IDF) reports that nearly half of all diabetes mellitus, (mainly T2D) patients, totaling 240 million, are undiagnosed. In 2021, there were 537 million diagnosed cases, with projections suggesting an increase to 643 million by 2030 and 783 million by 2045 [1]. While insulin resistance (IR) and β-cell dysfunction are recognized as key pathogenic players, obesity is one of the predominant risk factors in the development of T2D and its associated vascular complications [2]. Weight loss has been demonstrated to ameliorate the metabolic complications inherent to T2D. Personalized management of T2D demands the development of a clinical strategy individualized to the patient's specific requirements, complemented by an optimal weight-loss approach tailored to each individual [3]. However, achieving persistent weight loss and complete or partial remission of T2D can be challenging in certain cases.

Bariatric surgery has emerged as a robust alternative for patients with T2D concomitant with obesity, leading to weight loss, glycemic control, and, often, T2D remission [4–7]. The primary mechanism underpinning these outcomes is the anatomical alteration of the gastrointestinal tract, which results in modifications of gut hormones, bile acids, and the microbiome. Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), biliopancreatic diversion with duodenal switch (BPD/DS), and one anastomosis gastric bypass (OAGB) [8] may modify the anatomy and influence the entero-insular axis, enhancing insulin sensitivity and modulating postprandial glycemic excursions [9, 10]. Both RYGB and SG are considered the gold standard bariatric interventions due to their durable weight loss outcomes and associated metabolic benefits [11–14].

Despite evidence that surgical treatments can promote weight loss and help manage T2D, the long-term durability of these benefits remains uncertain. In a subset of patients, bariatric surgery may not lead to sustained improvement, as some individuals experience weight regain and a subsequent decline in glycemic control. [15]. While bariatric surgery offers promising results, comprehensive patient evaluation and post-operative management are imperative to optimize metabolic outcomes, cardiovascular disease (CVD) risk and minimize complications, especially in patients with T2D. [16].

Leroy Hood and other pioneers have championed systems medicine, an approach often referred to as P4 medicine due to its focus on prediction, prevention, personalization, and participation [17]. This paradigm aims to reduce mortality and morbidity from chronic diseases by implementing a deep knowledge of disease mechanisms and systems of the human body, and evidence-based personalized interventions. In this context, the development of a comprehensive approach to support P4 has fostered new diverse fields of research, commonly referred to as "OMICS". Omics modalities including genomics, transcriptomics, proteomics, metabolomics, and microbiome with deep phenotypic data, are currently utilized to understand biological processes, disease phenotypes, biomarker discovery, and prognostic assessments (Fig. 1). Utilizing diverse omics data facilitates the identification of new molecular pathways and biomarkers for complex diseases, subsequently en0061bling the assessment of an individual's health and offering early indicators of potential disease progression [18].

The field of omics has been implemented to identify factors associated with the progression of T2D and its related conditions [19–23], as well as to improve our understanding of the pathophysiological significance of β-cell dysfunction and its role in metabolic disorders [24]. Currently, omics technologies can be utilized to outline the main outcomes of bariatric surgeries, investigate T2D biomarkers, and lay the groundwork for innovative T2D treatment approaches. This approach helps in determining which patients stand to benefit most from various therapeutic interventions, including bariatric surgery. Yet, limited pioneering research has explored multiple omics layers to define the impact of bariatric procedures on T2D and CVD outcomes.

This review aimed to systematically evaluate clinical studies that applied at least one omics layer to investigate patients with T2D undergoing bariatric surgery. Given the significant gap in current literature, we focused on identifying potential biomarkers associated with CVD and highlighted their relevance to future precision medicine strategies. To the best of our knowledge, this is the first systematic review to integrate multiple omics disciplines, offering a comprehensive perspective on the effectiveness of bariatric surgery in managing T2D and reducing CVD risk.

Methods

Selection strategy

This systematic review was registered in PROSPERO (ID: CRD420251090077). A search was conducted in April 2024 on the PubMed database for clinical studies that utilized omics methods to assess the effect of bariatric surgery on CVD in patients with T2D. The search was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guideline [25].

PICO method [26] was used to formulate the research question (population, intervention, control, and outcomes); Population of interest was patients with T2D

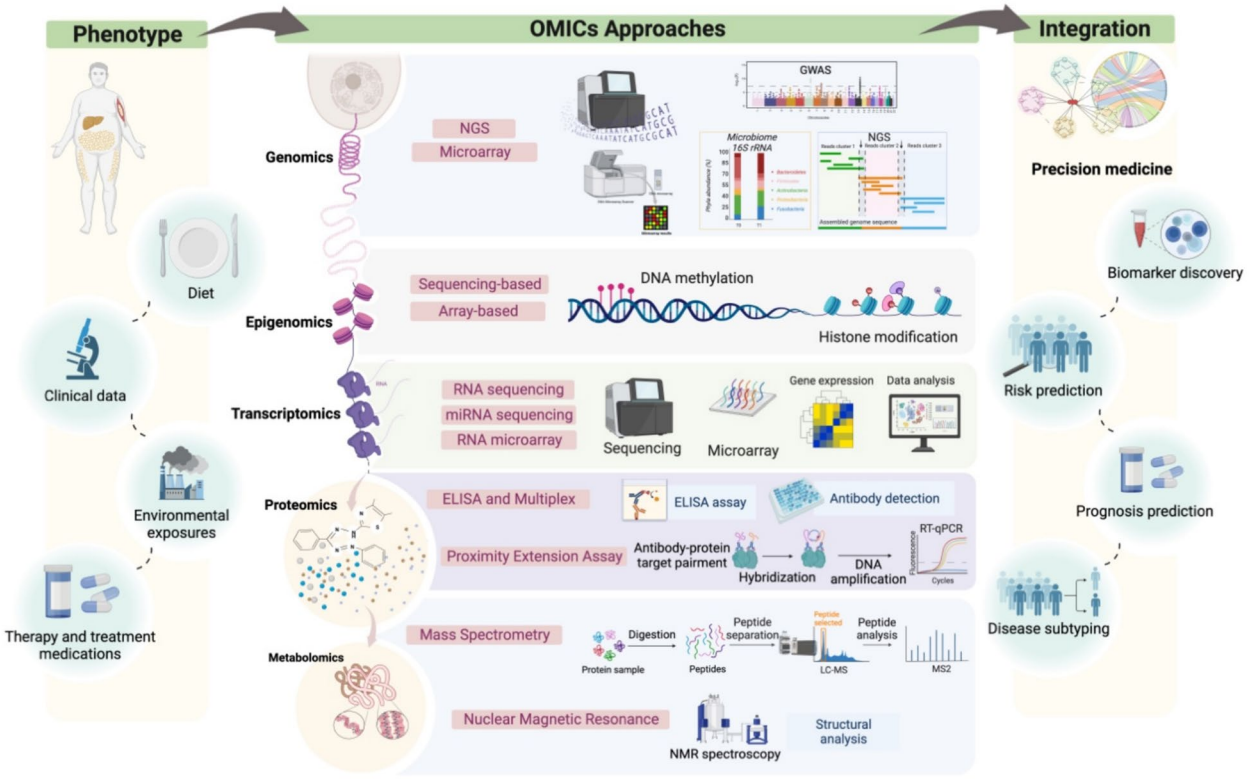

Fig. 1 Conceptual illustration of multi-OMICs integrating genomics, epigenomics, transcriptomics, microbiome, metabolomics, and proteomics to study disease. Genomics mainly studies DNA sequence and associated heritable biochemical modifications through rapid elucidation of an entire genome. Epigenomics studies factors affecting gene expression. Transcriptomics studies the detection and quantification of RNA molecules. Metabolomics captures comprehensive profiling of metabolite concentration in biological systems to investigate the chemical processes involved in metabolism. Proteomics analyze all expressed proteins in biological systems and their function. These disciplines' interaction leads to a phenotype change defined as any observable characteristic

with an age ≥ 18 years old, Intervention was bariatric surgery, Controls were patients with T2D at baseline pre-surgery, and outcomes were defined as OMICS integration to evaluate the impact of bariatric surgeries on T2D remission, inflammation and CVD changes between baseline and follow-up. Search terms included a combination of the following keywords and MeSH terms: "Bariatric surgery", "T2D", "OMICS", and "CVD". The detailed search strategy is described in the Supplementary file.

Data extraction and selection process

The inclusion process contained studies published in peer-reviewed journals written only in the English language. Review articles, conference abstracts, meta-analysis, case reports and comments were excluded from the search. Rayyan Software [27] was used to conduct the selection process. The selection was first implemented on the basis of evaluating the title and abstract where studies that do not match the selection criteria were excluded. Next, the remaining studies were selected after evaluating the full text by two reviewers.

The following study characteristics were extracted from the studies: publication year, study design, type of bariatric intervention, study cohort, sample type, analytical technique, number of patients, gender, mean age and Body mass index (BMI), major inclusion and exclusion criteria, follow-up period, omics approach, and outcome parameters. The extracted data were then documented in an Excel spreadsheet for analysis and reference.

Quality assessment

The quality assessment for each study included in the systematic review was performed using the National Institutes of Health (NIH) quality assessment tool by two independent reviewers [28]. Disagreement was resolved by a third reviewer. The classifications of each study were defined as "good", "fair", or "poor" quality according to the cutoff points defined by the NIH tool. A summary of the quality assessment is presented in the Supplementary file. Forty studies were "good" quality, nine studies of "fair" quality, and none of "poor" quality.

Statistical analysis

A meta-analysis was performed using the summarized data of the most frequently studied biomarkers. Biomarkers examined in three or more studies were analyzed

using Review Manager 5.4 software (RevMan). Mean differences and their 95% confidence intervals (CI) were calculated for continuous outcomes, and statistical heterogeneity was assessed using a random-effects model. Heterogeneity among studies was assessed using the Q statistical (Cochran's Q) test and I^2 statistic. I^2 of 50% or above was designated significant heterogeneity and 30–49% moderate heterogeneity. Forest plots demonstrate the pooled prevalence estimates of the meta-analysis results. $P < 0.05$ was used as the threshold for statistical significance.

Results

Screening and article selection

The search strategy reported a total of 6,103 studies, and 895 duplicate entries were identified. After a review of the titles and abstracts, 5,019 studies were excluded based on the inclusion criteria. The remaining 189 studies, a full-text review was conducted for eligibility. Out of these, 140 studies were excluded; 116 due to unrelated outcomes of interest and 24 because they focused on an unrelated patient population. A total of 49 studies were included in the review, comprising 35 prospective cohort studies (of which 7 were randomized controlled trials) and 7 retrospective case–control studies. The inclusion process is illustrated in the PRISMA flow diagram shown in Fig. 2a. Studies were grouped based on omics approaches. Out of the 49 studies, three focused on the genomics approach, three addressed epigenomics, and five explored the transcriptomics approach. Thirty-six studies focused on proteomics, six on metabolomics, and three on the gut microbiome. Six of the studies reported multiple omics approaches (Fig. 2b) [29–34]. Of the 49 studies included, 48 were rated as *good* and 1 as *fair* based on the NIH Quality Assessment Tool (Supplementary Table 2). A summary of all the included studies can be found in Table 1.

Genomics

Identifying genetic factors related to T2D may help to guide the establishment of novel interventions for patients and minimize the risk of CVD. It could provide weight management strategies pre- and post-bariatric surgery and influence CVD outcomes. Of the 49 studies included in this review, three addressed a genomic approach [35–37]. Benenati et al. [35] investigated the impact of the DIO2 p.Thr92Ala substitution in 32 T2D subjects which caused by a single nucleotide polymorphism (SNP) (rs225014) on the response to bariatric surgery in patients with T2D at 12 months follow-up. The study found that there was no association between the p.Thr92Ala polymorphism and the presence of T2D

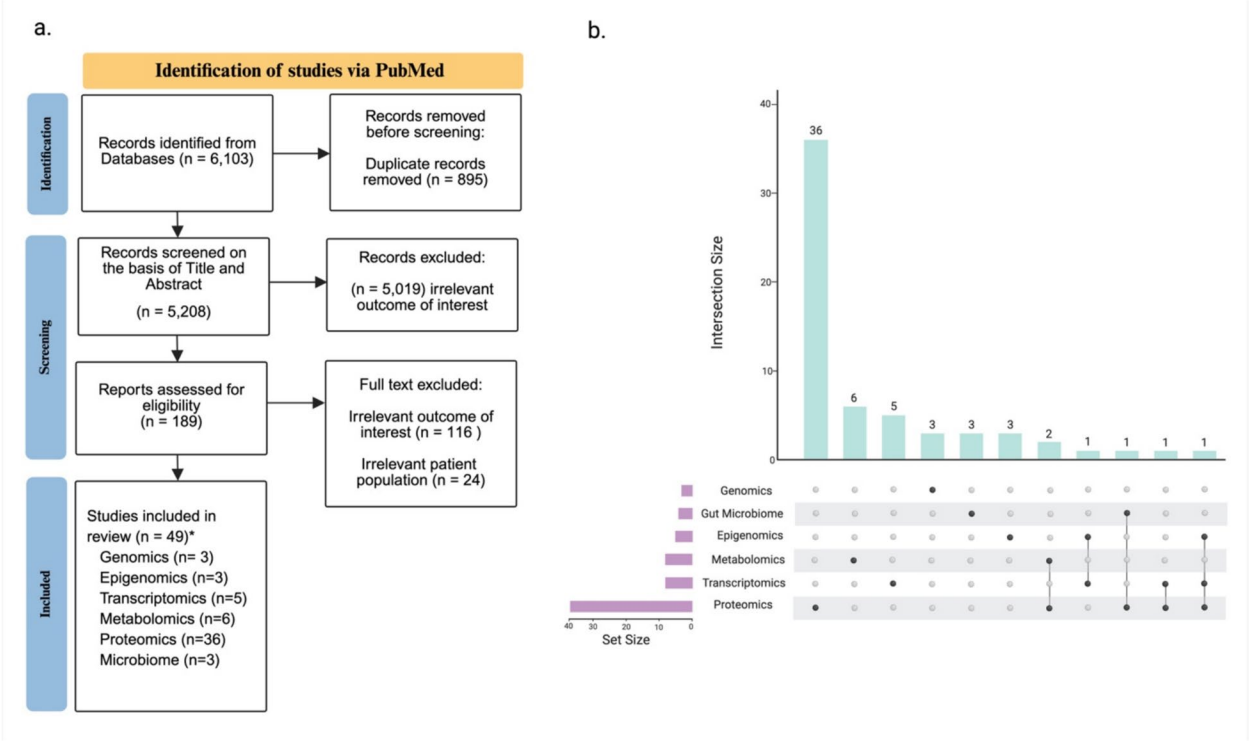

Fig. 2 PRISMA flowchart and upset plot of included studies.(**a**) PRISMA Flowchart illustrating the selection process. (* Note: Six studies included multiple approaches).(**b**) Upset plot summarizing shared OMICs approaches within the included studies. Overlapping OMICs approaches are indicated by intersections in the dot-and-line chart. The upper bar chart illustrates the number of studies per set intersection and the lower left bar chart shows the number of studies addressing each approach

Table 1 OMICS studies examining bariatric surgery effects on inflammation and cardiac health in T2D patients

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Benenati et al. [35]; 2022	Retrospective cohort study	RYGB, OAGB, SG and GB	Unit of Endocrinology, University of Siena, Italy	32	43 ± 11	45.3 ± 7.0	BMI 30–35 kg/m^2 and T2D with poor control despite optimal medical therapy	1	Peripheral blood leukocytes	Genotyping	No association between Thr92Ala polymorphism and the presence of T2D
Schnor N. et al. [36]; 2016	Prospective cohort study	RYGB	Brazilian	76 (100% female)	Not reported	Not reported	Female aged 20–50 years	1	Whole blood	Genotyping	The prevalence of T2D among Brazilian women with obesity was associated with the genetic variants rs3813929 ($p = 0.001$) in the 5-HT2C gene and rs1800849 ($p = 0.019$) in the UCP3 gene
Gatta-Cherifi B. et al.[37]; 2023	Prospective cohort study	SG	European	1	24	64	NA	1	Peripheral blood	Miseq sequencing	A novel loss-of-function variant in MRAP2 was found in a T2D patient with severe obesity
Zerrweck C. et al. [38]; 2016	Prospective cohort study	GB	Mexican	12	Not reported	38.5 ± 2.93	T2D patients with severe obesity	0.5	Subcutaneous adipose tissue biopsy	DNA methylation	A total of 1152 CpG sites differentially methylated
Vohl M-C et al. [33]; 2015	Prospective cohort study	BPD/DS	Quebec Heart and Lung Institute; Canada	20 (100% female)	28.9 ± 3.7	45.0 ± 7.2	Women with severe obesity and T2D	4–22	Whole blood, plasma, and buffy coat	ELISA, Microarray, Bisulfite conversion and quantitative DNA methylation	Differential methylation analysis identified 15,343 genes demonstrating at least one site ($p < 1.43 \times 10^{-7}$). *FKBP1A* and *ZNF323* genes showed the highest correlations with insulin and HOMA-IR ($p < 0.0001$)

Table 1 (continued)

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Benton M. et al. [30]; 2015	Prospective cohort study	GB	Wakefield Hospital, New Zealand	15 (100% female)	44 ± 10	47.6 ± 11.3	Women with obesity	1.5 ± 0.5	Subcutaneous and omental adipose tissue and whole blood	DNA methylation and mRNA qPCR	A greater proportion of CpGs are hypermethylated before weight loss. Robust correlations were identified between fasting glucose and *HDAC4*, *SLC37A3* and *DENND1C* in subcutaneous adipose
Almby K. et al. [29]; 2021	Randomized controlled trial	RYGB	Department of Endocrinology and Diabetes at Uppsala University Hospital; Sweden	13 (76.9% female)	51 ± 10	36.8 ± 3.9	T2D patients aged 18–60 years, with a BMI of 30–45 kg/m^2 and diabetes duration < 10 years and treated with < three antidiabetic agents but not insulin	2	Adipose tissue	mRNA qPCR	Adipogenesis genes (*PPARG, CEBPA, CEBPB, BMP4, FABP4,* and *FAS*) ($p < 0.05$), glucose transport (*GLUT1, GLUT4, AKT1,* and *IRS1* ($p < 0.1$)), and fatty acid oxidation (*CPT1B*) ($p < 0.001$) were increased. While *IL6* ($p < 0.1$) and *IL18* ($p < 0.01$) were decreased
Rega-Kaun et al. [39]; 2020	Prospective cohort study	RYGB	Caucasian; Austria	17	Not reported	Not reported	Not reported	1	Plasma and serum	miRNA qPCR	miR-122, miR-130, and miR-132 were significantly decreased, while miR-375 was increased ($p < 0.001$ for all miRNAs)
Fachim et al. [40]; 2020	Prospective cohort study	RYGB, and SG	Salford Royal Hospital; United Kingdom	5	Not reported	Not reported	Patients with impaired glucose regulation aged 18–80 years	0.5	Adipose tissue	mRNA qPCR	Caveolin-1 was discreetly increased ($p = 0.084$)
Lee SJ et al. [44]; 2021	Prospective cohort study	RYGB, and SG	Korean Obesity Surgical Treatment Study	18 (27.8% female)	43.8 ± 13	37.8 ± 5.9	BMI ≥ 35 kg/m^2 or 30.0–34.9 kg/m^2 and obesity-related comorbidities	0.5	Serum	UPLC/TQ-MS	Increased levels of TMAO ($p = 0.043$) and decreased levels of its precursor choline ($p = 0.091$) after RYGB; while no change after GB

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Härm A. et al. [31]; 2020	Prospective cohort study	RYGB	Oulu University Hospital; Finland	16 (63% female)	49.8 ± 8.1	41.8 ± 4.4	Adults aged 18–65 years undergoing bariatric surgery	0.5	Feces and serum	Not reported	Fecal short-chain fatty acids (SCFAs), especially acetate ($p < 0.002$) and butyrate ($p < 0.03$) levels, were significantly lower after surgery
Narath S. et al. [45]; 2016	Prospective cohort study	RYGB	Medical University of Graz Austria and Interdisciplinary Obesity Center in St. Gallen Switzerland	24	46.8 ± 11.3	43.9 ± 5.4	Adults aged > 18 yers	1	Serum	LC-HRMS	A significant decline in Sarcosine ($p = 0.031$), pyroglutamic acid ($p = 0.044$), alanine ($p = 0.005$) and leucyl-proline ($p = 0.049$) in patients with diabetes remission compared to patients without diabetes remission
Arora T. et al. [46]; 2015	Prospective cohort study	RYGB	Not reported	14 (71.4% female)	48.45 ± 2.87	49.1 ± 2.74	Patients undergoing RYGB	42 days	Plasma	GC/TOF–MS	T2D in remission exhibited higher pre-surgery levels of tricarboxylic acid cycle intermediates and TG with long-chain fatty acids compared to those not in remission
Thaker V. et al. [47]; 2024	Prospective cohort study	RYGB and GB	10 US hospitals	93 (69.9% female)	51.5 ± 9.83	46.63 ± 7.43	T2D adults aged ≥ 18 years undergoing RYGB or GB	2	Plasma	LC/MS	Changes in BCAAs and branched chain keto acids were positively linked with the change in A1c (false discovery rate $q < 0.001$)

Table 1 (continued)

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Zhao S. et al. [34]; 2024	Prospective cohort study	RYGB	Oulu University Hospital; Finland	16 (63% female)	49.8 ± 8.1	41.8 ± 4.4	Adults aged 18–65 years undergoing bariatric surgery	0.5	Faces and serum	ELISA and NMR	TG, cholesterol, Apo-B-100, lactate, and glycoprotein acetyls were decreased ($p < 0.0031$). The concentrations of BCAA (leucine, isoleucine, and valine) and aromatic amino acids (phenylalanine and tyrosine) decreased ($p < 0.0031$) by 17% for tyrosine and 23% for leucine
Song Z et al. [54]; 2022	Prospective cohort study	RYGB	Jinshazhou Hospital of Guangzhou University of Traditional Chinese Medicine	3	Not reported	40.41 ± 5.65	Adults with obesity aged between 18–70 years who are candidates for bariatric surgery	Not reported	Omental adipose tissue and serum	LC–MS/MS and ELISA	AIP1 was increased ($p < 0.05$) and TNF-α was decreased ($p < 0.05$) post-RYGB
Al Shawaf E et al. [51]; 2020	Prospective cohort study	SG	Dasman Diabetes Institute; Kuwait	11	Not reported	41 ± 3.35	Normal weight and patients with T2D and severe obesity	1	Plasma and serum	Immunoassay analyzer and ELISA	The Atherogenic Index of Plasma AIP (log TG/HDL) ($p < 0.01$) and hsCRP ($p < 0.01$) were significantly decreased after SG. No significant change was observed in Ox-LDL

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Adam S et al. [49]; 2019	Prospective cohort study	RYGB	Salford Royal Hospital; England	20	Not reported	Not reported	Not reported	1	Plasma and serum	Immunoturbidimetric assays and ELISA	hsCRP, IL-6, TG ($p<0.001$) and small, dense SD-LDL ApoB ($p<0.001$) decreased, while HDL cholesterol increased ($p<0.001$) significantly. No significant change was observed in total ApoB
Bonaventura A et al. [52]; 2019	Prospective cohort study	RYGB and BPD	Surgical Department of Genoa University; Italy	31 (16.13% female)	56 ± 7.77	34.9 ± 9.96	T2D patients aged between 35–70 years, with diabetes duration > 3 years, and A1c ≥ 7.5%	5	Serum	ELISA	Low NLR is associated with long-term T2D remission and CRP levels decreased after surgery
Wei J-H et al. [53]; 2022	Prospective cohort study	OAGB	Min-Sheng General Hospital; Taiwan	40 (57.5% female)	47.8 ± 11.3	39.3 ± 8.5	Adults with obesity aged between 18–65 years with a BMI of ≥ 27.5 kg/m^2 and A1c > 7% and who failed the medical control for obesity with acceptable operative risk	1	Serum	ELISA	FGF-19 and ox-LDL decreased significantly ($p<0.001$) and Corin increased significantly ($p=0.027$). Changes in FGF-21 and sRAGE were not significant
Ghanim H. et al. [55]; 2018	Prospective cohort study	RYGB	New York	15 (66.67% female)	53.8 ± 32.9	52.1 ± 18.6	T2D patients with severe obesity with a BMI of ≥ 40 kg/m^2	0.5	Plasma	ELISA	Neprilysin was decreased post-RYGB ($p<0.05$). LDL and TG were decreased while was HDL increased ($p<0.05$). No significant change was observed in total cholesterol level

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Ho JH. et al. [62]; 2020	Prospective cohort study	RYGB, SG and omega loop bypass	Salford Royal NHS Foundation Trust tertiary weight management centre; United Kingdom	37	51.4 ± 10.5	49.7 ± 10	Patients with severe obesity undergoing bariatric surgery	1	Plasma	chemiluminescent immunoassays and ELISA	Lp(a) levels were increased while OxPL-apoB ($p < 0.05$) levels were decreased. No significant change was observed in Ox-LDL
Lee P. et al. [56]; 2018	Retrospective cohort study	SG and GB (RYGB and mini GB)	Ethnic composition consists of Chinese, Malay, and Indian from recruited from a hospital in Singapore	145 (57.9% female)	47.6 ± 9.1	40.0 ± 7.6	T2D patients who underwent either primary SG or GB and who have at least 1 year of follow-up	1	Not reported	Not reported	HDL levels increased ($p < 0.001$), while TG decreased (in SG ($p = 0.003$) and in GB ($p < 0.001$). LDL increased ($p = 0.004$) after SG but was unchanged after GB ($p = 0.239$)
Huang Y. et al. [57]; 2022	Prospective cohort study	SG	Taipei Medical University Hospital, Taiwan	95 (53.7% female)	41.8 ± 8.78	42.5 ± 7	Undergoing the primary SG surgery	1	Serum	Not reported	According to the Framingham 10-year CHD risk model, the overall CVD risk decreased from 32.4 to 17.2% in the men and from 15.8 to 5.8% in the female, respectively, after SG ($p < 0.001$). TG decreased ($p < 0.05$) and HDL increased ($p < 0.05$)
Billington E. et al. [63]; 2019	Randomized controlled trial	SG	North Shore Hospital; New Zealand	22 (41% female)	49.3 ± 8.72	41.6 ± 7.92	Adults aged 22-55 years undergoing bariatric surgery with at least 6 months duration of T2D with a BMI of 35-65 kg/m^2 for at least 5 years	1	Plasma	ELISA	FGF23 ($p = 0.005$), PTH ($p = 0.009$) and leptin ($p = 0.01$) declined following SG

Table 1 (continued)

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Härm A. et al. [31]; 2021	Prospective cohort study	RYGB	Oulu University Hospital; Finland	16 (63% female)	49.8 ± 8.1	41.8 ± 4.4	Adults aged 18–65 years undergoing bariatric surgery	0.5	Faces and serum	Not reported	TG decreased ($p = 0.026$) and fecal calprotectin levels ($p < 0.001$), active LPS concentration ($p = 0.001$), ASCA ($p = 0.003$), and MG-H1 ($p < 0.001$) increased significantly, while the SCFA acetate ($p = 0.04$) was significantly lower
Iqbal Z. et al. [50]; 2022	Prospective cohort study	RYGB	Specialized and complex obesity/bariatric service in Manchester; United Kingdom	24	Not reported	52.29 ± 8.86	Not reported	1	Serum and plasma	ELISA and immunoturbidimetric assays	The levels of IL-6 ($p < 0.0001$), glycApoB ($p < 0.05$), HOMA-IR ($p < 0.001$), CRP ($p < 0.001$) decreased significantly, while HDL ($p < 0.001$) and total cholesterol ($p < 0.38$) increased
Lau E. et al. [32]; 2021	Randomized controlled trial	RYGB	Centro Hospitalar São João (CHSJ); Portugal	8 (50% female)	53.4 ± 8.78	33.6 ± 1.84	T2D adults aged between 20–65 years with a BMI ≥ 30 kg/m^2 and T2D duration > 3 months, overnight fasting C-peptide > 0.7 ng/ml and negative antiGAD autoantibody	1	Serum	Enzymatic colorimetric test, HPLC and electrochemiluminescence immunoassay	C-peptide, and HOMA-IR were significantly decreased ($p = 0.020$ and $p = 0.027$, respectively), while HDL ($p = 0.003$) increased significantly
Faramia J. et al. [64]; 2021	Prospective cohort study	RYGB, SG and BPD/DS	IUCPQ; Canada	20 per surgery type (70% female per surgery type)	49.5 ± 6.49	44.6 ± 5.46	Adults aged ≥ 18 years with a BMI > 40 kg/m^2 or > 35 kg/m^2 with a comorbidity	1	Plasma	ELISA	Plasma IGFBP-2 increased significantly ($p < 0.0001$) reaching higher levels after BPD-DS than after RYGB and SG

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Shah R. et al. [58]; 2019	Retrospective cohort study	SG and GB	Bariatric surgery and Framingham Heart Studies; United States	Bariatric cohort: 17 Framingham Heart cohort: 192 (42% female)	Bariatric cohort: Data not reported, Framingham Heart cohort: 56.3 ± 11.6	Bariatric cohort: data not reported. Framingham Heart cohort: 32.4 ± 6.3	Adults from Bariatric surgery and Framingham Heart cohorts	Bariatric cohort: 1 Framingham Heart cohort: 6.3	Plasma	Proximity Extension Assay and ELISA	More than 180 proteins were analyzed, and only IGFBP-2 protein was associated inversely with diabetes risk and increased after surgery ((OR = 0.63, 95% CI 0.49–0.79, $p = 0.0001$)
Jahansouz C. et al. [65]; 2019	Randomized controlled trial	RYGB	University of Minnesota, Columbia University in New York, and Mayo Clinic in Rochester	34 (65% female)	51 ± 9	36.1 ± 2.7	T2D adults aged > 30 years, with a BMI of 30.0–39.9 kg/m^2, undergoing treatment for T2D for at least 6 months, A1c ≥ 8.0%, and C-peptide > 1.0 ng/ml 90 min after a liquid mixed meal	1	Serum	ELISA	Circulating FABP4 decreased by 42% after surgery ($p = 0.002$)
Seki Y. et al. [59]; 2018	Retrospective cohort study	LSG-DJB	Japanese	72 (48.6% female)	46.8 ± 9.0	31.7 ± 2.0	T2D patients with Mild obesity with a BMI < 35 kg/m^2 underwent LSG-DJB B from September 2007 to March 2015, and the patients who presented for at least 1 year of follow-up	1	Not reported	Not reported	Fasting C-peptide, systolic BP, diastolic BP, LDL-C, and TGs decreased ($p < 0.001$); while HDL increased significantly from the baseline ($p < 0.001$)
Demyanets S. et al. [66]; 2020	Prospective cohort study	RYGB	Austrians	25	Not reported	Not reported	Adults aged ≥ 18 years with a BMI > 40 kg/m^2 or > 35 kg/m^2 with secondary disease and the failure or futility of a structured conservative program	1	Serum	ELISA	The pro-inflammatory marker sST2 decreased by 43% after surgery ($p = 0.0016$) and showed positive correlation with IL-33 (r = 0.44, $p = 0.05$)

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Almby K. et al. [29]; 2021	Randomized controlled trial	RYGB	Department of Endocrinology and Diabetes at Uppsala University Hospital; Sweden	13 (76.9% female)	51 ± 10	36.8 ± 3.9	T2D patients aged 18–60 years, with a BMI of 30–45 kg/m^2 and diabetes duration < 10 years and treated with < three antidiabetic agents but not insulin	2	Not reported	Enzymatic immunoassays	HDL increased ($p < 0.01$), while FFA, TGs and CRP reduced significantly ($p < 0.001$, $p < 0.01$, $p < 0.05$; respectively)
Istomin N. et al. [60]; 2022	Prospective cohort study	RYGB	Oulu University Hospital; Finland	16 (62.5% female)	49.8 ± 8.1	41.8 ± 4.4	Adults aged between 18–65 undergoing RYGB	0.5	Plasma and feces	Chemiluminescence immunoassay	Total fecal IgA was increased ($p = 0.020$), while total IgM and IgG were not affected by the surgery
Espinosa O. et al. [61]; 2018	Prospective cohort study	RYGB	Mexicans	23 (87% female)	44.4 ± 7.7	33.1 ± 1.1	Mexican patients with mild obesity (BMI 30–34.9 kg/m^2) aged 18–60 years with T2D who underwent laparoscopic gastric bypass between January 2014 and January 2015	1.5	Not reported	Not reported	Cardiovascular risk was improved significantly ($p = 0.03$) which was calculated by dividing total cholesterol by HDL. C peptide was decreased significantly ($p < 0.001$)
Munkonda et al. [87]; 2012	Prospective cohort study	BPD/DS	Bariatric surgery clinic of the Institut universitaire de cardiologie et de pneumologie de Que´bec (IUCPQ); Canada	22 (100% female)	42.0 ± 10.6	49.8 ± 7.9	Women, aged > 18 years, with BM ≥ 40 or BMI ≥ 35 kg/m^2 with associated comorbidities	1	Plasma	Turbidimetric inhibition immunoassay and ELISA,	Acylation stimulating protein was decreased ($p < 0.001$), as well as glucose, insulin, HOMA-IR, TG, cholesterol, LDL, HDL and hsCRP levels
Kim M. et al. [88]; 2013	Prospective cohort study	RYGB	Yeouido St. Mary's Hospital	57 (66.7% female)	43.5 ± 10.1	34.2 ± 4.1	T2D patients aged 19–64 years, with a BMI > 30 kg/m^2	1	Serum	ELISA	Levels of BMP-4 ($p = 0.024$), PAI-1, hsCRP, and FFAs were significantly decreased

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Zhao X. et al. [89]; 2017	Prospective cohort study	RYGB	Jiahe Surgical Hospita; China	20 (65% female)	42.70 ± 12.60	34.20 ± 6.22	Chinese patients with T2D and obesity undergoing RYGB surgery	1.5	Serum	Immunoassay analyzer	The 10-year cardiovascular risk of coronary heart disease decreased from 13.05% to 3.81% ($p = 0.001$) and the 10-year risk of stroke decreased from 19.66% to 14.22% ($p = 0.002$)
Shimizu H. et al. [90]; 2017	Prospective cohort study	SG	Tokyo Metropolitan Tama Medical Center; Japan	10 (50% female)	48.8 ± 2.7	40.9 ± 3.2	BMI > 35 kg/m^2	0.5	Serum	ELISA	hsCRP and plasminogen activator inhibitor-1 were decreased at 6 months. No significant changes were observed in IL-6, IL-8, TNF-α, serum amyloid A protein, and monocyte chemotactic protein-1
Liang Z. et al. [91]; 2013	Randomized controlled trials	RYGB	Southwest Hospital of Third Military Medical University; China	31 (29% female)	50.81 ± 5.44	30.48 ± 0.94	T2D patients aged 30–60 years with BMI > 28 kg/m^2	1	Plasma and serum	ELISA	Surgery group had the greatest degree of improvement ($p < 0.05$) compared to the usual care group in the inflammation index (hsCRP, TNF-a, and high molecular weight adiponectin)
Cazzo E. et al. [92]; 2014	Retrospective cohort study	RYGB	Hospital das Clínicas da Unicamp; Brazil	96 (23% female)	46 ± 10.8	44.3 ± 8.74	Subjects with obesity who underwent RYGB	1	Not reported	Not reported	Significant reductions ($p < 0.0001$) in fasting glucose, fasting insulin, A1c, LDL, and TG levels, along with an increase in HDL levels ($p < 0.0001$)

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Kota S. et al. [93]; 2012	Prospective cohort study	II-DSG	Kirloskar Hospital; India	17 (29.4% female)	29.2 ± 7.5	50.7 ± 8.1	T2D of 5 years duration aged 25–70 years with BMI ≥ 20 kg/m^2 and stimulated C-peptide level > 1 ng/ml	1.5	Serum and plasma	Chemiluminescence, Immunoturbidimetry assay and HPLC	Significant decrease in glycemic, lipid parameters, and microalbuminuria ($p < 0.05$)
Boza C. et al. [94]; 2011	Retrospective cohort study	RYGB	Pontificia Universidad Católica; Chile	30 (56.6% female)	48 ± 9	33.5 ± 1.2	T2D patients with a BMI 30–35 kg/m^2	2	Serum and plasma	Chemiluminescent immunoassay	Significant reductions ($p < 0.05$) in fasting glucose, fasting insulin, TG and A1c, along with an increase in HDL levels. No significant change in LDL, and TC levels
Courcoulas A. et al. [95]; 2024	Randomized controlled trial	RYGB, SG and GB	Cleveland Clinic, Joslin Diabetes Center, University of Pittsburgh, and University of Washington; US	166	49.0 ± 9.0	36.6 ± 3.6	T2D adults aged between 18–65 years with a BMI 27–45 kg/m^2	12	Not reported	Not reported	Patients who underwent bariatric surgery had better glycemic control, fewer diabetic medications, and greater rates of remission compared to those who received medical/lifestyle interventions
Pané A. et al. [96]; 2024	Prospective cohort study	RYGB and SG	Spain	18 (75% female)	51.0 ± 5.4	43.2 ± 4.3	Adults aged between 18–70 years with a BMI > 40 or > 35 kg/m^2 with obesity-related comorbidities	1	Plasma	Not reported	Significant decrease ($p < 0.001$) in fasting glucose, TG, hs-CRP and A1c
Martínez-Montoro J et al. [97]; 2023	Prospective cohort study	SG and BPD	Virgen de la Victoria University Hospital; Spain	98 (73.5% female)	48.08 ± 8.87	49.53 ± 7.18	T2D adults aged ≥ 18 years with a BMI ≥ 35 kg/m^2	1	Serum	Immunoassay	Significant differences in T2D remission were found between patients with TG ≥ 150 mg/dl and < 150 mg/dl ($p = 0.002$)

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Happonen N. et al. [98]; 2024	Prospective cohort study	RYGB	Oulu University Hospital; Finland	16 (62.5% female)	49.8 ± 8.1	41.8 ± 4.4	A medical indication for RYGB with an age of 18–65 years	0.5	Plasma and faces	Chemiluminescent immunoassay	Improvement in the systemic inflammation state evidenced by decreased levels of total plasma IgG, better hypertension and hyperglycemia, and their correlations with lower levels of certain plasma antibodies
Qi QYD et al. [99]; 2023	Randomized controlled trial	GB	Australia	21 (81% female)	53	29.5	T2D adults aged 18–65 years with a BMI 25–30 kg/m^2	10	Not reported	Not reported	HDL increased at 10 years ($p = 0.030$), but there was no significant change in blood pressure or other lipid measures
Chakaroun R. et al. [67]; 2021	Prospective cohort study	Not reported	University of Leipzig Medical Center; Germany	24 (70.83% female)	50.1 7.94	49.0 ± 6.68	BMI ≥ 40 kg/m^2, or ≥ 35 kg/m^2 with at least one obesity comorbidity	1	Whole EDTA blood	16S rRNA sequencing	At the phylum level: *(Proteobacteria, Firmicutes*, and *Patescibacteria)* - (*Cyanobacteria and Actinobacteria)* At the genus level: - (*Sphingomonas, Pseudomonas, Bacillaceae,* and *Burkholderiaceae*) (*CM1G08, Acinetobacter,* and *Acidibacter*)

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery
Lau E. et al. [32]; 2021	Randomized controlled trial	RYGB	Centro Hospitalar São João (CHSJ); Portugal	8 (50% female)	53.4 ± 8.78	33.6 ± 1.84	T2D adults aged between 20–65 years with a BMI ≥ 30 kg/m^2 and T2D duration > 3 months, overnight fasting C-peptide > 0.7 ng/ml and negative antiGAD autoantibody	1	Stool	16S rRNA sequencing	At the phylum level: *Proteobacteria* and *rPF;* No significant difference was observed in rFB At the genus level: prokaryotic genera richness ($p = 0.03$) and *(Klebsiella, Gammaproteobacteria, Enterobacter, unclassified Gammaproteobacteria,* and *unclassified Veillonellaceae)* ¯ *(Ruminococcus, unclassifed Lachnospiraceae family* and *Faecalibacterium)*
Assal K. et al. [68]; 2020	Prospective cohort study	RYGB	Coloproctology and Digestive Surgery Service of Hospital das Clínicas of the University of São Paulo, School of Medicine (HC-FMUSP); Brazil	25	45.80 ± 7.95	46.40 ± 5.48	Aged 18–60 years, BMI ≥ 35 kg/m^2, confirmed diagnosis of T2D with a fasting glucose ≥ 126 mg/dL, glycated hemoglobin (A1c) ≥ 7%, and current use of oral anti-diabetic drugs	1	Stool	16S rRNA sequencing	At the phylum level: *Proteobacteria* and ¯ rFB (rFB = 1.53 vs. 3.27, $p < 0.046$) At the genera level: (*Veillonella* and *Streptococcus*) and ¯ (*Flavonifractor, Blautia,* and *Butyricicoccus*) ($p < 0.005$) Only the *Oribacterium* ↓ between the 3- and 12-month time points postoperatively ($p < 0.003$)

Table 1 (continued)

Study	Study design	Intervention	Cohort	No. T2D subjects	Mean age (Years)	Mean BMI (kg/m^2)	Inclusion criteria	Follow-up (Years)	Sample type	Analytical technique	Biomarkers and outcomes post-surgery

aHR: adjusted hazard ratio; AIP: atherogenic index of plasma; AIP1: Abstract Actin-interacting protein 1; AMI: acute myocardial infarction; ApoB: Apolipoprotein B100; ASCA: anti-saccharomyces IgA antibodies; BCAAs: Branched-chain amino acids; BPD/DS: Biliopancreatic diversion with duodenal switch; CHD: coronary heart disease; CI, Cumulative incidence; CRP: C-reactive protein; ELISA: enzyme-linked immunosorbent assay; FABP4: Fatty acid binding protein 4; FFA: Free fatty acid; FGF: fasting serum fibroblast growth factor; GB: gastric bypass; GC/TOF–MS: gas chromatograph combined with time-of-flight mass spectrometer; HDL: high density lipoprotein; HF: heart failure; HOMA –IR: Homeostatic model assessment of insulin resistance; HPLC: High Performance Liquid Chromatography; hsCRP: Highly sensitive C-reactive protein; IGFBP-2: insulin-like growth factor binding protein-2; IGFBP: Insulin-like growth factor-binding protein; Il-DSG: Ileal interposition with diverted sleeve gastrectomy; LC-HRMS: liquid chromatography coupled to high resolution mass spectrometry; IL: interleukin; IUCPQ: Institut Universitaire de Cardiologie et de Pneumologie de Québec; LDL: low-density lipoprotein, Lp(a) lipoprotein(a); LPS: active lipopolysaccharide; LSG-DJB: Laparoscopic sleeve gastrectomy with duodenojejunal bypass; MG-H1: methylglyoxal-hydro-imidazolone; NLR: Neutrophil-to-lymphocyte ratio; NMR: Nuclear magnetic resonance; OAGB: one-anastomosis gastric bypass; ox-LDL: oxidized low-density lipoprotein; OxPL: oxidised phospholipids; PAD: peripheral artery disease; qPCR: quantitative polymerase chain reaction; *rFB*, Firmicutes/Bacteroidetes ratio; *rPF*, Proteobacteria/Firmicutes ratio; RYGB, Roux-en-Y Gastric bypass; SCFAs: short-chain fatty acids; SG, sleeve gastrectomy; SNP: single nucleotide polymorphism; sRAGE: soluble receptor for advanced glycation end-products; sST2: soluble suppression of tumorigenicity-2; TG: triglycerides; TMAO: Trimethylamine N-oxide; TNF-α: Tumor necrosis factor; UPLC/TQ-MS: ultra-high-performance liquid chromatography/triple quadrupole mass spectrometry

($p = 0.8$), hypertension, dyslipidemia or metabolic syndrome regardless of the different DIO2 gene expression forms (Thr/Thr, Thr/Ala, Ala/Ala). The p.Thr92Ala polymorphism is a common SNP in the DIO2 gene, resulting in a threonine-to-alanine substitution at codon 92. Another study by Schnor et al. [36] showed that rs3813929 ($p = 0.001$) and rs1800849 ($p = 0.019$) polymorphisms in the *5-HT2C* and *UCP3* genes are associated with the prevalence of T2D among 76 Brazilian women with obesity who were candidates for bariatric surgery. Additionally, Gatta-Cherifi B. et al. [37] reported a novel loss-of-function variant in *MRAP2* found in one T2D patient with severe obesity who had a successful outcome following bariatric surgery.

Currently, insufficient data at present on predicting patients' responses to bariatric surgery suggest that these genetic variations cannot yet be employed in clinical practice. Moreover, the genomics approach illustrates only one essential element of biological variation, which must be considered alongside novel biomarkers emerging from proteomics, metabolomics, and microbiomes approaches.

Epigenomics

In the context of bariatric surgery, understanding the epigenetic alterations that occur before and after the procedure can provide valuable insights into the mechanisms driving T2D remission. This knowledge can be leveraged to identify patients who are more likely to experience positive epigenetic changes following surgery, enabling further personalization of treatment plans. This review includes three studies that investigated the epigenetic impact of bariatric surgery on T2D, all of which indicated significant DNA methylation changes in adipose tissue and blood post-surgery [30, 33, 38]. In Mexican populations, 1152 CpG sites showed differential methylation in abdominal subcutaneous adipose tissue in patients with T2D and obesity compared to patients with obesity but without T2D [38]. Enrichment analysis indicated that genes associated with differentially methylated CpG sites are implicated in metabolic pathways, with DNA methylation remodeling correlating with improved metabolic status. Furthermore, whole blood DNA methylation analyses in women with obesity revealed variations in methylated genes at the gene body region after surgery, linked to diabetic and inflammatory functions, including *ABCF1*, *FKBP1A*, *IFIT2*, and *HTT*, indicating durable metabolic improvements post-surgery [33]. Another study found that a larger proportion of CpGs are hypermethylated prior bariatric surgery in 15 T2D women, and increased methylation is observed in the 3′ untranslated regions and gene bodies compared to the promoter regions [30]. In addition, they reported that bariatric surgery altered the methylation of *PRDM16* within adipose tissue.

These findings suggest that the benefits of bariatric surgery for patients with T2D can be partially explained by epigenetic remodeling. While DNA methylation is the most extensively studied epigenetic regulatory mechanism, other epigenetic mechanisms, such as microRNAs and long non-coding RNAs, may also contribute to the regulation of T2D, CVD, and body weight. Additionally, further research is needed to understand the relationship between genetic and epigenetic factors in bariatric surgery outcomes.

Transcriptomics

Five transcriptomic studies have investigated the impact of bariatric surgery on T2D [29, 30, 33, 39, 40]. Almby K. et al. [29] studied the mRNA expression of different genes in patients with T2D undergoing bariatric surgery. They reported an increase in the expression of genes involved in adipogenesis (*PPARG, CEBPA, CEBPB, BMP4, FABP4,* and *FAS*), glucose transport (*GLUT1, GLUT4, AKT1,* and *IRS1*), and fatty acid oxidation (*CPT1B*) 104 weeks after RYGB. In addition, the levels of pro/anti-inflammatory cytokines (*IL6* and *IL18*) were shown to be decreased

post-surgery. These changes suggest enhanced lipid oxidation after surgery and highlight the importance of systemic inflammation and adipose tissue function in preventing microvascular and cardiovascular comorbidities. Rega-Kaun et al. [39] reported a significant change in miRNA profiles after bariatric surgery in patients with T2D. Specifically, they observed a significant decrease in miR-122, miR-130, and miR-132 levels one-year post-surgery, while miR-375 was increased ($p < 0.001$ for all miRNAs). These miRNAs were previously found to be associated with insulin resistance and β-cell dysfunction in people with obesity [41, 42]. On the other hand, Fachim et al. [40] found that the gene expression of *Caveolin-1* in fat tissue increased slightly, but not significantly ($p = 0.084$), in five patients with T2D six months after bariatric surgery. *Caveolin-1* is known for its role in stimulating the production of major pro-inflammatory cytokines [43]. Vohl M-C et al. [33] identified 15,343 genes from differential methylation analysis demonstrating at least one site with significant correlation ($p < 1.43 \times 10^{-7}$). The *FKBP1A* and *ZNF323* genes showed the highest correlations with insulin and HOMA-IR. In addition, Benton M. et al. [30] examined the mRNA expression of five genes that are associated with obesity and T2D with differential promoter methylation (*ACACA, CETP, CTGF, S100A8, S100A9* and *PLIN4*) in 15 T2D women. Findings reveal that the mRNA expression of *CTGF* ($p = 0.002$), *S100A8* ($p = 0.0005$), *S100A9* ($p = 0.0009$) and *PLIN4* ($p = 0.0002$) was upregulated, while *ACACA* ($p = 0.001$) and *CETP* ($p = 0.00008$) downregulated.

The previous studies employed traditional transcriptomic techniques, such as Quantitative PCR method (qPCR) and microarray. However, single-cell RNA sequencing technology has emerged to overcome many limitations of these traditional techniques, especially in detecting low-expressed and novel transcripts. Despite the promise of the transcriptomic approach for understanding T2D, there are still insufficient data highlighting major modifications induced by bariatric surgery in patients with T2D.

Metabolomics

Detecting an individual's metabolomics profile has a key role in predicting metabolic outcomes of disease states and early changes in particular biochemical pathways. Six prospective studies have studied metabolites profile to evaluate the impact of bariatric surgery on CVD risk in patients with T2D [31, 34, 44–47]. Lee SJ et al. [44] reported elevated levels of the microbiota-derived metabolite, trimethylamine N-oxide (TMAO) ($p = 0.043$) and a trend toward decreased levels of its precursor choline ($p = 0.091$) six months after RYGB in seven patients with T2D. However, no change in TMAO metabolite was observed in 11 patients with T2D who underwent SG. Further, Härm A. et al. [31] found that fecal short-chain fatty acids (SCFAs), especially acetate ($p < 0.002$) and butyrate ($p < 0.03$), were significantly lower after RYGB. These SCFAs are recognized for their anti-inflammatory features, which therefore, could be key contributors to preventing gastric inflammation [48]. Narath S. et al. [45] reported significant declines in sarcosine ($p = 0.031$), pyroglutamic acid ($p = 0.044$), alanine ($p = 0.005$) and leucyl-proline ($p = 0.049$) in patients with diabetes remission compared to those without remission after bariatric surgery. In addition, Arora T. et al. [46] showed that patients with T2D remission exhibited higher pre-surgery levels of tricarboxylic acid cycle intermediates and triglycerides with long-chain fatty acids compared to those not in remission. Thaker V. et al. [47] found that changes in branched-chain amino acids (BCAAs) and branched-chain keto acids after surgery were positively linked with changes in A1c (false discovery rate $q < 0.001$). Moreover, Zhao S. et al. [34] reported that BCAAs were the most affected metabolites six months after RYGB, with concentrations of aromatic amino acids and BCAAs decreasing by 17% for tyrosine and 23% for leucine.

Bariatric surgery has beneficial impacts on attenuating risks of CVD; however, additional long-term studies are needed to better understand the role of different metabolites in predicting the outcomes of bariatric surgery in patients with T2D.

Proteomics

The search strategy identified 36 studies exploring proteomics technology to uncover a variety of proteins that are associated with CVD risk in patients with T2D undergoing bariatric surgery. Inflammatory profiles play a crucial role in the metabolic disturbances of T2D, with inflammatory adipocytokines exacerbating diabetic vascular complications and coagulation responses. Key mediators of diabetogenic inflammation include Interleukin-6 (IL)–6 [49, 50], C-Reactive Protein (CRP) [50], CRP-high-sensitivity CRP (hs-CRP) [32, 49, 51–53], Tumor necrosis factor-alpha (TNF)-α [54], and lipid profiles [29, 31, 51, 53, 55–61] all implicated in insulin resistance and modulated by bariatric surgery. Other markers such as IL-8, Adiponectin, Resistin and Leptin also exhibit significant changes post-surgery. However, inconsistent data on short- and long-term inflammatory marker levels post-procedure highlights variability in surgical interventions. Nevertheless, a consistent decline in CRP levels across studies supports the fact that substantial attenuation of inflammation occurs post-bariatric surgery.

Additional CVD-related biomarkers include B-type natriuretic peptides (BNP) [55], oxidized low-density lipoprotein (oxLDL) [62], total apolipoprotein B (ApoB) [49, 50], fibroblast growth factors (FGF) 19, 21 [53] and

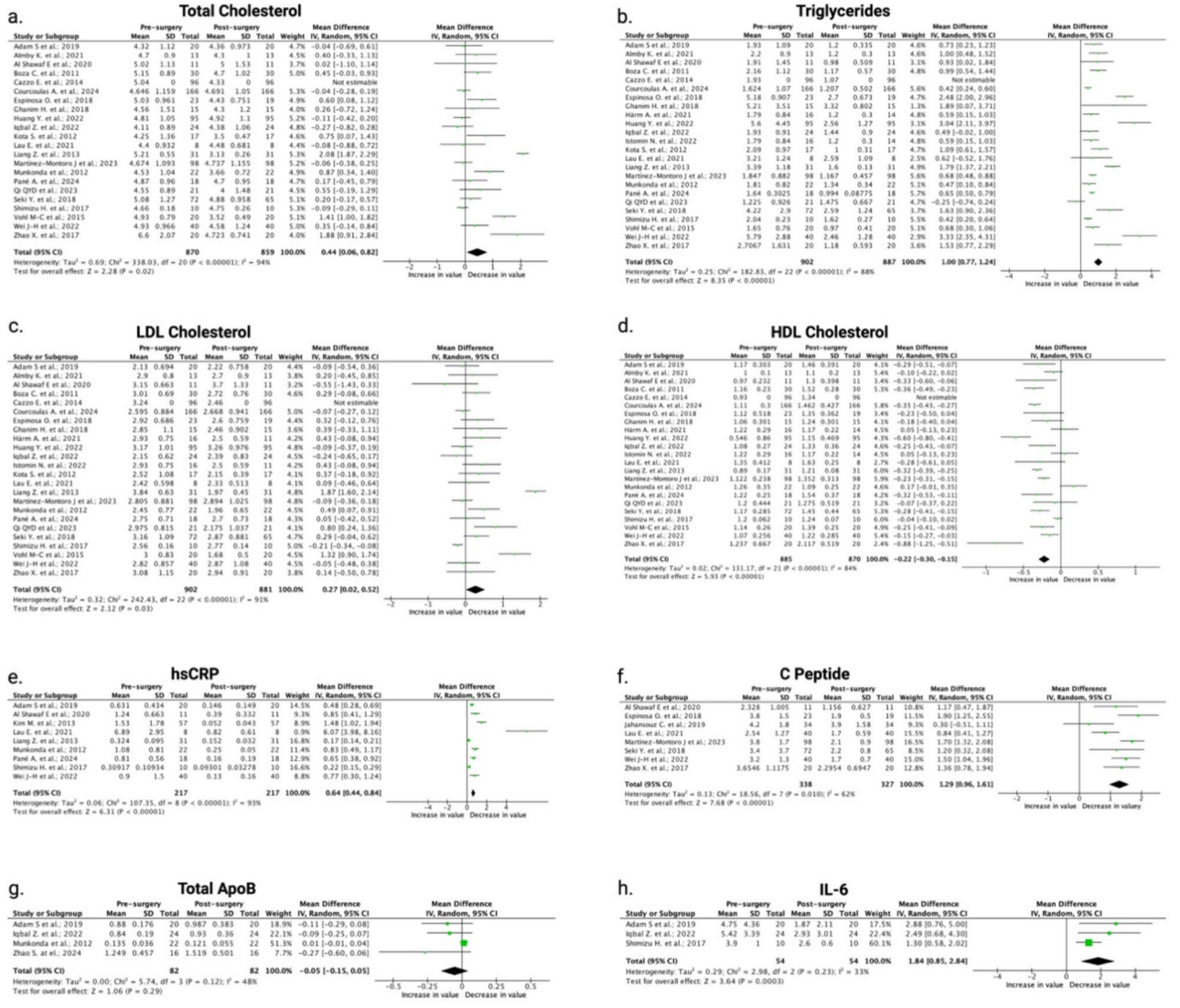

Fig. 3 Forest plots of mean differences and confidence intervals for inflammation biomarkers pre- and post-surgery. Analysis was performed at several postoperative time points using Random effects model of mean differences to assess the continuous data and statistical heterogeneity

23 [63], insulin-like growth factor-binding protein-2 (IGFBP-2) [64], fatty acid binding protein 4 (FABP4) [65], and soluble suppression of tumorigenicity-2 (ST2) [66]. These molecules hold promise as potential biomarkers for predicting CVD risk in patients with T2D and for the monitoring of patient responses to bariatric surgery.Fig 3 demonstrates the Forest plots of mean differences and confidence intervals for most redundant inflammation and CVD biomarkers (Total cholesterol, Triglycerides, LDL, HDL, hsCRP, C peptide, ApoB, and IL-6) across the studies that met the inclusion criteria for the meta-analysis. Total cholesterol levels were reported in 22 studies. Results showed that bariatric surgery significantly decreased total cholesterol levels (mean difference (MD) 0.44, 95% CI 0.06 to 0.82, $p = 0.02$, $I^2 = 94\%$) (Fig. 3a). Triglycerides and LDL cholesterol were reported in 24 studies. Their levels also decreased post-surgery (MD 1.00, 95% CI 0.77 to 1.24, $p < 0.00001$, $I^2 = 88\%$ for triglycerides; MD 0.27, 95% CI 0.02 to 0.52, $p = 0.03$, $I^2 = 91\%$ for LDL) (Fig. 3b and 3c). Conversely, HDL cholesterol increased (MD −0.22, 95% CI −0.30 to −0.15, $p < 0.00001$, $I^2 = 84\%$) (Fig. 3d), and hsCRP levels decreased (MD 0.64, 95% CI 0.44 to 0.84, $p < 0.00001$, $I^2 = 93\%$) (Fig. 3e) post-surgery. C peptide levels also significantly decreased (MD 1.29, 95% CI 0.96 to 1.61, $p < 0.00001$, $I^2 = 62\%$) (Fig. 3f), while ApoB levels increased but did not reach significance (MD −0.05, 95% CI −0.15 to 0.05, $p = 0.29$, $I^2 = 48\%$) (Fig. 3g). IL-6 was reported in three studies, with a I^2 value of 33%. Its levels were decreased post-surgery (MD 1.84, 95% CI 0.85 to 2.84, $p = 0.0003$, $I^2 = 33\%$) (Fig. 3h). These findings underscore the favorable impact of bariatric surgery on lipid profiles and inflammatory markers

crucial for cardiovascular health in patients with T2D. However, further research is needed to elucidate the mechanisms through which bariatric surgery mitigates inflammation and improves cardiometabolic outcomes in these individuals.

Microbiome

Three studies have investigated the impact of bariatric surgery on gut microbiota in patients with T2D [32, 67, 68]. Overall, these studies have shown that bariatric surgery leads to alterations in the gut microbiome and improvements in dysbiosis compared to baseline. Specifically, changes in the relative abundance of various bacterial phyla, orders, families, genera, and species have been observed post-surgery. At the phylum level, all three studies reported an increased relative abundance of *Proteobacteria* and a decrease in *Firmicutes* [32, 67, 68]. However, at the genus level, all studies reported contradictory results after bariatric surgery. Chakaroun R. et al. [67] observed reductions in *Sphingomonas, Pseudomonas, Bacillaceae,* and *Burkholderiaceae,* along with an increase in *CM1G08, Acinetobacter,* and *Acidibacter*, which are negatively associated with metabolic disease and inflammation markers, whereas positively associated with HDL cholesterol and blood bacterial quantity. In contrast, Lau E. et al. [32], reported an increase in *Klebsiella, Gammaproteobacteria, Enterobacter, unclassified Gammaproteobacteria,* and *unclassified Veillonellaceae,* while a decrease in *Ruminococcus, unclassifed Lachnospiraceae family* and *Faecalibacterium*. Assal K. et al. [68], found an increase in *Veillonella* and *Streptococcus* and a reduction in *Flavonifractor, Blautia, Butyricicoccus*, and *Oribacterium.*

These discrepancies likely stem from individual variations in how the gut microbiome responds to bariatric surgery. Therefore, further research is essential to comprehensively understand the mechanisms underlying these microbiota changes and their implications for improving metabolic outcomes in patients with T2D undergoing bariatric surgery. Clarifying these mechanisms could establish a foundation for targeted microbiome interventions to enhance the health benefits of surgical weight loss strategies in diabetes management.

Discussion

Postoperative outcomes of bariatric surgery show considerable heterogeneity among individuals, with patients achieving different responses. This systematic review, for the first time, identifies 49 studies from the existing literature that integrate omics datasets to provide a comprehensive analysis of the molecular and genomic determinants influencing individualized therapeutic responses to bariatric surgical interventions.

Genetic and epigenetic factors may influence how patients with T2D respond to bariatric surgery. Several SNPs, such as those in the MC4R, FTO, UCP2, ACSL5, 5-HT2C, UCP3, and MRAP2 genes, have shown associations with obesity, energy balance, and surgical outcomes [36, 37, 69–74]. However, the *DIO2* p.Thr92Ala polymorphism remain inconclusive [35]. While a global meta-analysis suggests it may be linked to poorer glycemic control and increased insulin resistance in patients with T2D [75]. Similarly, epigenetic signatures can also predict responses to bariatric surgery. Various epigenetic mechanisms can alter gene expression in response to environmental factors. Several studies have found significant DNA methylation changes in adipose tissue and blood following surgery [30, 33, 38]. In addition, the impact of bariatric surgery on specific gene promoter methylation has been reported in several candidate gene studies [76–78], although, none of these studies provided clear data specifically on patients with T2D undergoing bariatric surgery. It is crucial to note that the majority of epigenetic studies have been conducted with small sample sizes, therefore, the results should be interpreted carefully. The lack of sufficient genomics and epigenomics data on patients with T2D to fully explain the benefits of bariatric surgery presents a significant challenge. Overcoming this obstacle will require replication studies, as well as large-scale and longitudinal studies to pave the way for more effective and personalized healthcare solutions.

Transcriptomics is another key component of the omics approach to understanding gene expression changes in patients with T2D before and after surgery. Studies have identified altered expression in genes linked to obesity, T2D comorbidities, cardiovascular disease, adipogenesis, glucose regulation, inflammation, and fatty acid oxidation [29, 30, 33, 40, 79]. Bariatric surgery also affects miRNA levels related to pancreatic function and β-cell stress [39]. However, most studies rely on qPCR at single time points and lack RNA sequencing, limiting discovery of novel gene transcripts and dynamic changes over time. Moreover, transcriptomic data alone do not reveal functional effects, highlighting the need for complementary methods like proteomics or metabolomics for deeper biological insight.

Metabolomics can deliver a comprehensive view of these changes by spotting alterations in metabolite profiles coupled with improved insulin sensitivity, lipid metabolism, and inflammation; key factors in T2D and CVD. Bariatric surgery significantly alters amino acids, especially BCAAs, and reduces microbiota-derived metabolites like TMAO and SCFAs such as acetate and butyrate. [31, 34, 44, 47]. High TMAO levels are associated with T2D, obesity, and increased CVD risk, while SCFAs have anti-inflammatory properties that may help prevent gastric inflammation [48, 80–83]. Other

important metabolites like free fatty acids (FFAs) and lipids also need further study. However, variability in metabolite profiles due to genetics, lifestyle, and gut microbiome differences complicates identifying consistent metabolic patterns across patients.

The review meta-analyzed 36 proteomics studies and found that bariatric surgery improves metabolic health, reduces inflammation, and lowers cardiovascular risk in patients with T2D. Post-surgery, lipid profiles (total cholesterol, LDL, HDL, triglycerides) and inflammatory markers (IL-6, TNF-α, hs-CRP) improved, along with cardiac biomarkers like BNP, NT-proBNP, and adiponectin. Meta-analysis confirmed significant benefits, but high heterogeneity (>50%) was observed, likely due to differences in study design and assay techniques. Most studies used targeted immunoassays (e.g., ELISA), while others applied broader approaches such as the Proximity Extension Assay (PEA) or LC–MS, with LC–MS offering greater potential for discovery-based analysis [54, 58].

Microbiome dysbiosis is increasingly linked to T2D and its complications [84, 85]. Three studies using 16S rRNA sequencing found consistent phylum-level shifts post-bariatric surgery, including increased Proteobacteria and decreased Firmicutes, likely due to dietary and nutrient changes post-surgery [32, 67, 68]. However, findings at the genus level varied across studies, likely due to inherent inter-individual variability in microbial compositions. These variabilities create a challenge to identifying consistent microbial signatures associated with T2D, CVD, or bariatric surgery outcomes. While 16S rRNA provides limited resolution, advanced techniques like shotgun metagenomics offer deeper insight into microbial function and composition [86]. Such tools may uncover therapeutic targets, with microbiome modulation emerging as a promising adjunct to improve metabolic outcomes in T2D management.

Across the 49 studies, only six investigated multiple omics layers simultaneously [29–34]. Almby K. et al. [29] covered both transcriptomics and proteomics. Härm A. et al. [31] and Zhao S. et al. [34] covered both metabolomics and proteomics layers. Lau E. et al. [32] explored both gut microbiome and proteomics. Benton M. et al. [30] examined epigenomics and transcriptomics, while Vohl M-C et al. [33] integrated epigenomics, transcriptomics, and proteomics. With the ongoing advancements in systems biology, diabetes research is expected to become more systematic and in-depth. Multi-omics signatures offer a comprehensive view of the complex interplay of biological processes implicated in T2D remission and CVD risk reduction post-surgery. They promise the development of personalized diagnostics, predictive disease risk assessments, and targeted therapies that are not only more effective but also less likely to cause adverse effects in patients with T2D.

Despite these promising efforts, the critical appraisal of included studies reveals several methodological limitations. Follow-up durations were highly variable, ranging from a few weeks to several years, which complicates direct comparisons of post-surgical outcomes. Furthermore, inconsistencies in outcome definitions, such as T2D remission or CVD improvement were common ranging from short-term glycemic control to longer-term medication independence, or from surrogate biomarker changes to hard cardiovascular outcomes. This heterogeneity undermines the ability to draw unified conclusions across studies by limiting comparability, constraining meta-analytic power, and complicating translation into clinical practice. A notable limitation is the heavy reliance on surrogate endpoints rather than definitive clinical outcomes, which, while providing mechanistic insights, may not fully predict long-term patient benefit. Future research would benefit greatly from the adoption of harmonized, standardized, and clinically relevant endpoints. This would enhance reproducibility, strengthen evidence synthesis, and ultimately improve the applicability of findings to patient care. A significant imbalance in the application of omics technologies was also observed. Most studies focused heavily on proteomics, with relatively fewer examining genomics, epigenomics, metabolomics, transcriptomics, or microbiome data. This overrepresentation narrows the potential for discovering broader molecular pathways involved in surgical response. While proteomics has yielded valuable insights, expanding research into these underrepresented omics layers offers significant promise. Metabolomics can capture dynamic metabolic adaptations that underlie both glycemic improvements and cardiovascular risk reduction after surgery. While the gut microbiome represents a critical modifiable factor influencing host metabolism, energy balance, and surgical outcomes. Large, longitudinal cohorts that integrate these modalities alongside proteomics and other omics layers will be essential to achieve a more comprehensive systems-level understanding of T2D remission and cardiometabolic health after surgery. Additionally, selection and publication biases may limit generalizability. Beyond the statistical heterogeneity reported, additional variability likely arises from differences in assay platforms, cohort ethnicity, baseline T2D severity, and surgical techniques. Addressing these factors through standardized protocols and harmonized study designs will be essential to improve comparability and enhance the reliability of future findings.

It is crucial to be aware that the study of bariatric surgery outcomes in patients with T2D via omics technology poses some challenges. Clinical studies involving patients with T2D undergoing bariatric surgery often have limited sample sizes due to the invasive nature of these procedures, ethical considerations, and resource constraints.

Small sample sizes may reduce the statistical power and limit the extension of the findings into a broader context. In addition, ethnic diversity could influence individual responses to bariatric surgery, as genetic and epigenetic factors affecting T2D and CVD may vary among different populations. The clinical implementation of omics technologies also faces logistical and financial barriers. Robust infrastructure is required, including access to high-throughput platforms, bioinformatics expertise, and secure data storage. Multi-omics profiling, particularly in proteomics, metabolomics, and microbiome analysis, can be prohibitively expensive, especially in resource-limited settings. In addition, a lack of standardization in assay methods, data analysis pipelines, and result interpretation can introduce technical variability in biomarker quantification. Which, therefore, hinders the scalability of omics-based approaches across healthcare systems. Future research should explore the interplay between bariatric surgery and omics profiles in larger, ethnically diverse cohorts to better understand how these factors influence outcomes. Longitudinal studies with extended follow-up periods are necessary to capture the temporal dynamics of molecular and clinical changes following surgery. Omics-derived biomarkers must also be validated in independent populations to assess their reproducibility and predictive value for clinical outcomes such as T2D remission and cardiovascular risk reduction.

Emerging omics biomarkers have the potential to enhance personalized decision-making in bariatric surgery. In the future, clinicians could use these biomarkers to stratify patients according to their predicted likelihood of T2D remission, cardiovascular risk reduction, or weight-loss response, enabling tailored surgical planning and individualized preoperative counseling. For instance, specific metabolomic or microbial signatures may help identify patients who would benefit most from a particular surgical procedure or who require closer postoperative monitoring. Although routine clinical implementation is not yet established, integrating omics data into multidisciplinary care pathways could support precision medicine approaches, optimize patient outcomes, and guide postoperative follow-up strategies as the evidence base grows.

Successful regulatory approval and clinical adoption of OMICS technologies will require demonstrating added value beyond current standards of care. In addition, practical barriers such as high assay costs, infrastructure requirements, and variable regulatory frameworks, particularly in low- and middle-resource settings, pose significant challenges to translation. To overcome these limitations, future efforts should focus on developing cost-effective assays, establishing clinically standardized workflows, and fostering collaborative networks between researchers, clinicians, and regulatory bodies. Such coordinated initiatives will be essential to enable the integration of OMICS into personalized, evidence-based care across diverse healthcare environments.

Conclusion

This systematic review highlighted the pivotal role of omics disciplines in unraveling the impact of bariatric surgery on managing T2D and mitigating the risk of CVD. By exploring the realms of genomics, epigenomics, transcriptomics, metabolomics, proteomics, and additional omics disciplines, we ascertain profound understanding of the intricate molecular and physiological pathways underpinning a diverse spectrum of pathological conditions. This multifaceted data serves as a foundational pillar for precision medicine, facilitating the formulation of individualized diagnostic tools, predicting disease susceptibilities, and developing tailored therapeutic interventions. Integrating multi-dimensional omics data into clinical practice represents a significant advancement toward personalized medicine, enhancing therapeutic efficacy while reducing the risk of adverse events for patients with T2D.

Supplementary Information

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Supplementary file 1.

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Author contributions
BA: Writing – original draft. MM: Writing – review & editing. NM: Writing – review & editing. J.S.B.-G: Writing – review & editing. C.A: Writing – review & editing. H.A: Writing – review & editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Not applicable.

Competing interests
The authors declare no competing interests.

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