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Review

Mechanisms and Outcomes of Metabolic Surgery in Type 2 Diabetes

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Abstract: This review aimed at synthesizing the mechanisms and outcomes of metabolic surgery on hormones, adipokines, metabolomics, and at the molecular level. We reviewed the endocrine, microRNA, and metabolomics changes in human and animal models following metabolic surgery for the treatment of obesity and diabetes. PubMed, Science Direct, Scopus and Google Scholar databases were searched up to February 2022. The most relevant studies in the area over the past 17 years have been considered for this review. In most cases, metabolic procedures especially those that include intestinal bypass components, showed remission of type 2 diabetes. This involves a variety of weight-independent mechanisms to improve glucose homeostasis, improving insulin sensitivity and secretion. The miRNAs' dysregulated expressions have essential roles in metabolic processes. Metabolic surgery is a potentially sustainable treatment that can modify a patient's physiology and glucose regulation mechanism. The feasibility and role of miRNA are important for potential targeted genetic pathways in future obesity with type 2 diabetes management.

Keywords: diabetes; bariatric surgery; metabolic surgery; hormones; adipokines; microRNA; metabolomic

1. Introduction

Globally rising sedentary lifestyles and obesity have increased resulting in the burden of type 2 diabetes (T2D) tremendously worldwide. Bay et al (2017) reported in a study conducted in the US, that approximately 85% of patients with T2D are either overweight or obese [1]. Literature has shown that weight loss surgery (i.e., bariatric or metabolic surgery) has been proven to be effective, and provide good long-term glycemic control in patients with obesity and T2D. Metabolic surgery is now considered a well-supported treatment for T2D in patients with obesity and is endorsed by international diabetes and medical organizations [2].

Metabolic surgery exerts its physiological benefits by mediating intestinal physiology, bile acid metabolism, incretin hormone secretion, neuronal signaling and microbiome changes. Understanding the mechanism of metabolic procedures and their outcomes on diabetes will ensure optimal treatment and disease prevention strategies in T2D patients. Although the benefits of metabolic surgery for obesity-related comorbidities are well established, evidence of its molecular and metabolomics effects are still limited.

This review article summarizes the effects of metabolic surgery on endocrine, microRNA levels, and metabolomic for the treatment of obesity and diabetes, both in clinical trials as well as in animal models.

2. Search strategy

The references for this review were obtained from Pubmed, Science Direct and Scopus databases using the MeSH Terms: "diabetes", "bariatric surgery", "metabolic surgery", "diabetes and bariatric OR metabolic surgery", "bariatric OR metabolic surgery and hormones", "bariatric OR metabolic surgery and adipokines", "bariatric OR metabolic surgery and microRNA", "bariatric OR metabolic surgery and metabolomic". Papers

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on animal studies and clinical trials were included. Citation tracking was completed for all identified studies included in the refined library, using Zotero (ver. 2022).

3. Overview of Bariatric / Metabolic Surgery

Bariatric surgery was initially performed for weight loss (baros = weight) [3]. Bariatric surgical procedures included jejunoileal bypass (JIB), Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), biliopancreatic diversion (BPD), vertical-banded gastroplasty (VBG) or its familiar duodenal switch (DS) and adjustable gastric banding (AGB) [4]. The most commonly performed bariatric procedure worldwide and in Asia is SG followed by RYGB [5,6].

Many literatures have shown that bariatric surgery, which is now known as metabolic surgery, improved glucose homeostasis. Bariatric procedures especially with intestinal bypass components have shown to have remission in T2D. In a recent 2 years follow-up study by Abd Alla Salman M et al. (2022), complete remission of T2DM can be achieved in nearly half of the patients two years after metabolic surgery [7].

One of the important mechanisms of the improvement of T2D after metabolic surgery, is the change in gut microbiota. Gut microbiota structure has an important role in the improvement of islet β-cell function and the hypoglycemic effect. Body weight gain, blood serum lipids and fasting blood glucose are effectively decreased by the modified jejunoileal bypass [8]. This potential therapeutic strategy for T2D is explained by the jejunoileal bypass that has been modified and improved gut microbiota composition [8]. Additionally, insulin resistance, islet β-cell function, and glucose tolerance were significantly improved. In a T2D rat experimental model, it is suggested that the islet β-cell function might be contributed by amino acid metabolism [9].

Mingrone et al. published the effects of RYGB, VBG and BPD, on the glucose homeostasis principal determinants, which cover insulin secretion, insulin sensitivity and insulin-independent glucose disposal [10]. A comprehensive understanding of these effects helped to optimize surgical techniques and devices to provide maximum anti-diabetes impact.

4. Mechanisms involved in the postoperative weight and metabolic changes

3.2. Mechanisms involved in the postoperative weight and metabolic changes

Multiple mechanisms are responsible for postoperative weight and metabolic changes. These involve some degree of overlap involving the endocrine, digestive, nervous, and immune systems. Metabolic surgery has shown to have hormonal, adipokines and metabolomics changes and mechanisms at the molecular level.

4.1 Hormonal and adipokines changes

Metabolic surgery improves insulin secretion and sensitivity in patients with T2D, but the effect on patients with normal glucose tolerance or prediabetes (pre-DM) needs further understanding. Stenberg et al [11] followed up 742 RYGB patients for 2 years, where the glucometabolic control and insulin homeostasis improved in all these patients and were sustained 2 years after RYGB. Katsogiannos et al [12] conducted a study on 19 T2D patients with obesity after 4- weeks of RYGB. Patients were randomly selected for RYGB (study group, n=13) and standard-of-care medical treatment (control group, n=6). These suggested that following RYGB in T2D patients, there was a significant improvement in glycemia and insulin resistance and which could be due to neurohormonal mechanisms.

Absorption of glucose and protein was greatly accelerated after RYGB but only modestly accelerated after SG. Insulin, glucagon-like peptide-1 (GLP-1), cholecystokinin

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(CCK), and peptide YY (PYY) are appetite-inhibitors of which their secretions also differed markedly between the procedures [13]. The mechanisms underlying the benefits of metabolic surgery likely involve the bile acid–signaling pathway [14].

Sixty-nine subjects who underwent RYGB were compared with matched controls who had never been obese in a 2-years longitudinal study. RYGB group showed slightly increased HOMA-IR insulin sensitivity, a beneficial body composition, higher insulin clearance, lower atherogenic lipid or lipoprotein levels as well as benign adipocyte morphology ($p<0.0001$ for these parameters). This partly explained why long-term metabolic complications were protected by RYGB [15]. A cross-sectional study by Svane et al (2019) on 36 T2D patients was performed to study the absorption rates of glucose and protein, as well as profiles of gastro-entero-pancreatic hormones after metabolic surgery [13]. Metabolic surgery was performed in 24 patients (LSG, n=12; RYGB, n=12) and control group [n=12]. They received continuous infusions of stable isotopes of glucose, glycerol, phenylalanine, tyrosine, and urea before and during a mixed meal containing labeled glucose and intrinsically phenylalanine-labeled caseinate. The study showed that the systemic appearance of ingested glucose was faster after RYGB and SG vs controls, whilst the peak glucose appearance rate was 64% higher after RYGB, and 23% higher after SG (both $p<0.05$). Postprandial glucose and protein absorption and gastro-entero-pancreatic hormone secretions differ after SG and RYGB. RYGB was characterized by accelerated absorption of glucose and amino acids, whereas protein metabolism after SG did not differ significantly from controls, suggesting that different mechanisms explain improved glycaemic control and weight loss after these surgical procedures [13].

In a long-term study involving 163 patients with T2D, metabolic surgery was able to reduce obesity-related chronic low-grade inflammation. The acute-phase reactants C-reactive proteins (CRP, $p<0.001$) and high-sensitivity CRP (hs-CRP, $p<0.001$) are commonly used to monitor inflammation and are strongly associated with metabolic syndrome, atherosclerotic cardiovascular disease, and T2D. These markers were significantly reduced up to after 4-years of surgical intervention. The improvement was related to the change in BMI and remission of T2D in the long term [16].

Adipose tissue dysfunctionality could be caused by excessive visceral fat accumulation. This contributes significantly to the onset of obesity-related comorbidities [17]. Higher visceral fat at follow-up exam was significantly associated with reduced remission, which increased the incidence of diabetes, dyslipidemia and hypertension [18]. Hepatic, adipose and skeletal muscle tissues are the crucial endocrine organs that produce hepatokines, adipokines and myokines. They are biomarkers that can be beneficial or detrimental to an organism and act through the autocrine, endocrine and paracrine pathways [19].

Among the varieties of adipokines produced by adipose tissue are cytokines (TNF-α, TGFβ, IL-R1a, IL-6, IL-10), chemokines [MCP-1, CCL2, CCL5, macrophage inflammatory protein-2 (MIP-2), IL-8/CXCL8 IFNγ-inducible protein 10/ CXCL10], acute-phase reactants (haptoglobin, serum amyloid A, C-reactive protein, plasminogen activator inhibitor 1), damage-associated molecular pattern molecules (calprotectin, DAMPs, HMGB1, tenascin C, heat shock protein 72), pro-inflammatory (leptin, osteopontin, resistin, WNT5A, chemerin) as well as an anti-inflammatory (ghrelin, adiponectin, SRFP5, lipocalin-2 and omentin) (20). Obesity is associated with a changed secretion of adipokines that translates into increased cardiovascular risk in patients. These obese patients have an excess of dysfunctional adiposity (17). Among hormonal changes in metabolic surgery are adiponectin, ghrelin, leptin, glucagon-like peptide, secretin and oxyntomodulin [21,22].

Specific adipokines origins, functions and effects on metabolic surgery are further discussed.

4.1.1 Specific adipokines will be discussed below:

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a. Leptin

A product of the obesity gene, leptin takes part in the regulation of body weight by controlling food intake and energy expenditure [23]. It controls neuroendocrine function, which is a crucial hormone in energy homeostasis. Leptin activates a balanced effect on blood pressure control in the healthy state, by modulating the endothelial release of nitric oxide, as well as the sympathetic activity-dependent vasoconstriction and angiotensin II-dependent vasoconstriction [20,24]. In obesity, hyperleptinemia may emerge as a compensatory mechanism to control leptin resistance. This is due to obesity that activates an organ-specific leptin-resistant state [25]. Šebunova N et al (2022) analyzed 30 obese bariatric patients and found remarkable decrease in leptin levels changes in levels [26].

b. Adiponectin

Adiponectin is expressed only in adipose tissue, which is detectable in plasma. Plasma adiponectin concentrations are reduced in obese patients. Adiponectin exerts anti-inflammatory actions as well as increases insulin sensitivity [27]. It exists in 3 main oligomeric forms: a low, middle-, or high-molecular-weight adiponectin. Metabolic syndrome and insulin resistance in humans are best predicted by high-molecular-weight adiponectin [28].

Moreover, the adiponectin/leptin ratio has been recommended by Frühbeck G et al (2018) as a marker of adipose tissue dysfunction. The ratio correlates with insulin resistance more closely than a surrogate of insulin resistance like HOMA index, adiponectin or leptin alone [29]. Bariatric surgery resulted in weight loss and activated a constant decrease in leptin levels and an increase in adiponectin plasma levels in parallel [26]. There was an overall improvement of the metabolic profile corresponding with dipped leptin levels observed post-surgically [30].

c. Resistin and visfatin

Adipose-tissue resident-macrophages secrete resistin, which is a polypeptide. Its concentrations are elevated in obesity. It is because the pathophysiology of inflammation-induced insulin resistance in macrophages is regulated by resistin circulating levels [31]. Prospective case-control studies proved an association between increased risk of developing T2D in subjects with increased resistin levels at baseline. Its level was decreased after bariatric surgery [32,33].

Another adipocytokine secreted by adipocytes, inflamed endothelial tissue and macrophages is visfatin. It is increased in obesity, insulin resistance, and T2D. Visfatin acts as a pro-inflammatory intermediary, which has an important role in vascular inflammation pathogenesis in obesity and T2D, and contributes to atherosclerotic plaque instability. The plasma levels of visfatin were reported to steadily decrease after bariatric surgery-related weight loss [33]. An improvement in insulin resistance and diabetes was reflected in T2D patients who underwent RYGB, when visfatin serum level was decreased [34].

d. Ghrelin

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Main ghrelin functions are targeted at appetite, metabolism, and adiposity. The acylated and the deacyl ghrelin are the 2 main circulating isoforms of this hormone [35]. These isoforms consist of the main elements which are involved in the amelioration of non-alcoholic fatty-liver disease (NAFLD) after bariatric surgery [36]. In a ten-week diabetic rat study, RYGB and SG decreased leptin and ghrelin levels [37]. Ghrelin affects carbohydrate and lipid metabolism in obese patients. After RYGB and LSG surgeries, ghrelin was associated with elevated plasma levels of insulin, leptin, and glucagon [38].

e. Omentin-1 and apelin

Omentin-1, also known as intelectin-1, is an adipokine primarily secreted from visceral adipose tissue which consists of 313 amino acids, but it is also expressed in the heart, placenta, and ovaries [39,40]. It is an anti-inflammatory adipokine [41] that is expressed in omental, epicardial and perivascular adipose tissue [42]. The two genes, identified as omentin-1 and omentin-2, encode the omentin protein. In obesity, the omentin-1 level, which is the major circulating form, is reduced. It is also inversely correlated to waist circumference, BMI, and metabolic syndrome biomarkers [43]. Its expression is reduced in obesity [44]. During diet-induced weight loss, omentin-1 levels usually elevate over time, which showed evidence of the link between omentin and obesity [45].

The omentin circulating levels and the related mRNA expression in visceral adipose tissue are distinct in types of diabetes [43]. It might have a potential protective action of omentin in metabolic disorders [46]. In a recent study, omentin reduced insulin resistance in Goto-Kakizaki rats fed with a high-fat diet without affecting lipid profile [47]. Interestingly, a systematic review and meta-analysis found that serum omentin level is significantly lower in impaired glucose tolerance and T2DM patients but not in Type 1 diabetes (T1DM) [48].

In a study, bariatric surgery causes variable action in omentin-1 levels. Most patients display an elevation of omentin-1 levels in the immediate postoperative period. This condition occurs even before the induction of weight loss. The increment of omentin-1 levels was even maintained for one-year post-bariatric intervention [49].

Another novel adipokine, apelin, has a crucial role in the pathogenesis of insulin resistance as well as T2D. It is a peptide with many active isoforms ranging from 36-12 amino acids. Apelin is secreted from white adipose tissue and is associated with various functions including food intake and insulin sensitivity [50,51].

The level of apelin in obese patients with T2DM is significantly increased compared to healthy people [42]. In obesity and diabetes, insulin could control apelin [53].

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Long-term apelin treatment in insulin-resistant, obese mice has proven valuable effects on both glucose and lipid metabolism [54]. During a hyperinsulinemic-euglycemic clamp in non-diabetic human volunteers, apelin perfusion improved insulin sensitivity markedly without experiencing side effects [55].

f. Glucagon-like peptide-1 (GLP-1)

RYGB leads to profound changes in the secretion of gut hormones with effects on food intake, appetite as well as metabolism [56]. Several studies highlighted the important role of GLP-1, which plays an important role in achieving glycaemic control. GLP-1 is elevated after RYGB. Bile acid plasma concentrations were increased after RYGB. In this case, bile acids may act as molecular enhancers of GLP-1 secretion through activation of TGR5-receptors [57]. The improved glucose tolerance was due to a negative energy balance and resulting weight loss. In the beginning, these improve hepatic and later peripheral insulin sensitivity. Next, in combination with elevated postprandial insulin secretion, it is elicited particularly by magnified GLP-1 responses [56]. Additionally, post-RYGB causes a weight loss-independent postprandial insulin secretion which contributes to the improvement in glycemic control. This action is associated with a ~10-fold increment in the concentrations of the incretin hormone GLP-1 plasma [58].

A meta-analysis of 24 studies involving 368 patients by Pichamol Jirapinyo et al (2018) concluded that GLP-1 fasting levels remain unchanged but the levels increase after RYGB. Interestingly, shorter Roux limb length is associated with a greater increase in postprandial GLP-1, which may improve glycemic control [59].

Using a model of gastrectomy in lean mice, Pierre Larraufie et. al. (2019) showed that after bariatric surgery, GLP-1 is an enhancement factor of insulin secretion, which arises from fast nutrient delivery to the distal gut [60]. In an animal study mentioned earlier, RYGB and SG increased GLP-1 levels [37]. In a recent study by Abd Alla Salman M et al. (2022), complete remission of T2D was significantly associated with higher GLP-1 levels [7].

4.2 Molecular changes

4.2.1. Micro RNA

MicroRNAs (miRNAs) are expressed in various organs [61]. miRNAs are short pieces of RNA that are recognized as key gene expression regulators and have main roles in the regulation of many biological and pathological processes, including T2D [62]. Owing to their stability and practicality in non-invasive collection methods, the circulating miRNAs could be used as biomarkers. This is being explored in a wide range of pathologies, including diabetes dan cancer. Furthermore, their levels can be measured by quantitative RT-PCR, which utilizes straightforward, fast, and specific, with sensitive detection and quantification [63].

Differential expression of circulating miRNAs pre- and post- various dietary and bariatric surgery interventions have been reported in a few studies, identifying several weight loss-related candidate biomarkers. A range of dysregulated miRNA target pathways has also been identified. This is to understand the underlying obesity and obesity-related metabolic diseases pathophysiological mechanisms [64].

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Dysfunctional adipose tissue is extensively associated with T2D development and is the major source of circulating miRNAs. A specific miRNA, miR-122, distinctively found between visceral and subcutaneous adipose tissues was found in a study by [65]. They are involved in weight homeostasis as of the numerous metabolic processes [66]. The ratio of miR-122 between subcutaneous and visceral adipose tissues correlates with the outcome of bariatric surgery [65].

miRNA disorders are demonstrated in various studies involved in β cell development, insulin production, insulin secretion, insulin sensitivity, insulin resistance, insulin signaling pathways, and finally lead to the development of T2D [67]. These findings support the possible role of miR-33 to monitor pre-diabetes onset and progression.

Metabolic responses at early stages following weight loss after bariatric surgery are evident. These observations correspond with an improvement in diabetes. Seven microRNAs (let-7i-5p, let-7f-5p, miR-7-5p, miR-15b-5p, miR-205-5p, miR-320c and miR-335-5p) showed significant changes 3 weeks after RYGB surgery among 29 patients with severe obesity and T2D. Altered miRNAs functional pathways were associated with liver-, diabetes-, and pituitary-related diseases. Following bariatric surgery, miRNAs expressions in natural killer cells, and vital intestinal pathology imply mechanistic functions in early diabetes responses [68].

In a diet and cardiovascular study cohort, miR-223-3p baseline levels were found to be significantly related to insulin resistance in adipose tissue. Both preadipocytes and adipocytes miR-223-3p-secreting cells cause alteration of the circulation levels. This suggested that inflammation enhances the accumulation of miR-223-3p intracellularly. This possibly confers to preadipocyte dysfunction and body metabolic dysregulation [69].

The usefulness of identifying genetic differences between high and low weight loss groups after bariatric surgery by identifying specific serum miRNA has been demonstrated (66). miRNA profile in the serum of plasma is deregulated in the pre-DM state before the development of observable T2D. Undoubtedly, compared with controls, individuals with T2D or pre-DM have a differential profile of circulating miRNA [70]. Interestingly, a list of miRNAs has been identified in non-diabetic healthy individuals who proceeded to develop pre-DM or T2D [71]. Additionally, multiple circulating miRNAs plasma concentrations of healthy individuals have been identified as being markedly different between T2D patients and pre-DM individuals [72,73]. Deregulated plasma levels of miR-15a, miR-30a-5p, miR-150, and miR-375 were detected years before the onset of T2D and pre-DM and could be utilized to assess the risk of developing the disease. This may improve the prediction and prevention among high-risk individuals for T2D [74]. Eikelis et al (2021) also demonstrated that plasma levels of miR-9, miR-28-3p, miR29a, miR-103, miR-30a-5p, and miR-150 are powerful predictive biomarkers that can discriminate between Incident-T2D and non-T2D patients. A potential tool for the early detection of T2D has been developed. It is a multi-parameter diagnostic model consisting of miR-148b, miR-223, miR-130a, and miR-19a [75]. MicroRNA miR-132 (mir-132) is an important regulator of liver homeostasis and lipid metabolism. In the same experimental model, an association between miR-132 and markers of metabolic disease and cardiovascular was found [76]. Part of a blood biochemical changes of diabetes reversal was formed during the resolution of diabetes after bariatric surgery. This process occurred through the miRNA-gene interactions in the pancreatic islet, which is a novel mechanism [77].

Soon, informed decisions about surgery could be facilitated by these miRNAs. These potential miRNA biomarkers could also provide targets for future treatment by opening new genetic pathways that illustrate the pathophysiology of obesity. **Table 1** presents differentially expressed miRNA with their roles/targets after surgery.

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Table 1. Differentially expressed miRNA with their roles/targets after surgery.

Study	Intervention	Population	Source	Regulated miRNAs	Role/target
Ortega et al. 2013 (78)	RYGB	6 obese	Plasma	miR-221 and miR-199a-3p (↑) miR-16-1, miR-122, miR-140-5p, miR-193a-5p (↓)	–
Nunez-Lopez et al. 2017 (79)	RYGB	22 obese	Plasma	miR-15a (↑) miR-34a, miR-122 (↓)	Biomarkers of weight loss /glucose metabolism
Atkin et al. 2018 (68)	RYGB	29 T2D	Plasma	miR-7-5p, let-7f-5p, miR-15b-5p, miR-320c, miR-205-5p, miR-335-5p (↑) let-7i-5p (↓)	Inflammation, adipocyte proliferation, ß-cell function, thyroid and pituitary function
Hubal et al. 2017 (80)	RYGB	6 obese women	Plasma and serum adipocyte-derived exosomes	let-7a-5p, miR-16-5p	Insulin signaling
Bae et al. 2019 (81)	LSG ($n = 2$) RYGB ($n = 14$)	16 obese 18 CTRL	Serum exosomes	miR-424-5p	Biomarker of weight loss
Doyon L et al. 2020 (66)	LSG RYGP	20 obese	Serum	hsa-miR-375 hsa-miR-126-3 p	fatty acid biosynthesis obesity,

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				hsa-miR-663 a hsa-miR-30 c-5 p hsa-miR-100-5 p hsa-miR-27 a-3 p hsa-miR-590-5 p	adipocyte proliferation type 2 diabetes
Sangiao-Alvarellos S et al, 2020 (82)	Bariatric surgery	155 obese 47 CTRL	Se-rum/plasma	miR-122 miR-885-5 p miR-192	regulation of hepatic biochemical processes
Cereijo R et al, 2020 (83)	Bariatric surgery	26 obese	serum	miR-92a	Glucose homeostasis
Hulsmans et al. 2012 (84)	RYGB	9 obese 6 CTRL	PBMC	miR-181 (↑)	TLR-NFkB pathway
Macartney-Coxson et al. 2020 (85)	RYGB	15 obese women	SAT VAT	SAT: miR-23a-5p, miR-27a-5p, miR-200c-3p, miR-223-3p, miR-1246, miR-24-2-5p, miR-128, miR-421, miR-3178, miR-1224-5p, miR-221, miR-22, miR-762 (↓) VAT: miR-223-3p (↓)	Inflammation, glucose uptake
Liao et al. 2018 (65)	LSG	20 obese 8 CTRL	SAT VAT	VAT: miR-122 (↑)	PPAR-γ

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Kurylowicz et al. 2016 (86)	Bariatric surgery	20 obese 7 CTRL	SAT	miR-146b-3p, miR-146b-5p, miR-223-3p, miR-223-5p, miR-941 (↑)	BMPR2, FOXP1, IGF1R
Ortega et al. 2015 (87)	RYGB	16 obese	SAT	miR-155, miR-221, miR-130b (↓)	Inflammation
Ortega et al. 2015 (88)	RYGB	9 obese women	SAT	miR-19a/b, miR-146a/b, miR-155, miR-193b, miR-221, miR-222, miR-223, miR-376c, miR-411 (↓)	Glucose uptake, lipid metabolism, energy homeostasis
Nardelli et al. 2017 (89)	LAGB	3 obese 2 CTRL	SAT	miR-519d, miR-299-5p, miR-212, miR-671-3p (↓) miR-370, miR-487a (↑)	PPAR-α (miR-519d)
CTRL, control subjects; RYGP, Roux-en-Y gastric by-pass; PBMC, peripheral blood mononuclear cells; T2D, type 2 diabetes; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; LSG, laparoscopic sleeve gastrectomy; BMPR2, bone morphogenic protein receptor 2; FOXP, fork-head box protein P1; IGF1R, insulin-like growth factor receptor 1; LAGB, laparoscopic adjustable gastric banding; ↑ indicates increased expression level; ↓ indicates reduced expression level					

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4.2.2 Metabolomics

A relatively young science discipline, metabolomics shows great potential for the comprehensive study of the metabolome's dynamic alterations. Liquid chromatography–mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR) are the most frequently used techniques to study the main effects of RYGB or SG. NMR can uniquely identify and simultaneously quantify a wide range of analyses of amino acids, carbohydrates, vitamins, thiols, carbohydrates, peptides as well as nucleotides and nucleosides. The LC-MS technique has become a powerful tool for the analysis of the polar metabolites in a complex sample [90,91].

In an exploratory study among 17 diabetic and non-diabetic obese patients undergoing bariatric surgery, untargeted metabolomic profiling in subcutaneous adipose tissue was performed. However, among the 421 metabolites identified and analyzed, there were no significant differences between those patients [92]. Dysregulation of lipids and amino acids has been associated with insulin resistance and other pathophysiological processes of T2DM. This may be due to obesity which may influence subcutaneous adipose tissue metabolism masking T2DM-dependent dysregulation [93].

In another study of post-RYGB, alterations of basal metabolism among overweight diabetic subjects have been demonstrated by NMR metabolomic profiling. These changes were associated with energy homeostasis, alterations in lipid metabolism, and decreased branched-chain amino acids [94].

Most methods for the screening and prevention of T2D rely on prediabetes individuals already showing a steady decrease in insulin sensitivity. It is important to develop biomarker trajectory models that can complement accurately the existing individual risk assessment methods, because these methods may not be as effective as those developed to counter the disease [95].

In a 5-year diabetes remission study, metabolites in the branched-chain amino acids (BCAA) and trimethylamine-N-oxide (TMAO)-microbiome-related pathways were found to be predictive of T2D remission and weight loss amount in severely obese individuals [96]. These metabolites can be potentially used in the clinical management of T2DM patients undergoing bariatric surgery. Additionally, baseline levels of tryptophan, bilirubin, and indoxyl sulfate measured before surgery as well as levels of FFA 16:0, FFA 18:3, FFA 17:2, and hippuric acid measured at 6 months after surgery best predicted the suitability and efficacy of RYGB for patients with T2DM [97]. The summary of metabolomic profiles associated with metabolic surgery is presented in **Table 2.**

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Table 2. Metabolomic profiles of metabolic surgery.

Study	Intervention/ Surgery type	Population	Follow-up period	Role/target Metabolites	Outcomes
Zheng X et al, 2021 (98)	RYGB	38 individuals with T2D	12 months	Hyocholic acid (HCA)	Serum HCA levels increase in the patients after RYGB ($p < 0.05$) HCA species play critical roles in regulating glucose homeostasis and are protective against the development of T2DM in humans.
Ha J et al, 2020 (99)	SG RYGB	24 individuals with T2D	3 months	Amino acid metabolites (AAMs) : L-DOPA and 3-HAA	The prognostic performance of L-DOPA (AUROC = 0.97; 95% CI, 0.91 to 1.00) and 3-HAA (AUROC = 0.86; 95% CI, 0.63 to 1.00). AAMs are superior for predicting T2D remission postoperatively compared with existing prediction models.
Zhao, Linjing et al, 2017 (100)	RYGB	419 individuals -38 obese and T2D after RYGB - 381 T2D and CTRL with overweight or obesity)	12 months after RYGB	Targeted: Branched-chain amino acids (BCAAs), aromatic amino acids (AAAs), and acylcarnitines	Higher baseline stearic acid/palmitic acid (S/P) was associated with greater probability of diabetes remission after RYGB [odds ratio, 2.16 (95% CI 1.10–4.26)] - may serve as a diagnostic marker in preoperative patient assessment

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Study	Intervention/ Surgery type	Population	Follow-up period	Role/target Metabolites	Outcomes
Narath, Sophie H.et al, 2016 (101)	RYGB	44 obese; included 24 patients with T2D at baseline, 9 with diabetes remission	12 months	Untargeted: 36 metabolites are known markers for cardiovascular risk;	Trimethylamine-N-oxide, alanine, phenylalanine and indoxyl-sulfate which 4 metabolites significantly decline in patients with diabetes remission compared to patients without diabetes remission. (Sarcosine p = 0.031, pyroglutamic acid: p = 0.044, alanine: p = 0.005 and leucyl-proline: p = 0.049)
Lopes, Thiago I.B. et al, 2016 (94)	RYGB	10 obese & T2DM	12 months	Untargeted: Metabolic and lipoprotein profiles and fatty acid profile	Glucose levels decreased significantly after RYGB (from 159.8 ± 61.4 to 100.0 ± 22.9 mg/dL), demonstrating T2D remission ($p < 0.05$). Lower levels of metabolic profile: lactate, alanine, and branched chain amino acids The VLDL, LDL, N-acetyl-glycoproteins, and unsaturated lipid levels decreased but phosphatidylcholine and high-density lipoprotein increased after RYGB.

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Study	Intervention/ Surgery type	Population	Follow-up period	Role/target Metabolites	Outcomes
Sarosiek, Konrad et al, 2016 (102)	SG or full GB	15 patients Gastric sleeve with T2D (5); Gastric sleeve without T2D (5) and Gastric bypass with T2D (5)	28 days	Nontargeted global metabolomic: Glucose and lipid metabolism; histidine and its metabolites	62 compounds were significantly different in the post-surgery compared to baseline ($p<0.05$) Significant improvement in fat mobilization and oxidation ($p<0.05$), liver function ($p<0.05$) after surgery.
Nemati, Reza et al, 2016 (103)	LGB (Roux), LSG	38 obese with T2D GBP (11) SG (14) VLCD (13).	3 days	Targeted (NEFAs) Palmitic acid Monounsaturated/polyunsaturated ratio (MUFA/PUFA) Linoleic acid Unsaturated/saturated fat	Linoleic acid was positively correlated with total insulin secretion ($p = 0.03$). Glucose sensitivity correlated with palmitic acid ($p = 0.01$) GBP, SG and VLCD have similar acute effects on decreasing palmitic acid ($P<0.05$) Several NEFAs correlated with beta cell function parameters and HOMA-IR ($P<0.05$)
Luo, Ping. et al, 2016 (97)	RYGB	35 T2D -23 remission and 12 nonremission patients with T2D were measured at baseline, 6- and 12 months after RYGB	6 and 12 months	Untargeted: Free fatty acids (FFAs), acylcarnitines, amino acids, bile acids, and lipids species.	Insulin sensitivity, energy metabolism, and inflammation were related to metabolic alterations of free fatty acids (FFAs), acylcarnitines, amino acids, bile acids, and lipids species ($p<0.05$)

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Study	Intervention/ Surgery type	Population	Follow-up period	Role/target Metabolites	Outcomes
					Baseline levels of tryptophan, bilirubin, and indoxyl sulfate measured prior to surgery as well as levels of FFA 16:0, FFA 18:3, FFA 17:2, and hippuric acid measured at 6 months after surgery best predicted the suitability and efficacy of RYGB for patients with T2DM

CTRL, control subjects; RYGP, Roux-en-Y gastric by-pass; T2D, type 2 diabetes; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; LSG, laparoscopic sleeve gastrectomy; LAGB, laparoscopic adjustable gastric banding; BPD, Biliopancreatic diversion with duodenal switch; DJBL, duodenojejunal bypass liners; GB, Gastric Bypass; VLCD, very-low-calorie diet

HILIC - hydrophilic interaction liquid chromatography; UPLC–MS - ultra-performance liquid chromatography–mass spectrometry; UHPLC-MS/MS - Ultra-high performance liquid chromatography- tandem mass spectrometry; 1H NMR - proton nuclear magnetic resonance; LC-MS/MS - Liquid Chromatography with tandem mass spectrometry

VLDL, very low-density lipoprotein; LDL, low-density lipoprotein

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5. Conclusions

Metabolic surgery is a potential and sustainable treatment that can modify a patient's physiology and glucose regulation mechanism. In most cases, metabolic procedures especially those that include intestinal bypass components, showed remission of T2D. This involves a variety of weight-independent mechanisms to improve glucose homeostasis, improving insulin sensitivity and secretion.

The miRNAs' dysregulated expressions have crucial roles in metabolic processes. The feasibility and role of miRNA are important for potential targeted genetic pathways in future obesity management.

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References

1. Bays HE, Bazata DD, Clark NG, Gavin JR, Green AJ, Lewis SJ, et al. Prevalence of self-reported diagnosis of diabetes mellitus and associated risk factors in a national survey in the US population: SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes). BMC Public Health. 2007 Oct 3;7:277.
2. Hanipah ZN, Schauer PR. Bariatric Surgery as a Long-Term Treatment for Type 2 Diabetes/Metabolic Syndrome. Annu Rev Med. 2020 Jan 27;71(1):1–15.
3. Pollard S. The current status of bariatric surgery. Frontline Gastroenterol. 2011 Apr;2(2):90–5.
4. Buchwald H. The Evolution of Metabolic/Bariatric Surgery. Obes Surg. 2014 Aug 1;24(8):1126–35.
5. Ohta M, Seki Y, Wong SKH, Wang C, Huang CK, Aly A, et al. Bariatric/Metabolic Surgery in the Asia-Pacific Region: APMBSS 2018 Survey. Obes Surg. 2019 Feb;29(2):534–41.
6. Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Fourth IFSO Global Registry Report 2018. Obes Surg. 2019 Mar;29(3):782–95.
7. AbdAlla Salman M, Rabiee A, Salman A, Elewa A, Tourky M, Mahmoud AA, et al. Predictors of type-2 diabetes remission following bariatric surgery after a two-year follow up. Asian J Surg [Internet]. 2022 Mar 4 [cited 2022 Jul 21]; Available from: https://www.sciencedirect.com/science/article/pii/S1015958422001324
8. Tan C, Zheng Z, Wan X, Cao J, Wei R, Duan J. The role of gut microbiota and amino metabolism in the effects of improvement of islet β-cell function after modified jejunoileal bypass. Sci Rep. 2021 Feb 26;11:4809.
9. Alejandro EU, Gregg B, Blandino-Rosano M, Cras-Méneur C, Bernal-Mizrachi E. Natural history of β-cell adaptation and failure in type 2 diabetes. Mol Aspects Med. 2015 Apr;42:19–41.
10. Mingrone G, Cummings DE. Changes of insulin sensitivity and secretion after bariatric/metabolic surgery. Surg Obes Relat Dis. 2016 Jul 1;12(6):1199–205.
11. Stenberg E, Rask E, Szabo E, Näslund I, Ottosson J. The Effect of Laparoscopic Gastric Bypass Surgery on Insulin Resistance and Glycosylated Hemoglobin A1c: a 2-Year Follow-up Study. Obes Surg. 2020;30(9):3489–95.
12. Katsogiannos P, Kamble PG, Boersma GJ, Karlsson FA, Lundkvist P, Sundbom M, et al. Early Changes in Adipose Tissue Morphology, Gene Expression, and Metabolism After RYGB in Patients With Obesity and T2D. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2601–13.
13. Svane MS, Bojsen-Møller KN, Martinussen C, Dirksen C, Madsen JL, Reitelseder S, et al. Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy. Gastroenterology. 2019 May 1;156(6):1627-1641.e1.

14. Xu G, Song M. Recent advances in the mechanisms underlying the beneficial effects of bariatric and metabolic surgery. Surg Obes Relat Dis. 2021 Jan 1;17(1):231–8.
15. Andersson DP, Dahlman I, Hogling DE, Bäckdahl J, Toft E, Qvisth V, et al. Improved metabolism and body composition beyond normal levels following gastric bypass surgery: a longitudinal study. J Intern Med. 2019;285(1):92–101.
16. Lautenbach A, Stoll F, Mann O, Busch P, Huber TB, Kielstein H, et al. Long-Term Improvement of Chronic Low-Grade Inflammation After Bariatric Surgery. Obes Surg. 2021 Mar 5;
17. Landecho MF, Tuero C, Valentí V, Bilbao I, de la Higuera M, Frühbeck G. Relevance of Leptin and Other Adipokines in Obesity-Associated Cardiovascular Risk. Nutrients. 2019 Nov;11(11):2664.
18. Hunt SC, Davidson LE, Adams TD, Ranson L, McKinlay RD, Simper SC, et al. Associations of Visceral, Subcutaneous, Epicardial, and Liver Fat with Metabolic Disorders up to 14 Years After Weight Loss Surgery. Metab Syndr Relat Disord. 2021 Mar 1;19(2):83–92.
19. de Oliveira Dos Santos AR, de Oliveira Zanuso B, Miola VFB, Barbalho SM, Santos Bueno PC, Flato UAP, et al. Adipokines, Myokines, and Hepatokines: Crosstalk and Metabolic Repercussions. Int J Mol Sci. 2021 Mar 5;22(5):2639.
20. Rodríguez A, Ezquerro S, Méndez-Giménez L, Becerril S, Frühbeck G. Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. Am J Physiol Endocrinol Metab. 2015 Oct 15;309(8):E691-714.
21. Luo JN, Tavakkoli A. Physiologic Mechanisms of Weight Loss Following Metabolic/Bariatric Surgery. Surg Clin North Am. 2021 Apr 1;101(2):223–37.
22. Estienne A, Bongrani A, Reverchon M, Ramé C, Ducluzeau PH, Froment P, et al. Involvement of Novel Adipokines, Chemerin, Visfatin, Resistin and Apelin in Reproductive Functions in Normal and Pathological Conditions in Humans and Animal Models. Int J Mol Sci. 2019 Sep 9;20(18):E4431.
23. Muruzábal FJ, Frühbeck G, Gómez-Ambrosi J, Archanco M, Burrell MA. Immunocytochemical detection of leptin in non-mammalian vertebrate stomach. Gen Comp Endocrinol. 2002 Sep 1;128(2):149–52.
24. Gómez-Ambrosi J, Catalán V, Rodríguez A, Andrada P, Ramírez B, Ibáñez P, et al. Increased Cardiometabolic Risk Factors and Inflammation in Adipose Tissue in Obese Subjects Classified as Metabolically Healthy. Diabetes Care. 2014 Oct 1;37(10):2813–21.
25. Sweeney G. Cardiovascular effects of leptin. Nat Rev Cardiol. 2010 Jan;7(1):22–9.
26. Šebunova N, Štšepetova J, Kullisaar T, Suija K, Rätsep A, Junkin I, et al. Changes in adipokine levels and metabolic profiles following bariatric surgery. BMC Endocr Disord. 2022 Feb 3;22(1):33.
27. Huypens PR. Leptin and adiponectin regulate compensatory beta cell growth in accordance to overweight. Med Hypotheses. 2007;68(5):1134–7.
28. Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell Metab. 2013 Feb 5;17(2):185–96.
29. Frühbeck G, Catalán V, Rodríguez A, Ramírez B, Becerril S, Salvador J, et al. Adiponectin-leptin Ratio is a Functional Biomarker of Adipose Tissue Inflammation. Nutrients. 2019 Feb 22;11(2):E454.
30. Unamuno X, Izaguirre M, Gómez-Ambrosi J, Rodríguez A, Ramírez B, Becerril S, et al. Increase of the Adiponectin/Leptin Ratio in Patients with Obesity and Type 2 Diabetes after Roux-en-Y Gastric Bypass. Nutrients. 2019 Sep 3;11(9):2069.
31. Park HK, Kwak MK, Kim HJ, Ahima RS. Linking resistin, inflammation, and cardiometabolic diseases. Korean J Intern Med. 2017 Mar;32(2):239–47.
32. Doulamis IP, Konstantopoulos P, Tzani A, Antoranz A, Minia A, Daskalopoulou A, et al. Visceral white adipose tissue and serum proteomic alternations in metabolically healthy obese patients undergoing bariatric surgery. Cytokine. 2019 Mar 1;115:76–83.
33. Arica PC, Aydin S, Zengin U, Kocael A, Orhan A, Zengin K, et al. The Effects on Obesity Related Peptides of Laparoscopic Gastric Band Applications in Morbidly Obese Patients. J Investig Surg Off J Acad Surg Res. 2018 Apr;31(2):89–95.
34. Liu Y, Xiong J, He H, Zhu S, Mo Z. [Visfatin level after laparoscopic Roux-en-Y gastric bypass surgery in patients with Type 2 diabetes]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2013 Mar;38(3):258–61.
35. Gauna C, Delhanty PJD, Hofland LJ, Janssen JAMJL, Broglio F, Ross RJM, et al. Ghrelin stimulates, whereas des-octanoyl ghrelin inhibits, glucose output by primary hepatocytes. J Clin Endocrinol Metab. 2005 Feb;90(2):1055–60.
36. Ezquerro S, Méndez-Giménez L, Becerril S, Moncada R, Valentí V, Catalán V, et al. Acylated and desacyl ghrelin are associated with hepatic lipogenesis, β-oxidation and autophagy: role in NAFLD amelioration after sleeve gastrectomy in obese rats. Sci Rep. 2016 23;6:39942.
37. Kornyushin O, Sonin D, Polozov A, Masley V, Bulavinova N, Chervyak M, et al. Effect of sleeve gastrectomy, Roux-en-Y gastric bypass, and ileal transposition on myocardial ischaemia-reperfusion injury in non-obese non-diabetic rats. Sci Rep. 2021 Dec 13;11(1):23888.
38. Skuratovskaia D, Vulf M, Chasovskikh N, Komar A, Kirienkova E, Shunkin E, et al. The Links of Ghrelin to Incretins, Insulin, Glucagon, and Leptin After Bariatric Surgery. Front Genet. 2021;12:612501.
39. Tok A, Ozer A, Kanat-Pektas M, Aral M, Sakalli H, Aydogdu S, et al. The role of omentin in early pregnancy losses. J Obstet Gynaecol J Inst Obstet Gynaecol. 2020 Jan;40(1):107–10.
40. Watanabe T, Watanabe-Kominato K, Takahashi Y, Kojima M, Watanabe R. Adipose Tissue-Derived Omentin-1 Function and Regulation. Compr Physiol. 2017 Jun 18;7(3):765–81.

41. Tan YL, Zheng XL, Tang CK. The protective functions of omentin in cardiovascular diseases. Clin Chim Acta Int J Clin Chem. 2015 Aug 25;448:98–106.
42. Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab. 2006 Jun;290(6):E1253-1261.
43. Goodarzi G, Shirgir A, Alavi S, Khoshi A. Effect of insulin–glucose metabolism compared with obesity on adipose omentin gene expression in different models of diabetic C57BL/6 mice. Diabetol Metab Syndr [Internet]. 2019 Aug 14 [cited 2020 Jan 30];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6694498/
44. Zhou H, Zhang Z, Qian G, Zhou J. Omentin-1 attenuates adipose tissue inflammation via restoration of TXNIP/NLRP3 signaling in high-fat diet-induced obese mice. Fundam Clin Pharmacol. 2020 Jun 1;
45. Moreno-Navarrete JM, Catalán V, Ortega F, Gómez-Ambrosi J, Ricart W, Frühbeck G, et al. Circulating omentin concentration increases after weight loss. Nutr Metab. 2010 Apr 9;7:27.
46. Lis I, Pelczyńska M, Miller-Kasprzak E, Kujawska-Łuczak M, Mądry E, Bogdański P. Association of serum omentin concentration with anthropometric, physiological, and biochemical parameters in obese individuals. Nutrition. 2020 Nov 1;79–80:110866.
47. Leandro A, Queiroz M, Azul L, Seiça R, Sena CM. Omentin: A novel therapeutic approach for the treatment of endothelial dysfunction in type 2 diabetes. Free Radic Biol Med. 2021 Jan 1;162:233–42.
48. As´habi A, Sadeghi M, Arab A, Hajianfar H. The association between omentin and diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab Syndr Obes Targets Ther. 2019 Jul 31;12:1277–86.
49. Lapointe M, Poirier P, Martin J, Bastien M, Auclair A, Cianflone K. Omentin changes following bariatric surgery and predictive links with biomarkers for risk of cardiovascular disease. Cardiovasc Diabetol. 2014 Aug 21;13:124.
50. Alipour FG, Ashoori MR, Pilehvar-Soltanahmadi Y, Zarghami N. An overview on biological functions and emerging therapeutic roles of apelin in diabetes mellitus. Diabetes Metab Syndr. 2017 Dec;11 Suppl 2:S919–23.
51. Elsehmawy AAEW, El-Toukhy SE, Seliem NMA, Moustafa RS, Mohammed DS. Apelin and chemerin as promising adipokines in children with type 1 diabetes mellitus. Diabetes Metab Syndr Obes Targets Ther. 2019;12:383–9.
52. Cavallo MG, Sentinelli F, Barchetta I, Costantino C, Incani M, Perra L, et al. Altered Glucose Homeostasis Is Associated with Increased Serum Apelin Levels in Type 2 Diabetes Mellitus. PLOS ONE. 2012 Dec 5;7(12):e51236.
53. Yu Y, Fernandez ID, Meng Y, Zhao W, Groth SW. Gut hormones, adipokines, and pro- and anti-inflammatory cytokines/markers in loss of control eating: A scoping review. Appetite. 2021 Nov 1;166:105442.
54. Bertrand C, Valet P, Castan-Laurell I. Apelin and energy metabolism. Front Physiol [Internet]. 2015 [cited 2021 Apr 12];6. Available from: https://www.frontiersin.org/articles/10.3389/fphys.2015.00115/full
55. Gourdy P, Cazals L, Thalamas C, Sommet A, Calvas F, Galitzky M, et al. Apelin administration improves insulin sensitivity in overweight men during hyperinsulinaemic-euglycaemic clamp. Diabetes Obes Metab. 2018 Jan;20(1):157–64.
56. Holst JJ, Madsbad S, Bojsen-Møller KN, Svane MS, Jørgensen NB, Dirksen C, et al. Mechanisms in bariatric surgery: Gut hormones, diabetes resolution, and weight loss. Surg Obes Relat Dis Off J Am Soc Bariatr Surg. 2018 May;14(5):708–14.
57. Nielsen S, Svane MS, Kuhre RE, Clausen TR, Kristiansen VB, Rehfeld JF, et al. Chenodeoxycholic acid stimulates glucagon-like peptide-1 secretion in patients after Roux-en-Y gastric bypass. Physiol Rep. 2017 Feb;5(3).
58. Hindsø M, Svane MS, Hedbäck N, Holst JJ, Madsbad S, Bojsen-Møller KN. The role of GLP-1 in postprandial glucose metabolism after bariatric surgery: a narrative review of human GLP-1 receptor antagonist studies. Surg Obes Relat Dis [Internet]. 2021 Feb 9 [cited 2021 Apr 13]; Available from: https://www.sciencedirect.com/science/article/pii/S1550728921000800
59. Jirapinyo P, Jin DX, Qazi T, Mishra N, Thompson CC. A Meta-Analysis of GLP-1 After Roux-En-Y Gastric Bypass: Impact of Surgical Technique and Measurement Strategy. Obes Surg. 2018;28(3):615–26.
60. Larraufie P, Roberts GP, McGavigan AK, Kay RG, Li J, Leiter A, et al. Important Role of the GLP-1 Axis for Glucose Homeostasis after Bariatric Surgery. Cell Rep. 2019 Feb 5;26(6):1399-1408.e6.
61. Liu J, Yang D, Wang B, Zeng Y, Li W. The value of miRNAs in the prognosis of obese patients receiving bariatric surgery. Am J Transl Res. 2021;13(4):1905–14.
62. Flynt AS, Lai EC. Biological principles of microRNA-mediated regulation: shared themes amid diversity. Nat Rev Genet. 2008 Nov;9(11):831–42.
63. de Planell-Saguer M, Rodicio MC. Detection methods for microRNAs in clinic practice. Clin Biochem. 2013 Jul;46(10–11):869–78.
64. Catanzaro G, Filardi T, Sabato C, Vacca A, Migliaccio S, Morano S, et al. Tissue and circulating microRNAs as biomarkers of response to obesity treatment strategies. J Endocrinol Invest. 2021 Jun;44(6):1159–74.
65. Liao CH, Wang CY, Liu KH, Liu YY, Wen MS, Yeh TS. MiR-122 marks the differences between subcutaneous and visceral adipose tissues and associates with the outcome of bariatric surgery. Obes Res Clin Pract. 2018 Dec;12(6):570–7.
66. Doyon L, Das S, Sullivan T, Rieger-Christ K, Sherman J, Roque S, et al. Can genetics help predict efficacy of bariatric surgery? An analysis of microRNA profiles. Surg Obes Relat Dis Off J Am Soc Bariatr Surg. 2020 Jun 20;
67. Guay C, Regazzi R. MicroRNAs and the functional β cell mass: For better or worse. Diabetes Metab. 2015 Nov 1;41(5):369–77.
68. Atkin SL, Ramachandran V, Yousri NA, Benurwar M, Simper SC, McKinlay R, et al. Changes in Blood microRNA Expression and Early Metabolic Responsiveness 21 Days Following Bariatric Surgery. Front Endocrinol [Internet]. 2019 Jan 4 [cited 2020 Jan 31];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6338028/

69. Sánchez-Ceinos J, Rangel-Zuñiga OA, Clemente-Postigo M, Podadera-Herreros A, Camargo A, Alcalá-Diaz JF, et al. miR-223-3p as a potential biomarker and player for adipose tissue dysfunction preceding type 2 diabetes onset. Mol Ther - Nucleic Acids. 2021 Mar 5;23:1035–52.
70. Yang Z, Chen H, Si H, Li X, Ding X, Sheng Q, et al. Serum miR-23a, a potential biomarker for diagnosis of pre-diabetes and type 2 diabetes. Acta Diabetol. 2014 Oct;51(5):823–31.
71. Vasu S, Kumano K, Darden CM, Rahman I, Lawrence MC, Naziruddin B. MicroRNA Signatures as Future Biomarkers for Diagnosis of Diabetes States. Cells [Internet]. 2019 Nov 28 [cited 2020 Aug 18];8(12). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6953078/
72. Karolina DS, Tavintharan S, Armugam A, Sepramaniam S, Pek SLT, Wong MTK, et al. Circulating miRNA profiles in patients with metabolic syndrome. J Clin Endocrinol Metab. 2012 Dec;97(12):E2271-2276.
73. Kong L, Zhu J, Han W, Jiang X, Xu M, Zhao Y, et al. Significance of serum microRNAs in pre-diabetes and newly diagnosed type 2 diabetes: a clinical study. Acta Diabetol. 2011 Mar;48(1):61–9.
74. Jiménez-Lucena R, Camargo A, Alcalá-Diaz JF, Romero-Baldonado C, Luque RM, Ommen B van, et al. A plasma circulating miRNAs profile predicts type 2 diabetes mellitus and prediabetes: from the CORDIOPREV study. Exp Mol Med. 2018 Dec 26;50(12):1–12.
75. Yan LN, Zhang X, Xu F, Fan YY, Ge B, Guo H, et al. Four-microRNA signature for detection of type 2 diabetes. World J Clin Cases. 2020 May 26;8(10):1923–31.
76. Eikelis N, Dixon JB, Lambert EA, Hanin G, Tzur Y, Greenberg DS, et al. MicroRNA-132 may be associated with blood pressure and liver steatosis-preliminary observations in obese individuals. J Hum Hypertens. 2021 Aug 27;
77. Amouyal C, Castel J, Guay C, Lacombe A, Denom J, Migrenne-Li S, et al. A surrogate of Roux-en-Y gastric bypass (the entero-gastro anastomosis surgery) regulates multiple beta-cell pathways during resolution of diabetes in ob/ob mice. EBioMedicine. 2020 Aug 1;58:102895.
78. Ortega FJ, Mercader JM, Catalán V, Moreno-Navarrete JM, Pueyo N, Sabater M, et al. Targeting the circulating microRNA signature of obesity. Clin Chem. 2013 May;59(5):781–92.
79. Lopez YN, Coen P, Goodpaster B, Seyhan A. Gastric bypass surgery with exercise alters plasma microRNAs that predict improvements in cardiometabolic risk. Int J Obes 2005. 2017 Jul;41(7):1121–30.
80. Hubal MJ, Nadler EP, Ferrante SC, Barberio MD, Suh JH, Wang J, et al. Circulating adipocyte-derived exosomal MicroRNAs associated with decreased insulin resistance after gastric bypass. Obes Silver Spring Md. 2017 Jan;25(1):102–10.
81. Bae YU, Kim Y, Lee H, Kim H, Jeon JS, Noh H, et al. Bariatric Surgery Alters microRNA Content of Circulating Exosomes in Patients with Obesity. Obes Silver Spring Md. 2019 Feb;27(2):264–71.
82. Sangiao-Alvarellos S, Theofilatos K, Barwari T, Gutmann C, Takov K, Singh B, et al. Metabolic recovery after weight loss surgery is reflected in serum microRNAs. BMJ Open Diabetes Res Care. 2020 Oct;8(2):e001441.
83. Cereijo R, Taxerås SD, Piquer-Garcia I, Pellitero S, Martínez E, Tarascó J, et al. Elevated Levels of Circulating miR-92a Are Associated with Impaired Glucose Homeostasis in Patients with Obesity and Correlate with Metabolic Status After Bariatric Surgery. Obes Surg. 2020 Jan;30(1):174–9.
84. Hulsmans M, Sinnaeve P, Van der Schueren B, Mathieu C, Janssens S, Holvoet P. Decreased miR-181a expression in monocytes of obese patients is associated with the occurrence of metabolic syndrome and coronary artery disease. J Clin Endocrinol Metab. 2012 Jul;97(7):E1213-1218.
85. Macartney-Coxson D, Danielson K, Clapham J, Benton MC, Johnston A, Jones A, et al. MicroRNA profiling in adipose before and after weight-loss highlights the role of miR-223-3p and the NLRP3 inflammasome. Obes Silver Spring Md. 2020 Mar;28(3):570–80.
86. Kuryłowicz A, Wicik Z, Owczarz M, Jonas MI, Kotlarek M, Świerniak M, et al. NGS Reveals Molecular Pathways Affected by Obesity and Weight Loss-Related Changes in miRNA Levels in Adipose Tissue. Int J Mol Sci. 2017 Dec 27;19(1):66.
87. Ortega FJ, Mercader JM, Moreno-Navarrete JM, Nonell L, Puigdecanet E, Rodriquez-Hermosa JI, et al. Surgery-Induced Weight Loss Is Associated With the Downregulation of Genes Targeted by MicroRNAs in Adipose Tissue. J Clin Endocrinol Metab. 2015 Nov;100(11):E1467-1476.
88. Ortega FJ, Moreno M, Mercader JM, Moreno-Navarrete JM, Fuentes-Batllevell N, Sabater M, et al. Inflammation triggers specific microRNA profiles in human adipocytes and macrophages and in their supernatants. Clin Epigenetics. 2015 Apr 24;7(1):49.
89. Nardelli C, Iaffaldano L, Pilone V, Labruna G, Ferrigno M, Carlomagno N, et al. Changes in the MicroRNA Profile Observed in the Subcutaneous Adipose Tissue of Obese Patients after Laparoscopic Adjustable Gastric Banding. J Obes. 2017;2017:6754734.
90. Zhang J, Bowers J, Liu L, Wei S, Gowda GAN, Hammoud Z, et al. Esophageal cancer metabolite biomarkers detected by LC-MS and NMR methods. PloS One. 2012;7(1):e30181.
91. Lei Z, Huhman DV, Sumner LW. Mass Spectrometry Strategies in Metabolomics. J Biol Chem. 2011 Jul 22;286(29):25435–42.
92. Vizioli C, Jaime-Lara RB, Franks AT, Ortiz R, Joseph PV. Untargeted Metabolomic Approach Shows No Differences in Subcutaneous Adipose Tissue of Diabetic and Non-Diabetic Subjects Undergoing Bariatric Surgery: An Exploratory Study. Biol Res Nurs. 2021;23(1):109–18.
93. Samczuk P, Ciborowski M, Kretowski A. Application of Metabolomics to Study Effects of Bariatric Surgery. J Diabetes Res. 2018;2018:6270875.
94. Lopes TIB, Geloneze B, Pareja JC, Calixto AR, Ferreira MMC, Marsaioli AJ. Blood Metabolome Changes Before and After Bariatric Surgery: A (1)H NMR-Based Clinical Investigation. Omics J Integr Biol. 2015 May;19(5):318–27.

95. Vaishya S, Sarwade RD, Seshadri V. MicroRNA, Proteins, and Metabolites as Novel Biomarkers for Prediabetes, Diabetes, and Related Complications. Front Endocrinol [Internet]. 2018 Apr 23 [cited 2019 Oct 14];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5925339/
96. Kwee LC, Ilkayeva O, Muehlbauer MJ, Bihlmeyer N, Wolfe B, Purnell JQ, et al. Metabolites and diabetes remission after weight loss. Nutr Diabetes. 2021 Feb 24;11(1):10.
97. Luo P, Yu H, Zhao X, Bao Y, Hong CS, Zhang P, et al. Metabolomics Study of Roux-en-Y Gastric Bypass Surgery (RYGB) to Treat Type 2 Diabetes Patients Based on Ultraperformance Liquid Chromatography–Mass Spectrometry [Internet]. ACS Publications. American Chemical Society; 2016 [cited 2022 Jan 31]. Available from: https://pubs.acs.org/doi/pdf/10.1021/acs.jproteome.6b00022
98. Zheng X, Chen T, Zhao A, Ning Z, Kuang J, Wang S, et al. Hyocholic acid species as novel biomarkers for metabolic disorders. Nat Commun. 2021 Mar 5;12(1):1487.
99. Ha J, Jang M, Kwon Y, Park YS, Park DJ, Lee JH, et al. Metabolomic Profiles Predict Diabetes Remission after Bariatric Surgery. J Clin Med. 2020 Dec 1;9(12):E3897.
100. Zhao X, Gang X, Liu Y, Sun C, Han Q, Wang G. Using Metabolomic Profiles as Biomarkers for Insulin Resistance in Childhood Obesity: A Systematic Review [Internet]. Journal of Diabetes Research. 2016 [cited 2018 Oct 11]. Available from: https://www.hindawi.com/journals/jdr/2016/8160545/
101. Narath SH, Mautner SI, Svehlikova E, Schultes B, Pieber TR, Sinner FM, et al. An Untargeted Metabolomics Approach to Characterize Short-Term and Long-Term Metabolic Changes after Bariatric Surgery. PloS One. 2016;11(9):e0161425.
102. Sarosiek K, Pappan KL, Gandhi AV, Saxena S, Kang CY, McMahon H, et al. Conserved Metabolic Changes in Nondiabetic and Type 2 Diabetic Bariatric Surgery Patients: Global Metabolomic Pilot Study. J Diabetes Res. 2016;2016:3467403.
103. Nemati R, Lu J, Tura A, Smith G, Murphy R. Acute Changes in Non-esterified Fatty Acids in Patients with Type 2 Diabetes Receiving Bariatric Surgery. Obes Surg. 2017 Mar 1;27(3):649–56.