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Review

Subcutaneous adipose tissue and skeletal muscle mitochondria following weight loss

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Obesity is a major global health issue with various metabolic complications. Both bariatric surgery and dieting achieve weight loss and improve whole-body metabolism, but vary in their ability to maintain these improvements over time. Adipose tissue and skeletal muscle metabolism are crucial in weight regulation, and obesity is linked to mitochondrial dysfunction in both tissues. The impact of bariatric surgery versus dieting on adipose tissue and skeletal muscle mitochondrial metabolism remains to be elucidated. Understanding the molecular pathways that modulate tissue metabolism following weight loss holds potential for identifying novel therapeutic targets in obesity management. This narrative review summarizes current knowledge on mitochondrial metabolism following bariatric surgery and diet-induced weight loss in adipose tissue and skeletal muscle, and sheds light on their respective effects.

Highlights

Bariatric surgery and dieting have distinct effects on mitochondrial metabolism in adipose tissue and skeletal muscle.

In adipose tissue, bariatric surgery may preserve or enhance mitochondrial metabolism, whereas dieting tends to reduce it.

In skeletal muscle, bariatric surgery may increase mitochondrial metabolism, but it typically remains unchanged after dieting. Dieting in combination with exercise, rather than dieting alone, plays a pivotal role in activating muscle mitochondria.

Adipose tissue shows greater responsiveness to weight loss interventions compared with skeletal muscle in terms of mitochondrial metabolism.

Why mitochondrial metabolism is meaningful in weight loss

Obesity is a major global health issue, with over 2.5 billion people living with overweight or obesity in 2022 [1]. Obesity is an important risk factor for various diseases, including type 2 diabetes (T2D), dyslipidemia, cancer, and cardiovascular disease [2].

A 5–10% reduction in body weight significantly decreases the risk of metabolic disease and improves glucose metabolism [3]. Obesity treatments include dieting, exercise, medications, and **bariatric surgery** (see Glossary), with the latter being the most effective for sustained weight loss [4]. Dieting with **very low-calorie diets (VLCDs)** often yields modest weight loss [5], and maintaining lost weight proves challenging. Up to 80% of individuals struggle to maintain even a 10% reduction in body weight [6]. However, surgery is not feasible or available for all individuals with obesity. As such, identifying mechanisms that maintain weight loss is important for discovering new targets for obesity treatments.

Subcutaneous white adipose tissue and skeletal muscle are dynamic organs that play a central role in whole-body energy metabolism and the success of weight loss [7,8]. Subcutaneous adipose tissue (referred to as adipose tissue in this text) acts as an energy reservoir and secretes various hormones that affect whole-body metabolism [7], whereas skeletal muscle is a highly active major site of energy expenditure and of glucose and lipid metabolism [8].

Mitochondrial metabolism in adipose tissue and skeletal muscle after weight loss can represent a significant mechanism underlying sustained weight loss. Mitochondria are the key organelles for cellular energy metabolism, as described in Box 1, and are thus perfectly positioned to mediate the metabolic adaptations after weight loss. Reduced mitochondrial metabolism in adipose tissue [9] and skeletal muscle [10] is observed in individuals with obesity.

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Box 1. Mitochondria and their metabolic features

Mitochondria are organelles with a double-membrane encompassing the intermembrane space and the matrix. The outer membrane acts as a barrier to the cytoplasm, whereas the highly convoluted inner membrane forms cristae that increase the surface area of the matrix. The intermembrane space serves various functions, including protein import, calcium signaling, and reactive oxygen species (ROS) production. The mitochondrial matrix contains metabolic products, enzymes, ribosomes, proteins, and mitochondrial DNA (mtDNA) that facilitate various biochemical reactions [14].

Mitochondria contain their own circular genome (i.e., mtDNA) which contains 37 unique genes. Thirteen mtDNA genes encode protein subunits of the oxidative phosphorylation (OXPHOS) system, and the others encode mitochondrial tRNAs and rRNAs. Most of the mitochondrial proteome (>1100 proteins) is encoded by the nuclear genome [14]. Mitochondria are highly dynamic and undergo continuous processes of fission (fragmentation), fusion (elongation), mitophagy (degradation), and transport inside and between cells that determine the morphology, quality, quantity and distribution of mitochondria within cells [120].

Mitochondria play a crucial role in cellular and overall body energy balance. They generate metabolites, electron donors, and ATP through the tricarboxylic acid (TCA) cycle and OXPHOS. They govern many reactions including long-chain fatty acid β-oxidation and catabolism of branched-chain amino acids (BCAAs), and are pivotal in maintaining cellular calcium homeostasis, stress signaling, ROS, cellular differentiation, and apoptosis – encompassing all the cellular functions essential for metabolic well-being [14].

The mechanisms driving sustained weight loss after bariatric surgery or dieting are not fully understood. Distinct responses to weight-loss methods (e.g., higher after surgery, lower after dieting, or vice versa) have been reported for gut hormones and their satiety effects in the brain [11], a well as changes in the gut microbiome [12] and serum bile acids [13]. However, importantly, the specific mechanisms mediating the changes to adipose tissue and muscle mitochondrial metabolism after surgery and dieting remain to be elucidated.

Given these open questions and recent findings in the field, we outline the impact of surgery- and diet-induced weight loss on human adipose tissue and skeletal muscle mitochondrial metabolism, and also discuss potential mediating mechanisms. While we acknowledge the significant contributions of preclinical studies to our understanding of mitochondrial metabolism [14], in this review we focus on the results of human interventions to directly address clinical implications.

Mitochondria in adipose tissue and skeletal muscle in obesity

Reduced mitochondrial metabolism in adipose tissue has been shown in human obesity [9]. In short, there is lower expression of mitochondria-related and nucleic transcripts [15], as well as reduced levels of the main **mitochondrial biogenesis** regulator PGC-1α [16]. In addition, a decrease in **mitochondrial DNA amount**, subunits of mitochondrial proteins of the **oxidative phosphorylation (OXPHOS)** complex, the activities of OXPHOS complexes (C)I to IV, and mitochondrial membrane potential are observed [9]. Increased mitochondrial fragmentation is seen in mice [17]. Furthermore, mitochondrial **fatty acid oxidation**, **branched-chain amino acid (BCAA) catabolism**, lipolysis, lipogenesis, and adipogenesis are all downregulated in obesity and lower **mitochondrial respiration** rates are seen in isolated adipocytes [18]. This lower mitochondrial metabolism has been linked to a reduction in the hyperplastic capacity (expandability) of the adipose tissue, as well as to the development of metabolic diseases including T2D and insulin resistance [19], and increased inflammation [15]. However, in obesity, a higher mitochondrial mass, larger mitochondrial area, and increased mitochondrial transcript expression have also been found [20] that could potentially act as a compensatory mechanism.

The focus on mitochondrial metabolism in skeletal muscle has been more related to insulin resistance and T2D rather than to obesity *per se* [21]. However, in short, mitochondrial metabolism is reduced in obesity [10] and the mitochondria-related transcriptional signature is downregulated [15]. Other findings include lower skeletal muscle mitochondrial amount, lower mitochondria-

Glossary

Bariatric surgery: different surgical techniques that induce rapid and long-lasting weight reduction. Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG, either open or laparoscopic), and laparoscopic sleeve gastrectomy (LSG, similar to VSG, but laparoscopic) are the most common surgery approaches. Other techniques include biliopancreatic diversion (BPD) and adjustable gastric banding (AGB).
Branched-chain amino acid (BCAA) catabolism: breakdown of these amino acids (leucine, isoleucine, and valine) primarily occurs in the mitochondrial matrix. It involves transamination to generate α-keto acids, followed by oxidative decarboxylation and further oxidation to produce intermediates which enter the TCA cycle.
Electron transport chain: this chain is located in the inner mitochondrial membrane and comprises a series of protein complexes (CI–IV) and electron carriers (ubiquinone and cytochrome *c*). Its primary function is to transfer electrons from electron donors (e.g., NADH and $FADH_2$ from the TCA cycle) to the final electron acceptor, oxygen.
Fatty acid oxidation: fatty acids are broken down in the mitochondria to produce ATP, including **β-oxidation** which is the enzymatic process of breaking down fatty acids into acetyl-CoA units, which enter the TCA cycle.
Mitochondrial amount: the amount of mitochondria in the cells, typically measured by mitochondrial DNA in relation to nuclear DNA (mtDNA:nDNA ratio) or citrate synthase activity and/or cardiolipin levels.
Mitochondrial biogenesis: increases in the number and size of mitochondria within cells. It includes mtDNA replication, transcription and translation of mitochondrial and nuclear DNA, import of nucleus-encoded proteins into mitochondria, and an increase in mitochondrial membrane components.
Mitochondrial dynamics: changes in the morphology, quantity, distribution, and position of mitochondria within cells. It involves mitochondrial fission (fragmentation), fusion (elongation), mitophagy (degradation), and transport within the cell.
Mitochondrial respiration: organic molecules are oxidized in the presence of an inorganic electron acceptor, oxygen, to produce ATP. It is typically

related protein levels, lower respiratory capacity, reduced **mitochondrial dynamics**, and higher production of reactive oxygen species (ROS) [8].

The reduced mitochondrial metabolism observed in both adipose tissue and skeletal muscle in obesity presents an opportunity to combat metabolic diseases and facilitate weight loss by enhancing mitochondrial function. A thorough understanding of the impact of different weight loss methods on mitochondrial metabolism in peripheral tissues is needed.

Adipose tissue mitochondrial metabolism after bariatric surgery-induced weight loss

Bariatric surgery induces significant beneficial changes in adipose tissue that affect whole-body metabolism [22], but its specific impact on adipose tissue mitochondrial metabolism remains incompletely understood. Roux-and-Y gastric banding (RYGB) surgery may increase mitochondrial metabolism in adipose tissue (Figure 1A and Table 1). Increased transcription of genes related to mitochondrial biogenesis and metabolism has been reported [23], as well as mitochondrial number [24,25] and respiration [24], on both short- and long-term follow-up. Upregulation of genes related to fatty acid transport, β-oxidation, and mitochondrial uncoupling has been reported within 1 week of surgery [26]; likewise, upregulation of single genes involved in mitochondrial biogenesis occurs as early as 1 week after surgery [27] and is sustained up to 3 [28] or 6 months [29],

measured as oxygen consumption of the tissues or isolated mitochondria from these tissues. Mitochondrial respiration can be determined through the strategic use of various mitochondrial substrates, inhibitors, and stimulating agents.

Oxidative phosphorylation (OXPHOS): involves the electron transport chain and ATP synthase. As electrons are transported through the chain, energy is released, driving the pumping of protons (H^+ ions) from the mitochondrial matrix into the intermembrane space, creating a gradient. The ATP synthase (CV) uses this gradient to drive protons back into the mitochondrial matrix, generating ATP.

Tricarboxylic acid (TCA) cycle: this cycle in the mitochondrial matrix produces the high-energy electron carriers NADH and $FADH_2$ that are used in the electron transport chain to generate ATP.

Very low-calorie diet (VLCD): typically contains <800 kcal/day, whereas an LCD typically comprises 1000–1500 kcal/day. This dietary approach is sustained for 6–8 weeks to induce rapid weight loss. Following this phase, a gradual transition back to a normal weight-sustaining diet is implemented.

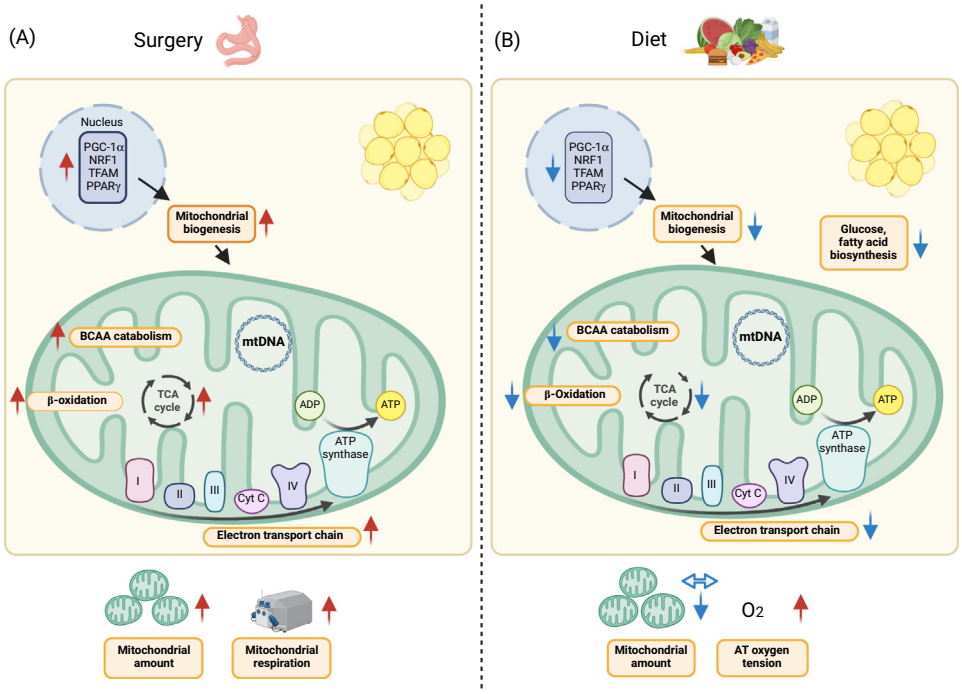

Figure 1. Mitochondrial metabolism in adipose tissue after bariatric surgery and diet-induced weight loss. (A) After bariatric surgery, increases are observed across various mitochondrial parameters, including increases in mitochondria-related transcriptional signature, mitochondrial amount, mitochondrial branched-chain fatty acid (BCAA) metabolism, fatty acid oxidation, tricarboxylic acid (TCA) cycle, individual oxidative phosphorylation (OXPHOS) complex subunits, and mitochondrial respiration. (B) Following diet-induced weight loss, decreases are observed in mitochondria-related transcriptional signatures, mitochondrial amount, and TCA cycle, BCAA, and fatty acid biosynthesis pathways. Increased oxygen tension represents reduced oxygen consumption of adipose tissue (AT). Abbreviations: Cyt C, cytochrome *c; mtDNA, mitochondrial DNA.*

Table 1. Mitochondria in adipose tissue after bariatric surgery and dieting[a,b]

Refs	Participants (*n*)	Reported weight loss	Surgery type or dieting trial	Study length	Enzyme activity	Gene expression	Protein expression	Mt amount/microscopy	*Ex vivo* respirometry	Other
Bariatric surgery										
Van der Kolk *et al.* 2021 [23]	172 RYGB 49 RYGB	22.4% 27.5%	RYGB RYGB	1, 2, 5 years	–	1 year and 2 years: **OXPHOS**, **FAO**, **TCA cycle**, **BCAA catabolism** 5 years: OXPHOS, FAO, TCA cycle, BCAA catabolism	**OXPHOS**	–	–	–
Hansen *et al.* 2015 [24]	Ob: 43 T2D: 15	Ob: 40 kg T2D: 35 kg	RYGB	4, 18 months	–	–	–	4 and 18 months: **mtDNA/nDNA**, mtDNA/adipocyte	18 months: **tissue mass normalized CI**, **CI+II**, and **maximal CI+CII respiration in the presence of octanoyl-carnitine**, **P/E ratio;** mtDNA and cell number normalized parameters NS	–
Camastra *et al.* 2017 [25]	T2D: 13 No T2D: 15	T2D: 46 kg No T2D: 43 kg	RYGB	1 year	–	–	–	T2D: Mt number No T2D: **Mt number**	–	–
Jahansouz *et al.* 2018 [26]	46	In graph reported	RYGB/sleeve (VSG)	1 week	–	VSG: **PPARδ**, **ANGPTL4**, **CPT1**, **PDK4**, **PLIN2**, PPARα, CPT2, UCP1 RYGB: **PPARδ**, **CPT1**, PDK4	–	–	–	–
Jahansouz *et al.* 2015 [27]	16	NS	RYGB/AGB	1 week	–	RYGB: **eNOS**, **NRF1**, **TFAM**, **PCG-1α**, **CytC** AGB: eNOS, NRF1, TFAM, PCG-1α, CytC	–	–	–	–
Henegar *et al.* 2008 [28]	10	18.5 kg	RYGB	3 months	–	**OXPHOS**	–	–	–	–

Ferraz-Bannitz *et al.* 2021 [29]	13	21.8%	RYGB	3, 6 months	–	3 months and 6 months: **PGC-1α**, **SIRT1**, **SIRT3**, **NRF2**, **SOD2**, *PPARG*	–	–	–	–
Moreno-Navarrete *et al.* 2014 [30]	6	21.1 kg	DGR	2 years	–	**PCG-1β**, **TFAM**, **MT-CO3**, PGC-1α, PRDM16	–	–	–	–
Varela-Rodriguez *et al.* 2021 [31]	4	21.4 kg/m^2	RYGB/sleeve (VSG)	22–33 months	**HK**	–	**TCA cycle**, **ETC**, **ATP formation**, **pyruvate metabolism**, **glycolysis**, **thermogenesis**, **FAS**, **(p)ACC**, **(p)AMPK**, (p)**AKT**	**Mt density**, **coverage**, *aspect ratio*	–	–
Mardinoglu *et al.* 2015 [32]	6	42 kg	Sleeve/RYGB	1 year	–	SAT: **BCAT2**, **CIDEA**, **NMNAT2**, **MPC1**, **MPC2**, *BCAT1* VAT: **BCAT2**, **CIDEA**	–	–	–	–
Dankel *et al.* 2010 [33]	16	59.1 kg	BPD/DS	1 year	–	**ATP5G**, **COX5B**, *SLC25A25*, *SLC25A37*, *SLC25A44*	–	–	–	–
Ngo *et al.* 2018 [34]	10	62.5 kg	RYGB	10–30 months	SAT: SDH VAT: **SDH**	–	–	–	–	–
Moreno-Castellanos *et al.* 2016 [35]	18 NGT: 9 IR: 9	NGT: 14.2 kg/m^2 IR: 17.5 kg/m^2	RYGB/sleeve (LSG)	13 months	–	–	NGT: **DLDH**, **PLIN**, **vimentin 49**, **TCPB**, *IMMT*, *PGC1A*, vimentin 53 IR: **DLDH**, **IMMT**, **TCPB**, *PLIN*, vimentin 53, vimentin 49, PGC-1α	–	–	–
Dieting										
Vink *et al.* 2017 [36]	15	10.4%	YoYo	5 weeks plus 4 weeks	–	*Glucose and pyruvate metabolism*, *fatty acid*	–	–	–	*AT pO2*

(continued on next page)

Table 1. (continued)

Refs	Participants (*n*)	Reported weight loss	Surgery type or dieting trial	Study length	Enzyme activity	Gene expression	Protein expression	Mt amount/microscopy	*Ex vivo* respirometry	Other
				WM		*biosynthesis*, *OXPHOS*, *TCA cycle*, *ETC*, **Mt biogenesis**				
Viguerie *et al.* 2005 [37]	50	6.8%	Nugenob	10 weeks	–	*UCP2*, *PPARG*, **PGC-1α**	–	–	–	–
Rappou *et al.* 2016 [38]	19	WM: 17.1% WR: 5.1%	Cryo	5, 12 months	12 months: *PARP*	5 months: SIRT3 **SIRT1**, **SIRT7**, **NAMPT**, SIRT2, SIRT5 12 months: SIRT3, **SIRT1**, **SIRT7**, SIRT2, SIRT5, NAMPT	–	–	–	–
Magkos *et al.* 2016 [5]	40	5.1% with 3.5month, 10.8% with 6.8month, 16.4%	–	3.5, 6.8, and 10.4 months	–	Oxidative stress: *NQO1*, *DHCR24*, *and UCHL1*	–	–	–	–
Vink *et al.* 2017 [39]	53	LCD: 8.1% VLCD: 8.9%	YoYo	5 or 12 weeks plus 4 weeks WM	–	*TCA cycle*, *OXPHOS*, *lipid and glucose metabolism*, **Mt biogenesis**, **Mt-related genes**	–	–	–	–
Van der Kolk *et al.* 2021 [23]	314 19	11.9% 9.0%	Diogenes Cryo	2, 8, or 12 months	–	2, 8, 12 months: *OXPHOS*, *FAO*, *TCA cycle*, *BCAA*	–	–	–	–
Jokinen *et al.* 2018 [40]	19	WM: 17.1% WR: 5.1%	Cryo	5, 12 months	–	*TCA cycle*, *OXPHOS*, *FAO*, *BCAA*, **16S**, ND5, CYTB, COX1, 12S	*CIII/porin*, porin, CII, CV	*mtDNA/nDNA*	–	–
Barquissaeu *et al.* 2018 [41]	289	11.5 kg	Diogenes	2, 8 months	–	2 months: *browning*	–	–	–	–

						markers, *ETC* 8 months: browning markers				
Mutch *et al.* 2011 [42]	40	2 months: >8% WR +3.9kg WM –2.6 kg	Diogenes	2, 8 months	–	WR plus WM: *OXPHOS*, *TCA cycle*, *FAO* WM: *BCAA*, *TCA cycle*, *OXPHOS*	–	–	–	–
Urbanová *et al.* 2017 [43]	T2D: 16	12 kg	–	3 weeks	–	*CS*, *DLAT*, *MT-ND5*, *SDHA* ATP50, COX4, CYC1, NDUF12	–	–	–	–
Marquez-Quinones *et al.* 2010 [44]	77	2 months: >8% WR +3.9 kg WM –2.6 kg	Diogenes	2, 8 months	–	WR: Mt-related genes WM: **Mt-related genes**	–	–	–	–
Hansen *et al.* 2015 [24]	Ob: 43 T2D: 15	Ob: 7 kg T2D: 7 kg	–	2 months	–	–	–	mtDNA/nDNA, mtDNA/adipocyte	CI, CI+II, and maximal CI+CII respiration in the presence of octanoyl-carnitine	–

[a]Text in bold font indicates significant upregulation after intervention; text in italic font indicates significant downregulation after intervention. Text in normal font indicates no significant changes.
[b]Abbreviations: AGB, adjustable gastric banding; BCAA, branched-chain amino acid; BPD/DS, biliopancreatic diversion with duodenal switch; CI, complex 1, CII, complex 2; CIII, complex 3; CytC, cytochrome *c*; DGR, distal gastric resection; ETC, electron transport chain; FAO, fatty acid oxidation; IR, person living with insulin resistance; LCD, low-calorie diet; LSG, Laparoscopic sleeve gastrectomy; Mt, mitochondria; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; NGT, person living with normal glucose tolerance; NS, not significant; Ob, person living with obesity; OXPHOS, oxidative phosphorylation; PARP, poly(ADP-ribose) polymerase; Qmax, maximal mitochondrial function; RYGB, Roux-en-Y gastric bypass; SAT, subcutaneous adipose tissue; sleeve, sleeve gastrectomy; TCPCr, phosphocreatine recovery time constant; T2D, person living with type 2 diabetes; TCA cycle, tricarboxylic acid cycle; VAT, visceral adipose tissue; VLCD, very low calorie diet; VSG, vertical sleeve gastrectomy; WM, person who maintained weight loss; WR, person who regained weight.

and expression of mitochondria-related genes [**tricarboxylic acid (TCA) cycle**, OXPHOS, fatty acid oxidation and BCAA catabolism] and OXPHOS complex subunit protein levels are increased after RYGB surgery at 1 year follow-up [23].

After RYGB, increased adipose tissue mitochondrial number is seen in individuals with obesity, as assessed by electron microscopy, but this effect was not found in individuals with obesity and T2D [25]. At a functional level, adipose tissue mitochondrial respiration was increased in individuals both with and without T2D when respiration was expressed relative to adipose tissue weight [24], but when the values were normalized to mitochondrial amount, no differences in oxidative capacity were seen. Interestingly, the P/E ratio [the ratio of OXPHOS capacity (P) to electron transfer pathway capacity (E) – a measure of mitochondrial coupling capacity] remained elevated, which suggests an increased ability to oxidize substrates after RYGB [24]. Overall, these studies indicate upregulation or at least a partial preservation of mitochondrial metabolism after RYGB surgery.

The upregulation of mitochondrial metabolism seen after weight loss has also been reported for other bariatric procedures (Table 1). Patients undergoing distal gastric resection surgery showed increased expression of genes related to mitochondrial biogenesis and the **electron transport chain** at 2 years follow-up [30]. After sleeve gastrectomy surgery, upregulation of genes related to fatty acid transport, β-oxidation, and mitochondrial uncoupling has been reported [26]. Proteins involved in the TCA cycle and OXPHOS complexes have been shown to be increased after sleeve gastrectomy, and the latter was accompanied by increased mitochondrial density and coverage [31]. Moreover, at 1 year follow-up after surgery, mitochondrial genes involved in BCAA catabolism were upregulated, but cytosolic BCAT1 was downregulated [32], whereas fatty acid oxidation transcripts and pyruvate transport into mitochondria were both increased [32]. At 1 year follow-up after biliopancreatic diversion (BPD) with duodenal switch surgery, an upregulation of genes involved in the electron transport chain was observed [33].

Some controversy remains regarding the increased mitochondrial metabolism after surgery. When adipose tissue depots were compared after 19 months post-RYGB surgery, OXPHOS CII enzyme activity was unchanged in subcutaneous adipose tissue and downregulated in visceral adipose tissue [34] (Table 1), indicating that mitochondrial metabolism may be differentially affected across adipose tissue depots after surgery.

The baseline phenotype of the patients (glycemic or metabolic status) may also influence the results of surgery on adipose tissue mitochondrial metabolism. Some mitochondria-related proteins have been suggested to be differentially regulated by insulin resistance status, and there were greater improvements in mitochondrial dynamics and mitochondrial biogenesis proteins in insulin-resistant than in insulin-sensitive individuals [35]. However, mitochondrial measures were not different when individuals with or without T2D were compared [24] or in individuals with T2D [25].

Overall, after various bariatric surgeries, adipose tissue mitochondrial metabolism appears to increase (Figure 1A), as indicated by mitochondrial number, expression of genes related to mitochondrial biogenesis, and possibly mitochondrial respiration. However, mitochondrial dynamics is still largely unexplored. Variations in duration of follow-up, sample size, and inclusion of T2D participants may influence the mitochondrial outcome. Nonetheless, current evidence suggests that there is partial restoration of adipose tissue mitochondrial metabolism post-surgery.

Adipose tissue mitochondrial metabolism after diet-induced weight loss

Weight loss induced by dieting has profound beneficial metabolic effects on adipose tissue [5], but how adipose tissue mitochondria are affected by dieting remains unclear. Diet-induced

weight loss has been associated with upregulation of adipose tissue mitochondrial metabolism (Table 1). In a clinical trial comparing two rates of weight loss – a 12 week LCD and a 5 week VLCD – on weight regain, the VLCD led to upregulation of genes related to mitochondrial biogenesis accompanied by a decrease in adipose tissue oxygen tension (pO2) [36]. These results indicate higher oxygen consumption in the tissue upon diet-induced weight loss. Increased mitochondrial biogenesis was also observed after a 10 week LCD [37], as well as upregulated gene expression of mitochondria-related sirtuins and NAD^+ metabolism after a 5 month diet intervention [38], and lower oxidative stress after progressive weight loss [5]. Upregulated mitochondrial biogenesis may act as a compensatory mechanism for the lower expression of mitochondrial oxidative pathways (e.g., OXPHOS, TCA cycle), as discussed later.

Dieting is mostly associated with downregulation of nuclear and mitochondrial RNA transcripts related to oxidative metabolism (Figure 1B and Table 1). Nuclear gene expression of mitochondrial pathways for the TCA cycle, OXPHOS, and fatty acid biosynthesis were downregulated, and a VLCD led to a greater number of gene alterations than an LCD [39]. Transcripts of the nucleus-encoded mitochondrial pathways were also downregulated by a 6 week LCD at 5 and 12 months follow-up [23,40]. Mitochondrial amount and protein levels of the CIII subunit of OXPHOS were reduced after weight loss at 12 months [40]. In addition, genes related to mitochondrial oxidative metabolism were downregulated in a trial with an 8 week VLCD followed by 6 months weight maintenance follow-up [23,41]. Genes connected to the TCA cycle, OXPHOS, and fatty acid metabolism were reduced both in individuals who maintained their weight loss and those who regained it [42]. A decline in the expression of *UCP1* and other browning markers in adipose tissue, that are known to associate with improved mitochondrial function, has been observed [41], as well as downregulated genes connected to the TCA cycle and OXPHOS [43]. Mitochondrial amount and respiration was unchanged after a 2 month diet phase [24]. Collectively, these studies at the gene expression level indicate downregulation of mitochondrial metabolism after dieting.

Weight-loss success by dieting may also be dependent on adipose tissue mitochondrial metabolism. Individuals maintaining weight loss exhibit higher baseline expression of nucleus-encoded mitochondrial oxidative pathways, a mitochondria-encoded gene for a CIV subunit, and mitochondrial DNA (mtDNA) amount compared with those regaining weight [40]. Moreover, mitochondria-related gene expression changes during the VLCD [42] and weight maintenance phases [44] were associated with weight-loss success. For instance, during the weight-maintenance phase, enhanced OXPHOS complex subunit gene expression was the major pattern associated with continued weight loss [44].

Overall, most studies report downregulated adipose tissue mitochondrial metabolism after dieting (Figure 1B); however, these studies primarily rely on transcriptome data and lack other measures such as functional assays or mitochondrial dynamics. Variability in VLCD durations and compositions, as well as in weight maintenance post-dieting, may affect mitochondrial outcomes.

Skeletal muscle mitochondrial metabolism after bariatric surgery-induced weight loss

Bariatric surgery enhances skeletal muscle metabolism, yet the exact mechanisms behind these improvements and mitochondrial involvement in them are unclear [45]. RYGB has been reported to upregulate mitochondrial metabolism (Figure 2A and Table 2). After the operation, mitochondrial respiration was normalized without changing mitochondrial amount or the levels of subunit proteins of the OXPHOS complex [46]. Moreover, abnormalities in mitochondrial network and morphology were improved along with a reduction in mitochondrial fission and unchanged mitochondrial amount [47]. In isolated mitochondria, when normalized against citrate synthase (CS) activity (a

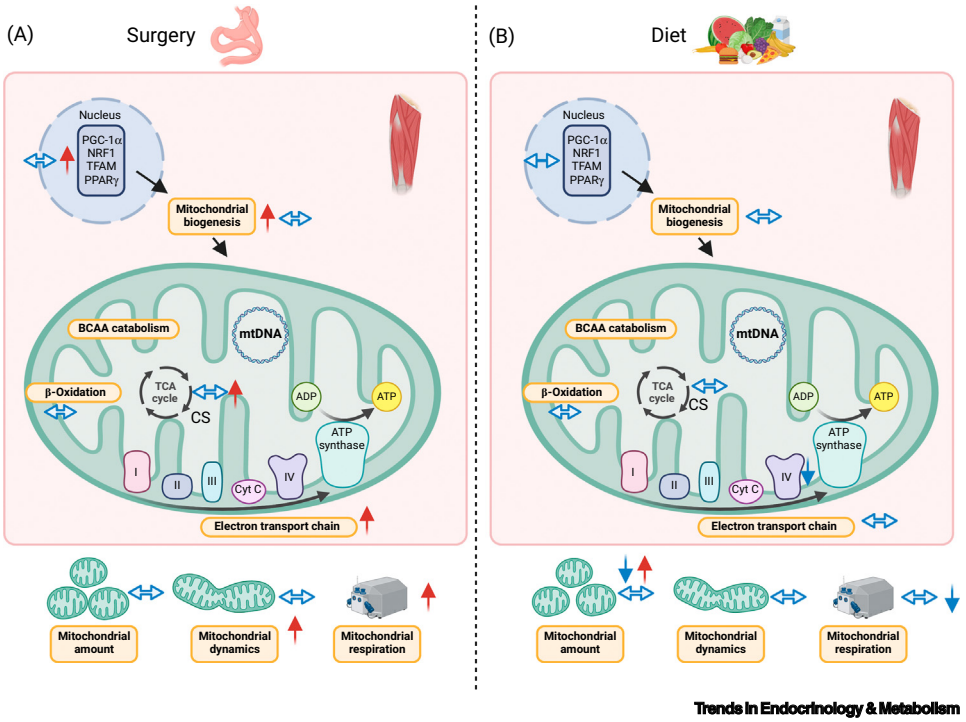

Figure 2. Mitochondrial metabolism in skeletal muscle following bariatric surgery and diet-induced weight loss. (A) After bariatric surgery, increases are observed across various mitochondrial parameters, including increases in mitochondrial transcriptional signatures, tricarboxylic acid (TCA) cycle enzymes, oxidative phosphorylation (OXPHOS) complex subunits, mitochondrial dynamics, and mitochondrial respiration. However, it is noteworthy that many studies also report no alterations in these measures or in other mitochondrial metabolic processes such as fatty acid β-oxidation and branched-chain fatty acid (BCAA) catabolism. (B) After diet-induced weight loss, unchanged levels of mitochondrial gene expression and enzyme activities are evident, and both increased or decreased levels are reported in parameters such as mtDNA amount, mitochondria-related gene expression, and *in vivo* and *ex vivo* respiration. Abbreviations: CS, citrate synthase; Cyt C, cytochrome *c*; mtDNA, mitochondrial DNA.

marker of mitochondrial amount), RYGB has led to an increase in ADP-stimulated coupled mitochondrial respiration and the phosphate/oxygen (P/O) ratio, which indicate improved mitochondrial efficiency. Uncoupled respiration (i.e., leak respiration or oxygen consumption without ATP production) was not changed [48]. In addition, expression of mitochondria-related genes, which was suppressed in obesity, was restored to levels comparable with those found in lean individuals following RYGB [49]. This finding was accompanied by altered methylation of the promoter region of the gene encoding the primary mitochondrial regulator PGC-1α, indicating that epigenetic modifications could potentially contribute to the effects of surgery [49]. Consistently, upregulated mitochondrial biogenesis was observed after surgery, as well as increased mitochondrial fusion transcripts [50].

Other surgical procedures besides RYGB have also demonstrated upregulated mitochondrial parameters in skeletal muscle. Gastric banding exhibited similar results in mitochondrial respiration compared with RYGB. Mitochondrial respiration was initially lower in individuals with obesity, but it recovered to levels comparable with those of lean controls, accompanied by unchanged mtDNA amounts [51]. In a recent meta-analysis, bariatric surgery was associated with increased levels of both mitochondrial amount and mitochondrial CI-linked ADP-coupled respiration [52].

However, the effects of bariatric surgery on skeletal muscle mitochondrial metabolism remain controversial (Table 2). Unchanged skeletal muscle basal and maximal mitochondrial

Table 2. Mitochondria in skeletal muscle after bariatric surgery and dieting[a,b]

Authors	Participants (*n*)	Reported weight loss	Surgery type	Study length	Enzyme activity	Gene expression	Protein expression	Mt amount/microscopy	*Ex vivo* respirometry	*In vivo* respirometry
Bariatric surgery										
Coen *et al.* 2015 [46]	101	RYGB: 22.1 kg +EX: 23.6 kg	RYGB + EX	8 months	RYGB: SDH, CS, NADH oxidase, CK	–	Both: NDUFB8, SDHB, UQCRC2, COX2, ATP5A	Both: cardiolipin	with CHO substrates RYGB: leak, CI, CI+CII, CytC, ETS	–
	RYGB: 50 +EX: 51		–	–	+EX: SDH, **CS**, **NADH oxidase**, CK	–	–	–	with FA substrates RYGB: leak, **FAO**, FAO and CI, **FAO and CI+CII**, **CytC** Both groups: **C1/ETS**, **CI+CII/ETS**, **CI/CI+CII**, leak/ETS	–
Kristensen *et al.* 2018 [47]	15	20 kg	RYGB	20 months	CS	–	*Fis1*, Mfn1/2, Drp1, OPA1	**Mt network**, *LD size with IMCL*, IMCL	–	–
Fernström *et al.* 2016 [48]	11	25.5kg	RYGB	6 months	–	–	–	–	Isolated mitochondria, per CS activity: **CI**, leak, **P/O ratio**	–
Barres *et al.* 2013 [49]	8	34.2 kg	RYGB	6 months	–	896 genes altered; **lipid metabolic process** **plus** **mitochondrion** **PDK4**, pgc-1alpha	–	–	–	–
Gastaldi *et al.* 2007 [50]	17	3 months: 22.2 kg 12 months: 41.9 kg	RYGB	3 and 12 months	–	3 months: **PGC-1α**, **MFN2**, CPT1, UCP3 12 months: **PGC-1α**, **MFN2**, *UCP3*,	–	–	–	–

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Table 2. (continued)

Authors	Participants *(n)*	Reported weight loss	Surgery type	Study length	Enzyme activity	Gene expression	Protein expression	Mt amount/microscopy	*Ex vivo* respirometry	*In vivo* respirometry
						CPT1				
Vijgen *et al.* 2013 [51]	8	27.9%	AGB	1 year	–	–	–	mtDNA/nDNA	**FAO (CI+CII)**, **CI+CII)**, LeakOmy, uncoupling ratio, maximum CI+CII, baseline	–
Pérez-Rodríguez *et al.* 2023 [52]	155	Meta-analysis	RYGB/sleeve	–	–	PGC-1α	–	**CS**	**CI**, CI+CII, uncoupled	–
Nijhawan *et al.* 2013 [53]	20	eWL: 30.3%	RYGB/sleeve	3 months	–	–	–	–	Basal and maximum respiration	–
Lund *et al.* 2018 [54]	Ob: 24T2D: 14	Ob: 40 kgT2D: 34 kg	RYGB	4.5 and 21 months	Both: CS, HADH	–	–	–	Both groups and timepoints: per weight or CS activity: FAO CI+CII, CI+CII, CI+CII max	–
Berggren *et al.* 2008 [55]	6		RYGB	1 year	–	PDK4, CPT1, PGC-1α	–	–	–	–
Campbell *et al.* 2016 [56]	7	6.8 kg/m^2	RYGB	3 months	–	*OXPHOS*, *TCA cycle*	**Desmin**, **SOD2**, OXPHOS, TCA cycle, CS, CytC	–	–	–
Fabris *et al.* 2004 [57]	10	48.6 kg	BPD	18 months	–	*CPT1*, *PPARA*, *ACOX1*, *ACACB*, SREBF1	–	–	–	–
Bariatric surgery: time and metabolic phenotype effects										
Barberio *et al.* 2021 [58]	No T2D: 12 T2D: 5	17.7 kg/m^2 T2D: 12.2 kg/m^2	RYGB	1 year	–	No T2D: OXPHOS, ETC T2D: **OXPHOS**, **ETC**	–	–	–	–
Hernandez-Alvarez *et al.* 2009 [59]	21	NGT: 63.1 kg	BPD	2 year	–	NGT: **MFN2**, **CS**, **porin**, **PGC-1β**, **SIRT1**, COX3, PGC-1α, PPARδ,	–	–	–	–

						ERRA				
		T2D: 62.9 kg	–	–	–	T2D: *MFN2*, CS, Porin, COX3, PGC-1β, PGC-1α, PPARD, ERRA, SIRT1	–	–	–	–
Gancheva *et al.* 2019 [60]	49	33.0%	RYGB/sleeve	2 weeks up to 1 year	2 weeks: *CS*	2 weeks: **mitochondrial function**, **FA metabolism**	2 weeks: Mfn2, Opa1, Fis1, LC3, p62, SDH, NDUFB8, UQCR2, **ATP5F1A**, pPink1, pParkin, pDRP1	2 weeks: *Mt density*	2 weeks: *maximum CI+CII max*, *respiratory control ratio*, leak control ratio, **CI+CII per CS activity**, CI+CII per SHD content	–
	T2D: 13	–	–	–	52 weeks: CS	52 weeks: 49 Mt-related genes transiently expressed	52 weeks: **Mfn2, Opa1, Fis1, LC3, p62, SDH, NDUFB8, UQCR2, ATP5F1A**, pPink1, pParkin, pDRP1	52 weeks: Mt density	52 weeks: maximum CI+CII, respiratory control ratio, leak control ratio, CI+CII per CS activity, *CI+CII per SHD content*	–
Dieting										
Civitarese *et al.* 2007 [61]	12	8.3 kg	–	6 months	CS, HADH, COX2	**TFAM**, **PGC-1α**, **SIRT1**, **eNOS**, **PARL**, **AMPKa2**	CS	**mtDNA/nDNA**	–	–
Sparks *et al.* 2017 [62]	51	8.8 kg	–	12 months		29 Mt-related genes, **SIRT1**	CIII, CIV	*mtDNA/nDNA*		ATPmax, resting ATP flux, O_2 uptake, P/O, EMCL, IMCL subgroup, **ATPmax**, **P/O**
Das *et al.* 2023 [63]	90	12%	–	24 months		**Mt biogenesis**	–	–	–	–
Kern *et al.* 1999 [64]	9	20.8%	–		**SDH**	–	–	–	–	–

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Table 2. (continued)

Authors	Participants *(n)*	Reported weight loss	Surgery type	Study length	Enzyme activity	Gene expression	Protein expression	Mt amount/microscopy	*Ex vivo* respirometry	*In vivo* respirometry
Kempen *et al.* 1998 [65]	28	10.8 kg		8 weeks	CS, **H-FABP**, HADH	–	–	–	–	–
Simoneau *et al.* 1999 [66]	40	F: 12.2 kg	–	13 weeks plus 3 weeks WM	F: *COX*, *HADH*, PFK, GAPDH	–	–	–	–	–
–	–	M: 17.5kg	–		M: COX, HADH, PFK, GAPDH	–	–	–	–	–
–	–	–	–	–	Both: CS, FABPpm, FABPc, LPL, CPT	–	–	–	–	–
Blaak *et al.* 2001 [67]	7	15.3 kg	–	10 weeks plus 2 weeks	CS, HADH, FABPc	–	–	–	–	–
Blaak *et al.* 2001 [68]	35	12 kg	–	8 weeks plus 2 weeks	CS, HADH	–	–	–	–	–
Imbeault *et al.* 2002 [69]	37	F: 9 kg M: 11 kg	–	15 weeks	CS, PFK, HADH, COX	–	–	–	–	–
Doucet *et al.* 2003 [70]	19	9%	–	15 weeks plus 4–6 weeks WM	CS, COX, HADH, PFK/CS	–	–	–	–	–
Metz *et al.* 2008 [71]	10	9.2 kg	–	15 weeks plus 4–6 weeks WM	PFK, GAPDH, LDH, HK, CK, CS, COX, HADH, MCT	–	–	–	–	–
Konings *et al.* 2010 [72]	12	15.5 kg	–	12 weeks	CS, HADH	PGC-1α	–	–	–	–
Kelley *et al.* 1999 [73]	32	14 kg	–	12 weeks plus 4 week WM	*COX*, CPT	–	–	–	–	–

Larson-Meyer *et al.* 2000 [74]	12	11.1 kg	–	4 months plus 3 months WM	–	–	–	–	–	TCPCr, TCADP, OXPHOS
Newcomer *et al.* 2001 [75]	24	12.3 kg	–	4 months plus 3 months WM	–	–	–	–	–	AnGly, CK, OXPHOS, VPCr, *TCADP*, **Qmax**
Rabøl *et al.* 2009 [76]	17	11.5%	–	10 weeks	CS	–	UCP3	mtDNA/nDNA	*CI*, CI+CII, *CI+CII maximum*	
Johnson *et al.* 2016 [77]	11	10.1%	–	17 weeks plus 2 weeks WM	–	–	–	–	CI, CII, CI+CII, CytC, CI+CII leak, CI+CII max, ROX	PCr
Nylén *et al.* 2019 [78]	8	–	–	3 weeks	–	PGC-1α, TFAM, **MLYCD**	–	–	–	–
Liu et al 2020 [79]	20	3.9 kg	–	2 months	–	PGC-1α, SIRT3, MFN2, TFAM, GPX1, SOD1, SOD2, CD36, PPARα, CPT1, PDK4, ACAT1, MCT1, MCT4, OXCT1	–	–	–	–
Smith *et al.* 2016 [80]	10	~10%	–	26.4 weeks	–	COX4I1, CPT1-b, PDK4, PGC-1α, UCP2, SOD1	–	–	–	–
Kristensen *et al.* 2018 [47]	15	9 kg	–	Until 8% body weight loss	CS	–	–	Mfn1/2, Drp1, Fis1, OPA1 IMCL, Mt network, LD size with IMCL	–	–
Lund *et al.* 2018 [54]	Ob: 24 T2D: 14	Ob: 7 kg T2D: 4 kg	–	Until 8–10% body weight loss at ~2 months	Both: CS, HADH	–	–	–	Both: per CS activity: FAO CI+CII,CI+CII, CI+CII max	–
Pérez-Rodríguez *et al.* 2023 [52]	520	Meta-analysis	–	–	*CIV activity*	–	–	Mt content; CIV	*Maximal CI-linked ADP coupled respiration*	–

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Table 2. (continued)

Authors	Participants (*n*)	Reported weight loss	Surgery type	Study length	Enzyme activity	Gene expression	Protein expression	Mt amount/microscopy	*Ex vivo* respirometry	*In vivo* respirometry
Diet versus diet plus exercise studies (only diet results are shown in this table)										
Svendsen *et al.* 1996 [81]	51	9.5 kg	–	12 weeks	CS, HK, GAPDH	–	–	–	–	–
Nordby *et al.* 2015 [82]	11	5.2 kg	–	12 weeks	–	–	CII–CV, CS, HADH	–	–	–
Toledo *et al.* 2008 [83]	7	10.8%	–	5 months	NADH-oxidase	–	–	mtDNA/ nDNA, cardiolipin Mt density, *Mt size*, *IMCL*	–	–
Menshikova *et al.* 2017 [84]	7	7,5 kg	–	4 months	**CS**, HADH, NADH oxidase, HADH/CS and NADH/CS ratio's	–	–	Cardiolipin, volume density	–	–
Beals *et al.* 2023 [85]	8	10.4%	–	20.6 weeks	–	No changes in DIET group	–	–	–	–
Ortmeyer *et al.* 2017 [86]	34	7.0 kg	–	6 months	CS, HADH	–	–	–	–	–
Diet-sensitive (DS) versus diet-resistant (DR)										
Harper *et al.* 2002 [87]	12	DR: 12% DS: 22%	–	–	–	DS: **UCP3**, UCP2 DR: UCP3, UCP2	–	–	DS versus DR: **leak**, **Mt oxygen consumption**	–
Gerrits *et al.* 2010 [88]	12	–	–	–	SDH	*SLC25A3*, *IRS2*, *GPAM*, *PPARD* GSEA: *ETC genes*	–	–	–	–

[a]Text in bold font indicates significant upregulation after intervention; text in italic font indicates significant downregulation after intervention. Text in normal font indicates no significant changes.
[b]Abbreviations: AGB, adjustable gastric banding; AnGly, anaerobic glycolysis; BCAA, branched-chain amino acid; BPD, biliopancreatic diversion; CI, complex 1; CII, complex 2, CIII, complex 3; CIV, complex 4; CK, creatine kinase; COX, cytochrome *c* oxidase; CS, citrate synthase; CV, complex 5; CytC, cytochrome *c*; DR, diet-resistant; DS, diet-sensitive; EMCL, extramyocellular lipid content; ETC, electron transport chain; eWL, excess weight loss; EX, exercise; F, female; FAO, fatty acid oxidation; HADH, hydroxyacyl-CoA dehydrogenase; HK, hexokinase; IMCL, intramyocellular lipids; IR, person living with insulin resistance; LCD, low-calorie diet; M, male; microscopy; Mt, Mitochondria; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; NGT, person living with normal glucose tolerance; NS, not significant; Ob, person living with obesity; OXPHOS, oxidative phosphorylation; RYGB, Roux-en-Y gastric bypass; SDH, succinate dehydrogenase; T2D, person living with type 2 diabetes; TCA cycle, tricarboxylic acid cycle; VLCD, very low calorie diet; WM, weight maintenance.

respiration [53], respiratory capacity and mitochondrial amount [54], gene expression for mitochondrial biogenesis or nutrient provisioning [55], and downregulated TCA cycle and OXPHOS genes with unchanged protein expression [56] have been reported after RYGB. BPD surgery was associated with reduced mitochondrial biogenesis, fatty acid transport, and fatty acid oxidation which were linked to impaired lipid oxidation [57].

Mitochondrial metabolism post-bariatric surgery may also vary depending on the presence of T2D. Females with T2D have lower expression of OXPHOS genes, including subunits of mitochondrial OXPHOS CI, before RYGB compared with controls without T2D. At 1 year post-RYGB, these pathways were upregulated in individuals with T2D but not in controls; this change was related to improvements in glucose metabolism [58]. By contrast, for individuals without T2D who underwent BPD surgery, there was increased expression of genes responsible for the TCA cycle, mitochondrial fusion, mitochondrial amount, and mitochondrial biogenesis, whereas individuals with T2D had unchanged expression of these genes – except for a downregulated mitochondrial fusion marker gene [59]. In addition, glucose oxidation was increased and lipid oxidation was decreased in individuals without T2D, compared with a blunted response in glucose oxidation in T2D after surgery [59], which may suggest better mitochondrial improvement in T2D and a shift towards glucose oxidation in individuals without T2D.

The effects of surgery on mitochondrial metabolism are also dependent on the time of follow-up [60]. Two weeks after sleeve or RYGB surgeries, in comparison to baseline, mitochondrial amount and maximal uncoupled respiration were decreased, which was paralleled by a lower respiratory control ratio, indicating impaired mitochondrial efficiency. At 12 weeks, measures of mitochondrial function and content returned towards baseline and there was higher expression for mitochondrial fusion genes. At 1 year, measures of mitochondrial function and amount returned towards baseline. The involvement of epigenetic mechanisms was suggested as mediators for these changes [60].

Overall, skeletal muscle mitochondrial amount and respiration appear to improve following surgery (Figure 2A), particularly in the long term [52]. However, the results are not consistent and factors such as mitochondrial dynamics remain largely unexplored. Post-operation intervals [60], exercise levels [46], and metabolic phenotype may influence mitochondrial outcomes. Moreover, a debate persists about whether the improvement is more significant in individuals without T2D versus those with the condition.

Skeletal muscle mitochondrial metabolism after diet-induced weight loss

Weight loss through dieting has profound effects on skeletal muscle. However, dieting is often coupled to exercise, which is a known trigger for mitochondrial biogenesis and dynamics in skeletal muscle. Understanding and separating the effects of weight loss through dieting alone, or in conjunction with exercise, on muscle mitochondrial metabolism is essential.

Only a few studies have reported an increase in mitochondrial markers in skeletal muscle following dieting, including the CALERIE study [61–63] that measured the most comprehensive range of mitochondrial parameters. An increase in skeletal muscle CII activity was seen in women who underwent moderate weight loss through dietary intervention [64]; however, they were encouraged to lose as much weight as possible and the study did not control for physical activity, which might affect the mitochondrial outcome, as discussed in more detail later.

No changes or a decline in mitochondrial function following dieting have been observed in studies with only enzymatic activity assays (Figure 2B and Table 2). Unchanged enzyme activities related to the TCA cycle [65–72], β-oxidation [65,67–72], mitochondrial fatty acid transport [66,73], and/

or OXPHOS CIV [69–71] have been reported. OXPHOS CIV activity was decreased after a 4 month dietary program [73]. Moreover, in women, but not in men, OXPHOS CIV and β-oxidation enzyme activities decreased significantly, questioning a uniform mitochondrial response after dieting in the two sexes [66].

No changes or a decline in mitochondrial function following dieting were also observed when multiple metrics to assess mitochondria were employed (Table 2). For instance, in sedentary overweight women who underwent VLCD, *in vivo* mitochondrial function remained unaltered, as measured with magnetic resonance spectroscopy during an exercise bout [74,75]. Unchanged *ex vivo* skeletal muscle mitochondrial respiration accompanied with unchanged mtDNA amount and TCA cycle activity after 10 weeks of dieting [76] was reported, as well as unchanged *ex vivo* mitochondrial respiration and *in vivo* mitochondrial function after a 16 week diet [77]. In addition, gene expression associated with mitochondrial biogenesis [78–80] and mitochondrial fusion/fission [47] did not change, nor did mitochondrial respiration [54]. A recent meta-analysis concluded that there was a decrease in mitochondrial maximal respiration without altering mitochondrial amount after dieting [52]. This finding was mainly supported by a reduction in OXPHOS CIV activity but not in the levels of CIV components [52].

The CALERIE study [61–63], a trial with 25% caloric restriction for 6 months, measured the most extensive range of different mitochondrial markers in a single trial, and also included longer follow-up timepoints (Table 2). This trial gives mixed results on the overall picture, but mostly suggests minor changes regarding skeletal mitochondrial metabolism after dieting. At the 6 month timepoint there were increases in the expression of mitochondrial biogenesis genes and decreases in whole-body oxygen consumption, oxidative stress, and DNA damage, although the enzymatic activities of the TCA cycle, β-oxidation, and OXPHOS CIV were not increased [61]. Biogenesis of 'efficient' mitochondria was suggested to act as an adaptive mechanism, which in turn lowers oxidative stress. After 12 months, reduced levels of mtDNA, unchanged mitochondrial biogenesis, but increased *SIRT1* expression were observed [62]. However, no changes in *in vivo* markers of muscle mitochondrial O_2 uptake and ATP fluxes reflecting mitochondrial phosphorylation capacity and mitochondrial efficiency were reported [62]. Recently, after a 2 year follow-up and a 12% weight loss, the individuals again presented with increased levels of mitochondrial biogenesis transcripts [63]. Collectively, most mitochondrial markers remained unchanged in the CALERIE trial, which suggests that the duration of follow-up and the amount of weight loss may play a role in interpreting the results.

The separate effects of dieting and exercise on skeletal muscle mitochondria have been explored by including both diet-only (Table 2) and diet plus exercise groups. After 12 weeks of intervention, no changes in TCA cycle activity [81] and expression of OXPHOS complex subunit proteins [82] were reported in the diet-only group, but these mitochondrial markers were increased in the diet plus exercise group [81,82], and exercise alone was able to explain the results of the latter study [82]. Moreover, after 16 weeks dieting, unchanged OXPHOS CI activity and mitochondrial amount, reduced mitochondrial size, and decreased intramyocellular lipid content were observed in the diet-only group, although mitochondrial density was maintained [83]. However, the combined exercise and diet group exhibited improvements in these mitochondrial markers [83]. Recent results showed improvements in insulin sensitivity accompanied by increased expression of genes involved in mitochondrial biogenesis and energy metabolism [84,85] and TCA cycle and β-oxidation activity [86] in groups who combined diet and exercise compared with diet alone. These findings suggest that exercise, rather than diet alone, plays a pivotal role in activating mitochondria in skeletal muscle.

Weight loss in response to dieting is highly variable; however, only one trial has addressed mitochondrial differences in skeletal muscle between diet-sensitive and diet-resistant individuals [87,88]. After a 6 week VLCD, mitochondrial uncoupled respiration was higher and the expression of the uncoupler *UCP3* was greater in diet-sensitive than in diet-resistant individuals, whereas there were no changes in *UCP2* expression [87]. Genes related to OXPHOS were upregulated in diet-sensitive compared with diet-resistant participants, accompanied by an increased proportion of oxidative fibers [88]. Primary myotubes from diet-resistant individuals had a lower capacity to adapt to oxidative stress compared with diet-sensitive individuals [89]. These results suggest that mitochondrial metabolism in skeletal muscle may depend on weight maintenance.

Overall, most studies show limited or no changes in skeletal muscle mitochondrial metabolism following dieting (Figure 2B). However, only a few studies have measured mitochondrial respiration, and data on mitochondrial dynamics are mostly lacking. Variability in dieting approaches, follow-up durations, and exercise control likely affects mitochondrial outcomes. Despite these differences, combining diet and exercise, rather than diet alone, appears to be crucial for activating skeletal muscle mitochondria.

Potential mechanisms behind the mitochondrial changes in adipose tissue and skeletal muscle after surgery and diet

Surgery and dieting affect mitochondrial metabolism in adipose tissue and skeletal muscle differently (Figure 3, Key figure). While many of the mechanisms behind these changes remain unclear, some potential connections are briefly discussed.

Gut hormones

Gut hormones may mediate the distinct effects of surgery and dieting on tissue mitochondria. The gut secretes >20 hormones that are released during fasting (e.g., ghrelin) or after meals [e.g., glucagon-like peptide 1 (GLP-1), peptide YY (PYY), gastric inhibitory polypeptide (GIP)], and these influence satiety, glucose homeostasis, and energy levels in various tissues [90]. Following bariatric surgery, most studies report increased levels of anorectic hormones such as GLP-1, GIP, and PYY [90], and decreased levels of hunger-related ghrelin [91]. Conversely, after dieting, secretion of anorectic hormones decreases whereas ghrelin levels rise [92], leading to reduced satiety sensation. Postprandial levels of PYY and GLP-1 tend to be higher after RYGB in comparison to LCD, and an increased incretin effect was observed after RYGB but not after weight loss induced by a LCD [93]. However, studies directly comparing gut hormone responses to surgery versus dieting remain limited.

Several gut hormones (e.g., GLP-1, GIP, and ghrelin) have been identified as regulators of adipose tissue and possibly skeletal muscle function. In adipose tissue, they influence lipid uptake, utilization, and storage in both humans and rodents [94]. Moreover, these hormones can induce thermogenesis and elevate energy expenditure, particularly in rodent models [90]. GLP-1, for instance, mediates diet-induced thermogenesis and sympathetic activation in rodent brown adipose tissue [95]. The GLP-1R agonist liraglutide enhanced mitochondrial dynamics and thermogenic gene expression in rodent adipose tissue [96] and semaglutide increased mitochondrial number and area in rodent skeletal muscle [97].

Indeed, in recent years, gut-hormone-based obesity medications, including GLP-1R agonists, have become an essential factor for weight loss and metabolic improvement. In a human adipocyte model, liraglutide improved mitochondrial respiration and biogenesis, and induced smaller lipid droplets and browning-like features *in vitro* [98]. However, human adipose tissue GLP-1R expression has not been linked to metabolic improvements after bariatric surgery [99], warranting

Key figure

Mitochondrial metabolism following bariatric surgery or diet-induced weight loss in adipose tissue and skeletal muscle

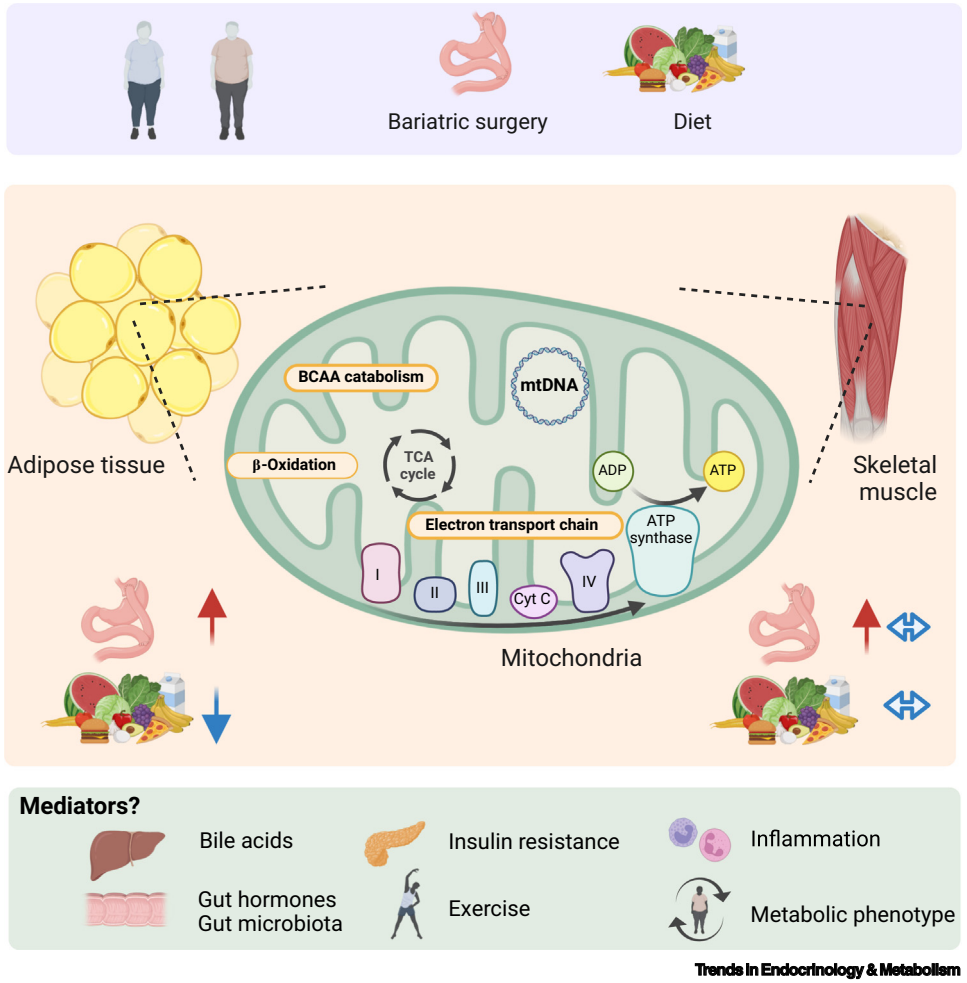

Figure 3. Weight loss induced by bariatric surgery or dieting has distinct effects on mitochondrial metabolism in adipose tissue and skeletal muscle. After surgery, adipose tissue often shows improved mitochondrial characteristics compared with before weight loss, in contrast to findings following dieting. Skeletal muscle responses vary after both forms of weight loss, yielding mixed results and suggesting an increase in mitochondrial metabolism after surgery, but not after dieting. Factors such as bile acids, gut hormones, microbiota composition, insulin sensitivity, metabolic phenotype, inflammatory status, and exercise emerge as potential factors influencing changes in mitochondrial metabolism after weight loss. Abbreviations: BCAA, branched-chain amino acid; Cyt C, cytochrome *c; mtDNA, mitochondrial DNA; TCA cycle, tricarboxylic acid cycle.*

further studies. Recently, the GIP/GLP-1R dual agonist tirzepatide was shown to increase transcripts related to mitochondrial biogenesis, the TCA cycle, and OXPHOS in both human and mouse adipocytes, primarily through long-acting activation of GIP rather than GLP-1R [100]. In the future, the therapeutic effects of gut-hormone and GLP-1R based medications on human adipose tissue and skeletal muscle will need to be further unraveled.

Bile acids

Bile acids – cholesterol-derived molecules that are modified by liver and gut – may mediate the differing effects of surgery and dieting on tissue mitochondria. They are major regulators of lipid metabolism and have pleiotropic effects by activating energy metabolism, improving insulin sensitivity, and regulating appetite signals such as GLP-1 [101]. In obesity, fasting and postprandial bile acid responses are blunted [102]. Both fasting and postprandial bile acid levels increase after bariatric surgery [102], and reduced bile acid levels have been observed after dieting [103].

Activation of the bile acid receptor TGR5 appears to enhance mitochondrial function in white and brown adipose tissue of mice, and bile acid receptor FXR agonism promotes thermogenesis, mitochondrial biogenesis, and fatty acid oxidation in mouse adipose tissue [101]. Supplementation with chenodeoxycholic acid (CDCA) increases energy expenditure, induces transcription of thermogenic *UCP1* in mouse adipose tissue [104], and increases mitochondrial activity in human brown adipose tissue [105]. In rodent skeletal muscle, bile acids can regulate skeletal muscle mitochondrial metabolism [106].

Gut microbiota

Weight loss leads to significant changes in gut microbiota composition, both after surgery [12] and dieting [107]. After surgery, increased microbial α-diversity has been reported which is linked to beneficial metabolic changes of adipose tissue [108]. Dieting also increases the diversity of the gut microbiota and induces favorable metabolic changes [107].

Gut bacteria ferment dietary fiber and produce short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. SCFAs can modulate energy metabolism by acting as signaling molecules and influencing the release of gut hormones, including GLP-1 and PYY [109]. The shift in gut microbiota composition may contribute to beneficial effects through alterations in SCFA production. Some SCFAs decrease after dieting [110] and increase after surgery [111], but the findings are inconsistent. SCFAs can enhance adipose tissue browning and may modulate skeletal muscle lipid and glucose metabolism possibly through activation of AMPK [112].

Other factors

In skeletal muscle, reduced levels of intramuscular triglycerides may distinguish between the metabolic changes induced by surgery and dieting. Lipid partitioning within cells is dependent upon mitochondria and can shift toward different metabolic pathways based on nutritional status. Studies have shown decreases in intramuscle triglyceride content after RYGB [47] and BPD [57] at varying intervals over 3–18 months. However, after 7 weeks of VLCD no changes in intramuscular triglycerides were observed [76], and after 10 weeks no alterations in fatty acid-binding protein (FABP) or muscle oxidative enzymes were found [68]. In addition, intramuscular triglyceride levels showed differential results depending muscle fiber type [62].

Muscle mass loss upon weight loss may affect mitochondrial metabolism in skeletal muscle. Bariatric surgery can result in up to 20% muscle mass loss due to rapid weight reduction [113], although increased exercise post-surgery may mitigate this [46]. Dieting also leads to muscle mass loss but to a lesser extent, and it can be reduced through increased protein intake and resistance training [84,114]. Despite the significant metabolic benefits of both interventions, further studies will be necessary to explore the relationship between muscle mass loss and mitochondrial metabolism upon weight loss.

In adipose tissue, reduced low-grade inflammation post-surgery, rather than after dieting, may link weight loss to improved tissue metabolism. Obesity often presents simultaneously with

both reduced mitochondrial metabolism and low-grade inflammation [15]. After surgery there is a decrease in adipose tissue inflammation-related transcriptome [22]. However, dieting outcomes vary: some studies show increased inflammatory mediators with VLCD [39] whereas others report no changes or reductions [5]. One study noted no immediate change in proinflammatory genes during VLCD but observed increased levels during follow-up [115]. These differential inflammatory responses may affect tissue mitochondrial metabolism.

Increased adipose tissue browning may be linked to enhanced mitochondrial metabolism after surgery. In mice, there is a connection between adipose tissue browning and increased thermogenic activation of brown adipose tissue following RYGB [116]. However, these findings have not been confirmed in humans. To date, studies have not shown increased thermogenic activity in brown adipose tissue [117] nor has there been evidence of adipose tissue browning after RYGB [118] or dieting [41].

Additional factors that may influence mitochondrial metabolism in adipose tissue and skeletal muscle following both surgery and dieting include enhanced insulin sensitivity [3], reduced oxidative stress [5], altered extracellular matrix remodeling [28], reduced endoplasmic reticulum stress [119], and modulation of nuclear DNA methylation [49]. In the future, additional mediators between weight loss and tissue metabolism may be found.

Concluding remarks

Both bariatric surgery and dieting lead to weight loss and improved whole-body and tissue metabolism. Comparing their effects on mitochondrial parameters presents challenges owing to varying follow-up following weight loss, unreported exercise levels, obesity-related comorbidities, and a diverse array of mitochondrial marker measurements (see Outstanding questions). Moreover, important mitochondrial features including mitochondrial dynamics are often unexplored after weight loss.

Nevertheless, mitochondria in adipose tissue and skeletal muscle respond differently to surgery- and diet-induced weight loss (Figure 3). Adipose tissue typically shows increased mitochondrial metabolism after surgery, whereas dieting tends to downregulate mitochondrial metabolism, at least at the gene expression level (Figure 1). Results on skeletal muscle are mixed, and the majority of studies suggest increased mitochondrial metabolism after surgery and mostly unchanged parameters after dieting (Figure 2). Exercise, rather than dieting alone, plays a pivotal role in activating mitochondria in skeletal muscle.

Potential mechanisms for the differences in mitochondrial metabolism between the two weight-loss methods may be linked to a variety of factors (see Outstanding questions). The changes in mitochondrial function and content after bariatric surgery could also be secondary to weight loss rather than a driving mechanism, and the initial metabolic status of people with obesity, including the obesity timecourse, can affect mitochondrial metabolism. Detailed assessment of mitochondrial metabolism following weight loss may provide targets and biomarkers for more tailored nutritional or pharmacological interventions in the prevention or treatment of obesity. Future studies are warranted to obtain detailed insights into these differential metabolic phenotypes as well as their related biomarkers.

Outstanding questions

What implications do the differential effects of weight loss through bariatric surgery versus dieting have for our understanding of metabolic responses, particularly in adipose tissue, skeletal muscle, and their mitochondria?

Which specific factors lead to improvements in mitochondrial metabolism in adipose tissue and skeletal muscle after weight loss?

How can mitochondrial metabolism in peripheral tissues be targeted for developing future obesity medications?

Authors contributions

B.W.v.d.K. and S.H. wrote the manuscript, created the figures, and generated the tables. E.P. and K.H.P. were responsible for the original review design and supervision of the work. All authors were included in the writing and read and approved the final manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to improve readability and check grammar. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of interests

The authors declare no competing interests.

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