

Review

Perspectives on whole body and tissue-specific metabolic flexibility and implications in cardiometabolic diseases

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SUMMARY

Metabolic flexibility is the body's ability to switch between fuel sources in response to changing supply. This adaptability is crucial for maintaining energy balance and metabolic homeostasis, involving key processes like insulin signaling, organ-specific hormone regulation, and mitochondrial function. Initially thought to be determined by skeletal muscle, metabolic flexibility is now recognized as a systemic process affecting multiple organs, including the brain, liver, heart, and adipose tissue. In cardiometabolic diseases, metabolic inflexibility often occurs early, contributing to disease progression. Insulin resistance, a key factor in metabolic inflexibility, impairs fuel utilization and exacerbates metabolic syndrome. Understanding and addressing metabolic flexibility is critical for early detection and prevention. This review emphasizes the significance of metabolic flexibility in cardiometabolic health, underscoring the importance of endocrine regulation and organ crosstalk. However, knowledge gaps remain regarding the mechanisms linking metabolic inflexibility to disease, the need for better clinical assessments, and the relationship with insulin resistance.

INTRODUCTION

Optimal health can be defined as an organism's ability to maintain or restore homeostasis in response to environmental changes and stressors. This unpredictable exposome requires a high degree of flexibility to adjust physiological processes as needed, with metabolic flexibility—shifting between available fuel sources to meet energy demands—being central to this adaptability.^{1,2} Initially thought to be primarily determined by skeletal muscle,^{3,4} metabolic flexibility is now recognized as a systemic feature relevant across the whole body, impacting organs, tissues, cells and even organelles.⁵ Studies have demonstrated that organs and tissues, such as the heart and adipose tissue, must also dynamically shift fuel sources to match fuel availability to energy demands, relying on nutrient sensing, uptake, transport, storage, and utilization.^{6–8} This adaptability is crucial for preserving energy homeostasis and supporting metabolic health.

Cardiometabolic diseases arise from a complex interaction of tissue-specific dysfunctions leading to whole-body metabolic disorders.⁹ In obesity, these diseases often begin with a gradual and heterogeneous loss of function in key metabolic tissues (i.e., adipose tissue, skeletal muscle, liver, and pancreas),⁹ which, over time, affect other organs, particularly the brain, heart, and kidneys, progressing to systemic metabolic syndrome and eventually end-stage organ failure and death.^{9,10} With healthcare's growing emphasis on preventive care over late-stage treatments, understanding early metabolic dysfunction has become critical. Early detection enables the identification of at-risk individuals and the development of pre-emptive interventions to prevent irreversible organ damage.⁸ Mechanistically, the early stages of systemic metabolic syndrome, often discernible by a loss of metabolic flexibility,^{2,6,8} precede cardiometabolic disease, marking critical disruptions in global energy homeostasis and nutrient metabolism.^{2,6} Given the central role of metabolic flexibility in maintaining health and the profound consequences



Table 1. Factors contributing to metabolic flexibility

Factor	Example	Effect
Nutritional state, fed	Consumption of western diet	Exaggerated and prolonged carbohydrate metabolism, reduced metabolic flexibility ^{11,12}
Nutritional state, fasted	Overnight fasting, or fasting for more than 8 h	Decrease in circulating dietary carbohydrates and lipids; decrease in insulin-glucagon ratio; production of ketone bodies, body predominantly reliant on fatty acid oxidation instead of carbohydrates ¹³
Energy needs	Vigorous physical exercise	Increase in energy needs leading to an increase in energy demand, results in increased AMP/ATP ratio, upregulation of oxidative phosphorylation activity in-place of glycolysis ^{14–17}
Substrate availability	Consumption of a carbohydrate-rich meal	In the availability of glucose, a metabolically flexible individual will be able to transit from fat oxidation to carbohydrate ^{18–20}
Hormonal regulation	Secretion of hormones during specific circumstances, leading to increased insulin action (e.g., times of stress—cortisol, thyroid hormones; while consuming a meal—GLP-1, GIP, CCK, cortisol, leptin) Secretion of hormones that decrease insulin secretion: somatostatin, glucagon, growth hormone (e.g., after a meal)	Modulation of metabolic flexibility directly or indirectly via increased insulin secretion (also see Table 2 for more elaboration) ²¹

of its impairment, this review will focus on the molecular and physiological underpinnings of this essential process. We will discuss how disruptions in metabolic flexibility contribute to the development and progression of cardiometabolic diseases, emphasizing the potential for targeting metabolic flexibility as an early therapeutic strategy to prevent or mitigate the development of these devastating conditions.

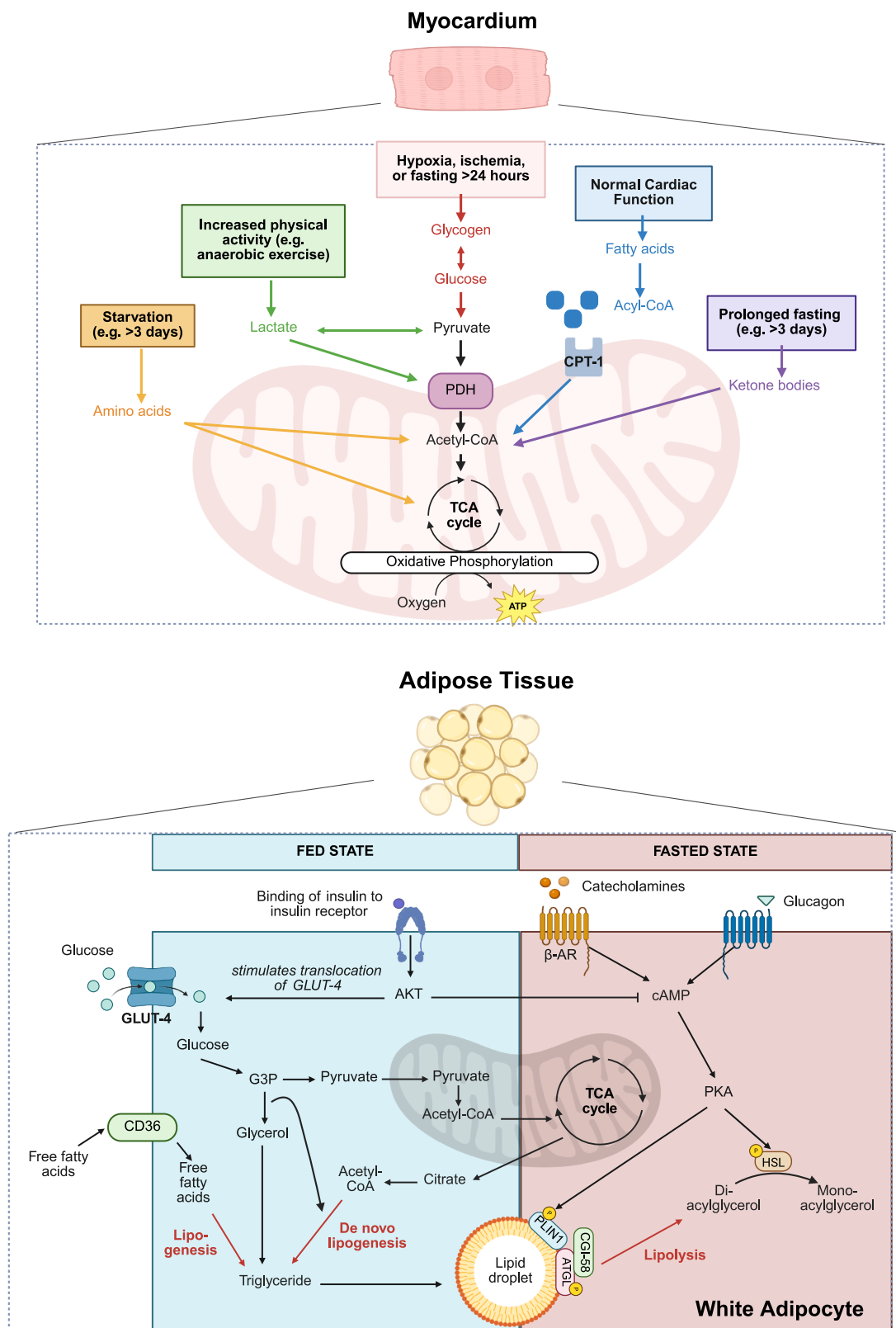
METABOLIC FLEXIBILITY IN WHOLE BODY AND INDIVIDUAL TISSUES

Metabolic flexibility can be influenced by several factors, including nutritional state (fasted or fed), energy demands from physical activity, substrate availability, and hormonal regulation^{11–21} (Table 1). Assessment of metabolic flexibility can be conducted at the whole-body level but is shaped by the integrated adaptive capacity of individual tissues, including skeletal muscle, liver, adipose tissue, and heart (Figure 1).²² In the fasted state, the body predominantly relies on fat for energy, as low glucose availability inhibits insulin secretion, promoting fatty acid oxidation.²² Conversely, after a carbohydrate-rich meal, carbohydrates become the primary energy source due to a rise in glucose levels that stimulate insulin secretion.⁸ Insulin then acts on the liver, adipocytes, and skeletal muscles to promote nutrient storage and utilization, maintaining energy homeostasis across different physiological states. In situations of poor circulation, such as ischemia, hypotension, and low oxygen tension, glucose metabolism primarily reaches pyruvate and is then reduced to lactate, resulting in less efficient ATP production. However, in a healthy state with good blood flow, carrying oxygen to tissues allows complete oxidation phosphorylation to occur in the mitochondria, thereby achieving maximum production of ATP through glucose oxidation. Optimized glucose oxida-

tion obviously requires insulin to drive glucose into cells via GLUT4, which benefits from optimized insulin sensitivity. Otherwise, defective insulin sensitivity will compromise glucose uptake, which will limit glucose oxidative capacity.

Figure 1 illustrates how cardiac substrate utilization shifts under various physiological and pathological conditions, including fasting, exercise and hypoxia. These scenarios are representative and intended to highlight the dynamic adjustments in fuel contribution from glucose, fatty acids, ketones, lactate, and amino acids in response to metabolic demands. Importantly, these shifts do not occur in an all-or-none manner; instead, substrates are utilized concurrently, with their relative contributions varying in a metabolic-context-dependent and tissue-specific manner, reflecting their functional capabilities. For example, physical activity does not solely involve the use of lactate for energy production. The type of fuel utilized is dependent on the exercise intensity and duration, which are determinants of substrate utilization. It is well established that for exercise requiring large amounts of energy, the primary fuel utilized would be fatty acids in place of lactate, owing to their greater ATP yield and capacity to sustain energy production over extended periods.²³ In addition, inter-species differences, such as in metabolic rate, enzyme expression, and hormonal regulation, may affect substrate preference and limit the direct translation of findings between animal and human models. Therefore, this figure should be interpreted as a conceptual framework to illustrate the principle of metabolic flexibility rather than an absolute depiction of substrate dominance under each condition.

Metabolic processes such as lipogenesis, lipolysis, mitochondrial dynamics, oxidation, and muscle contractility depend on the coordinated crosstalk between adipose tissue, which serves as a primary energy supplier; and skeletal muscles, which act as the effectors of physical work.²⁴ This



(legend on next page)

interaction, known as the “muscle-adipose axis,” is coordinated by myokines released by skeletal muscle and adipokines released by adipose tissue. The nature of this communication is also influenced by the specific topographic location of adipose tissue, whether subcutaneous, visceral, intermuscular, or intramuscular.²⁴ One prominent example is interleukin-6 (IL-6), a pleiotropic myokine that mediates inflammation responses and metabolism. IL-6 is closely associated with skeletal muscle contraction and is upregulated after prolonged exercise.²⁵ Following its secretion by muscles, IL-6 travels to adipose tissue and stimulates lipolysis to provide the energy required for physical exercise.²⁵ Studies have reported an association between IL-6 and exercise duration, training intensity, and the amount of muscle mass involved during the exercise period, with the release of Ca²⁺ ions by skeletal muscle driving the stimulation of exercise-induced IL-6 and its subsequent release into plasma.²⁶ Failure to stimulate IL-6 secretion can result in visceral adipose tissue accumulation as lipolysis is inhibited, a feature observed in the aging process.²⁷ The ectopic accumulation of lipid droplets in muscle tissues (extramyocellular vs. intramyocellular fat), particularly in the context of obesity and lipotoxicity, can impair muscle insulin sensitivity and hinder its ability to oxidize lipids as a fuel source.⁸

A study by Tahergorabi et al. demonstrated that excess nutrients are first stored in peripheral fat before being deposited ectopically in multiple organs.²⁶ However, fat storage in muscle is not always harmful, as seen in marathon runners,²⁸ suggesting that the biochemical qualitative composition of lipids and their topology within muscle fibers might determine their impact. Additionally, recent findings indicate that gut hormones secreted in response to nutrients also play a role in controlling the system’s adaptive capacity. An increase in GLP-1 levels was associated with a facilitated shift to postprandial carbohydrate oxidation, suggesting that GLP-1 directly contributes to diet-induced metabolic flexibility.²⁹

Metabolic flexibility in cardiometabolic disease

Metabolic flexibility seems to play an essential role in the early pathogenesis of cardiometabolic diseases,³⁰ which are a leading cause of death globally.³¹ These clinical conditions, including cardiovascular disease (CVD), metabolic dysfunction-associated fatty liver disease (MAFLD), and type 2 diabetes (T2DM), are typically associated with central obesity.⁹ In their subclinical stages, they are characterized by metabolic abnormalities such as insulin resistance, impaired glucose tolerance, dyslipidemia, and hypertension.³² When occurring together, these conditions fulfill the criteria for “metabolic syndrome.”³³ Several studies have demonstrated that metabolic syndrome is strongly associated with the development of multiple cardiometabolic diseases, increasing the risk of complications due to the pathogenic convergence of common metabolic pathways.¹⁰

In heart failure with preserved ejection fraction (HFpEF), commonly associated with metabolic syndrome, the heart’s ability to convert chemical energy from alternative fuels into mechanical energy is constrained, leading to reduced diastolic function.³⁴ While energetic deficits can impact both systolic and diastolic function, HFpEF, the most common form in metabolic syndrome, is primarily characterized by diastolic dysfunction, which we focus on here as a key example due to its growing prevalence and clinical relevance. Under physiological conditions, the heart primarily generates energy from lactate and fatty acid oxidation. However, in the failing heart, metabolic inflexibility manifests as a shift toward greater reliance on ketone body oxidation and glycolysis, resulting in a reduction of up to 40% in oxidative phosphorylation and ATP production in human studies.^{35,36} This disruption in energy production directly compromises cardiac function.^{2,37} The human heart was shown to rely on ketone bodies in proportion to what is available in circulation.³⁸ Ketone consumption was nearly tripled in patients with a reduced vs. preserved ejection fraction.³⁹ Additionally, impaired metabolic flux and incomplete fatty acid oxidation produce harmful byproducts, such as acylcarnitine, ceramides, or diacylglycerols, which may act as lipotoxic mediators during starvation, contributing to the induction of metabolic stress and insulin resistance. These byproducts can further disrupt mitochondrial dynamics, reduce energy synthesis efficiency, and contribute to contractile dysfunction, eventually leading to ventricular hypertrophy.

In the context of MAFLD and T2DM, inefficient fuel usage typically leads to metabolic inflexibility, as evident in the accumulation of liver fat and the onset of insulin resistance during the prediabetic stage.^{30,38} An experimental study investigating the mechanisms linking liver fat accumulation to T2DM found that individuals with steatosis but without fibrosis or necro-inflammation exhibited skeletal muscle insulin resistance similar to that seen in patients with T2DM.⁴⁰ Compared to individuals with normal intrahepatic lipid content, those with steatosis had reduced rates of insulin-stimulated glucose disposal and inappropriate low FAO for the excess of lipid accumulation.^{41,42} The role of liver fat in the development of T2DM was first suggested by Taylor et al.⁴³ and has since formed the rationale for weight loss interventions aimed at reversing T2DM.^{44,45} Indeed, reducing liver fat content in individuals with T2DM has been shown to restore glucose homeostasis, likely by directly modulating the cross-talk between the “liver-muscle” axis.⁴⁶

Metabolic flexibility vs. insulin resistance

Insulin resistance is widely recognized as one of the key factors leading to T2DM, and it is the most direct link between obesity, T2DM, and CVD. Insulin resistance is a prominent contributor to metabolic inflexibility, which can develop in various tissues and organs, particularly in the context of obesity and type 2

Figure 1. Mechanistic pathways involved in fuel adaptation in the heart and white adipocyte

(A) illustrates the ability of the myocardium to effectively utilize different types of fuels in different circumstances to ensure sufficient energy production to sustain contractile function. CPT-1 refers to carnitine-palmitoyl transferase-1; PDH, pyruvate dehydrogenase; and TCA, tricarboxylic acid. (B) illustrates the ability of white adipocytes to regulate lipid metabolism during fasted and fed state. AKT refers to protein kinase B; ATGL as adipose triglyceride lipase; β AR as β -adrenergic receptor; CD36 cluster of differentiate 36; CGI-58 as comparative gene identification-58; G3P as glyceraldehyde-3-phosphate; GLUT4 as a glucose transporter; HSL as hormone sensitive lipase; PKA as protein kinase A; PLIN1 as Perilipin 1. Created in <https://biorender.io>.

diabetes mellitus (T2DM), characterized by defective glucose uptake and metabolism. Metabolic inflexibility often results from reduced responsiveness to insulin signaling, impairing the body's ability to switch from lipid to glucose oxidation in the context of refeeding.⁶ This rigidity in fuel switching and utilization creates a vicious cycle, where insulin resistance and insufficient lipid utilization result in, and are mutually reinforced by, metabolic inflexibility, driving the organism toward metabolic dysfunction, particularly in the context of chronic overnutrition.

While insulin resistance has traditionally been seen as both a cause and a predictor of CVD in both the general population and individuals with diabetes, it offers a limited perspective by primarily focusing on its effect on glucose metabolism. In contrast, the concept of metabolic (in)flexibility offers a broader view, encompassing a range of metabolic processes that determine the body's ability to adapt available fuel utilization to meet energy demands and biosynthesis. This flexibility is also influenced by hormonal regulation and mitochondrial function, which control energy homeostasis beyond just the insulin and glucose pathways.^{2,8,47} For a more in-depth exploration of the connections between metabolic flexibility and insulin resistance, readers are referred to previous reviews that focus on insulin-regulated metabolic pathways.^{2,6,8,48,49}

Endocrine regulation of metabolic flexibility

Hormones play a crucial role in regulating whole-body metabolism by controlling how the body processes energy, stores nutrients, and maintains homeostasis. These processes are modulated by various tissue-derived endocrine factors such as incretins (e.g., GLP-1 and GIP), adipokines (e.g., leptin and adiponectin), hepatokines (e.g., IGF1, IGFBPs, SHBG, FGF21, fetuin-A, GDF15, activin E, and ANGPTLs), and myokines (e.g., IL-6, irisin, myostatin, and IL-15), which act as chemical messengers facilitating communication between organs.²⁴ Insulin, secreted by pancreatic beta cells, plays a crucial role in influencing the adaptive capacity of an organism. It facilitates glucose uptake and regulates the shift between carbohydrate and lipid metabolism. Although most commonly studied in the context of insulin resistance, insulin's broader effects on metabolic flexibility are crucial for maintaining proper energy balance and efficient fuel utilization. A consolidation of these hormones and their effects are listed in Table 2.^{9,24,50–58}

Current knowledge gaps

Current research on metabolic flexibility in cardiometabolic disorders has primarily focused on individual conditions, such as T2DM, MAFLD and CVD.¹⁰ Much of the research focuses on how "metabolic inflexibility" exacerbates insulin resistance and contributes to its detrimental downstream effects, including the suppression of hepatic glucose production, the promotion of excessive very low-density lipoprotein (VLDL) production, and the elevation of plasma triglyceride levels. Several meta-analyses in populations across Asia, Europe, and America⁵⁹ have established strong links between MAFLD and subclinical cardiovascular disease, highlighting mechanistic pathways of metabolic dysregulation postulated to unify these metabolic disorders.^{6,60}

Despite these advances, significant knowledge gaps and controversies persist. For instance, the precise mechanisms linking

metabolic flexibility to cardiometabolic disease remain unclear. There is also a need for the development of accurate, non-invasive, and easily implementable methods for assessing metabolic flexibility in clinical settings. Moreover, current research lacks effective techniques for measuring metabolic flexibility in specific organs such as the heart and the brain. Lastly, there is ongoing debate regarding the interaction between metabolic flexibility and insulin resistance, as well as whether these factors should be prioritized in the prevention and treatment of cardiometabolic disease.

Methods to measure metabolic flexibility

Metabolic flexibility, the body's ability to efficiently switch between fuel sources, is primarily assessed using calorimetry. While both direct and indirect calorimetry can be employed, indirect calorimetry is favored for its practicality. Calorimetry, the measurement of heat change, provides crucial insights into metabolic processes. Direct calorimetry measures heat loss from the body within a specialized, insulated environment.^{49,50} While calorimetry is comprehensive, its complexity results in it being less commonly used. Indirect calorimetry estimates energy expenditure by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2) and is preferred due to its relative ease of use. Two main types exist: the ventilated hood, which is more uncomplicated and more comfortable for participants; and the whole-body chamber, which is considered the gold standard because it captures all metabolic processes, including physical activity and thermogenesis.

Although they measure different aspects of energy expenditure, both direct and indirect calorimetry provide similar estimates of calorie expenditure due to the principle that all energy in the body is primarily generated by oxidation.^{47,48} Indirect calorimetry focuses on measuring VO_2 and VCO_2 to derive key metabolic parameters. The respiratory exchange ratio (RER), the ratio of VCO_2 to VO_2 , indicates the primary fuel being used: RER ~ 0.7 signifies primarily fat oxidation, while RER ~ 1.0 indicates primarily carbohydrate oxidation. Other derived measures include energy expenditure (EE) and the oxidation rates of carbohydrates, protein, and fat. In healthy individuals, RER fluctuates between fasting and fed states. During fasting, fat oxidation predominates (RER ~ 0.7). After a carbohydrate-rich meal, the body switches to carbohydrate utilization (RER ~ 1.0).⁹ A positive change in RER (ΔRER) between these states signifies good metabolic flexibility. Conversely, individuals with metabolic dysfunctions like obesity or MAFLD often exhibit impaired metabolic flexibility. They may experience insulin resistance, unopposed lipolysis, increased hepatic gluconeogenesis, and disrupted nutrient flux regulation.⁷ These factors lead to inappropriate fuel utilization: excessive lipid oxidation in the fed state and inappropriately elevated carbohydrate utilization in the fasted state. Consequently, their ΔRER is reduced, reflecting their inability to switch between fuel sources efficiently.

Beyond RER, other markers are being explored to assess metabolic flexibility, including lactate levels and advanced imaging techniques to quantify metabolic pathways. These innovative approaches hold promise for both research and clinical applications. Building on this understanding of the measurements and their significance, further exploration of the diverse applications

Table 2. Classes and effects of hormones on metabolic flexibility

Class of hormone	Site of production	Function	Examples
Incretins	Endocrine cells in epithelium of small intestine ⁴⁶	Increase insulin secretion following meal consumption ⁴⁶	GLP-1: inhibits glucagon secretion and stimulates insulin secretion ⁵⁸ GIP: inhibits lipolysis and stimulates lipogenesis, acts directly on pancreatic islets to stimulate insulin secretion ⁵⁸
Adipokines	Adipocytes in adipose tissue ⁴⁷	Involved in various processes such as inflammation, appetite modulation, lipid and glucose metabolism ⁴⁷	Leptin: involve in appetite control and regulates energy balance ⁵⁹ Adiponectin: reduces gluconeogenesis and enhances glycolysis and fatty acid oxidation ⁵⁹
Hepatokines	Hepatocytes in the liver ⁴⁵	Involved in the regulation of glucose and lipid metabolism in the liver, skeletal muscle and adipose tissue ⁴⁵	IGF1: inhibit secretion of growth hormone (GH), and inhibits insulin secretion at supraphysiologic concentrations ⁶⁰ IGFBPs: modulate cell signaling through multiple pathways, includes the regulation of IGF bioavailability, cell survival, migration and metabolism ⁶⁰ SHBG: regulates bioavailability of steroid hormones, shown to correlate with insulin resistance ⁶¹ FGF21: stress-inducible hormone that regulates energy balance, as well as glucose and lipid homeostasis ⁶² Fetuin-A (also known as AHSG): involved in the regulation of calcium metabolism and insulin signaling pathway ⁶³ GDF15: increases during exercise and is regulated by glucagon-to-insulin ratio ⁶⁴ Activin E: regulates glucose and lipid metabolism, enhances thermogenesis through emergence of beige adipocytes ⁶⁵
Myokines	Myocytes of muscle fibers ⁵³	Involved in organ crosstalk to mediate whole-body metabolism; regulates lipid metabolism during exercise ⁵³	IL-6: stimulates AMPK and increases glucose uptake and b-oxidation in muscle and adipose tissue ⁶⁶ IL-15: facilitates glucose metabolism in skeletal muscle, improves insulin sensitivity ²⁵ Irisin: converts white adipose tissue into brown adipose tissue to regulate energy expenditure ²⁵ Myostatin: regulates myoblast proliferation and prevents hypertrophy of muscles ²⁵

of indirect calorimetry and its contributions to understanding metabolic processes and improving clinical practice is warranted.

Clinical implications of metabolic inflexibility

Metabolic inflexibility in these individuals may have significant clinical implications. For example, cardiac lipid accumulation has been linked to the worsening of cardiac dysfunction.⁶¹ In both *in-vivo* and *in-vitro* models of heart failure, reduced expression of fatty acid transporters has been observed.⁶² As the disease progresses, further reductions in key proteins like PPAR α result in a decrease in fatty acid mitochondrial transporter proteins such as CPT1 or CPT2.⁶³ In advanced heart failure, while fatty acid uptake remains unchanged, the rate of fatty oxidation

declines, leading to intracellular lipid accumulation and the generation of toxic lipid species that contribute to mitochondrial dysfunction and further deterioration of heart failure.⁶⁴ In addition, lipid accumulation has been shown to worsen insulin resistance by disrupting the insulin signaling pathway, impairing glucose metabolism, and promoting cardiac dysfunction and overall metabolic dysregulation.⁶⁵ However, further investigations are required to understand better how metabolic inflexibility contributes to the initiation and progression of a wide range of cardiometabolic diseases.

Recent work has moved beyond the traditional, organ-centric view of metabolic disease to examine how distinct pathologies intersect and potentiate one another. This network perspective—captured in the term “systemic metabolic

disorders”—posits that discrete metabolic abnormalities converge to disrupt multiple organ systems, thereby amplifying morbidity and mortality from both cardiovascular and non-cardiovascular causes.⁶⁶ Conceptually, three progressive stages have been proposed: (1) a prodromal phase marked by laboratory or imaging evidence of metabolic derangement in the absence of overt organ injury; (2) an intermediate phase characterized by early, often subclinical, structural or functional organ changes; and (3) an advanced phase in which cumulative damage manifests as clinically apparent end-organ failure.⁶⁶ Crucially, at each stage the underlying defect is a loss of metabolic flexibility—an impaired capacity to match substrate utilization to energetic demand—that feeds forward to accelerate disease progression.

Building on this framework, the next section explores how targeted nutritional interventions, particularly intermittent fasting paradigms, can restore metabolic flexibility and interrupt this pathogenic cascade.

Effect of fasting on metabolic flexibility

A recent study showed that the effects of a seven-day water-only diet on the human body can lead to adaptation during periods of starvation. In addition to a reduction in lean muscle mass and average body weight, results from the indirect calorimeter suggested a switch from protein to fat oxidation during resting metabolic rates. In fact, total energy turnover from fat was quantified to be at 73%, while carbohydrate contribution fell from 53% to 19%. Interestingly, in another study looking into metabolic flexibility during sleep, it was reported that the body shifts toward carbohydrate utilization prior to awakening, in contrast to the assumption that there is a gradual shift from carbohydrate to fat utilization.⁶⁷ Furthermore, metabolically inflexible men were found to have a blunted decrease in their respiratory exchange ratio (RER) during sleep, with a 10-year age difference having a significant impact on RER. Furthermore, the study demonstrated inter-individual differences in RER during sleep. Altogether, these suggest that understanding fasting RER may provide insights into the early development of metabolic inflexibility.

Effect of high-fat/high-carbohydrate diet on metabolic flexibility

In another study conducted on male athletes, the consumption of a high-fat diet was found to improve metabolic flexibility during progressive exercise to exhaustion, as well as during 5 km running time trials. Mice studies have also demonstrated the effects of time-restricted feeding on metabolic flexibility, with high-fat diets improving metabolic flexibility on a short-term basis⁶⁸ and even in mice with excess adiposity.⁶⁹ However, current studies exploring the effects of a high-fat diet on metabolic flexibility are not in agreement. In a group of twenty overweight men, it was reported that a 3-week high-fat diet led to increased intrahepatic lipid accumulation and decreased metabolic flexibility, consistent with studies conducted in rodents.⁷⁰ Although current studies on the effects of high-fat diets on metabolic flexibility show conflicting results, these discrepancies are likely due to differences in the study models utilized and the health status of the subjects. Such variations make direct comparisons challenging,

underscoring the need for further research to better understand the impact of high-fat diets on metabolic flexibility across diverse populations and conditions.

Regarding the consumption of high-carbohydrate diets, studies in humans have shown that healthy children and adolescents can adapt to high-fat and high-carbohydrate diets, thereby reducing their likelihood of developing obesity and diabetes.⁷¹ More recently, studies have investigated the effects of glycemic indices on metabolic flexibility and reported that consumption of a high-carbohydrate, low glycemic index diet is consistent with improved metabolic flexibility and exercise performance in male athletes.⁷² On the flip side, another study demonstrated that metabolic flexibility is defective in obese youth with dysglycemia due to a defect in insulin sensitivity.⁷³ Table 1 summarizes the factors contributing to metabolic flexibility.

Metabolic flexibility as a predictor of weight gain

Calorimetry has also been used to provide insights into one's propensity toward obesity. In a study conducted on seventy-nine healthy individuals using a whole-room calorimeter, lower lipid oxidation rates in response to a high-fat diet (60% fat, 20% carbohydrate) were reported to be a possible predictor of weight gain after 6 months and 12 months. The study found that impaired metabolic flexibility in response to high-fat meals may be used to identify individuals prone to weight gain due to a reduced capacity to effectively oxidize dietary fat.⁷⁴ Similarly, in another study utilizing metabolic cages, it was reported that early differences in metabolic flexibility were observed in mice after weaning, where obesity-resistant mice had higher glucose tolerance and were more metabolically flexible than obesity-prone mice.⁷⁵

Emerging indicators of metabolic flexibility via non-invasive methods

Lactate levels

While blood lactate testing is commonly used to diagnose lactic acidosis⁷⁶ and assess acute illnesses or injury,⁷⁷ fasting lactate levels may also serve as indicators of metabolic health.⁷⁸ Traditionally viewed as a metabolic byproduct of anaerobic metabolism, lactate has recently been shown to be produced under aerobic conditions as well.⁷⁹ Studies in sports medicine have revealed significant differences in fasting lactate levels among elite athletes, individuals with metabolic syndrome, and healthy but sedentary men and women.⁷⁸ Elevated blood lactate levels have been associated with reduced aerobic oxidation and impaired tricarboxylic acid (TCA) cycle flux, leading to a compensatory increase in glycolysis and a shift toward glycolytic metabolism.⁷⁸ This suggests that fasting lactate levels could be helpful indicators of metabolic efficiency. Measuring such biochemical intermediates as lactate, ketones, and free fatty acids is possible. However, there are no developed and standardized protocols yet that define cutoffs for metabolic flexibility versus metabolically inflexible states and how effectively they correlate with delta RER and clinical metabolic flexibility. These biomarkers of metabolic flexibility need to be studied in experimental physiology using both preclinical and clinical models, including healthy subjects and those with insulin resistance, to establish cutoffs.

AMPK and mTOR Signalling Pathway

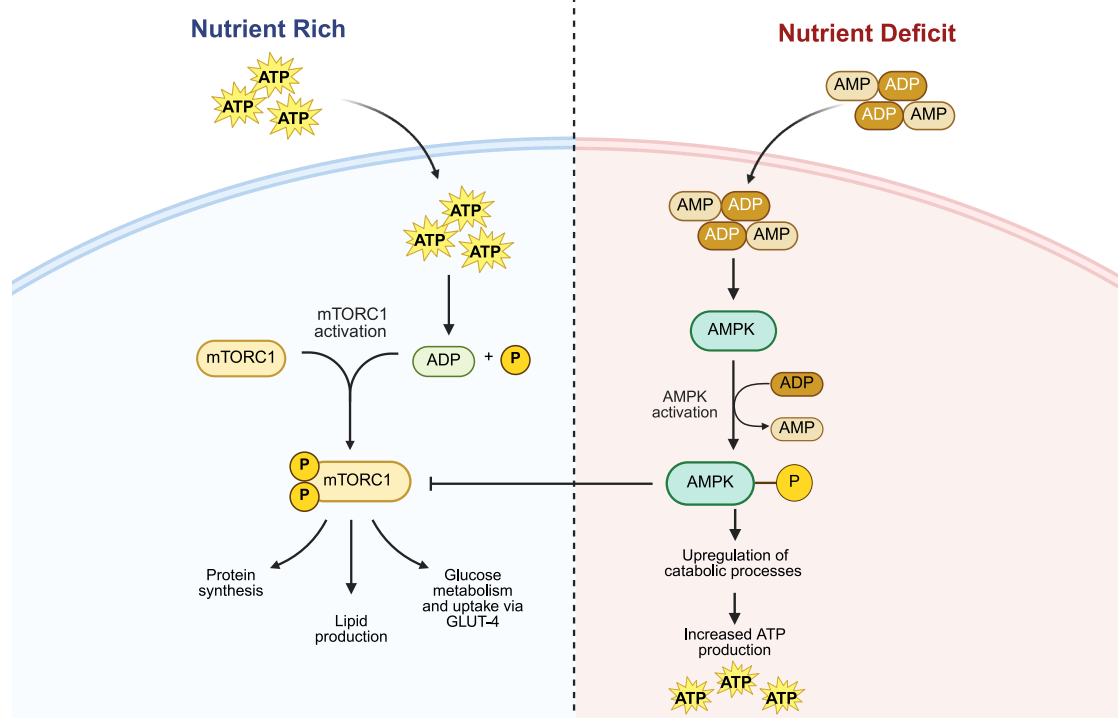


Figure 2. Integration of AMPK and mTORC1 signaling pathways

Under nutrient rich conditions, mTORC1 complex is activated via phosphorylation and results in the upregulation of anabolic pathways. In contrast to nutrient deficit conditions, AMPK pathway is upregulated and inhibits the mTORC1 pathway. Created in <https://biorender.io>.

Quantifying metabolically active pathways

Another emerging approach for assessing metabolic flexibility involves quantifying the activity of molecular pathways that regulate energy metabolism, such as AMP-activated protein kinase (AMPK) and nutrient sensing by mechanistic target of rapamycin complex 1 (mTORC1) (Figure 2). These pathways function as the “yin and yang” of nutrient sensing and growth control, working in opposition to maintain energy balance.⁸⁰ For example, under low-energy conditions, AMPK is activated, promoting catabolic processes to increase ATP production and conserve cellular energy.⁸⁰ Simultaneously, AMPK inhibits anabolic processes by inhibiting the mTORC1 pathway, which helps conserve energy⁸⁰ by limiting energy-intensive functions like protein synthesis, a process that can account for up to 20% of cellular energy expenditure.⁸¹ By suppressing mTORC1 and its downstream effectors, AMPK can achieve significant energy savings.⁸⁰

Conversely, when energy and nutrients are abundant, mTORC1 activation promotes anabolic processes, such as protein and lipid biosynthesis, thereby supporting cell growth.⁸² Although mTORC1 does not directly inhibit AMPK, the activation of mTORC1-driven anabolic processes can deplete cellular energy reserves, eventually triggering AMPK activation to restore balance.⁸² Figure 3 illustrates the complementary functions of AMPK and mTORC1 pathways in managing energy balance under both nutrient-deficient conditions and nutrient-rich condi-

tions. Research has previously suggested a link between AMPK activity and metabolic flexibility, particularly in the context of exercise.³⁰ Pharmacological activation of AMPK has been shown to induce gene expression changes similar to those seen during exercise.³⁰ As exercise intensity rises, glucose oxidation accelerates through oxidative phosphorylation, eventually shifting to anaerobic glycolysis at higher intensity,⁸³ an adaptation that occurs independently of insulin and corresponds with a proportional decline in energy production from free fatty acid oxidation.⁸⁴ While the link between mTOR and metabolic flexibility is less established, and most studies have focused on mTOR’s role in neurodegeneration,⁸⁵ though interest in the interaction between AMPK and mTORC1 in metabolic regulation is now growing.⁸⁶

We propose that the dynamic interaction between AMPK and mTORC1 pathways may largely explain systemic metabolic flexibility. Under nutrient-deficient conditions, healthy individuals typically exhibit elevated AMPK activity and reduced mTORC1 activity, facilitating energy conservation. However, with carbohydrate intake, the body shifts toward glucose utilization, leading to decreased AMPK activity and increased mTORC1 activation. In cases of metabolic inflexibility, however, the regulatory balance between anabolic mTORC1 and catabolic AMPK might be disrupted, resulting in an improper activation pattern that skews the ratio between these two pathways. This imbalance can manifest in two ways: (1) elevated fat oxidation and (2) ectopic fat

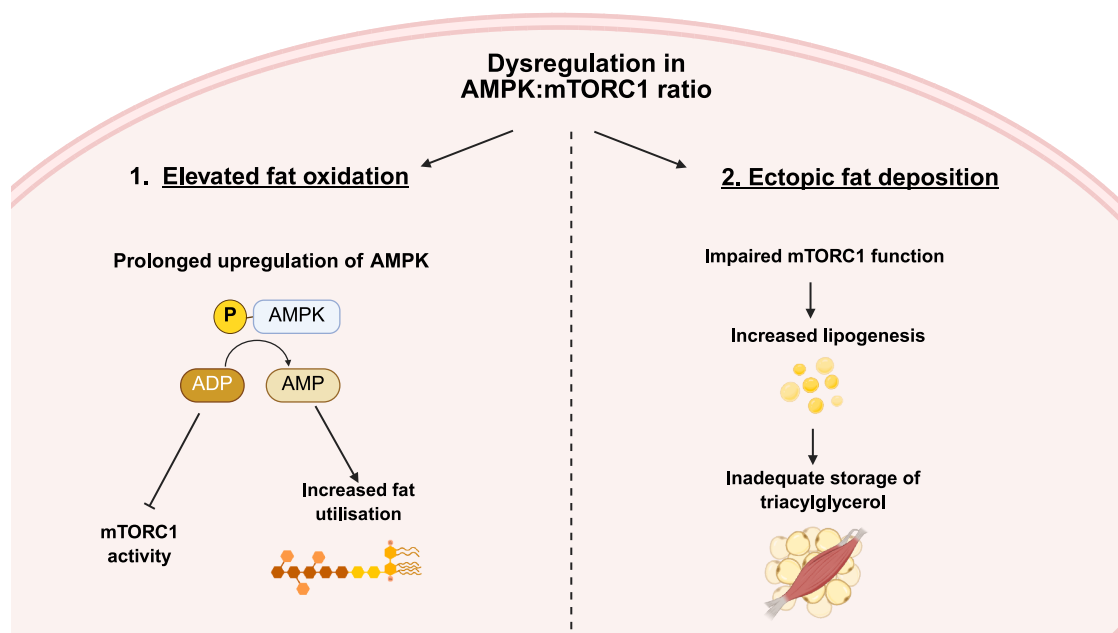


Figure 3. Effects of dysregulation in AMPK: mTORC1 ratio

We postulate that a dysregulation in AMPK: mTORC1 ratio results in two different scenarios—in the upregulation of fat oxidation, as well as ectopic fat deposition due to inappropriate storage of fatty acids. Created in <https://biorender.io>.

deposition. In the first scenario, elevated fat oxidation may result from prolonged postprandial upregulation of AMPK, which suppresses mTORC1 activity and increases lipid utilization. Clinical studies on patients with MAFLD have reported higher fasting fat oxidation rates compared to those without the condition, potentially as an adaptive response to mitigate lipotoxicity and prevent excessive lipid accumulation.⁸⁷ The second scenario involves ectopic fat deposition as a consequence of metabolic inflexibility, possibly due to impaired mTORC1 function. In this case, while lipid production is upregulated, the synthesized triacylglycerols are inadequately stored in adipose tissues, leading to abnormal fat deposits. A 2022 study linked metabolic inflexibility to sarcopenia, a condition characterized by reduced muscle mass and myosteatosis, which impacts strength and physical function.⁸⁸

Additionally, insulin, upon binding to the insulin receptor, triggers phosphorylation of insulin receptor substrates, which then activate a chain of signaling events downstream, particularly converging upon the PI3K-AKT-mTORC1 pathway, which leads to increased intracellular calcium trafficking and the translocation of GLUT4 proteins from the cytosol to be inserted into the cell membranes of insulin-sensitive tissues, whereupon glucose can then be transported into the cells for glycolysis and oxidation of pyruvate via PDH and shuttling of acetyl-CoA into the mitochondria for further oxidation via the TCA cycle.⁸⁹ Lipids undergo lipolysis, releasing free fatty acids for beta-oxidation when glucose reserves are low and suppressing insulin.⁸⁹ However, in an insulin-resistant state and elevated plasma insulin, the conserved anabolic action of insulin stimulates acetyl CoA carboxylase, which increases malonyl CoA, an inhibitor of carnitine palmitoyltransferase 1 (CPT-1), which reduces free fatty acids translocation into the mitochondria

for free fatty acids oxidation.⁹⁰ The increased free fatty acids then form triglycerides, which contribute to hypertriglyceridemia. Via the PI3K-AKT-mTORC1 pathway, insulin can lead to increased lipid biosynthesis via SREBP1c and also increased protein synthesis via 4EBP and p70S6K1 activation.⁹¹ mTOR is a cellular nutrient sensor, and upon activation by insulin signaling, it causes increased lipogenesis, including cholesterol biosynthesis via SREBP1c and HMG-CoA reductase, as well as increased adipogenesis.⁹¹ At the same time, it inhibits lipolysis, beta-oxidation, and ketogenesis.⁹¹ Currently, evidence linking these molecular pathways to clinical phenotypes remains limited, partly due to the complex study design required for such investigations. Consequently, more focus has been placed on elucidating the mechanisms of AMPK and mTORC1 in both *in vitro* and *in vivo* models. Modulating these central metabolic regulators has shown promise for treating cardiometabolic diseases, and recent reviews underscore their potential as therapeutic targets.^{91,92}

Imaging metabolic inflexibility using positron emission tomography (PET)

Advanced imaging techniques such as positron emission tomography (PET) offer the potential to track metabolic fluctuations and assess an organism's fuel preference and metabolic activity. Currently, PET scans are widely used in clinical settings to visualize cellular and molecular processes⁹³ with radioactive tracers labeled with a positron-emitting isotope (such as carbon-11, fluorine-18, or oxygen-15) to measure biological activity through the accumulation in target tissues.⁹³ A commonly used tracer, fluorodeoxyglucose (FDG), allows for the tracking of glucose metabolism, while fatty acid-specific PET tracers (FFA-PET) are used to assess fatty acid uptake.⁹³

Hyperpolarized carbon-11 imaging has recently emerged as a powerful tool for real-time, non-invasive visualization of metabolic fluxes.⁹⁴ This technique hyperpolarizes carbon-11 labeled compounds, greatly enhancing their magnetic resonance signal and enabling the detection of low-concentration metabolites.⁹⁴ Several studies have focused on hyperpolarized pyruvate, a key metabolite in glycolysis and the citric acid cycle,⁹⁴ with applications in cardiac imaging⁹⁵ as well as oncology,⁹⁶ where metabolic pathways alterations are prominent. Hyperpolarized carbon-11 imaging holds promise as a potential measure of metabolic flexibility, allowing the tracking of hyperpolarized glucose or pyruvate as the body transitions between fasted and fed states. This technique enables the quantification of up-regulated metabolic pathways, such as glycolysis or oxidative phosphorylation, thereby providing a detailed view of substrate utilization at a molecular level.

Limitations of using PET scans include the non-specific uptake of elevated FDG and the confounding effects of pharmacological agents on PET interpretation. Since glucose is metabolized by most human cells, elevated FDG uptake may arise from both increased metabolic activity and underlying inflammatory or infectious processes, thereby complicating the distinction between physiological and pathological states.⁹⁷ This poses a challenge in the context of metabolic flexibility—systemic or tissue-specific inflammation is known to impair insulin signaling and mitochondrial substrate switching and may independently contribute to altered FDG uptake. As such, reliance on PET imaging alone may not allow for the distinction between these two states. Instead, it should be coupled with complementary biochemistry assessments such as plasma metabolite profiling and hormone quantification to provide a more comprehensive evaluation of whole-body and tissue-specific metabolic function.

Furthermore, as FDG and glucose bind competitively to glucose transporters and hexokinase, FDG-PET scans are typically recommended for individuals with fasting blood glucose below 11 mmol/L.⁹⁸ This criterion presents a challenge in patients with diabetes, who may require exogenous agents to maintain glycemic control. Insulin administration can enhance FDG uptake in insulin-sensitive tissues, potentially confounding the interpretation of PET results. Notably, individuals with diabetes are also more likely to exhibit metabolic inflexibility, characterized by impaired substrate switching and insulin resistance. As such, altered FDG distribution may reflect both pharmacological effects and underlying metabolic dysfunction, limiting the reliability of FDG-PET in metabolic flexibility assessment. To mitigate these limitations, careful management of pre-scan insulin administration is essential. Current recommendations advise withholding rapid-acting insulin for at least 4 h, short-acting insulin for at least 6 h, and avoiding intermediate- or long-acting insulin entirely on the day of the FDG-PET scan.⁹⁸ Such precautions help minimize insulin-induced alterations in FDG uptake and may improve the validity of metabolic assessments in patients with diabetes.

Although PET imaging is not yet practical for routine clinical use, it has strong potential as an advanced secondary measure to complement other standard metabolic assessments. Insights gained through this method could improve our understanding of organ-specific metabolic flexibility and inform targeted therapeutic approaches. Importantly, the use of PET

scans is part of a non-exhaustive catalog of available imaging techniques, with other techniques including the use of magnetic resonance spectroscopy (MRS), computed tomography (CT), or magnetic resonance imaging (MRI). Despite their potential, validation of these techniques is still required for metabolic flexibility assessment.

Therapeutic approaches targeting metabolic flexibility

Advances in understanding metabolic flexibility suggest that specific molecular pathways and mechanisms could be targeted to enhance fuel selection while promoting energy expenditure and insulin sensitivity, making them promising candidates for therapeutic intervention.

Enhancing fuel switching and mitochondrial fatty acid flux

Accumulating evidence supports the role of peroxisome proliferator-activated receptor (PPAR) α as a key target for improving metabolic flexibility and cardiovascular health outcomes, given its pivotal function in lipid oxidation, an essential process in myocardial energy metabolism.⁹⁹ PPAR α regulates the expression of target genes involved in fatty acid uptake and oxidation by binding to direct repeat response elements in association with its retinoid X receptor (RXR). The activity of the PPAR α /RXR complex is determined by the availability of long-chain fatty acids and their metabolites, which act as ligands. Upon ligand binding, transcriptional coactivators are recruited, initiating gene transcription through histone acetylase activity.⁹⁹

A well-characterized coactivator is PPAR γ coactivator-1 α (PGC-1 α), which is highly expressed in the skeletal and heart muscles. Although PGC-1 α lacks histone acetylase activity, it acts through PPAR α and other transcription factors to initiate gene transcription and regulate energy metabolism. In cardiomyocytes, PGC-1 α activation increases the transcription of PPAR α target genes involved in fatty acid oxidation.^{100,101} PGC-1 α also serves as a coactivator for other transcription factors involved in mitochondrial biogenesis and the electron transport chain, promoting enhanced ATP production.¹⁰²

In a metabolically inflexible heart, the body shifts from oxidative catabolism to anaerobic glycolysis. This metabolic change is believed to result from the decreased expression of genes encoding regulatory enzymes involved in fatty acid oxidation and oxidative phosphorylation pathways, which are downregulated due to the deactivation of the PPAR α /PGC-1 α axis.¹⁰³ Furthermore, preclinical studies in murine models of ischemic heart disease and concentric cardiac hypertrophy have demonstrated significant downregulation of the PPAR α -RXR complex's expression and DNA binding activity. Similar inactivation of PPAR α has also been observed in patients with heart failure, suggesting that findings from animal models are likely relevant to human conditions.^{100,104,105}

Medications like trimetazidine, used to treat angina pectoris,¹⁰⁶ have been shown to modulate metabolic flexibility. Although the precise mechanism is still under investigation, *in vitro* and *in vivo* models suggest that trimetazidine reduces free fatty acid and ketone body levels. This effect is likely mediated through increased glucose and pyruvate levels, which are regulated via the AMPK and PPAR α pathways.^{107,108} Fibrates,

a class of amphipathic carboxylic acids drugs used to treat dyslipidemia, also target PPAR α .¹⁰⁹ Multiple studies in rat models have highlighted the beneficial effects of PPAR α or PPAR γ agonists, including reducing infarct size, promoting anti-inflammation responses, and increasing myocardial glucose utilization.¹¹⁰ Prior clinical studies utilizing PPAR α agonists in CVD treatment have demonstrated reductions in coronary heart disease progression and major adverse cardiovascular event (MACE).¹¹¹ However, combining fibrates with statins has failed to significantly reduce the rates of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.¹¹² In a study involving 9,795 patients with diabetes and dyslipidemia, daily administration of PPAR α agonists did not significantly reduce coronary events.¹¹³ These results suggest that additional regulatory pathways may contribute to PPAR/PGC-1 α activity and the metabolic remodeling of the heart, highlighting the need for further research to understand the underlying mechanisms better.⁹⁹

Restoring and improving mitochondrial function

Mitochondria, commonly referred to as the “powerhouse” of the cell, are responsible for producing ATP through coupling oxidative phosphorylation and chemiosmosis in the electron transport chain.¹¹⁴ As metabolically active tissue, the skeletal and heart muscles are enriched with mitochondria and are highly adaptable to changes in fuel availability to meet energy demands.⁴⁸ However, the inability of skeletal muscle to adapt to fluctuations in fuel availability plays a significant role in metabolic inflexibility, which is particularly evident in individuals with obesity and insulin resistance.¹⁸

Metabolic inflexibility in these individuals is characterized by an impaired ability to switch between fat to glucose oxidation, especially during the transition from fasting to the postprandial state. Additionally, the mitochondrial capacity in their skeletal muscle tends to be low, contributing to mitochondrial dysfunction.^{18,115–117} This dysfunction has been proposed as a key factor in the development of metabolic inflexibility; however, the precise mechanisms linking mitochondrial dysfunction to ectopic lipid accumulation and insulin resistance remain unclear.⁴⁸ One hypothesis, proposed by Muoio, suggests that excess nutrient intake overloads mitochondria. The intake of additional carbon substrates contributes to expanding intracellular stores of triacylglycerol and glycogen depots,¹¹⁸ increasing nutrient pressure, disrupting carbon flux, and producing reactive oxidative species as the demand for ATP exceeds the supply.¹¹⁸

To address these issues, therapeutic targets have focused on lowering mitochondrial import and uptake via several means, such as (1) reducing nutrient uptake, (2) increasing energy expenditure, and (3) using medications like glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors.

Interventions to enhance metabolic flexibility

Calorie restriction and fasting

Reducing nutrient intake through dietary interventions, such as calorie restriction and intermittent fasting, can promote metabolic flexibility by shifting fuel utilization and improving metabolic and cellular functions. Calorie restriction, which involves reducing daily calorie consumption without malnutrition, has

been shown to improve metabolic flexibility by enhancing glucose tolerance, insulin sensitivity, lipid metabolism, and mitochondrial function while also reducing inflammation and oxidative stress in animal models and humans.^{119,120} In human skeletal muscle, long-term calorie restriction has been shown to inhibit AKT activation and improve protein quality control by markedly increasing chaperone (e.g., HSP70 and GRP78) and autophagic (i.e., LC3 and Beclin 1) protein levels.¹⁰³ Additionally, calorie restriction promotes a PGC-1 α -dependent upregulation of genes involved in mitochondrial biogenesis, thereby enhancing the cell’s ability to produce energy efficiently.¹²¹ Similarly, intermittent fasting, which typically involves fasting periods exceeding 24 h,¹⁰² has been shown to promote a shift in fuel utilization, switching from glucose to fatty acids and ketone bodies during fasting, especially when coupled with exercise.¹²² However, a recent clinical trial found that consuming a typical Western diet during the feasting days may blunt the anti-inflammatory and metabolic benefits of fasting-induced weight loss.¹²³ Excessive protein intake, especially high in BCAAs, can worsen insulin resistance and increase risks for type 2 diabetes by overstimulating the AKT-mTOR pathway and disrupting FGF21 signaling.¹²⁴ In a weight loss trial, a high-protein diet (1.3 g/kg/day) prevented improvements in insulin sensitivity with a normal-protein diet (0.8 g/kg/day) despite similar weight, visceral fat loss, and liver fat loss.¹²⁵ This suggests that high protein intake may negate the benefits of calorie restriction, promoting metabolic inflexibility and elevating risks for cardiovascular disease, cancer, and accelerated aging. Importantly, caloric restriction needs to be complemented with exercise to prevent the compromise of muscle mass.

Exercise training

Exercise training, especially endurance exercise, is a powerful intervention for improving metabolic flexibility by increasing energy expenditure and optimizing fuel utilization. Endurance exercise promotes mitochondrial biogenesis and enhances oxygen and energy consumption, which markedly reduces visceral adiposity.¹²⁶ It also improves muscle insulin sensitivity and insulin responsiveness, primarily through increased adiponectin levels resulting from visceral fat loss, as well as the up-regulation of the insulin-responsive glucose transporter GLUT4 and enhanced glycogen synthase activity.¹²⁷ These adaptations result in improved glucose tolerance, even at lower circulating insulin levels, due to increased insulin sensitivity of active muscle tissues. Exercise training also enhances the expression of lipoprotein lipase in skeletal muscle, resulting in a decrease in serum triglyceride levels and an increase in HDL cholesterol concentrations, thereby promoting metabolic health. In two separate clinical studies, exercise training was found to improve fatty acid oxidation and restore mitochondrial function, insulin sensitivity, and metabolic flexibility.¹²⁸ One of the significant roles of IL-6 in exercise is the stimulation of hepatic glucose output and lipolysis to ensure sufficient energy production to sustain increased muscular contraction during exercise. In fact, the absence of IL-6 has been shown to negate the effects of exercise training on reducing visceral adipose tissue mass.¹²⁹ Aerobic and muscle-strengthening exercises were also reported to have a dose-response association with mortality.¹³⁰

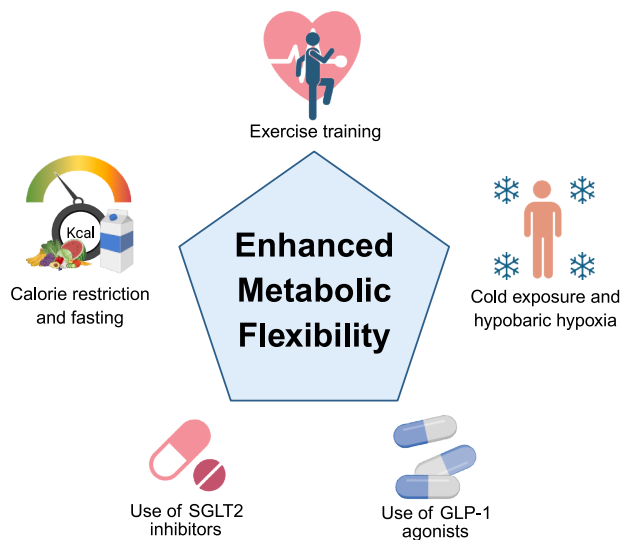


Figure 4. Interventions to enhance metabolic flexibility

Calorie restriction is often coupled together with exercise training to improve metabolic flexibility in an individual. Other interventions include cold exposure and hypobaric hypoxia, as well as the use of medications. Created in <https://biorender.io>.

Cold exposure and hypobaric hypoxia

Cold exposure, typically studied through cold water immersion¹³¹ or exposure to extreme cold temperatures,¹³² has been shown to induce metabolic adaptations in humans. Multiple studies have demonstrated that cold exposure causes metabolic remodeling, including alterations in body adipose tissue storage^{132,133} and improved cardiovascular risk factors.¹³⁴ Similarly, hypobaric hypoxia, which simulates low-oxygen environments, has been observed to shift metabolism toward glycolysis in humans^{132,135} and stimulate muscle angiogenesis in animal models.¹³⁶ These findings suggest that increasing energy expenditure by targeting mitochondrial activity could be a viable strategy for improving metabolic flexibility.

SGLT2 inhibitors

SGLT2 inhibitors represent another promising therapeutic approach for modulating metabolic flexibility. SGLT2, almost exclusively expressed in the proximal convoluted tubules of the kidneys, is a secondary-active glucose transporter that facilitates glucose reabsorption by coupling glucose transport with sodium reabsorption.¹³⁷ Inhibiting SGLT2 reduces both glucose and sodium reabsorption, leading to suppression of the renin-angiotensin-aldosterone system, which confers cardioprotective effects and alleviates cardiovascular strain.¹³⁸ Clinical use of SGLT2 inhibitors in heart failure has been shown to reduce the risk of death from cardiovascular events or non-fatal myocardial infarction.^{138,139} More recently, the role of SGLT2 inhibitors in enhancing metabolic flexibility has been observed during long-term drug administration in patients, demonstrating a shift in fuel utilization from carbohydrate to fatty acids and ketone bodies.^{140,141} Elevated circulating fatty acids provide precursors for ketone production in the liver, which are then utilized by the heart to support sustained myocardial contraction.^{142,143}

GLP-1 agonists

GLP-1 receptor agonists are an exciting novel therapeutic with potential for improved metabolic flexibility. These drugs mimic the action of GLP-1, a naturally occurring incretin hormone secreted in response to food consumption.¹⁴⁴ Mainly produced in the gut and pancreas, GLP-1 regulates appetite and blood glucose levels by stimulating insulin secretion and inhibiting glucagon release. GLP-1 agonists also promote beta-cell proliferation and regeneration,¹⁴⁵ further supporting glucose homeostasis. In addition to their effects on glucose regulation, GLP-1 agonists slow gastric emptying and lower blood pressure.^{144,146} Recent cardiovascular outcome trials have demonstrated their ability to reduce cardiovascular mortality as well as the incidence of non-fatal myocardial infarction and non-fatal stroke.^{147–150} Through these physiological actions, GLP-1 receptor agonists reduce chronic overnutrition and activate metabolic pathways that contribute to improved metabolic flexibility.

Figure 4 summarizes these five interventions and their role in enhancing metabolic flexibility.

Conclusions and future directions

Metabolic flexibility extends beyond insulin resistance, encompassing the body's ability to adapt fuel utilization in response to metabolic challenges, a process heavily influenced by endocrine regulation. Current clinical methods to measure metabolic flexibility include indirect calorimetry and various blood-based metabolic indices. The mitochondria play a crucial role in regulating fuel selection and endocrine function, thereby influencing metabolic flexibility. Modulating mitochondrial activity has the potential to enhance metabolic adaptability. However, significant limitations remain in our understanding of metabolic flexibility, particularly in terms of its generalizability across populations and the metabolic pathways involved. Most studies have relied on indirect calorimeters in highly controlled research settings, and there is a lack of reliable methodology for measuring metabolic flexibility in clinical practice. Furthermore, the precise mechanisms underlying metabolic flexibility and its downstream targets remain unclear, underscoring the need for further research to identify potential pharmacological targets involved in this process.

In summary, we propose that measures of metabolic flexibility can serve as valuable predictors of cardiometabolic disease outcomes, providing a more comprehensive assessment of metabolic health in conjunction with existing clinical markers. While short-term studies on dietary restriction or exercise interventions show promise in improving metabolic flexibility,^{102,119,122} long-term, well-powered clinical trials are needed to evaluate their sustainability and broader health benefits. Metabolic inflexibility is already linked to the development of cardiometabolic disease,³⁰ underscoring its potential as a predictive tool. Future research should focus on diverse populations and various disease stages to better understand how metabolic flexibility evolves in relation to disease progression.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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