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Exercise intervention for obesity via modulating metabolic flexibility: A molecular perspective (review)

JUN LIU[1]*, JING-JING FAN[1] and BEI ZHOU[2]

[1] College of Sports Medicine, Wuhan Sports University, 430079, Wuhan, China

[2] Graduate School, Wuhan Sports University, 430079, Wuhan, China

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ABSTRACT

Obesity has become one of the main risk factors threatening human health, and it is the core cause of various major chronic diseases. Although the efficacy of exercise intervention on obesity remains controversial, it has long been considered one of the most effective and safest approach for managing obesity and providing benefits to patients with obesity. Metabolic flexibility, especially skeletal muscle metabolic flexibility, has a profound impact on exercise weight loss due to its association with muscle fiber types. To understand the effect of exercise intervention on obese individuals with different muscle types, this review emphasizes high calorie diet induced obesity, investigates the interrelationships among obesity, exercise, and metabolic flexibility, and identifies potential molecular targets within this framework to inform future combined therapeutic strategies targeting metabolic inflexibility.

KEYWORDS

obesity, exercise, metabolic flexibility, molecular mechanism, molecular target

INTRODUCTION

Obesity is a chronic and complex disease, defined by the World Health Organization as excessive fat deposits that can impair health, diagnosed through a Body Mass Index (BMI) $\geq$30 kg m^{-2}

* Corresponding author. No. 461, Luoyu Road, Hongshan District, Wuhan City (430079), Hubei Province, China. Tel.: +86 15926306578. E-mail: liujun@whsu.edu.cn

(https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight, accessed on August 31,2025). Individuals with obesity exhibit metabolic rigidity, characterized by a blunted ability to increase fatty acid oxidation in response to high-fat intake [1]. The fundamental problem for many obese individuals is not just the excess body weight but also impaired metabolic flexibility (metabolic inflexibility), which leads to the ineffective fat burning [2]. As a hub of nutrient storage, energy use and locomotion, exercise-induced skeletal muscle function exerts influence on skeletal muscle metabolic flexibility and even systemic metabolic flexibility through the improvement of ectopic fat deposition within skeletal muscle [3, 4]. Metabolic flexibility refers to the ability of the body to adapt to physiological and environmental changes [5]. Impaired metabolic flexibility in skeletal muscles primarily manifests as carbohydrate/fat transport/storage/metabolism dysfunction which is usually associated with physical inactivity, excessive energy intake, obesity, and genetic predisposition [6–8]. Reduced fuel utilization capacity in skeletal muscles—such as decreased mitochondrial size and density, serves as a hallmark of metabolic syndrome and forms the fundamental component of metabolic inflexibility [9]. Broskey et al. demonstrated that impaired fat oxidation and metabolic inflexibility could be used to predict weight gain [10]. In an oral glucose tolerance testing research, metabolic flexibility is compared with metabolic health differences in overweight or obese individuals, no significant difference was found in the main metabolic health indicators between individuals with high and low metabolic flexibility, indicating that metabolic flexibility change occurred prior to metabolic health parameters, and those overweight individuals may have the impaired metabolic flexibility already [11]. Resistance exercise could activates metabolic pathways and multiple peripheral and central signaling pathways in multiple organs or tissues to achieve fat reduction [12–16]. In patients with impaired glucose tolerance (IGT), a 4-month low-intensity unsupervised walking exercise intervention could normalize metabolic regulation by increasing mitochondrial activity and enhancing the expression of metabolic genes in skeletal muscles such as ATP5J, CYC1, peroxisome proliferator-activated receptor alpha (PPARα), peroxisome proliferator-activated receptor delta (PPARδ), peroxisome proliferator activated receptor-γ coactivator (PGC)-1α and PGC1β [17]. Physical inactivity reduces mitochondrial phosphatidylethanolamine (PE) content in skeletal muscle by downregulating phosphatidylserine decarboxylase expression. PE deficiency inhibits mitochondrial pyruvate carrier activity, leading to impaired mitochondrial pyruvate uptake and oxidation, and glucose metabolism shifts towards lactate production, ultimately resulting in systemic metabolic flexibility abnormalities [18]. Therefore, the fundamental problem for majority of obese population is not just excess energy but impaired metabolic flexibility, which leads to the body "not being able" to burn energy substance effectively, while safe and effective exercise prescription may enhance or even reestablish metabolic flexibility. The core population of weight loss mentioned in this study is the obese population with different types of muscle fibers. This review aims to synthesize evidence that repositioning metabolic flexibility, particularly in skeletal muscle, as the central therapeutic target can unify our understanding of exercise interventions and guide combination therapies.

MUSCLE FIBER TYPE AND METABOLIC FLEXIBILITY

Generally, humans exhibit two primary types of muscle fibers: red muscle fibers (Type I) and white muscle fibers (Type II). The proportion of muscle fiber types varies among individuals, those who have a higher proportion of Type I red muscle fibers tend to accumulate fat droplets

within skeletal muscle tissue (both within red muscle fibers and in capillaries between the muscle interstitium) during obesity. Modulating specific metabolic factors in skeletal muscle can reverse metabolic inflexibility and effectively control obesity. Kdm2a is an enzyme that specifically catalyzes H3K36me2 demethylation—an enzyme here to close H3K36me2 gene expression so as to elevate H3K36me2 level which in turn reflects the main characteristics of mitochondria in type I muscle fibers. When Kdm2a was deficient or inhibited, the number of functional type I muscle fibers would increase in mitochondria. This shifts fuel utilization from glucose under cold conditions to lipids in obese states, protecting mice from cold damage and preventing obesity-induced insulin resistance caused by high-fat diet [19]. Given that type I muscle fibers exhibit superior metabolic flexibility and a higher density of mitochondria, they are likely to have a more adaptable intramyocellular lipid (IMCL) content storage and usage capacity compared to type II muscle fibers. Other types of ectopic lipid accumulation may synchronize with IMCL/intermyocellular adipose tissue (IMAT) such as subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and Inguinal fat, for differences in fat intake do not change adipose tissue health and whole body energy balance [20].

EXERCISE AND SKELETAL MUSCLE IMCL/IMAT

The influence of exercise on IMCL/IMAT in skeletal muscle of different populations (such as the young, middle-aged, elderly and atheletes) is different. For instance, for the general adult, various long-term exercises and a single bout of exercise of different intensities, durations and modes can all lead to varying degrees of reduction in IMCL and IMAT in skeletal muscle of unhealthy populations [21–25]. Nevertheless, the content of IMCL/IMAT in skeletal muscle is exactly the opposite among athletes compared to unhealthy populations. This is called ‘athlete paradox’. It means that compared to ordinary people, athletes’ muscle lipids are superior in quality rather than quantity. The synthesis of IMTG affects muscle diacylglycerol (DAG) localization and ceramide accumulation, which in turn affects insulin sensitivity [26]. It is recommended to use high-intensity resistance training (HIRT) in osteosarcopenia to prevent thigh muscle degeneration [27]. The mechanisms underlying could be skeletal muscle metabolism imbalance and fat metabolism disorder. Skeletal muscle IMCL/IMAT decreased during prolonged exercise. This was particularly obvious in the elderly population who undergo long-term strength training [27]. Increased IMCL saturation and higher IMAT content may affect fasting blood glucose levels in middle-aged and elderly adults with obesity or overweight [28]. This metabolic flexibility within the skeletal muscle adipose tissue may play a crucial role in maintaining systemic metabolic homeostasis. The decomposition rate of IMAT is similar to that of VAT, while both are three times faster than the breakdown rate of SAT. The principal reason for this is the modification of the local muscle microenvironment by elevated interstitial free fatty acid concentrations, thereby promoting insulin resistance in the muscle [29]. By reviewing literature on IMCL/IMAT and exercise from 2015 to 2025, we found that the healthier the population, the more IMCL and IMAT increase in the muscles after exercise (including athletes), while the weaker the population, the more IMCL/IMAT decreases after exercise. However, Hasegawa and Sjöros in 2016 and 2019 obtained completely opposite results possibly due to experimental design for different exercise interventions respectively [30, 31] (Table 1).

Table 1. The influence of exercise on IMCL/IMAT in skeletal muscle of different populations during 2015–2025

IMCL/IMAT	Age	Sex	Types of exercise			Variation
			Intensity	Duration	Mode	
IMCL						
Hasegawa et al., 2016	61.0 ± 1.3 (Cross-Sectional Comparison)	18 men and 42 women (healthy)	Aerobic exercise	Implied by the measure of VO_2peak	Habitual (regular, long-term)	The high-fitness group had a significantly higher VO_2peak and higher IMCL levels
Tsintzas et al., 2017	Young: 23 ± 2	Healthy males	Resistance exercise	Single bout	leg press and leg extension at 75% 1-RM	Young men: IMCL increased significantly at 48 h post-exercise
	Older: 72 ± 1					Older men: IMCL was higher at baseline and 12 h post-exercise but showed no change at 48 h
Fischer et al., 2018	45.2 ± 10.8	17 women, 2 men	Combined endurance and resistance training equally	each session lasting 90 min weekly for total 26 weeks	Aerobic and resistance training were conducted respectively using power bicycles and equipment	Significantly decreased by nearly 50%
Loher et al., 2018	GHD patient: 46.9 ± 11.7	Males	Aerobic exercise	Single bout	2 h of cycling at 50% VO_2max	Immediately post-exercise: Decreased in both GHD patients and control subjects but not statistically significant
	Control subjects: 39 ± 12.6					24 h post-exercise: Further decreased in GHD patients. Partially repleted in control subjects

(continued)

Table 1. Continued

IMCL/IMAT	Age	Sex	Types of exercise			Variation
			Intensity	Duration	Mode	
Otten et al. 2018	60	9 men/4 women with Type 2 Diabetes and obesity	Dietary intervention			IMCL decreased significantly
	61	8 men/5 women with Type 2 Diabetes and obesity	Combined Aerobic and Resistance training	3 sessions per week for 12 weeks	Aerobic: Low-intensity on a cross-trainer and moderate/high-intensity interval training on a cycle ergometer Resistance: Upper and lower body exercises for multiple muscle groups	IMCL decreased, but less than the diet-only group
Sjöros et al. 2019	48 years (SD 5) for healthy men; 49 years (SD 4) for T2D/ prediabetic subjects	Healthy group: 28 untrained men	sprint interval training, SIT	6 sessions over 2 weeks		Increased significantly after SIT compared to MICT in both healthy and T2D/prediabetic subjects
		T2D/prediabetic group: 10 women, 16 men	Moderate-intensity continuous training, MICT			No significant increase in IMCL after MICT; the change was less pronounced compared to SIT
Park et al., 2019	49 ± 2	Overweight and Obese Men	Aerobic exercise	3 days per week for 12 weeks	walking and/or light jogging	Improvement in arterial stiffness is associated with a reduction in EMCL, while there is no significant correlation with IMCL

(continued)

Table 1. Continued

IMCL/IMAT	Age	Sex	Types of exercise			Variation
			Intensity	Duration	Mode	
Shaw et al. 2020	Endurance Trained: 28 ± 7 Untrained: 25 ± 4	Healthy males	Chronic Endurance Training	Using the maximum oxygen uptake (VO_2 peak) and the maximum fat oxidation rate (MFO) to define the intensity	specifically cycling and/or triathlon(the trained group had "several years of training experience" and competed regularly)	Higher resting IMCL content in both type I and type II muscle fibres in endurance-trained individuals compared to untrained individuals
IMAT						
Konopka et al., 2018	Young Men (YM): 20 ± 1 Older Men (OM): 74 ± 3 Older Women (OW): 69 ± 2	Healthy, sedentary	Aerobic Exercise	4 days per week for 12 weeks	on a stationary, upright cycle ergometer	IMAT infiltration (IMAT CSA/Thigh Muscle CSA) and IMAT Cross-Sectional Area (CSA) significantly decreased after AET The decrease in IMAT infiltration was more pronounced in Older Women compared to Young Men
Chambers et al. 2019	Men: 74 ± 2 women: 72 ± 2	healthy	Aerobic Exercise	5 days $week^{-1}$, 7 h $week^{-1}$, on average over 52 ± 1 years	primarily running and cycling	Thigh IMAT was attenuated significantly
	74 ± 1	Healthy men	High-Intensity Lifelong Aerobic Exercise (LLE-P)	5 days $week^{-1}$, 8.5 h $week^{-1}$	performance-oriented, including competitive events	IMAT decreased compared to lower-intensity group

(continued)

Table 1. Continued

IMCL/IMAT	Age	Sex	Types of exercise			Variation
			Intensity	Duration	Mode	
	75 ± 2	Healthy men	Low-Intensity Lifelong Aerobic Exercise (LLE-F)	5 days week^{-1}, 7.4 h week^{-1}	fitness-oriented, not competitive	IMAT increased compared to high-intensity group
	25 ± 1	Healthy men and women	Aerobic exercise	4–6 days week^{-1}, 7 h week^{-1}		Lowest IMAT levels
Aas et al. 2020	86.6 ± 6.9	Frail elderly	Strength Training (ST)	2 times per week for 10 weeks	leg press and knee extension exercises	No change
	84.5 ± 7.2		Non-exercising control group (CON)	Non-exercising	Non-exercising	
Ghasemikaram et al., 2021	77.8 ± 3.6	Elderly men diagnosed with osteosarcopenia	High-Intensity Resistance Training (HIRT)	2 times per week for 16 months	The training was a periodized, single-set program performed on machines, targeting major and minor muscle groups	The exercise intervention significantly attenuated the age-related increase in IMAT
Waters et al., 2021	70 ± 4	Obese older adults	Aerobic exercise	3 times per week for 26 weeks	treadmill, bike, or elliptical trainer	IMAT decreased
	70 ± 5		Resistance exercise		weight-lifting machines for upper and lower body	
			Combined aerobic and resistance exercise			

(continued)

Table 1. Continued

IMCL/IMAT	Age	Sex	Types of exercise			Variation
			Intensity	Duration	Mode	
Fairfield et al. 2022	53 ± 1	Middle-aged women without chronic diseases	Resistance exercise training Sedentary	3 times per week for 12 weeks		IMAT decreased with HMB + D supplementation
Kircher et al. 2024	78–79	Elderly males with osteosarcopenia	High-Intensity Resistance Training, HIRT	Twice weekly for 16 months		IMAT remained stable in HIRT group while it increased in the control group

EXCESSIVE LIPID ACCUMULATION IN SKELETAL MUSCLE AND METABOLIC FLEXIBILITY

The distribution of lipid accumulation associated with metabolic flexibility is found in the skeletal muscle, as well as in the adipose tissue, liver, and heart. Impaired metabolic flexibility is mainly reflected in fat transport/storage/metabolism impairment (we generally refer to this kind of fat storage as ectopic lipid storage) of the skeletal muscle. Studies have shown that severely obese individuals with type 2 diabetes exhibit reduced insulin sensitivity and impaired metabolic flexibility compared to severely obese individuals without diabetes. Fuel conversion defects in skeletal muscles coexist with impaired mitochondrial content and function [32–35]. In the aspect of medical treatments, Yinchen extract PMI5011 reduces lipid accumulation in skeletal muscle, whereas *Momordica charantia* exhibites a decreasing trend in lipid accumulation in both skeletal muscle and liver and both supplements can increase skeletal muscle metabolic flexibility [36]. Moreover, reduced diacylglycerol kinase delta (DGKd) expression directly causes peripheral insulin resistance, decreased metabolic flexibility, mild obesity, and subsequent metabolic disorders, potentially contributing to the obesity phenotypes. Laboratory-based closed circuit spirometry—respiratory exchange ratio (RER) measurement, was a general gold standard of indirect calorimetry for accuracy. RER is the molar ratio of carbon dioxide produced (VCO_2) to oxygen consumed (VO_2) by the body during cellular respiration, reflecting substrate oxidation (carbohydrate vs. fat) and metabolic efficiency. This measurement demonstrates that reduced DGKd expression in DGKd+/− mice impaired fat utilization during rest and nighttime activity, resulting in elevated resting respiration (increased aerobic glucose oxidation) but insufficient nighttime activity-induced respiration (lactate production remains limited due to exercise-induced exhaustion) [37]. Studies in overweight men have shown that baseline fast plasma triglyceride (TG) concentrations correlate positively with the respiratory quotient (RQ), indicating that impaired fat oxidation during rest increases the proportion of glucose aerobic oxidation and elevates plasma TG levels [38]. It's worth noting that significant differences between active individuals and sedentary populations suggest that exercise-enhanced adipose tissue may possess greater lipid storage efficiency. However, it should be emphasized that improved lipid storage capacity does not equate to increased fat mass, since the formation of the latter requires an energy surplus. In fact, enhanced lipid storage capacity in adipose tissue, for example, overexpressing adipose tissue secreting adiponectin also shows enhanced clearance of circulating fatty acids and increased subcutaneous adipose tissue expansion after long-term high-fat diet feeding, can reduce the risk of excessive lipid accumulation in organs such as the liver, heart, and muscles, where ectopic lipid buildup poses serious health risks [39, 40]. In addition to subcutaneous and visceral adipose tissue, ectopic lipids can also be stored in non-adipose tissues such as intrahepatic lipids (IHCL), intracellular lipids of myocardial cells (ICCL), and skeletal muscles (IMCL/IMAT), which can be used as a flexible fuel storage and diminished through various long-term exercises [26]. These studies highlight that molecular regulators of lipid handling in various tissues are integral to maintaining systemic metabolic flexibility (Fig. 1).

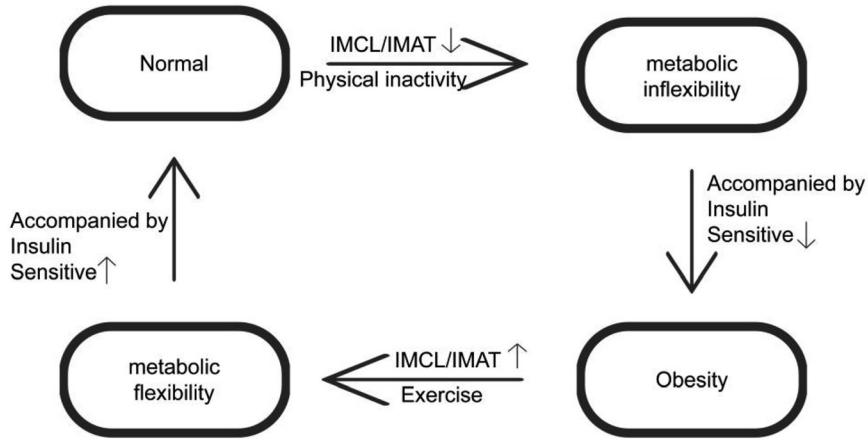

Fig. 1. Obesity and metabolic flexibility

EXERCISE AND METABOLIC FLEXIBILITY

Obese individuals with mainly type I fibers demonstrated greater proficiency in aerobic exercise and a preference for aerobic oxidation for energy production. They also have better insulin sensitivity and metabolic capacity, resulting in more significant weight loss [16, 41]. Based on these, different types of exercise-mediated different types of muscle fibers can improve skeletal muscle metabolic flexibility by altering ectopic fat deposition (e.g., fat metabolism/fat storage) within skeletal muscle. Besides, progressive resistance training (PRT) can increase thigh muscle density while effectively reducing IMAT in elderly, indicating greater aptitude for anaerobic exercise and favoring anaerobic glycolysis. Older adults with higher muscle lipid content derive the most physical function and performance benefit from PRT [42]. As type I fibers exhibit greater metabolic flexibility, studying the signaling pathways involved in their exercise intervention can aid in improving the metabolic flexibility of individuals primarily composed of type II fibers. By regulating the peripheral and central pathways, we can improve metabolic regulatory pathways, restore impaired metabolic flexibility, and create conditions for weight loss in patients with obesity. This is achieved in five ways: improving insulin sensitivity, optimizing energy substrate utilization, promoting capillary regeneration, repairing mitochondrial dysfunction, and affecting central nervous system function (Fig. 2).

IMPROVING INSULIN SENSITIVITY

Generally speaking, slow-twitch type I fibers are rich in mitochondria and have greater insulin sensitivity than fast-twitch type II skeletal muscles [43]. It is worth noting that different type of exercise involves preferential mechanisms. Endurance training in mice activates the AMP-activated Protein Kinase (AMPK)/PGC1α signaling pathway, while high-intensity or resistance training activates the phosphatidylinositol 3-kinase/serine-threonine kinase (PI3K/AKT)

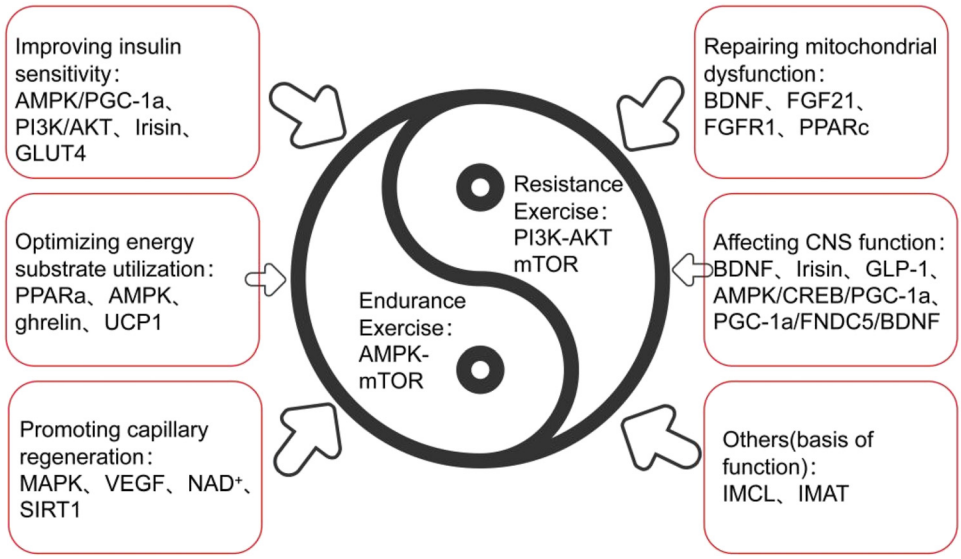

Fig. 2. The different exercise-induced signaling pathways for weight loss

signaling pathway [44]. More evidence from both rats and humans indicates that high-intensity exercise facilitates intracellular glucose transporter-4 (GLUT4) translocation to the cell membrane to enhance glucose uptake and alleviate diet-induced hyperinsulinemia [45, 46]. After 12 weeks of high-intensity interval training (HIIT) and 4 weeks of detraining in males without and with prediabetes or type 2 diabetes (T2D), the benefits in liver insulin sensitivity and ectopic lipid content induced by HIIT persisted, while the improvement in whole-body insulin sensitivity was eliminated after detraining [47]. Ectopic lipid storage is highly correlated with insulin resistance, possibly due to cellular dysfunction caused by the loss of metabolic flexibility and lipotoxicity [3]. Irisin is a myokine which protects C2C12 myotubes against insulin resistance by activating the p38 mitogen-activated protein kinase (p38MAPK)-PGC1α signaling pathway. In L6 myotubes, Irisin activates AMPK and p38MAPK, inducing GLUT4 translocation to enhance glucose uptake. Research has found that Irisin treatment enhances the phosphorylation of AMPK subunit alpha and extracellular signal-regulated kinase 1/2 (ERK1/2), thereby improving insulin sensitivity in mouse soleus muscle and C2C12 myoblasts stimulated by high glucose and palmitic acid [5].

OPTIMIZING ENERGY SUBSTRATE UTILIZATION

AMPK is a major regulator of nutritional homeostasis and can be activated by exercise. It phosphorylates over 100 different substrates, which are crucial for controlling autophagy, carbohydrate, fatty acid, cholesterol, and protein metabolism [48]. Low-intensity treadmill exercise can significantly upregulate the AMPK signaling pathway in obese mice, markedly reducing obesity caused by high-fat diet consumption. It also regulates gut microbiota, improves intestinal

barrier function, enhances gut homeostasis, reduces inflammation, and optimizes glucose-lipid metabolism [49, 50]. Exercise also enhances the ratio of mitochondria fusion to fission in skeletal muscle, fostering a more interconnected tubular network, which is positively associated with improved glucose handling. These changes may contribute to the improvement of insulin sensitivity and substrate utilization observed after exercise [51, 52]. Exercise can directly reduce the IMAT content and increase the fat storage capacity in skeletal muscle, improve the adaptability of adipose tissue, avoid lipid toxicity and inflammation caused by ectopic fat, and reverse fat oxidation impairment [3, 53, 54].

PROMOTING CAPILLARY REGENERATION

Following the activation of the AMPK signaling pathway, exercise not only enhance insulin sensitivity and optimize energy substrate utilization as previously mentioned, but also facilitates angiogenesis [55–57]. Hypoxia and inflammatory factors, such as Interleukin-1β (IL-1β) and Tumor Necrosis Factor α (TNFα), activate downstream nuclear factor kappa-light-chain-enhancer of activated B cells/Activator Protein-1 (NFκB/AP-1), which further stimulates cyclooxygenase 2 (COX2) to produce prostaglandin E2 (PGE2). This activates MAPK, promotes vascular endothelial growth factor (VEGF) release, and induces angiogenesis, with newly formed blood vessels effectively improving metabolic function in the contractive muscle [58, 59]. Exercise involving chronic hypoxia has been proven to improve the vascular structure and function of the peripheral circulation, reverse microvascular remodeling, and normalize capillary density, which may promote capillary growth by increasing angiogenic stimuli, such as VEGF [60]. Exhaustive exercise consumes large amounts of ATP, leading to an increase in the nicotinamide adenine dinucleotide (NAD+)/NADH ratio. Exercise can also enhance NAD + to promote NAD + - dependent deacetylase silent information regulator 1 (SIRT1) dependent capillary density increase, improve blood flow, increase endurance, promote angiogenesis, enhance insulin sensitivity, and provide other health benefits across various ages in-related cardiovascular and metabolic disease models [61–64]. The characteristic feature of obesity is the enlargement/proliferation of adipose tissue in which cells of distinct localization, turnover, and phenotypes show different functions; however, not all forms of adipose tissue expansion are identical to each other. The expansion of healthy adipose tissue is marked by sufficient capillary generation and mitochondrial-centered metabolic integrity, while the expansion of unhealthy adipose tissue presents the opposite characteristics, namely, capillary and mitochondrial disorders, resulting in deposition of inflammatory immune cells and excess production of pro-inflammatory cytokines. Exercise may facilitate the development and progression of healthy fat production by modifying angiogenesis in the adipose tissue [65, 66]. Both exercise and liraglutide (a GLP-1 receptor agonist) could increase muscle insulin sensitivity, enhance insulin-mediated muscle microvascular perfusion, reduce the accumulation of macrophages and superoxide production around muscle vessels, alleviate vascular inflammation, improve endothelial function, increase nuclear factor erythroid 2-related factor 2 (Nrf2) translocation in endothelial nuclei, and increase endothelial AMPK phosphorylation [67].

REPAIRING MITOCHONDRIAL DYSFUNCTION

A study demonstrates that brain-derived neurotropic factor (BDNF) is an essential myokine to maintain mitochondrial quality and provokes mitochondrial fission and clearance in skeletal muscle via the PRKAA/AMPK-PINK1-PRKN/Parkin and PRKAA-DNM1L/DRP1-MFF pathways. Muscle-specific bdnf knockout (MBKO) mice induced lack of BDNF expression in myotubes reduced fatty acid-induced mitofission and mitophagy, which impairs mitochondrial remodeling and lipid handling [68]. Compared with the untrained mice, exercise group exhibits better ability to counteract weight gain, adipose tissue hypertrophy, insulin resistance, fatty liver, and mitochondrial dysfunction caused by high-fat diet (HFD). The effects of exercise persist due to the PPARα-fibroblast growth factor 21 (FGF21)-fibroblast growth factor receptor 1 (FGFR1) signaling pathway [69]. Exercise-induced peroxisome proliferator-activated receptor γ (PPARγ) and PGC1α are key regulatory factors in mitochondrial biogenesis in wild-type C57BL/6J mice [70]. All these factors, BDNF, FGF21, FGFR1, PPARγ and so on, are associate with mitochondrial function.

AFFECTING CENTRAL NERVOUS SYSTEM FUNCTION

The melanocortin system serves as a key mechanism that regulates feeding behavior and energy balance. The dorsal medial hypothalamic nucleus (DMH), a critical region governing satiety, contains neurons with glucagon-like peptide-1 (GLP-1) receptors that directly respond to GLP-1 signals [71, 72]. Proopiomelanocortin (POMC) neurons in the dorsal arcuate nucleus can be activated by anorexic hormones such as leptin, GLP-1, cholecystokinin (CCK), and peptide tyrosine-tyrosine (PYY), but are inhibited by orexic hormones like ghrelin, asprosin, and insulin-like peptide 5 (ILP-5) [73–78]. Furthermore, defects or overexpression of anorexic/orexic hormone receptors may lead to severe obesity [79, 80]. After low-intensity treadmill exercise, MBKO mice exhibited impairments in PPARδ-regulated metabolic gene expression, decreased IMTG, reduced β-oxidation, and dysregulated mitochondrial dynamics which is consistent with the function of BDNF produced by fasting induction, may also resulting in metabolic inflexibility [81, 82]. Another study demostrates that compared with non-exercise and light-intensity exercise but not moderate-intensity exercise conditions, high-intensity exercise (HIE) interventions induce higher BDNF levels [83]. Recent studies have highlighted the critical roles of BDNF and tropomyosin receptor kinase B (TrkB) in the regulation of feeding behavior and energy balance in mammals, particularly in the hypothalamus. Some evidence indicates that this regulation also partially influences downstream pathways of the melanocortin signaling system, though nutritional deficiencies reduce BDNF expression, whereas leptin upregulates it in the ventromedial nucleus (VMN). Crucially, genetic disruption of BDNF and TrkB in both humans and mice results in hyperphagia and severe obesity [84]. Irisin participates in learning and memory through the PGC1α/fibronectin type III domain-containing protein 5 (FNDC5)/BDNF pathway and serves as a key regulatory factor for antidepressant genes. Irisin injection of central nervous system can reduce appetite by stimulating the expression of POMC, cocaine- and amphetamine-regulated transcript (CART), and orexin. However, some studies have found that intraventricular infusion of Irisin increases daily food intake, which may be related to its regulation of leptin and ghrelin levels [5]. Exercise-induced Irisin or peripheral Irisin

overexpression significantly increased BDNF expression in the hippocampus of stroke rats, ultimately improving post-stroke cognitive impairment (PSCI) [85]. Acute exercise inhibits acylated ghrelin and increases GLP-1 and PYY, which are related to the satiety control center, centralized in DMH, and respond to GLP-1 signals [86].

IMPROVING THE SKELETAL MUSCLE METABOLIC FLEXIBILITY: AN EFFECTIVE WAY TO ACHIEVE WEIGHT LOSS THROUGH EXERCISE

Diet-sensitive mice exhibit significantly higher susceptibility to obesogenic enviroment (eg.HFD) compared to diet-resistant mice and display a highly plastic metabolic phenotype; however, when external interventions (such as exercise) alter the energy balance, their metabolic system can respond rapidly, demonstrating stronger metabolic flexibility. In a voluntary treadmill exercise study, lower insulin-glucose index (IG index) and higher circulating levels of leptin were detected in obese-sensitive OM rats in the exercise group than that of the control group, indicating improved insulin sensitivity in OM rats, whereas no significant improvement is observed in obesity-resistant S5B/Pl rats [87]. Findings focus on human reach the same conclusion as those on mice. A study on 11 obese individuals who developed resistance to conventional dieting showed that exercise alone can help a significant proportion of individuals achieve significant weight loss [88, 89]. Studies have shown that individuals undergoing rapid weight loss subjects demonstrate higher oxidative fiber ratios, mitochondrial proton leakage rates, UCP3 mRNA abundance, and reduced glutathione (reduced and oxidized forms) in their femoral rectus and vastus lateralis muscles. These characteristics may explain their weight-loss advantages [90–93]. Exercise training exerts significant effects on improving body composition and enhancing mitochondrial function in obese women with dietary resistance (DR). Although diet sensitive (DS) phenotypes demonstrate advantages in weight reduction, their higher visceral fat levels and metabolic syndrome risks highlight the need to pay attention to metabolic health in this population [93]. These results imply that obese individuals who are resistant to traditional diets composed mainly of carbohydrates but responsive to such dietary modifications as nutritional supplementation may also benefit from exercise.

CONCLUSIONS

With the global surge in obesity rates, scientific weight management has become increasingly urgent. Exercise regimens beyond voluntary participation have gained significant attention. Various long-term exercises of different intensities, durations and modes can lead to varying degrees of reduction in IMCL and IMAT in skeletal muscle except for athletes that comply with ‘athlete paradox’. Endurance and resistance exercise through preferential factors and signaling pathways change molecular switches and downstream physiological functions. This article takes metabolic flexibility as the starting point, and by analyzing the signaling molecules, signaling pathways, and mechanisms involved in exercise-based weight loss, it elucidates that exercise can function through different muscle fiber types and skeletal muscle characteristics of various populations, thereby improving metabolic flexibility and achieving the goal of weight loss. By leveraging the fundamental principle of energy deficit for weight loss, we propose integrating

metabolism as the entry point, combining exercise with potential metabolic molecular targets, for example, AMPK, PGC-1a, PI3K, Irisin, GLUT4, UCP1, SIRT1, BDNF, GLP-1, *etc*. to search for new therapeutic approaches for obesity management through combined medication and exercise therapy.

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ABBREVIATIONS

AF	Atrial Fibrillation
AKT	Serine-Threonine Kinase
AMPK	AMP-activated Protein Kinase
AP-1	Activator Protein-1
ATP	Adenosine Triphosphate
BCB	Blood CNS Barrier
BDNF	Brain-Derived Neurotropic Factor
BMI	Body Mass Index
CART	Cocaine- and Amphetamine-Regulated Transcript
CCK	Cholecystokinin
CDX2	Caudal-Type Homeobox 2
CMT2Q	Type 2Q Muscular Dystrophy
COX2	Cyclooxygenase 2
DAG	Diacylglycerol
DGKd	Diacylglycerol Kinase delta
DMH	Dorsomedial Hypothalamus
DR	Diet Resistant
DS	Diet Sensitive
ER	Endoplasmic Reticulum
ERK1/2	Extracellular signal-Regulated Kinase 1/2
FAO	Fatty Acid Oxidation

FG	Fasting Glucose
FGF21	Fibroblast Growth Factor 21
FGFR1	Fibroblast Growth Factor Receptor 1
FNDC5	Fibronectin Type III Domain-Containing Protein 5
FTO	Fat mass and Obesity-associated
GDM	Gestational Diabetes Mellitus
GIR	Glucose Infusion Rate
GLP-1	Glucagon-Like Peptide-1
GLUT4	Glucose Transporter-4
GWAS	Genome-Wide Association Studies
HIIT	High-Intensity Interval Training
IG index	Insulin-Glucose index
IGT	Impaired Glucose Tolerance
IL-1β	Interleukin-1β
ILP-5	Insulin-Like Peptide 5
IMAT	Intermuscular Adipose Tissue
IMCL	Intramyocellular Lipid
IMTG	Intramuscular triglyceride
IR	Insulin Resistance
KO	Knockout
MAM	Mitochondria-Associated Endoplasmic Reticulum Membrane
MAPK	Mitogen-Activated Protein Kinase
MOTS-c	Mitochondrial Open Reading Frame of the 12S rRNA Type-c
mTOR	mammalian Target Of Rapamycin
NADH	Nicotinamide Adenine Dinucleotide (reduced form)
NFκB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
p38MAPK	p38 Mitogen-Activated Protein Kinase
PDGF-B	Platelet-Derived Growth Factor-B
PE	Phospholipid Ethylamine
PGC1	Peroxisome Proliferator Activated Receptor-γ Coactivator-1
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositol 3-Kinase
POMC	Proopiomelanocortin
PPAR	Peroxisome proliferator-activated receptor
PSD	Phosphatidylserine Decarboxylase
PYY	Peptide Tyrosine-Tyrosine
RER	Respiratory Exchange Ratio
RQ	Respiratory Quotient
SAT	Subcutaneous Adipose Tissue
SG	Sleeve Gastrectomy
SIRT1	Silent Information Regulator 1
SNP	Single Nucleotide Polymorphisms
T2D	Type 2 Diabetes
T2DM	Type 2 Diabetes Mellitus

TG	Triglyceride
TNFα	Tumor Necrosis Factor α
TrkB	Tropomyosin Receptor Kinase B
UCP	Uncoupling Protein
VAT	Visceral Adipose Tissue
VEGF	Vascular Endothelial Growth Factor
VMN	Ventromedial Nucleus

REFERENCES

1. Fritzen AM, Lundsgaard AM, Kiens B. Tuning fatty acid oxidation in skeletal muscle with dietary fat and exercise. Nat Rev Endocrinol 2020 Dec; 16(12): 683–96. https://doi.org/10.1038/s41574-020-0405-1
2. Goodpaster BH, Sparks LM. Metabolic flexibility in health and disease. Cell Metab 2017 May 2; 25(5): 1027–36. https://doi.org/10.1016/j.cmet.2017.04.015
3. Zacharewicz E, Hesselink M, Schrauwen P. Exercise counteracts lipotoxicity by improving lipid turnover and lipid droplet quality. J Intern Med 2018 Nov; 284(5): 505–18. 2018. https://doi.org/10.1111/joim.12729
4. Smith J, Murach KA, Dyar KA, Zierath JR. Exercise metabolism and adaptation in skeletal muscle. Nat Rev Mol Cell Biol 2023 Sep; 24(9): 607–32. 2023. https://doi.org/10.1038/s41580-023-00606-x
5. Shen S, Liao Q, Chen X, Peng C, Lin L. The role of irisin in metabolic flexibility: beyond adipose tissue browning. Drug Discov Today 2022 Aug; 27(8): 2261–7. https://doi.org/10.1016/j.drudis.2022.03.019
6. Thyfault JP, Rector RS, Noland RC. Metabolic inflexibility in skeletal muscle: a prelude to the cardiometabolic syndrome. J Cardiometab Syndr 2006 Summer; 1(3): 184–9. https://doi.org/10.1111/j.1559-4564.2006.05629.x
7. Galgani JE, Heilbronn LK, Azuma K, Kelley DE, Albu JB, Pi-Sunyer X, et al. Metabolic flexibility in response to glucose is not impaired in people with type 2 diabetes after controlling for glucose disposal rate. Diabetes 2008 Apr; 57(4): 841–5. 2008. https://doi.org/10.2337/db08-0043
8. Galgani JE, Moro C, Ravussin E. Metabolic flexibility and insulin resistance. Am J Physiol Endocrinol Metab 2008 Nov; 295(5): E1009–17. 2008. https://doi.org/10.1152/ajpendo.90558.2008
9. Storlien L, Oakes ND, Kelley DE. Metabolic flexibility. Proc Nutr Soc 2004 May; 63(2): 363–8. 2004. https://doi.org/10.1079/PNS2004349
10. Broskey NT, Obanda DN, Burton JH, Cefalu WT, Ravussin E. Skeletal muscle ceramides and daily fat oxidation in obesity and diabetes. Metabolism 2018 May; 82: 118–23. https://doi.org/10.1016/j.metabol.2017.12.012
11. Fernández-Verdejo R, Malo-Vintimilla L, Gutiérrez-Pino J, López-Fuenzalida A, Olmos P, Irarrazaval P, et al. Similar metabolic health in overweight/obese individuals with contrasting metabolic flexibility to an oral glucose tolerance test. Front Nutr 2021; 8: 745907. 2021. https://doi.org/10.3389/fnut.2021.745907
12. Wiklund P. The role of physical activity and exercise in obesity and weight management: time for critical appraisal. J Sport Health Sci 2016 Jun; 5(2): 151–4. https://doi.org/10.1016/j.jshs.2016.04.001
13. Lark DS, Kwan JR, McClatchey PM, James MN, James FD, Lighton J, et al. Reduced nonexercise activity attenuates negative energy balance in mice engaged in voluntary exercise. Diabetes 2018 May; 67(5): 831–40. https://doi.org/10.2337/db17-1293
14. O'Neal TJ, Friend DM, Guo J, Hall KD, Kravitz AV. Increases in physical activity result in diminishing increments in daily energy expenditure in mice. Curr Biol 2017 Feb 6; 27(3): 423–30. https://doi.org/10.1016/j.cub.2016.12.009

15. Ahn C, Zhang T, Yang G, Rode T, Varshney P, Ghayur SJ, et al. Years of endurance exercise training remodel abdominal subcutaneous adipose tissue in adults with overweight or obesity. Nat Metab 2024 Sep; 6(9): 1819–36. 2024. https://doi.org/10.1038/s42255-024-01103-x
16. Harper ME, Dent R, McPherson R. High-quality weight loss in obesity: importance of skeletal muscle. Diabetes 2025 Dec 01; 74(12): 2191–8. 2025. https://doi.org/10.2337/dbi25-0003
17. Osler ME, Fritz T, Caidahl K, Krook A, Zierath JR, Wallberg-Henriksson H. Changes in gene expression in responders and nonresponders to a low-intensity walking intervention. Diabetes Care 2015 Jun; 38(6): 1154–60. https://doi.org/10.2337/dc14-2606
18. Siripoksup P, Cao G, Cluntun AA, Maschek JA, Pearce Q, Brothwell MJ, et al. Sedentary behavior in mice induces metabolic inflexibility by suppressing skeletal muscle pyruvate metabolism. J Clin Invest 2024 Apr 23; 134(11). 2024. https://doi.org/10.1172/JCI167371
19. Wang Y, Xie H, Liu Q, Wang N, Luo X, Sun F, et al. Kdm2a inhibition in skeletal muscle improves metabolic flexibility in obesity. Nat Metab 2025 Feb; 7(2): 383–400. 2025. https://doi.org/10.1038/s42255-024-01210-9
20. Duivenvoorde LP, van Schothorst EM, Swarts HM, Kuda O, Steenbergh E, Termeulen S, et al. A difference in fatty acid composition of isocaloric high-fat diets alters metabolic flexibility in male C57BL/6JOlaHsd mice. PLoS One 2015; 10(6): e0128515. 2015. https://doi.org/10.1371/journal.pone.0128515
21. Park J, Choi Y, Myoenzono K, Yoshikawa T, Tagawa K, Isobe T, et al. Effects of aerobic exercise training on the arterial stiffness and intramyocellular or extramyocellular lipid in overweight and obese men. Clin Exp Hypertens 2020 May 18; 42(4): 302–8. https://doi.org/10.1080/10641963.2019.1649686
22. Fischer M, Oberänder N, Kaufmann J, Kirsche V, Prodehl G, Schäfer AO, et al. Changes in intra- and extramyocellular lipids in morbidly obese patients after non-surgical weight loss-a pilot study using magnetic resonance spectroscopy. Clin Nutr ESPEN 2018 Dec; 28: 121–6. https://doi.org/10.1016/j.clnesp.2018.08.018
23. Tsintzas K, Stephens FB, Snijders T, Wall BT, Cooper S, Mallinson J, et al. Intramyocellular lipid content and lipogenic gene expression responses following a single bout of resistance type exercise differ between young and older men. Exp Gerontol 2017 Jul; 93: 36–45. 2017. https://doi.org/10.1016/j.exger.2017.03.018
24. Loher H, Jenni S, Bucher J, Krüsi M, Kreis R, Boesch C, et al. Impaired repletion of intramyocellular lipids in patients with growth hormone deficiency after a bout of aerobic exercise. Growth Horm IGF Res 2018 Oct - Dec; 42–43: 32–9. 2018. https://doi.org/10.1016/j.ghir.2018.08.001
25. Fairfield WD, Minton DM, Elliehausen CJ, Nichol AD, Cook TL, Rathmacher JA, et al. Small-scale randomized controlled trial to explore the impact of β-Hydroxy-β-Methylbutyrate plus vitamin D3 on skeletal muscle health in middle aged women. Nutrients 2022 Nov 04; 14(21). 2022. https://doi.org/10.3390/nu14214674
26. Bergman BC, Perreault L, Strauss A, Bacon S, Kerege A, Harrison K, et al. Intramuscular triglyceride synthesis: importance in muscle lipid partitioning in humans. Am J Physiol Endocrinol Metab 2018 Feb 1; 314(2): E152–64. https://doi.org/10.1152/ajpendo.00142.2017
27. Kircher K, Chaudry O, Nagel AM, Ghasemikaram M, Uder M, Jakob F, et al. Effects of high-intensity training on fatty infiltration in paraspinal muscles in elderly males with osteosarcopenia - the randomized controlled FrOST study. BMC Geriatr 2024 Feb 08; 24(1): 141. 2024. https://doi.org/10.1186/s12877-024-04736-5
28. Kim JE, Dunville K, Li J, Cheng JX, Conley TB, Couture CS, et al. Intermuscular adipose tissue content and intramyocellular lipid fatty acid saturation are associated with glucose homeostasis in middle-aged and older adults. Endocrinol Metab (Seoul) 2017 Jun; 32(2): 257–64. 2017. https://doi.org/10.3803/EnM.2017.32.2.257
29. Goodpaster BH, Bergman BC, Brennan AM, Sparks LM. Intermuscular adipose tissue in metabolic disease. Nat Rev Endocrinol 2023 May; 19(5): 285–98. https://doi.org/10.1038/s41574-022-00784-2
30. Hasegawa N, Fujie S, Kurihara T, Homma T, Sanada K, Sato K, et al. Effects of habitual aerobic exercise on the relationship between intramyocellular or extramyocellular lipid content and arterial stiffness. J Hum Hypertens 2016 Oct; 30(10): 606–12. 2016. https://doi.org/10.1038/jhh.2016.28

31. Sjöros T, Saunavaara V, Löyttyniemi E, Koivumäki M, Heinonen I, Eskelinen JJ, et al. Intramyocellular lipid accumulation after sprint interval and moderate-intensity continuous training in healthy and diabetic subjects. Physiol Rep 2019 Feb; 7(3): e13980. 2019. https://doi.org/10.14814/phy2.13980
32. Mensink M, Hesselink MK, Russell AP, Schaart G, Sels JP, Schrauwen P. Improved skeletal muscle oxidative enzyme activity and restoration of PGC-1 alpha and PPAR beta/delta gene expression upon rosiglitazone treatment in obese patients with type 2 diabetes mellitus. Int J Obes (Lond) 2007 Aug; 31(8): 1302–10. https://doi.org/10.1038/sj.ijo.0803567
33. Corpeleijn E, Saris WH, Blaak EE. Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle. Obes Rev 2009 Mar; 10(2): 178–93. 2009. https://doi.org/10.1111/j.1467-789X.2008.00544.x
34. van de Weijer T, Sparks LM, Phielix E, Meex RC, van Herpen NA, Hesselink MK, et al. Relationships between mitochondrial function and metabolic flexibility in type 2 diabetes mellitus. PLoS One 2013; 8(2): e51648. https://doi.org/10.1371/journal.pone.0051648
35. Bakke SS, Feng YZ, Nikolić N, Kase ET, Moro C, Stensrud C, et al. Myotubes from severely obese type 2 diabetic subjects accumulate less lipids and show higher lipolytic rate than myotubes from severely obese non-diabetic subjects. PLoS One 2015; 10(3): e0119556. https://doi.org/10.1371/journal.pone.0119556
36. Fuller S, Yu Y, Mendoza T, Ribnicky DM, Cefalu WT, Floyd ZE. Potential adverse effects of botanical supplementation in high-fat-fed female mice. Biol Sex Differ 2018 Sep 12; 9(1): 41. 2018. https://doi.org/10.1186/s13293-018-0199-1
37. Jollet M, Tramontana F, Jiang LQ, Borg ML, Savikj M, Kuefner MS, et al. Diacylglycerol kinase delta overexpression improves glucose clearance and protects against the development of obesity. Metabolism 2024 Sep; 158: 155939. 2024. https://doi.org/10.1016/j.metabol.2024.155939
38. Siri-Tarino PW, Woods AC, Bray GA, Krauss RM. Reversal of small, dense LDL subclass phenotype by weight loss is associated with impaired fat oxidation. Obesity (Silver Spring) 2011 Jan; 19(1): 61–8. 2011. https://doi.org/10.1038/oby.2010.142
39. Long-term exercise training has positive effects on adipose tissue in overweight or obesity. Nat Metab 2024 Sep; 6(9): 1657–8. 2024. https://doi.org/10.1038/s42255-024-01102-y
40. Asterholm IW, Scherer PE. Enhanced metabolic flexibility associated with elevated adiponectin levels. Am J Pathol 2010 Mar; 176(3): 1364–76. 2010. https://doi.org/10.2353/ajpath.2010.090647
41. Duan Y, Li F, Tan B, Yao K, Yin Y. Metabolic control of myofibers: promising therapeutic target for obesity and type 2 diabetes. Obes Rev 2017 Jun; 18(6): 647–59. https://doi.org/10.1111/obr.12530
42. Long DE, Peck BD, Tuggle SC, Villasante Tezanos AG, Windham ST, Bamman MM, et al. Associations of muscle lipid content with physical function and resistance training outcomes in older adults: altered responses with metformin. Geroscience 2021 Apr; 43(2): 629–44. 2021. https://doi.org/10.1007/s11357-020-00315-9
43. da Costa TS, Pontes J, García Delgado G, Omage FB, de Oliveira Santana G, Rodrigues GT, et al. Systemic and skeletal muscle metabolic signatures associated with early insulin resistance in just-weaned non-obese Goto-Kakizaki diabetic rats. Biomed Pharmacother 2025 Dec; 193: 118826. 2025. https://doi.org/10.1016/j.biopha.2025.118826
44. Feng L, Li B, Xi Y, Cai M, Tian Z. Aerobic exercise and resistance exercise alleviate skeletal muscle atrophy through IGF-1/IGF-1R-PI3K/Akt pathway in mice with myocardial infarction. Am J Physiol Cell Physiol 2022 Feb 01; 322(2): C164–164C176. 2022. https://doi.org/10.1152/ajpcell.00344.2021
45. Joseph A, Parvathy S, Varma KK. Hyperinsulinemia induced altered insulin signaling pathway in muscle of high fat- and carbohydrate-fed rats: effect of exercise. J Diabetes Res 2021: 5123241. 2021. https://doi.org/10.1155/2021/5123241
46. Sullivan BP, Nie Y, Evans S, Kargl CK, Hettinger ZR, Garner RT, et al. Obesity and exercise training alter inflammatory pathway skeletal muscle small extracellular vesicle microRNAs. Exp Physiol 2022 May; 107(5): 462–75. https://doi.org/10.1113/EP090062

47. Mastrototaro L, Apostolopoulou M, Hartwig S, Strassburger K, Lipaeva P, Trinks N, et al. The role of exosomes for sustained specific cardiorespiratory and metabolic improvements in males with type 2 diabetes after detraining. EBioMedicine 2024 Dec; 110: 105471. 2024. https://doi.org/10.1016/j.ebiom.2024.105471
48. Townsend LK, Steinberg GR. AMPK and the endocrine control of metabolism. Endocr Rev 2023 Sep 15; 44(5): 910–33. https://doi.org/10.1210/endrev/bnad012
49. Quiroga R, Nistal E, Estébanez B, Porras D, Juárez-Fernández M, Martínez-Flórez S, et al. Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. Exp Mol Med 2020 Jul; 52(7): 1048–61. https://doi.org/10.1038/s12276-020-0459-0
50. Wang J, Zhang Q, Xia J, Sun H. Moderate treadmill exercise modulates gut microbiota and improves intestinal barrier in high-fat-diet-induced obese mice via the AMPK/CDX2 signaling pathway. Diabetes Metab Syndr Obes 2022; 15: 209–23. https://doi.org/10.2147/DMSO.S346007
51. Axelrod CL, Fealy CE, Mulya A, Kirwan JP. Exercise training remodels human skeletal muscle mitochondrial fission and fusion machinery towards a pro-elongation phenotype. Acta Physiol (Oxf) 2019 Apr; 225(4): e13216. https://doi.org/10.1111/apha.13216
52. Slivka DR, Heesch MW, Dumke CL, Cuddy JS, Hailes WS, Ruby BC. Human skeletal muscle mRNAResponse to a single hypoxic exercise bout. Wilderness Environ Med 2014 Dec; 25(4): 462–5. https://doi.org/10.1016/j.wem.2014.06.011
53. Little JP, Chilibeck PD, Ciona D, Vandenberg A, Zello GA. The effects of low- and high-glycemic index foods on high-intensity intermittent exercise. Int J Sports Physiol Perform 2009 Sep; 4(3): 367–80. 2009. https://doi.org/10.1123/ijspp.4.3.367
54. Nosaka N, Tsujino S, Honda K, Suemitsu H, Kato K, Kondo K. Effect of ingestion of medium-chain triglycerides on substrate oxidation during aerobic exercise could depend on sex difference in middle-aged sedentary persons. Nutrients 2020 Dec 24; 13(1): 36. https://doi.org/10.3390/nu13010036
55. Milkiewicz M, Mohammadzadeh F, Ispanovic E, Gee E, Haas TL. Static strain stimulates expression of matrix metalloproteinase-2 and VEGF in microvascular endothelium via JNK- and ERK-dependent pathways. J Cell Biochem 2007 Feb 15; 100(3): 750–61. 2007. https://doi.org/10.1002/jcb.21055
56. Hulmi JJ, Oliveira BM, Silvennoinen M, Hoogaars WM, Ma H, Pierre P, et al. Muscle protein synthesis, mTORC1/MAPK/Hippo signaling, and capillary density are altered by blocking of myostatin and activins. Am J Physiol Endocrinol Metab 2013 Jan 01; 304(1): E41–50. 2013. https://doi.org/10.1152/ajpendo.00389.2012
57. Da Silva ND, Fernandes T, Soci UP, Monteiro AW, Phillips MI, De Oliveira EM. Swimming training in rats increases cardiac MicroRNA-126 expression and angiogenesis. Med Sci Sports Exerc 2012 Aug; 44(8): 1453–62. 2012. https://doi.org/10.1249/MSS.0b013e31824e8a36
58. Fu P, Zhu R, Jia J, Hu Y, Wu C, Cieszczyk P, et al. Aerobic exercise promotes the functions of brown adipose tissue in obese mice via a mechanism involving COX2 in the VEGF signaling pathway. Nutr Metab (Lond) 2021 Jun 3; 18(1): 56. https://doi.org/10.1186/s12986-021-00581-0
59. Garner RT, Weiss JA, Nie Y, Sullivan BP, Kargl CK, Drohan CJ, et al. Effects of obesity and acute resistance exercise on skeletal muscle angiogenic communication pathways. Exp Physiol 2022 Aug; 107(8): 906–18. https://doi.org/10.1113/EP090152
60. Banchero N. Cardiovascular responses to chronic hypoxia. Annu Rev Physiol 1987 1987; 49: 465–76. https://doi.org/10.1146/annurev.ph.49.030187.002341
61. De Ciuceis C, Rizzoni D, Palatini P. Microcirculation and physical exercise in hypertension. Hypertension 2023 Apr; 80(4): 730–9. 2023. https://doi.org/10.1161/HYPERTENSIONAHA.122.19465
62. Das A, Huang GX, Bonkowski MS, Longchamp A, Li C, Schultz MB, et al. Impairment of an endothelial NAD+-H2S signaling network is a reversible cause of vascular aging. Cell 2018 Mar 22; 173(1): 74–89.e20. 2018. https://doi.org/10.1016/j.cell.2018.02.008

63. Aldiss P, Betts J, Sale C, Pope M, Budge H, Symonds ME. Exercise-induced 'browning' of adipose tissues. Metabolism 2018 Apr; 81: 63–70. 2018. https://doi.org/10.1016/j.metabol.2017.11.009
64. Kane AE, Sinclair DA. Sirtuins and NAD+ in the development and treatment of metabolic and cardiovascular diseases. Circ Res 2018 Sep 14; 123(7): 868–85. 2018. https://doi.org/10.1161/CIRCRESAHA.118.312498
65. Meister BM, Hong SG, Shin J, Rath M, Sayoc J, Park JY. Healthy versus unhealthy adipose tissue expansion: the role of exercise. J Obes Metab Syndr 2022 Mar 30; 31(1): 37–50. 2022. https://doi.org/10.7570/jomes21096
66. Yu X, Hu Y, Lim HY, Li Z, Jaitin DA, Yang K, et al. Septal LYVE1+ macrophages control adipocyte stem cell adipogenic potential. Science 2025 Aug 28; 389(6763): eadg1128. 2025. https://doi.org/10.1126/science.adg1128
67. Liu J, Aylor KW, Liu Z. Liraglutide and exercise synergistically attenuate vascular inflammation and enhance metabolic insulin action in early diet-induced obesity. Diabetes 2023 Jul 1; 72(7): 918–31. https://doi.org/10.2337/db22-0745
68. Ahuja P, Ng CF, Pang B, Chan WS, Tse M, Bi X, et al. Muscle-generated BDNF (brain derived neurotrophic factor) maintains mitochondrial quality control in female mice. Autophagy 2022 Jun; 18 (6): 1367–84. 2022. https://doi.org/10.1080/15548627.2021.1985257
69. Kim YJ, Kim HJ, Lee SG, Kim DH, In Jang S, Go HS, et al. Aerobic exercise for eight weeks provides protective effects towards liver and cardiometabolic health and adipose tissue remodeling under metabolic stress for one week: a study in mice. Metabolism 2022 May; 130: 155178. https://doi.org/10.1016/j.metabol.2022.155178
70. Brendel H, Shahid A, Hofmann A, Mittag J, Bornstein SR, Morawietz H, et al. NADPH oxidase 4 mediates the protective effects of physical activity against obesity-induced vascular dysfunction. Cardiovasc Res 2020 Aug 01; 116(10): 1767–78. 2020. https://doi.org/10.1093/cvr/cvz322
71. Lenharo M. How blockbuster obesity drugs create a full feeling - even before one bite of food. Nature 2024 Jun 27. 2024. https://doi.org/10.1038/d41586-024-02106-0
72. Kim KS, Park JS, Hwang E, Park MJ, Shin HY, Lee YH, et al. GLP-1 increases preingestive satiation via hypothalamic circuits in mice and humans. Science 2024 Jul 26; 385(6707): 438–46. 2024. https://doi.org/10.1126/science.adj2537
73. Wen X, Zhang B, Wu B, Xiao H, Li Z, Li R, et al. Signaling pathways in obesity: mechanisms and therapeutic interventions. Signal Transduct Target Ther 2022 Aug 28; 7(1): 298. 2022. https://doi.org/10.1038/s41392-022-01149-x
74. Tadross JA, Steuernagel L, Dowsett G, Kentistou KA, Lundh S, Porniece M, et al. A comprehensive spatiocellular map of the human hypothalamus. Nature 2025 Mar; 639(8055): 708–16. 2025. https://doi.org/10.1038/s41586-024-08504-8
75. Geloneze B, de Lima-Júnior JC, Velloso LA. Glucagon-like Peptide-1 receptor agonists (GLP-1RAs) in the brain-adipocyte axis. Drugs 2017 Apr; 77(5): 493–503. 2017. https://doi.org/10.1007/s40265-017-0706-4
76. Borer KT, Lin PJ, Wuorinen E. Timing of meals and exercise affects hormonal control of glucoregulation, insulin resistance, substrate metabolism, and gastrointestinal hormones, but has little effect on appetite in postmenopausal women. Nutrients 2021 Dec 1; 13(12): 4342. https://doi.org/10.3390/nu13124342
77. Ullah R, Shen Y, Zhou YD, Fu J. Perinatal metabolic inflammation in the hypothalamus impairs the development of homeostatic feeding circuitry. Metabolism 2023 Oct; 147: 155677. 2023. https://doi.org/10.1016/j.metabol.2023.155677
78. Duerrschmid C, He Y, Wang C, Li C, Bournat JC, Romere C, et al. Asprosin is a centrally acting orexigenic hormone. Nat Med 2017 Dec; 23(12): 1444–53. 2017. https://doi.org/10.1038/nm.4432
79. Wasim M, Awan FR, Najam SS, Khan AR, Khan HN. Role of leptin deficiency, inefficiency, and leptin receptors in obesity. Biochem Genet 2016 Oct; 54(5): 565–72. 2016. https://doi.org/10.1007/s10528-016-9751-z

80. Zigman JM, Nakano Y, Coppari R, Balthasar N, Marcus JN, Lee CE, et al. Mice lacking ghrelin receptors resist the development of diet-induced obesity. J Clin Invest 2005 Dec; 115(12): 3564–72. 2005. https://doi.org/10.1172/JCI26002
81. Yang X, Brobst D, Chan WS, Tse M, Herlea-Pana O, Ahuja P, et al. Muscle-generated BDNF is a sexually dimorphic myokine that controls metabolic flexibility. Sci Signal 2019 Aug 13; 12(594). 2019. https://doi.org/10.1126/scisignal.aau1468
82. Chan WS, Ng CF, Pang B, Hang M, Tse M, Iu E, et al. Exercise-induced BDNF promotes PPARδ-dependent reprogramming of lipid metabolism in skeletal muscle during exercise recovery. Sci Signal 2024 Mar 19; 17(828): eadh2783. 2024. https://doi.org/10.1126/scisignal.adh2783
83. Fernández-Rodríguez R, Álvarez-Bueno C, Martínez-Ortega IA, Martínez-Vizcaíno V, Mesas AE, Notario-Pacheco B. Immediate effect of high-intensity exercise on brain-derived neurotrophic factor in healthy young adults: a systematic review and meta-analysis. J Sport Health Sci 2022 May; 11(3): 367–75. 2022. https://doi.org/10.1016/j.jshs.2021.08.004
84. Loos R, Yeo G. The genetics of obesity: from discovery to biology. Nat Rev Genet 2022 Feb; 23(2): 120–33. 2022. https://doi.org/10.1038/s41576-021-00414-z
85. Wei J, Cai Y, Jiang Z, Xie J, Xie D, Ouyang F, et al. Targeting the muscle-brain axis to improve post-stroke cognition via the FNDC5/irisin/BDNF pathway. J Adv Res 2025 Oct 25. 2025. https://doi.org/10.1016/j.jare.2025.10.027
86. Ribeiro FM, Silva MA, Lyssa V, Marques G, Lima HK, Franco OL, et al. The molecular signaling of exercise and obesity in the microbiota-gut-brain axis. Front Endocrinol (Lausanne) 2022; 13: 927170. https://doi.org/10.3389/fendo.2022.927170
87. Zachwieja JJ, Hendry SL, Smith SR, Harris RB. Voluntary wheel running decreases adipose tissue mass and expression of leptin mRNA in osborne-mendel rats. Diabetes 1997 Jul; 46(7): 1159–66. 1997. https://doi.org/10.2337/diab.46.7.1159
88. Editorial. Effect of exercise alone on obesity. Br Med J 1976 Feb 21; 1(6007): 417–8. 1976. https://doi.org/10.1136/bmj.1.6007.417
89. Gwinup G. Effect of exercise alone on the weight of obese women. Arch Intern Med 1975 May; 135(5): 676–80. 1975.
90. Harper ME, Dent R, Monemdjou S, Bézaire V, Van Wyck L, Wells G, et al. Decreased mitochondrial proton leak and reduced expression of uncoupling protein 3 in skeletal muscle of obese diet-resistant women. Diabetes 2002 Aug; 51(8): 2459–66. 2002. https://doi.org/10.2337/diabetes.51.8.2459
91. Thrush AB, Zhang R, Chen W, Seifert EL, Quizi JK, McPherson R, et al. Lower mitochondrial proton leak and decreased glutathione redox in primary muscle cells of obese diet-resistant versus diet-sensitive humans. J Clin Endocrinol Metab 2014 Nov; 99(11): 4223–30. 2014. https://doi.org/10.1210/jc.2014-1726
92. Gerrits MF, Ghosh S, Kavaslar N, Hill B, Tour A, Seifert EL, et al. Distinct skeletal muscle fiber characteristics and gene expression in diet-sensitive versus diet-resistant obesity. J Lipid Res 2010 Aug; 51(8): 2394–404. https://doi.org/10.1194/jlr.P005298
93. Pileggi CA, Blondin DP, Hooks BG, Parmar G, Alecu I, Patten DA, et al. Exercise training enhances muscle mitochondrial metabolism in diet-resistant obesity. EBioMedicine 2022 Sep; 83: 104192. https://doi.org/10.1016/j.ebiom.2022.104192