

## The Effect of Aerobic Exercise on Insulin Resistance: Narrative review of the Molecular Mechanisms

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### Abstract

Insulin resistance (IR) is a central pathophysiological hallmark of type 2 diabetes mellitus (T2D) and related cardio-metabolic disorders. This narrative review explores the impact of regular physical activity, particularly aerobic and resistance exercise, on the mitigation of IR through various molecular mechanisms. Genetic predispositions, chronic low-grade inflammation, dysregulated circulating metabolites, hormonal imbalances, oxidative stress, and abnormal enzymatic activities collectively contribute to the pathogenesis of IR. Physical activity, especially aerobic exercise, has significant anti-IR effects by modulating inflammatory processes. This includes suppression of pro-inflammatory cytokines (e.g., TNF- $\alpha$ , IL-6) and adipokines (e.g., resistin, visfatin), as well as an increase in anti-inflammatory myokines (e.g., irisin, muscle-derived IL-6) and adiponectin/emilin-1 profiles. These changes create an anti-inflammatory environment that enhances insulin signaling in skeletal muscle, liver, and adipose tissue. Hormonal adjustments, such as improved insulin secretion, beta-cell function, and tissue sensitivity, further support these metabolic adaptations. Additionally, exercise reduces oxidative stress by strengthening antioxidant defenses and inhibiting key IR-promoting enzymes like PTP1B and 11 $\beta$ -HSD1. This preservation of tyrosine phosphorylation of the insulin receptor and downstream IRS-1/PI3K/Akt pathway activation leads to increased GLUT4 translocation and glucose uptake. In summary, regular exercise is a cost-effective, non-pharmacological intervention that targets interconnected molecular factors in the etiology of IR. These diverse effects highlight its therapeutic potential in personalized prevention and management strategies for IR and associated metabolic diseases, warranting its integration into clinical guidelines.


**Keywords:** Aerobic exercise, Insulin resistance, Molecular mechanisms

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## Introduction

Insulin resistance (IR) occurs when tissues do not respond adequately to insulin stimulation, leading to an increased need for insulin to maintain normal function (1). The liver, skeletal muscle and adipose tissue are particularly prone to insulin resistance compared to other tissues (2). Elevated blood glucose levels result in increased insulin production, causing hyperinsulinemia (elevated circulating insulin). IR is often associated with both hyperglycemia and hyperinsulinemia (3). Its development can be influenced by genetic factors, such as mutations in insulin signaling genes, as well as environmental factors like physical activity and nutrition (4,5).

Key factors contributing to the development of IR include increased inflammatory mediators, dysregulated circulating metabolites, hormonal imbalances, oxidative stress, and altered enzymatic activity. Regular physical activity, especially aerobic exercise, has been shown to counteract these disturbances by enhancing insulin signaling and metabolic homeostasis through interconnected molecular adaptations. IR is a complex metabolic disorder associated with the pathophysiology of various chronic diseases. Therefore, identifying effective non-pharmacological strategies for its prevention and management is crucial. Among these strategies, regular physical activity, particularly aerobic exercise, has emerged as a potent intervention that improves insulin sensitivity through multiple molecular mechanisms.

### Molecular mechanisms of IR

Understanding IR requires a brief examination of the insulin signaling pathway in cells that are sensitive to IR, such as skeletal muscle cells, liver cells, and adipocytes. Insulin, an anabolic hormone, plays a crucial role in regulating cell growth and differentiation through gene expression and metabolic proteins. It promotes the absorption,

storage, and synthesis of nutrients while inhibiting the release of glycogen, proteins, and triglycerides into the bloodstream (6). The metabolic effects of insulin begin with the auto-phosphorylation of the insulin receptor, leading to the activation of insulin receptor substrate proteins (7). This process primarily activates the PI3K/Akt pathway, which controls glucose uptake, glycogen synthesis, lipid metabolism, and protein synthesis. Additionally, the ERK/MAPK pathway mainly influences cell growth and differentiation (8,9). Disruption of these signaling pathways can impair insulin action and contribute to the development of IR (10,11). While the main molecular mechanism of IR may involve disruptions in cell signaling through the insulin receptor, research suggests that any abnormalities in the proteins of the insulin pathway can disrupt insulin signal transmission within the cell, reducing or eliminating the regulatory effects of insulin. Various factors, including genetics, inflammatory mediators, circulating metabolites, hormones, oxidative stress, and obesity, play significant roles in the development of IR (12-14).

### 1. Genetics

Genetics is a key factor in determining susceptibility to insulin resistance. Research on twins indicates that 30–50% of the variability in insulin sensitivity and related characteristics is due to genetic factors (15). Studies show that there are common genetic factors influencing fasting insulin levels, HOMA-IR, insulin sensitivity measured by clamp tests, and various components of IR/metabolic syndrome phenotype, including obesity and dyslipidemia (16).

At the monogenic level, mutations in genes such as INSR and PPARG can significantly hinder insulin function and contribute to insulin resistance. Furthermore, research has shown that various genetic loci linked to insulin signaling, adipocyte biology, lipid

metabolism, and body fat distribution, play a role in determining an individual's risk of developing insulin resistance and type 2 diabetes (T2D) (16).

## 2. Inflammation

Chronic low-grade inflammation is now recognized as a major contributor to IR, particularly in obesity, where adipose tissue and skeletal muscle overexpress pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which are associated with, and predictive of, impaired insulin action (17). Evidence indicates that both systemic and tissue-specific inflammation can induce IR by interfering with the insulin signaling pathway. Although multiple tissues can contribute to the development of IR in the context of obesity, adipose tissue appears to play the predominant role. Adipocyte hypertrophy, which underlies obesity, is accompanied by structural and functional alterations in these cells. Hypertrophic fat cells produce significant amounts of inflammatory mediators and release them into the blood circulation. Inflammatory mediators released from adipose tissue, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , disrupt insulin signaling in skeletal muscle, liver, and adipose tissue through activation of stress-related serine kinases (18). These alterations impair IRS-1 signaling, reduce glucose uptake, and ultimately promote IR (19). Leukotriene B4 may also reduce insulin signaling in myocytes and hepatocytes (20,21). Collectively, human and animal studies support a causal role of this inflammation in the pathogenesis of IR and T2D (22).

## 3. Circulating metabolites

Circulating metabolites, by contributing to fundamental disturbances in the metabolism of energy-yielding substrates, play a pivotal role in the pathogenesis of IR. Elevated levels of free fatty acids and complex lipid species such as ceramides and diacylglycerols, derived from adipose tissue and dietary intake, accumulate in the liver and skeletal muscle, where they activate stress kinases and inhibit

Akt signaling, thereby impairing insulin-stimulated glucose uptake and exacerbating "lipotoxic" IR (23). Metabolomic studies further indicate that branched-chain and aromatic amino acids are consistently elevated in individuals with IR and prediabetes and that these elevations predict the future development of T2D (24). In obesity, excessive fatty acid metabolites activate PKC and protein phosphatase 2A, particularly in skeletal muscle and liver tissue (25). These molecular alterations impair IRS and Akt signaling, weaken insulin action, and promote lipotoxic IR (26).

## 4. Hormones

Multiple hormones modulate insulin action, and disturbances in their secretion or signaling play a fundamental role in the development of IR. Adipose tissue-derived hormones (adipokines) such as leptin and adiponectin are of particular importance: obesity is characterized by elevated circulating leptin with leptin resistance and reduced adiponectin, a profile that independently predicts impaired insulin sensitivity and the metabolic syndrome (27). Leptin resistance and pro-inflammatory adipokines enhance lipolysis, ectopic lipid deposition, and low-grade inflammation, whereas hypo-adiponectinemia diminishes AMPK activation and fatty acid oxidation, collectively disrupting insulin signaling in the liver and skeletal muscle (28). Counter-regulatory hormones-including glucocorticoids, growth hormone, glucagon, and catecholamines-oppose insulin action by stimulating hepatic glucose production and lipolysis; chronic elevations of these hormones in conditions such as Cushing's syndrome, acromegaly, stress states, or with exogenous glucocorticoid and growth hormone therapy lead to systemic IR and an increased risk of diabetes (29,30). Sex steroids also influence insulin sensitivity. Estrogens generally exert protective metabolic effects, whereas androgen excess is associated with impaired insulin action and hyperinsulinemia, particularly in conditions such as polycystic ovary syndrome

(31). Dysregulation of adipokines, counter-regulatory hormones, and sex steroids, together with nutrient oversupply and inflammation, drives the onset and progression of IR.

## 5. Oxidative stress

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, is a major contributor to IR. Obesity and chronic inflammation increase mitochondrial and NADPH oxidase-derived ROS in insulin-sensitive tissues, which in turn activate stress-responsive serine/threonine kinases such as JNK, IKK $\beta$ , and ASK1. These kinases phosphorylate insulin receptor substrate (IRS) proteins on inhibitory serine residues, thereby impairing downstream PI3K–Akt signaling and reducing glucose uptake (32). Mitochondrial oxidative stress can independently induce IR, as demonstrated in experimental models in which increased mitochondrial ROS disrupt insulin signaling in skeletal muscle and liver even before overt mitochondrial dysfunction becomes apparent (33). ROS-induced damage to mitochondrial DNA, lipids, and proteins further decreases oxidative capacity, promotes the accumulation of lipotoxic intermediates, and amplifies inflammatory signaling, establishing a vicious cycle that links oxidative stress, inflammation, dyslipidemia, and  $\beta$ -cell dysfunction to the onset and progression of IR and T2D (34). Excessive ROS production in adipocytes further impairs PI3K/Akt signaling, GLUT4 translocation, and glucose uptake, thereby exacerbating IR (35).

## 6. Enzymes activity

Multiple enzymes that regulate insulin signaling and local hormone or lipid metabolism play key roles in the development of IR. Stress-activated serine/threonine kinases such as JNK, IKK $\beta$ , mTOR/S6K1, and specific PKC isoforms are induced by inflammatory cytokines, free fatty acids, and oxidative stress, and they phosphorylate

insulin receptor substrate-1 (IRS-1) on specific serine residues (e.g., Ser307), thereby uncoupling IRS-1 from the insulin receptor and attenuating downstream PI3K–Akt signaling (36). Protein tyrosine phosphatase 1B (PTP1B), an endoplasmic reticulum–anchored phosphatase, dephosphorylates the insulin receptor and IRS proteins, acting as a major negative regulator of insulin action; overexpression or activation of PTP1B promotes IR, whereas its genetic deletion or pharmacological inhibition enhances insulin signaling (37). Enzymes that control local glucocorticoid activation, particularly 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1), increase intracellular cortisol levels in adipose tissue and muscle, leading to JNK activation, lipolysis, ectopic fat accumulation, and impaired Akt signaling. Overexpression of 11 $\beta$ -HSD1 induces glucocorticoid- and diet-induced IR in animal and cellular models, while its genetic or pharmacological inhibition ameliorates glucocorticoid- and diet-induced IR (38). Collectively, these findings indicate that enzymatic regulators at the level of insulin receptor signaling, phosphatase counter-regulation, and intracellular hormone metabolism integrate inflammatory and nutritional cues to initiate and maintain IR.

## Physical activities affect IR

If genetic reasons are ignored, IR is mostly due to a positive energy balance. This can originate from two sources: increased energy intake, lack of physical activity, or a combination of both. Regular physical activity, as one of the most effective non-pharmacological interventions to decrease IR incidence and control, has attracted researchers' attention. Studies show that various forms of physical activity reduce IR (39).

### 1. Effect on inflammation

One of the mechanisms by which physical activity reduces IR is its effect on systemic and tissue inflammation. Existing evidence suggests that physical activity reduces

inflammation by decreasing pro-inflammatory mediators and increasing anti-inflammatory mediators, thereby preventing the development and progression of IR.

### 1.1. Pro-inflammatory mediators

Regular physical activity reduces circulating levels of pro-inflammatory mediators, with much of this effect mediated through improvements in IR and the underlying inflammatory-metabolic milieu. Findings from a meta-analysis of 23 randomized clinical trials (n= 1350) demonstrated that in patients with T2D, regular physical activity significantly lowered CRP, TNF- $\alpha$ , and IL-6 levels—changes that correlated with improved glycemic status (40).

Hayashino et al. (2014) analyzed the results of 14 randomized controlled trials with 824 patients and concluded that physical activities, especially aerobic exercise, reduce CRP and IL-6 (41). These results have been confirmed in the studies of Xing et al. (2020), Papagianni et al. (2023), and Hejazi et al. (2023), who all reported reductions in TNF- $\alpha$ , IL-6, and CRP (42-44). Since circulating inflammatory mediators are among the most prominent factors in creating IR in tissues, it can be concluded that regular physical activities, especially aerobic exercises, prevent systemic inflammation from disrupting the insulin signaling pathway in peripheral tissues.

Several mechanisms may explain the anti-inflammatory effects of aerobic exercise. Regular aerobic activity improves adipocyte function, enhances mitochondrial activity, and reduces adipocyte size and lipid accumulation, thereby decreasing the release of inflammatory adipokines and free fatty acids into the circulation (45). Consequently, circulating TNF- $\alpha$  and IL-6 levels decline, reducing inflammation-induced disruption of insulin signaling in peripheral tissues (46-48). Aerobic exercise may also suppress inflammatory responses through negative regulation of TLR4 signaling in peripheral blood mononuclear cells (49).

### 1.2. Inflammatory adipokines

Obesity and physical inactivity increase the levels of pro-inflammatory adipokines such as resistin and leptin, leading to low-grade chronic inflammation and disruption of insulin signaling, followed by the development of insulin resistance (IR). Regular physical activity reduces IR by shifting the adipokine profile from a pro-inflammatory to an anti-inflammatory state (50). Evidence indicates that in obese young individuals, regular physical activity decreases circulating levels of leptin, resistin, and visfatin, and these changes are associated with improved markers of IR (51). In obesity and IR, resistin is generally regarded as a pro-inflammatory factor and a promoter of IR by enhancing NF- $\kappa$ B activity and increasing the expression of TNF- $\alpha$ , IL-6, and adhesion molecules (50).

A decrease in circulating resistin levels has been reported after eight weeks of aerobic exercise in postmenopausal women with high blood pressure. These findings show that aerobic exercise can reduce the adipokine resistin (52). Evidence suggests that in individuals with type 2 diabetes (T2D), resistance training (in combination with aerobic exercise) tends to induce a greater reduction in resistin levels compared to aerobic training alone or control conditions. A 52-week combined program of aerobic exercise (70–80% VO<sub>2</sub> max, 40 minutes, twice weekly) and high-intensity resistance training (80% of 1RM) significantly improved leptin, adiponectin, and resistin levels (53). The reduction in resistin observed with exercise is thought to result from decreased visceral fat mass and adipocyte size (50), attenuation of systemic inflammation (54), and diminished glucotoxic and lipotoxic stimuli that typically elevate resistin and other pro-inflammatory adipokines (50). Moreover, regular physical activity generally lowers circulating visfatin levels, which contributes to a reduction in IR by alleviating visfatin's pro-inflammatory effects and its desensitizing influence on insulin signaling. Several randomized controlled trials (RCTs) and meta-analyses have shown that regular exercise decreases plasma visfatin concentrations in populations with obesity, metabolic syndrome, or T2D. For instance, a 12-week combined aerobic and resistance training program in middle-aged obese women significantly reduced visfatin levels, accompanied by improvements in body composition and IR (55). Similarly, findings from

a meta-analysis indicated that in patients with T2D, regular physical activity, particularly combined aerobic and resistance training, significantly reduced visfatin levels and glycemic indices (56). Regular exercise appears to directly downregulate visfatin production by reducing visceral adipose tissue mass, as visfatin mRNA and protein expression are highest in VAT and positively correlated with adipocyte size. Through adipocyte atrophy, enhanced mitochondrial biogenesis, and increased fatty acid oxidation, physical activity mitigates lipotoxic stress and subsequently suppresses visfatin production (50).

Chemerin adipokine is also increased in obesity and increases IR by affecting the insulin signaling pathway. Increased concentrations of chemerin in circulation have been reported in obesity (57) and related diseases such as metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), and T2D (58). In addition, a positive correlation between serum chemerin and BMI, blood triglyceride level, waist-to-hip ratio, blood pressure, and IR, as well as an inverse correlation with HDL-cholesterol, has been observed in different populations (59,60). It has been reported that aerobic exercise in diabetic rats reduces chemerin. The reduction of chemerin plays a significant role in improving glucose and fat metabolism and fatty liver induced by aerobic exercise in diabetic rats. This is probably mediated by PPAR $\gamma$  to increase ATGL, lipoprotein lipase, and GLUT4 in peripheral metabolic organs. These changes can reduce diabetic metabolic complications (61). In overweight women, twelve weeks of aerobic exercise decreased the concentration of chemerin. This indicates the effect of aerobic exercise on improving the adipokine profile in overweight people (62).

### 1.3. Anti-Inflammatory adipokines

Aerobic exercise, along with the reduction of inflammatory adipokines, causes an increase in anti-inflammatory adipokines that can exert very positive effects on metabolism, especially the insulin signaling pathway. One of the most potent anti-inflammatory adipokines that increases with aerobic exercise is adiponectin. Obesity reduces adiponectin levels, which is associated with IR, cardiovascular diseases, NAFLD, and inflammation-related diseases (63,64). Adiponectin improves the insulin

signaling pathway in skeletal muscle cells and liver cells and reduces IR and other metabolic disorders. On the other hand, adiponectin inhibits the production of TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , exerting its anti-inflammatory effect. It has been reported that aerobic exercise is one of the most significant stimuli for adiponectin production and release. An increase in adiponectin after aerobic exercise has been reported in premenopausal women (65), obese children (66), obese postmenopausal women (67), and diabetic rats (68). The key point regarding the increase of adiponectin with aerobic exercise is that it creates significant changes in glucose uptake and IR in peripheral tissues. The reason for this, apart from increased release, is the increased expression of its receptors in skeletal muscle tissue. This leads to glucose absorption and fatty acid oxidation in the muscle (69).

Regular physical activity, particularly aerobic, resistance, or combined exercise, elevates circulating levels of other anti-inflammatory adipokines such as emilin-1, vaspin, and apelin in obese, overweight, and T2D populations, thereby mitigating IR. Emilin-1, primarily secreted from the stromal vascular fraction of visceral adipose tissue, decreases in obesity and exhibits an inverse correlation with IR (70). In male smokers, eight weeks of aerobic exercise increased emilin-1 levels, improved the lipid profile, and reduced IR (71). Similar findings have been reported in obese men (72). Thus, exercise-induced elevations in emilin-1 enhance muscle glucose uptake, suppress hepatic gluconeogenesis and adipose tissue inflammation, and improve insulin sensitivity.

### 1.4. Anti-Inflammatory myokines

Changes in the myokine profile represent another key mechanism by which physical activity attenuates IR. Regular physical activity substantially enhances insulin sensitivity by modulating myokine secretion increasing insulin-sensitizing myokines while suppressing those that impair insulin action. These myokines exert effects on skeletal

muscle, adipose tissue, liver, and even the brain through well-defined signaling pathways (e.g., AMPK, JAK/STAT, p38-MAPK, PI3K-Akt), thereby reducing lipotoxicity and inflammation while promoting glucose uptake (73). Skeletal muscle serves as the primary site of insulin-stimulated glucose disposal and a major endocrine organ. Muscle contraction during exercise triggers the release of multiple myokines (e.g., IL-6, irisin, IL-15, myonectin), which act in autocrine, paracrine, and endocrine fashions to regulate glucose and lipid metabolism. Physical inactivity blunts this myokine response, fostering an inflammatory milieu that exacerbates IR, whereas regular exercise restores a "healthy" myokine profile (74,75). Among exercise-induced myokines, IL-6 and irisin play central roles in improving insulin sensitivity. Muscle-derived IL-6 exerts anti-inflammatory effects by suppressing TNF- $\alpha$  expression and activating AMPK-mediated oxidative metabolism (76). Irisin, released following PGC-1 $\alpha$  activation during aerobic exercise, enhances GLUT4 translocation, promotes glucose uptake, and stimulates browning of white adipose tissue, collectively improving systemic insulin sensitivity (73,77,78). Accordingly, exercise-induced irisin improves IR both locally (via enhanced muscle glucose uptake/oxidation) and systemically (via adipose browning).

IL-15 is another exercise-responsive myokine involved in glucose homeostasis. Increased circulating IL-15 following aerobic and resistance exercise promotes GLUT4 translocation, mitochondrial oxidative activity, and skeletal muscle glucose uptake, thereby contributing to improved insulin sensitivity (79,80).

Myostatin negatively regulates skeletal muscle mass and is closely associated with obesity and IR. Regular aerobic exercise reduces myostatin expression while improving insulin-stimulated glucose disposal, suggesting that suppression of myostatin contributes to exercise-induced improvements in insulin sensitivity (81,82).

## 2. Circulating metabolites

### 2.1. Circulating free fatty acids

Regular physical activity partially improves insulin sensitivity by altering the release, uptake, storage, and oxidation of circulating free fatty acids (FFAs) in tissues. These changes mitigate the chronic "lipotoxic" stress imposed by FFAs on the liver and skeletal muscle, modulate inflammation, and thereby attenuate IR. A single bout of sympatho-adrenergic activation enhances adipose tissue lipolysis and blood flow, elevating circulating FFAs during moderate-to-long-duration aerobic exercise to supply fuel for active muscles. This transient elevation is physiologically adaptive and accompanied by robust mitochondrial oxidation, preventing the accumulation of lipotoxic intermediates (83).

In contrast, a period of aerobic training enhances muscle capacity for FFA oxidation both at rest and during activity (84). Regular aerobic exercise also improves adipose tissue insulin sensitivity, thereby more effectively suppressing insulin-mediated lipolysis; consequently, postprandial or clamp-level insulin infusions elicit greater reductions in circulating FFAs. A systematic review and meta-analysis further indicate that regular physical activity enhances adipose tissue insulin sensitivity, particularly when assessed via tracer-based FFA appearance rates or the ADIPO-IR index (85). Aerobic exercise elevates circulating adiponectin and muscle adiponectin receptor expression, activating AMPK to boost FFA oxidation and insulin sensitivity, ultimately lowering circulating FFA levels. Consequently, the reduction in circulating FFAs following regular physical activity is associated with attenuated IR.

### 2.2. Circulating branched-chain and aromatic amino acids

Favorable alterations in branched-chain amino acids (BCAAs; leucine, isoleucine, valine) and aromatic amino acids (AAAs; phenylalanine, tyrosine, tryptophan) induced by aerobic exercise are associated with

improved IR. Elevated BCAA and AAA levels are consistently linked to obesity, IR, and future T2D risk, with physical activity modulating both their concentrations and metabolism to support enhanced insulin function (86,87). Exercise interventions that improve insulin sensitivity often normalize or modulate BCAA/AAA profiles, although findings across studies are heterogeneous. In individuals with PCOS, eight weeks of moderate-intensity aerobic exercise improved the IR-associated amino acid profile (both BCAAs and AAAs) in parallel with better insulin action, independent of weight loss (86). In obese American Indian youth, obesity correlated with markedly elevated BCAAs and AAAs positively with body fat and negatively with insulin sensitivity. Sixteen weeks of aerobic exercise enhanced fitness but did not significantly alter insulin sensitivity or most amino acid levels, suggesting that when exercise elicits modest metabolic effects, BCAA/AAA concentrations may remain relatively stable (88). In adults with T2D or NAFLD, 12 weeks of combined aerobic and resistance exercise reduced intrahepatic fat and improved peripheral insulin sensitivity without significantly lowering plasma BCAA levels. A cross-sectional association between higher BCAAs and greater intrahepatic fat persisted irrespective of physical activity levels. Overall, regular physical activity reliably improves IR, whereas its effects on fasting circulating BCAA/AAA levels are variable: in some contexts, they decrease relative to controls or normalize; in others, they remain unchanged despite enhanced insulin action. Aerobic exercise upregulates the activity and expression of key mitochondrial BCAA catabolic enzymes, particularly the branched-chain  $\alpha$ -keto acid dehydrogenase (BCKDH) complex and its regulatory phosphatase PP2Cm, in skeletal muscle and liver. This promotes greater BCAA oxidation and ketoacid derivative clearance, lowering circulating BCAAs and their accumulation in insulin-sensitive tissues, especially in obese and IR individuals (89,90). Aerobic exercise

prevents the buildup of BCAA-derived acylcarnitines and other mitochondrial stress/IR-linked intermediates via enhanced BCAA disposal. By reducing BCAA availability and boosting their catabolism, aerobic exercise attenuates tonic mTORC1 activation by amino acids and facilitates IRS-1-AKT signaling recovery. In obese mice, exercise enhanced insulin-stimulated AKT phosphorylation in muscle and liver, an effect largely abolished by BCAA supplementation during training (89,90). In this context, it has been reported that 12 weeks of aerobic exercise in diet-induced obese mice reduced body weight and plasma branched-chain amino acid (BCAA) concentrations, changes that were associated with improved insulin sensitivity in subcutaneous white adipose tissue (sWAT) (91).

Aromatic amino acids (AAAs) are strongly associated with IR and with future risk of developing diabetes, and frequently rise in parallel with BCAAs in insulin-resistant states (86). Mechanistically, elevated AAAs may reflect impaired hepatic amino acid catabolism, altered splanchnic extraction, and broader metabolic inflexibility. In women with PCOS, baseline phenylalanine and tyrosine concentrations were higher than in controls and accompanied by IR; after 8 weeks of moderate-intensity aerobic training, these differences disappeared in parallel with improvements in insulin sensitivity and cardiorespiratory fitness, suggesting that exercise can normalize AAA levels as part of broader hepatic and systemic metabolic adaptation (86).

Direct molecular data on exercise-induced changes in AAA metabolism are more limited than for BCAAs. Nevertheless, by reducing intrahepatic fat, enhancing hepatic insulin signaling, and improving mitochondrial function, regular physical activity likely augments hepatic uptake and oxidation of AAAs and thereby contributes to lowered or normalized circulating levels in insulin-resistant individuals. In addition, exercise-induced improvements in gut barrier integrity

and microbiome composition may decrease the production of AAA-derived metabolites implicated in metabolic disease (92,93).

### 2.3 Hormones

Regular physical activity acutely elevates counter-regulatory hormones such as glucocorticoids (cortisol), growth hormone (GH), glucagon, and catecholamines to mobilize fuels and maintain blood glucose levels during exercise, whereas chronic training improves insulin sensitivity by attenuating excessive responses, enhancing tissue adaptations, and optimizing metabolic signaling (94). Regular exercise (e.g., aerobic/resistance,  $\geq 150$  min/week) reduces resting insulin levels and HOMA-IR in a dose-dependent manner, with counter-regulatory responses to the same absolute intensity becoming blunted indicative of improved efficiency and reduced stress (95,96). Exercise-induced changes in catecholamine/GH/cortisol/glucagon concentrations enhance cAMP/PKA signaling while upregulating PGC-1 $\alpha$ /NRFs to lower ROS/ceramides that serine-phosphorylate and inhibit IRS-1. Concurrently, elevated GH/glucagon activates JAK-STAT and PKA, synergizing with increased AMPK to boost GLUT4/AS160 and Akt activation, thereby preventing mTORC1 overactivation and associated negative feedback on insulin signaling. Collectively, these adaptations enhance peripheral tissue insulin signaling and attenuate IR (96).

### 2.4 Oxidative stress

Regular physical activity attenuates oxidative stress and improves insulin sensitivity by enhancing antioxidant defenses and modulating ROS-related signaling pathways. Moderate aerobic exercise increases physiological ROS production, which activates adaptive pathways, thereby promoting GLUT4 translocation, mitochondrial biogenesis, and glucose uptake (97-99). Concurrently, regular exercise reduces pathological oxidative stress markers and lipid peroxidation, ultimately

restoring insulin signaling and improving glycemic control (100,101).

### 2.5 Enzymes activity

Regular physical activity reduces the levels and activity of protein tyrosine phosphatase 1B (PTP1B) a negative regulator of insulin signaling thereby alleviating insulin resistance (IR) in tissues such as the liver and skeletal muscle. This reduction enhances the tyrosine phosphorylation of the insulin receptor and IRS-1/2, strengthening downstream PI3K/Akt activation to improve glucose uptake and suppress hepatic glucose production (102). Both aerobic and strength training lower PTP1B protein content and its binding to IR/IRS-1 in the liver and muscle of obese and aged models, with effects persisting for up to 16 hours post-exercise. Strength training (15 sessions) reduces both basal and insulin-stimulated PTP1B independently of weight loss while improving pyruvate tolerance (103,104). Regular physical activity lowers PTP1B through anti-inflammatory pathways, including decreased NF- $\kappa$ B/TNF- $\alpha$  recruitment to the PTP1B promoter and increased SIRT1 expression, which suppresses PTP1B transcription. The reduction in PTP1B enhances IRS-1<sup>Y612</sup> phosphorylation, Akt<sup>S473</sup> activation, and FOXO1 phosphorylation while downregulating PEPCK/G6Pase to inhibit gluconeogenesis. EGR-1/PTP1B signaling is also diminished in muscle (103).

Conversely, regular physical activity decreases the expression and activity of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) in skeletal muscle and liver, thereby curtailing local cortisone-to-cortisol conversion and mitigating glucocorticoid excess and IR. This tissue-specific adaptation suppresses cortisol-induced lipogenesis, gluconeogenesis, and IRS-1 serine phosphorylation while enhancing insulin signaling via PI3K/Akt. Four weeks of voluntary wheel running reduced skeletal muscle and hepatic 11 $\beta$ -HSD1 protein levels. In hamsters, these changes decreased visceral

fat mass by approximately 66% while concurrently elevating hepatic 11 $\beta$ -HSD1 activity to limit ectopic cortisol action (105). Exercise suppresses 11 $\beta$ -HSD1 transcription through AMPK/SIRT1 activation and NF- $\kappa$ B downregulation, reducing cortisol access to the glucocorticoid receptor (GR) and thereby inhibiting FOXO1/PEPCK-mediated gluconeogenesis; lower GR desensitizes glucocorticoid signaling. In muscle, this enhances IRS-1 tyrosine phosphorylation and Akt activation, improving glucose uptake independently of weight loss.

## Conclusion

Regular physical activity, especially aerobic and resistance exercise, significantly enhances insulin sensitivity through various interconnected molecular mechanisms. Exercise reduces pro-inflammatory cytokines and adipokines while boosting anti-inflammatory myokines and adipokines. It also improves lipid and amino acid metabolism, lowers oxidative stress, and modulates hormonal and enzymatic pathways involved in insulin resistance (IR).

These adaptations work together to restore insulin signaling, enhance GLUT4-mediated glucose uptake, and improve metabolic homeostasis. Consequently, regular exercise serves as an effective non-pharmacological

strategy for preventing and managing IR and related metabolic disorders.

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## Authors' contributions

F.S: Conceptualization, literature review, and original draft preparation.

M.A A and S. A: Supervision, methodological oversight, validation, and writing-review & editing.

M. P and S. R: Consultation and writing-review & editing.

All authors contributed to the final approval of the manuscript.

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