REVIEW ARTICLE

Exercise, GLUT4 and Skeletal Muscle Glucose Uptake: Advances and Emerging Directions

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ABSTRACT

Skeletal muscle is the principal site of postprandial glucose disposal, and its exercise-stimulated glucose uptake is a cornerstone of metabolic health. This process depends on the glucose transporter GLUT4, which is regulated by both insulin- and contraction-stimulated pathways. Understanding exercise-driven GLUT4 dynamics is crucial for combating insulin resistance and type 2 diabetes. Over the past decades, research has progressed from descriptive physiology to a mechanistic framework, identifying key insulin-independent regulators such as AMPK, Rab GTPases, SNAREs, Rac1, and redox mediators. Emerging methodologies, including high-resolution imaging, quantum dot tracking, and proteomics profiling, have provided insight into vesicle docking, fusion, and signalling convergence. Comparative exercise studies reveal modality-specific effects (e.g., HIIT) and that regulation varies by age, sex, and metabolic status, highlighting the need for population-specific approaches. Nevertheless, important questions remain: the kinetics of GLUT4 exocytosis and endocytosis in human muscle remain incompletely defined, and the integration of redox signalling with canonical kinases such as AMPK and CaMKII is poorly understood. Moreover, most mechanistic insights are derived from rodent models or young male subjects, limiting generalisability to elderly, female, or insulin-resistant populations. Addressing these gaps requires translational studies combining advanced imaging, CRISPR reporters, and molecular phenotyping with human exercise interventions. Integrating exercise with pharmacological or nutritional strategies may also unlock synergistic effects on glucose regulation. In conclusion, GLUT4 sits at the nexus of exercise biology and metabolic disease. Elucidating its regulation across diverse populations is pivotal for advancing precision exercise medicine and developing targeted interventions for insulin resistance and type 2 diabetes.

Keywords:
Exercise, skeletal muscle, glucose uptake, GLUT4, insulin resistance.

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INTRODUCTION

The ability of skeletal muscle to increase glucose uptake during exercise has been recognised for nearly a century, with early studies using arteriovenous balance and isotopic tracers establishing muscle contraction as a potent driver of glucose disposal.[1] This foundational work laid the groundwork for later discoveries that muscle glucose uptake can be stimulated independently of insulin, offering key insights into how exercise preserves glycemic control in insulin-resistant states.[2] Central to this process is the glucose transporter type 4 (GLUT4), identified in the late 20th century as the primary mediator of insulin- and contraction-stimulated glucose uptake.[3] GLUT4 accounts for the majority of postprandial glucose disposal in skeletal muscle and is tightly regulated by two complementary pathways: insulin signaling, which mobilizes GLUT4 via phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) cascades and SNARE-mediated vesicle fusion,[4] and contraction-stimulated pathways involving AMP-activated protein kinase (AMPK), calcium-calmodulin signaling, and nitric oxide (NO).[5] In the long term, chronic exercise enhances GLUT4 expression through transcriptional regulators such as myocyte enhancer factor 2 (MEF2), contributing to improved insulin sensitivity and metabolic health.[6]

Rapid advances have refined our understanding of GLUT4 regulation, revealing a complex interplay between energy sensors (AMPK), vesicle trafficking proteins such as Ras-related protein in brain (Rab8a, Rab10), and cytoskeletal elements such as Ras-related C3 botulinum toxin substrate 1 (Rac1) and soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNAREs).[7] Despite these developments, key gaps remain, particularly regarding the kinetics of GLUT4 trafficking in human tissues, the roles of reactive oxygen species (ROS) and NO, and regulatory differences across sex, age, and metabolic status.[8] This review aims to synthesise recent insights into exercise-regulated GLUT4 dynamics, emphasizing molecular mechanisms, methodological innovations, and translational implications for metabolic disease. Particular focus is given to vesicle trafficking kinetics, redox signaling, and population-specific adaptations, to inform personalised strategies for improving skeletal muscle glucose uptake.[9] The next section outlines the current consensus on exercise-regulated GLUT4 dynamics, setting the stage for recent advances and future directions.

Current Understanding

To understand recent advances in the next section, it is first important to outline current knowledge of how exercise influences skeletal muscle glucose uptake through tightly integrated vascular and metabolic mechanisms. For instance, in moderate to intense exercise, vasodilatory signals such as NO and prostacyclin increase skeletal muscle blood flow, thereby enhancing substrate delivery.[10] This rise in perfusion is accompanied by greater capillary recruitment, expanding the exchange surface for glucose and insulin. Although these adaptations are impaired in obesity and insulin resistance, they can be restored with regular exercise training.[11] At the systemic level, hepatic glucose output also rises as insulin levels fall, ensuring adequate arterial glucose availability to sustain contractile activity.[12] Additionally, redistribution of blood flow toward nutritive microvascular pathways further optimises glucose access at the tissue level.[13]

At the cellular level, these hemodynamic adaptations converge with contraction-induced mobilisation of GLUT4 to the sarcolemma, coupling increased delivery with enhanced transporter availability.[14] Classic studies established that GLUT4 trafficking involves small guanosine triphosphatase (GTPases) and SNARE fusion machinery, with signaling input from both insulin- and contraction-activated pathways.[15] Insulin drives vesicle fusion through endomembrane trafficking routes, whereas contraction engages distinct, parallel signaling processes to achieve GLUT4 translocation.[16] Contraction also recruits mediators such as AMPK, Rac1, and reactive oxygen/nitric oxide species, which operate independently of insulin to ensure glucose uptake[17] (Figure 1).

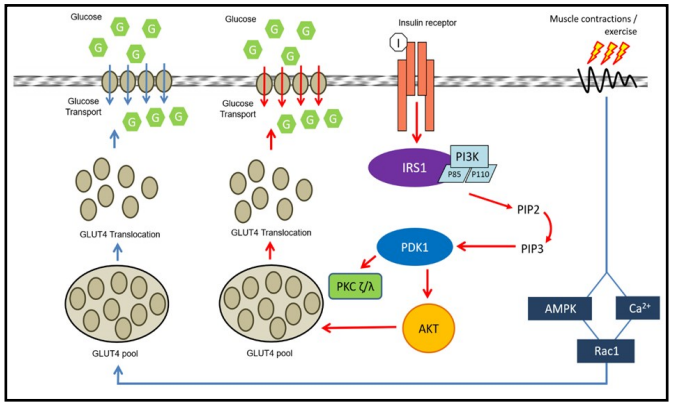

Figure 1: Dual Pathways of GLUT4-Mediated Glucose Uptake in Skeletal Muscle. Glucose uptake in skeletal muscle occurs through two major, complementary mechanisms. Insulin signaling activates the insulin receptor and downstream IRS–PI3K–PDK1–Akt signaling, promoting translocation of GLUT4 vesicles from intracellular pools to the sarcolemma. In parallel, muscle contraction/exercise stimulates insulin-independent pathways involving AMPK, Ca^{2+}-related signaling, and Rac1, which also drive GLUT4 translocation. These converging pathways increase the number of GLUT4 transporters at the cell surface, enhancing glucose entry into muscle cells.

Following GLUT4 translocation, glucose enters the myofiber and is rapidly phosphorylated by hexokinase II (HKII), the rate-limiting enzyme for intracellular glucose metabolism. Exercise enhances HKII expression and activity through AMPK-dependent mechanisms, ensuring efficient trapping of glucose as glucose-6-phosphate (G-6-P).[18] This step is subject to feedback inhibition by G-6-P to avoid excess metabolite accumulation.[19] Muscle glycogen availability also modulates these processes: low glycogen amplifies AMPK activation and GLUT4 translocation, while high glycogen suppresses these responses, reflecting a substrate-sensing mechanism that helps balance energy supply and demand.[20]

Nutritional status further shapes exercise-mediated glucose metabolism. Short-term high-fat feeding, for example, impairs glycogen repletion and alters post-exercise glucose handling, highlighting the importance of diet–exercise interactions in metabolic regulation.[21] These coordinated responses become especially critical at higher exercise intensities, where AMPK activation enhances both GLUT4 translocation and HKII activity to maximize glucose disposal.[22]

Together, this body of work establishes a framework in which vascular adaptations, GLUT4 trafficking, and intracellular metabolism act in concert to facilitate glucose uptake during exercise. Chronic adaptations, such as increased GLUT4 abundance and improved muscle oxidative capacity, further enhance both basal and stimulated glucose uptake, contributing to long-term improvements in insulin sensitivity and metabolic health.[6] Despite these advances, questions remain regarding how contraction-specific signals uniquely regulate GLUT4, the degree of redundancy between insulin- and exercise-activated pathways, and the influence of muscle fiber type on glucose handling.[23]

Recent Advances

Advances in Exercise-Stimulated Signaling Pathways

Over the past decade, substantial progress has been made in understanding how exercise stimulates GLUT4 translocation in skeletal muscle through insulin-independent signaling. A key player in this process is AMPK, particularly the α2 isoform, which becomes activated during muscle contraction and initiates GLUT4 mobilization independently of insulin.[24] One major way AMPK promotes GLUT4 trafficking is by phosphorylating Rab GTPase-activating proteins (RabGAPs), including Tre-2/Bub2/Cdc16 domain family members (TBC1D1 and TBC1D4). This phosphorylation inhibits their suppressive effects on Rab proteins such as Rab8A and Rab10, which in turn coordinate the movement of GLUT4-containing vesicles toward the sarcolemma for membrane fusion and glucose uptake.[7]

Furthermore, phosphorylation of TBC1D4 by both AMPK and AKT also reveals an important signaling convergence point. For instance, AMPK-mediated phosphorylation at specific sites can modulate or enhance subsequent AKT-dependent phosphorylation, forming a molecular basis for the additive effects of exercise and insulin on skeletal muscle glucose uptake.[25] Moreover, beyond Rab GTPase regulation, vesicle docking and fusion at the membrane are coordinated by soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) complexes. Hence, vesicle-associated membrane protein 2 (VAMP2) and the syntaxin-binding protein Munc18c play key roles in vesicle fusion in insulin -responsive tissues. While the roles of VAMP2 and Munc18c in contraction-stimulated trafficking are less well-defined than in insulin-mediated pathways, the underlying mechanisms have been characterized largely in adipose and cellular model systems and are thought to extend to skeletal muscle, where these proteins are believed to contribute meaningfully to GLUT4 vesicle fusion.[26]

Muscle contraction also engages multiple insulin-independent signaling modules that promote GLUT4 mobilization. These include calcium-sensitive messengers (e.g., nicotinic acid adenine dinucleotide phosphate (NAADP) and cyclic ADP-ribose), Rac1-dependent actin remodeling, and the CaMKII–Kalirin–Rac1 signaling cascade. Together, these pathways bypass classical insulin signaling to support glucose uptake during exercise.[27] Collectively, these findings underscore the robustness of the exercise-activated GLUT4 pathway, driven by redundant and complementary signaling systems that ensure glucose uptake even under insulin-resistant conditions.

Redox Biology in GLUT4 Regulation

Redox signaling, particularly involving ROS and NO, has emerged as a potential modulator of contraction-induced GLUT4 translocation, although its role in humans remains less well established than in experimental models. Much of the mechanistic insight currently derives from rodent studies. In these models, both hydrogen peroxide (H_2O_2) and NO, especially that produced by neuronal nitric oxide synthase (nNOS), enhance skeletal muscle glucose uptake during contraction via pathways that can

operate independently of AMPK. This redox-mediated effect is attenuated by antioxidant treatment such as N-acetylcysteine, particularly during high-intensity exercise, supporting a physiological signaling role for ROS rather than purely oxidative damage.[28] However, glucose uptake is preserved in nNOS-deficient mice, suggesting compensatory mechanisms, possibly involving AMPK or other parallel pathways, can sustain glucose transport in the absence of nNOS.[29]

In humans, evidence for redox involvement is more limited and largely functional rather than mechanistically resolved. Studies indicate that NADPH oxidase 2 (NOX2)-derived ROS contribute to contraction-stimulated glucose uptake, and pharmacological inhibition of NO synthase can reduce exercise-induced skeletal muscle glucose transport.[30] These findings suggest that redox signaling participates in human muscle glucose regulation, but the precise molecular targets and their relationship to canonical GLUT4 trafficking pathways remain unclear. The relative contribution of ROS versus NO also appears to depend on exercise intensity, with ROS-related signaling becoming more prominent at higher workloads.[31]

Overall, while redox modulation of glucose uptake is well supported in rodent muscle, translation of specific molecular mechanisms to humans remains incomplete, and current human data should be interpreted as evidence for involvement rather than definitive pathway mapping. Further research is needed to determine how redox signals integrate with established contraction-mediated pathways and whether mechanisms defined in animal models apply directly to human skeletal muscle physiology.

Conceptual Integration of Proposed Mechanisms

Current evidence supports several, not mutually exclusive, models for how redox signals influence GLUT4 trafficking during contraction.[28] One model proposes that ROS, particularly H_2O_2 derived from NOX2, act upstream of canonical metabolic kinases, modulating AMPK, CaMKII, or other contraction-sensitive kinases to amplify established GLUT4 trafficking pathways.[27] A second model suggests more direct redox effects on cytoskeletal remodelling and vesicle trafficking proteins, potentially influencing Rac1 activation or SNARE-associated processes involved in GLUT4 vesicle docking and fusion.[27] A third possibility is that NO-related signalling operates through cyclic GMP- and Ca^{2+}-dependent mechanisms that intersect with contraction-stimulated pathways at multiple nodes.[28] Importantly, these mechanisms are not mutually exclusive and may vary with exercise intensity, redox load, and muscle metabolic state.[31]

At present, the strongest mechanistic support for these pathways comes from rodent models, whereas in humans, redox signalling is supported mainly by functional and pharmacological evidence rather than direct molecular mapping.[31]

Methodological Innovations in GLUT4 Trafficking Research

Recent advances in imaging and proteomic technologies have significantly enhanced our ability to study GLUT4 regulation in skeletal muscle at both molecular and cellular resolution. High-resolution fluorescence microscopy and live-cell imaging now allow direct visualization of GLUT4 dynamics in intact human muscle fibers, moving beyond earlier reliance on indirect markers.[32] In addition, quantum dot labeling has further improved temporal resolution by enabling long-term, high-fidelity tracking of individual GLUT4 vesicles during docking and fusion at the plasma membrane.[33]

Proteomic profiling has also yielded new insights, identifying previously unrecognised GLUT4 interactors such as vacuolar protein sorting-associated protein 13A / 13C (VPS13A and VPS13C), which suggest that the regulatory network extends beyond the canonical Rab–SNARE machinery.[34] Proximity labeling combined with mass spectrometry has revealed dynamic phosphorylation sites on TBC1D1 and TBC1D4, providing greater resolution of AMPK- and Akt-dependent signaling mechanisms.[25] Importantly, many of these methods have been applied in both rodent and human systems, increasing the translational relevance of basic discoveries. However, caution is warranted when interpreting findings

from studies that rely on protein overexpression cell lines, as these conditions may not fully capture the behavior of GLUT4 vesicles in native muscle tissue.

Differential Effects of Exercise Modalities

Different types of exercise training exert modality-specific effects on GLUT4 expression, translocation, and glucose uptake capacity in skeletal muscle. Aerobic endurance training consistently enhances insulin sensitivity and GLUT4 translocation, primarily by increasing muscle capillarization and mitochondrial function, which together improve glucose delivery and oxidation efficiency.[35] Resistance training, while less studied in this context, promotes glucose uptake by increasing skeletal muscle mass and total glucose disposal capacity. Some evidence also suggests that resistance exercise may activate distinct intracellular signaling pathways, such as those involving mechanical stress or mechanistic target of rapamycin complex 1 (mTORC1), which could contribute to GLUT4 mobilization. Notably, detraining reduces insulin-stimulated glucose uptake when normalized to muscle mass, underscoring the metabolic importance of maintaining muscle tissue.[36]

High-intensity interval training (HIIT) has emerged as a particularly potent stimulus for GLUT4 upregulation. Remarkably, as few as six HIIT sessions can increase GLUT4 protein expression by up to 369% in individuals with type 2 diabetes, alongside improvements in mitochondrial function and glycolipid metabolism.[37] Clinical trials also show that HIIT enhances skeletal muscle glucose extraction not merely through increased perfusion, but by improving intracellular glucose uptake mechanisms, including both insulin receptor signaling and insulin-independent pathways such as AMPK activation. These adaptations make HIIT a promising intervention for insulin-resistant individuals.[38] While these findings clearly demonstrate the distinct benefits of different exercise modalities, future studies should investigate whether combining aerobic and resistance training produces additive or synergistic effects on GLUT4 regulation, particularly in populations at risk for type 2 diabetes.

GLUT4 Regulation Across Special Populations

Recent studies suggest that GLUT4 regulation is strongly influenced by factors such as age, sex, and metabolic status, although the underlying mechanisms are not yet fully understood. In insulin-resistant and obese individuals, GLUT4 expression is reduced in both skeletal muscle and adipose tissue, contributing to impaired glucose disposal, possibly through chronic inflammation, lipid accumulation, and disruptions in insulin signaling.[39] Importantly, exercise can bypass these signaling defects by activating contraction-induced pathways such as AMPK, thereby restoring GLUT4 translocation and improving glycemic control.[40] Aging is also associated with reduced GLUT4 abundance and diminished insulin sensitivity. However, both endurance and resistance training have been shown to restore GLUT4 function and improve metabolic health in elderly muscle.[40] This finding suggests that exercise remains a viable intervention across the lifespan, even when basal GLUT4 expression is compromised.

Sex differences further contribute to variability in GLUT4 regulation. Women generally exhibit higher GLUT4 expression and greater insulin sensitivity despite higher adiposity, which may be explained by hormonal influences such as estrogen-mediated enhancement of glucose uptake and potential differences in muscle fiber composition.[41] Nevertheless, the evidence is not uniform, with some studies reporting that men display distinct hepatic and peripheral insulin responses.[42] Collectively, these findings underscore the importance of tailoring exercise strategies to specific populations. Future mechanistic studies that account for sex, age, and metabolic phenotype will be critical for optimising exercise-based interventions targeting GLUT4 regulation.

Future Directions

Clarifying GLUT4 Trafficking Kinetics in Human Skeletal Muscle

A major unresolved challenge in the field is the incomplete understanding of GLUT4 trafficking kinetics in human skeletal muscle. Rodent studies using intravital and confocal imaging have demonstrated that GLUT4 vesicles rapidly insert into the membrane during

contraction but are reinternalized more slowly afterward, providing key insights into the temporal sequence of trafficking events.[43] Whether these dynamics accurately represent human physiology, however, remains uncertain.

Although recent imaging platforms have begun to visualize GLUT4 movement in human muscle fibers, most data still come from indirect measures or model systems that may not fully capture endogenous vesicle cycling.[8] The next step is to establish how GLUT4 exocytosis, docking, and reinternalization are quantitatively regulated in intact human tissue during and after exercise.

Future studies should aim to integrate real-time imaging with in situ biochemical assays to resolve how the timing of GLUT4 cycling contributes to both normal glucose tolerance and pathological states such as insulin resistance. Defining these kinetics in humans would provide a critical translational bridge between cellular mechanisms described in animal models and clinical exercise interventions.

Resolving the Role of Redox Signaling in Exercise-Induced Glucose Uptake

ROS and NO are consistently generated during muscle contraction, but their direct contributions to GLUT4 translocation in vivo remain unclear. Rodent studies show that hydrogen peroxide and nNOS-derived NO promote GLUT4 mobilization through AMPK-independent pathways, and antioxidant treatment can blunt this effect.[28] In humans, NOX2-derived ROS has been implicated as a regulatory signal, and pharmacological NOS inhibition has been shown to reduce exercise-stimulated glucose uptake.[30] A major challenge is disentangling redox-dependent effects from canonical signaling cascades such as AMPK, Rac1, and CaMKII, which are often co-activated during exercise. Future progress will require models that enable selective inhibition or knockout of specific redox enzymes, ideally in human muscle or advanced translational systems, to determine whether ROS and NO function as primary effectors, permissive cofactors, or modulatory amplifiers of contraction-mediated GLUT4 trafficking.

Mechanistic Studies in High-Risk Populations

A significant translational knowledge gap exists in understanding GLUT4 regulation in populations at highest metabolic risk, including obese, prediabetic, and elderly individuals. These groups consistently exhibit reduced GLUT4 abundance and defects in vesicle trafficking, yet few studies have pinpointed the precise molecular disruptions or identified the signaling nodes where regulation fails.[9] This lack of mechanistic insight limits the development of targeted therapies. Future research should prioritize in vivo analyses using human muscle biopsies and engineered muscle constructs derived from high-risk individuals. Key questions include whether AMPK and Rac1 signaling remain responsive to contraction, whether SNARE complex assembly is impaired, and whether chronic training can reverse vesicle tethering or membrane fusion defects. Addressing these questions will be essential for translating GLUT4 biology into precision exercise prescriptions and novel pharmacological strategies to combat metabolic diseases.

Integrative Exercise-Pharmacological Strategies

Advances in GLUT4 biology now open the possibility of combining exercise with pharmacological or nutritional agents to amplify glucose uptake. AMPK activators such as 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), although limited in clinical applicability, have demonstrated the potential to mimic contraction-induced GLUT4 translocation in both rodents and humans.[44] Emerging evidence also suggests that natural bioactives like tectorigenin can upregulate GLUT4 through AMPK and protein kinase A catalytic subunit alpha (PKACα) signaling, highlighting nutritional compounds as possible adjuncts to exercise.[45] In addition, NO donors may enhance GLUT4-mediated uptake indirectly by improving skeletal muscle perfusion.[46]

Biotechnological approaches such as gene modulation of transcriptional regulators (e.g., MEF2 and GLUT4 enhancer factor) and the development of engineered muscle constructs represent exciting opportunities for precision upregulation of GLUT4.[47] Future studies should systematically evaluate these interventions in combination

with exercise, particularly in insulin-resistant populations, to determine whether they can yield additive or synergistic improvements in glucose regulation.

Personalised Exercise Medicine for GLUT4 Regulation

A key future direction is the personalisation of exercise interventions for GLUT4 regulation, guided by genetic, epigenetic, demographic, and health-related factors. Polymorphisms in metabolic genes, including those influencing GLUT4 expression and signaling efficiency, have been linked to differences in both insulin sensitivity and exercise responsiveness.[48] Age-specific training protocols have already demonstrated improvements in GLUT4 expression and muscle quality in elderly populations [49], while sex-specific differences in GLUT4 regulation and insulin sensitivity suggest that tailored exercise strategies may be needed for women and men.[41]

In addition, patients with comorbidities such as diabetic kidney disease demonstrate variable responses to aerobic, resistance, and HIIT protocols, underscoring the importance of individualised intervention frameworks.[50] Moving forward, integrating genomics, molecular phenotyping, and clinical profiling will be critical to realize precision exercise medicine strategies that optimize GLUT4 regulation and improve metabolic health outcomes.

CONCLUSION

In summary, exercise-induced regulation of GLUT4 represents one of the most powerful natural mechanisms for maintaining glucose homeostasis. Through converging insulin and contraction pathways, skeletal muscle ensures continuous glucose uptake under both fed and fasting conditions. Advances in molecular and imaging techniques have revealed the complexity of this system, where AMPK, redox mediators, small GTPases, and SNARE proteins operate in an integrated network that sustains glucose transport even in insulin-resistant states.

While significant mechanistic insight has been gained, key challenges remain, particularly in bridging cellular mechanisms with human physiological responses and in addressing underrepresented populations, including women, older adults, and metabolically diverse individuals. Overcoming these gaps will require multidisciplinary and translational approaches that combine molecular profiling with clinical exercise research.

Therefore, understanding and harnessing GLUT4 biology offers a pathway to more precise and equitable strategies for metabolic health. This approach could transform exercise science from general recommendations into targeted, evidence-based interventions for metabolic disease prevention and management.

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