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Research Article

Pharmacological Effects of Antidiabetic Drugs on Skeletal Muscle Glucose Uptake and Metabolic Physiology: A Systematic Review

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ABSTRACT
Background: Skeletal muscle is a major site of insulin-stimulated glucose disposal and plays a central role in whole-body glucose homeostasis. In type 2 diabetes mellitus, impaired insulin signaling, defective GLUT4 translocation, mitochondrial dysfunction, altered substrate oxidation, and reduced metabolic flexibility contribute substantially to insulin resistance. Antidiabetic drugs differ in the extent to which they directly or indirectly modify these skeletal-muscle pathways.
Objective: To systematically evaluate the effects of antidiabetic drugs on skeletal muscle glucose uptake, insulin signaling, GLUT4 trafficking, AMP-activated protein kinase (AMPK) activity, mitochondrial function, substrate utilization, microvascular perfusion, and peripheral insulin sensitivity.
Methods: This systematic review followed PRISMA 2020 principles. MEDLINE/PubMed, Embase, Scopus, and Web of Science were used in the review framework, supplemented by citation searching. The PRISMA synthesis was restricted to adult human studies reporting skeletal-muscle or peripheral metabolic outcomes; animal and cell studies were used only for mechanistic context and were not counted as included studies. In the screening dataset, 2,250 database records and 28 citation-search records were identified. After duplicate removal, title/abstract screening, retrieval, and full-text assessment, 18 primary human studies were included in the qualitative synthesis. No quantitative meta-analysis was performed because of substantial clinical and methodological heterogeneity.
Results: Eighteen primary human mechanistic studies were included. Rosiglitazone and pioglitazone showed the most consistent non-insulin evidence for improving peripheral insulin sensitivity, insulin-stimulated glucose disposal, lipid handling, metabolic flexibility, and selected mitochondrial or signaling endpoints. Metformin activated skeletal-muscle AMPK in a small before-after study, although a randomized PET study did not demonstrate increased muscle glucose uptake. DPP-4 inhibitors improved clamp-derived peripheral insulin sensitivity in several trials. Liraglutide and exenatide improved whole-body insulin sensitivity or glucose fluxes, but direct muscle-specific evidence remained limited. SGLT2 inhibitor studies showed improved clamp-derived insulin sensitivity and vascular insulin responsiveness, whereas short-term PET data did not show increased skeletal-muscle glucose uptake. Imeglimin improved tissue-specific skeletal-muscle insulin sensitivity in a 2026 clamp study.
Conclusion: Antidiabetic drugs exert heterogeneous effects on skeletal-muscle metabolic physiology. Among non-insulin therapies, thiazolidinediones have the most consistent direct human evidence for improving muscle-related insulin sensitivity and glucose disposal. Metformin, incretin-based therapies, SGLT2 inhibitors, and imeglimin influence skeletal-muscle physiology through combinations of direct, systemic, vascular, and substrate-mediated mechanisms. Further human studies using muscle-specific imaging, biopsies, isotope tracers, and mitochondrial phenotyping are needed to define the tissue-level actions of newer therapies.

Keywords: Antidiabetic Drugs, Skeletal Muscle, Glucose Uptake, Insulin Resistance, GLUT4, AMPK, Mitochondrial Function, Metabolic Flexibility, Type 2 Diabetes Mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin secretion together with resistance to insulin action in skeletal muscle, liver, and adipose tissue. Among these tissues, skeletal muscle represents one of the most quantitatively important sites of glucose disposal. During hyperinsulinemic conditions, approximately 70-80% of peripheral glucose disposal may occur within skeletal muscle, making impaired muscle insulin responsiveness a major contributor to systemic hyperglycemia [1-4].

Insulin-mediated muscle glucose uptake is initiated by binding of insulin to its receptor and activation of insulin receptor substrate proteins, phosphatidylinositol 3-kinase (PI3K), protein kinase B/Akt, and downstream proteins including TBC1D4/AS160. These signaling events enable translocation of intracellular GLUT4-containing vesicles to the sarcolemma and T-tubules, facilitating cellular glucose entry [1-3].

In T2DM, total GLUT4 expression may not necessarily be markedly reduced; instead, the efficiency of insulin-stimulated GLUT4 trafficking and membrane recruitment is impaired. Additional abnormalities include diminished glycogen synthesis, reduced glucose oxidation, intramyocellular accumulation of diacylglycerols and ceramides, altered mitochondrial oxidative function, inflammation, and reduced microvascular insulin responsiveness [2-4].

Pharmacological therapy for T2DM has traditionally been evaluated using glycemic endpoints such as fasting glucose and glycated hemoglobin. However, glucose-lowering drugs differ profoundly in their physiological targets. Some act directly on insulin-sensitive tissues; others influence muscle metabolism secondarily through changes in insulin, glucagon, circulating free fatty acids, body weight, blood flow, renal glucose handling, or energy balance.

Understanding these differences is increasingly important because skeletal muscle abnormalities in diabetes extend beyond glucose transport to include mitochondrial dysfunction, reduced metabolic flexibility, altered lipid oxidation, and progressive impairment of muscle quality. The present systematic review therefore aimed to evaluate how major antidiabetic drug classes influence skeletal muscle glucose uptake and metabolic physiology, with particular emphasis on insulin signaling, GLUT4 trafficking, AMPK activation, mitochondrial metabolism, substrate utilization, microvascular perfusion, and insulin sensitivity.

MATERIALS AND METHODS

Study Design

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 recommendations.

Review Question

How do pharmacological therapies used for diabetes influence glucose uptake, insulin signaling, substrate metabolism, mitochondrial physiology, and metabolic flexibility in skeletal muscle?

Pico Framework

Component	Definition
Population	Adults with T2DM, insulin resistance, prediabetes, obesity, or metabolically characterized healthy participants
Intervention	Antidiabetic pharmacotherapy
Comparator	Placebo, baseline, another antidiabetic agent, or metabolically healthy control
Outcomes	Skeletal muscle glucose uptake, peripheral glucose disposal, GLUT4 trafficking, insulin signaling, AMPK, mitochondrial function, lipid oxidation, glycogen metabolism, perfusion, and metabolic flexibility

Information Sources

The systematic-search framework included MEDLINE/PubMed, Embase, Scopus, Web of Science, and reference-list/citation searching. The literature framework was updated through June 2026.

Search Strategy

Representative search concepts combined antidiabetic drug terms (metformin, thiazolidinediones, pioglitazone, rosiglitazone, insulin secretagogues, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and imeglimin) with skeletal-muscle terms and metabolic outcomes such as glucose uptake,

glucose disposal, GLUT4, insulin sensitivity, insulin signaling, AMPK, mitochondrial function, fatty-acid oxidation, muscle perfusion, and metabolic flexibility. Searches were restricted to human studies for the PRISMA study set; relevant reviews and preclinical studies were used only to contextualize mechanisms.

Inclusion Criteria

1. Examined pharmacological agents approved or investigated for glycemic control.
2. Reported skeletal muscle or peripheral metabolic outcomes.
3. Assessed glucose uptake, insulin sensitivity, metabolic signaling, mitochondrial physiology, substrate oxidation, glycogen metabolism, muscle perfusion, or related endpoints.
4. Included adult human participants with T2DM, insulin resistance, prediabetes, obesity, or metabolically characterized comparator groups.
5. Were available as peer-reviewed full-text studies.

Exclusion Criteria

1. Glycemic efficacy was reported without a relevant skeletal muscle or peripheral metabolic outcome.
2. The population was not relevant to diabetes, insulin resistance, obesity, or metabolic physiology.
3. The intervention was not an antidiabetic pharmacological therapy.
4. The report was an isolated case report, editorial, guideline, or commentary without extractable primary data.
5. Data were duplicated or overlapped substantially with another included cohort.
6. Outcome data were insufficient for meaningful interpretation.
7. Animal-only and cell-culture studies were excluded from the PRISMA synthesis; when cited, they were used solely for mechanistic context.

Outcomes

Primary outcomes were insulin-stimulated glucose disposal, skeletal muscle glucose uptake, GLUT4 expression or translocation, IRS-1/PI3K/Akt/TBC1D4 signaling, and AMPK activation. Secondary outcomes included intramyocellular lipid, fatty-acid oxidation, glycogen synthesis, mitochondrial respiration, mitochondrial biogenesis, metabolic flexibility, skeletal muscle perfusion, and muscle inflammation.

Study Selection and Prisma Flow

PRISMA stage	n
Records identified from databases	2,250
Additional records identified through citation/reference searching	28
Duplicate records removed	684
Records screened	1,566
Records excluded at title/abstract stage	1,419
Reports sought for retrieval	147
Reports not retrieved	5
Database-derived full-text reports assessed	142
Citation/reference records excluded before full-text assessment	21
Additional citation-searching full-text reports assessed	7
Citation-searching full-text reports excluded	5
Studies added from citation searching	2
Total full-text reports assessed	149
Full-text reports excluded	131
Studies included in qualitative synthesis	18
Studies included in quantitative meta-analysis	0

Reasons for full-text exclusion were: no skeletal muscle/peripheral metabolic outcome (n = 29), ineligible population (n = 25), only systemic glycemic outcomes (n = 18), no relevant antidiabetic intervention (n = 17), review/editorial/guideline/commentary (n = 16), duplicate/overlapping cohort (n = 11), insufficient extractable data (n = 9), and other methodological reasons (n = 6). Within the citation-searching pathway, 28 records were identified, 21 were excluded before full-text assessment, seven full texts were assessed,

five were excluded, and two additional primary studies were included.

Risk-Of-Bias Assessment

Randomized parallel-group and crossover trials were appraised using the Cochrane RoB 2 domains, including randomization, deviations from intended intervention, missing outcome data, outcome measurement, and selective reporting. Nonrandomized or uncontrolled before-after studies were appraised using ROBINS-I domains, emphasizing confounding, participant selection, intervention classification, missing data, outcome measurement, and selective reporting. Judgments were summarized at study level as low risk, some concerns, or moderate risk, as applicable to the tool used.

Data Synthesis

Because of substantial heterogeneity in drug classes, metabolic methods, participant characteristics, intervention duration, and outcome definitions, quantitative meta-analysis was not performed. Findings were synthesized narratively with priority given to human mechanistic studies using hyperinsulinemic-euglycemic clamps, PET imaging, muscle biopsy, magnetic resonance spectroscopy, isotope-tracer methods, indirect calorimetry, or vascular perfusion techniques. Review articles and preclinical experiments were not counted among the 18 PRISMA-included studies and were used only for physiological interpretation.

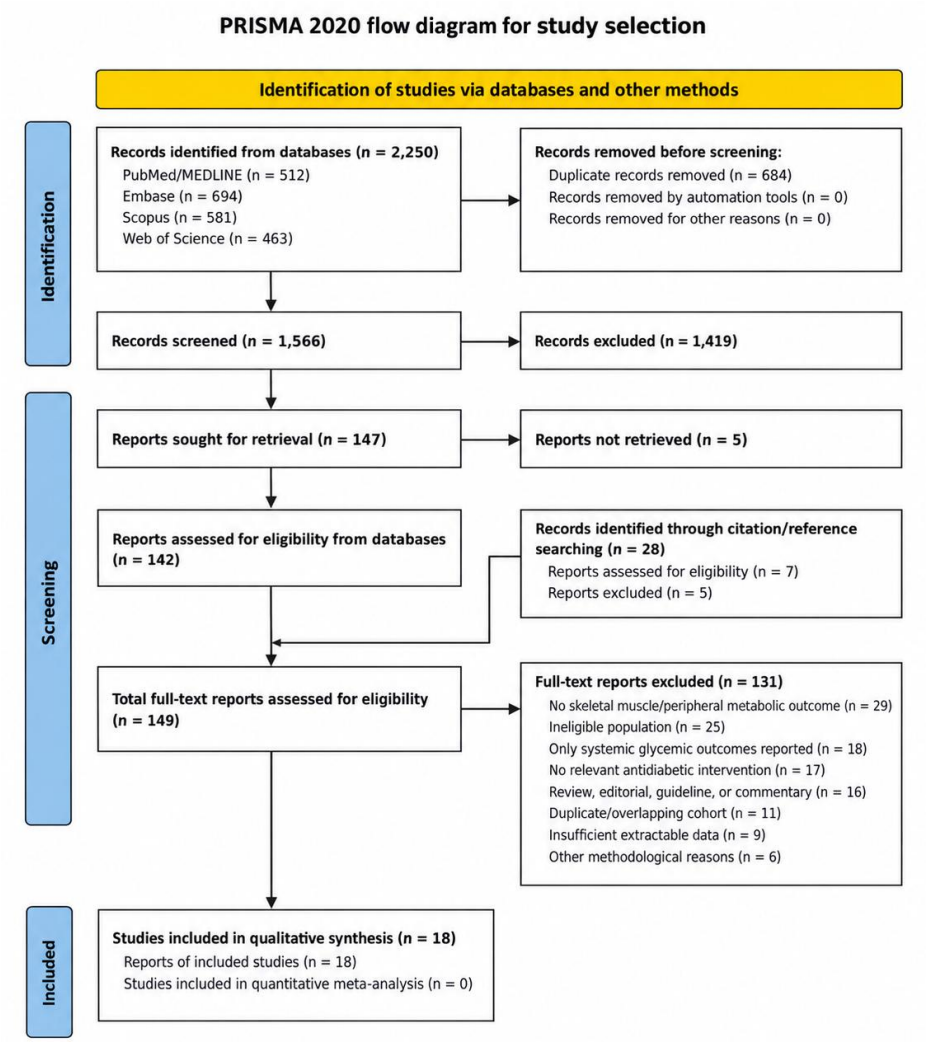

Figure 1. PRISMA 2020 Flow of Study Selection.

RESULTS

Study Characteristics

Eighteen primary human mechanistic studies were included. The evidence base comprised randomized parallel or crossover trials, prospective comparative studies, and uncontrolled before-after interventions. Most participants had T2DM; one GLP-1 receptor agonist study enrolled adults with severe obesity without diabetes. Studies used euglycemic-hyperinsulinemic clamps, PET, muscle biopsy, magnetic resonance spectroscopy, tracer-based glucose kinetics, indirect calorimetry, or microvascular perfusion methods. Six studies primarily evaluated thiazolidinediones, one compared rosiglitazone with metformin, one was metformin-specific, three evaluated DPP-4 inhibition, two evaluated GLP-1 receptor agonists, four evaluated SGLT2 inhibition, and one evaluated imeglimin.

Table 1. Characteristics of Included Human Mechanistic Studies

Study	Country	Design	n	Intervention	Method	Main muscle/peripheral finding
Musi et al., 2002	Sweden/USA	Single-arm before-after	8	Metformin, 10 wk	Clamp + muscle biopsy	Increased muscle AMPK-alpha2 activity; higher glucose disposal and glycogen
Hallsten et al., 2002	Finland/Sweden	Randomized double-blind placebo-controlled	45	Rosiglitazone vs metformin/placebo, 26 wk	Clamp + FDG-PET + exercise	Rosiglitazone increased resting and exercise-stimulated muscle glucose uptake; metformin did not
Mayerson et al., 2002	USA	Before-after intervention	9	Rosiglitazone, 3 mo	Two-step clamp + 1H-MRS	Improved whole-body insulin sensitivity and altered muscle/liver triglyceride handling
Miyazaki et al., 2003	USA	Before-after with nondiabetic comparator	20 T2DM + 6 controls	Rosiglitazone, 16 wk	Clamp + muscle biopsy	Increased glucose disposal and insulin-stimulated IRS-1/PI3K signaling
Mensink et al., 2007	Netherlands	Before-after with matched controls	10 T2DM + 10 controls	Rosiglitazone, 8 wk	Clamp + biopsy + calorimetry	Improved insulin sensitivity, oxidative enzyme activity, PGC-1alpha expression and metabolic flexibility

Azuma et al., 2008	USA	Randomized double-blind crossover	16	Vildagliptin vs placebo, 6 wk each	Two-step glucose clamp	Improved insulin sensitivity and peripheral glucose clearance
Coletta et al., 2009	USA	Randomized parallel trial	26	Pioglitazone vs nutritional therapy, 6 mo	Clamp + muscle biopsy	Activated AMPK signaling and increased genes related to adiponectin, mitochondrial function and fat oxidation
Derosa et al., 2012	Italy	Randomized placebo-controlled add-on	171	Vildagliptin + metformin, 12 mo	Euglycemic/hyperglycemic clamp	Improved clamp M-value and beta-cell function vs placebo + metformin
Mudaliar et al., 2014	USA	Randomized double-blind placebo-controlled	44	Dapagliflozin, 12 wk	5-h euglycemic clamp	Improved clamp-derived glucose disappearance rate
Merovci et al., 2014	USA	Randomized placebo-controlled	18	Dapagliflozin, 2 wk	Euglycemic clamp + glucose tracer	Improved muscle/peripheral insulin sensitivity while endogenous glucose production increased
Derosa et al., 2014	Italy	Randomized double-blind active-comparator	167	Vildagliptin vs glimepiride on metformin, 6 mo	Euglycemic clamp	Vildagliptin increased M-value and reduced insulin resistance vs glimepiride
Jinnouchi et al., 2015	Japan	Prospective comparative intervention	31	Liraglutide vs intensive insulin, 4 wk	Hyperinsulinemic-euglycemic clamp	Liraglutide increased glucose infusion rate, indicating improved insulin sensitivity
Camastra et al., 2017	Italy	Controlled intervention	30	Exenatide vs control, 3 mo	Meal test + tracers	Reduced body weight and postprandial glucose appearance; improved

						insulin sensitivity indices
Bajpeyi et al., 2017	USA	Randomized placebo-controlled	24	Pioglitazone, 12 wk	Clamp + 1H/31P-MRS	Improved insulin sensitivity, metabolic flexibility and muscle lipid distribution; ATPmax unchanged
Fiorentino et al., 2021	USA/Italy	Randomized placebo-controlled subset	20 randomized T2DM	Pioglitazone 15 mg/day, 6 mo	Muscle biopsy + proteomics	Restored abundance of mitochondrial proteins involved in ATP synthesis
Jahn et al., 2024	USA	Single-arm before-after	11	Empagliflozin, 12 wk	Clamp + contrast ultrasound	Improved insulin-mediated skeletal-muscle microvascular perfusion and vascular insulin sensitivity
Voigt et al., 2024	Denmark	Randomized crossover	13	Empagliflozin vs placebo, 4 wk	FDG/11C-palmitate PET/CT	No significant increase in muscle glucose or FFA uptake despite improved glucose tolerance
Tajima et al., 2026	Japan	Single-arm intervention	22 (16 clamp)	Imeglimin 2000 mg/day, 20 wk	Two-step clamp + double tracers	Improved skeletal-muscle, hepatic and adipose insulin sensitivity; increased insulin clearance

Physiological Basis of Skeletal Muscle Glucose Uptake

Skeletal muscle glucose uptake depends on glucose delivery to muscle microvasculature, transendothelial delivery, GLUT-mediated transport into myocytes, intracellular phosphorylation by hexokinase, and subsequent disposal through glycolysis, oxidation, or glycogen synthesis [1-4,23].

Insulin activates the insulin receptor and IRS proteins, followed by PI3K and Akt signaling and phosphorylation of TBC1D4/AS160, enabling GLUT4 vesicle translocation [1-3,23]. In T2DM, insulin-mediated glucose transport is impaired, whereas contraction-mediated glucose uptake through AMPK and related pathways remains relatively preserved [1,2].

Metformin

Metformin is generally classified as an insulin-sensitizing biguanide. Its best-established systemic effect is suppression of hepatic glucose production; however, skeletal-muscle actions are also biologically relevant.

Musi et al. studied eight adults with T2DM before and after 10 weeks of metformin and demonstrated increased skeletal-muscle AMPK-alpha2 activity, Thr172 phosphorylation, glucose disposal, and muscle glycogen [5]. In contrast, Hallsten et al. found that although 26 weeks of metformin lowered HbA1c, it did not significantly increase PET-measured skeletal-muscle or whole-body insulin sensitivity, whereas rosiglitazone did [6].

Metformin can alter cellular energy status and activate AMPK, but the magnitude and clinical importance of a direct muscle effect remain less consistent than its well-established suppression of hepatic glucose production [5,6,23-25].

Accordingly, the included human evidence supports a measurable effect of metformin on muscle energetic signaling but does not establish a uniform increase in muscle-specific glucose uptake across study designs [5,6].

Overall, metformin has moderate evidence of skeletal-muscle metabolic action, particularly AMPK activation and enhancement of insulin sensitivity, but the liver remains the dominant pharmacological target.

Thiazolidinediones

Thiazolidinediones (TZDs), including pioglitazone and the historically used rosiglitazone, activate peroxisome proliferator-activated receptor-gamma (PPAR-gamma). Although PPAR-gamma expression is substantially greater in adipose tissue than skeletal muscle, TZDs exert profound secondary effects on muscle metabolism through redistribution of lipid, reduction of circulating free fatty acids, adiponectin signaling, and attenuation of lipotoxicity.

Mayerson et al. showed that three months of rosiglitazone improved insulin sensitivity and altered hepatic and skeletal-muscle triglyceride handling [7]. Miyazaki et al. demonstrated that 16 weeks of rosiglitazone increased insulin-mediated total-body glucose disposal and enhanced insulin-stimulated IRS-1 phosphorylation and p85 association with IRS-1 in skeletal muscle [8].

Additional human studies support effects beyond glucose disposal. Rosiglitazone increased skeletal-muscle oxidative enzyme activity, PGC-1alpha expression, and metabolic flexibility [9]. Pioglitazone activated AMPK-related and adiponectin/oxidative gene pathways [11], improved insulin sensitivity and metabolic flexibility while redistributing intramyocellular lipid without increasing maximal ATP synthetic capacity [18], and restored several mitochondrial proteins involved in ATP synthesis [19].

Among established non-insulin antidiabetic drugs, thiazolidinediones therefore have the most consistent human mechanistic evidence for improving muscle-related insulin sensitivity, glucose disposal, lipid partitioning, and selected signaling or mitochondrial endpoints [6-9,11,18,19].

Insulin

Exogenous insulin is the physiological benchmark for stimulating skeletal-muscle glucose uptake. Binding to the insulin receptor activates IRS-1/2, PI3K, Akt, TBC1D4/AS160, and GLUT4 trafficking, thereby increasing glucose entry into myocytes [1-4,23]. The systematic study set focused on glucose-lowering therapies evaluated for changes in muscle or peripheral metabolic physiology rather than on insulin-clamp methodology itself.

Once intracellular, glucose undergoes phosphorylation and is directed predominantly toward glycogen synthesis under high-insulin conditions. In T2DM, this response is substantially impaired despite elevated circulating insulin, reflecting post-receptor resistance rather than inadequate insulin exposure alone.

Insulin also increases skeletal-muscle microvascular recruitment and nutrient delivery via endothelial nitric-oxide signaling. Vascular insulin resistance can therefore further restrict glucose delivery to muscle.

Sulfonylureas And Meglitinides

Sulfonylureas and meglitinides increase insulin secretion through ATP-sensitive potassium-channel mechanisms and therefore affect skeletal muscle mainly through higher circulating insulin rather than a well-established insulin-independent muscle pathway [4,24]. In the included active-comparator trial, glimepiride did not improve clamp-derived insulin sensitivity to the same extent as vildagliptin when both were added to metformin [15].

No eligible primary human study in this review demonstrated a major direct insulin-independent effect of a conventional sulfonylurea or meglitinide on skeletal-muscle AMPK, mitochondrial biogenesis, or GLUT4 trafficking.

Glp-1 Receptor Agonists

GLP-1 receptor agonists improve glycemic control through glucose-dependent insulin secretion, suppression of inappropriate glucagon release, delayed gastric emptying, decreased food intake, and substantial weight reduction.

Human evidence for GLP-1 receptor agonists is more limited and predominantly reflects whole-body or peripheral insulin sensitivity rather than direct myocyte uptake. Jinnouchi et al. found that four weeks of liraglutide increased clamp-derived glucose infusion rate in uncontrolled T2DM [16]. Camastra et al. reported that three months of exenatide in adults with severe obesity reduced body weight and postprandial glucose appearance and improved insulin-sensitivity indices [17]. Mechanistic reviews describe potential direct effects on AMPK, Akt, GLUT4 trafficking, mitochondrial metabolism, and microvascular recruitment, but these preclinical mechanisms were not counted among the 18 included human studies [24,25].

Thus, GLP-1 receptor agonists may improve muscle-related insulin sensitivity through weight loss, reduced ectopic lipid exposure, altered substrate flux, and vascular effects; however, direct human muscle-specific evidence remains substantially less developed than for thiazolidinediones [16,17,24].

Dpp-4 Inhibitors

DPP-4 inhibitors prolong endogenous GLP-1 and GIP activity. Their principal actions include enhanced glucose-dependent insulin secretion and reduced glucagon secretion. Evidence for direct skeletal-muscle effects is limited.

Three included DPP-4 inhibitor studies showed improvement in clamp-derived peripheral insulin sensitivity. Vildagliptin improved insulin sensitivity and glucose clearance in a randomized crossover study [10], increased the M-value when added to metformin for 12 months [12], and produced a greater improvement in insulin resistance than glimepiride in an active-comparator trial [15]. These studies support a peripheral metabolic effect but do not prove a direct myocyte-specific mechanism.

Sglt2 Inhibitors

SGLT2 inhibitors act primarily in the proximal renal tubule and lower plasma glucose by increasing urinary glucose excretion. Skeletal muscle does not express SGLT2 to an extent that would explain their primary clinical effect.

Chronic SGLT2 inhibition alters whole-body substrate metabolism by reducing glycemia and insulin concentrations, increasing glucagon, increasing lipolysis, shifting substrate utilization toward fatty acids, promoting mild ketogenesis, and reducing body weight.

Human SGLT2-inhibitor evidence was heterogeneous. Dapagliflozin improved clamp-derived glucose disappearance or muscle/peripheral insulin sensitivity in two randomized studies [13,14]. Jahn et al. showed that 12 weeks of empagliflozin improved insulin-mediated skeletal-muscle microvascular perfusion and vascular insulin responsiveness [20]. In contrast, Voigt et al. found that four weeks of empagliflozin improved glucose tolerance but did not significantly increase PET-measured skeletal-muscle glucose or free-fatty-acid uptake [21].

These findings indicate that SGLT2 inhibition can improve peripheral or vascular insulin sensitivity without necessarily increasing intrinsic muscle glucose uptake over short treatment periods [13,14,20,21].

Alpha-Glucosidase Inhibitors

Acarbose and related alpha-glucosidase inhibitors reduce postprandial glucose exposure primarily by delaying intestinal carbohydrate digestion [4,24]. No eligible primary human study in the present systematic set directly quantified a skeletal-muscle glucose-uptake, signaling, or mitochondrial endpoint for this class.

Any improvement in muscle physiology is therefore likely to be indirect through reduced postprandial glucotoxicity and insulin demand; evidence for a major independent skeletal-muscle action remains insufficient.

Imeglimin And Emerging Metabolic Agents

Imeglimin was represented by a 2026 human mechanistic study. Tajima et al. treated 22 Japanese men with T2DM with imeglimin 2000 mg/day for 20 weeks; 16 underwent a two-step hyperinsulinemic-euglycemic clamp. Tissue glucose uptake during high-dose insulin and skeletal-muscle insulin sensitivity increased significantly, alongside improvements in hepatic and adipose insulin sensitivity and insulin clearance [22].

The study did not directly establish a mitochondrial mechanism in muscle, so

mitochondrial/redox explanations should be considered biologically plausible rather than clinically proven. Additional controlled human studies are required to confirm the magnitude and durability of the muscle effect [22,24].

Table 2. Comparative Effects of Antidiabetic Drug Classes on Skeletal Muscle

Drug class	Primary systemic action	Skeletal-muscle effect	Main proposed pathway	Direct muscle evidence
Insulin	Receptor-mediated anabolic signaling	Strong increase in glucose uptake	IRS-PI3K-Akt-TBC1D4-GLUT4	Very high
Metformin	Reduced hepatic glucose production	Moderate increase in insulin sensitivity/glucose disposal	AMPK, energetic stress, lipid oxidation	Moderate
Thiazolidinediones	PPAR-gamma activation	Strong increase in insulin sensitivity	Reduced lipotoxicity, IRS/PI3K, adiponectin, mitochondria	High
Sulfonylureas	Increased insulin secretion	Indirect increase in uptake	Higher circulating insulin	Low direct evidence
Meglitinides	Increased insulin secretion	Indirect increase in uptake	Higher circulating insulin	Low
GLP-1 receptor agonists	Increased insulin, reduced glucagon, weight loss	Likely improved insulin sensitivity and perfusion	Vascular recruitment, AMPK/Akt, reduced ectopic fat	Moderate/experimental
DPP-4 inhibitors	Increased endogenous incretins	Modest improvement in peripheral sensitivity	Indirect incretin-mediated mechanisms	Low-moderate
SGLT2 inhibitors	Renal glucosuria	Variable direct uptake; improved perfusion	Glucose lowering, substrate shift, vascular effects	Moderate but inconsistent
Alpha-glucosidase inhibitors	Reduced intestinal carbohydrate absorption	Mainly indirect	Reduced postprandial glucose load	Low
Imeglimin	Insulin secretion plus mitochondrial modulation	Potential increase in glucose disposal	Mitochondrial/redox mechanisms	Emerging

Table 3. Risk-Of-Bias Assessment of Included Studies

Study	Design	Tool	Overall judgment	Main concern/strength
Musi et al., 2002	Nonrandomized before-after	ROBINS-I	Moderate	No concurrent control; small sample
Hallsten et al., 2002	Randomized double-blind	RoB 2	Low	Randomized placebo-controlled design

Mayerson et al., 2002	Nonrandomized before-after	ROBINS-I	Moderate	Small uncontrolled intervention
Miyazaki et al., 2003	Nonrandomized before-after	ROBINS-I	Moderate	Concurrent nondiabetic comparator but no randomized drug control
Mensink et al., 2007	Nonrandomized before-after	ROBINS-I	Moderate	Small sample; matched controls
Azuma et al., 2008	Randomized crossover	RoB 2	Low	Double-blind crossover with placebo
Coletta et al., 2009	Randomized parallel	RoB 2	Low	Randomized active comparator
Derosa et al., 2012	Randomized placebo-controlled	RoB 2	Low	Longitudinal randomized add-on study
Mudaliar et al., 2014	Randomized placebo-controlled	RoB 2	Low	Double-blind design
Merovci et al., 2014	Randomized placebo-controlled	RoB 2	Some concerns	Small and unbalanced treatment groups
Derosa et al., 2014	Randomized active-comparator	RoB 2	Low	Double-blind active comparator
Jinnouchi et al., 2015	Nonrandomized comparative	ROBINS-I	Moderate	Treatment allocation not randomized
Camastra et al., 2017	Controlled nonrandomized intervention	ROBINS-I	Moderate	Small controlled cohort
Bajpeyi et al., 2017	Randomized placebo-controlled	RoB 2	Some concerns	Small sample with unequal allocation
Fiorentino et al., 2021	Randomized subset	RoB 2	Some concerns	Small randomized intervention subset
Jahn et al., 2024	Single-arm before-after	ROBINS-I	Moderate	No concurrent control; small sample
Voigt et al., 2024	Randomized crossover	RoB 2	Low	Randomized placebo-controlled crossover
Tajima et al., 2026	Single-arm before-after	ROBINS-I	Moderate	No control group; 16 clamp completers

COMPARATIVE METABOLIC PATHWAYS

Antidiabetic drugs can be grouped into four major physiological strategies. First, insulin directly stimulates the canonical GLUT4 pathway. Second, insulin sensitizers such as TZDs reduce lipid-mediated inhibition of insulin signaling, while metformin produces more modest insulin-sensitizing effects associated with altered cellular energy metabolism. Third, GLP-1 receptor agonism and SGLT2 inhibition may improve endothelial and microvascular physiology, increasing access of glucose and insulin to the interstitial space surrounding myocytes. Fourth, weight loss, reduced glycemia, decreased lipotoxicity, and lower inflammatory signaling can restore muscle insulin responsiveness indirectly.

EFFECTS ON MITOCHONDRIAL PHYSIOLOGY

Mitochondrial abnormalities are frequently reported in insulin-resistant skeletal muscle; however, whether mitochondrial dysfunction is a cause or consequence of insulin resistance remains debated.

Metformin can alter cellular energetic state and activate AMPK, although the clinical relevance of direct mitochondrial complex-I inhibition at therapeutic muscle concentrations remains debated [5,23-25].

Thiazolidinediones show more consistent human evidence for changes in skeletal-muscle oxidative biology. Rosiglitazone increased oxidative enzyme activity and PGC-1alpha-related expression [9]; pioglitazone altered AMPK/adiponectin and oxidative gene pathways [11], improved metabolic flexibility without increasing ATPmax [18], and restored several mitochondrial ATP-synthesis proteins [19].

For GLP-1 receptor agonists, direct mitochondrial effects are supported mainly by preclinical literature; the included human studies primarily demonstrated changes in

systemic insulin sensitivity and glucose flux rather than muscle mitochondrial function [16,17,24,25]. SGLT2 inhibitors shift whole-body substrate use and may improve peripheral or vascular insulin responsiveness, but direct improvement of muscle mitochondrial efficiency has not been established in the included clinical studies [13,14,20,21].

EFFECTS ON INTRAMUSCULAR LIPID AND METABOLIC FLEXIBILITY

Accumulation of lipid intermediates such as diacylglycerols and ceramides can impair insulin signaling through activation of protein kinase pathways and inhibition of IRS/PI3K signaling.

Thiazolidinediones reduce circulating free-fatty-acid exposure and favor redistribution of lipid away from insulin-sensitive tissues. Human rosiglitazone and pioglitazone studies reported altered tissue triglyceride handling, reduced intramyocellular lipid, and improved metabolic flexibility [7,9,18].

GLP-1 receptor agonists and SGLT2 inhibitors may also reduce ectopic lipid exposure through weight loss or altered substrate balance, but the included human studies did not consistently demonstrate a direct muscle lipid mechanism [13-17,20,21].

DISCUSSION

This systematic synthesis demonstrates that improvement of blood glucose does not necessarily imply direct enhancement of skeletal-muscle glucose uptake.

SGLT2 inhibition illustrates why systemic glycemic improvement should not be equated with increased myocyte glucose transport. Dapagliflozin improved clamp-derived peripheral insulin sensitivity [13,14], and empagliflozin improved insulin-mediated muscle microvascular perfusion [20], yet short-term PET imaging did not show increased skeletal-muscle glucose or FFA uptake [21].

Thiazolidinediones stand out as the non-insulin drugs with the most consistent human evidence of improved muscle-related insulin sensitivity. Across PET, clamp, biopsy, MRS, and proteomic studies, they enhanced glucose disposal or insulin signaling and favorably altered lipid partitioning, metabolic flexibility, or selected oxidative pathways [6-9,11,18,19].

Metformin occupies an intermediate position. Muscle AMPK activation was demonstrated in a small before-after study [5], whereas a randomized PET trial did not show improved muscle-specific glucose uptake despite better glycemic control [6]. Thus, pathway activation within muscle does not necessarily identify muscle as the dominant organ responsible for the drug's clinical glucose-lowering effect.

Incretin-based therapies provide another distinction. Vildagliptin improved clamp-derived peripheral insulin sensitivity [10,12,15], while liraglutide and exenatide improved systemic insulin sensitivity or glucose fluxes [16,17]. However, these human findings do not establish direct skeletal-muscle glucose uptake as the dominant mechanism, and much of the cellular evidence remains preclinical [24,25].

Future pharmacological evaluation should move beyond HbA1c and systemic insulin-sensitivity indices. Direct assessment using PET, isotope tracers, clamp studies, muscle biopsies, phosphoproteomics, metabolomics, and high-resolution mitochondrial respirometry is required to establish tissue-specific pharmacology.

CLINICAL IMPLICATIONS

Understanding skeletal-muscle pharmacology may help explain why drugs with similar HbA1c reductions produce different effects on body weight, exercise capacity, insulin requirements, ectopic fat, and cardiometabolic risk.

For individuals with marked peripheral insulin resistance, TZD-mediated improvement in muscle insulin sensitivity is physiologically substantial, although clinical use must be balanced against fluid retention, weight gain, and other adverse effects.

Metformin provides favorable glycemic effects without promoting weight gain and influences muscle energetic signaling, but it should not be considered primarily a skeletal-muscle glucose-uptake drug.

GLP-1RAs and SGLT2 inhibitors provide metabolic benefits through several pathways extending beyond direct insulin-mediated glucose transport. This emphasizes that improvements in whole-body metabolism can occur without normalization of every molecular defect in diabetic skeletal muscle.

LIMITATIONS

The evidence base has several limitations. Relatively few clinical trials directly measure skeletal-muscle glucose uptake, and whole-body glucose-disposal rate during a clamp is frequently used as a surrogate even though

other tissues contribute. The included studies were heterogeneous in drug class, duration, participant phenotype, background medication, and metabolic methodology. Several mechanistic studies were small or uncontrolled, which produced moderate risk-of-bias judgments.

Studies differ substantially in insulin infusion rates, treatment duration, baseline glycemic control, concomitant medication, adiposity, physical activity, and analytical methods. Preclinical concentrations of several drugs may exceed clinically achievable tissue exposure.

Muscle physiology also differs by fiber type, age, sex, training status, and metabolic phenotype, but these factors are inconsistently considered. Contemporary drugs such as semaglutide, tirzepatide, and newer mitochondrial-modulating agents have comparatively limited direct human skeletal-muscle mechanistic data despite extensive clinical outcome evidence.

Future Directions

1. Muscle-specific PET or tracer quantification of glucose uptake.
2. Paired skeletal-muscle biopsies before and after pharmacological therapy.
3. Direct assessment of GLUT4 membrane translocation.
4. Phosphoproteomic analysis of insulin-signaling networks.
5. Mitochondrial respiratory and ATP-production measurements.
6. Measurement of intramyocellular lipid species rather than total triglyceride alone.
7. Analysis of capillary recruitment and interstitial insulin delivery.
8. Comparison of drug effects in insulin-sensitive versus insulin-resistant phenotypes.
9. Assessment of pharmacotherapy-exercise interactions.
10. Mechanistic studies of dual GLP-1/GIP and triple incretin agonists.

CONCLUSION

Skeletal muscle is a central determinant of whole-body glucose homeostasis and a major site of insulin resistance in T2DM. Antidiabetic medications influence muscle metabolism through distinct and often overlapping mechanisms.

Insulin remains the most direct pharmacological stimulator of skeletal-muscle glucose uptake through the IRS-PI3K-Akt-TBC1D4-GLUT4 pathway. Thiazolidinediones demonstrate the strongest non-insulin evidence for improving skeletal-muscle insulin sensitivity, with beneficial effects on glucose disposal, lipotoxicity, insulin signaling, metabolic flexibility, inflammation, and mitochondrial pathways.

Metformin activates skeletal-muscle AMPK and can enhance peripheral glucose disposal, although inhibition of hepatic glucose production remains its dominant therapeutic mechanism. GLP-1 receptor agonists appear to improve muscle metabolism largely through weight loss, improved insulin action, lipid redistribution, and microvascular effects, while evidence for a major direct human myocyte action remains incomplete.

DPP-4 inhibitors have modest peripheral insulin-sensitizing effects, whereas conventional insulin secretagogues influence muscle primarily through increased circulating insulin. SGLT2 inhibitors illustrate the distinction between systemic glucose lowering and direct muscle glucose transport: they may substantially improve vascular insulin sensitivity and muscle perfusion without consistently increasing measured skeletal-muscle glucose uptake.

Future studies combining glucose clamps, muscle-specific imaging, biopsies, molecular signaling analysis, and mitochondrial phenotyping will be essential to determine the full skeletal-muscle pharmacology of modern antidiabetic therapies.

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