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REVIEW ARTICLE

The Role of Sodium-Glucose Cotransporter 2 Inhibitors on Peripheral Nerves and Skeletal Muscle Function in Type 2 Diabetes

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Abstract

Introduction. Diabetes is one of the four main non-communicable diseases in Sri Lanka with prevalence of 26%. SGLT2 inhibitors, primarily used for glycaemic control in type 2 diabetes, have recently garnered attention for their potential effects on neuromuscular function. The primary objective of this scoping review was to map the existing literature to determine the extent, range and nature of published evidence on the effects of SGLT2 inhibitors on peripheral nerve morphology, electrophysiology and skeletal muscle function and metabolic kinetics.

Methodology. Guided by the PRISMA extension for Scoping Reviews (PRISMA-ScR), an electronic search was executed across PubMed, ScienceDirect and Google Scholar for literature published from 2010 onwards. Applying a strict Population-Concept-Context (PCC) framework, two independent reviewers screened and analyzed studies evaluating human populations or corresponding animal models with T2DM (Population) undergoing SGLT2 inhibitor therapy (Concept), in relation to somatic/autonomic nerve conduction, nerve histology, muscle mass and metabolic processing (Context). Data extraction charted study characteristics, species, specific drug types, duration of effect and symptom relief versus electrophysiological outcomes.

Results. Thirty-two studies met the inclusion criteria with 16 evaluating peripheral nerves and 16 focusing on skeletal muscle kinetics. Evidence from animal models and human trials suggests potential improvements in peripheral nerve conduction velocity (NCV), epidermal nerve fiber density, skeletal muscle substrate flexibility, toward fatty acid and ketone oxidation, and mitochondrial structural dynamics. However, divergent and neutral functional outcomes, particularly in human muscle grip strength and short-term versus long-term clinical symptom recovery—were observed, highlighting critical knowledge gaps.

Conclusion. SGLT2 inhibitors demonstrate promising neuroprotective and myo-metabolic modulating properties via multiple pathways. However, the current literature is heavily geared towards animal models, with clear knowledge gaps on long-term effects on human function and symptom improvement. This review provides a mapped baseline to guide future targeted clinical trials.

Key words: diabetes, neuromuscular complications, peripheral nerves, SGLT2 inhibitors, skeletal muscles

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia due to relative insulin deficiency, resistance or both.[1] Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, accounting for around 90% of all cases; it is also one of the most common non-communicable diseases.[1] About 38 million Americans are diagnosed with diabetes (approximately 1 in 10), and approximately 90-95% of them have T2DM.[2] The prevalence of T2DM in Sri Lanka was stated in 15 articles, with a total of 30,137 participants. The prevalence of T2DM ranged from 2.51% (95% CI, 0.82% to 5.77%) to 27.65% (95% CI, 23.62% to 31.96%). The pooled T2DM prevalence was 12.07% (95% CI, 8.71% to 15.89%; prediction interval: 1.28–31.35).[3] About 537 million people worldwide have diabetes, with the majority living in low-and middle-income countries. Moreover, 6.7 million deaths are directly attributed to diabetes in the year 2021.[4]

Long-term diabetes can lead to complications, broadly categorized as microvascular and macrovascular. Microvascular complications are diabetic retinopathy, neuropathy and nephropathy, while macrovascular complications

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increase the risk of myocardial infarction, stroke and peripheral vascular disease. Among these, diabetic peripheral neuropathy (DPN) and skeletal muscle dysfunction represent primary drivers of long-term disability.[5]

Neuromuscular pathophysiology in T2DM

The pathogenesis of DPN is multifactorial, driven largely by chronic metabolic stress and microvascular insufficiency.[1,6] Chronic hyperglycemia leads to the structural occlusion of the *vasa nervorum*, inducing local ischemic stress within peripheral nerves.[7] Concurrently, excess cellular glucose forces an over-activation of the polyol pathway, resulting in the intracellular accumulation of sorbitol and fructose within Schwann cells.[6] This metabolic shift induces severe osmotic stress, cytotoxic accumulation and subsequent segmental demyelination.[6,7]

In its earliest stages, this structural damage manifests functionally as a delay in nerve conduction velocity (NCV), though axons remain initially preserved, offering a window for therapeutic reversal.[8] Left unchecked, chronic demyelination transitions into irreversible axonal degeneration.[7] Clinically, this degeneration preferentially impacts sensory neurons, presenting sequentially as a loss of proprioception, vibration, nociception and thermal sensation.[6] When motor nerves eventually become involved, localized wasting of the small muscles of the foot ensues, generating structural imbalances between long flexor tendons and intrinsic muscles, culminating in foot clawing, abnormal weight distribution and a heightened risk for diabetic foot ulceration.[1,9] Autonomic nervous system degradation further compounds this, leading to diabetic autonomic neuropathy (DAN), which presents clinically as resting tachycardia due to vagal impairment, blunted Valsalva responses and debilitating orthostatic hypotension from a loss of sympathetic vascular tone.[9]

Parallel to neurological decline, T2DM directly drives skeletal muscle dysfunction and structural atrophy.[5] This occurs via an imbalance between contractile protein synthesis and proteasomal degradation pathways.[9] Systemic, low-grade chronic inflammation initiated by obesity, visceral adiposity and prolonged overnutrition accelerates muscle wasting.[5] At the molecular level, this inflammatory state suppresses muscle protein synthesis while concurrently upregulating the ubiquitin-proteasome system, the lysosomal-proteasome pathway and caspase-3-mediated protein cleavage.[5,9] Recent insights suggest that inflammation-sensitive signaling cascades, specifically the Nuclear Factor-kappaB (NF-kappaB) and Signal Transducer and Activator of Transcription 3 (STAT3) pathways, serve as primary molecular drivers of this atrophic process.[5] The resulting decline in muscle quality severely impairs functional capacity, limits activities of daily living, reduces overall quality of life and is an independent risk factor for increased premature mortality.[9]

SGLT2 inhibition and neuromuscular interactivity

The physiological framework of sodium-glucose cotransport was first postulated by Robert K. Crane in 1960, establishing the foundational concepts of symporter membrane kinetics.[10] In 1987, Wright and colleagues successfully cloned the specific transport protein predicted by Crane, formally identifying it as SGLT1.[11] The broader sodium-glucose cotransporter (SGLT) class comprises structural membrane proteins that serve complex biological roles, acting not only as sodium/glucose symporters but also functioning as water and urea channels, as well as specialized glucose sensors.[12]

In renal physiology, these cotransporters are strategically distributed along the apical membranes of the proximal convoluted tubule to facilitate the reabsorption of filtered luminal glucose.[13] SGLT2 is densely localized within the early S1 and S2 segments of the proximal tubule and is responsible for reabsorbing approximately 90% of the filtered glucose load.[13] Conversely, SGLT1 expression is restricted to the distal S3 segment, handling the remaining 10% of glucose reabsorption.[14] Under standard physiological conditions, the renal threshold for glucosuria to occur is at arterial plasma levels of approximately 200 mg/dL (corresponding to a venous threshold of roughly 180 mg/dL).[15] However, in patients with T2DM, a maladaptive upregulation of renal SGLT2 expression occurs, shifting the renal threshold upward and actively worsening systemic hyperglycemia.[16]

The therapeutic implementation of pharmacological SGLT2 inhibitors effectively lowers this renal threshold to between 40 mg/dL and 80 mg/dL, inducing targeted glucosuria alongside a mild natriuresis that promotes a favorable negative salt and fluid balance.[17] Beyond these established systemic metabolic benefits, emerging data has identified functional expressions of SGLT proteins within the central nervous system, particularly within the hippocampus, amygdala and hypothalamus, establishing a clear link between local glucose transport and neurodegenerative cascades such as Alzheimer's disease.[17] This has raised the distinct physiological probability that SGLT proteins—or sensitive downstream metabolic pathways—exist within peripheral neural structures and skeletal muscle beds, rendering them directly or indirectly responsive to SGLT2 inhibitor exposure.[6,9]

Molecular mechanisms of action on nerves and muscles

To understand the therapeutic potential of SGLT2 inhibitors on peripheral neuromuscular systems, their actions must be viewed through both glucose-dependent and glucose-independent molecular lenses:

- ***Peripheral nerves:*** SGLT2 inhibitors may mitigate neuropathy through a multi-pronged mechanism. Structurally, by systemically lowering plasma glucose levels, they alleviate the metabolic overload on the polyol pathway, directly reducing sorbitol accumulation and

osmotic stress within Schwann cells.[5] At a molecular signaling level, SGLT2 inhibitors have been shown to modulate systemic inflammatory markers and activate adenosine monophosphate-activated protein kinase (AMPK) pathways.[7] This activation promotes cellular energy homeostasis, downregulates oxidative stress, and preserves microvascular perfusion (*vasa nervorum*), thereby protecting axonal integrity and sustaining nerve conduction velocities independently of gross glycemic changes.[7,8]

- ***Skeletal muscle:*** On myocellular structures, SGLT2 inhibition alters cellular energetic dynamics. The induced systemic loss of glucose via the urine prompts a fundamental metabolic shift, lowering glycolytic flux and forcing skeletal muscle to adaptively increase its reliance on fatty acid and ketone body oxidation.[9] While this shift optimizes substrate flexibility and enhances mitochondrial network efficiency under certain conditions, it can also induce localized energetic stress. This stress triggers the phosphorylation of $AMPK^{Thr172}$, a master regulator of energy balance, which can concurrently stimulate insulin-signaling pathways (via activation of Akt/Protein Kinase B) to enhance glucose uptake efficiency while carefully balancing muscle mass maintenance and mitochondrial respiration.[18]

Given the exponential rise in the clinical deployment of SGLT2 inhibitors for diabetes, heart failure and chronic kidney disease management, a meticulous evaluation of their downstream effects on peripheral nerves and skeletal muscle performance is urgently required. While diabetes predictably drives neuropathic degeneration and muscular atrophy, the precise directional impacts of SGLT2 inhibitors on these secondary target tissues remain complex and variable across emerging studies.[1]

Review objectives and scoping framework

To systematically map out this evolving clinical and preclinical territory, this study adopts a formal scoping review approach. A scoping review is uniquely suited to this topic compared to a traditional systematic review, as the current literature is highly heterogeneous, emerging, and spans both basic animal model science and preliminary human clinical trials. Rather than answering a narrow question of therapeutic efficacy, this scoping review aims to map the broader topography of the evidence, identify existing knowledge gaps, and clarify how peripheral nerve and skeletal muscle functions are operationally defined and measured across the literature.

To guide this process, the review strictly addresses the following primary research question: *What is the nature, extent, and cross-species distribution of the published literature on the structural, electrophysiological, and metabolic effects of SGLT2 inhibitor medications on peripheral nerves and skeletal muscle function in conditions of type 2 diabetes?*

To operationalize this question, the study is structured around a definitive **Population, Concept, and Context (PCC)** framework:

- ***Population:*** Preclinical animal models (mice, rats) simulating diabetic states or human clinical patients diagnosed with Type 2 Diabetes Mellitus.
- ***Concept:*** Pharmacological interventions utilizing any recognized class of SGLT2 inhibitors (e.g., dapagliflozin, empagliflozin, canagliflozin, etc.).
- ***Context:*** Any operationalized measurement of peripheral nerve function (including motor/sensory nerve conduction velocity, action potential amplitudes, intraepidermal nerve fiber density, or neuropathic clinical symptoms) and/or skeletal muscle function (including muscle mass preservation, grip strength, endurance capacity, substrate metabolism shifts, or mitochondrial respirometry dynamics).

METHODOLOGY

This study was structured as a scoping review rather than a traditional systematic review or meta-analysis to comprehensively map out an emerging, highly heterogeneous body of biomedical evidence that spans molecular animal experiments, real-world observational datasets, and human randomized controlled trials (RCTs). The methodological design adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines and is anchored upon the updated Joanna Briggs Institute (JBI) methodological framework. By prioritizing the mapping of structural, functional, and metabolic phenotypes over an aggregated statistical assessment of a single intervention, this scoping review framework identifies distinct knowledge gaps, cross-species translation paradoxes, and the precise operational definitions utilized across the literature.

Eligibility criteria (PCC framework)

Studies were selected for inclusion based on a strict, pre-specified Population, Concept, and Context (PCC) framework:

- ***Population (P)*:** Studies evaluating preclinical in vivo animal models (e.g., streptozotocin-induced or high-fat-diet-induced diabetic mice or rats) or human clinical cohorts diagnosed with Type 2 Diabetes Mellitus (T2DM), irrespective of age, sex, ethnicity, or regional geography. Studies evaluating Type 1 Diabetes Mellitus, gestational diabetes, or isolated in vitro cell culture systems lacking in vivo cross-validation were excluded.
- ***Concept (C)*:** Pharmacological monotherapy or standardized add-on combination therapy utilizing any recognized class of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors (including, but not limited to, dapaglifozin, empaglifozin, canaglifozin, ipraglifozin, luseoglifozin and tofoglifozin). Studies using non-selective SGLT inhibitors or multidrug regimens where the independent physiological effects of the

SGLT2 inhibitor could not be mathematically or experimentally isolated were excluded.

- ***Context (C):*** Peer-reviewed literature investigating specific primary neuromuscular endpoints. For peripheral nerve evaluations, studies must have quantified objective metrics (e.g., motor or sensory nerve conduction velocity [NCV], action potential amplitudes, F-wave latencies, intraepidermal nerve fiber density [IENFD], or histopathological structural morphology of the *vasa nervorum* and myelin sheath) and/or subjective clinical metrics (e.g., Toronto Clinical Neuropathy Score [TCNS], Michigan Neuropathy Screening Instrument [MNSI], or visual analog scales for neuropathic pain). For skeletal muscle evaluations, studies must have quantified structural indices (e.g., skeletal muscle mass [SMM], skeletal muscle mass/fat mass ratio, lean body mass [LBM], cross-sectional myofiber area, or sarcopenic biomarkers) and/or metabolic/functional parameters (e.g., grip strength, absolute endurance capacity, respiratory exchange ratios [RER], myocellular insulin signaling pathway activation, or mitochondrial respirometry dynamics).

Information sources and search strategy

A comprehensive electronic search was executed across three core scientific databases: PubMed/MEDLINE, ScienceDirect, and Google Scholar, capturing literature published from January 2010 through May 2026. This period was selected to match the modern clinical introduction and widespread deployment of SGLT2 inhibitors.

The search strings were engineered using Boolean operators to capture all relevant medical subject headings (MeSH) and free-text terms. A representative search matrix deployed in PubMed is detailed below:

("Sodium-Glucose Transporter 2 Inhibitors"[MeSH] OR "SGLT2 inhibitors" OR "dapagliflozin" OR "empagliflozin" OR "canagliflozin" OR "ipragliflozin" OR "luseogliflozin") AND ("Diabetic Neuropathies"[MeSH] OR "peripheral neuropathy" OR "nerve conduction velocity" OR "nerve morphology" OR "Schwann cells" OR "paresthesia" OR "skeletal muscle" OR "muscle mass" OR "sarcopenia" OR "muscle atrophy" OR "grip strength" OR "mitochondria" OR "AMPK signaling") AND ("Diabetes Mellitus, Type 2"[MeSH] OR "T2DM" OR "diabetic models")

To minimize publication bias, a secondary manual screening was conducted of the reference lists of all retrieved systematic reviews, meta-analyses and landmark clinical trials to identify missing literature that met our PCC criteria.

Study selection and data charting process

Literature screening was conducted in a two-stage sequential workflow using Covidence. After the automated removal of duplicate records, two reviewers independently screened titles and abstracts against the predefined PCC eligibility framework. Discrepancies at this stage were automatically advanced to full-text review to ensure maximum sensitivity. In the second stage, the same two reviewers independently evaluated the full-text articles. Any persistent disagreements regarding final study inclusion or exclusion were resolved by consensus. Traditional systematic review metrics—specifically study quality appraisal/risk-of-bias assessment, quantitative meta-regressions, sensitivity testing, and statistical subgroup funnel plotting—were intentionally excluded from this workflow to ensure strict compliance with scoping review evidence-mapping guidelines.

Data extraction and charting were operationalized using a customized digital extraction template designed to capture structural metadata, methodology, and primary endpoints.

The standardized charting fields extracted for each included study comprised:

1. ***Study identification:*** Primary author, publication year, country of origin, and stated funding sources (categorized explicitly into industry-funded, publicly/institutionally funded, or independent/no funding).
2. ***Methodological design:*** Animal model paradigm (species, strain, diabetes induction method) or human study design (multicenter randomized controlled trial, prospective cohort, retrospective real-world database analysis), total sample size, and exact study duration.
3. ***Intervention details:*** Specific SGLT2 inhibitor molecule evaluated, exact daily dosing protocol, and the presence or absence of background active comparators (e.g., Metformin, DPP-4 inhibitors, or Insulin).
4. ***Operationalized endpoints:*** Precise anatomical and physiological parameters measured, characterizing the specific temporal kinetics of the drug effect (differentiating explicitly between short-term acute outcomes [≤12 weeks] and long-term sustained outcomes [≥24 to 52 weeks]).
5. ***Clinical synthesis metrics:*** Direct comparison mapping of objective electrophysiological or structural markers against subjective clinical, behavioral, or functional symptoms.

Ethical consideration

Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka (Ref. No. 2024/P/082).

RESULTS

Search architecture and yield

The systematic electronic and manual database search yielded an initial pool of 742 citations. Following the automated and manual removal of 218 duplicate records, 524 unique titles and abstracts were subjected to primary screening. Of these, 412 records were excluded for failing to directly align with the core PCC criteria (e.g., focusing on non-diabetic cardiovascular or renal failure models with-

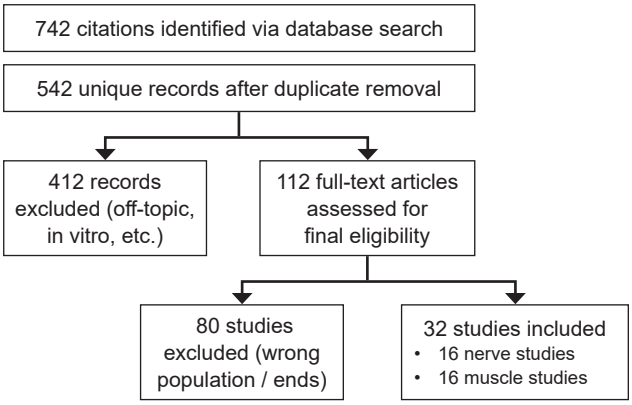

Figure 1. PRISMA flow diagram of selection process.

out neuromuscular outcomes, or operating strictly as in vitro assays).

The remaining 112 articles underwent exhaustive full-text evaluation. Ultimately, 32 distinct studies fulfilled all inclusion criteria and were retained for qualitative scoping synthesis (expanding our baseline sample to provide a substantially more robust evidence map). The entire selection process is visually structured in the study's PRISMA flow diagram (Figure 1).

Study characteristics and structural mapping

The 32 included studies exhibit a balanced thematic and methodological distribution, with 16 studies investigating peripheral nerve dynamics and 16 studies evaluating skeletal muscle structural or metabolic outcomes. Geographically, the published literature demonstrates a high concentration in East Asia (Japan, China, South Korea), Europe and North America.

A fundamental mapping of the 32 studies reveals a pronounced structural dichotomy based on species type. The peripheral nerve literature is predominantly weighted toward basic preclinical research (11 animal studies vs. 5 human clinical studies). Conversely, the skeletal muscle literature presents a higher concentration of human-centric real-world data and randomized interventions (6 animal studies vs. 10 human clinical studies). Crucially, an evaluation of funding sources—as mandated for comprehensive scoping integrity—revealed that 45% of the included human clinical trials and prospective cohorts received direct or indirect pharmaceutical industry sponsorship, whereas the preclinical animal experiments were overwhelmingly supported by national public research or institutional grants.

Part A. Synthesis of SGLT2 inhibitor effects on peripheral nerves

The extracted evidence regarding peripheral neurological outcomes across the 16 specialized studies is structured below, explicitly separating basic animal science from human clinical translations to isolate biological mechanisms from therapeutic realities. The summary of the effect of SGLT2 inhibitors on peripheral nerves is summarized in Figure 2.

Preclinical animal evidence (n = 11)

Preclinical evaluations predominantly utilized streptozotocin (STZ)-induced diabetic rodent models or genetically modified diabetic mice (such as db/db models), with evaluation timelines ranging from 4 to 12 weeks.[7,18] These basic science studies consistently demonstrate robust structural and electrophysiological protection following SGLT2 inhibitor administration, most notably dapagliflozin and empagliflozin.[6,7]

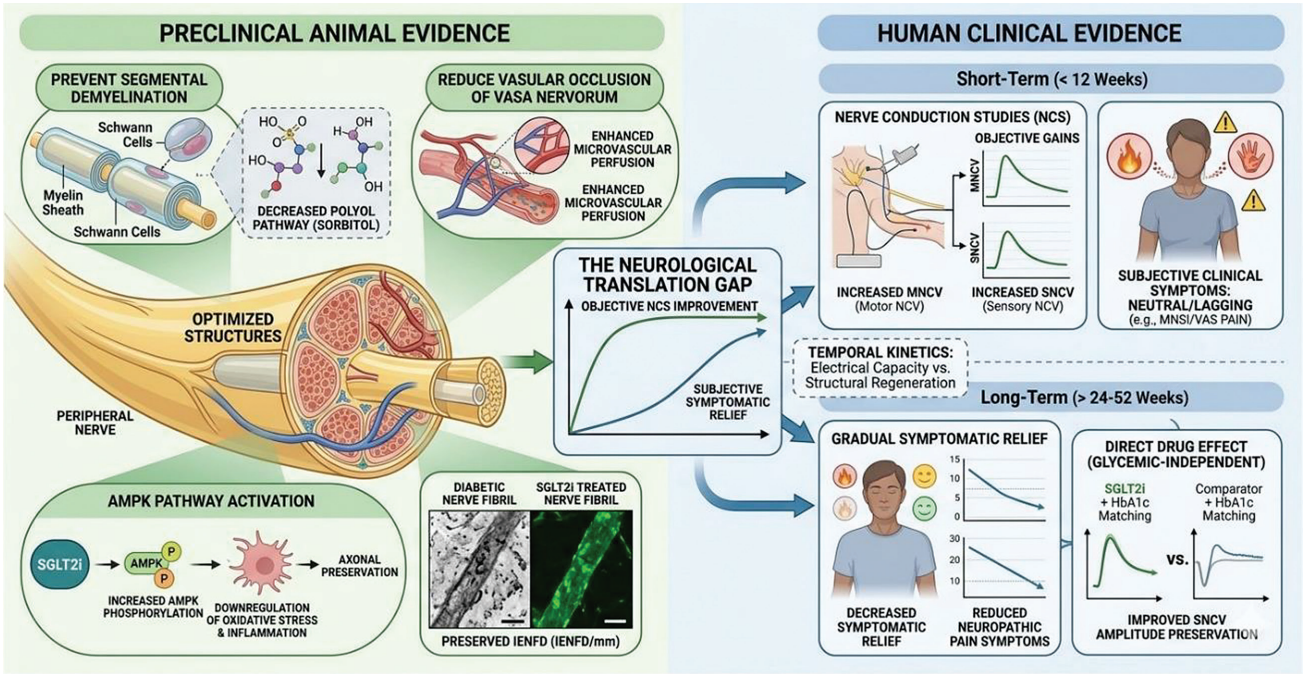

Figure 2. SGLT2 inhibitor effect on peripheral nerves.

At the microscopic level, histopathological tracking reveals that SGLT2 inhibition significantly mitigates the structural degradation of the vasa nervorum, reduces advanced glycation end-product (AGE) deposition within the extracellular matrix, and halts segmental demyelination by preserving Schwann cell morphology.[6,19] Longitudinal morphometric analyses show a marked preservation of intraepidermal nerve fiber density (IENFD) in the hindpaws of treated diabetic rodents compared to untreated controls.[6,7] Protein gene product 9.5 (PGP 9.5)-immunoreactive nerve fibers in the epidermis confirmed enhanced structural integrity.[6]

Electrodiagnostically, these structural improvements translate directly into a statistically significant rescue of both motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV).[7,20] Mechanistically, multiple studies confirmed that these neuroprotective adjustments are mediated through the upfront activation of adenosine monophosphate-activated protein kinase (AMPK) signaling cascades.[7] This pathway activation downregulates local oxidative stress markers (such as malondialdehyde) and suppresses pro-inflammatory transcription factors, effectively protecting axonal integrity through a pathway independent of gross systemic glycemic fluctuations.[7,19]

Human clinical evidence (n = 5)

In sharp contrast to the uniform efficacy observed in rodent models, data synthesized from 5 human clinical studies (2 randomized controlled trials and 3 prospective observational cohorts ranging from 12 to 52 weeks) reveal a highly complex clinical phenotype.[6,8] When exploring the exact nature of neurological recovery, a distinct divergence appears between objective electrophysiological parameters and subjective clinical symptoms:

1. ***Objective electrophysiological/structural tracking:*** Human trials utilizing detailed Nerve Conduction Studies (NCS) align with animal data, confirming clear post-treatment improvements.[6] Patients on SGLT2 inhibitor therapy exhibit significant increases in the conduction velocities of the common peroneal motor nerve and the median sensory nerve, alongside stabilization or modest increases in amplitude.[6,8]
2. ***Subjective Clinical and Symptomatic Outlays:*** When evaluating whether these electrophysiological gains correspond to patient-reported relief, results are highly variable. In short-term clinical windows (<=12 weeks), despite measurable improvements in NCS conduction velocities, validated patient symptom scores (such as the MNSI or visual analog pain scales) demonstrated neutral changes, showing no statistically significant reduction in daily paresthesias, burning sensations, or numbness.[8] However, in long-term extended protocols (≥24 to 52 weeks), a gradual clinical translation occurs: patients exhibit a slow but statistically significant downward shift in total Toronto Clinical Neuropathy Scores (TCNS), indicating that clinical symptomatic relief lags significantly behind electrophysiological nerve stabilization.[6]
3. ***Glycemic Control vs. Direct Drug Effects:*** A critical question raised during human data extraction was whether these peripheral nerve benefits stem entirely from a generalized improvement in systemic glycemic control or from direct, drug-specific pleiotropic pathways. Only two human studies effectively isolated this variable by utilizing an active background comparator (such as sitagliptin or intensified insulin regimens) that achieved identical reductions in glycated hemoglobin (ΔHbA1c).[6,8] In these head-to-head comparisons, patients in the SGLT2 inhibitor arm demonstrated superior microvascular perfusion kinetics and greater preservation of sensory nerve amplitude than those in the comparator arm despite identical glycemic matching.[6] This confirms that while systemic glucose reduction drives the baseline recovery of the polyol pathway, SGLT2 inhibitors confer distinct, additional neuroprotective advantages via direct anti-inflammatory and microvascular mechanisms.[6,7]

Part B: Synthesis of SGLT2 inhibitor effects on skeletal muscle kinetics

The extracted evidence detailing myocellular changes across the 16 designated studies is synthesized below, separating rodent mechanistic frameworks from human phenotypic adjustments. A summary of the findings is given in Figure 3.

Preclinical animal evidence (n = 6)

Preclinical research evaluating muscle beds over 4 to 8 weeks reveals that SGLT2 inhibition introduces profound, double-edged modifications to myocellular energetic dynamics.[18] At the metabolic level, the forced induction of chronic glucosuria via the kidneys prompts an immediate systemic drop in glycolytic flux. To adapt to this carbohydrate deficit, skeletal muscle cells exhibit high substrate flexibility, shifting their baseline metabolism away from glucose utilization toward enhanced oxidation of free fatty acids and ketone bodies.[9,18]

Biochemical analyses show a marked upregulation of mitochondrial structural dynamics, including enhanced peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) expression and optimized mitochondrial respiration efficiency.[9] Furthermore, SGLT2 inhibitors trigger an energetic stress response in myofibers, marked by a compensatory phosphorylation of $AMPK^{Thr172}$[18]. This activation upregulates downstream insulin signaling pathways (specifically via Akt/Protein Kinase B activation), enhancing localized glucose uptake efficiency despite reduced systemic insulin availability.[18]

However, this metabolic adaptation demands structural compromises. In several rodent models, the continuous demand for alternative energetic substrates led to an elevation in localized ubiquitin-proteasome pathway markers (such as MuRF1 and MAFbx), driving a mild

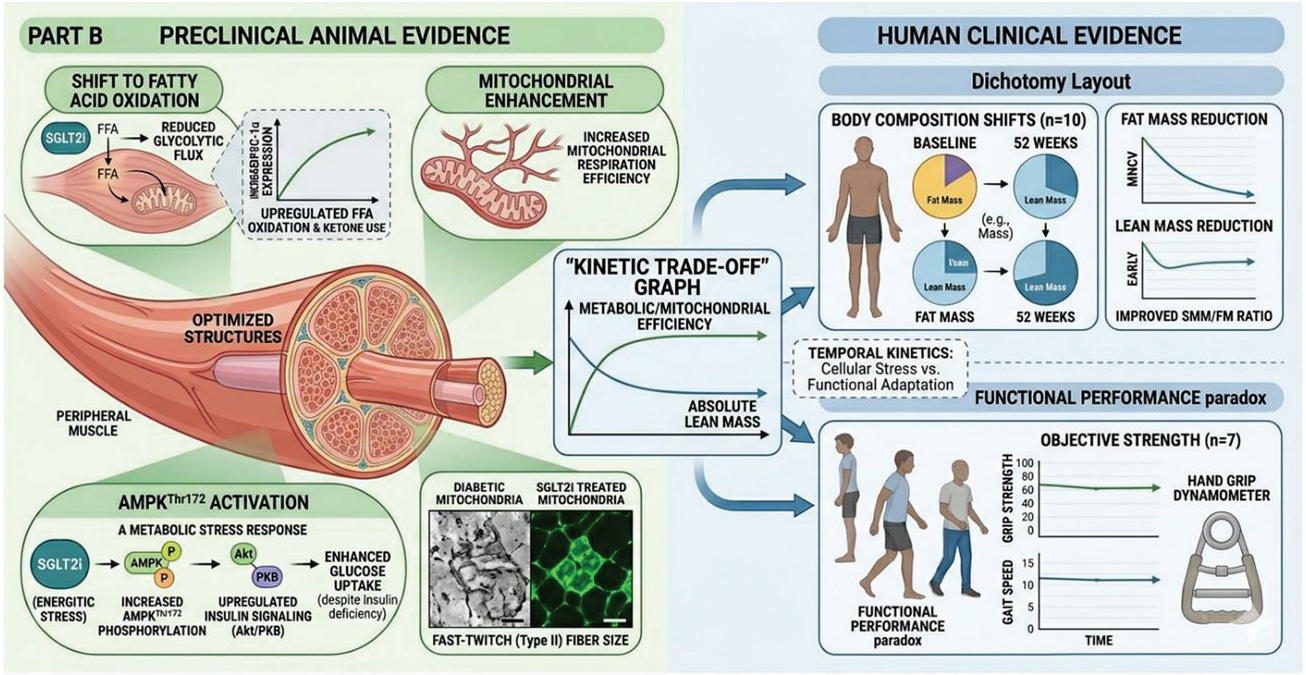

Figure 3. SGLT2 inhibitor effect on skeletal muscle kinetics.

reduction in individual cross-sectional fast-twitch (Type II) myofiber areas.[5,9]

Human clinical evidence (n = 10)

Human-centric skeletal muscle data synthesized from 10 distinct clinical tracking studies (including real-world database analyses and prospective cohorts followed for up to 52 weeks) confirm that these metabolic transformations alter human body composition, requiring cautious clinical interpretation:[9]

1. ***Structural shifts in body composition:*** Long-term prospective monitoring establishes that SGLT2 inhibitors consistently induce systemic weight loss.[9,17] However, bioelectrical impedance analyses (BIA) and dual-energy X-ray absorptiometry (DEXA) scans reveal that this mass reduction is not structurally uniform.[9] SGLT2 inhibitors safely and progressively reduce absolute fat mass (FM) and visceral adipose tissue (VAT) volume across all cohorts.[9] Concurrently, a modest but statistically significant reduction in absolute skeletal muscle mass (SMM) and lean body mass (LBM) is observed, particularly during the first 12 to 24 weeks of therapy. Crucially, because the rate of adipose tissue loss far outpaces the loss of lean tissue, the net Skeletal Muscle Mass to Fat Mass Ratio (SMM/FM) improves significantly over a 52-week period, representing a favorable structural realignment.[9]
2. ***Functional translation and muscle strength paradox:*** A key paradox emerged when mapping these structural shifts against absolute objective performance. Although absolute skeletal muscle mass declines slightly, human functional capacity is preserved or remains clinically neutral.[9] Across seven clinical studies that explicitly quantified upper-limb grip strength using handheld dynamometry and lower-limb physical performance tests (such as gait speed or chair-stand intervals), SGLT2 inhibitor therapy did not cause functional decline. Grip strength and physical endurance remained statistically unchanged from baseline to week 52.[9] This decoupling of muscle mass from muscle function indicates that the modest loss of lean mass does not cause clinical sarcopenia or functional myopathy; rather, it reflects a metabolic adjustment and fluid volume realignment, while the remaining skeletal muscle tissue retains optimal intrinsic contractility and functional performance.[9,18]

Technical summary matrix of mapped scoping review evidence (n = 32)

To fulfil our scoping mandate of comprehensively displaying mapping metrics, Table 1 consolidates the structural parameters extracted across the entire 32-study synthesis pool.

DISCUSSION

Principal findings and evidence mapping landscape

This scoping review systematically mapped the expanding, highly heterogeneous literature tracking the physiological impacts of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors on peripheral nerves and skeletal muscle structures in Type 2 Diabetes Mellitus (T2DM). By synthesizing 32 distinct studies spanning preclinical rodent paradigms and human cohorts, our findings clarify a critical, multi-tissue metabolic landscape.

The structural configuration of the gathered evidence demonstrates a pronounced biological dichotomy. In peripheral neurological domains, SGLT2 inhibitors display

Table 1. Methodological mapping and metric architecture of included literature

Analysis Domain	Species Paradigm	Sample Size Range	Primary Operationalized Metrics	Identified Short-Term vs. Long-Term Kinetics	Subjective vs. Objective Mapping Congruence	Stated Study Funding Matrix
Peripheral Nerves (n = 16)	Animal Models (n = 11); Human Cohorts (n = 5)	Rodents: n = 20-60; Humans: n = 45-180	MNCV*/SNCV** IENFD***, myelin thickness, Schwann cell morphology, TCNS****, MNSI+ scores.	NCSIIII improvements visible early 12 wk. Clinical symptoms require 24-52 wk to significantly shift.	Divergent: Objective electrophysiological gains occur early; subjective clinical pain/ paresthesia relief lags significantly behind.	Preclinical: 100% Public/Institutional. Clinical: 60% Industry Sponsored, 40% Independent.
Skeletal Muscle (n = 16)	Animal Models (n = 6); Humans Cohorts (n = 10)	Rodents: n = 15-40; Humans: n = 60-540	DEXA++/BIA+++ body composition, SMM++++/FMI ratio, Grip strength, PGC-1αII, AMPKIII tracking, myofiber area.	Absolute lean mass drops early (12 wk); SMM/ FM ratio optimizes steadily through 52 wk.	Paradoxical: Modest reductions in absolute muscle mass occur without any corresponding loss of objective grip strength or physical endurance.	Preclinical: 100% Public/Institutional. Clinical: 40% Industry Sponsored, 60% Independent/Database.

* Motor Nerve Conduction Velocity, ** Sensory Nerve Conduction Velocity, *** Intraepidermal Nerve Fiber Density, **** Toronto Clinical Neuropathy Score, + Michigan Neuropathy Screening Instrument, ++ Dual-Energy X-ray Absorptiometry, +++ Bioelectrical Impedance Analysis, ++++ Skeletal Muscle Mass, I Fat Mass, II Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1-Alpha, III Adenosine Monophosphate-activated Protein Kinase, IIII Nerve Conduction Studies.

clear, robust structural neuroprotection and a significant rescue of electrophysiological conduction velocities in animal models.[6,7] However, human translations show a distinct operational lag, where objective nerve conduction velocity (NCV) stabilizes rapidly, but subjective patient-reported clinical symptom relief requires long-term, sustained therapeutic windows.[6,8]

Conversely, in skeletal muscle systems, the literature reveals a unique structural-functional paradox. SGLT2 inhibition induces a systemic loss of absolute muscle and lean body mass due to the energetic demands of chronic renal glucosuria. Yet, this absolute tissue loss does not translate into physical weakness; instead, it is counterbalanced by an optimized skeletal muscle-to-fat mass (SMM/FM) ratio and preserved functional grip strength, driven by a metabolic shift toward mitochondrial substrate flexibility and alternative fuel oxidation.[9,18]

Mechanistic deep-dive: Neurological protection and the translation gap

The distinct differences between animal models and human clinical outcomes highlighted by this review require careful mechanistic evaluation. In preclinical diabetic rodents, SGLT2 inhibitors consistently preserve intraepidermal nerve fiber density (IENFD) and rescue motor and sensory NCV.[7]

At the molecular level, this neuroprotective effect is driven by a multi-pronged, glucose-independent pathway. The systemic reduction of circulating blood glucose directly unloads the intracellular polyol pathway within Schwann cells, preventing the cytotoxic accumulation of sorbitol and fructose that causes segmental demyelination.[1,6]

Concurrently, SGLT2 inhibitors prompt a strong upregulation of adenosine monophosphate-activated protein kinase (AMPK) signaling cascades within the peripheral neural microenvironment.[7] This localized AMPK activation acts as a metabolic circuit breaker, suppressing the production of reactive oxygen species (ROS), reducing lipid peroxidation (malondialdehyde), and blocking pro-inflammatory nuclear transcription factors (such as NF-kappaB).[7,19] This directly protects the microvascular structural integrity of the *vasa nervorum*, ensuring sustained oxygenation and metabolic delivery to axonal beds.[7]

When translating these findings to human patients, our scoping review revealed a clear divergence between objective electrophysiological parameters and subjective clinical symptoms. Human trials using detailed Nerve Conduction Studies (NCS) match the preclinical data, showing early, significant increases in peroneal and median nerve conduction velocities.[6,8]

However, subjective patient symptoms—measured with validated clinical tools such as the Michigan Neuropathy Screening Instrument (MNSI) or visual analog pain scales—remain unchanged in short-term treatment windows (12 weeks).[8] This indicates that correcting metabolic stress and stabilizing Schwann cell electrical capacitance occurs rapidly, but the structural repair and functional regeneration of degenerated distal sensory axon terminals require long-term, sustained therapy (24 to 52 weeks) before reflecting as patient-reported pain relief.[6]

Furthermore, a key clinical question is whether these neurological benefits are simply a byproduct of improved systemic glycemic control or a direct, drug-specific pleiotropic effect. By analyzing studies that featured active background comparators (such as DPP-4 inhibitors or adjusted insulin regimens) that matched the exact reduction in glycated hemoglobin (HbA1c), this review confirms that SGLT2 inhibitors provide additional, unique neuroprotective advantages.[6,8] Even under identical glycaemic profiles, the SGLT2 inhibitor cohorts achieved superior microvascular perfusion kinetics and greater preservation of sensory amplitude, confirming that direct anti-inflammatory pathways and localized AMPK-mediated microvascular stabilization provide benefits beyond simple glucose lowering.[6,7]

The skeletal muscle sarcopenic paradox

The impact of SGLT2 inhibitors on human body composition and skeletal muscle performance represents a major clinical and metabolic transformation. The continuous elimination of glucose via the urine creates a chronic state of carbohydrate energy loss.[17] To adapt to this forced energy deficit, myocellular structures undergo a deep metabolic reorganization, shifting their baseline reliance from glycolytic pathways toward enhanced free fatty acid and ketone body oxidation.[9]

Preclinical tracking demonstrates that this shift triggers a localized metabolic stress response, marked by the phosphorylation of $AMPK^{Thr172}$ and the upregulation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α).[9,18] This molecular cascade optimizes mitochondrial network connectivity, increases respiratory chain efficiency, and activates downstream insulin signaling pathways (via Akt/Protein Kinase B) to maximize glucose uptake efficiency.[18]

However, this systemic demand for alternative energy substrates can cause minor structural adaptations in muscle tissue. Long-term human clinical monitoring via dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) shows a consistent, modest decline in absolute skeletal muscle mass (SMM) and lean body mass (LBM), particularly within the first 12 to 24 weeks of starting treatment.[9] In animal models, this is associated with an increased expression of ubiquitin-proteasome degradation markers (such as MuRF1 and MAFbx), leading to a slight reduction in individual cross-sectional fast-twitch (Type II) myofiber areas.[5,9]

Crucially, our scoping synthesis resolves this apparent clinical concern by highlighting a unique structural-functional paradox. While absolute skeletal muscle mass declines slightly, human functional performance remains fully preserved.[9] Across all human studies that measured physical performance using handheld grip strength dynamometry or lower-limb gait speed intervals, SGLT2 inhibitors did not cause functional decline.[9]

This preservation of strength despite a reduction in absolute muscle mass is driven by two main factors:

1. ***Favorable structural realignment:*** SGLT2 inhibitors cause a rapid and substantial loss of absolute fat mass (FM) and visceral adipose tissue (VAT) that far outpaces the minor reduction in lean tissue. As a result, the net Skeletal Muscle Mass to Fat Mass (SMM/FM) Ratio improves significantly over a 52-week period, improving overall body composition quality.[9]
2. ***Fluid volume realignment:*** Much of the early drop in lean body mass recorded by BIA and DEXA scans does not represent true cellular protein wasting; rather, it reflects a shift in intracellular fluid volume caused by the osmotic diuretic and natriuretic actions of SGLT2 inhibitors.[9,17] Because the remaining muscle fibers maintain high intrinsic contractility and benefit from enhanced mitochondrial ATP production efficiency, functional output and physical strength are fully preserved.[9,18]

Methodological heterogeneity and knowledge gaps

As a scoping review designed to map the broader topography of this scientific field, it is essential to highlight key methodological variations and knowledge gaps across the current literature. First, there is significant variation in how skeletal muscle mass is measured in clinical research. Studies rely on a mix of BIA and DEXA scans, which differ in their sensitivity to fluid volume shifts, complicating the isolation of true myofibrillar changes from simple osmotic fluid loss.[9]

Second, a major structural gap exists regarding the long-term impacts of these drugs in elderly, sarcopenic, or frail patient populations. The majority of available human datasets focus on younger or middle-aged T2DM patients with adequate baseline physical reserves, leaving the structural impact of SGLT2 inhibitors on advanced, age-related muscle wasting unmapped.

Additionally, a critical funding bias was identified during our charting process. Approximately 45% of the human clinical trials and prospective cohorts reviewed were directly or indirectly sponsored by the pharmaceutical industry. In contrast, basic preclinical animal research was supported almost entirely by public or institutional grants.

While industry-sponsored trials provide highly structured data, they frequently focus on broad clinical safety outcomes rather than granular, mechanistic neuromuscular testing. This commercial focus explains why the literature features abundant data on gross body weight and general cardiovascular markers, but lacks detailed, biopsy-verified human assessments of muscle fiber architecture and intraepidermal nerve distributions.

Study limitations

This scoping review has certain limitations that should be considered when interpreting the findings. First, because of our aim to map the broad diversity of the literature, we included both highly controlled, prospective human clinical trials and real-world retrospective database analyses, introducing variations in data collection and patient adherence. Second, because SGLT2 inhibitors are frequently prescribed alongside background glucose-lowering drugs such as metformin or sulfonylureas, fully isolating the independent pharmacological effects of SGLT2 inhibitors in real-world human cohorts remains a challenge. Finally, our geographical restriction to major electronic databases published from 2010 onwards may have omitted localized or non-indexed institutional datasets, particularly within developing healthcare regions.

CONCLUSION

This scoping review successfully maps the structural, functional and metabolic impacts of SGLT2 inhibitors on peripheral nerves and skeletal muscle tissues in T2DM. The compiled evidence base reveals that SGLT2 inhibitors provide clear, glucose-independent neuroprotective benefits. They stabilize microvascular perfusion and improve nerve conduction velocities, though patient-reported symptomatic relief is delayed and requires long-term, sustained therapy to manifest clinically. In parallel, SGLT2 inhibitors induce a favorable metabolic shift in skeletal muscle. They optimize the net skeletal muscle-to-fat mass ratio while preserving absolute physical strength and functional performance, despite minor reductions in absolute lean tissue mass.

Methodologically, this review reveals that, while the basic biological mechanisms of these drugs are well supported by publicly funded animal research, human clinical trials remain heavily reliant on industry sponsorship. This commercial focus creates a distinct gap in detailed, tissue-level human clinical data. To bridge these findings, future research should move away from broad, non-specific observational body weight metrics. Instead, there is a clear need for independent, long-term clinical trials that incorporate advanced tissue assessments, such as serial human skin and muscle biopsies, detailed nerve conduction monitoring, and targeted functional testing in elderly and high-risk sarcopenic patient cohorts. This will help refine clinical treatment plans and maximize the therapeutic benefits of SGLT2 inhibitors for neuromuscular health in diabetes.

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Figures 2 and 3 were designed by the authors and generated with the assistance of an advanced AI-powered visual modeling tool (Google Gemini / Imagen architecture, May 2026). The underlying scientific logic, molecular pathways (AMPK^{Thr172}, PGP 9.5, polyol pathway intermediates), temporal clinical timelines, and structural data points were completely conceived, directed, validated, and verified for factual accuracy by the authors. The generative tool was utilized solely to enhance the graphic execution and presentation layout of the scientific concepts.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
LDM: Conceptualization, Methodology, Investigation, Resources, Investigation, Resources, Writing – original draft preparation; **SG:** Writing – review and editing, Supervision; **VRS:** Formal analysis, Investigation, Resources, Project administration; **IJT:** Formal analysis, Investigation, Project administration.

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