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The Role of Metformin in Skeletal Muscle Healing: A Comprehensive Review

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Abstract

BACKGROUND: Skeletal muscle disorders, which comprise numerous rare diseases, are primarily genetic. To improve patients' quality of life, novel treatment discovery for neuromuscular illness is needed, given the psychological and financial strain caused by the disease's progression and limited therapeutic options. Metformin has garnered attention beyond its glucose lowering effects for its ability to improve skeletal muscle repair. Therefore, this review aims to gather and evaluate recent studies on the impact of metformin on the regeneration of skeletal muscle. **Methods**: A systematic search was conducted in January 2025 using multiple databases (i.e., ScienceDirect, Scopus, Web of Science, IEEE, and others) to identify primary research that focused on the effects of metformin on skeletal muscle or mechanism related to skeletal muscle healing. After applying exclusion criteria, the abstracts were screened to assess their eligibility for the review, followed by full-text screening. **Results:** A total of 115 studies were identified, and 40 studies were included in the final data synthesis. Metformin's ability on muscle healing involved satellite cell activation, inflammatory modulation, and mitochondrial regulation. Research results are still inconsistent; some studies show that it positively impacts regeneration, while others show delayed healing or compromised function. Metformin has various effects on the repair of skeletal muscle; most of which are mediated by AMPK activation, decreased inflammation, and oxidative stress regulation. **Conclusion:** This review highlights the potential of metformin in skeletal muscle healing. Nevertheless, the type of injury, dosage, and timing of administration are critical factors influencing outcomes.

Keywords: skeletal muscle; metformin; inflammation; macrophages; satellite cells.

Introduction

Skeletal muscle is among the most dynamic and adaptable tissues in the human body. Skeletal muscle tissue also has the largest mass, accounting for 45% of total body weight. However, it is also susceptible to injury caused by various factors, including sports trauma, overuse or certain medical conditions, leading to pain, weakness and loss of muscle mass. The nature and severity of the injury determine the healing response, which is primarily based on the muscle's intrinsic regenerative capacity [1]. Both chronic muscle disorders and muscle injuries have similar regenerative mechanisms; therefore,

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understanding the mechanism behind skeletal muscle healing is essential not only for improving recovery after acute injuries but also for developing strategies to alleviate progressive muscle wasting in neuromuscular disease and lead to functional recovery. Moreover, detecting novel therapeutic targets for alleviating the progression of neuromuscular disease and reducing patient discomfort is vital [2].

Metformin was introduced into clinical practice after research evaluating its tolerance, as well as its longer-term safety [3]. Metformin inhibits gluconeogenesis through multiple pathways, thereby lowering blood glucose levels [3]. Metformin, along with its hypoglycemic effect, could augment skeletal muscle mass and strength via different mechanisms, thus delaying disease progression. Muscle degeneration in both injuries and neuromuscular diseases often involves mechanisms such as mitochondrial dysfunction, oxidative stress, inflammation and impaired glucose and lipid metabolism. While conventional drugs that target a single pathological process, such as corticosteroids (i.e., prednisone and dexamethasone) that are widely used to reduce inflammation or non-steroidal anti-inflammatory drugs (NSAIDS; i.e., ibuprofen and diclofenac) targeting cyclooxygenase (COX), provide short-term relief, their prolonged use often leads to adverse outcomes, including muscle atrophy, metabolic imbalance, and impaired regeneration [4]. In contrast, through the activation of AMP-activated protein kinase (AMPK), metformin can counteract these mechanisms. Due to its well-established safety profile, low cost, and multifaceted mechanisms, metformin emerges as a promising alternative to conventional drugs for promoting muscle repair and functional recovery.

To the best of our knowledge, we have not identified any article that specifically address the use of metformin in skeletal muscle healing or its underlying mechanisms. Therefore, this review details literature examining non-conventional applications of metformin in tissue repairs, focusing on the molecular and cellular mechanisms underlying its effects on skeletal muscle healing. By integrating data from in vitro studies, animal models, and preliminary clinical trials, this review examines how metformin modulates key processes of muscle repair, including satellite cell function, inflammation, fibrosis, and functional recovery. Consolidating these findings, this low-cost and widely available drug presents potential for further research and clinical translation, particularly in sports medicine, rehabilitation, geriatric medicine, diabetes-related muscle pathology, and neuromuscular diseases, where it may promote recovery after injury or surgery, preserve muscle mass in the elderly, and prevent muscle atrophy in chronic conditions.

Following the introduction (Section 1), the review paper is organized as follows: Section 2 includes the research questions (RQs) and the article selection process; Section 3 depicts the literature review; Section 4 represents a summary and problem definition; Section 5 provides the conclusion.

Material and Methods

Clearly defined RQs are crucial for the evaluation process since they form the foundation of the entire investigation. The defined RQs for the review are given as follows:

- ✓ RQ1: What are the research articles related to skeletal muscle healing?
- ✓ RQ2: What is the importance of metformin and inflammation in muscle healing?
- ✓ RQ3: What are the effects of metformin on satellite cells?
- ✓ RQ4: What are the challenges of the role of metformin in skeletal muscle healing?

We searched across databases such as Science Direct, Scopus, IEEE, Web of Science, and others for studies published from January 1, 2015 to June 30, 2025. The list of keywords used for the search strategy was “skeletal muscle healing”, “metformin”, “skeletal muscle”, and “anti-inflammatory effects”. A total of 115 studies were identified.

First screening

The citations retrieved from the search were imported into EndNote™ (Clarivate, Philadelphia, USA), a reference management software. After removing duplicates and records deemed ineligible for various reasons, 85 studies were screened based on the inclusion and exclusion criteria outlined in Table 1. We used the PRISMA framework to screen the studies as shown in Figure 1. The search outcomes from year 2015 to 2024 are shown in Figure 2.

Second screening

After removing the articles according to the inclusion and exclusion criteria outlined in Table 1 (n = 15), a total of 70 studies underwent the second screening, which involved reviewing the titles and abstracts of the articles. Subsequently, 50 reports were retrieved during this stage, and full-text assessments were conducted for studies deemed potentially relevant. The following reasons were used to exclude the studies:

1) Did not include mechanism related to muscle healing.

2) For in vitro project, the cell type used is irrelevant to muscle healing (e.g., β-cells).

3) Outcomes are limited to glucose uptake or insulin signaling without incorporating any injury model.

Data extraction and charting

Data from the eligible articles were extracted and organized into tables for comprehensive analysis. Table 2 provides an overview of skeletal muscle healing based on underlying mechanisms. Table 3 summarizes studies examining the effects of metformin on inflammation, while Table 4 focuses on its role in satellite cell activation. Finally, Table 5 presents the parameters of metformin treatment applied in studies on skeletal muscle healing.

Literature Review

This literature review aims to critically analyze and combine current scientific evidence on the potential role of metformin in skeletal muscle healing. Given metformin's well-established use in managing type 2 diabetes and its emerging effects on cellular metabolism, inflammation, and tissue regeneration, it is important to explore its implications in muscle repair processes. This review seeks to present an extensive overview of the molecular processes involved, note observations from preclinical and clinical research, and determine current gaps in knowledge as well as the therapeutic uses and limitations of metformin during muscle regeneration

Overview of Skeletal Muscle Healing

Skeletal muscle repair is a highly regulated biological process that involves three intersecting phases: the inflammatory phase, the regenerative phase, and the remodeling phase [6]. The inflammatory phase, which is initiated immediately after injury, is distinguished by necrosis of damaged muscle fibers and invasion of immune cells such as neutrophils and macrophages. These cells remove cellular debris and secrete pro-inflammatory cytokines that condition the microenvironment for tissue repair. With inflammation resolution, the regenerative process begins with the activation and growth of satellite cells (muscle stem cells), which are then differentiated and fused to create new muscle fibers [7]. Angiogenesis and reorganization of the extracellular matrix (ECM) accompany tissue reformation. Ultimately, in the remodeling phase, newly generated myofibers mature, orient, and are incorporated structurally and functionally into mature muscle tissue.

The relationship between inflammation and skeletal muscle regeneration was explored [8]. Resolution of inflammation occurred through a shift from pro-inflammatory macrophages to anti-inflammatory macrophages. As per the research, cross-talk occurred during this transition, combining signals for cellular metabolism, efferocytosis, resolution, and signaling pathways. Macrophages reduced inflammation throughout the restorative phase while promoting matrix remodeling, angiogenesis, and stem cell differentiation. Depleting macrophages can impair skeletal muscle regeneration by delaying the expression of pro-fibrotic factors, inflammatory cytokines, chemokines, and oxidative stress-related enzymes [9].

Cyclooxygenase-2 (COX-2) also plays a role in the inflammatory response of skeletal muscle healing by converting arachidonic acid to prostaglandins (i.e., PGE2), which recruits inflammatory cells and activates satellite cells [10]. In acute muscle healing, NSAIDs that act as COX inhibitors (i.e., indomethacin and ibuprofen) reduced proliferation, differentiation, and fusion of satellite cells. The treatment also inhibited plantaris hypertrophy following overloading [4]. Conversely, in chronic muscle healing, prednisone — a steroidal anti-inflammatory drug — has positive effects by dampening chronic inflammatory conditions, decreasing transforming growth factor-beta (TGF-β) production, and diminishing muscle fibrosis [11]. It restored the balance in the inflammatory process and improved muscle regeneration. In addition to the inflammatory condition underlying muscle atrophy (acute vs. chronic), the effectiveness of anti-inflammatory drugs in promoting muscle healing also depends on the origin of the inflammatory process, whether local or systemic [4].

Another protein called hepatocyte growth factor (HGF) is also activated during muscle regeneration. It activates quiescent satellite cells in skeletal muscle and facilitates the transition of infiltrated macrophages [12, 13]. Inhibiting HGF signaling leads to increased M1 macrophage inflammatory markers, such as interleukin-1 beta (IL-1β) and inducible nitric oxide synthase (iNOS), and diminished M2 macrophage markers, such as IL-10 and TGF-β, resulting in compromised muscle repair. Delivering exogenous HGF promoted the transition to M2 macrophages, thus facilitating muscle regeneration [13]. This demonstrates HGF's potential usage as a basis when developing therapeutics for muscle degenerative diseases.

Every phase of muscle healing depends on cellular energy in the form of adenosine triphosphate (ATP). Hence, decreasing the availability of ATP impairs every aspect of the healing process. ATP and other derivatives of adenine nucleotides are reduced in atrophic skeletal muscle across different diseases, including diabetes [14]. Intracellular ATP delivery promoted rapid tissue regeneration via the upregulation of cytokines, chemokines, and stem cells [15]. The greater healing effect was achieved through energy supply via magnesium-ATP intracellular delivery, although other functions of ATP might also contribute to this effect.

Myostatin, a member of the TGF-β family and an inhibitor of muscle growth, interacts with activin type II receptors ACVR2B, which recruits and activates myostatin/activin type 1 receptor (ALK4).

Then, ALK4 phosphorylates Smad2 and Smad3 proteins. Activated Smad2 and Smad3 proteins form a complex with Smad4, which regulates gene transcription that inhibits muscle growth and promotes muscle protein degradation [16]. Knocking out myostatin leads to muscle overgrowth, making it a promising target for muscle-wasting disorders [16]. However, down-regulating ALK4 led to decreased muscle mass in mice, which subsequently showed signs of muscle atrophy. The treatment promoted muscle regeneration; however, the muscle fiber size decreased markedly, leading to decreased muscle mass [16]. Therefore, caution must be exercised when developing therapies that interfere with myostatin/ALK4 pathways, as the protein regulates a tight balance of protein synthesis and degradation.

Insulin-like growth factor-1 (IGF-1) is a key growth factor that regulates both anabolic and catabolic pathways in skeletal muscle. It increases skeletal muscle protein synthesis with phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. Activation of Akt in rat muscle prevents denervation-induced atrophy. Myostatin has been found to inhibit Akt phosphorylation, resulting in decreased protein synthesis and reduced cell size. Studies in relation to ALK4 and myostatin/Smad pathways suggested that IGF-1 cross-talks with the pathways at different levels, suggesting a delicate balance between these pathways is critical to maintaining muscle mass [17]. In relation to IGF-1, microRNAs such as miR-29b were identified that contribute to muscle atrophy by targeting IGF-1 and P13K [18]. In aging-induced muscle atrophy, miR-29b was upregulated, making it a potential therapeutic target for counteracting this condition [18]. The significance of research articles related to skeletal muscle healing is depicted in Table 2.

The important role of macrophage polarization from M1 to M2 phenotype in promoting tissue repair through anti-inflammatory cytokines such as IL-10 and TGF-β during the inflammatory phase was emphasized [8]. The heterogeneity of macrophage populations complicates this process. The inflammation modulation in animal models was also investigated and observed individual variability in response to the treatment [4]. Other work examining the role of HGF in inflammatory responses found that its effects on cytokine expression via the AMPK pathway may vary depending on the cell type [13]. Studies focusing on the regenerative phase, particularly angiogenesis and myofiber development, have shown enhanced monocyte chemoattractant protein-1 (MCP-1) expression and myogenesis through vascular endothelial growth factor (VEGF) and TGF-β signaling, although the underlying molecular mechanisms remain poorly understood [15, 16].

Additionally, investigations into the role of miR-29b in muscle via the IGF-1/PI3K pathway demonstrated that inhibition of this microRNA altered fiber-type composition and reduced muscle strength, highlighting the complexity of therapeutic strategies for muscle healing [18]. These studies underscore the complexity of skeletal muscle healing, marked by coordinated cellular responses, signaling cascades, and context-specific outcomes. They also highlight critical challenges, including variability in experimental models, difficulties in therapeutic targeting, and the need for deeper mechanistic insight to optimize muscle repair strategies.

Metformin and Muscle Inflammation and Healing

Metformin can exert significant anti-inflammatory effects that may enhance muscle healing [19]. One of its key mechanisms involves macrophage polarization modulation, shifting the balance from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype [20]. The shift plays a critical role in resolving inflammation and promoting tissue regeneration. Metformin influences the expression of various cytokines by reducing levels of pro-inflammatory markers such as TNF-α and IL-6 and augmenting anti-inflammatory cytokines such as IL-10 [21]. Metformin supports a more favorable milieu for effective muscle repair and regeneration by modulating immune cell activity and the inflammatory environment.

AMPK activation and cytokine expression

The effect of metformin on pro-inflammatory cytokine production (tumor necrosis factor-alpha (TNF-α), IL-1β and IL-6) was investigated in a rotator cuff injury model [22]. Metformin treatment significantly increased cytokine levels, while simultaneously suppressing supraspinatus fatty infiltration. In contrast, metformin was shown to attenuate renal inflammation in db/db mice by regulating autophagy through the AMPK/ mammalian target of rapamycin (mTOR) signaling pathway. This mechanism led to downregulation of IL-1β and TNF-α, suppression of NF-κB activity, and inhibition of reactive oxidative species (ROS)-induced apoptosis [23]. The contrasting result suggests that the immunomodulatory ability of metformin is not strictly anti-inflammatory; it can also have a pro-inflammatory effect, which is context-dependent. For example, metformin may have an anti-inflammatory effect in an already inflamed renal environment, where simulated inflammation would be more detrimental [23]. On the other hand, metformin has a pro-inflammatory effect on normal injuries, augmenting the healing process [22].

In muscle atrophy, excessive activation of the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome leads to excessive inflammation and cell damage, and it has been implicated in the pathogenesis and progression of inflammation-related skeletal muscle wasting. In a model of myocardial infarction, metformin provided cardioprotective effects against ischemia/reperfusion injury. It activated phosphorylated AMPK, decreased pro-inflammatory cytokines, TNF-α, IL-6, and IL-1β, and decreased NLRP3 inflammasome activation [24]. In vitro studies showed that the NLRP3 activator nigericin eliminated the anti-inflammatory effects of metformin, while having minimal influence on AMPK phosphorylation. The inflammatory response induced by myocardial ischemia/reperfusion injury was mediated mainly through activation of the AMPK pathway, which in turn suppressed NLRP3 inflammasome activation [24]. In muscle atrophy, excessive activation of the NLRP3 inflammasome causes excessive inflammation and cell damage, and the NLRP3 inflammasome was shown to be involved in the pathogenesis and development of inflammation-related skeletal muscle wasting [24].

Zinc finger E-box-binding homeobox (ZEB1)

The mechanism of metformin on skeletal muscle atrophy has also been linked to zinc finger E-box-binding homeobox (ZEB1) [25]. Metformin treatment not only increased myotube diameter and reduced the expression of atrophy-marker proteins, but also upregulated ZEB1. While ZEB1 generally promotes inflammatory responses through TGF-β/signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B (NF-κB) signaling [26], in an inflammation-induced atrophy model, metformin-mediated ZEB1 upregulation was beneficial, consequently contributing to muscle repair [25]. This suggests that the effect of metformin is context-dependent.

Inflammatory cells

The immunomodulatory ability of metformin was demonstrated in herpes simplex virus-induced inflammatory lesions [27] The treatment induced metabolic reprogramming within the lesions. Compared to other metabolic therapy such as 2-deoxy-D-glucose (2DG), metformin was more favorable as it reduced the pro-inflammatory response without inhibiting interferon-γ (IFN-γ)–releasing inflammatory cells, such as Th1 and $CD8^+$ T cells. In the context of inflammatory lesions caused by viral infection, the initial inflammatory response mediated by IFN-γ plays an important role in controlling viral replication and preventing disease progression. In contrast, in a metabolic disease model.

Chemokines expression

A study reported that metformin inhibited the expression of chemokines such as CCL2, CXCL10, and CXCL11 [28]. Compound C, an AMPK inhibitor, reversed this inhibitory effect, suggesting that metformin acts via the AMPK pathway. They also found that metformin suppressed the phosphorylation of IκBα and p65, which are crucial in the signaling cascade. IκBα in particular binds to NF-κB, and its activity is elevated during skeletal muscle atrophy. NF-κB inhibited myoblast differentiation into myotubes and in skeletal muscle atrophy, and its activity increased [29]. By preventing IκBα degradation, NF-kβ activation is blocked; consequently, its inhibitory effects on myoblast differentiation were reversed [30]

A detailed summary of six research studies that evaluate the role of metformin on inflammation and skeletal muscle repair using both in vitro and in vivo models to decipher its multifunctional effect is outlined in Table 3. These investigations had diverse methodologies such as gene expression profiling, histological analysis, and analytical approaches to evaluate pivotal stages of muscle repair, spanning acute inflammation to regeneration and atrophy. Metformin exhibited effects across various cell types, namely macrophages [22, 27, 28], C2C12 myoblasts [25], and NVRM [24]. Metformin has been shown to have protective effects across different tissue injury and disease models. In skeletal muscle, while the treatment promoted the pro-inflammatory cytokines production, it also contributed to better preservation of muscle tissue following muscle atrophy [22]. In ocular-lesion models, metformin reduced lesion severity, while in cardiovascular injuries, it decreased infarct size, apoptosis, and fibrosis while improving the markers of myocardial damage. Its anti-inflammatory actions are also evident through the suppression of pro-inflammatory cytokines such as TNF-α and IL-1β, as well as the inhibition of NF-κB– and AMPK-mediated chemokine expression. Thus, these studies suggested the potential of metformin not only as a metabolic drug but also as a modulator of inflammation and muscle remodeling, However, further investigations are needed to elucidate its mechanism and therapeutic potential in muscle repair.

Effects of Metformin on Satellite Cells

Metformin acts on satellite cells, the endogenous stem cells responsible for skeletal muscle repair and regeneration [31]. Satellite cells are important for the initiation of myogenesis following muscle damage, and their proliferation and differentiation capacities determine the efficacy of regeneration [32]. Research has proven that metformin can regulate satellite cell function by activating AMPK, an important energy sensor that increases cellular resistance to metabolic stress and mitochondrial biogenesis [33]. Metformin improves the muscle stem cell niche by enhancing the local microenvironment, suppressing inflammation, and restricting fibrotic signals [34]. These modifications promote a more favorable environment for muscle stem cell function and tissue repair.

Satellite cells activation and function decline with age. While the young muscle niche maintains satellite cells in a quiescent state, the aged niche tends to provide signals that drive their activation and differentiation [35]. Hence, aged satellite cells fail to maintain quiescence; consequently, they differentiate into muscle fibers at the expense of self-renewal. The stem cell population becomes depleted over time; consequently, fewer satellite cells are available for future muscle repair. The loss of satellite cells in aged muscle is especially more pronounced in fast-twitch (type II) fibers [36]. In addition, aged satellite cells displayed a significant decline in migratory ability, migrating at less than half the speed observed in young cells and their activation was notably delayed, as indicated by the low expression of MyoD, a marker for satellite cell activation [37].

One study found that metformin can delay satellite cells activation and maintain their quiescence [38]. The study suggested that the metabolic perturbation induced by metformin forced satellite cells into a lower metabolic state, thereby maintaining them in a quiescent state. In aged muscles, this capability is especially relevant since aged satellite cells lose their ability to remain quiescent. Another study by the same author [39] showed that metformin can slow down the replication of C2C12, a mouse myoblast cell line, by delaying them in G2/M phase of the cell cycle through modulation of cyclins and cyclin inhibitors, consequently inhibiting their permanent exit from the cell cycle. These findings highlight the potential of metformin as a pharmacological intervention for maintaining muscle stem cell function during repeated regeneration cycles, particularly in conditions such as Duchenne muscular dystrophy and sarcopenia, where satellite cell depletion contributes to disease progression.

Metformin was able to reduce muscle atrophy after heat injury by increasing Pax7-positive muscle progenitor cells proliferation [40] Treatment with metformin significantly reduced the myofiber cross-sectional area of burn injury compared to sham. In addition, the treatment also enhanced the proliferation of satellite cells [40]. The importance of metformin in regulating and enhancing satellite cells was also highlighted [41]. They found that uric acid induced ROS production and inhibited insulin receptor substrate 1 (IRS1)–Akt signaling, leading to insulin resistance in C2C12 cells. Metformin was found to reverse this process by increasing glucose uptake.

One study investigated the combined effects of metformin and leucine on collagen deposition and found that the treatment increased both collagen deposition and the satellite cell population [42]. The study also found that the dual treatment alleviated collagen turnover caused by hindlimb unloading by altering the hallmark pathways related to inflammation and myogenesis. Similarly, combined treatment with gallic acid and metformin reduced inflammatory mediators, including TNF-α, IL-6, and NF-κB [43]. These results highlight the increasing popularity of combination therapies, which target multiple pathways simultaneously and may exert synergistic effects.

A study reported that short-term exposure to a clinical dose of metformin augmented H_2O_2 production and release in skeletal muscle of healthy older adults [44]. These changes in H_2O_2 corresponded positively with alterations in type I fiber satellite cell content, consistent with previous findings [42]. During hindlimb unloading, metformin significantly increased the proportion of gastrocnemius type I fibers compared to ambulatory controls, while leucine showed a similar but non-significant trend [42]. This suggests that metformin may help preserve slow-twitch, oxidative fibers, which are more resistant to disuse-induced atrophy.

Table 4 summarizes seven studies examining the effects of metformin across diverse biological models, illustrating its multifaceted roles in muscle regeneration, inflammation, oxidative stress, and immune modulation. In vitro, treating C2C12 myoblasts with 2 mM metformin for 2–8 days delayed satellite cell activation via AMPK activation and mTOR inhibition, potentially hindering rapid muscle repair [38]. The same author observed consistent results in a different study, noting that high doses of metformin inactivated mTOR and that its effect on myogenic differentiation was dose-dependent [39]. In a burn injury, metformin improved satellite cell proliferation and muscle cross-sectional area [40]. However, metformin did not attenuate inflammation, suggesting that the improvement in muscle atrophy was primarily due to enhanced satellite cell proliferation rather than its anti-inflammatory effects [40]. In C57BL/6J mice and C2C12 myoblasts, metformin reversed uric acid–induced insulin resistance, reduced ROS production, and activated IRS1–AKT signaling [41]

The combinatory treatment of metformin and leucine proved effective, as shown by the increased of satellite cells proliferation [42]. Likewise, administration of 200 mg/kg/day metformin and 100 mg/kg gallic acid for 25 days significantly reduced TNF-α and IL-6 levels, preserved tissue architecture, and sustained satellite cell integrity via AMPK activation; however, further studies were required for clinical translation [43]. Lastly, metformin may contribute to the regulation of type I muscle fibers via AMPK activation and oxidative signaling [44]. Collectively, these findings underscore the therapeutic potential of metformin, while also emphasizing that its benefits and limitations are context-dependent.

Challenges on the Role of Metformin in Human Muscle Healing

Several issues with metformin's function in human skeletal muscle repair restrict its use in therapeutic settings. The variation in study designs is one significant problem; it is challenging to develop precise therapy guidelines due to variations in dose, timing, and model systems [45]. Metformin can have suppressive effects on early-phase muscle regeneration, including satellite cell activation and required inflammatory responses, which can postpone recovery, even if it activates AMPK and modifies inflammation as well as mitochondrial function [46]. Most current research is based on animal models or in vitro systems with little human data and few clinical trials that directly measure functional recovery, including muscle strength or mobility. Also, patient-specific characteristics, such as age, sex, metabolic state, and comorbidities, affecting the effects of metformin are not known [47].

Dose-dependent effects

The effect of metformin appears to be dose-dependent [39]. They showed that metformin can slow down the replication of C2C12 and alter the production of cyclins and cyclin inhibitor, therefore inhibit their permanent exit from the cell cycle. High doses of metformin (5 mM and 10 mM) inhibited myogenic differentiation, while low doses appeared to stimulate it, although the latter finding was not statistically significant [39]. This effect is beneficial for long-term muscle maintenance, especially for muscular dystrophy patients where continuous needs for satellite cells leads to depletion of the stem cell pool [48]. However, in the early phase of muscle injury, satellite cell activation and differentiation are needed to generate new myofibers and repair damage. If metformin inhibits this, it may delay muscle regeneration. Given that low and high doses of metformin exert stimulatory or inhibitory effects, respectively, further studies are needed to determine its optimum dosage.

Dosage variability

The dosage and duration of metformin administration (Table 5) varied substantially among studies, suggesting the lack of a standardized treatment protocol across experimental models, shown in Table. In vivo studies applied a wide range of doses, from 50 mg/kg in rotator cuff injury to over 300 mg/kg in models of muscle crush injury or hindlimb unloading [Yoon, Pavlidou]. Some protocols combined metformin with other treatments such as gallic acid and leucine, further complicating direct comparison [Mohamed and Hafez, Petrocelli]. In vitro experiments also showed marked inconsistency, with concentrations ranging from 100 μM to as high as 10 mM, and treatment durations ranging from several hours to multiple days [Pavlidou, Pavlidou, Yuan, Ye]. In several studies, metformin was administered prior to injury induction, which may not accurately reflect clinical conditions where treatment usually begins after injury or disease onset [Pavlidou, 2019, Mohamed and Hafez, Yuan]. These variations in dosage, frequency, and exposure time limits the direct comparisons between studies.

Model limitations

Some studies did not extend their experiments over a sufficient duration. For example, a study utilizing the metformin-loaded PLGA microspheres combined with an in situ–molded injectable sodium alginate/Bioglass (SA/BG) hydrogel to alleviate rotator cuff muscle degeneration was only limited to 6 weeks [49]. To fully evaluate the effect, a longer duration with additional time points would be necessary. The effect of metformin also appeared to differ depending on the health status of the individual. On the other hand, a study of combinatory treatment on Duchenne muscular dystrophy was only conducted on five patients, and no placebo was introduced [Hafner et al. [50]. Despite that, the combinatory treatment of L-arginine and metformin was shown to improve mitochondrial protein expression and reduced oxidative stress, shown by reduction in nitric oxide.

In an insulin-resistant model of C2C12 cells, metformin treatment increased myostatin mRNA level compared to the control [51] Combinatory treatment of metformin, TNF-α and insulin led to greater increase. As myostatin plays a crucial role in muscle atrophy, these findings suggested that metformin could impair muscle function under insulin-resistant conditions. In db/db mice, myostatin mRNA increased significantly only in metformin-treated gastrocnemius muscle, whereas other hindlimb muscles showed no significant differences compared to controls. A similar but more pronounced effect was observed in wild-type mice. Metformin was found to increase the levels of p-AMPK, and enhanced the binding of FoxO3A to the myostatin promoter, consequently upregulating myostatin expression [51]. These findings suggest that metformin exerts complex regulatory effects on muscle, with outcomes differing between diabetic and non-diabetic conditions.

Human data gaps

Although preclinical studies using in vitro and in vivo models provide valuable insights into the potential of metformin in enhancing muscle regeneration through satellite cell maintenance and immunomodulatory ability, clinical evidence supporting these findings remains limited. Some of the clinical evidence provided negative capability of metformin instead. One study reported that metformin reduced ADP-stimulated respiration in low-capacity runner rats [52]. Interestingly, washout of metformin unexpectedly doubled respiratory capacity in high-capacity runners, raising questions about whether the beneficial effects of metformin are broadly applicable.

Considering that the positive effects of metformin are often observed primarily in unhealthy patients or experimental models, an important question arises as to whether its efficacy is dependent on the health status of the individual. One study reported that metformin blunted muscle hypertrophy following advanced resistance exercise training in older adults. They observed that metformin not only attenuated the hypertrophic response but also did not increase the satellite cell population [53]. This effect may be mediated by inhibition of mTORC1, leading to decreased muscle protein synthesis or increased autophagy. Both acute and chronic reductions in mTORC1 activation may lead to decreased lean mass gains in subjects treated with metformin. These findings suggest that, in healthy older individuals, metformin may exert adverse rather than beneficial effects, emphasizing the challenge of defining its precise role in skeletal muscle disease.

Summary and Problem Definition

Metformin's effects on skeletal muscle healing remain poorly understood, although its anti-inflammatory and metabolic functions are established concerning diabetes and aging. Current investigations have reported metformin's influence on satellite cells, mitochondrial biology, and inflammation signaling. Yet, several significant gaps exist, such as inconsistent findings between studies that utilize different models (in vitro vs. in vivo), doses, and treatment durations. There are also a limited number of translational studies. Most studies are based on rodent or cell culture models, with limited validation in human clinical environments. However, scant research has been done on how metformin interacts with muscle-specific conditions, such as sarcopenia, cachexia, or inflammation due to injury. Despite encouraging molecular evidence, whether metformin supports or inhibits skeletal muscle regeneration in various physiological or pathological states is unknown.

Experimental design variability, including dosing regimens, model systems, and endpoint measurements, makes comparisons and more sweeping conclusions challenging. Research concentrates on biomarkers or histology without correlating to muscle strength or function recovery. The action of metformin may differ by age, metabolic state, or the presence of comorbidities, but this individualization is not typically explored. The methodology for translating preclinical understanding into practice is underdeveloped, and standardized protocols and well-conducted human trials are thus needed. This review sought to fill these gaps by integrating recent findings, highlighting limitations and future directions for future research aimed to maximize the therapeutic application of metformin in muscle repair.

Conclusion

Here, the emerging role of metformin, a well-established antidiabetic drug, in skeletal muscle healing was explored. The aim is to analyze metformin's effects on muscle regeneration through various biological mechanisms, such as satellite cell activity, inflammation control, oxidative stress modulation, and mitochondrial function, using both in vitro and in vivo studies. The analyzed research articles found that metformin modulated critical regenerative pathways primarily through AMPK activation and mTOR inhibition, which serve as the most promising molecular target for intervention. By targeting these pathways, metformin could reduce oxidative stress and inflammation, preserve satellite cell viability, and enhance long-term muscle remodeling. Nevertheless, evidence also suggested that reducing necessary acute inflammatory responses and slowing satellite cell activation, especially during the early phases of injury, might delay early-stage muscle repair. These findings were significant as they suggested that metformin could be a cost-effective adjunct therapy to promote muscle health, particularly in aging populations, chronic disease states, or muscle-wasting conditions. In rehabilitation settings, metformin could support recovery after sports injuries or surgical interventions. In older adults, it may help mitigate sarcopenia by preserving muscle mass and function, while in patients with diabetes, it could improve delayed muscle healing associated with chronic hyperglycemia. While preclinical studies provide mechanistic insights into metformin’s effects on muscle regeneration, clinical translation is limited by species differences, dosing inconsistencies, short-term observations, and the scarcity of human trials. Therefore, while current evidence highlights promising mechanisms, well-designed clinical trials are necessary to validate metformin’s therapeutic potential in muscle-related diseases and to establish optimal dosing, treatment duration, and target populations.

Abbreviations

ALK4, activin receptor-like kinase 4; AMPK, AMP-activated protein kinase; Akt, protein kinase B; COX-2, cyclooxygenase-2; ECM, extracellular matrix; IFN-γ, interferon-gamma; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; 2DG, 2-deoxy-D-glucose.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical approval

Not applicable

TABLE 1. Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Language	English	Other than English
Year of Publication	2015-2025	Published before 2015
Type of Publication	Peer-reviewed journal articles and reviews	Grey literature (e.g., theses, dissertations, conference proceedings), book and book chapters

TABLE 2. Overview of studies on skeletal muscle healing.

Author's name	Method	Phase	Cell Types	Proteins	Findings	Challenges
Chazaud et al. [8]	Inflammatory	Inflammatory	M1→ M2 macrophage transition	IL-10, TGF-β	- Macrophages reduce inflammation while promoting stem cell differentiation and matrix remodeling	Complex and dynamic nature of inflammation and the heterogeneity of macrophage populations
Duchesne et al., [4]	Animal models	Inflammatory and Regenerative	Macrophages and satellite cells	IL-6	- Anti-inflammatory drugs were effective to dampen local inflammation but not systemic inflammation.	Individuals respond differently to injuries and treatments, making it challenging
Choi et al. [13]	Animal models	Inflammatory and Regenerative	Macrophages	TNF-α, IL-1β, iNOS and IL-10	- HGF decreased TNF-α, IL-1β, and iNOS, while enhancing IL-10 expression. It also increased the phosphorylation of AMPKα	The regulatory effect of HGF on AMPK is complex and appears to occur through distinct pathways depending on the cell type.
Mo et al. [15]	Real-time PCR and immunohistochemical staining	Regenerative	Endothelial cells and platelet	VEGF-A, VEGF-D, and VEGFR-2	- Wounds treated with ATP-vesicles depicted higher expression of MCP-1 along with stem cell markers	Less mechanism was explored so, there should be more mechanism should be explored
Pasteuning-Vuhman et al. [16]	Myogenic differentiation assay and Luciferase reporter assay	Regenerative	Myofibers and fibroblasts	TGF-β	- ALK4 inhibition controlled the delicate balance between protein production and degradation. - ALK4 inhibition also increased myogenesis	Difficulty in targeting ALK4 specifically for therapeutic purposes
Li et al. [18]	Animal models and in vitro	Regenerative	Myofibers	miR-29b	- MiR-29b contributed to multiple types of muscle atrophy by targeting IGF-1 and P13K.	The fiber-type composition shifted from type I fibers towards type IIB fibers, leading to overall decrease in strength.

IL-10, interleukin-10; TGF-β, transforming growth factor-beta; IL-6, interleukin-6; HGF, hepatocyte growth factor; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; AMPK, AMP-activated protein kinase; PCR, polymerase chain reaction; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2; ATP, adenosine triphosphate; MCP-1, monocyte chemoattractant protein-1; ALK4, activin receptor-like kinase 4; IGF-1, insulin-like growth factor 1; P13K, phosphoinositide 3-kinase.

TABLE 3. Overview of studies on the role of metformin on inflammation and healing of muscle.

Author's name	**Methods**	**Importance**	**Phase**	**Cell Types**	**Cytokines**	**Time duration**	**Impacts**	**Outcomes**	**Challenges**
Yoon et al., [22]	Animal model and analytical techniques	Modulating inflammation and inhibiting fatty infiltration	Acute inflammatory and early regenerative phase	Macrophages and Myofibers	IFN-γ, IL-6 and TNF-α	5 days and 14 days	Metformin administration led to a significant upregulation of proinflammatory cytokines.	Better preservation of muscle tissue suggests potential benefits for muscle healing	More research was needed to translate these findings into clinical applications for human patients
Jia et al., [25]	In vitro model, In vivo model, and analytical techniques	Protective effects against skeletal muscle atrophy	Inflammatory	C2C12 Myoblasts	IL-1β	In vitro: 4 days and In vivo: 4 weeks	Metformin treatment increased the diameter of myotubes in C2C12 cells.	Metformin treatment partially alleviated muscle atrophy and stimulated differentiation.	Long-term impact of metformin on muscle regeneration was not explored completely
Berber and Rouse [27]	Animal model	Modulating inflammation	Inflammatory	Leukocyte, neutrophils, macrophages and T cells.	CD45, CD11b, Ly6G, F4/80, CD4, CD8, IFN-γ, and Foxp3	9 to 15 days	The severity of HSV-induced ocular lesions was reduced when treatment began at lesion onset. Both 2DG and metformin were effective, with metformin showing slightly greater efficacy.	Metformin reduced ocular lesion severity	Need further studies to optimize dosing and timing.
Sun et al. [23]	Animal model	Impact of metformin om diabetic nephropathy	Inflammation	-	IL-1β, TNF-α and NF-κB	7 days	Protective effect of metformin may involve regulation of the AMPK–mTOR–autophagy signaling pathway	Reduced T NF-α and IL-1β	Further studies are needed to confirm whether these findings translate to diabetic patients.
Zhang et al. [24]	Rat heart Langendorff model and in vitro	Cardioprotective effects of metformin on I/R injury	Inflammation	NRVM	TNF-α, IL-6, IL-1β and NLRP3 inflammasome	30 minutes before ischemia and continued until the reperfusion phase	Metformin protects the heart during I/R injury by enhancing AMPK signaling and suppressing NLRP3 inflammasome activation.	Reduced infarct size, apoptosis and fibrosis Improved markers of myocardial damage	Precise therapeutic window and optimal dose of metformin for post-ischemic treatment need clarification.
Ye et al. [28]	In vitro model	Regulatory effects of metformin on chemokine expression	Inflammation	RAW264.7	CCL2, CXCL10, CXCL11, IL-1 and IL-6	8 to 24 hours	Metformin treatment decreased the expression of chemokines along with IL-1 and IL-6.	Metformin inhibited NF-κB and AMPK signaling, leading to reduced chemokine expression.	The inhibitory effect of metformin on NF-κB remain unclear as Ser536 was greatly suppressed compared to Ser276

IFN-γ, interferon-gamma; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; NF-κB, nuclear factor-kappa B; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; I/R, ischemic/reperfusion; NRVM, neonatal rat ventricle myocytes NLRP3, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; RAW264.7, murine macrophage cell line; CCL2, chemokine ligand 2; CXCL10, C-X-C chemokine ligand 10; CXCL11, C-X-C chemokine ligand 11; IL-1, interleukin-1.

TABLE 4. Overview of studies on the effect of metformin on satellite cells. AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; MyoD, myoblast determination protein 1; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; H_2O_2 , hydrogen peroxide.

Author's Name	Models	Dose of Metformin	Duration	Cytokines	Effect	Mechanism	Outcomes	Challenges
Pavlidou et al., [38]	C2C12 myoblasts	2 mM	2–8 days	-	Delayed satellite cell activation.	AMPK activation and mTOR inhibition	Metformin administration led to delayed regeneration of cardiotoxin-damaged skeletal muscle.	In situations requiring rapid muscle repair, such as acute injuries, the delayed effects of metformin might not be beneficial.
Pavlidou et al., [39]	C2C12 myoblasts and satellite cells	100 µM, 500 µM, 2 mM, 5 mM and 10 mM (added every 24h)	3 days	-	Metformin treatment led to decreased levels of MyoD, myogenin.	AMPK activation and mTOR inhibition	Metformin treatment activated AMPK, a key regulator of energy metabolism, contributed to the observed effects on differentiation.	Higher dose of metformin inactivated mTOR, highlighting the need to determine optimal dosing for therapeutic applications
Yousuf et al. [40]	Burn injury model	100 mg/kg	24h after injury to 14 days	-	Metformin attenuated muscle catabolism, preserved muscle cross-sectional area and increased satellite cells proliferation	AMPK	Metformin increased Pax-7 positive muscle progenitor cells, therefore enhanced the regenerative capacity of skeletal muscle	Impact of metformin n regeneration varied with the nature of the injury model.
Yuan et al., [41]	C57BL/6J and C2C12 myoblasts	-	7 days	-	Reduced cardiotoxin-induced intracellular calcium influx.	AMPK activation	Results demonstrated an interaction between metformin and uric acid-induced insulin resistance that could be important for knowing effects of metformin on patients.	Study did not specify the exact dose of metformin administered to mice, making it difficult to compare with clinical dosing.
Petrocelli et al., [42]	Animal model	0.5 mg/mL	-	-	Increased satellite cell abundance in the gastrocnemius muscle during disuse.	RNA sequencing	Altered muscle transcriptional pathways related to inflammation and myogenesis.	Combinatory treatment did not alter muscle or fiber size during disuse or recovery conditions.
Mohamed and Hafez [43]	Animal model	200 mg/kg metformin and 100 mg/kg gallic acid a day	25 days	TNF-α and IL-6	Suppressed the expression of pro-inflammatory cytokines.	AMPK activation	Showed normal architecture with intact satellite cells.	Additional studies, including clinical trials, were still needed.
McKenzie et al., [44]	Homeostatic model	-	5 weeks	-	Change in H_2O_2 emission was positively correlated with the change in type 1 myofiber satellite cell content.	AMPK activation	Positive correlation between increased H_2O_2 emission and satellite cell content in type 1 muscle fibers.	Skeletal muscle all sample size (16 participants).

TABLE 5. Summary of studies evaluating metformin dosage, treatment duration and experimental model.

Study	Model/Condition	Experimental Type	Duration of Treatment	Dose	Focus
Yoon et al. [22]	Rotator cuff injury	In vivo	5 days (after injury)	50 mg/kg	Immunomodulatory
Jia et al. [25]	Muscle atrophy	In vitro and in vivo	In vitro: Day 3 after myotube differentiation In vivo: 4 weeks	In vitro: 1 mM In vivo: 320 mg/day	Immunomodulatory
Berber and Rouse [27]	HSV-1	In vivo	Twice a day, up to day 9 or 14	100 mg/kg	Immunomodulatory
Sun et al. [23]	Diabetic nephropathy	In vivo	7 days	200 mg/kg	Immunomodulatory
Zhang et al. [24]	Ischemia/ reperfusion	In vivo and in vitro	-	-	Immunomodulatory
Ye et al. [28]	-	In vitro	8 to 24 hours	10 mM	Immunomodulatory
Pavlidou et al. [38]	Muscle crush injury	In vivo In vitro	In vivo: Pretreated before injury In vitro: Every 48 h	In vivo: 300 mg/kg In vitro: 2 mM	Satellite cells
Pavlidou et al. [39]	-	In vitro	3 days, metformin was added every 24h	100 µM, 500 µM, 2 mM, 5 mM and 10 mM	Satellite cells
Yousuf et al. [40]	Burn injury model	In vivo	24h after injury to 14 days	100 mg/kg	Satellite cells
Yuan et al., [41]	-	In vitro	24 h	1 mM (added 2 h before UA)	Satellite cells
Petrocelli et al. [42]	Hindlimb unloading	In vivo	7 to 14 days	336.6 mg/kg	Satellite cells
Mohamed and Hafez [43]	Hepatic encephalopathy (HE)	In vivo	25 days	200 mg/kg metformin and 100 mg/kg gallic acid a day (given before HE induction)	Satellite cells
McKenzie et al. [44]	-	Controlled trials	14 days	2 grams per day. No capsule on the morning of data collection	Satellite cells

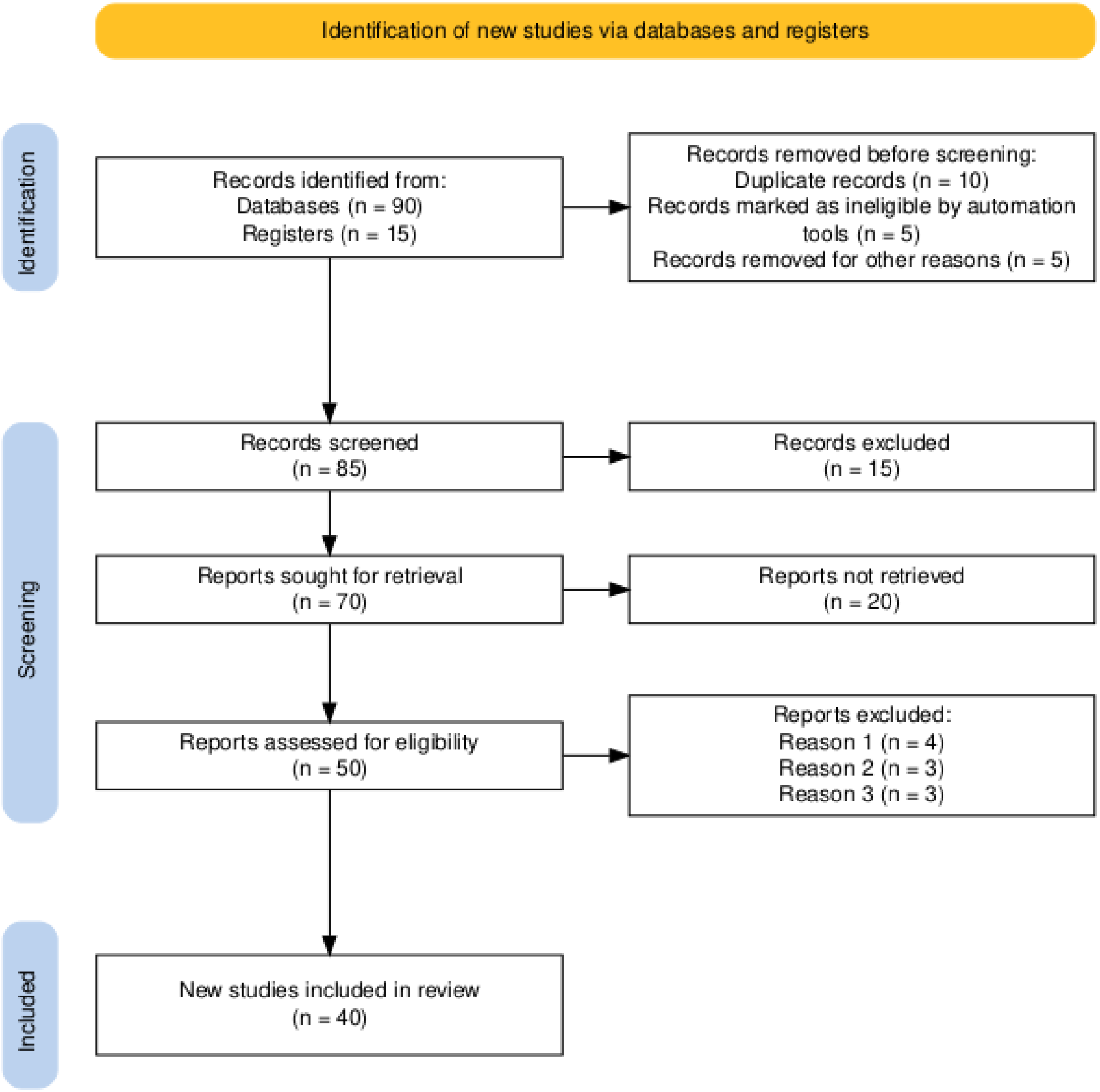

Fig. 1. PRISMA flowchart of study selection [5]. The database search yielded 105 searches, spanning from January 1, 2015 to June 30, 2025. 40 articles were included in the final data analysis.

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