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REVIEW ARTICLE OPEN ACCESS

A Systematic Review of the Effects of Exercise Training on Oxidative Stress, Inflammatory Signaling, and Inflammasome Pathways in Diabetic Animal Models

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ABSTRACT

Background: Oxidative stress, chronic inflammation, and inflammasome activation contribute substantially to the progression of diabetes mellitus and its complications. Exercise training has emerged as a potential non-pharmacological strategy to modulate these pathological mechanisms. This systematic review aimed to evaluate the effects of exercise training on oxidative stress, inflammatory signaling, antioxidant defense, and inflammasome-related biomarkers in diabetic animal models. **Methods:** PubMed and ScienceDirect were systematically searched from database inception to April 2026 in accordance with PRISMA 2020. In vivo diabetic rodent studies evaluating exercise and reporting oxidative stress, inflammatory, antioxidant, or inflammasome-related biomarkers were included. Risk of bias was assessed using SYRCLE's tool, and findings were synthesized qualitatively because of methodological heterogeneity. The review was not prospectively registered. **Results:** Twenty studies were included. Exercise training generally reduced oxidative and nitrosative stress markers, enhanced endogenous antioxidant defenses, attenuated pro-inflammatory mediators, and modulated NLRP3 inflammasome- and pyroptosis-related signaling across multiple diabetic tissues. Six studies were categorized as low risk of bias, 13 as moderate risk, and one as high risk. **Conclusions:** Preclinical evidence indicates that exercise training exerts multi-tissue protective molecular effects through coordinated redox, inflammatory, antioxidant, and inflammasome-related mechanisms. Interpretation is limited by methodological heterogeneity across diabetic models, exercise protocols, target tissues, and biomarker assessments. Standardized, methodologically rigorous studies are needed to clarify integrated redox–inflammasome–pyroptosis pathways and improve translational relevance. No specific funding was received for this review.

Keywords: *diabetes; exercise training; inflammation; oxidative stress; inflammasome*

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both, ultimately leading to multiorgan damage[1,2]. In 2024, approximately 589 million adults aged 20–79 years were living with diabetes, and this number is projected to increase to 853 million by 2050[3]. This growing burden is largely driven by type 2 diabetes mellitus (T2DM), which continues to rise across both high-income and low to middle income countries[4]. Beyond hyperglycemia, diabetes is strongly associated with cardiovascular, renal, hepatic, neural, and metabolic complications that substantially contribute to morbidity and mortality.

These complications indicate that diabetes is not only a disorder of glucose homeostasis, but also a systemic condition involving persistent cellular and molecular injury.

At the cellular and molecular levels, one of the key mechanisms linking hyperglycemia to diabetic complications is the interaction between oxidative stress and chronic inflammation. Persistent hyperglycemia promotes excessive reactive oxygen species (ROS) production, mitochondrial dysfunction, lipid peroxidation, and impairment of endogenous antioxidant systems, resulting in tissue injury and metabolic dysregulation[1,2]. Oxidative stress further amplifies inflammatory pathways involving mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), thereby contributing to insulin resistance, β-cell dysfunction, and tissue fibrosis[5]. These redox–inflammatory interactions are regulated by molecular pathways implicated in diabetic complications, including nuclear factor erythroid 2-related factor 2 (Nrf2) as a major regulator of antioxidant and cytoprotective responses through the Nrf2/HO-1 pathway[6], as well as the NLRP3 inflammasome, which promotes inflammatory injury and pyroptotic cell death across diabetes-associated tissues[7,8]. Thioredoxin-interacting protein (TXNIP) has also been proposed as a molecular link between oxidative stress and NLRP3 inflammasome activation, suggesting a mechanism through which redox imbalance may amplify inflammatory injury in diabetes[9,10]. Therefore, therapeutic strategies that modulate oxidative stress, inflammatory signaling, and inflammasome-related pathways may be important for reducing diabetes-associated tissue injury.

Among non-pharmacological strategies, exercise training is widely recognized as an effective approach for improving glycemic control and metabolic health in DM. Beyond its metabolic benefits, exercise has been shown to improve redox balance, enhance antioxidant defense, attenuate inflammatory mediators, and protect pancreatic βcells from oxidative and endoplasmic reticulum stress[11,12]. These effects suggest that exercise may regulate immunometabolic and inflammasomeassociated pathways, thereby contributing to broader tissue protection in diabetic conditions[8]. Although numerous animal studies have examined the effects of exercise on oxidative stress and inflammatory biomarkers in diabetes, evidence related to Nrf2 signaling, redox regulation[13,14], NLRP3 inflammasome activation[15,16], and pyroptosis-related pathways[17] remains fragmented across different diabetic models, exercise protocols, target tissues, and biomarker assessments. Therefore, this systematic review aimed to evaluate and synthesize current evidence regarding the effects of exercise training on oxidative stress, inflammatory signaling, antioxidant defense systems, and inflammasome-related pathways in diabetic animal models, while identifying potential molecular mechanisms underlying exercise-mediated protection against diabetes-associated tissue injury.

MATERIALS AND METHODS

Search Strategy and Study Selection

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Systematic literature searches were performed in PubMed and ScienceDirect from database inception to April 2026. The search strategy was developed based on the PICO framework: diabetic rodent models as the population, exercise training as the intervention, non-exercise diabetic groups as the comparison, and oxidative stress, inflammatory signaling, antioxidant defense, and inflammasome-related biomarkers as outcomes.

The main search terms included combinations of “diabetes” OR “diabetic,” “exercise training,” “oxidative stress,” “inflammation,” “inflammasome,” “gene expression,” and “animal model,” with Boolean operators adapted to each database. The PubMed search string was: (diabetes OR diabetic) AND exercise training AND (inflammation OR oxidative stress OR inflammasome) AND gene expression AND (rat OR mice OR animal). The ScienceDirect search string was: (diabetes OR diabetic)

AND exercise training AND oxidative stress AND inflammasome AND gene expression AND animal. No publication year restriction was applied.

All identified records were screened independently by two reviewers based on titles and abstracts, followed by full-text assessment of potentially eligible studies according to predefined inclusion and exclusion criteria. Disagreements were resolved through discussion until consensus was reached. The study selection process is presented in the PRISMA 2020 flow diagram. The completed PRISMA 2020 checklist and PRISMA 2020 for Abstracts checklist are provided in Online Resources 1 and 2, respectively. The PICO framework and complete database search strategies are provided in Online Resource 4.

Eligibility Criteria

Studies were considered eligible if they met the following criteria: (1) in vivo experimental study design; (2) use of diabetic rodent models representing type 1 or type 2 diabetes mellitus; (3) exercise training or physical activity as the primary intervention; and (4) assessment of at least one oxidative stress, inflammatory signaling, antioxidant defense, and inflammasome-related biomarkers.

Studies were excluded if they involved non-diabetic animal models, in vitro experiments, review articles, editorials, letters to the editor, conference abstracts without complete data, or duplicate publications.

Data Collection Process

Data extraction was performed independently by two reviewers using a standardized extraction form developed prior to the review process. Extracted data included study characteristics, animal species or strain, diabetes induction model, exercise modality, intensity, frequency, duration, intervention protocol, target organs, assessed biomarkers, molecular pathways, and principal findings. Any discrepancies between reviewers were resolved through discussion until consensus was reached. When methodological details or outcome data were unclear, the original articles were re-evaluated to ensure data accuracy.

Extracted data were organized into standardized evidence tables summarizing study characteristics, diabetes models, exercise type, exercise protocols, target organs, principal molecular findings and major biological effect. Biomarkers were grouped according to biological function into oxidative stress, inflammatory signaling, antioxidant defense, and inflammasome-related categories to facilitate qualitative synthesis and comparison across studies.

Data Items and Outcomes

The primary outcomes were molecular biomarkers associated with oxidative stress, inflammatory signaling, antioxidant defense, and inflammasome-related pathways in diabetic tissues. Oxidative stress and antioxidant-related outcomes included reactive oxygen species (ROS), malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), glutathione balance (GSH/GSSG), antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as antioxidant and cytoprotective signaling pathways including Nrf2/HO-1, AMPK, SIRT1, and miR-126-related mechanisms.

Inflammatory outcomes included tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-10 (IL-10), NF-κB signaling, adiponectin, irisin, and Meteorin-like (METRNL)-related pathways. Inflammasome and pyroptosis-associated outcomes included NLRP3, caspase-1, IL-18, gasdermin D (GSDMD), and purinergic signaling pathways involving P2X4 and P2X7 receptors.

Risk of Bias Assessment

Methodological quality and risk of bias were assessed independently by two reviewers using SYRCLE's Risk of Bias tool for animal intervention studies[18]. The assessment covered selection, performance, detection, attrition, reporting, and other potential sources of bias. Each domain was categorized as "Low risk," "High risk," or "Unclear risk" based on the methodological transparency reported in each study. Discrepancies between reviewers were resolved through discussion until consensus was reached. Studies were considered to have low overall risk of bias when most domains were rated as low risk and no major methodological concerns were identified. The detailed study-level SYRCLE risk-of-bias assessment is provided in Online Resource 3.

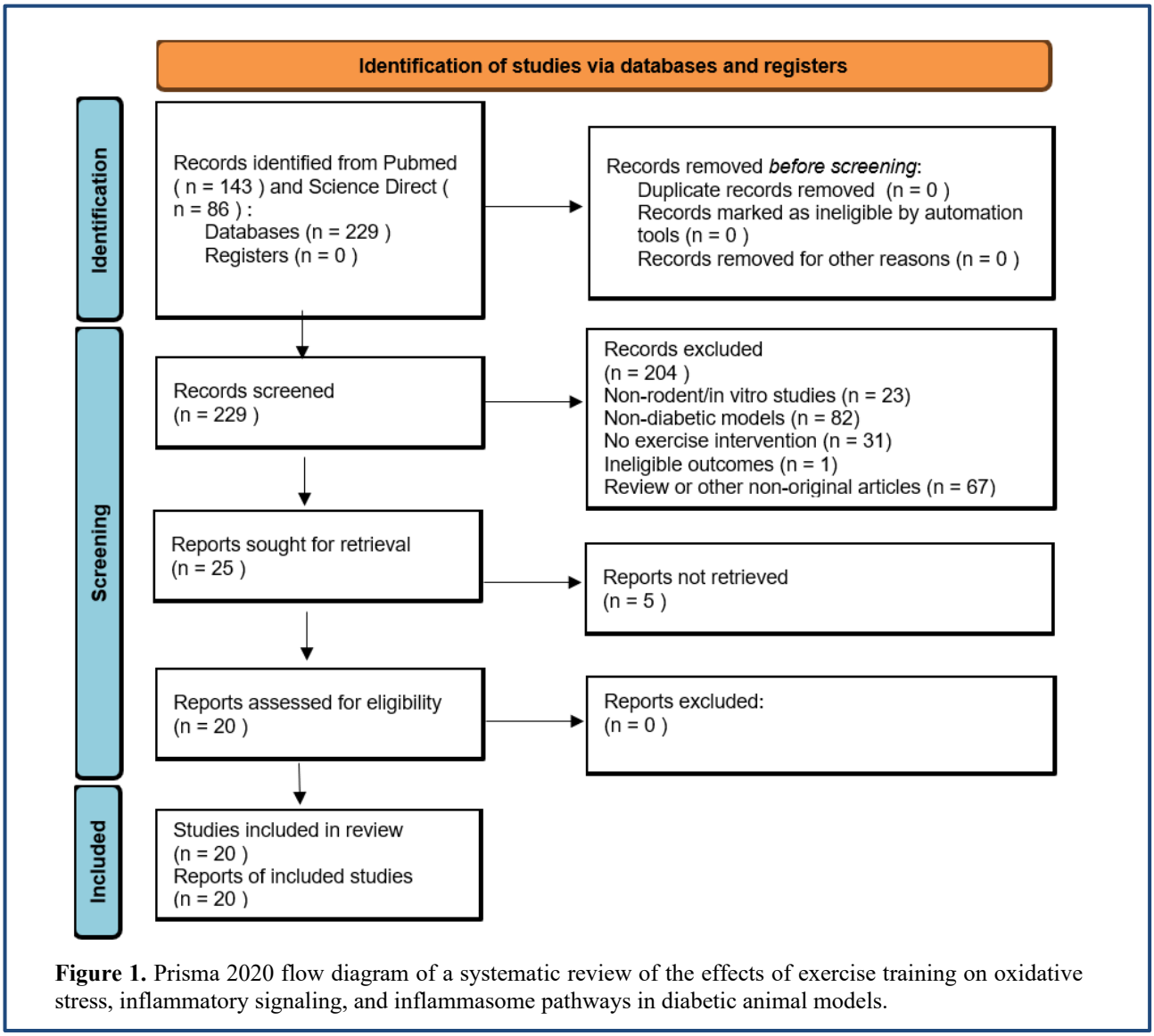


Figure 1. Prisma 2020 flow diagram of a systematic review of the effects of exercise training on oxidative stress, inflammatory signaling, and inflammasome pathways in diabetic animal models.

Synthesis of Results

Due to substantial heterogeneity among included studies in terms of animal species and strains, diabetes induction methods, exercise protocols, target organs, and assessed biomarkers, quantitative meta-analysis was not performed. Accordingly, standardized effect measures such as mean differences, risk ratios, or pooled estimates were not calculated. Findings were synthesized descriptively using evidence tables and qualitative narrative synthesis.

Study characteristics, exercise protocols, molecular biomarkers, principal findings, and risk of bias assessments were summarized in table and figure to facilitate comparison across diabetic models and exercise interventions. Studies were grouped according to shared molecular and biological pathways, including oxidative stress regulation, antioxidant signaling, inflammatory modulation, and inflammasome-related mechanisms.

Potential sources of heterogeneity were explored qualitatively by comparing differences in animal models, diabetes induction methods, exercise modality, intervention duration and intensity, target organs, and assessed molecular biomarkers. Sensitivity analyses, formal reporting bias assessment, and certainty of evidence evaluation were not performed because quantitative pooling was not feasible.

Registration and Protocol

This systematic review was not prospectively registered, and no review protocol was publicly published.

RESULTS

Study selection

The database search identified 229 records from PubMed and ScienceDirect. After title and abstract screening, 25 reports were considered potentially eligible and selected for full-text retrieval. Five reports could not be retrieved for full-text assessment. The remaining 20 full-text articles were assessed for eligibility and all met the predefined inclusion criteria; therefore, 20 studies were included in the qualitative synthesis. The study selection process is illustrated in the PRISMA 2020 flow diagram.

Study characteristics

The 20 included studies were published between 2011 and 2025 and investigated exercise interventions in various diabetic animal models, including streptozotocin (STZ)induced, high-fat diet (HFD)-induced, HFD/STZ-induced, and genetic diabetic models. The studies used different rodent species and strains, with target tissues including the heart, liver, kidney, skeletal muscle, pancreas, adipose tissue, and neural tissue. Treadmill exercise was the most frequently applied intervention, although swimming, voluntary wheel running, resistance training, and high-intensity interval training (HIIT) protocols were also reported. Overall, the studies evaluated oxidative stress markers, antioxidant enzymes, inflammatory mediators, and inflammasome-related pathways. Detailed study characteristics and principal molecular findings are presented in Table 1.

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Table 1. Characteristics, exercise protocols, and principal molecular findings of included studies investigating exercise interventions in diabetic animal models (n = 20).

No	Author (Year)	Diabetes Model	Species / Strain	Exercise Type / Modality	Target Organ / Tissue	Exercise Protocol	Principal Molecular Findings	Major Biological Effect
1	Asgari et al. (2022)[19]	T1DM (STZ 65 mg/kg)	Wistar rats	Moderate interval treadmill training	Kidney	Interval training, 40 min/session, 5 days/week for 10 weeks	Activated miR-126/Nrf2 signaling; reduced MDA; increased GPx and CAT activity	Antioxidant signaling activation
2	Botta et al. (2013)[20]	T2DM (db/db)	db/db mice	Moderate aerobic motorized wheel running	Heart	Voluntary wheel running, 60 min/session, 5 days/week for 2 weeks	Increased cardiac PGC-1α expression and reduced inflammatory cytokines and iNOS signaling	Anti-inflammatory and metabolic regulation
3	Ghiasi et al. (2019)[21]	T2DM (HFD + STZ)	Wistar rats	Aerobic swimming training	Pancreas	Swimming, 60 min/session, 5 days/week for 12 weeks	Increased pancreatic SIRT1, SOD, GPx, and CAT activity; reduced MDA	Redox homeostasis improvement
4	Javaid et al. (2021)[22]	T2DM (HFD-induced)	C57BL/6 mice	Aerobic treadmill training	Adipose tissue	Progressive treadmill, 20–50 min/session, 5 days/week for 12 weeks	Suppressed NLRP3, caspase-1, IL-1β, and IL-18 signaling through METRNL-associated pathways	Inflammasome inhibition
5	Khoramipour et al. (2024)[23]	T2DM (HFD + STZ)	Wistar rats	HIIT treadmill training	Skeletal muscle	HIIT, 5 days/week for 8 weeks	Modulated arginine and glutathione metabolism and P2X7R-related purinergic signaling	Purinergic and redox pathway modulation
6	Lima et al. (2015)[24]	T1DM (STZ 60 mg/kg)	Wistar rats	Moderate aerobic treadmill training	Liver	Progressive treadmill, 15–60 min/session, 5 days/week for 9 weeks	Normalized hepatic SOD1 and GPX1 expression and increased SOD and GPx activity	Enhanced antioxidant defense

7	Liu et al. (2025)[25]	T2DM (HFD + STZ)	Mice	Aerobic treadmill training	Heart	Treadmill, 60 min/session, 5 days/week for 8 weeks	Suppressed P2X4/P2X7-mediated NLRP3 activation and GSDMD-associated pyroptosis	Inflammasome and pyroptosis inhibition
8	Pourmousavi et al. (2023)[26]	T1DM (STZ 50 mg/kg)	Wistar rats	Moderate aerobic treadmill training	Heart	Treadmill, 60 min/session, 5 days/week for 8 weeks	Reduced cardiac MDA, increased SOD and GPx, improved Bcl-2/Bax ratio	Antioxidant and anti-apoptotic effect
9	Qi et al. (2011)[27]	T2DM (non-obese)	Goto-Kakizaki rats	Endurance aerobic treadmill training	Skeletal muscle	Treadmill, 30–60 min/session, 6 days/week for 8 weeks	Improved GSH/GSSG balance and reduced p53 and TIGAR expression	Redox balance restoration
10	Rao et al. (2014)[28]	T2DM (HFD-induced)	C57BL/6 mice	Endurance aerobic downhill treadmill	Adipose tissue & muscle	Downhill treadmill, 60 min/session, 5 days/week for 8 weeks	Induced METRNL secretion and promoted thermogenic and IL-10-associated anti-inflammatory signaling	Immunometabolic modulation
11	Riahi et al. (2016)[29]	T1DM (STZ 50 mg/kg)	Wistar rats	Moderate aerobic swimming training	Heart	Swimming, 30 min/session, 5 days/week for 8 weeks	Reduced cardiac LOX-1 expression, MDA, and nitrosative stress (NOx)	Oxidative stress reduction
12	Ribeiro et al. (2017)[30]	T1DM (STZ 60 mg/kg)	Wistar rats	Resistance ladder-climbing training	Adipose tissue (RPAT)	Resistance training every 48 h for 8 weeks	Increased adiponectin mRNA and IL-10 expression in adipose tissue and serum	Anti-inflammatory adipokine regulation
13	Rodrigues et al. (2014)[31]	T1DM (STZ 60 mg/kg)	Wistar rats	Moderate aerobic treadmill training	Kidney	Treadmill, 60 min/session, 5 days/week for 8 weeks	Reduced renal TBARS and suppressed iNOS and P2X7 receptor expression	Oxidative stress and inflammasome suppression
14	Saiyin et al. (2019)[32]	Maternal diabetes (STZ)	Mice	Voluntary aerobic wheel running	Fetal heart	Maternal voluntary wheel running during gestation	Reduced fetal cardiac DHE and 4-HNE and restored developmental Gata4 expression	Developmental oxidative stress protection

15	Sharma et al. (2016)[33]	T1DM (STZ 65 mg/kg)	Sprague-Dawley rats	Endurance aerobic treadmill training	Heart	Progressive treadmill up to 60 min/session, 5 days/week for 3 weeks	Suppressed NADPH oxidase subunits p47phox and p67phox and normalized cardiac collagen III	Oxidative stress attenuation
16	Tan et al. (2024)[34]	T2DM (HFD + short photoperiod)	Psammomys obesus (sand rats)	Low-to-moderate voluntary aerobic wheel running	Heart & adipose tissue	Daily ad libitum wheel access for 10 weeks	Downregulated cardiac Ccl2, Tgfb1, Bax/Bcl2 and suppressed NF-κB activation in visceral fat	Anti-inflammatory and anti-apoptotic effect
17	Wang B. et al. (2024)[35]	T2DM (HFD + STZ 30 mg/kg)	Wistar rats	Aerobic treadmill training	Heart	Treadmill, 45 min/session, 5 days/week for 8 weeks	Increased irisin and p-AMPK; decreased TNF-α, IL-1β, and TGF-β1	Anti-inflammatory signaling modulation
18	Wang et al. (2025)[36]	T2DM (db/db) & HFD+STZ	C57BL/6J mice	Voluntary/forced aerobic treadmill or wheel running	Heart	Treadmill or wheel, 60 min/session, 5 days/week for 8 weeks	Increased METTL3 and YBX1, stabilizing Nrf2 mRNA and reducing cardiac oxidative stress	Antioxidant signaling activation
19	Yoon et al. (2015)[37]	T1DM (STZ 50 mg/kg)	Sprague-Dawley rats	Moderate aerobic motorized wheel running	Neural tissue (DRG)	Moderate treadmill exercise, 5 days/week for 6 weeks	Reduced TNF-α and IL-1β while increasing protective HSP70 in DRG	Anti-inflammatory neuroprotection
20	Zhang et al. (2022)[38]	T2DM (db/db)	BKS-db/db mice	Moderate aerobic treadmill training	Liver	Progressive treadmill, 15–40 min/session, 5 days/week for 8 weeks	Activated hepatic AMPK/Nrf2/HO-1 signaling and reduced ER stress and apoptosis	Cytoprotective antioxidant signaling

Abbreviations: 4-HNE, 4-hydroxynonenal; AMPK, AMP-activated protein kinase; CAT, catalase; DHE, dihydroethidium; DRG, dorsal root ganglion; GSDMD, gasdermin D; HFD, high-fat diet; HIIT, high-intensity interval training; HO-1, heme oxygenase-1; IL, interleukin; MDA, malondialdehyde; METRNL, Meteorin-like; NF-κB, nuclear factor-kappa B; NLRP3, NOD-like receptor pyrin domain-containing protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; SIRT1, sirtuin 1; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Exercise-mediated regulation of oxidative stress and antioxidant signaling

Most included studies indicated that exercise training attenuated oxidative stress and enhanced endogenous antioxidant defense across diabetic tissues. Various exercise modalities, including treadmill running, swimming, interval training, and voluntary wheel running, were associated with reduced oxidative or nitrosative stress markers such as malondialdehyde (MDA)[19,21,26,29], thiobarbituric acid reactive substances (TBARS)[31], dihydroethidium (DHE)[32], and NOx[29], together with increased antioxidant enzymes including superoxide dismutase (SOD)[21,24,26], glutathione peroxidase (GPx)[19,21,24,26], catalase (CAT)[19,21], and glutathione-related pathways[23,24,27].

At the signaling level, exercise-mediated redox improvements were linked to activation of cytoprotective pathways, including miR-126/Nrf2[19], SIRT1[21], AMPK/Nrf2/HO-1[38], and METTL3/YBX1-mediated Nrf2 regulation[36]. Exercise also modulated oxidative stress-related metabolic pathways, including improved GSH/GSSG balance, reduced p53 and TIGAR expression[27], suppression of NADPH oxidase subunits[33], and decreased LOX-1-associated lipid peroxidation[29]. Collectively, these findings indicate a consistent pattern of exerciseassociated improvement in redox homeostasis, characterized by reduced oxidative stress markers, enhanced antioxidant defenses, and activation of cytoprotective signaling pathways in diabetic animal models.

Exercise-mediated modulation of inflammatory signaling

Exercise training attenuated inflammatory signaling across multiple diabetic tissues, particularly in cardiac, adipose, and neural tissues. Several studies reported reduced pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β)[35,37], inducible nitric oxide synthase (iNOS)[20,31], transforming growth factor-beta 1 (TGF-β1), Ccl2, Tgfb1, and NF-κB-related signaling components[34,35], together with activation of regulatory pathways such as irisin/AMPK and PGC-1α signaling[20,35].

In addition to suppressing pro-inflammatory responses, exercise enhanced antiinflammatory and immunometabolic pathways. Resistance training increased adiponectin and interleukin-10 (IL-10) expression in adipose tissue[30], while exercise-induced Meteorinlike (METRNL) secretion was associated with thermogenic and anti-inflammatory signaling[28]. In neural tissue, moderate exercise reduced TNF-α and IL-1β expression while increasing protective heat shock protein 70 (HSP70), suggesting an exercise-associated anti-inflammatory neuroprotective response[37].

Exercise-mediated suppression of inflammasome and pyroptosis pathways

Exercise training was associated with suppression of inflammasome-related and pyroptotic pathways in diabetic tissues. Treadmill exercise reduced NLRP3 inflammasome activation, as reflected by decreased caspase-1, interleukin-1 beta (IL-1β), and interleukin-18 (IL-18) signaling through Meteorin-like (METRNL)-associated mechanisms in adipose tissue[22]. In diabetic cardiac tissue, exercise attenuated P2X4/P2X7-mediated NLRP3 activation and gasdermin D (GSDMD)associated pyroptosis[25]. Exercise also modulated purinergic and redoxrelated pathways, including reduced renal P2X7 receptor expression[31] and altered P2X7R-related signaling in skeletal muscle[23].

Overall, the included studies indicate that exercise exerts protective molecular effects in diabetic conditions by targeting interconnected redox, inflammatory, antioxidant, and inflammasome-related pathways.

Risk of bias assessment

The included studies showed predominantly low-to-moderate risk of bias based on SYRCLE's risk of bias tool. Six studies were categorized as low risk, thirteen as moderate risk, and one as high risk. Random sequence generation and baseline comparability were generally adequately reported, whereas allocation concealment, random housing, blinding of caregivers and investigators, and random outcome assessment were frequently rated as unclear due to insufficient methodological reporting.

One study was classified as high risk because animals that were unable to complete treadmill adaptation were reassigned into sedentary groups, potentially introducing selection bias[31]. Despite these limitations, most studies demonstrated relatively standardized experimental procedures and consistent outcome reporting. The summary of the risk of bias assessment is presented in Figure 2.

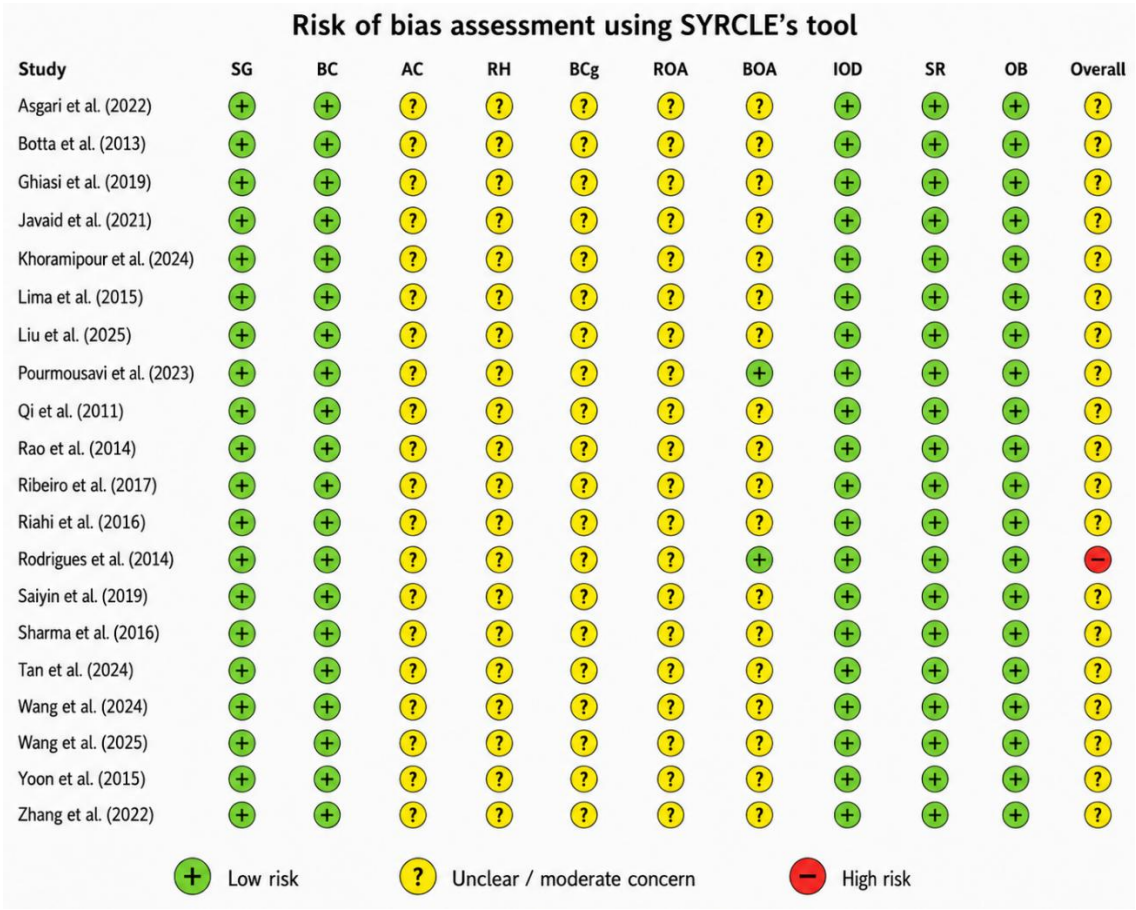


Figure 2. Risk of bias assessment using SYRCLE's tool of included studies investigating exercise-interventions in diabetic animal models. SG, sequence generation; BC, baseline characteristics; AC, allocation concealment; RH, random housing; BCg, blinding of caregivers; ROA, random outcome assessment; BOA, blinded outcome assessment; IOD, incomplete outcome data; SR, selective reporting; OB, other bias.

DISCUSSION

The present systematic review summarizes current evidence regarding the molecular effects of exercise on oxidative stress, inflammatory signaling, and inflammasome-related pathways in diabetic animal models. Overall, the included studies indicate that exercise training confers multi-tissue protection by targeting interconnected oxidative, inflammatory, antioxidant, and pyroptosis-associated

pathways. These findings support the growing concept that exercise functions not only as a metabolic intervention, but also as an important immunometabolic regulator in diabetes mellitus.

Oxidative stress remains a central mechanism in diabetic complications. Across the included studies, exercise consistently reduced oxidative and nitrosative stress markers, including malondialdehyde (MDA)[19,21,26,29], thiobarbituric acid reactive substances (TBARS)[31], dihydroethidium (DHE), 4-hydroxynonenal (4-HNE)[32], and NOx[29], while enhancing antioxidant defenses such as superoxide dismutase (SOD)[21,24,26], glutathione peroxidase (GPx)[19,21,24,26], catalase (CAT)[19,21], and glutathione-related pathways[23,24,27]. This pattern suggests that exercise helps restore redox homeostasis in diabetic tissues through coordinated suppression of oxidative damage and enhancement of endogenous antioxidant capacity.

Several studies further demonstrated that exercise activated antioxidant, cytoprotective, and metabolic signaling pathways in diabetic tissues. Stabilization of Nrf2 signaling through METTL3/YBX1-mediated regulation was observed in diabetic cardiac tissue[36], while activation of the AMPK/Nrf2/HO-1 pathway was accompanied by reduced endoplasmic reticulum stress and apoptosis in the liver[38]. Nephroprotective effects were also associated with miR-126/Nrf2 signaling after interval training[19], supporting the role of Nrf2-related pathways in exercise-mediated antioxidant protection[6]. In parallel, exercise associated improvements included increased pancreatic SIRT1 expression[21], improved glutathione balance, suppression of p53/TIGAR-related oxidative stress signaling[27], attenuation of NADPH oxidase-related pathways[33], and reduced LOX-1 receptor expression with lower lipid peroxidation[29]. Together, these findings indicate that exercise-mediated protection extends beyond direct antioxidant effects and may involve broader regulation of cytoprotective, mitochondrial, metabolic, and oxidative signaling networks.

Beyond oxidative stress modulation, exercise also attenuated inflammatory signaling across multiple diabetic tissues. Reduced expression of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β)[35,37], inducible nitric oxide synthase (iNOS)[20,31], and NF-κB-related signaling components[34], was observed after exercise training. Increased irisin signaling was associated with suppression of TNF-α and IL-1β in diabetic cardiac tissue[35]. Downregulation of Ccl2, Tgfb1, and Rela/NF-κB p65 was also observed after voluntary wheel running[34]. Similarly, reduced inflammatory cytokine expression was accompanied by increased PGC-1α signaling in diabetic cardiac tissue[20]. These observations support the interpretation that exercise exerts broad antiinflammatory effects that may contribute to attenuation of diabetic tissue injury.

Several studies additionally demonstrated enhancement of anti-inflammatory mediators and immunometabolic signaling pathways. Increased adiponectin and IL-10 expression was observed after resistance training[30]. Exercise-induced secretion of Meteorin-like (METRNL) was associated with anti-inflammatory and thermogenic responses in adipose tissue[28]. Emerging evidence suggests that exercise-induced myokines and adipokines, such as irisin, adiponectin, and METRNL, may mediate crosstalk between skeletal muscle, adipose tissue, and immune signaling pathways, thereby contributing to improved metabolic homeostasis in diabetes. This supports the role of exercise as a systemic immunometabolic modulator rather than solely a glucose-lowering intervention.

An important emerging finding of this review is that several studies identified exercise-associated modulation of inflammasome-related and pyroptotic signaling pathways. The included evidence showed suppression of NLRP3 inflammasome activation, reduced caspase-1 signaling, and attenuation of IL-1β and IL-18 production after exercise training. Inhibition of NLRP3 inflammasome activation through METRNLassociated mechanisms was observed in adipose tissue[22]. Suppression of P2X4/P2X7-mediated NLRP3 activation and gasdermin D (GSDMD)-associated pyroptosis was also reported in diabetic cardiomyopathy after treadmill exercise[25]. In addition, exercise modulated purinergic signaling involving P2X7 receptors, as reflected by decreased renal P2X7 receptor expression and reduced

oxidative stress markers after treadmill exercise[31], as well as exercise-associated changes in glutathione and arginine metabolic pathways linked to P2X7R-related signaling in skeletal muscle[23]. These findings are supported by previous evidence showing that oxidative stress and NLRP3 inflammasome activation contribute to diabetic cardiovascular and metabolic complications[7,8]. Collectively, the available evidence suggests that exercise may protect diabetic tissues partly by suppressing inflammasome-driven inflammatory injury and pyroptotic cell death.

The interaction between oxidative stress and inflammasome activation may represent an important mechanistic link underlying the protective effects of exercise in diabetic complications. Oxidative stress can promote NLRP3 inflammasome activation through mitochondrial dysfunction, ROS accumulation, TXNIP signaling, and purinergic receptor activation. Previous studies have demonstrated that TXNIP functions as a critical molecular bridge between oxidative stress and inflammatory signaling pathways in diabetes[9,10]. Therefore, exercise-induced improvement of redox balance may indirectly attenuate inflammasome activation and downstream inflammatory injury, thereby contributing to tissue protection across diabetic models.

However, the available preclinical evidence remains fragmented, as few studies have directly examined the redox–inflammasome–pyroptosis axis as an integrated molecular pathway following exercise interventions. In particular, simultaneous assessment of upstream redox regulators such as TXNIP together with downstream inflammasome and pyroptosis markers remains limited. A summary of the integrated molecular effects of exercise training identified across the included studies is presented in Figure 3.

Several limitations should be acknowledged. The included studies were heterogeneous in animal strains, diabetes induction methods, exercise protocols, target organs, and biomarker assessments, which precluded quantitative meta-analysis. Most studies used male rodents and frequently provided limited reporting on allocation concealment, blinding, and sample size calculation, potentially affecting reproducibility. At the review level, the search was limited to PubMed and ScienceDirect, only published preclinical studies were included, and the findings therefore have limited direct translational applicability to human diabetes.

Overall, these findings support exercise training as a potential immunometabolic intervention that modulates oxidative stress, inflammatory signaling, and inflammasomerelated pathways in diabetic animal models. However, further standardized and methodologically rigorous preclinical studies are needed to clarify the integrated molecular mechanisms underlying exercise-mediated tissue protection.

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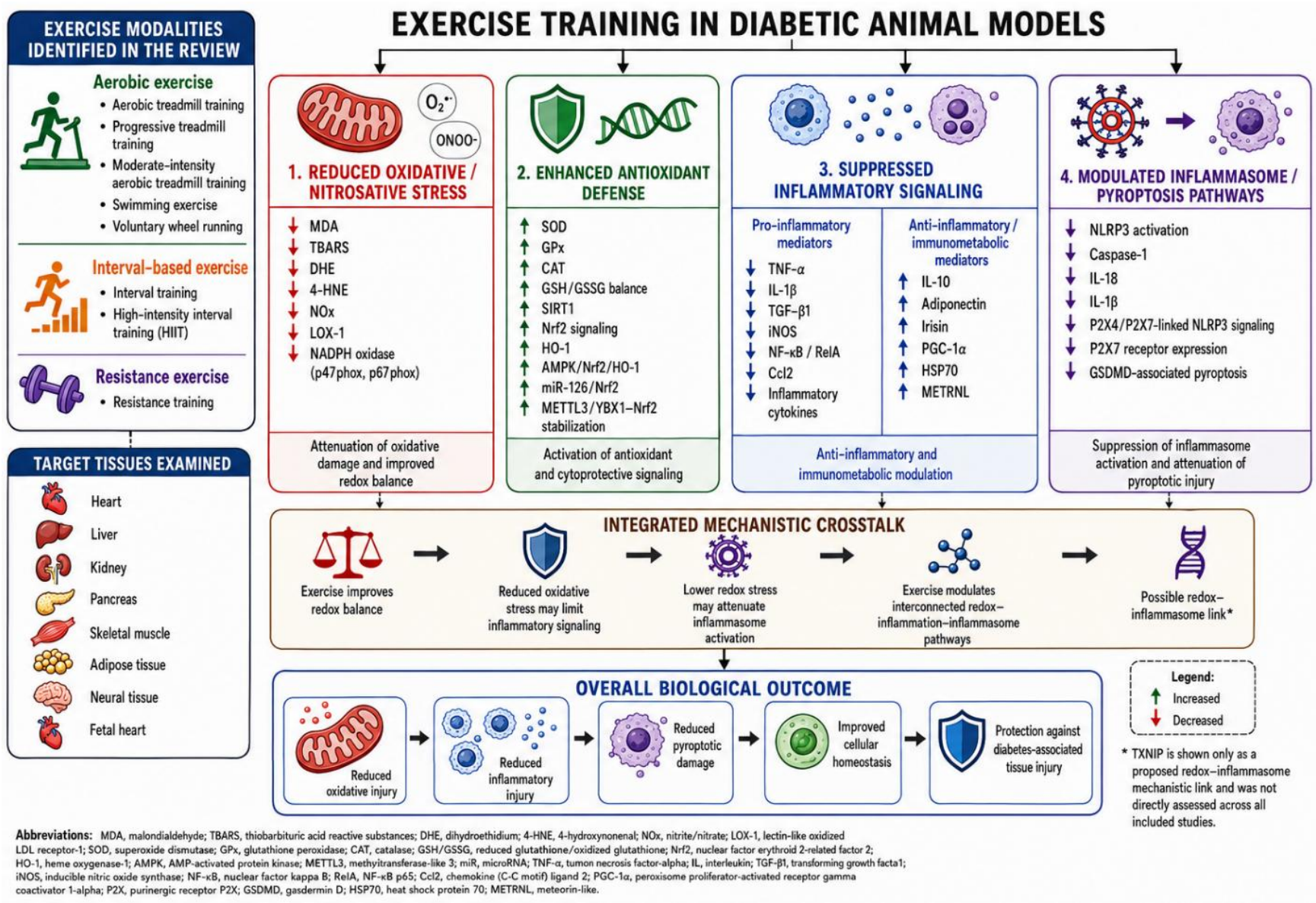


Figure 3. Integrated molecular effects of exercise training in diabetic animal models: a schematic summary.

CONCLUSION

Exercise training exerts protective molecular effects in diabetic animal models by attenuating oxidative stress, enhancing antioxidant defenses, suppressing inflammatory signaling, and modulating inflammasome- and pyroptosis-related pathways. These effects appear to involve interconnected mechanisms, including Nrf2/HO-1 signaling, AMPK activation, SIRT1 regulation, purinergic signaling, and exercise-associated mediators such as irisin and Meteorin-like (METRNL), supporting the role of exercise as an immunometabolic regulator with potential translational relevance for preventing diabetes-related organ dysfunction. However, substantial heterogeneity across exercise protocols, diabetic models, target tissues, and biomarker assessments limits direct comparison among studies; therefore, future preclinical research should apply standardized exercise interventions, improve methodological rigor, include both sexes, and assess redox, inflammasome, and pyroptosis-related biomarkers more comprehensively.

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Authors' contributions

ABH conducted the literature search, study selection, data extraction, qualitative synthesis, and drafted the manuscript. CI contributed to the conception of the review, provided methodological guidance on the design and conduct of the systematic review, supervised the review process, and critically reviewed and revised the manuscript. MR and AA contributed to the critical interpretation of the findings and critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Availability of data

Supporting materials for this review are provided as Online Resources 1–4: the PRISMA 2020 checklist (Online Resource 1), PRISMA 2020 for Abstracts checklist (Online Resource 2), detailed SYRCLE risk-of-bias assessment (Online Resource 3), and PICO framework with complete database search strategies (Online Resource 4). The PRISMA flow diagram and study-level characteristics are presented within the main manuscript.

List of abbreviations

4-HNE, 4-hydroxynonenal; AMPK, AMP-activated protein kinase; CAT, catalase; DHE, dihydroethidium; DM, diabetes mellitus; DRG, dorsal root ganglion; ER, endoplasmic reticulum; GSDMD, gasdermin D; GSH/GSSG, reduced/oxidized glutathione ratio; GPx, glutathione peroxidase; HFD, high-fat diet; HIIT, high-intensity interval training; HO-1, heme oxygenase-1; HSP70, heat shock protein 70; IL, interleukin; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; METRNL, Meteorin-like; NF-κB, nuclear factor-kappa B; NLRP3, NOD-like receptor pyrin domain-containing protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TBARS, thiobarbituric acid reactive substances; TGF-β1, transforming growth factor-beta 1; TNF-α, tumor necrosis factor-alpha; TXNIP, thioredoxin-interacting protein.

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