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Systematic Review

Comparative Effects of Exercise and GLP-1 RAs on Type 2 Diabetic Rat Model: A Systematic Review

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Abstract

International Journal of Exercise Science 18(6): 363-378, 2025. https://doi.org/10.70252/FHZH8622 Type 2 diabetes mellitus (T2D) is a major health problem worldwide having life-threatening complications causing mortality and a rise in prevalence. Effective treatment strategies are vital for managing diabetes and its associated complications including cardiovascular disease (CVD), nephropathy, neuropathy, and retinopathy. This systematic review aims to evaluate effective treatment approaches, focusing on the comparative effects of exercise and GLP-1 receptor agonists (GLP-1RAs) in T2D rat models. Current pharmacological therapies primarily target glycemic control and insulin sensitivity. However, there is a growing concern in non-traditional approaches that involve exercise and GLP-1 RAs for managing T2D. These therapies are crucial as they have the potential to improve pancreatic β-cell efficiency to secrete insulin, control blood glucose levels, decrease insulin resistance, and manage diabetes-related issues. Studies were searched in seven electronic databases including Google Scholar, MEDLINE, PubMed, Cochrane Library, Scopus, PEDro, and Web of Science from inception till 2024. Out of 16,500 documents retrieved between 2020 and 2024, 58 full-text articles were assessed in detail, and 13 studies met the inclusion criteria that include Male Wistar, Male Sprague Dawley and Adult female Wistar albino rats weighing 200-250 grams. These experimental studies examined the effects of exercise and different GLP-1 RAs on 103 diabetics and 103 non-diabetic rats. Overall, synthesized findings revealed a promising effect on glucose control, insulin sensitivity, and metabolic health in diabetic rats. Further research is needed to elucidate the cellular and molecular mechanism(s) through which exercise and GLP-1 RAs manage T2D and its associated complications including cardiovascular disease (CVD), nephropathy, neuropathy, and retinopathy.

Keywords: Exercise, Type 2 diabetes, glucose, insulin, diabetes complications

Introduction

Diabetes is a metabolic illness instigated by insulin resistance, β-cell dysfunction, and hyperglycemia.[1] Diabetes is associated with an increase in various comorbidities such as cardiovascular disease (CVD), nephropathy, neuropathy, and retinopathy, which all increase morbidity and mortality.[2] Diabetes affects an estimated 537 million people globally, a number expected to rise to 783 million by 2045. According to the IDF 10th edition, the incidence of diabetes has been increasing in South East Asian (SEA) countries for at least 20 years, and current figures have surpassed all previous predictions. In 2021, more than one in every ten persons globally will get diabetes. The expected prevalence of diabetes in adults aged 20 to 79 years will be 537.5 million by 2024. Pakistan ranks highest among the countries with 33 million cases and a comparative prevalence rate of 30.8% in 2021 globally.[3] This increasing prevalence and burden of problems despite treatment indicate need for additional treatments.[4]

Treatments for diabetes include pharmacological drugs such as thiazolidinedione, sulfonylurea, biguanide, metformin, and Glucagon-like peptide-1 receptor agonists (GLP-1 Ras). GLP-1 RAs are efficient and durable in glycemic control in patients with T2D.[5] GLP-1 RAs replicate the effects of native compromised GLP-1 in diabetes. It increases insulin secretion, inhibits glucagon release, and slows stomach emptying.[6] GLP-1 RAs are classified into two categories, Short-acting GLP-1 RAs (such as exenatide and lixisenatide) and Long-acting GLP-1 RAs (such as albiglutide, dulaglutide, liraglutide, and semaglutide). Once or twice daily doses of short-acting GLP-1 RAs reduce postprandial glucose levels by slowing stomach emptying after meals.[7] The long-acting GLP-1 RAs after starting initial dose of 0.5 mg reduces blood glucose levels by stimulating insulin production and suppressing glucagon levels. The dose is then adjusted based on the patient's response and tolerance.[8]

It has been shown that non-pharmacological therapies, including intensive lifestyle modifications, are beneficial for managing T2D.[9] By adopting a healthy lifestyle, diabetic patients might lose weight and decrease the risk of associated complications. Lifestyle interventions, especially those focusing on diet, physical activity, and behavioral modification, have an important role in T2D management.[10] Exercise is essential for regulating blood glucose levels. Exercise enhances muscle glucose uptake and metabolism via both insulin-dependent and independent signalling pathways. Insulin binds to its receptor in the insulin-dependent pathway, beginning a series of events that activate "IRS (Insulin Receptor Substrate) and PI3K (Phosphoinositide 3-Kinase) signalling cascade". This chain of reaction finally activates Akt, a crucial protein involved in the transport of GLUT4 translocation to the membrane. Once at the membrane, GLUT4 allows glucose to enter the cell.[11] During muscle contraction, glucose is absorbed *via* the insulin-independent pathway, which stimulates "AMPK (AMP-Activated Protein Kinase), facilitating GLUT4 translocation to the cell membrane". Furthermore, elevated calcium levels during contraction activate CaMKII (Calmodulin-Dependent Protein Kinase II), increasing glucose absorption. This insulin-independent route is especially important during physical activity, as it allows muscles to absorb glucose efficiently.[12] Additionally, exercise prevents the synthesis of glucose by the liver by decreasing gluconeogenesis and glycogenolysis. Exercise also promotes lipid metabolism and lowers visceral fat. Exercise can also increase

insulin sensitivity, support weight management, and improve overall health.[13]Additionally, effective T2D management through exercise is determined by frequency, intensity, duration, and type of exercise. American Diabetes Association (ADA) recommends that individuals with T2D should performing "at least 150 minutes of moderate to vigorous physical exercise at least three days a week".[14,15]

Previous studies and new evidence showed that GLP-1 RAs and exercise improve β-cell function and play an effective role in controlling T2D and limiting its complications.[16] In obese individuals with or without diabetes GLP-1 RAs and exercise have shown cardiometabolic improvement.[17] GLP-1 RAs and exercise both help with weight management and glucose control by reducing visceral fat and improving insulin sensitivity. Exercise directly affects skeletal muscle glucose uptake and liver glucose production, while GLP-1 RAs improve pancreatic function and regulate glucose and hunger hormones. Combining GLP-1 RAs with exercise may work even better, improving metabolism and preventing complications such as cardiovascular disease and diabetic nephropathy. Thus, the complementary effects of GLP-1 RAs and exercise highlight the importance of using both in the treatment of diabetes. This multimodal strategy addresses both physiological mechanisms and lifestyle factors. Incorporating exercise and GLP-1 RAs in daily routines provides metabolic advantages and manages blood glucose levels.

Methods

Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed in the accomplishment of the current systematic review. This research was carried out by the ethical standards of the *International Journal of Exercise Science*.[18] To ensure the laboratory animal's moral and humane treatment Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) recommendations were used.[19]

Search strategy

Seven electronic databases, i.e., Google Scholar, MEDLINE, PubMed, Cochrane Library, Scopus, PEDro, and Web of Science were searched for the studies from September to December 2023 with a language and publishing dates filter applied. The Medical Subject Headings (MeSH) terms for "Aerobic Exercise," "Resistance Exercise", "Glucose", "Insulin", "Diabetic Complications" and "GLP-1RAs" were searched. The first author (S.A) used predetermined eligibility criteria which include only articles that show relevance to the research topic, quality work, and show adherence to the study outcomes. The primary screening and literature search was carried out by the first author (S. A). The other authors HA, AH, and SF were finally examined the selected studies and resolved any differences among the reviewers.

Inclusion and exclusion criteria

The selection criteria were based on the PICO strategy, which is based on the population of concern, type of intervention, type of comparison, and qualitative results observed. This is the

widely used method supported by the Cochrane Collaboration that identifies the constituents of systematic reviews in evidence-based medicine.

Thus, the qualifying studies for review included healthy control rats and T2D rats with an average weight range of 200-250 g. Studies involving randomized controlled trials (RCTs) published 2014-2024 investigating the effect of exercise and GLP-1 RAs on diabetic rat models were chosen. Outcome measure comprised Fasting Blood Glucose (FBG), Plasma Insulin, and HOMA IR. After applying inclusion and exclusion criteria, a total of 13 studies were identified, which are examined in this study for further analysis.

*Data extraction and quality a*ssessment

All data were obtained as provided by the included studies following CRD and Cochrane's advice. The provided information for the included RCTs was divided into (i) the Author and Year of publication, (ii) the Diabetic Rats' Characteristics, (iii) the Experiment and Control Groups, and (iv) the Outcome. Independent performance by two reviewers followed by a discussion was used to eliminate potential bias and improve the review's quality because it corresponds to the methodology, evaluates the study's internal and external validity, ensures that the findings are applicable in practice, and represents a commonly used method in high-quality sources. The reviewers used the SYRCLE tool (Systematic Review Centre for Laboratory Animal Experimentation) to assess the animal studies that involved the possibility of tool-type biases. Types of risks assessed for quality measurement including selection bias – randomization, and allocation concealment; performance bias – blinding, and detection; attrition bias – incomplete outcome data; and reporting bias – selective reporting of outcome are listed.

Results

A total of 16,500 records were retrieved from seven electronic databases, including Google Scholar, MEDLINE, PubMed, Cochrane Library, Scopus, PEDro, and Web of Science from inception from 2020 to 2024. The initial screening process began by reviewing the titles and abstracts, leading to the exclusion of 15,500 records due to mismatched titles and abstracts that did not align with the review's focus. Additionally, 1000 records were excluded because of duplication. 197 full articles were identified as potentially relevant after a laborious review and were subjected to a more detailed analysis. The inclusion criteria were specifically tailored to studies that examined the effects of exercise and GLP-1 RAs in the treatment of T2D and associated complications in rat models. After applying the inclusion criteria only 13 studies were found to be eligible. A total of 103 diabetic rat models were used in these studies and examined various outcomes related to the efficacy of treatment exercise and GLP-1 RAs therapy in treating complications from diabetes.

Figure 1 shows the selection criteria for these studies were used in several stages, which represents the conception of the review process. Helping to better understand the potential contribution of these interventions or to compare their outcomes the selected studies provide insight into the effects of exercise and GLP-1 RAs on general health in diabetic rat models.

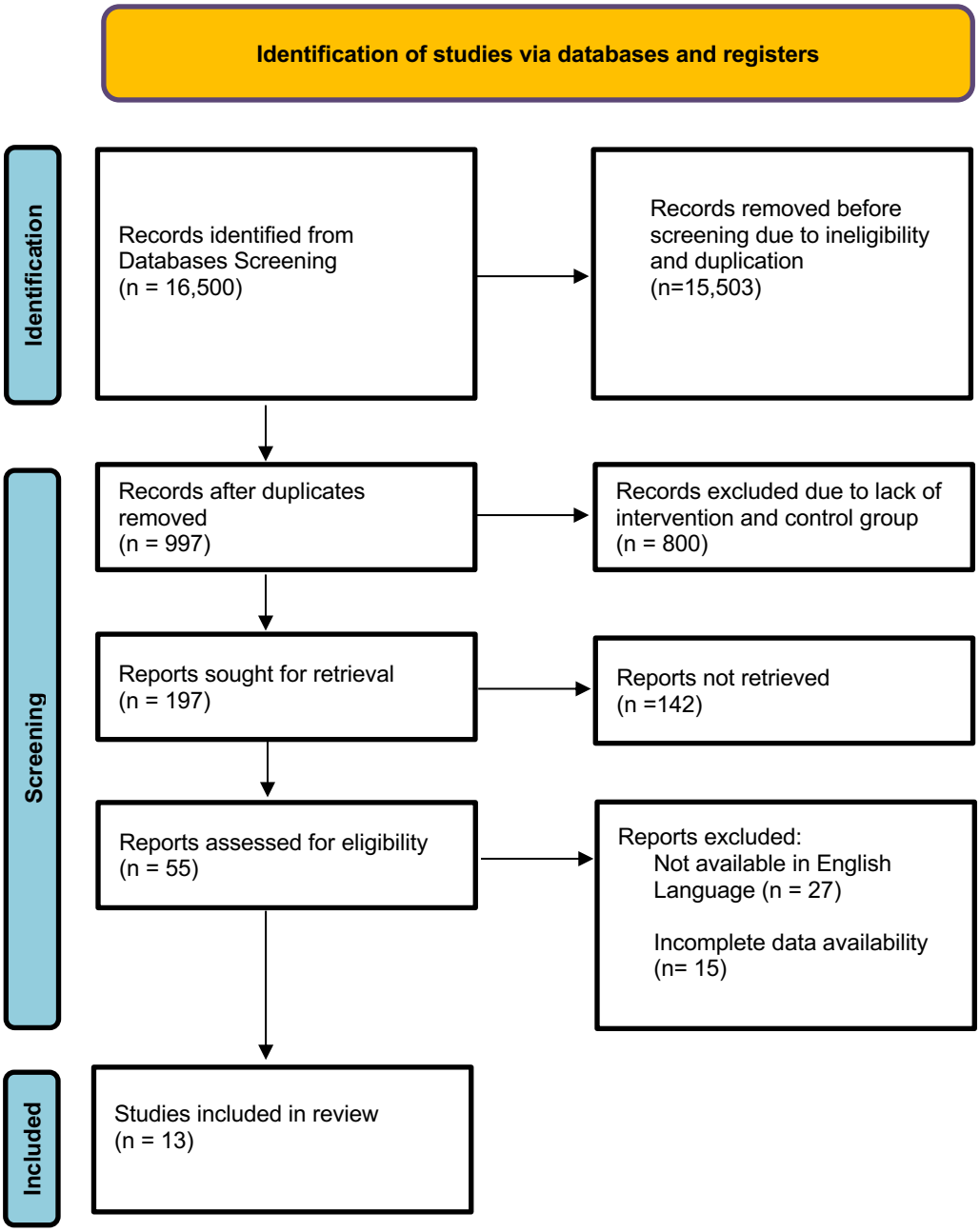


Figure 1. Represents the conceptualization of the review process.

Synthesized Findings

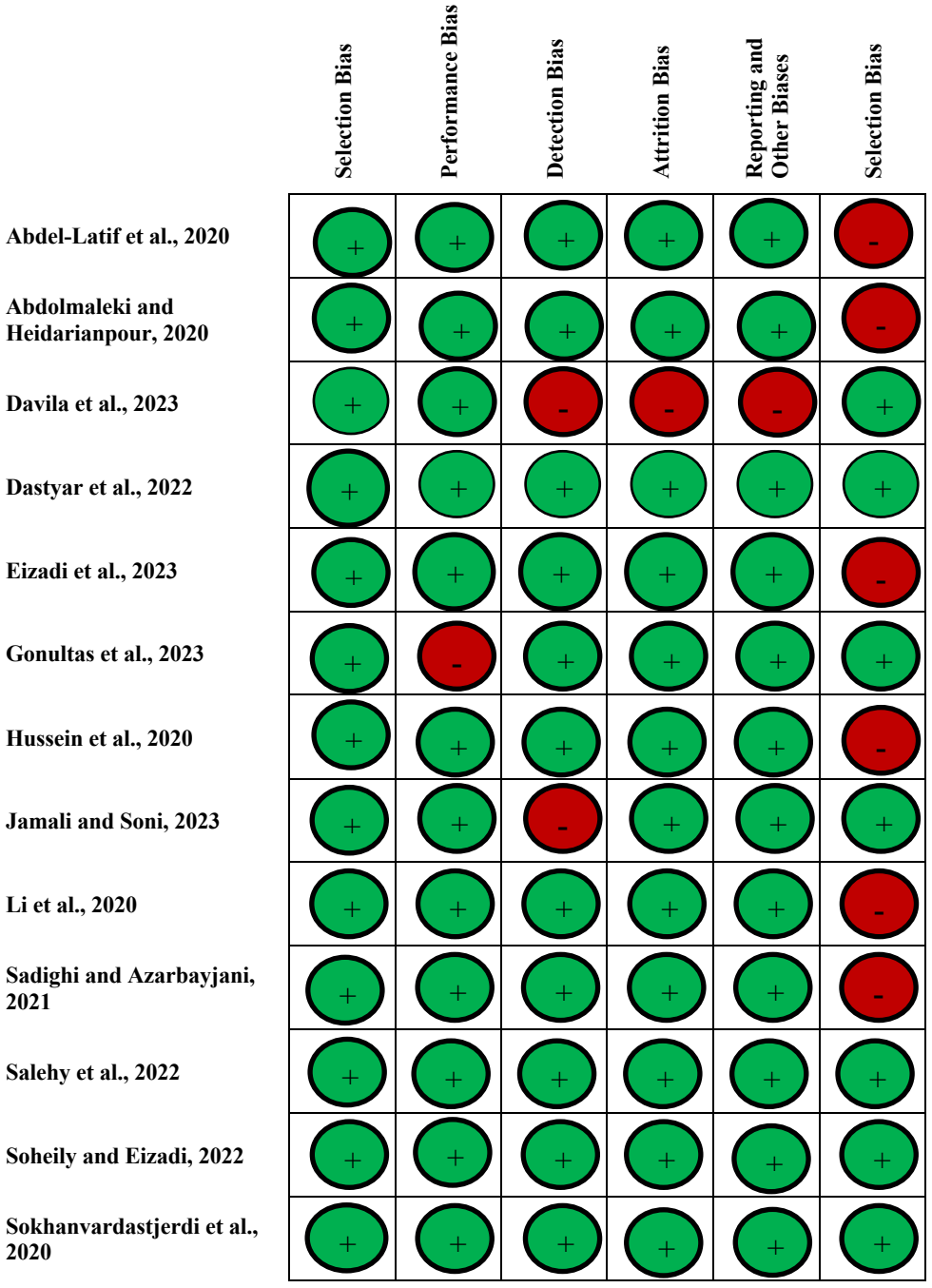
Effects of Exercise.

This systematic review examined the comparative effects of exercise and GLP-1 RAs in T2D rat models to evaluate the beneficial response of these therapies. Abdolmaleki and Heidarianpour observed that physical activity can efficiently reverse the changes in glycosylphosphatidylinositol-specific-phospholipase D1 (GPLD1) levels, which was complemented by decreased blood glucose concentration and decreased glucose tolerance indicating its importance in glucose homeostasis.[20] Sokhanvardastjerdi et al study has reported that PDX-1 and GLUT-2, of two critical genes, dramatically increase following aerobic exercise which ultimately regulates glucose uptake and insulin production.[21] Furthermore, Sadighi and Azarbayjani reported that aerobic exercise reduced apoptosis in cardiomyocytes of T2D rats.[22] This shows that exercise is beneficial in preserving cardiac function and lowers risk of cardiovascular complications of T2D.[22] Additionally, Eizadi et al found that TCF7L2, a significant genetic risk factor for T2D, lowered following three months of high-intensity interval training (HIIT), resulting in lower blood glucose levels and improved insulin sensitivity.[23] Dastyar et al found that resistance training improved cardiac hypertrophy in diabetic rats, through activation of the PI3K/AKT1 signalling pathway, which is critical for cell development and survival.[24] Furthermore, Salehy et al proved that resistance training significantly lowered glucose levels in T2D rats, due to the downregulation of PEPCK expression, which is a critical enzyme in gluconeogenesis, suggesting a potential mechanism for improved glucose management in T2D rats.[25] Soheily and Eizadi study has shown a reduction in FOXO1 gene expression in T2D rats after six weeks of resistance training, which leads to improved insulin sensitivity and lower fasting glucose levels.[26] This effect is significant as its proves that exercise can reduce insulin resistance, hyperglycemia and β-cell dysfunction associated with T2D.[26]

Effects of GLP-1 RAs.

Abdel-Latif et al reported that a low dose of GLP-1 RAs, lixisenatide, has a significant effect on antioxidant activity and reduces kidney levels of malondialdehyde and total NOx, it shows potential therapeutic value of GLP-1 RAs in lowering oxidative damage and improving renal function in T2D patients.[27] Hussein et al revealed that GLP-1 RAs has potential for addressing diabetic cardiomyopathy T2D by increasing myocardial glucose absorption, decreasing lipid buildup, and reducing inflammation and oxidative stress.[28] Li et al showed that GLP-1 RAs protects against Cardiomyopathy in T2D rats by reducing hyperglycemia while enhancing vascular endothelial dysfunction via downregulating Caveolin-1, a protein that contributed to its anti-oxidative actions and improved endothelial function.[29] This provide evidence that GLP-1 RAs is beneficial for diabetes-related cardiac complications.[29] D'Avila et al revealed that liraglutide reduces body weight and blood triglycerides and protect small blood vessels from structural and functional damage, lowering the likelihood of nephropathy and retinopathy.[30] Histological findings showed increased vascular integrity and decreased fibrosis.[30] Furthermore, Gönültaş et al reported that liraglutide, a GLP-1 RAs, improves erectile function in T2D rats by increasing eNOS activity.[31] These findings highlight liraglutide's ability to treat diabetes-related erectile dysfunction.[31] Jamali and Soni observed that Exenatide outperformed advanced medicines in lowering blood glucose levels in streptozotocin-induced T2D rats, demonstrating its potential as a superior therapy alternative for hyperglycemia management.[32]

To ensure the transparency of the studies used in this review, the risk of bias was assessed using the SYRCLE standards. This evaluation took into account biases in randomization, allocation concealment, blinding, and outcome reporting in the included trials, as shown in Figure 2.



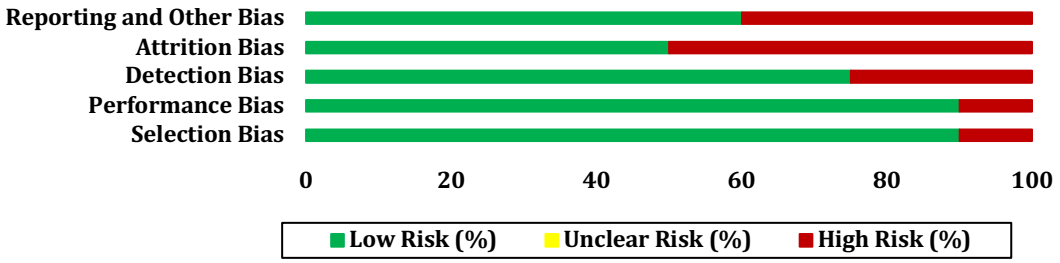


Figure 2. Summary of Risk of Bias of the selected studies.

Table 1. Characteristics of included studies (n=13).

S.No	Author (Year)	Target Population	Rat Model	Study Design	Type of Therapy	Sample Size	Duration
Aerobic Exercise							
1	Abdolmaleki and Heidarianpour, 2020[20]	Male Wistar rats	T2D	RCT	Aerobic	24	5 days/week for 14 weeks
2	Sokhanvardastjerdi et al, 2020[21]	Male Wistar rats	T2D	RCT	Aerobic	14	five days/Week for 12 weeks
3	Sadighi and Azarbayjani, 2021[22]	Male Wistar rats	T2D	RCT	Aerobic	16	five days/Week for 6 weeks
4	Eizadi et al, 2023[23]	Male Wistar rats	T2D	RCT	Aerobic	14	5 days/week for 6
Resistance Exercise							
5	Dastyar et al, 2022[24]	Male Wistar rats	T2D	RCT	Resistance	14	5 days/week for 6 weeks
6	Salehy et al, 2022[25]	Male Wistar rats	T2D	RCT	Resistance	14	5 days/week for 6 weeks
7	Soheily and Eizadi, 2022[26]	Male Wistar rats	T2D	RCT	Resistance	14	5 days/week for 6 weeks
GLP-1 RAs							
8	Abdel-Latif et al, 2020[27]	Male Sprague Dawley rats	T2D	RCT	Lixisenatide	16	2 weeks
9	Hussein et al, 2020[28]	Male Sprague Dawley rats	T2D	RCT	Liraglutide	16	4 weeks
10	Li et al, 2020[29]	Male Wistar rats	T2D	RCT	Liraglutide	30	4 weeks

11	D'avila et al, 2023[30]	Male Wistar rats	T2D	RCT	Liraglutide	20	5 weeks
12	Gönültaş et al, 2023[31]	Male Wistar rats	T2D	RCT	Liraglutide	20	12 weeks
13	Jamali and Soni, 2023[32]	Adult female Wistar albino rats	T2D	RCT	Exenatide	12	7 days

Table 2. Description of included studies (n=13).

S.No	Author (Year)	Rat Model	Intervention Groups		Findings
			Experimental	Control	
Aerobic Exercise					
1	Abdolmaleki and Heidarianpour, 2020[20]	Male Wistar rats, aged 3 months and weighing 210 to 230 grams	Exercise was performed for five days/week for 14 weeks at 0% grade on treadmill at 26 m/min (n=12)	Non-diabetic sedentary (n=12)	Decrease in GPLD1 by exercise training modifying in glycemic and insulin profile
2	Sokhanvardastjerdi et al, 2020[21]	Male Wistar rats, age 10 weeks, weight, 220 grams	Exercise was performed on a treadmill with five sessions per week for 12 weeks with a steady increase in time (10 to 55 minutes) and speed (18 to 26 m/min) (n=7)	Non-diabetic sedentary (n=7)	Significant lowers serum glucose by increasing the expression of PDX1 and GLUT-2
3	Sadighi and Azarbayjani, 2021[22]	Male Wistar rats, 4–6 weeks old	Exercise was performed for five days/Week for 6 weeks on a treadmill, starting at 0° of the slope and gradually increasing the time and speed (n=8)	Non-diabetic sedentary (n=8)	Aerobic exercise reduce diabetes-related apoptosis in cardiomyocytes
4	Eizadi et al, 2023[23]	Male Wistar rats, 9 to 10-week-old, weighing 220 grams	Resistance exercise on climbing ladder was performed for 5 days/week for 6 weeks (n=7)	Non-diabetic sedentary (n=7)	Increases serum insulin and β-cell function in obese diabetic rats.
Resistance Exercise					
5	Dastyar et al, 2022[24]	Male Wistar rats, 10 weeks old rats,	Resistance exercise was performed for 5 days/week for 6 weeks on vertical ladder of 1-meter with an 80% gradient and 4	Non-diabetic	Improvement physiological cardiac hypertrophy in diabetic rats

		weighing 220 grams	repetitions while weights were attached to the rat's tail (n=7)	sedentary (n=7)	
6	Salehy et al, 2022[25]	Male Wistar rats, 10 weeks old rats, weighing 220 grams	Resistance exercise was performed for 5 days/week for 6 weeks on vertical ladder of 1-meter with an 80% gradient and 4 repetitions while weights were attached to the rat's tail (n=7)	Non-diabetic sedentary (n=7)	Improve glucose homeostasis diabetes rats and this effect may be attributed decrease PEPCK expression in response to exercise
7	Soheily and Eizadi, 2022[26]	Male Wistar rats, 10 weeks old rats, weighing 220 grams	Resistance exercises was performed for 5 days/week for 6 weeks on vertical ladder of 1-meter with an 80% gradient while weights were attached to the rat's tail (n=7)	Non-diabetic sedentary (n=7)	In obese diabetic rats may be rooted in decreased insulin expression following exercise
GLP-1 RAs					
8	Abdel-Latif et al, 2020[27]	Male Wistar rats, weighing 200–250 grams	Diabetic + Lixisenatide (n=6) (intraperitoneally at two dose levels (1 and 10 nmole/kg/day) every 3 days)	Non-diabetic (n=6)	Treatment with low doses of lixisenatide proved effective in preventing early diabetic nephropathy
9	Hussein et al, 2020[28]	Male Sprague Dawley rats, weighing 200–250 grams	Diabetic + Lixisenatide (n=8) (subcutaneously at a dosage of 75 µg/kg once daily)	Non-diabetic (n=8)	Dulaglutide by boosting the anti-oxidant defense system, restoring kidney functioning parameters, and reducing histological alterations
10	Li et al, 2020[29]	Male Sprague Dawley rats, weighing 120-160 grams	Diabetic+ liraglutide (n=8) (intraperitoneally at a dosage of 0.2 mg/kg per day)	Non-diabetic (n=8)	LIRA improves vascular endothelial dysfunction in rats with T2D by inhibiting oxidative stress and activating eNOS through the downregulation of Cav-1
11	D'avila et al, 2023[30]	Male Wistar rats, weighing 200–210 grams	Diabetic+ liraglutide (n=10) (subcutaneously at a dosage of 100 µg/kg)	Non-diabetic (n=10)	GLP-1 RAs may serve as effective therapeutic options to avoid microvascular problems related to diabetes
12	Gönültaş et al, 2023[31]	Male Wistar rats, weighing	Diabetic+ liraglutide (n=10) (subcutaneously at a dosage of 0.3 mg/kg every 12 hours)	Non-diabetic (n=10)	Liraglutide, has protective effects on diabetic rats' erectile tissues

		240-335 grams			
13	Jamali and Soni, 2023[32]	Adult female Wistar albino rats, weighing 200-250 g	Diabetic+ Exenatide (n=6) (subcutaneously at doses of 25 and 50 µg/kg)	Non-diabetic (n=6)	Exenatide has the potential to be utilized as an alternative antidiabetic drug to treat T2D

Discussion

This review highlights the distinct and complementary mechanisms by which exercise and GLP-1 RAs manage T2D and its associated complications in T2D rat models. Exercise is an important component of diabetes care because it improves glycemic control and insulin sensitivity by increasing GLUT4 translocation in skeletal muscle, which optimizes the uptake of glucose.[12] It decreases pro-inflammatory cytokines (TNF-α and IL-6) and boosts anti-inflammatory cytokines (IL-10). These effects are significant as they reduce insulin resistance and control long-term diabetic-related complications.[21] As a result, exercise is crucial for treating diabetes and improving long-term health outcomes. On another side, the antidiabetic emerging medicine, GLP-1 RAs is critical for the therapy of T2D as it provides beneficial results by increasing insulin secretion, glucagon suppression, and modulation of appetite.[33] A 2021 clinical trial has validated the efficacy of subcutaneous semaglutide by lowering HbA1c, managing weight loss, and providing cardiovascular benefits.[34] Moreover, their antioxidant and anti-inflammatory properties support β-cell insulin secretion and slow T2D progression.[7] While exercise and GLP-1 RAs use different mechanisms, they have complementing effects on glycaemic management, insulin sensitivity, and overall metabolic health. This review looks at their comparative effects in T2D rat models, emphasizing their synergistic potential for glycaemic management, insulin sensitivity, general metabolic health, and T2D-associated complications.

Amaravadi et al reported that a 12-week exercise efficiently decreases insulin resistance, and improves glycaemic management in diabetes, highlighting the significance of physical exercise in regulating blood glucose levels.[35] This finding is crucial because increasing insulin sensitivity increases glucose uptake while decreasing persistent hyperglycemia, a major cause of diabetic complications.[35] A study by Lino Rodrigues et al demonstrated that physical training significantly increased antioxidant activity to control microcirculatory dysfunction associated with T2D.[36] This antioxidant process is critical because oxidative stress is a major factor in the progression of diabetic problems such as neuropathy, cardiovascular disease, and retinopathy.[36] It complements the study by Lin et al that regular exercise improves insulin resistance mediated by decreased mitochondrial fission via the irisin/AMPK signalling pathway.[37] This is essential because it demonstrates the molecular basis of exercise benefits of mitochondrial dynamics *via* the irisin/AMPK signalling pathway can reduce insulin resistance, which is a key aspect in controlling and preventing diabetes complications.[37] According to the findings of Zare et al, physical activity may help to reduce diabetes-induced neuronal damage in the prefrontal cortex

by inhibiting apoptosis.[38] This neuroprotective impact emphasizes the importance of exercise beyond glycaemic management, extending to neurological health.[38] Furthermore, exercise has been demonstrated to provide significant cardioprotective benefits. A study conducted in 2024 reported that aerobic exercise training might exert a cardio-protective effect in T2D rats by reducing apoptosis and oxidative stress indices.[39] These are significant because these effects are beneficial for cardiovascular complications related to diabetes.[24] Rashidi et al observed that the diabetic-resistant training group had significantly lower fasting glucose levels than the diabetic group, as well as lower myocardial damage, fibrosis, oxidative stress, inflammation, and apoptosis, it is showed superior cardioprotective properties.[40] These properties could be attributed to its superior capacity to diminish fibrosis, oxidative stress, apoptosis, and inflammatory cytokines against diabetic cardiomyopathy (DCM) in T2D.[40] Furthermore, a study done in 2023 that long-term exercise protects pancreatic β-cell mass and islet shape by lowering circulating IL-1β and pancreatic inflammatory markers TNF-α, TGF-β, and NF-κB p65 phosphorylation, that crucially underlines the significance of exercise in decreasing inflammation and fibrosis, which contribute to β-cell dysfunction in T2D.[41]

Numerous studies revealed the beneficial effect of novel anti-diabetic GLP-1 RAs on the skeletal metabolism of T2D rats and patients.[32] Beyond glycaemic control, GLP-1 RAs emerged as a key treatment for T2D because of diverse effects in T2D patients where it provides cardio- protective effects and improvement in overall metabolic health.[30] Dhanapalaratnam et al study showed GLP-1 RAs improved neuropathy outcomes, evidenced by enhanced structural and morphological measures alongside better electrophysiological and clinical endpoints.[42] This is significant as it highlights the GLP-1 RAs potential in diabetes-related neuropathy.[42] Moreover, other than glucose management, GLP-1 RAs have an important role in a variety of tissues where this medication provides neuro-protective, anti-inflammatory, cardio-protective, and metabolic effects. This is beneficial because it specifies their potential for controlling diabetic angiopathy and minimizing associated complications.[43] GLP-1 RAs therapy by targeting GLP-1/leptin/kiss1/GnRH, steroidogenesis, and TGF-β/Smad pathways significantly improved functional and structural reproductive abnormalities in T2D rats. This is important because it shows that GLP-1 RAs can treat reproductive dysfunction in T2D by altering critical hormonal and signalling pathways, emphasizing their role in promoting fertility and reducing diabetes-induced reproductive problems.[19] Additionally, Liraglutide effectively lowers blood glucose levels, improves biochemical markers, and lowers HOMA-IR in T2D, enhancing metabolic outcomes. These improvements may help to enhance glycemic control, minimize the risk of diabetes-related complications, and perhaps improve long-term T2D management outcomes.[16] Ozeki et al findings indicate that GLP1-RAs, semaglutide, significantly decrease body fat while preserving the mass of skeletal muscle (MM) in obese T2D patients.[44] This is noteworthy because it tackles insulin resistance caused by obesity as well as muscle preservation, which is critical for glucose metabolism and overall health.[44] Despite the optimistic results, the evaluated studies have many limitations. Most notably, the heterogeneity of study designs, the variability in intervention durations, and the minimal emphasis on long-term effects limit the generalizability of these results. Future research should seek to standardize experimental techniques and lengthen intervention durations in order to fully understand the combined effects of exercise and GLP-1 RAs in diabetes management and complications.

The findings of our research align with previous literature highlighting the comparative effects of exercise and GLP-1RAs proved to be effective in maintaining glycaemic control and overall metabolic health in T2D. Considering all the aspects, our study adds to the expanding body of evidence emphasizing the importance of exercise and GLP-1 RAs in effectively controlling multiple complications associated with T2D.

In conclusion, all these experiments were shown to be effective and efficient in improving overall health in T2D rats. In the future, studies are required to understand the mechanism of GLP-1 RAs and exercise in managing T2D and limiting its complications.

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