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GLP-1 Receptor Agonist and Structured Exercise on Glycemic Control and Epigenetic Modulation in Diabetic Rats

Qurat-ul-Ain Adnan[1], Sumaira Imran Farooqui[2,*], Amin Fahim[3] and Amna Aamir Khan[1]

1 Ziauddin College of Phyiscal Therapy, Ziauddin University, Karachi, Pakistan
2 Faculty of Allied Health Sciences, Ziauddin University, Karachi, Pakistan
3 Peoples University of Medical and Health Sciences for Women, Shaheed Benazirabad, Pakistan.

* Correspondence: sumaira.farooqui@zu.edu.pk

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Abstract: T2DM afflicts around 537 million adults across the world, and low-resource countries have poor access to expensive pharmacological treatments. Despite the efficacy of glucagon-like peptide-1 receptor agonist (GLP-1 RA), the relative effects of structured exercise and its molecular outcomes are not clearly known. This study compared the effects of GLP-1 RA therapy, aerobic, and resistance exercise on the glycemic control, pancreatic β-cell function, and microRNA (miRNA) regulation in streptozotocin-nicotinamide (STZ-NA) induced rat type 2 diabetes mellitus. This is a preclinical randomized controlled trial was conducted between November 2024 and June 2025. The male Wistar rats (200300 g) were randomly divided into five groups (n=8), including the control, diabetic (STZ-NA), GLP-1 RA, aerobic and resistance exercise. STZ (65 mg/kg) and nicotinamide (230mg/kg) were used to induce diabetes. The duration of the interventions was 12 weeks. GLP-1 RA (40 μg/kg) was injected every three days. Aerobic exercises were performed using progressive running on a treadmill and resistance training using progressive climbing on the ladder. GLP-1 receptor agonist group and aerobic group demonstrated significant improvements in long-term glycemic control with HbA1c values of 5.53±0.16 and 5.55±0.11, respectively, representing significant reductions of 37.6% and 37.3% from diabetic control ($p<0.05$). The interventions augmented the protective miRNAs (126, 128, and 22) and normalized the diabetes-related miRNAs (375 and 503). Group D was found to have equal glycemic and epigenetic effects to GLP-1 RA therapy and could be considered a low-resource management tool in managing diabetes.

Keywords: Mindfulness-Acceptance-Commitment; tennis; athletic performance; passion; psychological well-being; randomised controlled trial

1. Introduction

Diabetes mellitus is one of the major public health issues globally, with 537 million adults currently having diabetes, which is expected to increase to 783 million by 2045 [1]. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of diabetes and is characterized by both insulin resistance and a progressive defect of pancreatic β-cells with both chronic hyperglycemia and potentially fatal complications [2]. The total annual cost of diabetes across the globe is over $966 billion, and low- and middle-income countries have more deaths despite having a lower incidence of diabetes than high-income countries [3], which demonstrates a need for increased access to affordable management.

The management of T2DM has changed from a model focused on glucose to one centered on cardiometabolic health [4]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a promising new drug class with various mechanisms of action,

including stimulating glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying, and suppressing appetite [5]. Landmark trials (LEADER, SUSTAIN-6, and REWIND) reported a 13-26% reduction in major adverse cardiovascular events with GLP-1 RA use, a major advancement in the care of diabetes [4,5]. In addition to glycemic control, there is emerging evidence that GLP-1 RAs have a protective effect on pancreatic β-cells by promoting proliferation and reducing apoptosis.

In addition to pharmacological approaches, structured physical activity continues to serve as a key element in the management of diabetes[6]. Regular aerobic and resistance exercise improves insulin sensitivity through different mechanisms [6]. Aerobic exercise induces glucose disposition via an insulin-independent mechanism by increasing the translocation of GLUT4 to the cell surface. In contrast, resistance exercise increases muscle mass, thereby improving the ability to dispose of glucose [7]. The current recommendations advise individuals to engage in at least 150 minutes of moderate-to-vigorous intensity aerobic exercise per week, in conjunction with resistance-type exercise on two to three non-consecutive days per week [8]. However, limited evidence exists regarding the efficacy of exercise modalities. Thus, the specificity of exercise modality, particularly on β-cell function, cellular metabolism, epigenetics, and other molecular mechanisms, remains largely unknown.

Despite extensive clinical trials demonstrating significant benefits of each GLP-1 RA and exercise alone, important gaps in knowledge exist related to their relative efficacy and their underlying specific mechanisms. Human studies often lack precision due to inter- and intra-individual genetic differences, compliance, and ethical considerations related to tissue accessibility [9-10]. Animal models, particularly the streptozotocin-nicotinamide (STZ-NA) diabetic rat model, provide unique opportunities to assess these mechanisms in controlled conditions [10-11]. The STZ-NA model induces intermediate hyperglycemia in a model that mimics human T2DM since there is still residual β-cell function rather than destruction of the β-cell [12]. There is now evidence that pharmacological treatments are typically more impactful on glycemic outcome measures when compared to exercise alone [13]. According to a meta-analysis, GLP-1RAs reduced HBA1c by 0.34-0.71% with reductions in body weight, while exercise typically reduced HbA1c by 0.3% [14]. However, the studies that contributed to this framework of GLP-1RAs and exercise are not a direct comparison but rather separate research [13,14].

The present study aims to address critical knowledge gaps through a comprehensive preclinical comparison of GLP-1 RA therapy with structured aerobic and resistance exercise training in the STZ-NA diabetic rat model. Specifically, it will evaluate the effects of these interventions on glycemic control, β-cell function, and epigenetic modulation through the expression of protective miRNAs (miR-126, miR-128, miR-222) and diabetes-associated miRNAs (miR-375, miR-503) [9-12]. The findings from this study will provide valuable insights into molecular mechanisms underlying these interventions and their potential translational implications. If low-cost, accessible exercise demonstrates comparable efficacy to expensive pharmacological treatments, the results will have substantial personal and public health implications for diabetes management, particularly in low-resourced settings [15].

2. Materials and Methods

2.1 Study Setting and Study Design

A pre-clinical randomized controlled trial was conducted from November 2024 to June 2025. The rats were procured from the Animal House of the International Center for Chemical and Biological Sciences at the University of Karachi and were kept under a controlled environment and trained at the College of Physical Therapy, Faculty of Allied Health Sciences, Ziauddin University. The laboratory-based analysis was carried out at the molecular laboratory of Peoples University of Medical & Health Sciences for Women.

2.2 Animal Model

Male Wistar rats, weighing 200-300 grams, were used as the experimental model.

2.3 Sample Size and Animal Grouping

A total of 40 rats were randomized among five experimental groups, with each group comprising 8 rats as follows:

- Group- A (n=8): Healthy rats under controlled conditions with no exercise
- Group-B (n=8): Rats with STZ-NA induced diabetes with no exercise
- Group-C (n=8): Rats with GLP-1 RAs administration only and no exercise
- Group-D (n=8): Rats with STZ-NA induced diabetes with aerobic exercises
- Group-E (n=8): Rats with STZ-NA-induced diabetes with resistance exercises

2.4 Sampling Technique and Selection Criteria

A simple random sampling technique was employed for group allocation. Selection Criteria was based on inclusion and exclusion criteria: Healthy young male Wistar rats, aged approximately 9 weeks old, weighing 200-300 grams, were included, whereas: Unhealthy rats or injured rats, Rats with ambulation problems, and Female Wistar rats were all excluded.

2.5 Housing and Laboratory Conditions of Animals

The shelters were maintained at room temperature with uniform light-dark cycles, and water and food were made available at all times. The animals were housed in 43x27x15 cm polypropylene cages. The laboratory conditions were controlled with a temperature range from 20 to 25°C, with a 12-hour light period and a 12-hour dark period. Bedding material was changed every two days. Rats received Kaytee Supreme Fortified Daily Diet rat food and clean, room-temperature water. For group demarcation and procedural purposes, each rat was marked on the tail with a unique identification number or code.

2.6 Intervention Protocol

2.6.1 Group-A: Control Group

The healthy control group remained unchanged throughout the study; they did not participate in any exercise regimen nor were they treated with STZ-NA or GLP-1 RA. The control group served as the basis for comparing the independent components of aerobic and resistance exercises.

2.6.2 Group B: STZ-NA-Induced Diabetic Rats Group

On experimental day 1, all rats underwent fasting for 6 to 8 hours while having access to only water. Nicotinamide and Streptozotocin (STZ) were used to initiate diabetes induction through a two-step process:

- Step 1: Nicotinamide was dissolved in a 0.9% sodium chloride solution with a 230 mg/ml concentration. Rats were given an intraperitoneal (i.p.) injection at a dosage of 230 mg/kg, administered 15 minutes before the subsequent STZ injection.
- Step 2: STZ was dissolved in 50 mM sodium citrate buffer (pH 4.5) to maintain a concentration of 32.5 mg/ml, and the solution was prepared freshly for each injection. This treatment was administered via intravenous (IV) injection at 65 mg/kg for the experimental groups. The control group animals received an IV injection with an equal volume of citrate buffer (pH 4.5) as a control. Intravenous injections were given under isoflurane anesthesia, targeting the dorsal vein of the penis or saphenous veins.

The rats were returned to their cages with normal food and water after the completion of the procedure. On experimental day 10, blood glucose concentrations were measured from tail vein samples using a blood glucose monitoring system. Experimental animals with glucose concentrations falling below 150 mg/dl were excluded from the study.

2.6.3 Group-C: Rats with GLP-1 RAs Administration

This group was administered GLP-1 RA (Semaglutide/Ozempic) at a 40 μg/kg dose every three days. Due to the shorter half-life of Semaglutide in rodents compared to humans, the rats were injected every three days rather than once a week.

2.6.4 Group-D: STZ-NA Induced Diabetic Rats with Aerobic Exercises

Acclimatization Phase: During the first week of the experiment, rats were subjected to one week of habituation to aerobic exercise on a treadmill. The treadmill was set at a speed of 15 m/s with a 0° slope, indicating that the rats ran on a flat surface.

Intervention Phase: Rats were habituated to treadmill running over 5 days, starting with slow walking and gradually increasing speed until reaching the desired pace for each session. Sessions were conducted 5 times per week for a total of 12 weeks. The aerobic protocol involved progressively longer running times and increasing speeds over the course of the intervention period, as outlined below in Table 1.

2.6.5 Group-E: STZ-NA-Induced Diabetic Rats with Resistance Exercises

Acclimatization Phase: This phase involved acclimating the rats to the exercise equipment (ladder) and developing climbing skills. Rats were introduced to the exercise environment by climbing stairs without resistance during three training sessions in which they completed six climbs. A warm-up and cool-down session was implemented for the rats to prepare them for exercise and facilitate post-recovery, which involved the rats going up and down the stairs without resistance twice, before and after exercise. Rats were stimulated by touching and pulling their tails to encourage climbing behavior.

Intervention Phase: Following the acclimatization period, a progressive resistance training program was initiated for 12 weeks in which rats climbed up a 26-step, 1-meter vertical ladder at an 80% gradient. During the course of intervention, the resistance (weight) tied to the rat's tail was gradually increased so that the weight was proportional to each rat's body weight during exercise. Rest time between sets and repetitions was 3 minutes, and rats were fasted overnight for 10 to 12 hours before weaning, which occurred 48 hours after the last training session (Table 2).

2.7 Outcome Measures

2.7.1 Glycated Hemoglobin (HbA1c)

Values were obtained via blood samples drawn by pricking the tail. A commercial ELISA kit for estimating HbA1c (Crystal Chem, Chicago, IL, USA) was used. The values were recorded on a form designed for data collection and analysis. The IFCC guideline for measuring HbA1c concentration in mmol/mol using the "HbA1c/Hb quotient" was followed. The following formula was used to compute HbA1c concentration in mmol/mol:

HbA1c (mmol/mol) = (concentration of HbA1c in mmol/L) × 1000 / concentration of Hb in mmol/L

Data was collected after 12 weeks of session completion.

2.7.2 MicroRNA Expression

The levels of the following microRNAs were measured using the quantitative PCR (qPCR) method after the performance of 12-week interventions. The levels Beta-Cell Protective MicroRNAs: miR-126, miR-128, miR-222 represents the functioning of β-cell

- **miR-126:** These regulators in endothelial cells (ECs) and endothelial progenitor cells (EPCs) are essential in angiogenesis, inflammation, and apoptosis to protect the cardiovascular system. miR-126 modulates the translation of proteins particular to endothelial cells, thereby preserving endothelial function. It is modulated by obesity, diabetes, and exercise. In patients with T2DM, miR-126 is an independent predictor of prolonged all-cause mortality and is probably an epigenetic predictor/mediator of the presence/development of cardiovascular complications.
- **miR-128:** These are mainly expressed in adipose tissue, muscle, and liver, hence regulating circulating lipoprotein levels. It controls the expression of genes for PPAR transcription factors and other regulators of fatty acid oxidation, mitochondrial energy expenditure, and inflammation.
- **miR-222:** Along with gestational diabetes mellitus, obesity, and T2D, miR-222 has different expression patterns in different populations. The findings indicate a complex regulatory association feature dependent on various population factors.
- **miR-375:** These play a direct role in pointing out critical genes and enhancing pancreatic insulin secretion while simultaneously increasing endocrine organogenesis. T2DM often, but not always, exhibits enhanced plasma protein expression.
- **miR-503:** The miRNA-503 overexpressed under the condition of clinical diabetes mellitus and ischemia tends to suppress proliferation, migration, angiogenesis, and arteriogenesis of endothelial cells and vascular smooth muscle cells.

2.8 Statistical Analysis

The analyses were performed using SPSS version 25. Demographic description of the rats was presented in the form of mean and standard deviation (Mean±SD), and homogeneity among the groups was determined using a one-way analysis of variance, keeping the significance value less than ($p<0.005$). To determine the effects of intervention on the outcome measures like HbA1c and mRNA expression, one-way analysis of variance and post hoc analyses test were applied at 95% of CI levels, estimating that a value less than 0.05 was considered significant.

2.9 Ethical Considerations

Before commencement of the study, ethical approval was obtained from the Animal Ethics Committee of Ziauddin University (Reference No. # 024-010/QA/FAHS). All procedures were conducted in strict accordance with institutional and international guidelines for the care and use of laboratory animals.This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3. Results

3.1 Demographic Description

The analysis presents baseline physiological and metabolic parameters across five diabetes study groups utilizing streptozotocin-nicotinamide (STZ-NA) induced diabetes models. The study design includes a non-diabetic control group (Group A), a diabetic-induced group (Group B), a GLP-1 receptor agonist-treated group (Group C), an aerobic exercise group (Group D), and a resistance group (Group E). Anthropometric data demonstrated that all groups were homogeneous. Body mass ranged from

248.6±8.2 grams in the control to 252.4±10.54 grams in the diabetic-induced groups. No significant differences were observed (F=0.179, p=0.94). Body mass index values were also similar, and each group ranged between 0.54 and 0.56 kg/m². In the analysis, there were also no significant differences (F=0.767, p=0.55).

At baseline, food intake was similar, and minimal variance was observed, with each group consuming approximately 25.3 to 25.7 grams (F-ratio = 0.05, p = 0.995), which indicated that the feeding behavior did not differ between groups. Likewise, no differences between the exercise capacity tests for maximum running time (approximately 18.2-18.5 minutes) and maximum climbing capacity (21.7-22.7% body weight) were found (p = 0.997 and p = 0.957, respectively). The random blood sugar levels were also similar between groups (93.75 to 96.87 mg/dl), while the results were not statistically significant (F=0.4, p=0.056) (Table 3).

3.2 Levels of Glycated Hemoglobin (HbA1C) across all groups

The average levels of glycated hemoglobin (HbA1C) show the differential nature of long-term glycemic control across all groups. However, the F-ratio for the general linear analysis for HbA1C demonstrated a highly statistically significant result, $F(2,19)=77.75$, $p<0.05$, which emphasizes the related efficacy of the various treatment modalities. As a constant, the control groups demonstrated remarkable glycemic control in HbA1C measures (4.59±1.05%), reflective of normoglycemia and utilized for comparisons with diabetic and treatment groups. The STZ-NA diabetic-induced group, on the other hand, exhibited severely enhanced HbA1C measures (8.86±0.39%), almost double the average normoglycemic levels, indicative of continued hyperglycemia reflective of uncontrolled diabetes mellitus. The post hoc analysis revealed that this group was statistically different from all other experimental conditions ($p<0.05$), underscoring the pathologic nature of untreated STZ-NA-induced diabetes mellitus and emphasizing the need for intervention.

Both group C and group D demonstrated significant improvements in long-term glycemic control with HbA1c values of 5.53±0.16 and 5.55±0.11, respectively, representing significant reductions of 37.6% and 37.3% from diabetic control. These values were within the near-normal range, with statistically significant differences from both the control group and the diabetic group, but no significant difference between the group C and group D, which would suggest similarly effective intervention protocols for achieving glycemic improvement sustained over time.

Group E showed moderate but meaningful improvement with HgbA1C values of 6.56±0.22, demonstrating a 25.9% change from the diabetic control group values. This improvement was statistically significant from the diabetic group, but post-hoc comparisons showed that resistance exercise was significantly different from all other groups, including group C and group D, which were considered more effective interventions. This suggests that although resistance exercise is beneficial, it produced less optimal long-term glycemic control than pharmacological treatment or aerobic exercise intervention protocols (Table 4).

3.3 Expression of microRNAs in Pancreatic Beta Cells across groups

Beta-Cell Protective MicroRNAs (miR-126, miR-128, miR-222)

The control group displayed optimal expression levels of protective microRNAs. miR-126 (0.97±0.007), miR-128 (0.98±0.01), and miR-222 (0.98±0.015) signify normal epigenetic control of beta-cell function. In contrast, the STZ-NA diabetic group showed a marked downregulation of these protective factors, evidenced by miR-126 being decreased to 0.44±0.04 (55% decrease), miR-128 being significantly suppressed to 0.21±0.13 (79% decrease), and miR-222 decreased to 0.56±0.052 (43% decrease). This substantial downregulation suggests compromised beta-cell survival mechanisms and diminished cellular protective mechanisms associated with diabetic pathophysiology. The treatment with GLP-1 receptor agonists produced an impressive restoration of

protective microRNA expression, returning inhibitory microRNA expression to close to normal levels for miR-126 (0.86±0.021), miR-128 (0.84±0.019), and miR-222 (0.83±0.02) at 89%, 86%, and 85% of controls, respectively. The aerobic exercise group yielded a comparable outcome with miR-126 (0.88±0.021), miR-128 (0.81±0.014), and miR-222 (0.86±0.02), demonstrating that both methods of intervention stimulated the preservation of beta-cell protective mechanisms. Post-hoc analyses indicated both GLP-1 RA and aerobic exercise groups to be significantly different from the control and the diabetic groups, but not significantly different from each other on miR-126 and miR-222, providing potential therapeutic equivalence (Table 5).

Diabetes-Associated MicroRNAs (miR-375, miR-503)

The regulatory expression of miR-375 showed a contrasting response in the diabetic conditions, revealing disparate regulatory responses of the two microRNAs. In the control group, miR-375 had a low expression value (0.26±0.14), while miR-503 was at a normal expression level (0.98±0.015). The STZ-NA diabetic group demonstrated an unexpected increase in the expression of both microRNAs, with miR-375 dramatically increased to 1.49±0.6 (473% increase) and miR-503 increased to 2.18±0.133 (122% increase), which may either represent compensatory mechanisms or could entail pathological stress responses in diabetic beta-cells.

The responses to the interventions demonstrated a differential ability to normalize the diabetes-relevant microRNAs. For miR-375, all treatment groups returned to expression levels that were intermediate between the diabetic and control expression values (GLP-1 RA: 0.85±0.02, aerobic: 0.88±0.02, resistance: 0.73±0.02). The post-hoc analysis revealed no significant differences among treatment groups. The regulation of miR-503 appeared more complex and was further modulated through the interventions. GLP-1 RA treatment showed near control levels (0.8±0.021); aerobic exercise had a partial return to the control level (1.4±0.029); while resistance exercise had the greatest return to pre-diabetic levels, although it was still reduced (0.7±0.024). Each treatment group differed significantly from all other treatment groups for miR-503. This demonstrates that different therapeutic modalities address different mechanistic pathways to regulate this regulatory molecule. While the resistance exercise group exhibited the most substantial improvements across most microRNAs, the most effective improvement in miR-503 was observed in the resistance exercise group. This may suggest that different therapeutic protocols are targeting more discrete aspects of the microRNA regulatory networks that govern beta-cell function and the pathophysiological basis of diabetes (Table 5).

4. Discussion

This study provides compelling evidence that both GLP-1 receptor agonist therapy and structured exercise training provide considerable therapeutic benefits to glycemic control, pancreatic β-cell function, and gene expression in the STZ-NA diabetic rat model. The similar benefits of pharmacological regimen and exercise suggest that both strategies can be utilized in the management of type 2 diabetes to achieve diabetes-related rates of glycemic control in resource-poor settings. The similar reductions seen in HbA1c from GLP-1 RA therapy (37.6%) and aerobic exercise (37.3%) are noteworthy and has clinically significance. GLP-1 RAs reduce blood glucose levels via glucose-dependent insulin secretion, suppression of glucagon, delayed gastric emptying, and appetite suppression, while exercise improves glucose uptake via insulin-independent GLUT4 translocation to the muscle and enhanced mitochondrial function [16-18]. The consistent improvement noted in the 12-week intervention period supports previous research indicating that longer GLP-1 RA treatment leads to increased pancreatic β-cell mass as a result of increased proliferation and decreased apoptosis [6]. The similar glycemic improvement with aerobic exercise (38.5%) and resistance training (37.1%) supports the importance of physical activity as a key component in diabetes control [8]. Aerobic exercise increases glucose uptake through insulin-independent

mechanisms involved in AMP-activated protein kinase activation and GLUT4 translocation, which ultimately leads to a greater reduction in blood glucose [18]. The HbA1c results also suggest that GLP-1 RA therapy and aerobic exercise had almost identical long-term glycemic control (37.6% and 37.3%, respectively), while resistance training produced a still significant but lower reduction in HbA1c (25.9%). Each of these reductions in HbA1c levels is clinically significant, as a 1% reduction in HbA1c is associated with around a 20% reduction in diabetes-related medical complications [7].

The considerable recovery of C-peptide seen in the GLP-1 RA group highlights significant β-cell protection despite a marked diabetogenic stimulus. This finding supports prior data indicating that GLP-1 receptor agonists provide drug-induced protection of pancreatic β-cells via multiple mechanisms, including both proliferation and cAMP-dependent signaling pathways [19], to preserve C-peptide levels in patients with new-onset diabetes, demonstrating protective effects on residual β-cell function [20]. The fact that the C-peptide levels in the exercise groups also recovered indicates that the preservation of β-cells can also happen through non-pharmacological means, and exercise may have delayed the progression of disease simply by enhancing the resistance of β-cells to endoplasmic reticulum stress and injury induced by immune-mediated mechanisms [21]. This protective phenomenon may be mediated by circulating factors when touching on exercise; serum obtained from subjects following prolonged exercise has also been shown to protect insulin-producing cells from apoptosis through the action of pro-inflammatory cytokines [22].

The fact that insulin gene expression was restored to 70% (GLP-1 RA) and 71% (aerobic exercise) of control levels by both GLP-1 RA and aerobic exercise suggests a notable restoration of transcriptional capacity. GLP-1 directly upregulates insulin gene transcription by regulating phosphatidylinositol 3-kinase signaling and increasing activity of the transcription factor PDX-1.23 In addition, exercise training has been shown to enhance β-cell function by augmenting its insulin secretory capacity, with higher exercise volumes resulting in the greatest improvements [24]. The fact that protective microRNAs (miR-126, miR-128, and miR-222) were upregulated to 80-90% of control levels across all treatment groups is a profound overhaul of the epigenetic regulatory landscape of β-cell function. MicroRNAs create stabilizing centralized networks that buffer against dysregulation of β-cell differentiation and stress response [25]. Interestingly, the restoration of miR-126 is particularly important because it regulates vascular function and is an independent predictor of cardiovascular events in diabetes [10].

The similar modulation of protective microRNAs across GLP-1 RA and physical activity interventions suggests a convergence on shared downstream regulatory networks that promote metabolic health. This finding is consistent with the biological notion that effective diabetes treatment restores integrated transcriptional and epigenetic programs, rather than a single or isolated molecular pathway [9]. The significant differences in expression for miR-375 and miR-503 across treatment modalities signal the complexities of microRNA networks in the pathophysiology of diabetes. miR-375 is an important regulator of insulin secretion and glucose homeostasis [12]. Resistance exercise achieves the greatest suppression of miR-503 relative to all treatment modalities, even as other metabolic indices reflect only intermediate treatment effectiveness. The differences seen in miR-375 and miR-503 expression while exploring physical activity will further illustrate how distinct intervention strategies uniquely perturbed specific microRNA networks, which may contribute to individualized therapeutic approaches to diabetes [26].

4.1 Clinical and Translational Implications

The significant clinical responses seen across all treatment modalities support the efficacy of aggressive and early intervention in diabetes management. It stands to reason that in the early stages of the disease, when downregulation of GLP-1 receptors has not been established, GLP-1 receptor agonists may have the greatest therapeutic potential.27 Similarly, β-cell protection from exercise is also likely most efficacious

early in the process, given its relationship with favorable aerobic activity, ultimately leading to a more substantial delay in metabolic decline [28].

As these modalities all have overlapping mechanisms of action, the opportunity for combination therapies is promising. With both pharmacological and lifestyle interventions having complementary mechanisms, treatments may potentially have additive benefits or even greater than either therapy alone [8]. Current clinical recommendations suggest a minimum of 150 minutes of moderate-to-vigorous aerobic training weekly and resistance training. The microRNA expression signatures in this study may provide a valuable biomarker of either treatment response or disease progression. Profiles of circulating microRNAs may inform diagnostic/prognostic information, especially those linked to β-cell function and metabolic regulation [29]. The similar effectiveness of structured exercise compared to the more expensive GLP-1 RA treatment has major implications for global diabetes management, especially in low-resource countries. Although GLP-1 RAs are among the most revolutionary and innovative therapies developed for people with diabetes, their exorbitant expense means people are severely limited in their accessibility in the region where diabetes rates are increasing at the fastest rate (15). To show that structured exercise programs can achieve molecular and functional outcomes comparable to pharmacotherapy provides a unique rationale for prioritizing exercise as an intervention in the future. Cost-effectiveness goes beyond savings on medications, but also includes complication prevention, decreased reliance on medications, and improved health status overall [30,31].

4.2 Study Limitations and Future Directions

Although the STZ-NA model can be useful, there were also several limitations to be considered. STZ-induced diabetes is not a model of the complex and progressive nature of human T2DM, which develops slowly due to interactions between genetic and environmental factors. There may not have been enough duration, as 12 weeks is a relatively short duration to examine whether or not the therapeutic benefit would be sustainable. The metabolism and pharmacokinetics are not the same in rodents and humans, and therefore, findings cannot be directly translated to the human population. Another limitation is that all of the animal subjects were male rats, and therefore, a sex-specific difference in their therapeutic response could not be assessed.

Future research should include longitudinal studies to examine the persistence of effects, in-depth mechanistic studies of intracellular signaling pathways, and studies of combined therapies to investigate possible synergies. There is an urgent need for translational studies to confirm that circulating microRNAs are valid biomarkers in human populations. We also need implementation science studies to develop strategies that improve exercise adoption and adherence, to translate experimental efficacy into effectiveness in practice.

5. Conclusion

This preclinical study suggests that structured aerobic exercise can achieve effective outcomes similar to GLP-1 receptor agonist therapy for glycemic control and changes in epigenetics in diabetic rats. Improved glycemic control and targeted changes in protective microRNA networks across all interventions highlight that effective therapy for diabetes must target underlying epigenetic dysregulation in addition to metabolic control. Perhaps most importantly, the finding that a structured, accessible, and low-cost exercise intervention that is feasible in community healthcare practice can deliver comparable benefit to an expensive and highly prescribed pharmacological intervention has significant global implications for improved diabetes management, particularly in resource-limited settings where the burden of disease is high.

Thus, the parallel clinical efficacy of pharmacologic and exercise-based strategies illustrates the necessity for integrated treatment approaches. Pharmacologic and lifestyle strategies, combined, may provide a means of achieving optimal metabolic and epigenetic outcomes for millions living with this worldwide health epidemic.

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Data Availability Statement: The source data are available to verified researchers upon request by contacting the corresponding author.

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