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GLP-1 RECEPTOR AGONIST VS. EXERCISE: EFFECTS ON INSULIN GENE EXPRESSION AND B-CELL RECOVERY IN DIABETIC RATS

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is estimated to affect 537 million adults worldwide, but the mechanisms at the molecular level whereby structured exercise and incretin-based pharmacotherapy affect pancreatic β-cell transcriptional activity and circulating microRNA (miRNA) profiles are not fully understood. In a diabetic rodent model, the effects of a GLP-1 receptor agonist (GLP-1 RA) were compared with those of aerobic and resistance exercise on glycemic control, β-cell function, and insulin-related miRNA expression.

Methods: Forty male Wistar rats were randomly assigned to five groups (eight per group): healthy controls, STZ-NA-induced diabetic, GLP-1 RA (semaglutide), aerobic exercise, and resistance exercise. Interventions were delivered for 12 weeks. Random blood sugar (RBS), glycated hemoglobin (HbA1c), serum C-peptide, insulin gene expression (RT-qPCR, $2^{-}\Delta\Delta Ct$ method), and five miRNAs (miR-126, -128, -222, -375, -503) were measured by RT-PCR and gel electrophoresis.

Results: All three interventions significantly decreased RBS levels compared with untreated diabetic animals (aerobic: 38.5%; resistance: 37.1%; GLP-1 RA: 39.3%; $p<0.001$). The HbA1c reductions were similar (~37%) for GLP-1 RA and aerobic exercise, and insulin gene expression was restored to ~70% of control values; resistance exercise had more modest improvements (25.9% reduction in HbA1c; 58% of control in insulin gene expression). Protective miRNAs (miR-126, -128, -222) increased in all treatment arms, pathological miRNAs (miR-375, miR-503) decreased, and resistance exercise normalized miR-503 the most.

Conclusion: Structured exercise and GLP-1 RA therapy have similar effects on glycemic control, β-cell preservation, and epigenetic regulation via miRNAs, suggesting that exercise is a valid molecular therapy in addition to pharmacologic therapy.

KEYWORDS: *Aerobic Exercise; Diabetes Mellitus; GLP-1 Receptor Agonist; Insulin Gene Expression; MicroRNA; Wistar Rats.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex and increasingly prevalent metabolic disorder characterized not only by elevated blood sugar levels but also by a range of serious complications affecting various organ systems.[1] Among these complications, cardiovascular and renal issues are well-documented, but the disease also leads to the progressive deterioration of pancreatic β-cells, which are crucial for insulin production.[2] In recent years, advancements in diabetes management have emphasized two main strategies: the use of pharmacological agents such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the integration of structured physical activity, including both aerobic and resistance training.[3] These approaches aim to improve glycemic control and enhance overall patient health, marking a significant shift in the management of T2DM.[4]

Exercise has insulin-independent effects on glucose disposal through AMPK (AMP-activated protein kinase) signaling and increased translocation of glucose transporters.[5] It also has a wide range of effects on hepatic insulin sensitivity and on β-cell preservation, extending beyond these immediate effects.[6]

It remains unclear whether these two interventions influence common molecular pathways at the level of the insulin gene or if they have a similar effect on the microRNA networks that regulate β-cell survival and function. The changes in molecular signature induced by exercise, compared with pharmacological therapies, have direct implications for the role of lifestyle interventions in diabetes management, making it crucial to understand whether exercise can achieve these effects.[7-8] In this context, comparative-effectiveness studies using relevant animal models offer a valuable means to explore the molecular effects of drug and lifestyle therapies before embarking on time-consuming human clinical trials. The STZ-NA rat model is particularly effective for examining recoverable β-cell function, rather

than fully destroyed cells. This model allows partial protection of β-cells through nicotinamide, thereby helping maintain a population of residual insulin-secreting cells.[9] As a result, it is well-suited for testing therapies aimed at rescuing transcriptional and epigenetic programs rather than solely lowering glucose levels.

The purpose of this study was to compare the effects of a GLP-1 receptor agonist, aerobic exercise, and resistance exercise on various health indicators in a streptozotocin-nicotinamide (STZ-NA)- induced model of diabetes in rats. These indicators included random blood glucose, HbA1c, serum c-peptide, pancreatic insulin gene expression, and a panel of five regulatory microRNAs (miRNAs). The study aimed to evaluate the extent to which exercise can be viewed as a molecular therapy rather than merely a behavioral one, and to investigate whether aerobic and resistance exercise engage distinct regulatory pathways.

METHODOLOGY

Study Design and Ethical Approval

The pre-clinical randomized controlled study was conducted on 40 male Wistar rats (200–300 g, 9 weeks old) obtained from the Animal House of the International Center for Chemical and Biological Sciences, University of Karachi. The animal training was conducted at the College of Physical Therapy, Ziauddin University, and the molecular analyses were carried out at the laboratory of Peoples University of Medical & Health Sciences for Women. The Animal Ethics Committee of Ziauddin University (2024-010/QA/FAHS) approved the study.

Animals and Diabetes Induction

Male rats without injury and able to move were included, but female rats and rats with mobility impairment were excluded. Animals were randomly assigned (n=8/group) to five groups: (A) healthy control, (B) STZ-NA diabetic (untreated), (C) STZ-NA diabetic treated with GLP-1 RA, (D) STZ-NA diabetic treated with aerobic exercise, and (E) STZ-NA diabetic treated with resistance exercise. Groups B–E were made diabetic using the two-step nicotinamide–streptozotocin protocol: Nicotinamide (230 mg/kg, i.p.) was given 15 minutes prior to streptozotocin (65 mg/kg, i.v. in citrate buffer, pH 4.5); control animals received the same volume of citrate buffer. On day 10, diabetes was confirmed by tail-vein glucose measurement (150 mg/dl was used as the cut-off).

Interventions

Group C received semaglutide at 40 μg/kg every 3 days; this dose was selected because the half-life of GLP-1 RAs in rodents is shorter than in humans.[10] Group D had a progressive treadmill protocol, starting with 10 minutes at 18 m/min in week 1, and increasing to 60 minutes at 28 m/min in weeks 11–12, five times weekly for 12 weeks.[11] Group E had resistance training using a weighted ladder climbing exercise, increasing from 10% of body weight in week 1 to 100% in weeks 10–12 and performed five sessions per week for 12 weeks; animals were fasted for 10–12 hours prior to weaning, which occurred 48 hours after the last exercise session.

Housing Conditions

Animals were kept in standard conditions: 12 hours light/dark cycle, 20-25°C, free access to standard rodent chow and water, bedding changed every 2 days, and each animal was given a unique identification code. The study period was 8–12 months from procurement to molecular analysis, with the main intervention period of 12 weeks being set for all treatment arms to enable direct temporal comparison.

Outcome Measures

Random blood sugar (RBS) was measured using a glucometer, HbA1c was quantified by ELISA (IFCC protocol), serum C-peptide was measured by ELISA (Mercodia), insulin gene expression was determined by RT-qPCR using the $2^{-}\Delta\Delta Ct$ method on pancreatic tissue taken at euthanasia, and five miRNAs (miR-126, -128, -222, -375, -503) were measured by RT-PCR with sequence-specific primers and gel electrophoresis. Animals were sacrificed using sodium pentobarbital (60 mg/kg) at week 12, and pancreatic tissue was snap frozen at −80°C for RNA extraction.[12]

Statistical Analysis

Data were analyzed using SPSS v25. The normality of the data was tested by the Shapiro-Wilk test. One-way ANOVA (or Kruskal-Wallis for non-normal data) with Bonferroni post-hoc was used for between-group comparisons. In contrast, paired t-tests (or Wilcoxon signed-rank test for non-normal data) were used for within-group comparisons. The level of statistical significance was determined at $p<0.05$.

RESULTS

Baseline Characteristics

No significant between-group differences were observed at baseline in body weight (248.6–252.4 g), BMI (0.54–0.56 kg/m²), food intake (25.3–25.7 g), maximum running time (18.2–18.5 minutes), maximum climbing capacity (21.7–22.7% body weight), or RBS (93.75–96.87 mg/dl; all $p>0.05$), confirming successful randomization and comparable baseline physiological and behavioral status across the five groups (Table 1).

Table 1. Baseline physiological and behavioral characteristics across groups (mean ± SD).

Variable	Control	Diabetic (STZ-NA)	GLP-1 RA	Aerobic Exercise	Resistance Exercise	F-ratio	p-value
Weight (g)	248.6±8.2	252.4±10.54	250.8±10.84	251.6±11.43	249.5±10.24	0.179	0.940
BMI (kg/m²)	0.54±0.02	0.56±0.03	0.55±0.02	0.55±0.03	0.55±0.02	0.767	0.554
Food intake (g)	25.33±1.39	25.69±1.6	25.4±1.58	25.5±1.43	25.4±1.59	0.05	0.995
Max. running time (min)	18.43±1.75	18.17±1.88	18.45±1.43	18.26±1.84	18.43±1.72	0.03	0.997
Max. climbing capacity (% BW)	22.46±2.67	21.7±2.87	22.22±2.68	21.95±2.75	22.66±2.59	0.161	0.957
RBS (mg/dl)	96.8±2.29	96.87±2.1	95.87±2.03	93.75±1.83	96.75±1.66	0.4	0.056

Glycemic Control

RBS differed markedly across groups over the 12 weeks (F-ratios 665.70–1025.44, $p<0.001$ at every time point). The control group remained stable (97.8-99.4 mg/dl). Untreated diabetic animals showed sustained hyperglycemia, falling only marginally from 284.9 to 276.2 mg/dl (a 3.0% change). By contrast, GLP-1 RA reduced RBS from 275.3 to 167.0 mg/dl (39.3% reduction), aerobic exercise from 273.5 to 167.8 mg/dl (38.5%), and resistance exercise from 278.6 to 175.1 mg/dl (37.1%). By weeks 11–12, the three active treatment arms no longer differed significantly from one another, indicating convergent glycemic efficacy despite distinct mechanisms (Figure 1).

HbA1c at week 12 confirmed this pattern ($F=77.75$, $p<0.001$): control 4.59±1.05%, diabetic 8.86±0.39%, GLP-1 RA 5.53±0.16% (37.6% reduction), aerobic exercise 5.55±0.11% (37.3%), and resistance exercise 6.56±0.22% (25.9%). Resistance exercise differed significantly from both GLP-1 RA and aerobic exercise, indicating a less complete restoration of long-term glycemic control despite similar reductions in RBS.

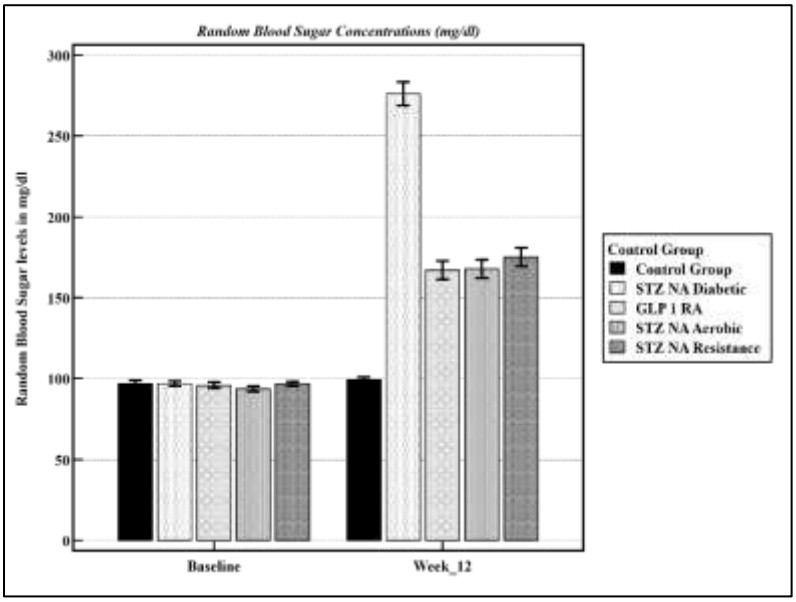

Figure 1. Random blood sugar (mg/dl) at baseline and week 12 across control, diabetic, and intervention groups

β-cells Secretory Function

Serum C-peptide, essentially abolished in untreated diabetic rats (0.002±0.001 nmol/L versus 0.73±0.10 nmol/L in controls, a 99.7% loss), was substantially recovered by GLP-1 RA (0.53±0.11 nmol/L, ~73% of control), aerobic exercise (0.50±0.14 nmol/L, 68%), and resistance exercise (0.45±0.20 nmol/L, 62%), with no significant differences among the three active arms ($F=33.33$, $p<0.001$).

Insulin Gene Expression

Transcriptional activity mirrored the C-peptide findings ($F=571.79$, $p<0.001$). Relative to control (0.97±0.007), diabetic animals showed a 68% reduction (0.31±0.03). GLP-1 RA restored expression to 0.68±0.02 (70% of control) and aerobic exercise to 0.69±0.01 (71%), with no significant difference between these two groups. Resistance exercise achieved a more modest 0.56±0.04 (58% of control), differing significantly from both other active interventions (Figure 2).

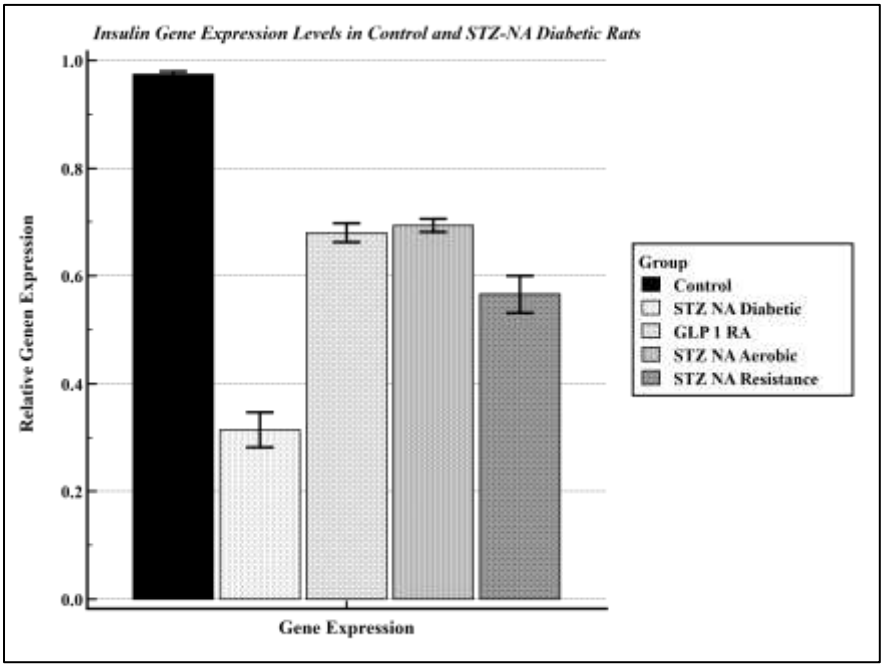

Figure 2. Relative pancreatic insulin gene expression (RT-qPCR, $2^{-}\Delta\Delta Ct$) after 12 weeks across groups

miRNA expression

All five miRNAs showed highly significant between-group variation ($F=20.26–691.46$, $p<0.001$). Protective miRNAs were suppressed in diabetic animals (miR-126: −55%; miR-128: −79%; miR-222: −43%) and substantially restored by GLP-1 RA (89%, 86%, 85% of control, respectively) and aerobic exercise (91%, 83%, 88%), with no significant difference between these two treatments for miR-126 and miR-222. Diabetes-associated miRNAs showed the opposite pattern: miR-375 rose 473%, and miR-503 rose 122% in untreated diabetic animals. All treatments normalized miR-375 to comparable intermediate levels. For miR-503, however, each treatment produced a distinct response—GLP-1 RA achieved near-normal suppression (0.80±0.021), aerobic exercise showed only partial normalization (1.40±0.029), and resistance exercise achieved the greatest suppression of all (0.70±0.024), significantly outperforming the other two arms. This divergence, occurring against a backdrop of otherwise convergent glycemic and transcriptional outcomes, suggests that resistance exercise engages a distinct regulatory node within the miRNA network governing vascular and endothelial protection in diabetes (Table 2, Figure 3).

Table 2. Full microRNA expression profile across groups at week 12 (mean ± SD).

miRNA	Control	Diabetic (STZ-NA)	GLP-1 RA	Aerobic Exercise	Resistance Exercise	F-ratio	p-value
miR-126	0.97±0.007	0.44±0.04	0.86±0.021	0.88±0.021	0.73±0.023	533.02	<0.001

miR-128	0.98±0.01	0.21±0.13	0.84±0.019	0.81±0.014	0.72±0.024	172.59	<0.001
miR-222	0.98±0.015	0.56±0.052	0.83±0.02	0.86±0.02	0.72±0.021	228.31	<0.001
miR-375	0.26±0.14	1.49±0.6	0.85±0.02	0.88±0.02	0.73±0.02	20.26	<0.001
miR-503	0.98±0.015	2.18±0.133	0.8±0.021	1.4±0.029	0.7±0.024	691.46	<0.001

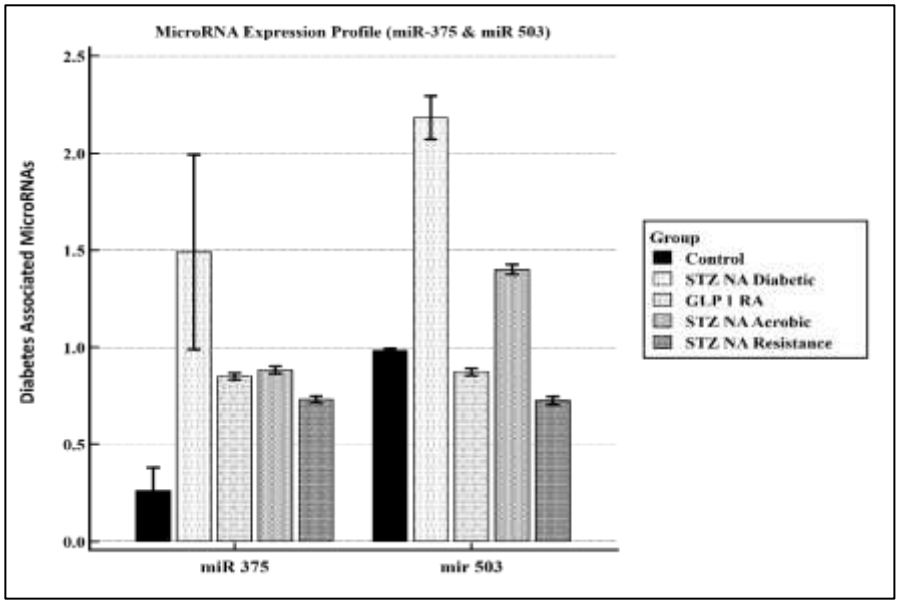

Figure 3. Expression of diabetes-associated miRNAs (miR-375, miR-503) at baseline and week 12 across groups

Table 3. Summary of key outcome measures across groups at week 12 (mean ± SD).

Outcome	Control	Diabetic (STZ-NA)	GLP-1 RA	Aerobic Exercise	Resistance Exercise
RBS, wk 12 (mg/dl)	99.4±1.72	276.21±8.72	167.02±6.84	167.83±6.91	175.12±7.01
HbA1c (%)	4.59±1.05	8.86±0.39	5.53±0.16	5.55±0.11	6.56±0.22
C-peptide (nmol/L)	0.73±0.10	0.002±0.001	0.53±0.11	0.50±0.14	0.45±0.20
Insulin gene expression (rel.)	0.97±0.007	0.31±0.03	0.68±0.02	0.69±0.01	0.56±0.04
miR-503 (rel.)	0.98±0.015	2.18±0.133	0.80±0.021	1.40±0.029	0.70±0.024

DISCUSSION

These findings demonstrate that a GLP-1 RA and structured exercise, despite operating through ostensibly distinct mechanisms, converge on comparable therapeutic endpoints in an STZ-NA rodent model of diabetes (Table 3). The near-equivalence of GLP-1 RA and aerobic exercise across RBS, HbA1c, C-peptide, and insulin gene expression supports the growing view that exercise is a genuine molecular therapy rather than a purely behavioral adjunct.[5,13]

The sustained glucose-lowering effect of GLP-1 RA is consistent with its multi-modal action on insulin secretion, glucagon suppression, and gastric emptying.[3,14] Chronic dosing, moreover, appears to support β-cell mass by enhancing proliferation and reducing apoptosis, effects that persist beyond active treatment.[4,15] The comparable RBS and HbA1c reductions achieved by aerobic exercise likely reflect AMPK-mediated GLUT4 translocation and improved hepatic insulin sensitivity, both of which enhance insulin-independent glucose disposal and produce a prolonged post-exercise glucose-uptake window.[6,16,17]

A particularly notable observation was the dissociation within the resistance exercise group between preserved C-peptide levels (statistically indistinguishable from those in the other active arms) and comparatively poorer HbA1c control. Because C-peptide reflects endogenous insulin biosynthesis while HbA1c integrates insulin secretion with peripheral insulin action over several weeks, this pattern suggests that resistance training preserved β-cell secretory function and insulin output without fully restoring peripheral glucose utilization to the same extent as aerobic training.[18] Resistance exercise increases the muscular reservoir available for glucose disposal but appears less effective than aerobic exercise at enhancing the intrinsic insulin sensitivity of muscle fibers, producing shorter, less consistent post-exercise glucose-uptake intervals.[19,20] This distinction has a practical implication: C-peptide alone is an incomplete predictor of glycemic outcome, and exercise prescription may need to be tailored to whether the predominant physiological deficit is impaired insulin secretion or impaired insulin action.

The miRNA data extend these findings to the epigenetic level. Restoration of miR-126, miR-128, and miR-222 across GLP-1 RA and aerobic exercise groups points to shared downstream regulatory programs governing endothelial integrity, lipid metabolism, and adipose tissue function, even though the upstream signals initiating these changes differ.[7,21] The divergent miR-503 response merits particular attention: while GLP-1 RA achieved the most complete normalization among pharmacologically comparable outcomes, resistance exercise produced the strongest suppression of this pathologically upregulated miRNA, suggesting that different therapeutic modalities may selectively engage distinct nodes of the same regulatory network.[8] This raises the possibility that combination regimens pairing GLP-1 RA or aerobic exercise with resistance training could achieve more complete correction of the miRNA network than any single intervention alone.[22] Such miRNA signatures may eventually support individualized treatment selection, an approach already proposed for predicting GLP-1 RA response in clinical populations.[23]

Taken together, the data support early initiation of either pharmacological or lifestyle intervention, given evidence that GLP-1 receptor density and β-cell reserve decline with disease duration, and that the protective benefits of exercise are likewise more effective before extensive β-cell loss occurs.[24] From a translational standpoint, the convergence of aerobic exercise on outcomes essentially indistinguishable from a pharmacological agent strengthens the case for prescribing structured exercise with the same clinical seriousness as medication, particularly given current guidance recommending at least 150 minutes of moderate-to-vigorous aerobic activity and two to three resistance sessions weekly for adults with T2DM.[25] Like most STZ-NA studies, this design used only male rodents, a convention adopted across metabolic research to limit estrous-cycle-related variability, though it constrains generalizability, as discussed below.[26]

Strengths

This study's principal strengths include its randomized, controlled design; the direct within-study comparison of a pharmacological agent against two distinct exercise modalities; and the use of convergent outcome measures spanning glycemic, hormonal, transcriptional, and epigenetic levels, which allowed a clear point of divergence between treatment arms, namely the miR-503 response, to be identified despite otherwise comparable efficacy.

Limitations

Several limitations warrant consideration. The STZ-NA model primarily reflects insulin deficiency through β-cell destruction rather than the mixed insulin resistance and secretory decline typical of human T2DM, and the 12-week intervention window may be insufficient to capture long-term durability or the emergence of therapeutic tolerance. Species differences in metabolism and pharmacokinetics also limit direct extrapolation of dosing regimens to humans. As this study used only male rats, the findings cannot be generalized to females, given known sex differences in glucose metabolism and diabetes susceptibility. Importantly, β-cell "recovery" and "preservation" in this study are inferred from functional and transcriptional endpoints, namely C-peptide, insulin gene expression, and glycemic

control, rather than from direct histological or morphometric assessment of β-cell mass, which was not performed; these findings should therefore be interpreted as evidence of preserved insulin secretory and transcriptional capacity, not confirmed structural preservation of β-cell mass.

Recommendations
Future work should test whether earlier initiation or longer duration can further narrow the gap left by resistance training on HbA1c while preserving its distinctive benefit on miR-503, and translational studies in humans are needed to confirm these molecular convergences.

CONCLUSION
In this pre-clinical model, GLP-1 receptor agonist therapy and structured exercise training produced comparable improvements in glycemic control, β-cell preservation, and miRNA-mediated epigenetic regulation, with aerobic exercise most closely matching pharmacological efficacy and resistance exercise offering distinct advantages in normalizing miR-503. These findings reinforce the therapeutic legitimacy of exercise as a molecular intervention in diabetes care, not merely a behavioral recommendation, and support further investigation of miRNA-based biomarkers for individualized treatment selection.

Author Contributions
QA: conceptualization, data collection, analysis, and drafting manuscript.
SIF: Study supervision, data collection, analysis and drafting manuscript.
AF: Statistical analysis, results interpretation and critical review of manuscript.
AAK: Data validation and critical review of manuscript.

All authors reviewed and approved the final manuscript and accepted responsibility for the integrity and accuracy of the work.

Funding
This research received no external funding.

Conflicts of Interest
The authors declare no conflict of interest.

Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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