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ORIGINAL PAPER

Guarding masculinity: Telmisartan and aerobic exercise preserve testicular histomorphometry in diabetic rats

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Summary ***Background: Diabetes mellitus (DM) is associated with testicular damage, leading to male infertility. This study investigates the effects of telmisartan, moderate-intensity aerobic exercise, and their combination on testicular histopathology in a streptozotocin-induced diabetic rat model.***

Methods: Male Wistar rats were divided into five groups: healthy control (K0), diabetic control (K1), telmisartan monotherapy (K2), aerobic exercise monotherapy (K3), and combination therapy (K4). Diabetes was induced using streptozotocin (STZ), and treatments were administered for 10 weeks. Testicular histopathology was assessed by evaluating Johnsen score, Sertoli cell count, Leydig cell count, and seminiferous tubule diameter.

Results: Diabetic rats (K1) showed significant declines in Johnsen score, Sertoli and Leydig cell counts, and seminiferous tubule diameter ($p < 0.05$). Telmisartan (K2) and combination therapy (K4) significantly improved all parameters, with values approaching those of healthy controls (K0). Aerobic exercise (K3) improved seminiferous tubule diameter but had limited effects on Johnsen score, Sertoli, and Leydig cells. Kruskal-Wallis, Mann-Whitney U, ANOVA, Games-Howell, and LSD tests confirmed these findings.

Conclusions: Telmisartan, either as monotherapy or in combination with moderate-intensity aerobic exercise, effectively ameliorates testicular damage in diabetic rats. Aerobic exercise alone has a partial protective effect. These findings suggest potential therapeutic strategies for preventing diabetes-induced male infertility.

KEY WORDS: *Diabetes mellitus; Telmisartan; Aerobic exercise; Testicular histopathology; Male infertility.*

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INTRODUCTION

Diabetes mellitus (DM) is known to impair male reproductive health, often leading to infertility (1). In diabetic conditions, testicular function is compromised, with significant reductions in testosterone levels, as well as impaired spermatogenesis and sperm motility (2). The prevalence of infertility among men with DM is reported to range from 35% to 51% (3).

Telmisartan, an angiotensin II receptor blocker with partial PPAR-γ agonist activity, has been shown to enhance testicular health and mitigate testicular damage in diabetic rat models (4). Furthermore, *moderate-intensity aerobic exercise* (MIAE) for ten weeks has been reported to improve Johnsen score and increase seminiferous tubule diameter by reducing *reactive oxygen species* (ROS) in diabetic rats (5, 6).

We selected moderate-intensity aerobic exercise over high-intensity protocols because the latter is widely recognized as a physiological stressor that may negatively impact overall health. High-intensity exercise has been linked to increased oxidative stress, which can detrimentally affect the male reproductive system (7).

Additionally, excessive training may induce overtraining syndrome, characterized by hormonal imbalances that disrupt spermatogenesis. Prior evidence indicates that high-intensity exercise impairs germ cell development and compromises the viability of germinal lineages and Sertoli cells within the seminiferous tubules (8, 9).

Therefore, based on previous studies, moderate-intensity aerobic exercise for ten weeks is considered the optimal regimen for supporting reproductive health while minimizing potential adverse effects (5, 6). Telmisartan (6 mg/kg body weight) has been shown to prevent diabetes-induced testicular damage when administered for a minimum of four weeks (4). However, to our knowledge, no prior study has directly investigated the combined effects of these two interventions.

This study examined the synergistic effects of telmisartan and moderate-intensity aerobic exercise on testicular histoarchitecture in STZ-induced diabetic rats.

MATERIALS AND METHODS

Study Design

This study used a true experimental, post-test-only control group design to evaluate the effects of telmisartan and MIAE on testicular histopathology in diabetic rats.

Thirty-nine healthy male Wistar rats (12 weeks old, 140-180 grams) were randomly assigned to five groups:

- K0: Healthy control
- K1: Diabetic control

- K2: Diabetic + telmisartan
- K3: Diabetic + MIAE
- K4: Diabetic + telmisartan + MIAE

After 10 weeks of intervention, all rats were euthanized via intraperitoneal injection of ketamine (300 mg/kg) and xylazine (30 mg/kg), followed by cervical dislocation and decapitation to ensure humane and complete sacrifice.

Induction of Diabetes Mellitus

Diabetes was induced by a single STZ injection (35 mg/kg, i.p.). Rats with fasting glucose > 150 mg/dL after 7 days were classified as diabetic.

Treatment protocols

- Telmisartan: 6 mg/kg/day orally via gavage for 10 weeks.
- Moderate intensity aerobic exercise: Rats in the K3 and K4 groups performed swimming exercises in a cylindrical tank (diameter 45 cm, water depth 55 cm) for 60 minutes/day, 5 days/week (Monday-Friday) for 10 weeks. Swimming was supervised, and sessions were terminated if rats could not keep their heads above water for more than 3 seconds without effort. Non-compliance in three consecutive sessions led to exclusion.

Sample collection and histological preparation

At week 10, after euthanasia testes were collected from rats, fixed, and embedded in paraffin. Sections (5 µm) were stained with H&E for analysis of:

- Johnsen score
- Sertoli cell count
- Leydig cell count
- Seminiferous tubule diameter

A single anatomical pathology specialist evaluated five non-overlapping fields per rat using a Leica Flexacam i5 microscope and Enersight software. Tubule diameter was assessed at 100×; Johnsen score, Sertoli, and Leydig cells at 400×.

Johnsen score

The Johnsen scoring system rates spermatogenesis from 1 to 10, with higher scores reflecting greater germ cell maturity and better testicular function (Table 1) (1).

Table 1.
Johnsen score criteria for histological evaluation of testicular damage.

Score	Histological criteria
10	Normal tubular epithelium, complete spermatogenesis, open lumen, ≥ 10 spermatozoa
9	Damaged tubular epithelium, closed lumen, ≥ 10 spermatozoa
8	Fewer than 10 spermatozoa
7	No spermatozoa, ≥ 10 spermatids
6	No spermatozoa, < 10 spermatids
5	No spermatozoa or spermatids, ≥ 5 spermatocytes
4	No spermatozoa or spermatids, < 5 spermatocytes
3	Only spermatogonia present
2	Only Sertoli cells present
1	No cells present in the tubule

Statistical analysis

Data were analyzed using SPSS. Normality was tested with Shapiro-Wilk; homogeneity with Levene's test. One-way ANOVA with Tukey's post hoc was applied for normal data, and Kruskal-Wallis with Mann-Whitney U for non-normal data. Significance was set at $p < 0.05$.

Ethical considerations

This study received ethical approval for animal experimentation from the institutional ethics committee 88/EC/KEPK/FKUA/2025.

RESULTS

Diabetic rat model

Thirty-nine healthy male Wistar rats (12 weeks old) were randomly assigned to five groups. Diabetes was induced in all except the healthy control group (K0) using a single STZ injection (35 mg/kg, intraperitoneal). Rats with fasting glucose > 150 mg/dL after 7 days were classified as diabetic. The groups were:

- K0: Healthy control
- K1: Diabetic control
- K2: Diabetic + telmisartan (6 mg/kg/day, oral) for 10 weeks
- K3: Diabetic + exercise (60 min/day, 5 days/week) for 10 weeks
- K4: Diabetic + telmisartan + exercise

All interventions were administered for a duration of 10 weeks. Final fasting glucose was measured before euthanasia, and testicular tissues were collected for analysis (Figures 1, 2).

Histological evaluation of testicular parameters

The histological evaluation focused on four key testicular parameters: Johnsen score, Sertoli cell count, Leydig cell count, and seminiferous tubule diameter.

Blood glucose levels

All STZ-induced groups (K1-K4) maintained fasting glucose levels > 150 mg/dL, confirming sustained hyperglycemia. No significant differences were found among diabetic groups ($p > 0.05$), indicating that treatments did not affect blood glucose levels (Table 2).

Johnsen score analysis

Shapiro-Wilk and homogeneity tests indicated a non-parametric distribution for Johnsen scores ($p < 0.05$).

Table 2.
Blood glucose level.

Group	Blood Sugar 7 days After STZ Injection	Blood Sugar Before Termination
K0		108.29 ± 9.84
K1	456.14 ± 137.001	490.43 ± 107.35
K2	349.13 ± 137.001	339.13 ± 156.76
K3	382.57 ± 136.15	381.42 ± 138.12
K4	344.71 ± 135.624	320.71 ± 131.35

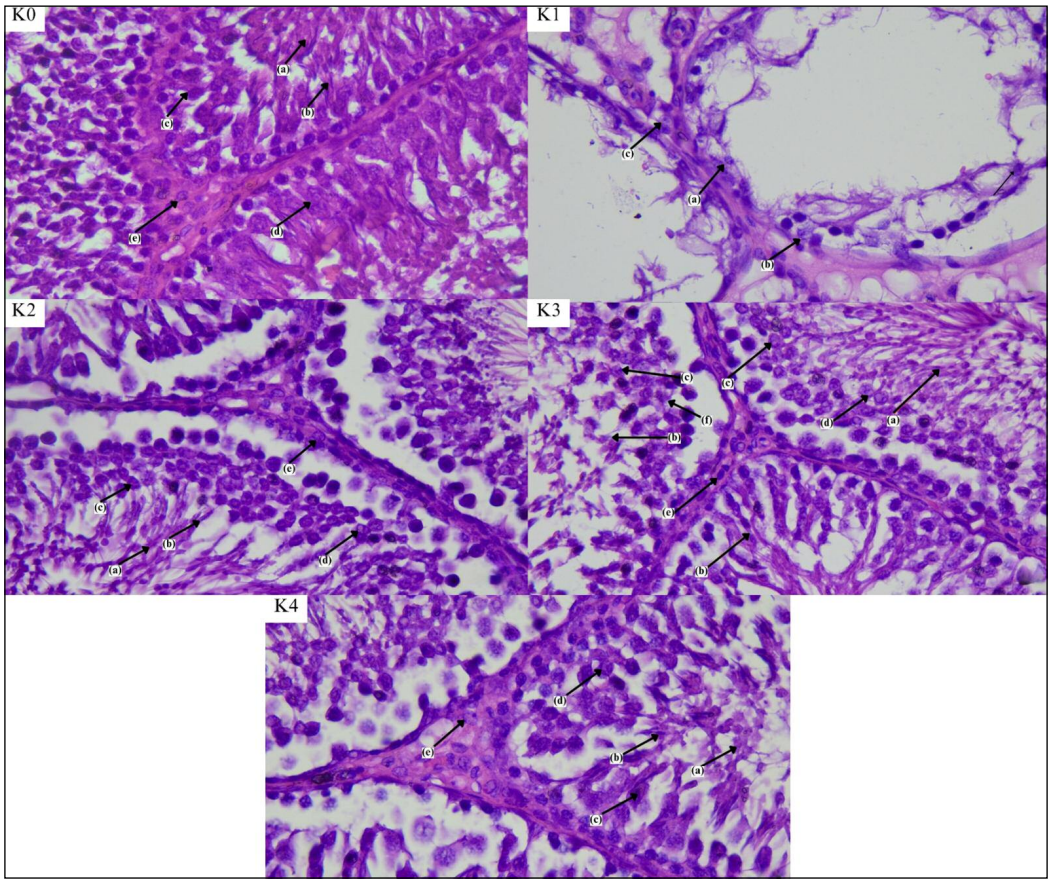

Figure 1.
Representative hematoxylin and eosin (H&E)-stained sections of seminiferous tubules at 400× magnification.
(a) Spermatozoa;
(b) Spermatids;
(c) Spermatocytes;
(d) Sertoli cells;
(e) Leydig cells.
K0: Healthy control with normal tubular architecture and spermatogenesis (Johnsen Score 10).
K1: Diabetic control showing degeneration of seminiferous epithelium (Johnsen Score 5).
K2: Telmisartan-treated group showing near-complete restoration (Johnsen Score 10).
K3: Exercise-treated group with partial recovery (Johnsen Score 9).
K4: Combination therapy group showing near-complete restoration (Johnsen Score 10).

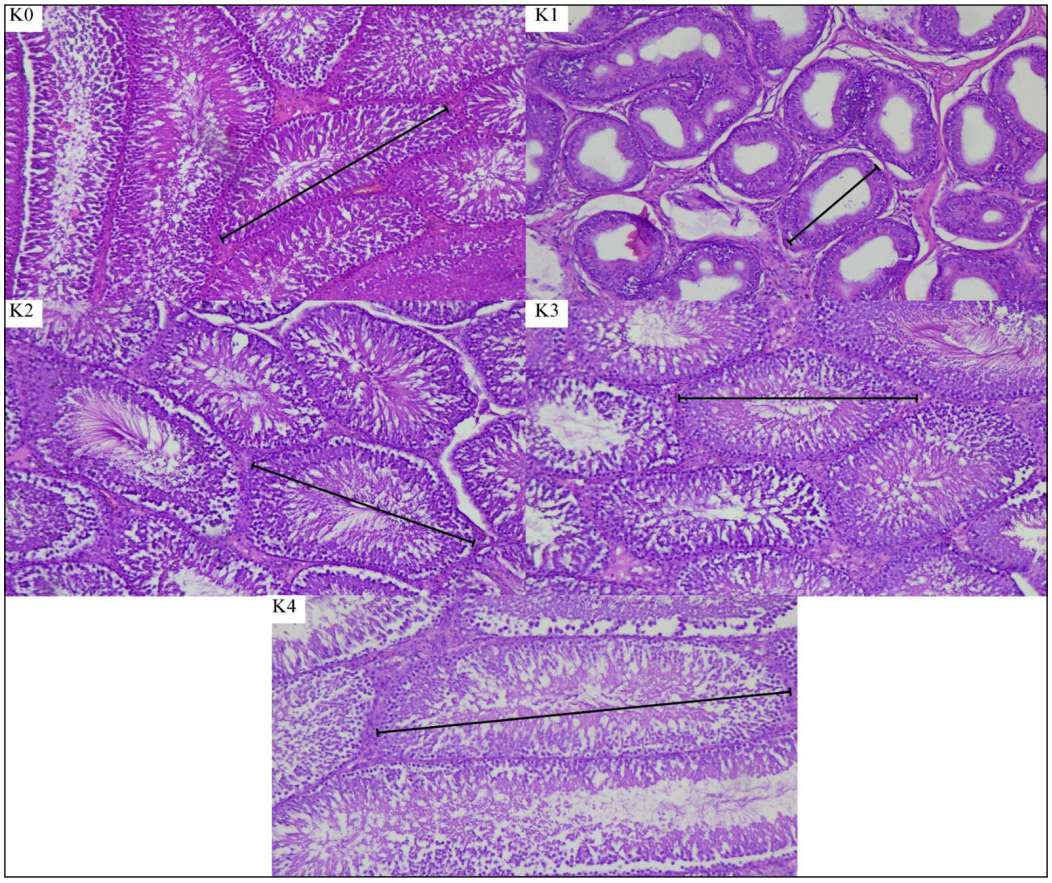

Figure 2.
Representative hematoxylin and eosin (H&E)-stained sections of seminiferous tubules at 100× magnification.
The K1 group (diabetic control) exhibited the smallest average seminiferous tubule diameter (0.17 mm), which was significantly lower than that of all other groups.
This reduction is visually apparent through the collapsed and irregular architecture of the seminiferous tubules, in stark contrast to the preserved tubular structure and normal diameter observed in groups K0, K2, K3, and K4.

Table 3.
Mean values of Johnsen score, Sertoli cell count, Leydig cell count, and seminiferous tubule diameter.

Group	Johnsen Score	Sertoli Cell	Leydig Cell	Seminiferous Tubule Diameter (mm)
K0	9.50 ± 0.70	4,40 ± 2.41	6.48 ± 1.97	0.33 ± 0.05
K1	4.53 ± 0.73	1.60 ± 1.15	1.70 ± 0.89	0.17 ± 0.04
K2	9.43 ± 0.37	5.11 ± 1.36	4.69 ± 0.63	0.28 ± 0.06
K3	8.44 ± 1.14	3.58 ± 1.07	3.18 ± 0.95	0.30 ± 0.05
K4	9.69 ± 0.32	6.00 ± 1.45	4.97 ± 1.02	0.32 ± 0.05

Table 4.
Mean, median, normality test, and Kruskal-Wallis test for Johnsen score.

Group	Mean ± SD	Median (Min-Max)	Normality (p-value)	Kruskal-Wallis (p-value)
K0	9.50 ± 0.70	9.80 (8.00 - 10.00)	0.013	< 0.001*
K1	4.53 ± 0.73	4.60 (3.20 - 5.60)	0.498	
K2	9.43 ± 0.37	9.60 (8.80 - 9.80)	0.271	
K3	8.44 ± 1.14	8.80 (5.80 - 9.60)	0.052	
K4	9.69 ± 0.32	9.80 (9.00 - 10.00)	0.011	

The Kruskal-Wallis test showed significant differences among groups ($p < 0.001$) (Table 4).
Diabetic controls (K1) had the lowest mean Johnsen score (4.53 ± 0.73), indicating severe testicular degeneration, while healthy controls (K0) showed normal spermatogenesis (9.50 ± 0.70).
All treatment groups improved significantly: K2 (9.43 ± 0.37), K3 (8.44 ± 1.14), and K4 (9.69 ± 0.32), with K4 achieving the highest score.
Post hoc Mann-Whitney U tests showed significant differences between K1 and all treatment groups ($p < 0.001$).
Johnsen scores in K2 and K4 were comparable to K0, indicating effective preservation of testicular histology (Figure 3).

Sertoli cell count

Shapiro-Wilk and homogeneity tests indicated non-parametric distribution for Sertoli cell counts ($p < 0.05$).
Kruskal-Wallis analysis revealed significant

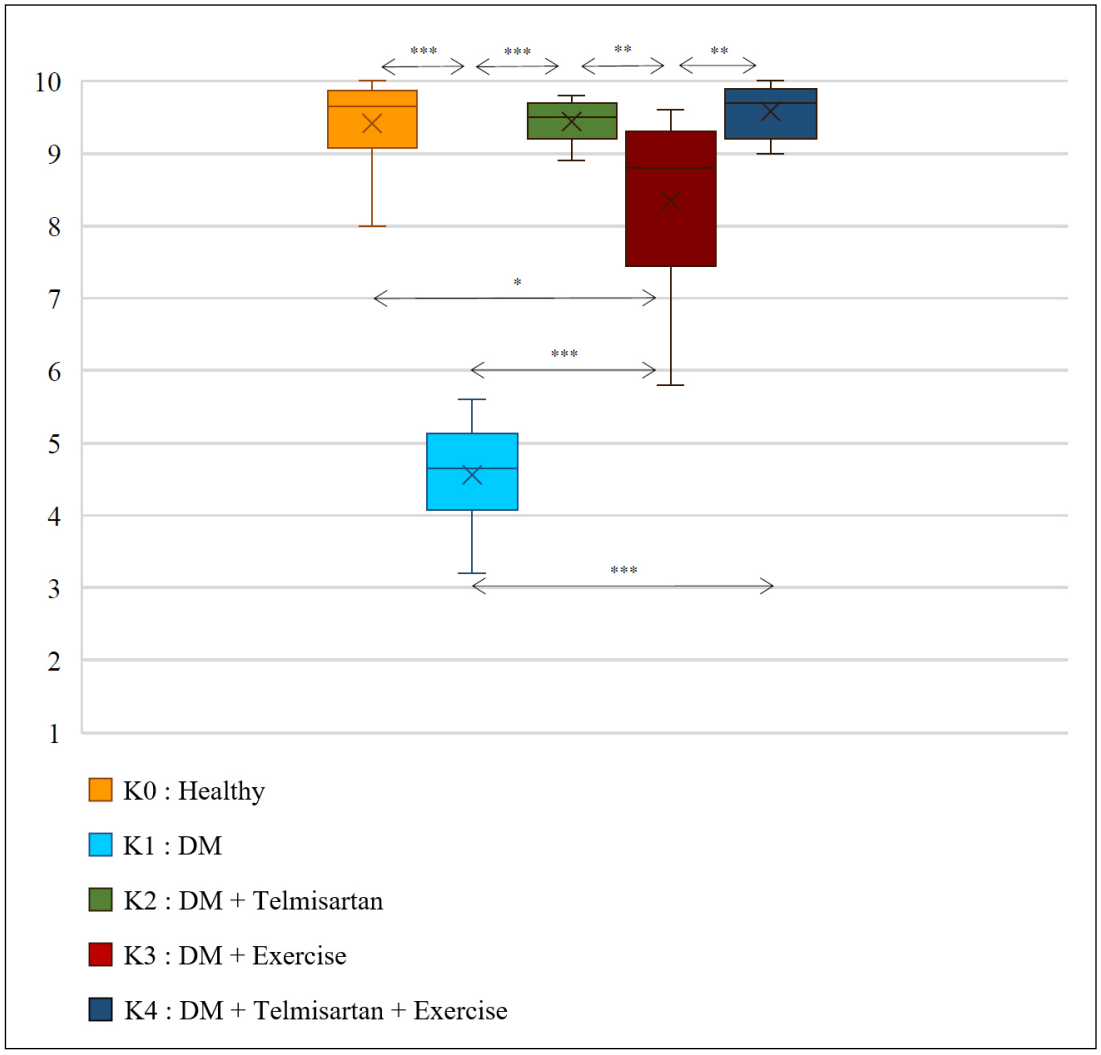

Figure 3.
Graphical presentation of the Mann-Whitney U test for Johnsen score. Significant differences are indicated as follows:
**P < 0.05,*
***P < 0.01,*
****P < 0.001.*

Table 5.
Mean, median, normality test, and Kruskal-Wallis test of Sertoli cell count.

Group	Mean ± SD	Median (Min-Max)	Normality (p-value)	Mann-Whitney (p-value)
K0	4.40 ± 2.41	4.70 (1.00 - 7.80)	0.241*	< 0.001*
K1	1.60 ± 1.15	1.50 (0.20 - 3.60)	0.665*	
K2	5.11 ± 1.36	5.40 (3.80 - 7.00)	0.116*	
K3	3.58 ± 1.07	4.00 (1.00 - 4.40)	0.002	
K4	6.00 ± 1.45	5.40 (4.00 - 8.60)	0.565*	

Table 6.
Mean, median, normality test, and Kruskal-Wallis test of Sertoli cell count.

Group	Mean ± SD	Median (Min-Max)	Normality (p-value)	ANOVA (p-value)
K0	6.48 ± 1.97	6.80 (3.20 - 8.80)	0.666*	< 0.001*
K1	1.70 ± 0.89	2.10 (0.20 - 2.80)	0.227*	
K2	4.69 ± 0.63	4.60 (4.00 - 6.00)	0.058*	
K3	3.18 ± 0.95	3.20 (1.00 - 4.40)	0.078*	
K4	4.97 ± 1.02	5.00 (3.00 - 6.20)	0.377*	

group differences ($p < 0.001$) (Table 5). The diabetic control group (K1) had the lowest mean Sertoli cell count (1.60 ± 1.15), indicating marked cellular impairment, while healthy controls (K0) showed significantly higher counts (4.40 ± 2.41). All treatments increased Sertoli cell numbers: K2 (5.11 ± 1.36), K3 (3.58 ± 1.07), and K4 (6.00 ± 1.45). Post hoc Mann-Whitney U tests confirmed significant differences between K1 and all treatment groups ($p < 0.05$). Counts in K2 and K4 were comparable to K0, suggesting effective preservation of Sertoli cells (Figure 4).

Leydig cell count

Shapiro-Wilk and homogeneity tests confirmed normal distribution of Leydig cell counts ($p > 0.05$), permitting parametric analysis. One-way ANOVA showed significant group differences ($p < 0.001$).

Diabetic controls (K1) had the lowest count (1.70 ± 0.89), indicating severe depletion, while healthy controls (K0) had substantially higher counts (6.48 ± 1.97) (Table 6).

All treatment groups showed significant increases in Leydig cell count: K2 (4.69 ± 0.63), K3 (3.18 ± 0.95), and K4 (4.97 ± 1.02). Post hoc Games-Howell tests confirmed significant differences between K1 and all treatment

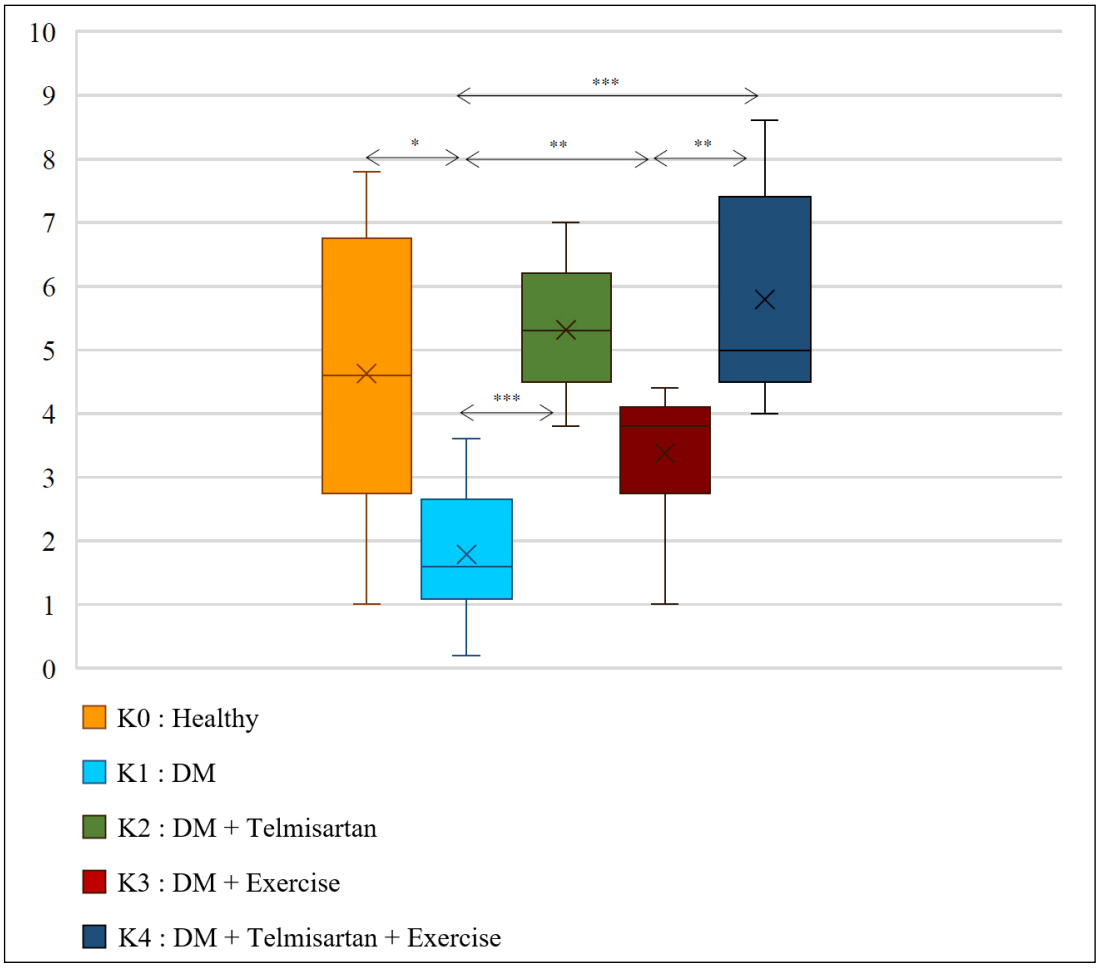

Figure 4.
Graphical presentation of the Mann-Whitney U test for Sertoli cell count. Significant differences are indicated as follows:
**P < 0.05,*
***P < 0.01,*
****P < 0.001.*

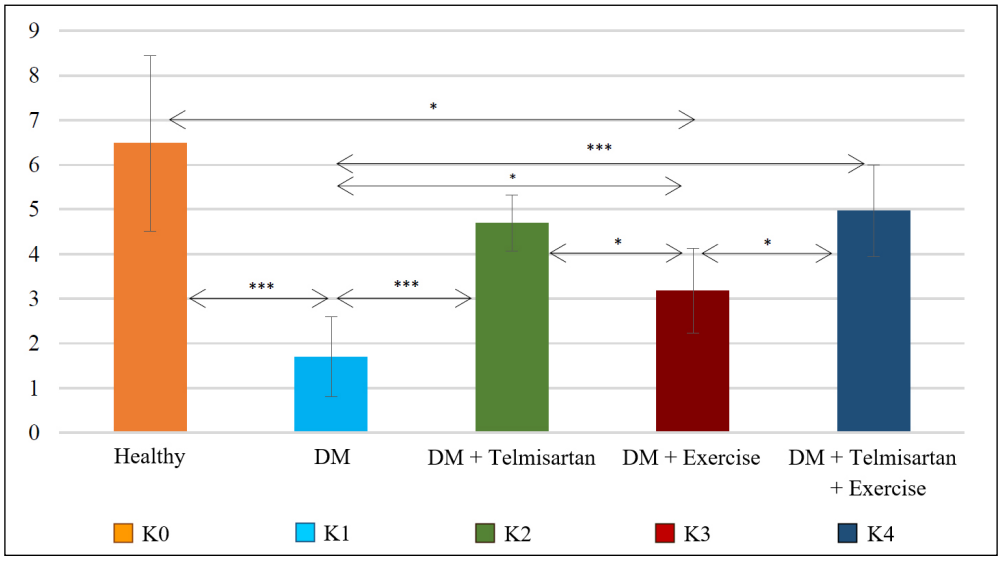

Figure 5.
*Graphical presentation of the Post Hoc Games-Howell test for Leydig cell count. Significant differences are indicated as follows: *P < 0.05, **P < 0.01, ***P < 0.001.*

groups ($p < 0.001$). Leydig cell counts in K2 and K4 were comparable to K0, indicating effective mitigation of diabetes-induced Leydig cell depletion (Figure 5).

Seminiferous tubules diameter

Shapiro-Wilk and homogeneity tests confirmed normal distribution of seminiferous tubule diameter data ($p > 0.05$), permitting parametric analysis. One-way ANOVA revealed significant differences among groups ($p < 0.001$) (Table 7).

The diabetic control group (K1) had the smallest seminiferous tubule diameter (0.17 ± 0.04 mm), while the healthy control (K0) had the largest (0.33 ± 0.05 mm).

Treatment groups showed significant improvements: K2 (0.28 ± 0.06 mm), K3 (0.30 ± 0.05 mm), and K4 (0.32 ± 0.05 mm). Post hoc LSD analysis confirmed significant differences between K1 and all treatment groups ($p < 0.05$).

Telmisartan (K2), aerobic exercise (K3), and combination therapy (K4) all restored seminiferous tubule diameters to levels comparable with healthy controls (K0), indicating reversal of diabetes-induced tubular atrophy (Figure 6).

Table 7.
Mean, median, normality test, and One-Way ANOVA analysis of seminiferous tubule diameter.

Group	Mean ± SD	Median (Min-Max)	Normality (p-value)	ANOVA (p-value)
K0	0.33 ± 0.05	0.32 (0.26 - 0.42)	0.284*	< 0.001*
K1	0.17 ± 0.04	0.17 (0,12 - 0.22)	0.561*	
K2	0.28 ± 0.06	0.26 (0,22 - 0.40)	0.185*	
K3	0.30 ± 0.05	0.28 (0,24 - 0.38)	0.193*	
K4	0.32 ± 0.05	0.32 (0.24 - 0.38)	0.568*	

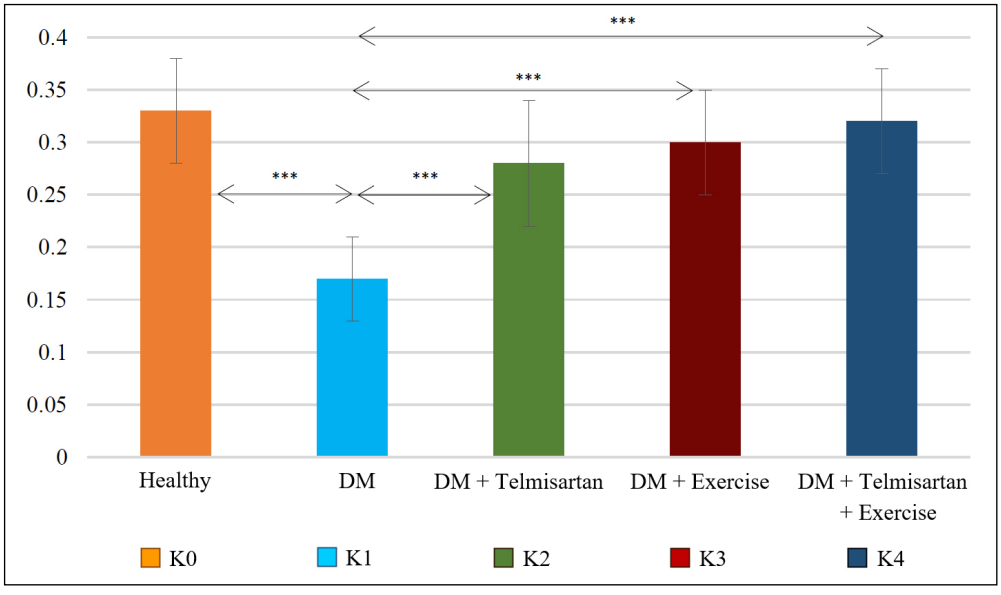

Figure 6.
*Graphical representation of the Post Hoc LSD test for seminiferous tubule diameter. Significant differences are indicated as follows: P < 0.05, P < 0.01, *P < 0.001.*

Discussion

This study evaluated the protective effects of telmisartan, moderate-intensity aerobic exercise, and their combination in STZ-induced diabetic rats. All interventions significantly improved Johnsen score, Sertoli and Leydig cell counts, and seminiferous tubule diameter compared to untreated diabetic controls.

In diabetic controls, histopathology showed marked testicular damage, with reduced Johnsen score (4.53 ± 0.73), Sertoli cells (1.60 ± 1.15), Leydig cells (1.70 ± 0.89), and seminiferous tubule diameter (0.17 ± 0.04 mm), indicating impaired spermatogenesis. These findings support prior evidence linking diabetes to oxidative stress, inflammation, and hormonal imbalance that disrupt testicular structure and function (1).

Rats with STZ-induced diabetes maintained blood glucose levels above 150 mg/dL. Compared to healthy controls, they showed significant reductions in Johnsen score (4.53 ± 0.73), Sertoli cell count (1.60 ± 1.15), Leydig cell count (1.70 ± 0.89), and seminiferous tubule diameter (0.17 ± 0.04 mm), indicating testicular dysfunction. These findings align with evidence that chronic hyperglycemia increases ROS, damages Sertoli cells, disrupts the blood-testis barrier, and downregulates FSH receptor expression, ultimately impairing spermatogenesis (1).

Testicular tissue is highly vulnerable to oxidative stress, which can trigger germ and Leydig cell apoptosis, impair function, and reduce sperm count and motility, as previously reported (12). Chronic oxidative stress induces morphological changes in the seminiferous tubules, including degeneration of various germ cells, such as Sertoli cell, spermatogonia, and spermatocytes (5, 13).

In this study, telmisartan (K2), aerobic exercise (K3), and combination therapy (K4) significantly improved all testicular histological parameters compared to diabetic controls (K1). Telmisartan alone markedly increased the Johnsen score (9.43 ± 0.37), Sertoli cells (5.11 ± 1.36), Leydig cells (4.69 ± 0.63), and seminiferous tubule diameter (0.28 ± 0.06 mm). These effects are likely due to its anti-inflammatory and antioxidant actions, including TNF-α, NF-κB, and ROS suppression, PPAR-γ activation, enhanced insulin sensitivity, and stimulation of the hypothalamic-pituitary-gonadal axis (14-16).

Moderate-intensity aerobic exercise (K3) significantly improved testicular histology, with increased Johnsen score (8.44 ± 1.14), Sertoli cells (3.58 ± 1.07), Leydig cells (3.18 ± 0.95), and seminiferous tubule diameter (0.30 ± 0.05 mm). These benefits are likely mediated by upregulation of Hsp70, Hsp90, GDNF, and enhanced GLUT-4-dependent glucose regulation (17-19).

Combination therapy (K4) produced the most favorable outcomes, with Johnsen score (9.69 ± 0.32), Sertoli cells (6.00 ± 1.45), Leydig cells (4.97 ± 1.02), and seminiferous tubule diameter (0.32 ± 0.05 mm). However, differences between K4 and telmisartan alone (K2) were not statistically significant, suggesting that telmisartan monotherapy may be sufficient to restore testicular histology in diabetic conditions.

Compared to exercise alone (K3), telmisartan (K2) showed superior efficacy. Aerobic exercise has limited ability to suppress pro-inflammatory mediators like TNF-α, caspase-3, COX-2, and iNOS, and does not significantly affect PPAR-γ or VEGF expression. As a result, exercise primarily enhances structural recovery, especially seminiferous tubule diameter, without fully restoring Johnsen score, Sertoli and Leydig cell count (14, 15, 20).

Telmisartan monotherapy (K2) significantly improved all histomorphometric parameters to levels comparable with healthy controls (K0). Its protective effect is likely due to modulation of oxidative stress and inflammation, including reduced TNF-α, IL-6, and ROS, along with enhanced antioxidant enzyme activity. Telmisartan also activates PPAR-γ, a key regulator of spermatogenesis and testicular homeostasis (4).

Moderate-intensity aerobic exercise (K3) offered partial protection, notably preserving seminiferous tubule diameter. While it modestly improved Johnsen score, Sertoli, and Leydig cell counts, the effects were less pronounced than with telmisartan or combination therapy. These findings suggest that exercise mainly supports structural integrity via improved blood flow and tissue remodeling but is insufficient for fully restoring spermatogenesis (5, 16, 21).

Combination therapy (K4) yielded the greatest improvements across all histomorphometric parameters, surpassing either monotherapy. This synergistic effect likely stems from telmisartan's anti-inflammatory and antioxidant actions coupled with exercise-induced enhancements in blood flow and tissue repair. Histological outcomes in K4 closely matched those of healthy controls, underscoring its potential as an effective strategy to preserve testicular function in diabetes (21).

Both telmisartan monotherapy and combination therapy effectively preserved testicular histology in diabetic rats, with outcomes comparable to healthy controls. In contrast, exercise alone primarily maintained seminiferous tubule diameter. These findings suggest that telmisartan's broader protective mechanisms, anti-inflammatory, antioxidant, and hormonal are essential for preventing testicular damage and supporting spermatogenesis.

Telmisartan provides broad and potent protection of testicular histomorphometry in diabetic conditions through multiple molecular pathways. Its key mechanisms include: (1) reducing oxidative stress; (2) activating the hypothalamic-pituitary-gonadal (HPG) axis via PPAR-γ and improving insulin sensitivity; (3) suppressing inflammatory mediators such as TNF-α, IL-6, NF-κB, caspase-3, COX-2, iNOS, ROS, NO, 3-nitrotyrosine, and p-ERK1/2; and (4) enhancing VEGF expression to support testicular vascularization and function.

In contrast, moderate-intensity aerobic exercise protects testicular tissue mainly through two mechanisms: (1) reducing oxidative stress and (2) enhancing insulin sensitivity via GLUT-4 activation, indirectly stimulating the HPG axis. While beneficial, its limited molecular targets likely account for its reduced efficacy in preserving Johnsen score, Sertoli and Leydig cell count compared to telmisartan.

Moderate-intensity aerobic exercise primarily improves testicular structure particularly seminiferous tubule diameter by enhancing blood flow, oxygenation, and tissue remodeling. These changes promote rapid morphological recovery even in diabetic conditions. However, full functional restoration reflected by Johnsen score and Sertoli and Leydig cell activity – depends on more complex endocrine and molecular adaptations, such as HPG

axis normalization, hormonal balance, and germinal epithelium regeneration, which are slower to respond to exercise alone (5, 16, 22).

While exercise may lead to early improvements in seminiferous tubule diameter, full restoration of Johnsen score as well as Sertoli and Leydig cell counts requires more targeted metabolic and hormonal modulation.

In comparison to the untreated diabetic group, all three therapies tested – telmisartan monotherapy, moderate-intensity aerobic exercise monotherapy, and the combined therapy – demonstrated significant improvements in Johnsen score, Sertoli and Leydig cell counts, and seminiferous tubule diameter.

When compared to the healthy control group, only telmisartan monotherapy (K2) and combination therapy (telmisartan + exercise, K4) restored Johnsen score, Sertoli and Leydig cell counts, and seminiferous tubule diameter to levels approaching those of healthy controls. Aerobic exercise (K3) improved seminiferous tubule diameter but had limited effects on other parameters.

Telmisartan monotherapy was as effective as combination therapy in restoring Johnsen score, normalizing Sertoli and Leydig cell counts, seminiferous tubule diameters in diabetic rats, with both approaches achieving near-complete recovery compared to healthy controls.

While this study provides valuable insights into the testicular protective effects of telmisartan and aerobic exercise, several limitations must be acknowledged. First, the study used a rat model, and caution is required when extrapolating these findings to human clinical contexts. Additionally, fertility-related outcomes, such as sperm quality, fertilization rates, and pregnancy success, were not assessed and should be the focus of future studies. The telmisartan dosage of 6 mg/kg body weight per day, while effective in the rat model, may not be directly translatable to human equivalents, necessitating dose optimization studies to determine the most appropriate and safe human dosage.

The use of Wistar rats, rather than human subjects, limits the broader applicability of these findings to clinical populations. Furthermore, the study did not evaluate direct fertility measures, such as sperm quality, sperm retrieval, or pregnancy rates. The relatively high dose of telmisartan administered in this study (6 mg/kg) may also present challenges for potential human application.

Conclusions

Both telmisartan and moderate-intensity aerobic exercise, whether individually or combined, offer protective effects against testicular damage in diabetic rats. Telmisartan monotherapy proved to be equally effective as the combined therapy in restoring testicular architecture and normalizing cellular profiles, with both approaches resulting in near-complete recovery of structural integrity and cell counts. These findings suggest promising therapeutic potential for mitigating diabetes-induced male infertility. However, further studies, including clinical trials, are required to confirm the applicability of these interventions in human populations.

Future studies should determine the minimum effective telmisartan dose and further explore combination therapy in clinical settings. Evaluating fertility outcomes – such as sperm quality, ICSI success, and pregnancy rates – will be crucial to to support clinical applicability. These findings warrant further investigation in clinical settings to evaluate whether similar protective effects are achievable in diabetic men at risk of infertility.

Declarations

Ethical approval: *This study received ethical approval for animal experimentation from the institutional ethics committee 88/EC/KEPK/FKUA/2025.*

Availability of data and material: *All data generated or analyzed during this study are available upon request.*

Competing interests: *The authors declare that they have no competing interests.*

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Authors' contributions: *AF, MS, and SW contributed to the conception and design of the study. AF organized the database, performed the data analysis, and wrote the first draft of the manuscript. GA and ASR contributed to data interpretation and literature review. MS, SW, and ASR critically revised the manuscript for important intellectual content. All authors contributed to manuscript revision, read, and approved the submitted version.*

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