Effects of Telmisartan and Moderated-Intensity Aerobic Exercise on Collagen Type I Expression in a Diabetes Melitus Model

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KEYWORDS

Telmisartan, Bladder, DM rat model, Collagen type I

Introduction: Diabetes Mellitus (DM) is an escalating global health issue that can lead to complications across various organs, including the urinary system. Diabetic Bladder Dysfunction (DBD) is a common urological complication of DM, characterized by increased collagen deposition in bladder tissue. Diabetes-induced bladder fibrosis results in loss of compliance and impaired contractility.

Objectives: This study aims to evaluate the effects of telmisartan administration and moderate-intensity aerobic exercise on collagen type I expression in a DM rat model.

Methods: To create a DM model, the Wistar rats were induced with 35 mg/kgBW of streptozotocin (STZ). The rats were divided into five groups: a control group, groups receiving telmisartan treatment, aerobic exercise groups, a combination of both treatments and an untreated DM group. Collagen type I expression was measured using immunohistochemistry. SPSS version 20 was performed for statistical analysis.

Results: Male Rattus norvegicus were divided into five groups: K0 (control), K1 (untreated DM), K2 (DM + telmisartan), K3 (DM + exercise), and K4 (DM + telmisartan and exercise). Body weight increased consistently with age, and all diabetic groups maintained fasting blood glucose levels above 150 mg/dL post-STZ injection. Type I collagen expression in the detrusor significantly differed among groups ($p < 0.05$). Similar results were observed in the lamina propria, where Group K4 significantly differed from all other groups ($p < 0.05$). Detrusor thickness also differed significantly between groups ($p < 0.05$), with Group K4 showing a significant reduction compared to K1 ($p < 0.05$). For lamina propria thickness, Welch ANOVA revealed significant intergroup differences ($p < 0.05$), with Group K4 significantly differing from K1 ($p = 0.001$).
Conclusions: Telmisartan and moderate-intensity aerobic exercise synergistically reduce DM-induced bladder fibrosis by lowering Collagen type I expression. These findings highlight the potential of combination therapy in preventing urological complications in DM patients.

1. Introduction

Diabetes Mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both. In 2021, over 463 million individuals globally were diagnosed with diabetes mellitus (DM), and this figure is projected to rise significantly in the coming decades.[1] Moreover, DM has been identified as a major contributor to various organ-related complications, including bladder dysfunction, which is commonly referred to as Diabetic Bladder Dysfunction (DBD). This condition affects up to 80% of DM patients and is often overlooked in diabetes care.[2]

Diabetic Bladder Dysfunction (DBD) is distinguished by impaired bladder compliance, diminished detrusor muscle contractility, and elevated collagen deposition in the bladder wall. One of the key factors in the bladder fibrosis process is the upregulation of Transforming Growth Factor Beta 1 (TGF-β1), which regulates the synthesis and degradation of type 1 and type 3 collagen.[3] This bladder fibrosis results in a loss of bladder elasticity and contractility, contributing to urinary storage and voiding dysfunction.[4]

Current treatments for DBD include various pharmacological agents, such as angiotensin II receptor blockers (ARBs) like telmisartan, which have demonstrated anti-fibrotic effects on bladder smooth muscle.[5] Additionally, regular exercise is known to provide benefits for DM patients, including reducing oxidative stress and improving insulin sensitivity. However, studies on the combined effects of these two therapies on bladder fibrosis and type 1 collagen expression remain limited.[6]

2. Objectives

This study investigates the mechanisms underlying the inhibition of bladder dysfunction progression in a diabetic mellitus (DM) rat model following the administration of telmisartan and moderate-intensity aerobic exercise. The findings are expected to provide in-depth insights into the preventive mechanisms against such dysfunctions through either moderate-intensity aerobic exercise intervention or telmisartan therapy. The outcomes of this research have the potential to support the development of strategies based on physical exercise or pharmacological therapy to prevent the progression of bladder dysfunction in DM patients, thereby improving their quality of life.

This study investigates the mechanisms underlying the inhibition of bladder dysfunction progression in a diabetic mellitus (DM) rat model following the administration of telmisartan and moderate-intensity aerobic exercise. The findings are expected to provide in-depth insights into the preventive mechanisms against such dysfunctions through either moderate-intensity aerobic exercise intervention or telmisartan therapy. The outcomes of this research have the potential to support the development of strategies based on physical exercise or pharmacological therapy to prevent the progression of bladder dysfunction in DM patients, thereby improving their quality of life.

3. Methods

This true-experimental study employed a randomized controlled design to investigate the effects of telmisartan and moderate-intensity aerobic exercise, individually and in combination, on bladder fibrosis in a diabetic rat model. Forty male Wistar rats (Rattus norvegicus) weighing 150–200 g were utilized and divided into five groups using block randomization. The study duration was 10 weeks, including a 1-week acclimatization and a 10-week intervention period.

The animals were housed in controlled environmental conditions at 22–25°C with a 12-hour light/dark cycle and provided ad libitum access to food and water. A one-week acclimatization period was conducted before the interventions.

Diabetes mellitus (DM) was induced using a single intraperitoneal injection of streptozotocin (STZ) at a dose of 35 mg/kg body weight, dissolved in citrate buffer (pH 4.5). On the third day post-injection, fasting blood glucose levels were measured from tail vein blood using a digital glucometer. Rats with fasting glucose levels >150 mg/dL were confirmed as diabetic and included in the study, while those below this threshold were excluded.

The diabetic rats were allocated into five groups (n=8 per group) through block randomization :

1. Non-diabetic Rats(K0): Healthy rats without DM induction or intervention.
2. DM Control (K1): Diabetic rats without intervention.
3. Telmisartan (K2): Diabetic rats treated with telmisartan (6 mg/kg body weight/day) via oral gavage for 10 weeks.
4. Aerobic Exercise (K3): Diabetic rats subjected to moderate-intensity swimming (60 minutes/day, 5 days/week) for 10 weeks in water maintained at 32°C.
5. Combination (K4): Diabetic rats receiving both telmisartan (6 mg/kg body weight/day) and swimming exercise (60 minutes/day, 5 days/week) for 10 weeks.

At the end of the 10-week intervention period, all rats were humanely terminated through an overdose of ketamine/xylazine anesthesia. Bladder tissues were excised, fixed in 10% formaldehyde for 24 hours, and processed for paraffin embedding. Histological sections (5 μm thick) were prepared for hematoxylin-eosin (H&E) staining to assess general bladder morphology and immunohistochemical staining to evaluate type 1 collagen expression.

Immunohistochemistry was performed on bladder tissue sections to detect type 1 collagen expression. Sections were incubated with primary antibodies against TGF-β1 and type 1 collagen, followed by secondary antibodies conjugated with peroxidase. Staining results were visualized using a polarized light microscope.

The immunohistochemical results were evaluated using one-way ANOVA and Welch ANOVA to determine the statistical significance of differences between the groups. Data were presented as mean ± standard deviation (SD), with a p-value <0.05 considered statistically significant. Post-hoc LSD test was performed for pairwise comparisons among the control, diabetic control, and intervention groups (telmisartan, aerobic exercise, and combination therapy).

Observed Parameters

1. Type 1 Collagen Expression: Type 1 collagen, a major extracellular matrix component, was measured to evaluate changes in bladder elasticity and wall thickening.
2. Bladder Wall Thickness: The thickness of the detrusor and lamina propria layers was analyzed to identify structural changes associated with fibrosis.

This structured methodology and targeted interventions aim to provide scientific evidence on the effects of telmisartan and moderate-intensity aerobic exercise in preventing diabetes-induced bladder fibrosis.

Ethical Approval

This study was conducted following ethical principles for animal research, and ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Airlangga University (Certificate No. 111/EC/KEPK/FKUA/2024).

Study Period and Location

The study was conducted over 12 weeks in the Biochemistry and Pathological Anatomy Laboratory, Faculty of Medicine, Airlangga University.

4. Results

White rats of the species Rattus norvegicus Wistar strain, male, aged 12 weeks, were included in this study. One rat from each group (K0, K1, K2, and K4) dropped out during the study. Body weight data showed an increase consistent with the rats' age progression from the start of the study at 12 weeks, followed by a 1-week acclimatization period, after which STZ injection was administered. Fasting blood glucose levels were first measured one week after the STZ injection when the rats reached 13 weeks of age. Subsequently, the groups were treated as follows: Group K0 received no treatment, Group K1 served as the untreated diabetes mellitus (DM) group, Group K2 received telmisartan, Group K3 performed moderate-intensity aerobic exercise until 22 weeks of age, and Group K4 received both telmisartan and moderate-intensity aerobic exercise until 22 weeks of age. Blood glucose data measured at each time point showed mean results exceeding 150 mg/dL **(Table 1)**.

Table 1 : Body Weight and Fasting Glucose.

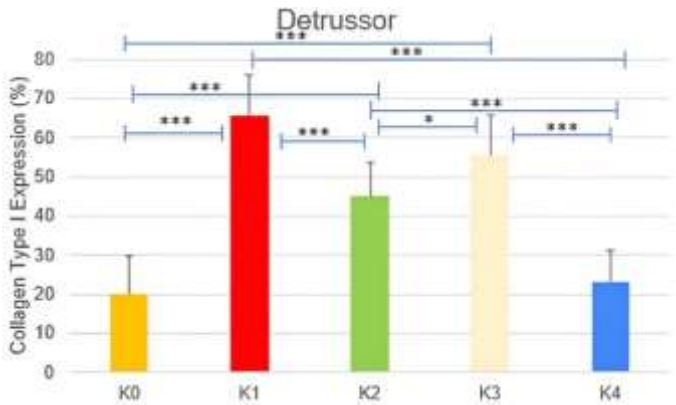
Group	K0 (Mean ± SD)	K1 (Mean ± SD)	K2 (Mean ± SD)	K3 (Mean ± SD)	K4 (Mean ± SD)
Initial Body Weight (g)	154.14 ± 10.88	150.29 ± 10.14	160.38 ± 19.15	153.71 ± 9.84	151.29 ± 14.11
Final Body Weight (g)	235.71 ± 52.05	238.29 ± 24.79	225.63 ± 37.79	187.00 ± 18.48	177.29 ± 24.95
Initial Fasting Blood Glucose (mg/dL)	-	456.14 ± 137.00	349.13 ± 137.00	382.57 ± 136.15	344.71 ± 135.62
Final Fasting Blood Glucose (mg/dL)	108.29 ± 9.84	490.43 ± 107.35	339.13 ± 156.76	381.42 ± 138.12	320.71 ± 131.35

Homogeneity and normality tests confirmed appropriate data distribution for type I collagen expression in the detrusor. One-way ANOVA revealed significant differences between groups ($p = 0.001$). DM control rats (K1) showed the highest collagen expression (65.71 ± 10.17), while non-diabetic controls (K0) showed the lowest (20 ± 9.57). Treatment groups showed progressively reduced expression: aerobic exercise (K3: 55.71 ± 10.17), telmisartan (K2: 45 ± 20.16), and combination therapy (K4: 23.13 ± 7.99). The Shapiro-Wilk test confirmed normal distribution across all groups ($p > 0.05$) **(Table 2)**. Post-hoc LSD analysis showed significant differences between K1 and all other groups ($p < 0.001$). Notably, the combination therapy (K4) demonstrated collagen expression levels most comparable to healthy controls (K0), suggesting effective treatment **(Figure 1)**

Table 2 : Mean, normality test, and one-way ANOVA test results for type I collagen expression in the detrusor of diabetic rat models

	Mean ± SD	Normality (p-value)	ANOVA (p-value)
K0	20 ± 9.57	0.380	
K1	65.71 ± 10.17	0.948	
K2	45 ± 20.16	0.278	0.001
K3	55.71 ± 10.17	0.948	
K4	23.13 ± 7.99	0.282	

Figure 1 : The graphical presentation of Post hoc LSD Test on the expression of Type I Collagen in the detrusor of DM mouse model. Significant difference P < 0,05 by Post hoc LSD test : * : < 0,05, ** : < 0,01, *** : < 0,001

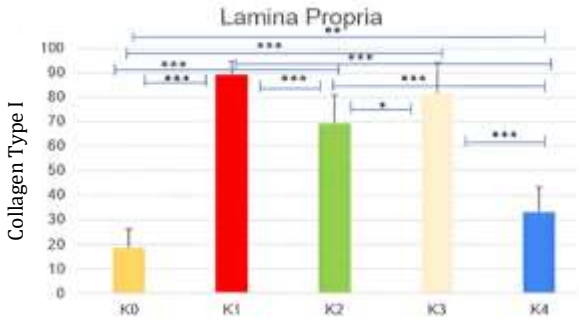


Type I collagen expression in the lamina propria showed significant differences by one-way ANOVA ($p = 0.001$). DM controls exhibited the highest expression (88.5 ± 3.2%), significantly higher than non-diabetic controls (18.7 ± 8.4%, $p < 0.001$). Telmisartan treatment (K2) reduced collagen expression to 68.4 ± 5.1%, while aerobic exercise (K3) showed levels of 78.2 ± 7.3%, both significantly lower than K1 ($p < 0.001$). The combination therapy (K4) demonstrated the lowest expression (32.5 ± 9.8%) among treatment groups, significantly different from K1, K2, and K3 (all $p < 0.001$). All intervention groups maintained higher collagen levels than K0 ($p < 0.05$). Shapiro-Wilk test confirmed normal distribution across all groups ($p > 0.05$) **(Table 3)**. Post hoc LSD analysis revealed significant differences between K4 and K0,K1,K2,K3 groups ($p < 0.05$) **(Figure 2)**.

Table 3 : Mean values, normality test, and one-way ANOVA results for type I collagen expression in the lamina propria of diabetic rat models in each group.

Group	Mean ± SD	Normality (p-value)	ANOVA (p-value)
K0	20 ± 9.57	0.380	
K1	65.71 ± 10.17	0.948	
K2	45 ± 20.16	0.278	0.001
K3	55.71 ± 10.17	0.948	
K4	23.13 ± 7.99	0.282	

Figure 2 : The graphical presentation of post hoc LSD test results for type I collagen expression in the lamina propria of diabetic rat models. Significant difference P < 0,05 by post hoc LSD test : * : < 0,05, ** : < 0,01, *** : < 0,001.

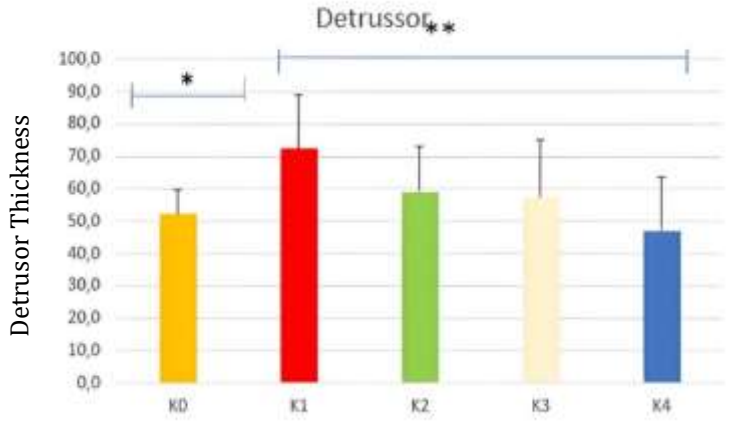


Analysis of detrusor thickness showed significant differences among groups by one-way ANOVA ($p = 0.045$). DM control rats exhibited the highest thickness (72.5 ± 16.8 µm) compared to non-diabetic controls (52.1 ± 7.42 µm). Telmisartan treatment (K2) and aerobic exercise (K3) reduced detrusor thickness to 59.06 ± 14.3 µm and 57.14 ± 18.22 µm, respectively. The combination therapy showed the lowest thickness (47.14 ± 16.67 µm). Shapiro-Wilk test confirmed normal distribution across all groups ($p > 0.05$, ranging from 0.054 to 0.579) **(Table 4).** Post hoc LSD analysis revealed significant differences between K1 and K4 ($p < 0.05$), with combination therapy demonstrating the most pronounced reduction **(Figure 3).**

Table 4. Mean values, normality test, and One-Way ANOVA test on detrusor thickness in diabetic rat models for each group.

Group	Mean ± SD	Normality (p-value)	ANOVA (p-value)
K0	52.1 ± 7.42	0.445	
K1	72.5 ± 16.8	0.054	
K2	59.06 ± 14.3	0.579	0.045
K3	57.14 ± 18.22	0.577	
K4	47.14 ± 16.67	0.244	

Figure 3. The graphical presentation of Post Hoc LSD test on detrusor thickness in diabetic rat models. Significant difference P < 0,05 by post hoc LSD test : * : < 0,05, ** : < 0,01, *** : < 0,001.

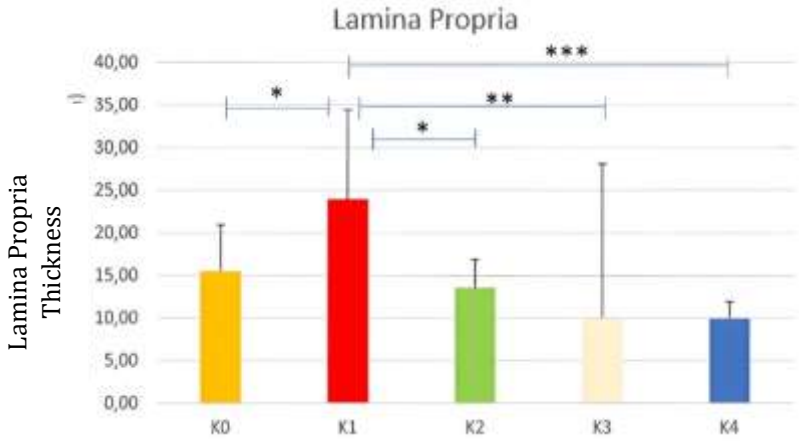


Lamina propria thickness aalysis revealed significant differences among groups by Welch ANOVA (p = 0.013). DM controls showed the highest thickness (23.9 ± 10.59 µm) compared to non-diabetic controls (15.54 ± 5.39 µm). Telmisartan treatment reduced thickness to 13.6 ± 3.43 µm, while both aerobic exercise and combination therapy groups showed the lowest values (10 ± 18.22 µm and 10 ± 2.04 µm, respectively). Shapiro-Wilk test confirmed normal distribution (p > 0.05, ranging from 0.061 to 0.590) **(Table 5)**. Post hoc LSD analysis demonstrated significant reductions in all treatment groups compared to K1 (K2: p < 0.05; K3: p < 0.01; K4: p < 0.001) **(Figure 4)**.

Table 5. Median values, normality test, and Welch ANOVA test on lamina propria thickness in diabetic rat models for each group.

Group	Mean ± SD	Normality (p-value)	ANOVA (p-value)
K0	15.54 ± 5.39	0.452	
K1	23.9 ± 10.59	0.175	
K2	13.6 ± 3.43	0.590	0.013
K3	10 ± 18.22	0.061	
K4	10 ± 2.04	0.144	

Figure 4. Post Hoc LSD test on lamina propria thickness in diabetic rat models. Significant difference P < 0,05 by post hoc LSD test : * : < 0,05, ** : < 0,01, *** : < 0,001.



Immunohistochemical analysis of type I collagen expression in bladder tissue sections revealed varying staining intensities across different regions (Figure 5). The staining intensity was categorized as negative (N), weak (W), moderate (M), and strong (S), as indicated by red arrows. The negative control showed minimal background staining, while weak staining demonstrated light collagen distribution. Moderate staining exhibited increased collagen density, and strong staining displayed intense brown coloration, indicating high collagen deposition.

Immunohistochemical analysis revealed varying type I collagen expression intensities in bladder tissue sections. The staining was categorized as negative (N), weak (W), moderate (M), and strong (S), with red arrows indicating representative areas. The intensity ranged from minimal background staining in negative controls to intense brown coloration in strong staining, reflecting different levels of collagen deposition **(Figure 5)**. Histological examination demonstrated distinct layers of detrusor muscle (D) and lamina propria (LP), with standardized thickness measurements shown by red measurement lines **(Figure 6)**.

Figure 5. Type I Collagen Staining in Detrusor and Lamina Propria. (N) Negative, (W) Weak, (M) Moderate, (S) Strong, Red Arrow: Type I Collagen Staining

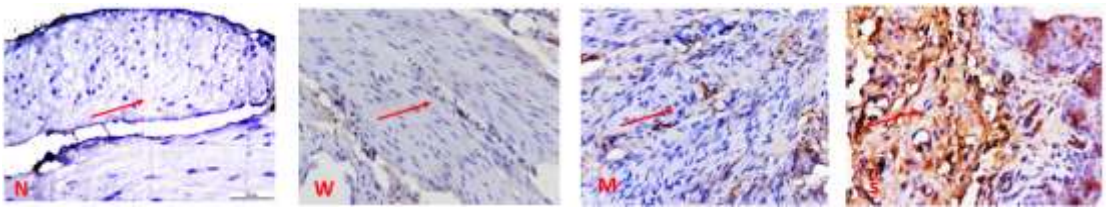
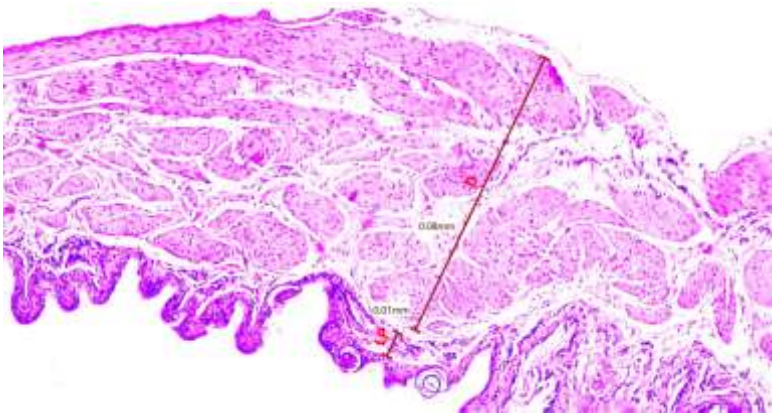


Figure 6. The detrusor and lamina propria thickness. (D) Detrusor, (LP) Lamina Propria.



5. Discussion

Diabetic Bladder Dysfunction (DBD) is a significant complication affecting up to 80% of diabetes patients[1], characterized by increased bladder capacity, post-void residual volume, and reduced bladder sensation and contraction. The progression of DBD typically follows a biphasic pattern, with an initial compensatory phase followed by a decompensated phase marked by impaired contractility and increased fibrosis.[2]

In this study, we successfully established a type 1 diabetes mellitus (T1DM) animal model using streptozotocin (STZ), as evidenced by blood glucose levels consistently exceeding 150 mg/dL across all diabetic groups **(Table 1)**. This finding aligns with established diabetes diagnostic criteria and previous studies using similar STZ doses of 35 mg/kgBW.[7,8,9]

Our results demonstrated significant alterations in both the detrusor and lamina propria layers of diabetic rat bladders. In the diabetic control group (K1), we observed markedly elevated type I collagen expression in both the detrusor (65.71 ± 10.17) and lamina propria (88.5 ± 3.2%) compared to non-diabetic controls (K0: 20 ± 9.57 and 18.7 ± 8.4%, respectively). This substantial increase in collagen deposition aligns with the pathophysiology of diabetic bladder dysfunction, where chronic inflammation leads to ECM modification and fibrosis.[15] The lamina propria showed particularly pronounced changes, likely due to its ECM-rich structure[14], supporting previous findings that this layer is highly susceptible to diabetic-induced alterations.

The structural changes were further evidenced by increased tissue thickness in both layers. The diabetic control group exhibited the highest detrusor thickness (72.5 ± 16.8 µm) and lamina propria thickness (23.9 ± 10.59 µm) compared to non-diabetic controls (52.1 ± 7.42 µm and 15.54 ± 5.39 µm, respectively). These findings are consistent with previous studies showing that diabetes leads to detrusor hypertrophy and increased connective tissue deposition by 16 weeks post-induction.[12,24]

Our intervention studies revealed differential effects of treatments. Telmisartan alone (K2) significantly reduced collagen expression in both detrusor (45 ± 20.16) and lamina propria (68.4 ± 5.1%), supporting its anti-fibrotic properties. This effect is likely mediated through telmisartan's dual action as an angiotensin receptor blocker and partial PPARγ agonist, which has been shown to suppress TGF-β1 expression and reduce oxidative stress in various tissue types.[19,21] Additionally, telmisartan has been demonstrated to inhibit myofibroblast activation and reduce the expression of fibrosis-related proteins such as α-SMA and fibronectin.[4]

Aerobic exercise intervention (K3) significantly reduced collagen expression
(detrusor: 55.71 ± 10.17; lamina propria: 78.2 ± 7.3%). The mechanism involves exercise-induced modulation of oxidative stress and inflammatory pathways[5], particularly through the reduction of TGF-β signaling, which is a key mediator of fibrosis in diabetic conditions.[6] Exercise has been shown to enhance antioxidant defense systems and reduce pro-inflammatory cytokines, which may help prevent excessive collagen deposition.[13,17]

Notably, the combination therapy (K4) demonstrated the most pronounced benefits, with collagen expression levels most closely approximating those of healthy controls in both detrusors (23.13 ± 7.99)

and lamina propria (32.5 ± 9.8%). This synergistic effect was also reflected in tissue thickness measurements, where K4 showed the lowest values for both detrusor (47.14 ± 16.67 µm) and lamina propria (10 ± 2.04 µm) thickness. The superior efficacy of combination therapy suggests that telmisartan and exercise work through complementary mechanisms. Telmisartan's direct anti-fibrotic effects through angiotensin receptor blockade and PPARγ activation,[19,23] are complemented by exercise's ability to enhance antioxidant capacity and reduce inflammatory mediators.[5,25] oreover, recent studies have shown that mechanical stress from exercise can modulate ECM remodeling through mechanotransduction pathways, potentially enhancing the tissue's response to pharmacological intervention.[16]

This synergistic effect may explain why the combination therapy achieved near-normal collagen levels in both tissue layers. The histological findings, particularly the immunohistochemical analysis (Figure 5), provided visual confirmation of these quantitative results. They showed varying intensities of collagen staining that corresponded with our numerical data. The standardized thickness measurements (Figure 6) further validated our morphometric findings.

These results have important clinical implications, suggesting that a combined pharmacological intervention and lifestyle modification approach may be more effective in managing diabetic bladder dysfunction than either treatment alone. The 10-week intervention period in our study proved sufficient to induce significant histological changes, contrasting with shorter-duration studies that showed limited effects.[22]

6. Conclusion

The study concluded that in the diabetic rat model, rats treated with both telmisartan and moderate-intensity aerobic exercise had significantly lower type I collagen expression in both the detrusor and lamina propria compared to those treated with either telmisartan or aerobic exercise alone, as well as the untreated diabetic rats. Additionally, the thickness of the detrusor and lamina propria was significantly thinner in the combination treatment group compared to all other groups, including those receiving only one treatment or no treatment. This finding suggests that telmisartan and aerobic exercise effectively reduce bladder fibrosis in diabetic rats.

7. Acknowledgment

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8. Author Contribution

MFF: Conceptualization, Methodology, Investigation, Resources, Writing Original Draft, Data Curation, Software. TD: Conceptualization, Supervision, Validation, Formal Analysis. MAS: Conceptualization, Supervision, Validation, Formal Analysis. ASR: Supervision, Validation, Formal Analysis. All authors have read, reviewed, and approved the final manuscript.

9. Declaration of Interest

The authors declare no conflicts of interest related to this study.

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