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EFFECT OF TAMSULOSIN IN A MODEL OF ADENINE-INDUCED CHRONIC RENAL DISEASE

Mariana Cecilia Pérez-Villalobos[1], Nicté García-Carrillo[1], Andrea Barba-González[1], Martín Humberto Muñoz-Ortega[2], Esperanza Sánchez-Alemán[1,3], Manuel Enrique Ávila-Blanco[1], Jorge Christopher Morones-Gamboa[1], Javier Ventura-Juárez[1*], Sandra Luz Martínez-Hernández[4*]

[1]Departamento de Morfología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, 20100, Aguascalientes, México.

[2]Departamento de Química, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, 20100, Aguascalientes, México.

[3]Unidad de Medicina Familiar #8 IMSS, 20180, Aguascalientes, México.

[4]Departamento de Microbiología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, 20100, Aguascalientes, México.

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Corresponding Author: Javier Ventura-Juárez[1] & Sandra Luz Martínez-Hernández[2]
[1]Departamento de Morfología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, Av. Universidad 940, 20100, Aguascalientes, México.
[2]Departamento de Microbiología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes, Aguascalientes, Av. Universidad 940, 20100, Aguascalientes, México. **[DOI: 10.5281/zenodo.10912230]**

ABSTRACT

Chronic kidney disease (CKD) encompasses a spectrum of structural and functional abnormalities in the kidneys, persisting for over three months with specific health implications. It is estimated to affect 10% of the global population. These include morphological changes based on the combined responses of glomeruli, renal tubules, renal blood vessels, and/or renal interstitium to continuous injury, leading to chronic inflammatory processes and renal fibrosis. While no specific treatment has been established, angiotensin-converting enzyme inhibitors, their receptor blockers to regulate blood pressure, metabolic modulators to reduce hyperglycaemia, and statins to lower fatty acids have been utilized. The aim of this study was to analyze the effect of tamsulosin on an adenine-induced chronic kidney disease model in rats.

KEYWORDS: Chronic kidney disease (CKD), abnormalities, morphological, hyperglycaemia.

2. INTRODUCTION

Chronic kidney disease (CKD) is defined as a collection of abnormalities in kidney structure or function, present for more than three months, with specific health implications.[1] It involves morphological changes resulting from the combined responses of glomeruli, renal tubules, renal blood vessels, and/or renal interstitium to continuous injury.[2,3] The disease is characterized by the presence of fibrosis, impacting various physiologically essential functions,

including the excretion of soluble impurities from the blood through urine and the maintenance of fluid and electrolyte homeostasis.[4] CKD is a public health issue, with its prevalence varying according to the stage of the disease. Of all individuals affected by CKD, 90% are unaware of their condition. It is estimated that between 2.284 and 7.083 million patients with kidney disease require replacement therapy. Moreover, the incidence of CKD is higher in developed countries, such as the United States (13.0%) and Norway (10.2%) (2). In Mexico, the morbidity and mortality rates due to CKD are alarming, with a prevalence of 11%, meaning approximately 13 million people suffer from some degree of kidney damage, many of whom are unaware.[5]

Tamsulosin is a selective α-1a adrenergic antagonist, blocking α-1A and α-1D adrenergic receptors.[6] As a specific α1 adrenergic receptor antagonist, it is used (generally as its hydrochloride salt, tamsulosin hydrochloride) in the treatment of prostatic hyperplasia, chronic prostatitis, urinary retention, and helps in the elimination of kidney stones. Additionally, it serves as an antineoplastic agent.[7] By blocking adrenergic receptors, it relaxes the smooth muscle of the prostate, the detrusor muscles of the bladder, improving urinary flow and preventing storage symptoms. This medication is pharmacologically related to doxazosin, prazosin, and terazosin; however, unlike these drugs, tamsulosin has greater affinity and selectivity for α1A adrenergic receptors, which are primarily found in non-vascular smooth muscle.[8] The α-1 adrenoceptors play a crucial role in modulating vascular tone and systemic hemodynamics, and blockers of these receptors have been widely used to treat hypertension. However, to date, there have been few studies to determine whether such drugs can convey a biological effect on the kidney. In studies conducted on mice with bilateral ureteral obstruction, as well as in cultures of proximal tubular cells from the HK-2 cell line, it was found that blocking α1 adrenergic receptors promoted a decrease in the production of the pro-inflammatory cytokine TGF-β, the p38/Smad 3 pathway, as well as the epithelial-mesenchymal transition, thereby significantly reducing the risk of renal damage and fibrosis.[9] On the other hand, it has been observed that tamsulosin inhibits fibrotic transcription factors such as TGF-β, extracellular matrix (ECM) proteins like collagen I, as well as Reactive Oxygen Species, which are significant in the progression of fibrosis and renal damage. Furthermore, tamsulosin was found to inhibit signaling pathways activated by the transcription factor NF-κB, as well as preventing the activation of the p38 protein, a molecule that induces the MAPK signaling pathway.[10] The aim of this study was to analyze the effect of tamsulosin on an adenine-induced chronic kidney disease model in rats.

3. MATERIALS AND METHODS

3.1. Experimental Animals

Male Wistar rats weighing between 150-250 g were obtained from the bioterium of the Center for Basic Sciences at the Autonomous University of Aguascalientes. The animals were kept in 12-hour light/dark cycles, with relative humidity and a controlled temperature of 25 °C. They were dewormed prior to the experiments (fenbendazole 55 mg, toltrazuril 20 mg, and praziquantel 10 mg) at a dose of 1 ml/kg, administered intragastrical for 3 days. Throughout the experimentation, a diet of Purina Rodent Chow & Ad libitum nutricubes and freely accessible purified water was provided. All conducted experiments adhered to the NOM-062-ZOO-1999 standard and were approved by the institutional bioethics committee for the management of laboratory animals, which follows the guidelines of the National Institutes of Health for the care and use of Laboratory animals.[11]

3.2. Experimental Design

Animals were allocated into five groups, each comprising five subjects (n=5): intact (healthy), fibrotic (diseased), tamsulosin (healthy treated with tamsulosin), R.E (endogenous regeneration, i.e., diseased without treatment), and

tam/adenine (diseased and treated with tamsulosin). To induce chronic renal failure, adenine (150 mg/kg, Sigma-Aldrich, ≥99%) was orally administered over four weeks using a stainless steel curved esophageal cannula (18 × 3", Cadence Science). The study employed two models: therapeutic and prophylactic. In the therapeutic model, following adenine induction, tamsulosin hydrochloride (0.4 mg/kg/day, pharmaceutical grade) in sterile purified wáter was orally administered every 24 hours for two weeks. In the prophylactic model, tamsulosin treatment commenced concurrently with adenine induction; after administering adenine, a 30-minute rest period preceded the oral tamsulosin administration, which continued for four weeks. Upon treatment completion, rats were anesthetized with intraperitoneal sodium pentobarbital (100 mg/kg). Renal tissues were harvested to analyze biomarkers of renal damage and gene expression.

3.3. Histopathological Analysis

Longitudinal kidney sections from each animal were collected and preserved in 4% paraformaldehyde at room temperature. They were subsequently processed using histological techniques to obtain 5-micrometer-thick sections, using a Leica RM 2125RT microtome. Staining was performed with hematoxylin/eosin, Masson's trichrome, and Sirius Red. Image analysis was conducted using an Axioscope 40/40 FL microscope and processed with Image ProPlus 4.5.1 software (Media Cybernetics, Bethesda).

3.4. Biomarkers of Renal Damage

Serum levels of various parameters commonly used to assess renal function, such as urea, creatinine, BUN, and uric acid, were measured using wet chemistry with the DimensionEXL-200 system by Siemens.

3.5. RT-qPCR

Total RNA was extracted using the Direct-zol™ RNA MiniPrep kit (Zymo Research, R2050), following the manufacturer's protocol. RNA concentration was determined using the Biodrop device (Isogen Life Science, 80-3006-51). The cDNA was synthesized from 1μg of RNA by reverse transcription using the GoScript™ Reverse Transcription System (Promega Corporation, A5000). Quantitative PCR (qPCR) was then performed using Maxima SYBR Green/ROX qPCR Master Mix (2X) (Thermo Scientific, K0221) in conjunction with the StepOne™ Real-Time PCR Systems (Applied Biosystems). The aim was to assess the relative gene expression levels of collagen 1, ACTA-2 and TGF-β (see Table 1). Expression levels were normalized with respect to β-actin, and was calculated differential expression using the 2-ΔΔCq method.

3.6. Statistical Analysis

The statistical analysis was conducted using GraphPad Prism 9 software for macOS. A non-parametric analysis of variance was performed with Dunn's PostHoc test for multiple comparisons. The confidence level was set at 0.05.

4. RESULTS

Tamsulosin improves renal function but does not reduce renal tissue damage in the therapeutic model. The tissues were analyzed to see histological changes and thereby assess the drug's effect in the different models (therapeutic and prophylactic). In the therapeutic model, the fibrotic group showed greater tubular luminal expansion, presence of collagen fibers, and a clear presence of 2,8-DHA (dihydroxyadenine) crystals. Conversely, in the group that received tamsulosin (tam/adenine), tubular damage was less, but with inflammatory infiltrate and a reduction in collagen fibers (Masson's Trichrome). With Sirius Red staining, the presence of type I collagen fibers, visualized in red, and type III in

green, was noted, as well as some yellow fibers, being a combination of both types. Animals treated with tamsulosin did not show a reduction in 2,8-DHA crystal deposits; however, there was less tubular luminal expansion compared to the fibrotic group. Regarding collagen fibers (Masson's trichrome and Sirius Red staining), no changes were observed when compared to the fibrotic group, although the presence of type I collagen was noted (Fig. 1). Conversely, when evaluating renal function markers, a decrease in BUN, urea, creatinine, and uric acid was seen in the groups that received tamsulosin (tam/adenine) compared to the fibrotic group (Fig. 2).

The analysis of the relative expression of three different fibrotic markers revealed that TGF-β expression was higher in the fibrotic group compared to the intact and tam/adenine groups. It is noteworthy that, although no significant differences were seen between the evaluated groups, the expression of TGF-β in the tam/adenine group was slightly lower than in the intact group. Regarding ACTA-2 (smooth muscle alpha-actin), no variations were observed in any of the groups. Lastly, the determination of COL-1 showed quite similar expression values, with the fibrotic slightly higher than the intact and fibrotic groups (Fig. 3).

Tamsulosin improves renal function and prevents the development of damage to the kidney tissue in the prophylactic model. In the prophylactic model, a normal structural conformation is observed in the intact and tamsulosin groups, with round tubular contours and normal tubular expansion. The fibrotic group exhibits tubular luminal expansion and a clear presence of 2,8-DHA crystals. The R.E. group presents the same characteristics as the fibrotic group. The tam/adenine group shows deformation in the tubular contours, although it is not very clear. Moreover, the presence of collagen fibers in the fibrotic and tam/adenine groups is almost equal, with a predominance in the fibrotic group. In the R.E group, there are collagen fibers, but in a smaller proportion, mostly type I collagen fibers (Fig. 4). Regarding renal function markers, the fibrotic group shows elevated levels of BUN, creatinine, urea, and uric acid, with statistically significant differences compared to the control. The group that received tamsulosin (tam/adenin) exhibits a clear decrease in creatinine and uric acid; however, about urea and BUN, it only showed values slightly below the fibrotic group (Fig. 5). Finally, the markers of relative expression indicate that TGF-β, ACTA-2, and COL-1 are decreased compared to the fibrotic and R.E. groups. This suggests that tamsulosin can promote the fibrotic process in the kidney (Fig. 6).

Table I: Primer sequences for RT-PCR.

GEN	PRIMER	SEQUENCE (5'-3')	AMPLICON (PB)
COL-1	FW	AGG CAT AAA GGG TCA TCG TG	157
	RV	ACC GTT GAG TCC ATC TTT GC	
ACTA 2	FW	GCC AGT CGC CAT CAG GAA C	74
	RV	CAC ACC AGA GCT GTG CTG TCT T	
TGF-B	FW	GAC TCT CCA CCT GCA AGA CCA	244
	RV	CGG GTG ACT TCT TTG GCG TA	
B-ACTIN	FW	GTC GTA CCA CTG GCA TTG TG	175
	RV	GCT GTG GTG GTG AAG CTG TA	

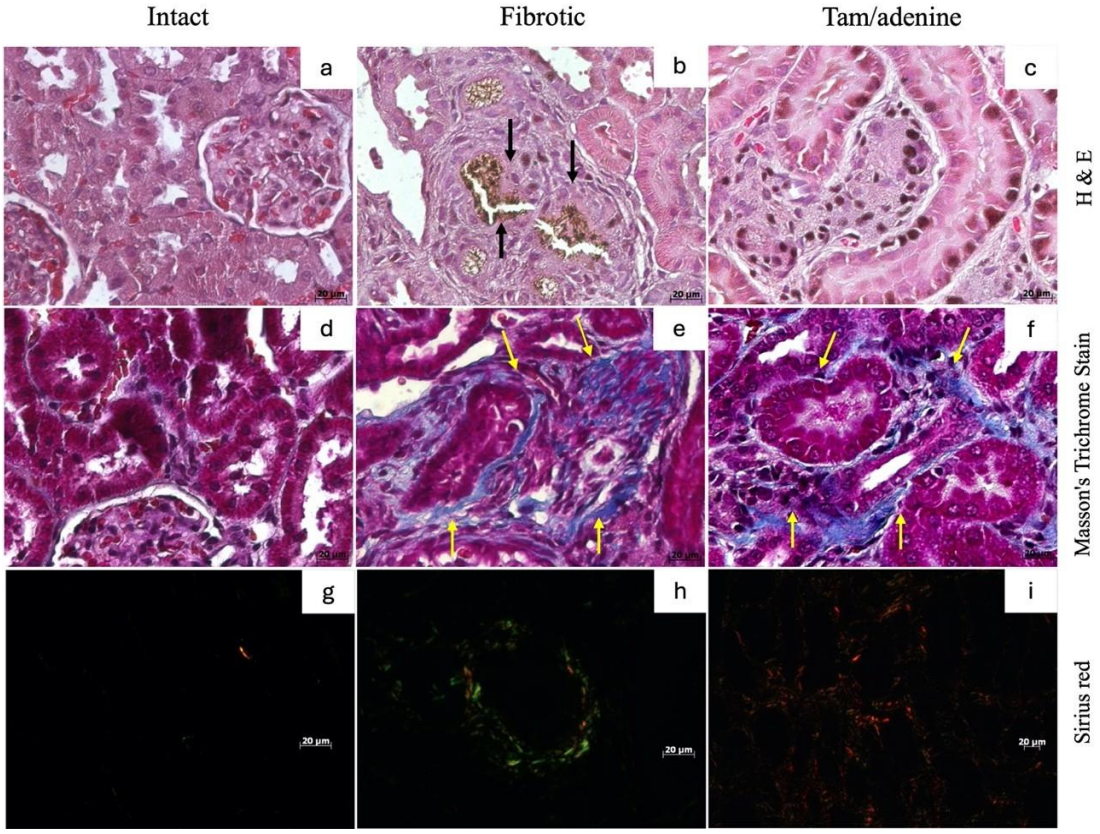

Figure 1: Tamsulosin does not enhance the renal tissue in the therapeutic model. Histopathological analysis of renal tissues stained with hematoxylin/eosin (H/E), Masson's trichrome, and Sirius Red revealed the following findings: Healthy group (a): No alterations in renal tissue structure. Fibrotic group (b): Tubular luminal expansion, presence of collagen fibers (showed by yellow arrows), and deposits of 2,8-DHA crystals (indicated by black arrows). Tam/adenine group (c) (received tamsulosin): Tubular damage was reduced, but with inflammatory infiltrate. Notably, there were no significant differences in collagen presence (yellow arrows) between type I and type III. Additionally, there was no decrease in 2,8-DHA crystal deposits (black arrows).

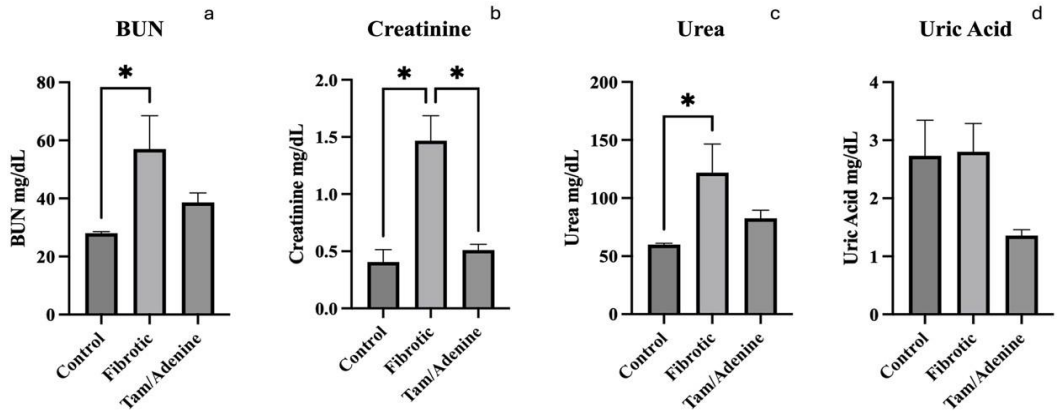

Figure 2: Tamsulosin improves renal function in the therapeutic model. By analyzing biochemical parameters, we evaluated the ability of tamsulosin to enhance renal function. It was observed that the group receiving tamsulosin (tam/adenine) exhibited a reduction in blood urea nitrogen (BUN), creatinine, urea, and uric acid concentrations compared to the fibrotic group.

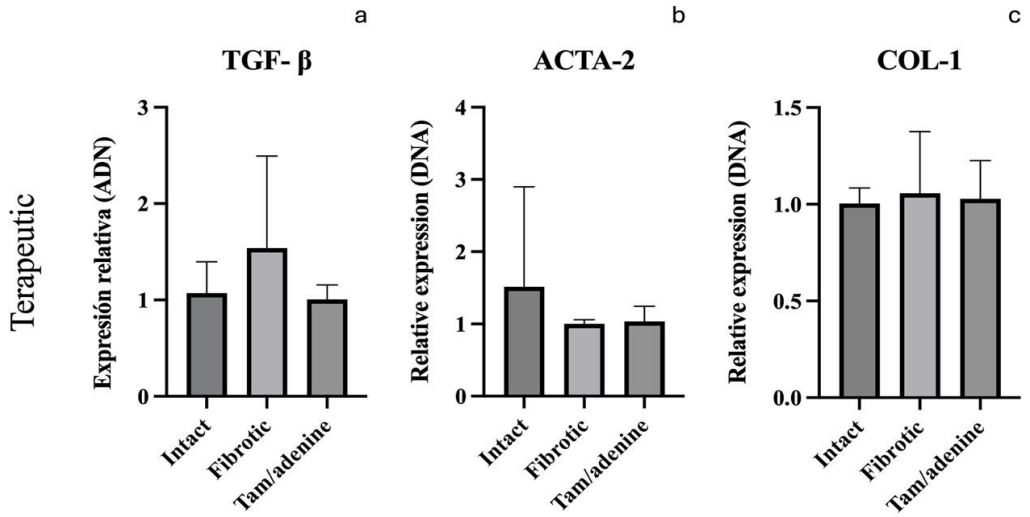

Figure 3: Analysis of the relative expression of fibrotic markers in the therapeutic model. By assessing the relative expression of fibrotic markers (TGF-β, ACTA-2, and COL-1), the effect of tamsulosin was evaluated. The healthy group showed no variations in any of the evaluated markers, while the fibrotic group exhibited increased expression of TGF-β and COL-1. In the group receiving tamsulosin, a decrease in TGF-β and COL-1 was observed. ACTA-2 did not show any changes in the evaluated groups.

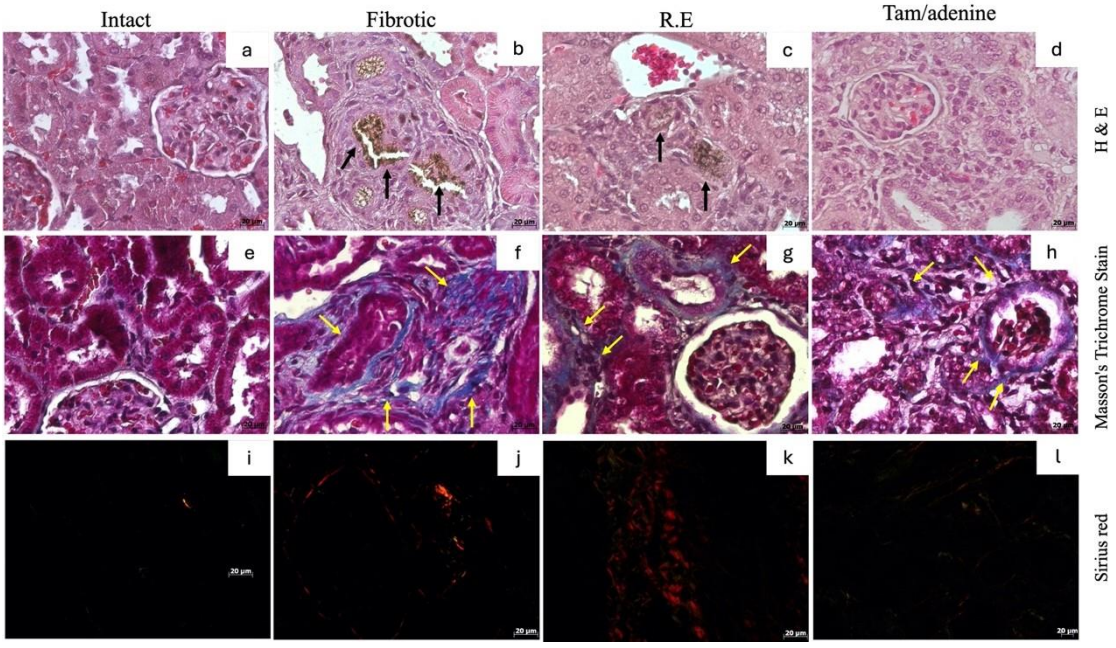

Figure 4: Tamsulosin prevents the development of renal damage in the prophylactic model. through histopathological analysis of renal tissues stained with hematoxylin/eosin (H/E), Masson's trichrome, and Sirius Red, the following observations were made: a) In the intact group; normal structural conformation is observed. b) The fibrotic group exhibits luminal tubular expansion, clear presence of 2,8-DHA crystals (black arrows), and abundant collagen fibers (yellow arrows). c) The R.E. group displays characteristics similar to the fibrotic group. d) The group treated with tamsulosin (tam/adenine) shows slight deformation in tubular contours and a marked reduction in collagen fibers (yellow arrows). Additionally, deposits of 2,8-DHA crystals are not observed (black arrows).

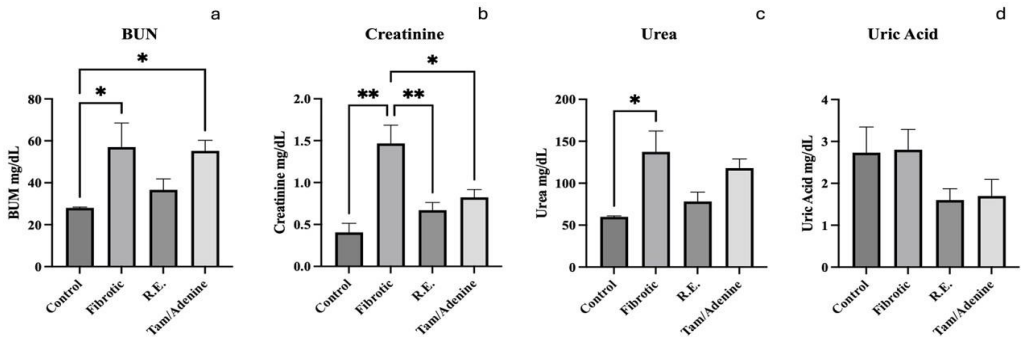

Figure 5: Tamsulosin Improves renal Function in the prophylactic Model. Biochemical parameter analysis was conducted to evaluate the ability of tamsulosin to enhance renal function. The fibrotic group exhibited elevated levels of BUN, creatinine, urea, and uric acid. In contrast, the tamsulosin-treated group showed a significant decrease in creatinine levels, along with a slight reduction in urea and uric acid levels. No differences in BUN were seen in the treated group compared to the fibrotic group.

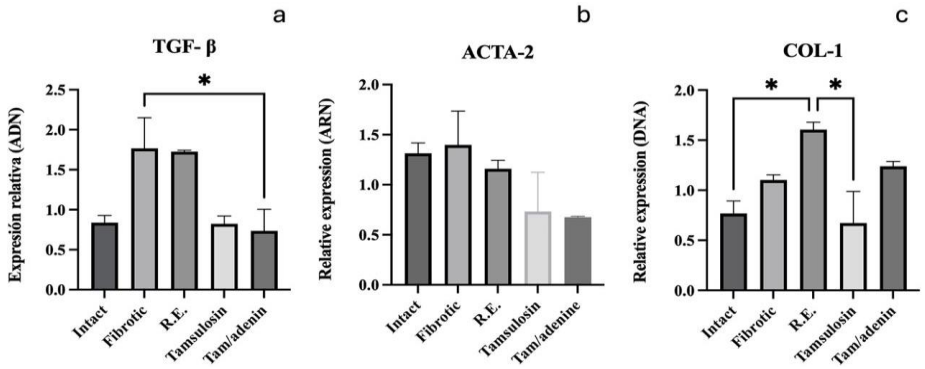

Figure 6: Analysis of the Relative Expression of fibrotic markers in the prophylactic model. The effect of tamsulosin was assessed through the analysis of the relative expression of fibrotic markers (TGF-β, ACTA-2, and COL-1). The healthy group showed no variations in any of the evaluated markers, while the fibrotic group exhibited increased expression of TGF-β and COL-1. In the tamsulosin-treated group, a decrease in TGF-β and COL-1 was observed. ACTA-2 did not show changes across the evaluated groups.

5. DISCUSSION

Recent investigations into new therapeutic approaches for tamsulosin have highlighted its significant role in reducing the expression of pro-fibrogenic factors in mouse models with unilateral ureteral obstruction[9], as well as its potential to mitigate oxidative stress and inflammatory response in diabetic nephropathy.[10] This study employed two experimental models, therapeutic and prophylactic, to notice the effects of tamsulosin, assessing morphological, biochemical, and molecular variables. In the therapeutic model, the fibrotic group shown deposits of 2,8-DHA crystals, inflammation of the renal tubules[12], and increased tubular lumen. Animals treated with tamsulosin show a light reduction in 2,8-DHA crystal deposits; however, they showed less tubular luminal expansion tan the fibrotic subjects. Some studies suggest that crystal size influences the ease of disposal, with adenine producing heterogeneous and amorphous crystals[13], Meltzer et al., (2018)[14] noted that tamsulosin does not positively affect renal calculi that vary in size and shape. Additionally, inflammatory cell infiltrations in the glomerular regions (tam/adenine group) were shown, which occurs as chronic kidney disease (CKD) develops and the glomeruli lose their selective filtration ability, activating the inflammatory process and subsequent cellular infiltration. While adenine-induced damage directly

affects the tubules, it is known that deterioration of renal tubule cells inevitably leads to glomerular damage.[15] Masson's trichrome and Sirius Red staining revealed the presence of collagen, particularly type I, in the group treated with tamsulosin. It is important to note that type I collagen is one of the primary markers for the development of fibrosis, along with type III collagen.[15] However, renal function markers such as BUN, urea, creatinine, and uric acid showed a significant decrease in the groups that received tamsulosin (tam/adenine) compared to the fibrotic group, suggesting an effect of tamsulosin on the recovery of renal function in this model.

In the molecular analysis, three distinct markers were utilized to assess fibrosis. The primary marker, transforming growth factor β (TGF-β), is recognized as a critical pro- fibrotic agent. Studies have shown that increased activity of the renal sympathetic nerve significantly contributes to interstitial fibrosis. This enhancement occurs as the nerve discharges norepinephrine, exacerbating the TGF-β-induced extracellular matrix production via the α1-AR/Gαq/p38/Smad3 pathway. Consequently, inhibiting the α1-AR receptor can effectively arrest the progression of fibrosis.[9]

Results and Molecular Analysis Expression levels of the marker in the tamsulosin-treated group (tam/adenine) remained comparable to the intact (healthy) group, while its expression was higher in the fibrotic group. Another aspect evaluated was smooth muscle actin (ACTA-2), which is used to understand the number of myofibroblasts present in the tissue (2), stimulating the production of the extracellular matrix and thereby collagen I, a crucial process in the progression of kidney disease. The expression of ACTA-2 in the tamsulosin-treated group is high, pointing that tamsulosin does not reduce the number of myofibroblasts. Lastly, when assessing the expression of collagen I (COL-1), the expression levels showed no significant differences, suggesting that tamsulosin does not have the capacity in this model to eliminate collagen I deposits when the disease is at advanced stages. In the prophylactic model, the histopathological analysis revealed that tamsulosin reduces cellular infiltration within the glomerular area. Additionally, it significantly diminishes the occurrence of 2,8-DHA crystal deposits. These findings suggest that tamsulosin's role as a specific α1 adrenergic receptor antagonist contributes to the relaxation of smooth muscle tissue. This action helps the urinary flow, which is instrumental in preventing the formation of renal calculi.[16] Regarding serum BUN and creatinine concentrations, high values write down a deficiency in the filtration process[17], suggesting that tamsulosin may improve kidney filtration by reducing their serum concentration. However, urea concentrations in the fibrotic group and the tamsulosin-treated group are very similar. Uric acid concentrations in the fibrotic group are twice as high as those in the group treated with tamsulosin, showing that tamsulosin might be involved in adenine metabolism, preventing the formation of uric acid stones (Longoni-Merino, 2018). Similarly, molecular analysis shows that tamsulosin decreases the expression of TGF-β, ACTA-2, and COL-1. This may can be attributed to an inhibition of TGF-β, as tamsulosin is known to inhibit collagen synthesis through the TGFβ1/SMAD pathway (18). Furthermore, a study by (9) on mice with unilateral ureteral obstruction (UUO), found that at a dose of 0.4 mg/kg/day, tamsulosin treatment shows a protective effect against renal tubular damage and extracellular matrix deposition. In addition to histological improvement, after 7 days, plasma creatinine and urea levels significantly decreased compared to controls. Also, levels of smooth muscle α-actin (a myofibroblast biomarker) and vimentin, a marker of EMT, decreased in animals treated with tamsulosin.

6. CONCLUSIONS

The findings from macroscopic, histopathological, biochemical, and molecular analyses during the first stages of the disease (prophylactic model) indicate that tamsulosin effectively halts fibrosis progression and bolsters renal

function, offering protection at both the molecular and tissue levels. It also diminishes the expression of ACTA-2 and type I collagen by targeting TGF-β inhibition. However, in the disease's later stages (therapeutic model), tamsulosin appears to solely enhance renal function.

7. ACKNOWLEDGEMENTS

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8. CONFLICTS OF INTEREST

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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10. AUTHOR CONTRIBUTIONS

Mariana Cecilia Pérez-Villalobos, Javier Ventura-Juárez, designed the article structure and revised the manuscript, Sandra Luz Martínez-Hernández, designed, revised and wrote the manuscript, Nicté García-Carrillo and Andrea Barba-González, carried out the experiments, drafted the initial manuscript and prepared the references and tables, Jorge Christopher Morones-Gamboa, experimental design, Martín Humberto Muñoz-Ortega and Esperanza Sánchez-Alemán contributed to acquisition, analysis and interpretation of the data. All authors have read and agreed to the published version of the manuscript. Manuel Enrique Ávila Blanco contributed to the formatting of the paper, revision of the manuscript, images, and statistics, as well as translation into English.

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