RESEARCH ARTICLE

Modulation of Histopathological Changes and Inflammatory Markers in the Testes of Hypertensive Male Rats by Fenofibrate Treatment

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ABSTRACT

Background: Hypertension impairs reproductive organs function, including the testes. As fenofibrate, a major drug used for treating dyslipidemia, improves endothelial function and has anti-inflammatory properties,

Aim: This study investigates the effects of fenofibrate on histopathological and inflammatory marker changes in induced by hypertension in rat's testis.

Methods: In this study thirty normal male rats, weighing between 120 and 140 grams and aged six to seven weeks, were used. The rats were divided into three groups: The control negative (n=10), rats that received a standard diet and water only. Control positive rats, the hypertensive group (n=10), received an oral Nω-nitro-l-arginine methyl ester (L-NAME) at a dosage of 40 mg/kg/day for 3 weeks. Treatment group (n=10), L-NAME was administered by the rats at a dosage of 40 mg/kg/day followed by Fenofibrate at a daily dose of 30 mg/kg for 4 weeks.

Results: Fenofibrate significantly decreased the proinflammatory markers and the pathological changes in the testes (testicular degeneration, necrosis, vascular congestion, interstitial edema, and hypospe-rmatogenesis) at a P – value < 0.001 compared with the hypertensive group. These changes were significantly increased in hypertensive group compared to the control group (P- value < 0.001). Fenofibrate also showed increased testosterone levels at a P – value < 0.001 compared to the hypertensive group, where testosterone levels were significantly decreased in hypertensive group compared to the control group (P value < 0.001). However, there was no significant effect of fenofibrate or hypertension on body and testicular weight.

Conclusion: Fenofibrate improves histopathological and inflammatory marker changes induced by hypertension in male rats.

Key words: Hypertension, Testes, Fenofibrate, Inflammatory Factors, Testosterone

INTRODUCTION

Hypertension is a chronic condition characterized by elevated arterial blood pressure [1]. It is a significant public health issue, affecting over 25% of the population and is considered a major risk factor for cardiovascular diseases, contributing to over 50% of the 17 million annual deaths worldwide [2]. This condition is complex, with various causes and numerous interacting genetic and environmental factors. Its occurrence changes with age, plasma renin activity, and sodium sensitivity [1]. Pre-clinical animal models have greatly enhanced our understanding of hypertension by allowing control over these contributing factors, though no single model is comprehensive [2]. The contemporary way of living significantly impacts personal health, with arterial hypertension being a major concern. It's a prevalent chronic condition globally, often symptomless and diagnosed late. This condition can cause various complications by affecting the structure and function of organs through changes in blood vessels including degeneration, vessels tone, and density [3]. Arterial hypertension is recognized to mainly affect organs like the Kidneys, parts of the brain, heart, and eyes, but there's limited research on its influence on the testes, which are vital for male fertility and sperm quality [4].

Studies indicate that hypertension is related to male sexual dysfunction, including issues with libido, erections, and ejaculation as well as male infertility due to reduced blood flow to the testicles. Although the precise mechanisms are not entirely clear, a significant aspect of hypertension is the reduced blood flow to essential organs caused by arterial vasoconstriction, and induces inflammation, leading to testicular (among other organs) damage [5, 6]. A study found that as cardiovascular disease becomes more prevalent, there's a noticeable decline in semen quality [7].

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While the association remains contentious, other studies suggest a correlation between hypertension and alterations in sperm quality parameters such as aberrant sperm morphology, motility, viability and increased sperm DNA damage. Experimental models of hypertension-induced stroke demonstrate changes in testicular architecture, including diminished blood perfusion and alterations in tissue composition [8].

The decline in semen quality is now a global public health concern due to its association with higher mortality rates in affected men in comparison to those with normal sperm quality.

As a result, semen quality is hypothesized to be a marker of man wellness, indicating a potential link between overall health and reproductive function [8]. Additionally, hypertension can increase oxidative stress and inflammation [9] and may impact inflammatory markers expression such as IL-1, IL-6, and TNF- α [10], further disrupting hormonal balance [3]. Nowadays, more attention has been paid to controlling hypertension and addressing the associated testicular changes.

Studies have found that treatment with fenofibrate improves endothelial function of the blood vessels by decreasing oxidative stress and increasing endothelial nitric oxide synthase [11, 12]. This suggests that fenofibrate's benefits on vascular health promotion in people are mediated by mechanisms other than reducing cholesterol. Fenofibrate, a fibric acid derivative, is primarily utilized as an anti-hyperlipidemic drug to manage dyslipidemia by binding to peroxisome proliferator-activated receptors-α (PPAR-α).

It is known to have multiple beneficial effects, including cell protection, lowering pro-inflammatory cytokines, and inhibiting mitogen-activated protein kinase (MAPK) activation, through both PPAR-α dependent and independent pathways [13].

Because of the limited studies and no clear explanation on the impact of hypertension on histopathological changes, inflammatory markers, and testosterone levels in male rats, as well as the effects of fenofibrate on modulating these changes post-hypertension, the aim of the present study is to investigate these aspects comprehensively.

SUBJECTS AND METHODS

Animal

Thirty normal, male, Sprague-Dawley (SD) rats were used in this study. Their weights ranged between 120-140 grams, and their ages spanned from six to seven weeks. The rats were sourced from Hawler Medical University - College of Pharmacy, Department of Animal House. Rats were housed in polypropylene cages under a 12-hour light/12-hour darkness, with ad libitum access to water and food.

Experimental design

A total of thirty male rats were divided into three groups. The control negative (n=10), rats that received a standard diet and water only throughout the experiment. Control positive or hypertensive group (n=10), rats were administered Nω-nitro-l-arginine methyl ester (L-NAME) at a dosage of 40 mg/kg/day for three weeks orally by gavage after dissolving it in distilled water. Treatment group (n=10), rats were administered L-NAME at a dosage of 40 mg/kg/day then received fenofibrate (Lipanthyl, 200 mg per micronized pill, Abbott, French) dissolved in distilled water and administered daily by gastric gavage at a dose of 30 mg/kg for 4 weeks. Throughout the experimental period, the body weights of all rats were recorded weekly, and their clinical status was monitored daily.

Blood pressure

Arterial pressure (diastolic, systolic, and mean blood pressure) and heartbeat were measured at the start and end of the experiment. The tail-cuff method (CODA non-invasive blood pressure monitor/Kent Scientific Corporation, USA), which uses volume pressure to record tail arterial pressure, was used for measurement of the blood pressure. The animal's tail was covered with a cuff to stop blood flow, once deflated, specially designed differential pressure transducers measured the blood volume in the tail, also known as VPR (volume pressure recording). The rats were put in a restraining Plexiglas cage for at least 30 minutes before recording each blood pressure. The occlusion cuff was put on the tail, and the VPR sensor cuff was tied near the occlusion cuff. Rats were adapted to the arterial pressure recording procedure four times before the first pressure measuring was made. During the procedure, at least five readings were recorded, with the highest and lowest values omitted, and the mean of the remaining values was recorded

Blood samples

Blood samples were collected by a cardiac puncture after the injection of ketamine and xylazine intraperitoneally at does 35mg/kg, 5mg/kg BW. Then the blood centrifuged and serum was used for the following analysis; Rat IL-6 ELISA Kit (ab234570), Rat TNF alpha ELISA Kit (ab236712) and Mouse/Rat Testosterone ELISA Kit (ab285350) in each group using ELISA.

Histopathologic scoring assessment

At the end of the experiment, the animals were sacrificed and the testes were removed for measurement and histopathological examination. The samples were preserved overnight in 10% neutral buffered formalin (NBF) followed by paraffin infiltration and embedding. Five sections of 4 µm from each region were put on charged and normal microscope slides (Fisher Scientific, PA).

A light microscopic examination (Leica, Germany) of serial Hematoxylin and Eosin (H&E)-stained sections

was performed. Histopathologic scoring assessment was conducted using AmScope TM software (China). The testicular changes in the seminiferous tubules were evaluated for the following: testicular degeneration or necrosis, organization of the germinal epithelium in a regular thickness lumen, sloughing of germinal layers accompanied by vascular congestion and interstitial edema, and the spermatogenesis process with the presence or absence of spermatozoa. Microscopic grading was carried out by calculating the proportion of morphologically abnormal areas relative to the total surface area of each seminiferous tubule. The following scoring system was used: score 0: no lesion, score 1: 1–25%, score 2: 26–50%, score 3: 51–75%, and score 4: ≥76% [14, 15].

Statical Analysis

The data from the results were presented as the means ± SEM. For the comparison of two variable measurements, unpaired t-tests were employed. For three variables, a one-way ANOVA was utilized. A significance level of $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using GraphPad Instat Version 8.02 (GraphPad Software, San Diego, California, USA)

RESULTS

The study found that giving 40 mg/kg of L-NAME daily for three weeks induced hypertension in male rats, with a significant increase ($P < 0.001$) in systolic blood pressure (153.42 ± 0.349 mmHg), diastolic blood pressure (115.71 ± 0.427 mmHg), and mean blood pressure (130.72 ± 0.375 mmHg) compared to the control group, which had systolic blood pressure of 112.92 ± 0.358 mmHg, diastolic blood pressure of 83.27 ± 0.328 mmHg, and mean blood pressure of 95.87 ± 0.235 mmHg. Additionally, the heart rate (beats per minute) decreased significantly ($p < 0.001$) in the hypertensive group (334.32 ± 0.673 bpm) versus the control group (381.75 ± 0.215 bpm).

Effect of Fenofibrate on body and testicular weight

The body weight in the hypertensive group decreased compared to the control negative group non-significantly. Fenofibrate increased rats' body weight compared to the hypertensive group non-significantly. Testicular weight decreased in the hypertensive group compared to the control negative group non-significantly. Fenofibrate improved in testicular weight vs. to the hypertensive group non-significantly,

Table 1.

Impact of Fenofibrate on Inflammatory Markers

The levels of the inflammatory markers IL-1, TNF-α, and IL-6 were significantly elevated ($P < 0.001$) in the hypertensive group compared to the control negative group. Fenofibrate use demonstrated a significant reduction ($P < 0.001$) in these inflammatory markers versus the hypertensive group (Figure 1a and 1c). The testosterone significantly reduced ($P < 0.001$) in rats of hypertensive group in comparison to the control negative group. While, fenofibrate significantly raised ($P < 0.001$) testosterone levels in hypertensive male rats, (Fig 1 d).

Table 1

Effect of Fenofibrate on Body and Testicular Weight in studied Groups

Parameters	Control negative Group	Hypertensive group	Hypertensive treated with Fenofibrate	P -value
Body weight (gm)	473.48± 3.123 [a]	455.85± 4.569 [a]	461.13± 5.743[a]	0.195
Testicular weight (gm)	2.932 ± 0.038 [a]	2.798 ± 0.0538 [a]	2.875 ± 0.037[a]	0.126

*The data expressed by Mean ± SE, the same letters indicate no significant difference ($p > 0.05$).

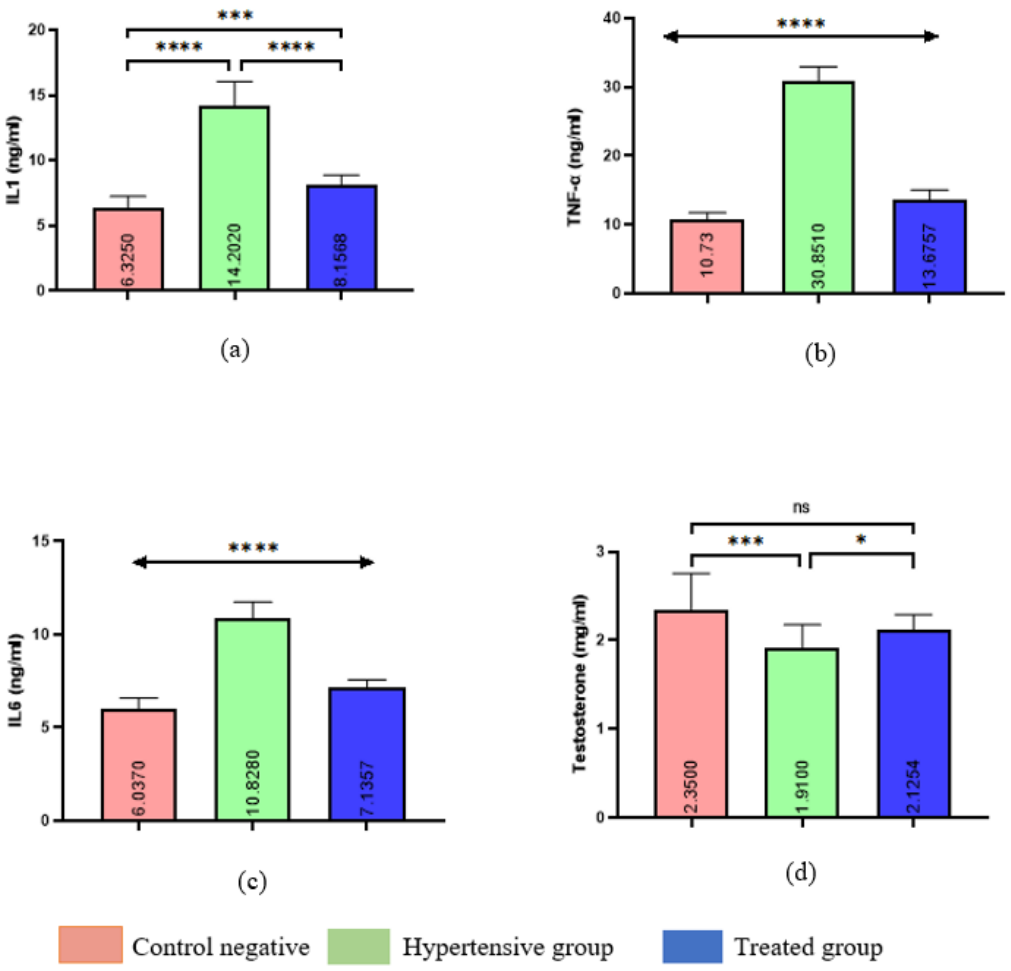

Fig 1. The impact of fenofibrate on the inflammatory markers (a) IL-1, (b)TNF-α (c) IL-6 and (d)Testosterone level in control negative, hypertensive and treated groups.

Attenuation of Histopathology Lesion by Fenofibrate

Testes from the control negative group showed several rounded seminiferous tubules with an ordered architecture under a microscope, along with normal parenchyma. Around four to six layers of spherical spermatids lined the germinal epithelium at a distinct stage of spermatogenesis (from spermatogonia to spermatozoa). Mature sperm's spinning flagella occupied the lumina of the seminiferous tubules. The normal vasculature supplied the interstitial areas between tubules, where intact Leydig cells were seen in Fig 2 a and Fig 2 b.

In contrast, testes in the hypertensive rats revealed dilation of seminiferous tubules, sloughing or detachment of spermatogonia and germinal epithelium, severe degeneration of primary and secondary spermatocytes with severe depletion of germ cells and decrease in the number of spermatozoa and reduction in round spermatids. Necrosis of spermatogonia exhibiting dark, small, and round pyknotic nuclear structures; and marked interstitial degeneration with pyknotic Leydig cells were also found (Fig 2 c and Fig 2 d).

After fenofibrate administration, however, only mildly enlarged seminiferous tubules with mild degeneration in germ cells, primary and secondary spermatocytes with Sertoli cells, and intact interstitial cells within normal organized interstitial space were found. Instead, it enhanced the mitotic activity of spermatogenic cells and Leydig cells against hypertensive effect (Figure 2e and f), the hypertensive group recorded the high score as seen in Table 2.

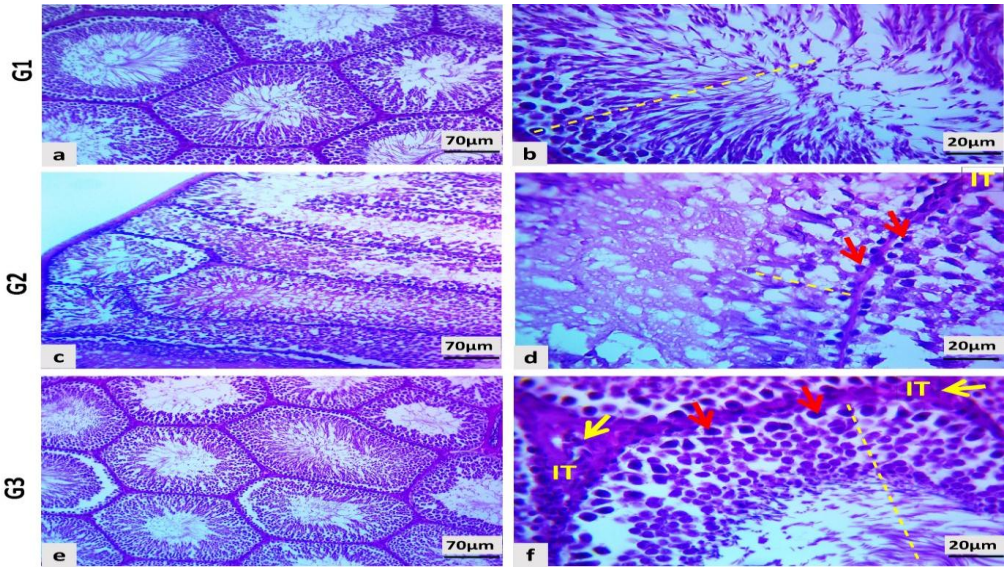

Fig 2. Light microscopic section of the testes in different studied groups revealed; a and b: Normal organization of seminiferous tubules at diverse spermatogenic stages (yellow dash lines) and spermatozoa that filled the lumen, well-organized interstitial space (IT) in control negative group. c and d: Distention of seminiferous tubules with a disorganized germinal epithelium, marked hypospermatogenesis (yellow dash line), detachment of spermatogonia that revealed pyknotic features (red arrows), marked degenerated Leydig cells within moderate interstitial edema (yellow arrow) in control positive group. e and f: Mild dilation of the seminiferous tubule, mild degeneration of spermatogenic cells and spermatogonia (red arrow), normal interstitial space, and intact Leydig cells in treatment group, (H&E stain).

Table 2
Effect of Fenofibrate on pathological scores.

Parameters	Control	Hypertensive group	Hypertensive treated with Fenofibrate	P- Value
Testicular degeneration	0.000	3.62 ± 0.112	1.036 ± 0.120	0.001
Testicular necrosis	0.000	3.09 ± 0.124	0.5357 ± 0.095	
Vascular congestion and interstitial oedema	0.000	2.31 ± 0.105	1.179 ±0.073	
Hypo spermatogenesis	0.000	3.78 ± 0.09177	1.107 ±0.05952	

DISCUSSION

Hypertension in male rats is a well-established area of research for understanding the pathophysiology and potential treatments for high blood pressure in humans [1,16]. Similar to the previous studies, the current study induced hypertension via L-NAME, which is a non-specific inhibitor of nitric oxide synthase (NOS). L-NAME reduces NO production, leading to vasoconstriction, increased vascular resistance and ultimately elevated blood pressure and hypertension [17, 18]. The mechanism of hypertension after NO deficiency is relevant to certain forms of human hypertension, making L-NAME a valuable tool for translational research [19]. The testes, as important male reproductive organs, are not exempt to the complications of hypertension. Some studies have shown that hypertension can alter its morphology and impair sperm quality [20 - 22]. A larger cohort study done in 2015 found that males with hypertensive conditions had a higher probability of sperm abnormalities, supporting the link between hypertension and male fertility [23].

The results of the present study found non-significant decrease in body weight in the hypertensive group, which is similar to the results of other researches whom documented the non-significant reduction in body weight and its stability recorded in the hypertensive rat [24, 25]. Hypertension increases metabolic demand, often associated with chronic inflammation, which can exacerbate catabolic processes, greater energy expenditure and potential weight loss due to the increased workload on the heart, kidneys, and other organs [24]. Additionally, hypertension can alter neuroendocrine function, including the regulation of appetite and feeding behavior [25]. Some studies suggest that hypertensive rats may experience changes in appetite-regulating hormones like leptin and ghrelin, resulting in reduced food intake and consequent weight loss. [25,26]. Fenofibrate administration at a dose of 30 mg/kg for 4 weeks improved non-significantly increase in body weight compared to the hypertensive group.

Although there is limited research on the effect of fenofibrate on body weight, and no direct literature is

present, this increase could be related to fenofibrate's anti-inflammatory characteristics, which can reduce inflammation and create an anabolic state that promotes weight maintenance or minor gain [26].This is corroborated by an investigation of [24], which found that fenofibrate's increase of lipid metabolism, enhances the general efficiency of energy and prevents the catabolic effects associated with hypertension [26]. Furthermore, Ghosh MK et al. [27] discovered that persistent inflammation can aggravate catabolic processes, leading to weight loss, as a result, lowering systemic inflammation can enhance the digestive system and nutrition absorption, contributing to a positive energy balance, this may contribute to a minor rise in body weight when the body transitions towards an anabolic state [27]. The current study discovered a non-significant decrease in testicular weight in hypertensive group compared to the control group. Although no direct studies are emphasizing the effect of hypertension on testicular size, and the disorder's effect on the testicles is still unclear, this slight drop in testicular weight could be attributed to hypertension, which increases oxidative stress in organs, including the testicles, potentially reducing blood flow, oxygen and nutrient distribution, and causing cellular damage [3]. Furthermore, Azu OO et al. [28] discovered that high blood pressure can disturb the hormonal balance such as testosterone and follicle-stimulating hormone (FSH), which are essential for maintaining testicular growth and function.

Testicular weight increased somewhat after fenofibrate treatment compared to the hypertensive group, but the difference was not statistically significant [28]. The explanation for this could be the enhancement of endothelial function, improvement of the testicular arteries, and the protection of testicular tissues from oxidative damage by lowering inflammation, as evidenced by study of Abdulzeez 2020 and Xue 2019 [29, 30]. According to our findings, male hypertensive rats showed significantly higher levels of pro-inflammatory cytokines (IL-6, IL-1, and TNF-alpha) than the control group. This result aligns with other research conducted under hypertension conditions by [10, 31, 32].

The complex interaction of oxidative stress, immunological activation, and vascular dysfunction is linked to the rise of inflammatory cytokines because endothelial dysfunction and reduced NO during hypertension produce Reactive Oxygen Species (ROS), a major cause of inflammation [11,33]. Additionally, ROS can trigger the transcription factor nuclear factor-kappa B (NF-κB), which increases the expression of pro-inflammatory cytokines such as TNF- α, IL-1, and IL-6 [34]. Furthermore, hypertension stimulates the innate and adaptive immune systems, attracting neutrophils, T cells, and macrophages which are major cells for producing inflammatory markers.

Furthermore, the renin-angiotensin-aldosterone system (RAAS) is frequently overactive during hypertension, leading to increased levels of angiotensin II, a strong vasoconstrictor and pro-inflammatory mediator that boosts the synthesis of TNF-alpha, IL-6, and other cytokines [35].

In agreement with other studies [35-37], the present study showed a significant reduction in the Pro-inflammatory cytokine levels in the fenofibrate-treated group compared to the hypertensive group. This is mainly due to fenofibrate ability to decrease the ROS, enhance endothelial function and inhibition of nuclear F-κB by activation of PPAR-α. Studies also demonstrated that activation of PPAR-α inhibits the activation of activator protein-1 (AP-1), nitric oxide synthase (iNOS) MAPKs, which are involved in the synthesis of pro-inflammatory cytokines and apoptosis [38- 41]. The results of the study revealed a significant decrease in testosterone levels in the hypertensive group. This finding is consistent with the study by Ketchem JM et al. [41], who demonstrated that the reduction in testosterone is primarily attributed to an increased pro-inflammatory state in the body.Such heightened inflammation contributes to testicular dysfunction by damaging Leydig cells, which are crucial for testosterone production [41].

Studies have found that hypertension can modify testicular morphology and affect the quality of the sperm primarily due to decrease blood supply, which contributes to the pathophysiology of infertility in men [20, 21, 22].

Our findings revealed a significant decrease in testosterone levels in the hypertensive group, which is consistent with the findings of Ketchem JM [41], who discovered that the decrease in testosterone is primarily due to pro-inflammatory state in the body contributes to damaging the Leydig cells which are essential for the production of testosterone and disrupts hormonal signaling pathways, particularly those involving luteinizing hormone (LH) and (FSH) [28].

Our study found that fenofibrate treatment significantly increased testosterone levels compared to hypertensive rats. While the exact mechanism by which fenofibrate modulates testosterone levels remains unclear and lacks literature support, it is hypothesized that this effect may be attributed to the drug's anti-inflammatory properties and its ability to enhance endothelial function which lead to improved blood flow in the testicular artery, potentially contributing to the observed elevation in testosterone levels [29,30]. The current study showed a pronounced effect of hypertension on seminiferous tubules characterized by marked degeneration of spermatogenic cells and depletion of germ cells with a decrease in the number of spermatozoa, marked degeneration of Leydig cells.

This agrees with other studies that showed hypertension is a major factor in the development of testicular dysfunction [3, 42, 43]. This dysfunction is mainly due to the noticed degeneration of seminiferous tubules and the loss of spermatogenetic cells impeding the function of Sertoli cells and ultimately resulting in the loss of spermatogenic cells.

As a result of changes in the local microcirculation, testicular injury was observed in hypertensive rats.

This was associated with elevated ROS activity, lower semen quality, and increased testicular hypoxia-induced protein expression [3, 42]. The Fenofibrate administration reduced the hypertensive effect and decreased the score lesion to only mild degeneration of seminiferous tubules and germ cells, primary and secondary spermatocytes with Sertoli cells, and intact interstitial cells which is similar to the study done by Gallucci et al., 2022 [38]. A related study indicated that Fenofibrate prevented lipid peroxidation, suggesting that Fenofibrate treatment of testicular injury may be an alternative treatment for testicular injury. However, the mechanism underlying favorable effect on ROS in the testis was not clarified [43]. It reduces tissue damage and increases hemeoxygenase-1, which normalizes vascular contractility in hypertension via lowering ROS and TNF-α [44].

CONCLUSIONS

The present research shows that fenofibrate treatment in hypertensive male rats decreases the proinflammatory markers (IL-1, IL-6, and TNF-alpha) and pathological changes in the testes, such as degeneration, necrosis, vascular congestion, interstitial edema, and hypospermatogenesis. It also causes an increase in testosterone levels with no significant effect on body or testicular weight.

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None

Conflict of interest statement

All authors declare that they have no conflict of interest.

Ethical Considerations

The study was approved Hawler Medical University – Collage of Medicine by the Research Ethics Committee and Institutional Animal Care, Kurdistan/Iraq, ID (HMU 9,10) ethical norms for animal experimentation.

Author contribution

The experiment was carried out by the first, second, third and sixth authors, who examined the data and produced the article. Data anaylsis, and double-checked the histopathological section with paper writing were also performed by all authors.

All authors have reviewed and approved the current version of the manuscript.

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