Clinical and Experimental Health Sciences

Morphological and Biochemical Investigation of the Healing Effects of Exercise on High Fat Diet Induced Kidney and Bladder Damage

Merve Acikel Elmas[1], Ozlem Bingol Ozakpinar[2], Meltem Kolgazi[3], Goksel Sener[4], Feriha Ercan[5]

[1] Acibadem University, School of Medicine, Department of Histology and Embryology, Istanbul, Türkiye.
[2] Marmara University, Faculty of Pharmacy, Department of Biochemistry, Istanbul, Türkiye.
[3] Acibadem University, School of Medicine, Department of Physiology, Istanbul, Türkiye.
[4] Fenerbahce University, Vocational School of Health Services, Istanbul, Türkiye.
[5] Marmara University, School of Medicine, Department of Histology and Embryology, Istanbul, Türkiye.

Correspondence Author: Feriha Ercan
E-mail: fercan@marmara.edu.tr
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ABSTRACT

Objective: The aim of this study was to evaluate the ameliorative effects of swimming training on renal and bladder damage caused by a high-fat diet (HFD) using morphological and biochemical measurements.

Methods: Sprague Dawley rats were fed either standard chow (CONT, 6% fat) or HFD (45% fat) for 18 weeks, these rats were divided into two subgroups at the last 6 weeks of the experiment. The exercise groups (CONT+EXC, HFD+EXC) were trained daily swimming sessions (1 h per day for 5 days/week) during the last 6 weeks. Kidney and bladder samples were prepared for light and electron microscopic examination at the end of experiment. Malondialdehyde, glutathione, interleukin-6, and tumor necrosis factor-α were measured by biochemically.

Results: Regular morphology of the renal cortex and bladder mucosa was observed in the CONT and CONT +EXC groups. Degenerated renal corpuscles and proximal tubules in the kidney and degenerated urothelium with leaky tight junctions and mast cell increase in the bladder mucosa were observed in the HFD group. Ameliorated renal cortex and bladder mucosa were observed in the HFD+EXC group. In addition, malondialdehyde, glutathione, interleukin-6, and tumor necrosis factor-α levels were also consistent with the histological findings.

Conclusion: HFD-induced renal and bladder damage may be related to increased oxidative damage. It was observed that the histological damage and altered oxidative stress parameters could be reversed by swimming training, and it is thought that moderate swimming exercise may play a role in regulating oxidative stress.

Keywords: High fat diet, exercise, kidney, bladder

1. INTRODUCTION

Obesity is one of the major epidemic problems in western countries (1). Diabetes and metabolic syndrome, cardiovascular disease, hypertension, non-alcohol-related liver disease, erectile dysfunction, glomerulonephritis, overactive bladder syndrome as well as obesity are important risk factors that cause the pathogenesis of urogenital tract (2). Oxidative stress is observed with an increase in reactive oxygen species (ROS). Additionally, several studies have shown that ROS is elevated in obese individuals (3). Obesity-induced oxidative stress has an important role in the pathogenesis of urogenital system disorders (4). There is a tendency for sodium to remain in obesity-associated hypertension in both human and animal models. So, this abnormality in sodium homeostasis, lead to the development of hypertension. Natriuretic and anti-natriuretic factors induce these failures. Since the renin angiotensin system (RAS) is the main regulator of sodium and water homeostasis, this can cause abnormalities, especially in the kidneys and other organs of the urogenital system (5). The most well-known abnormality of obesity affecting the kidney is obesity-associated glomerulopathy. It is characterized by glomerulomegaly and may be accompanied by glomerulosis lesions (5, 6). Bladder dysfunctions caused by obesity and/or diabetes (impaired bladder sensation and detrusor contractility) generate significant stress, resulting in increased bladder capacity, limiting normal daily activities, and lowering quality of life. (6). Recent studies have shown that symptoms such as restlessness (62%), incomplete emptying of the bladder (45%) is common in obesity-related urogenital problems. Metabolic syndrome lead to malfunction of bladder in animal models and obese patients because of the chronic inflammation (6). Obesity includes complex problems of metabolic changes

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such as chronic inflammation, and altered lipid metabolism (5). Metabolic alterations in the bladder tissue regarding obesity could be related to urothelial abnormality, and detrusor and autonomous nervous system overactivity (6).

Exercise is a non-pharmacological intervention to prevent or treat the symptoms of obesity-related diseases. Experimental studies have shown that moderate hypertension associated with obesity is reduced by exercise (7). Studies have shown that regular exercise has positive effects on obesity-related health parameters, even without weight loss (8, 9). It is also stated that regular exercise leads to a reduction in adipose tissue, thus reducing the negative effects of obesity on health parameters (9, 10). Swimming exercise was ameliorated morphology of adipose tissue and pancreatic islets of obese animals (11). In addition, several studies have shown strong associations between physical activity levels and circulating leptin and obesity gene expression in adipose tissue (12, 13). Experimental studies have shown that altered lifestyle factors such as exercise affect ROS levels in rats fed a high-fat diet (HFD) (3, 7). Exercise also has a positive effect on RAS by decreasing cardiac angiotensin-converting enzyme in healthy rats (2). Thus, exercise is an effective way to reduce oxidative stress without pharmacological treatment. The aim of this study was to investigate the ameliorative effect of exercise on renal and bladder tissue morphology and oxidative stress markers in HFD-induced obesity using histological, ultrastructural, and biochemical methods.

2. METHODS

2.1. Animals and Experimental Design

Male Sprague Dawley rats (8 weeks old, 200–300 g) were kept in normal plastic cages with free access to food and water. These animals were housed in a room (21 °C) and light–dark cycle (12:12 h). The Animal Care and Ethical Committee for Experimental Animals at Marmara University endorsed the experimental protocols (date: 15.08.2016, protocol code: 089.206.mar).

2.2. Experimental Design

Sprague Dawley male rats (n = 5 in each group) were randomly divided into two main groups according to diet type as standard chow (control: CONT, 6% fat) or HFD (45% fat). After 12 weeks these groups were divided into two subgroups as CONT+EXC and HFD+EXC. During the last 6 weeks of the experiment, these exercise groups maintained their diet for 18 weeks and were trained in daily swimming sessions (60 min/day, 5 days/week). Swimming exercise was done in a plastic tank (60 cm × 150 cm × 45 cm) with warm water at 32 ± 1 °C for 1 hour of 5 days a week. The weight of rats was measured periodically for weekly. At the end of the 18 weeks, ketamine and xylazine were injected intraperitoneally to euthanize the animals. Kidney and bladder samples were processed for histological, ultrastructural and biochemical evaluations.

2.3. Light Microscopic Preparation

Kidney and bladder samples were fixed in 10% neutral buffered formalin solution for light microscopic investigations. These samples were dehydrated with alcohol, cleared with xylene and incubated in paraffin. Paraffin sections were stained with hematoxylin and eosin (H&E) and with periodic acid Schiff (PAS) for histological evaluation. Stained sections were examined under a photomicroscope (Olympus BX51, Tokyo, Japan).

2.4. Transmission Electron Microscopic Preparation

The kidney samples were fixed with 2.5 % glutaraldehyde in phosphate buffered solution (PBS; 0.1 M, pH 7.2), then post-fixed in 1% osmium tetroxide (OsO_4) in PBS (0.1 M, pH 7.2), dehydrated in increasing concentration of ethyl alcohol series and embedded in Epon 812 (Fluka, Sigma–Aldrich Chemical, Steinheim, Switzerland). The urinary bladder samples were fixed in 2.5% glutaraldehyde in PBS (0.13 M and pH 7.4), these tissue samples were en bloc stained with ruthenium red and postfixed with OsO_4 (ratio used 1 part of stock ruthenium red solution: 4 parts of 1% OsO4) for 1 hour. Then dehydrated with alcohol series and embedded in Epon 812 resin (14). Toluidine blue (TB) was used to stain semithin sections, which were then examined under a light microscope. Uranyl acetate and lead citrate were used to contrast ultrathin sections. Ultrathin sections were evaluated under a transmission electron microscope (JEOL 1200 EXII, Tokyo, Japan).

2.5. Measurement of Malondialdehyde and Glutathione Levels

The thiobarbituric acid reactive compounds were determined using a spectrophotometric technique to evaluate tissue malondialdehyde (MDA) levels as an indicator of lipid peroxidation (15). Glutathione (GSH) levels in kidney and bladder samples were determined by the method of Ellman (16). Results of MDA and GSH level were expressed as nmol/g.

2.6. Measurement of Interleukin-6 and Tumor Necrosis Factor – α Levels

Tissue interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were measured with commercial rat TNF-α and rat IL-6 ELISA kits (Bioassay Technology Laboratory). Results were expressed as pg/mL.

2.7. Statistical Analysis

One-way analysis of variance was used to assess the data, followed by Tukey's multiple comparison tests. Prism 6.0 GraphPad software was used for statistical analysis (San Diego, CA, USA). $P<0.05$ was used as the statistical significance level.

3. RESULTS

3.1. Body Weight of Experimental Animals

The body weight of rats in the HFD (P<0.01) and HFD+EXC (P<0.001) groups was significantly higher than the CONT group in 12 weeks. The body weight of HFD (P<0.01) and HFD+EXC (P<0.01) groups was also significantly higher than the CONT group in 18 weeks (Table 1).

Table 1. *Body weight of experimental groups at the begining (1st week), before the exercise training (12th week) and at the end (18th week) of the study. **P < 0.001 and **P < 0.01 vs CONT group. Values are given as mean ± SEM.*

	0.day	12 Week (day 84)	18 Week (day 126)
CONT	224.5±16.5	291.7±6.35	321.4±4.6
CONT+EXC	231.7±6.9	325.9±14.8	356±21.7
HFD	221.1±11.7	353.8±11.7**	384.2±5.4**
HFD+EXC	245.8±13.8	380.4±14.2***	396.1±13**

3.2. Histopathological Results

Normal morphology of renal corpuscles and tubules was noticed in the kidney samples of the CONT and CONT+EXC groups. Degenerated renal corpuscles with dilatation and cellular debris in Bowman space, mild degeneration of tubule epithelium with decrease in PAS positive staining at the apical surface and the presence of cellular debris in the tubule lumen were noticed in the HFD group. Mild glomerular congestion and degeneration of tubule epithelium with PAS positive staining at the apical surface were observed in the HFD+EXC group (Figure 1).

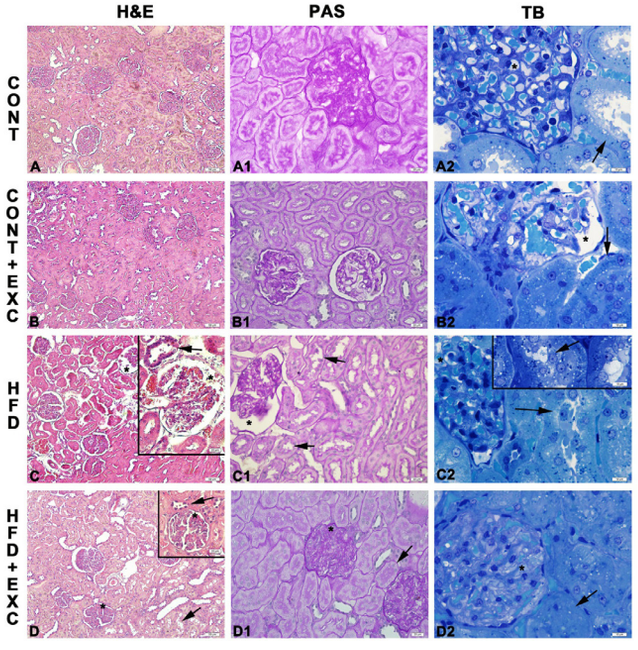

Figure 1. *Representative photomicrographs of kidney samples in the experimental groups. Regular renal corpuscles and tubules are seen in the CONT (A, A2) and CONT+EXC (B, B2) groups. Degenerated renal corpuscles with glomerular congestion and dilated Bowman's space with cellular debris (*), degenerated proximal tubules (arrow) are seen in the HFD group (C, C2). Quite normal morphology in renal corpuscles and decreased degenareted tubules (arrow) are seen in the HFD+EXC group (D, D2). Regular PAS positive stained glomerular (*) and tubular (arrow) basement membranes and apical cytoplasm of proximal tubules are seen in the CONT (A1), CONT+EXC (B1) and HFD+EXC (D1) groups. Degenerated renal corpuscle with dilated Bowman's space (*) and degenerated proximal tubules with decrease of PAS positive staining (arrow) are seen in the HFD group (C1). A-D: H&E staining, A1-D1: PAS staining; A2-D2: TB staining. Scale bars: A-D: 50 µm; insets in C and D and A1-D1: 20 µm; A2-D2: 10 µm.*

Normal bladder morphology with urothelium and a few numbers of mast cells in mucosa were recognized in CONT and CONT+EXC groups. Degeneration in urothelium with decrease of PAS positive staining in apical luminal surface and increase of mast cells in mucosa and migration of mast cells in urothelium were seen in the HFD group. Quite regular urothelium with increase of PAS positive staining in apical luminal surface and a few numbers of granulated mast cells in mucosa were seen in HFD+EXC group (Figure 2).

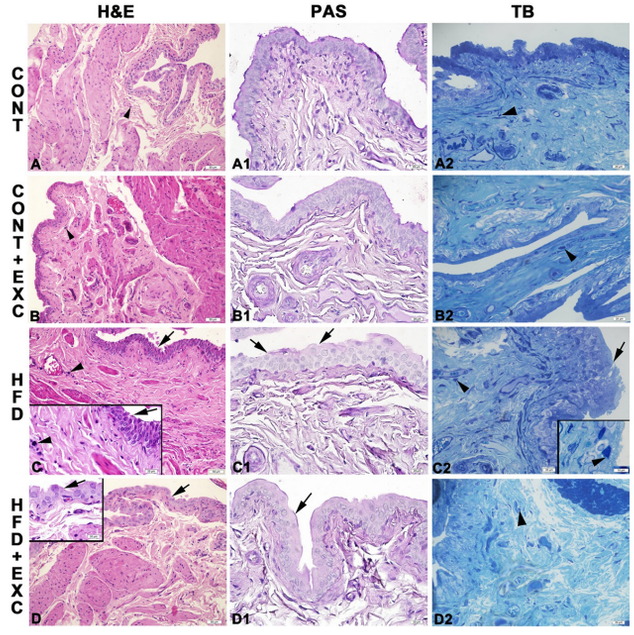

Figure 2. *Representative photomicrographs of bladder samples in the experimental groups. Regular mucosa with urothelium and a few numbers of mast cells (arrowhead) are seen in the CONT (A) and CONT+EXC (B) groups. Degenerated urothelium (arrow) and increase of mast cells (arrowhead) are seen in the HFD (C and C2) group. Quite regular mucosa with urothelium (arrow) is seen in the HFD+EXC (D) group. Regular urothelium with PAS positive stained apical luminal surface (arrow) are seen in the CONT (A1), CONT+EXC (B1) and HFD+EXC (D1) groups. Degenerated urothelium with decrease of PAS positive staining (arrow) in apical luminal surface (arrow) are seen in the HFD group (C1). Regular mucosa with a few number of mast cells (arrowhead) are seen in the CONT (A2), CONT+EXC (B2) and HFD+EXC (D2) groups. Increased mast cells (arrowhead) in mucosa and migrated mast cells (arrowhead) in urothelium (inset) are seen in the HFD group (C2). A-D: H&E staining, A1-D1: PAS staining; A2-D2: TB staining. Scale bars: A-D: 50 µm; insets in C and D, A1-D1 and A2-D2: 20 µm; inset in C2: 10 µm.*

3.3. Ultrastructural Results

Regular proximal tubules with apical microvillus structures and regular pedicels, glomerular capillaries and basement membrane were observed in CONT and CONT+EXC groups. Degenerated proximal tubules with desquamation of microvillus structures, irregular capillary endothelium of glomerulus were seen in the HFD group. Quite regular proximal tubules with microvilli and pedicels, glomerular capillaries and basement membrane were observed in the HFD+EXC group (Figure 3).

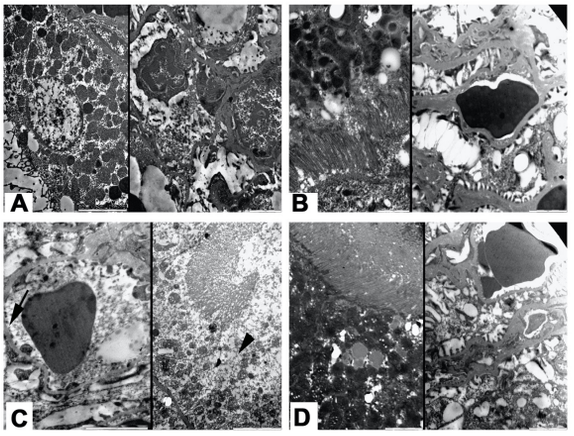

Figure 3. *Representative electronmicrographs of kidney samples in the experimental groups. Regular ultrastructure of proximal tubules, pedicels, glomerular capillaries and basement membrane are seen in the CONT (A), CONT+EXC (B) and HFD+EXC (D) groups. Degeneration in glomerular capillary endothelium (arrow) and degenerated proximal tubule cell with loss of microvilli (arrow head) are seen in the HFD group (D).*

Regular apical urothelial cells with impermeable tight junctions were observed in CONT and CONT+EXC groups. Degenerated apical urothelial cells with penetration of ruthenium red into the intercellular space were observed in the HFD group. Quite regular apical urothelial cells and impermeable tight junctions were observed in the HFD+EXC group (Figure 4).

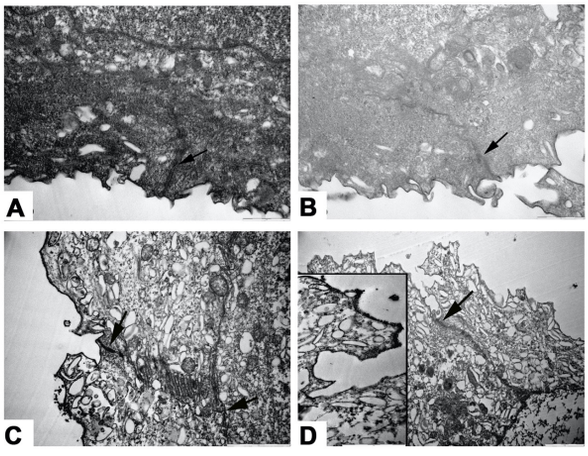

Figure 4. *Representative ruthenium red stained electronmicrographs of urothelium in the experimental groups. Regular ultrastructure of apical urothelial cells with impermeable tight junctions (arrow) are seen in the the CONT (A), CONT+EXC (B) and HFD+EXC (D) groups. Penetration of ruthenium red into the intercellular area (arrow) are seen in the HFD group (C).*

3.4. Biochemical Results

In kidney samples, MDA level was significantly higher (P<0.001) in the HFD group than the CONT and CONT+EXC groups. MDA level was reduced in the HFD+EXC group (P<0.001) compared to the HFD group. GSH level was significantly reduced in the HFD group compared to the CONT (P<0.05) and CONT+EXC (P<0.01) groups. Although statistically not significant, GSH level was increased in the HFD+EXC group compared to the HFD group. The HFD group had higher levels of renal IL-6 and TNF-α than the CONT (P<0.001) and CONT+EXC (P<0.01) groups. When compared to the HFD group, the HFD+EXC group had lower IL-6 (P<0.01) and TNF-α (P<0.001) levels (Figure 5).

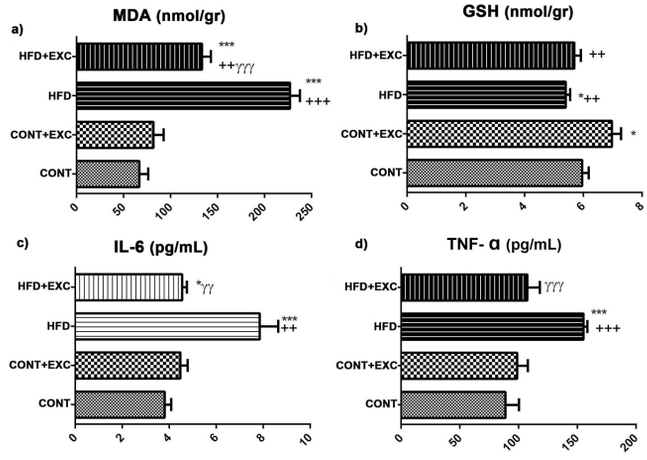

Figure 5. *MDA, GSH, IL-6 and TNF-α levels of kidney samples in the experimental groups. *P<0.05 and ***P<0.001 compared to CONT group; ++P<0.01 and +++P<0.001 compared to CONT+EXC group; γγP<0.01 and γγγP<0.001 compared to HFD group.*

In the bladder samples, MDA level was significantly higher (P<0.001) in the HFD group than the CONT and CONT+EXC groups. The HFD+EXC group had lower MDA levels (P<0.01) than the HFD group. GSH levels in the HFD group were significantly lower than the CONT (P<0.05) and CONT+EXC (P<0.01) groups. However, when compared to the HFD group, this value was higher in the HFD+EXC group (P<0.05). When compared to the CONT and CONT+EXC groups, the HFD group had a higher level of IL-6 (P<0.01). When compared to the HFD group, the HFD+EXC group (P<0.05) had a lower IL-6 level (Figure 6).

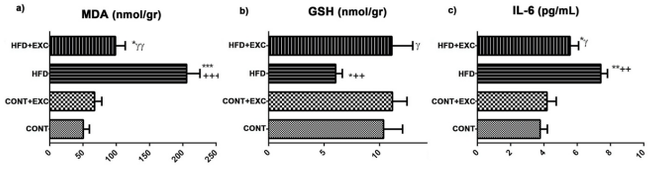

Figure 6. *MDA, GSH and IL-6 levels of bladder samples in the experimental groups. *P<0.05, **P<0.01 and ***P<0.001 compared to CONT group; ++P<0.01 and +++P<0.001 compared to CONT+EXC group; γP<0.05 and γγP<0.01 compared to HFD group.*

4. DISCUSSION

The findings of this study demonstrated that the weight of HFD and HFD+EXC groups higher than the CONT group. Glomerular and tubular morphological damage in kidney, and urothelial damage, increased mast cells in bladder mucosa were found in the HFD group. MDA, IL-6 and TNF-α levels in kidney and MDA and IL-6 levels in bladder were increased and GSH level was decreased in both tissues in the HFD group. However, all these histopathological and oxidative damage parameters were ameliorated in both kidney and bladder tissues in the HFD+EXC group.

Long-term HFD feeding may result in obesity and affect renal lipid metabolism in mice (17, 18). Chronic hyperglycemia and hyperlipidemia regarding obesity effects excess nutrient influx to the kidney (19). Altered lipid metabolism finally causes renal injury, glomerulosclerosis, interstitial fibrosis and albuminuria (17). Sun et al. (2020) reported that HFD induced hyperglycemia and hyperlipidemia and kidney cells imposed upon excess amount of nutrients (19). HFD fed mice showed degeneration in the proximal tubules because of the massive ROS production. Physical capacity, lipid metabolism, and oxidative status substantially improve with exercise (20, 21). Coelho et al (2010) showed that physical activity ameliorates oxidative stress parameters by lowering oxidant production (22). Park et al (2013) showed that regular exercise protects renal injury by reducing oxidative stress (23). Parallel to the previous studies tubular degeneration and altered renal corpuscles morphology were seen in the present study. These tubular and renal corpuscle degenerations might be associated with the increase of oxidative stress parameters in the HFD fed rats. It was observed that HFD induced renal degeneration was ameliorated by the moderate swimming exercise by inhibiting of oxidative stress generation.

Gasbarro et al. (2010) reported that HFD induced bladder dysfunction in the sense of obstruction rather than overactive bladder (24). Bladder fibrosis observed in HFD animals because of the bladder dysfunction (25). ROS are modify protein function by carbonylation in HFD (6). Oberbach et al. (2013) showed that carbonylated proteins were increased in HFD induced urinary bladder degeneration (5). Bladder overactivity is observed in HFD fed rats (26). However, if mice are fed with HFD more than 8 months, they develop voiding dysfunction and reduced urinary tract fibrosis. (27). Inflammation also reported in the fructose diet fed rat bladder (8). Obesity has been linked to increased TNF-α expression in adipose tissue and serum levels (28). But, the relation between the TNF-α and bladder dysfunction has rarely been reported (26). Fan et al. (2014) have been shown that impaired HFD mouse contractility could be ameliorated by TNF-α antogonist treatment (26). Morphological alterations especially for urethelium and the smooth muscle degeneration have been observed in hyperlipidemic rats and fructose fed rats (8, 26). Experimental studies showed that obesity alters blood flow of the bladder and so that causes bladder dysfunction. Exercise increases blood flow of the bladder and so that heals bladder function (29). Exercised animals have increased bladder capacity and larger volumes (7). Additionally, oxidative stress related mast cell degranulation is observed in HFD fed rats (30). Proinflammatory activity also induces mast cell degranulation (31). Parallel with the previous studies, urothelium degeneration, mast cell degranulation in mucosa and increase of MDA and IL-6 level in bladder samples were observed in this study. Moderate swimming exercise improved these morphological and biochemical changes in HFD fed rats by the regulation of oxidative stress generation.

HFD-induced obesity accelerates the production of ROS and oxidative stress. Glutathione S-transferase and MDA levels are important to evaluate lipid peroxidation index and GSH concentration. GSH is important to protect tissues from oxidative damage (3). MDA is an oxidative cell parameter and a product of lipid peroxidation in the cell membrane (32, 33). Increased blood plasma MDA and decreased GSH levels were observed in HFD induced obese rats (3). Moreover, exercise has been reduced MDA level and increased GSH level in heart and aorta tissues in HFD induced obese rats (34). Exercise might be effected for preventing obesity-induced oxidative stress in HFD fed rats by increasing antioxidant enzyme activity and decreasing lipid peroxidation (3). Pro-inflammatory cytokine IL-6 level in kidney was increased in the HFD fed rats (35). This increase in kidney samples might be regarding harmful effects of chronic inflammation and this effect may elevate the lipotoxicity development (35). It was shown that association exists between increased renal lipid accumulation and proinflammatory mediators IL-6 and TNF-α (36). Renal lipotoxicity is also related with glomerulonephritis and proteinuria development (37). TNF-α is also higher in bladder tissue of hyperlipidemic rats. In the present study, it has been observed that IL-6 and TNF – α levels were increased in HFD fed rats comparing to the standard chow fed rats. These parameters were decreased in moderate swimming exercise treated HFD fed rats.

5. CONCLUSION

Our findings showed increase of oxidative and morphological damage in both kidney and bladder in rats fed a high-fat diet. It was observed that the histological damage and altered oxidative stress parameters improved with swimming exercise. Moderate swimming exercise may play a role in the regulation of oxidant/antioxidant balance in obesity induced kidney and bladder damage.

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