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Various endurance training intensities improve GFR and Up-regulate AQP2/GSK3β in lithium-induced nephropathic rats

Shadan Saberi[1†], Mohammad Amin Rajizadeh[1*†], Mohammad Khaksari[2], Azadeh Saber[1], Mohammad Akhbari[1], Soheil Aminizadeh[1,3] and Forouzan Rafie[4,5]

Abstract

Background Lithium is extensively used for mood stabilization in bipolar disorder, but its long-term use can lead to nephrotoxicity, characterized by a reduction in glomerular filtration rate (GFR) and potential progression to end-stage renal disease (ESRD). Exercise has been shown to have protective effects on renal function, yet the impact of varying exercise intensities on lithium-induced nephropathy is not well understood.

Aim This study aimed to investigate the effects of different intensities of endurance training on kidney function and inflammation in a rat model of lithium-induced nephropathy, focusing on the expression of aquaporin 2 (AQP2), glycogen synthase kinase 3-beta (GSK-3β), and SIRT1.

Methods Thirty-five male Wistar rats were divided into five groups: control, lithium-only, lithium with low-intensity exercise (LIT), lithium with medium-intensity exercise (MIT), and lithium with high-intensity exercise (HIT). The lithium-induced nephropathy model was established by administering lithium in food. Exercise groups underwent treadmill training at specified intensities for eight weeks. Fractional excretion of sodium (FENa) was measured, and GFR was evaluated by Cr clearance. ELISA and Western blotting assessed inflammatory markers (TNF-α, IL-10), SIRT1, GSK-3β, and AQP2 expressions in kidney tissues.

Results Lithium significantly reduced Cr clearance and increased FENa compared to controls. All exercise intensities improved Cr clearance and reduced FENa, with HIT showing the most significant improvement. Exercise at all intensities reduced TNF-α levels and increased IL-10 levels, with MIT and HIT significantly enhancing SIRT1 levels. Lithium reduced the expression of GSK-3β and AQP2, whereas exercise increased their expression across all intensities.

Conclusion Endurance training, particularly at high intensity, significantly mitigates lithium-induced renal impairment by improving GFR, reducing inflammation, and enhancing the expression of renal protective proteins. These findings suggest that tailored exercise regimens could be beneficial for patients undergoing long-term lithium therapy to prevent renal damage.

[†]Shadan Saberi and Mohammad Amin Rajizadeh contributed equally to this work.

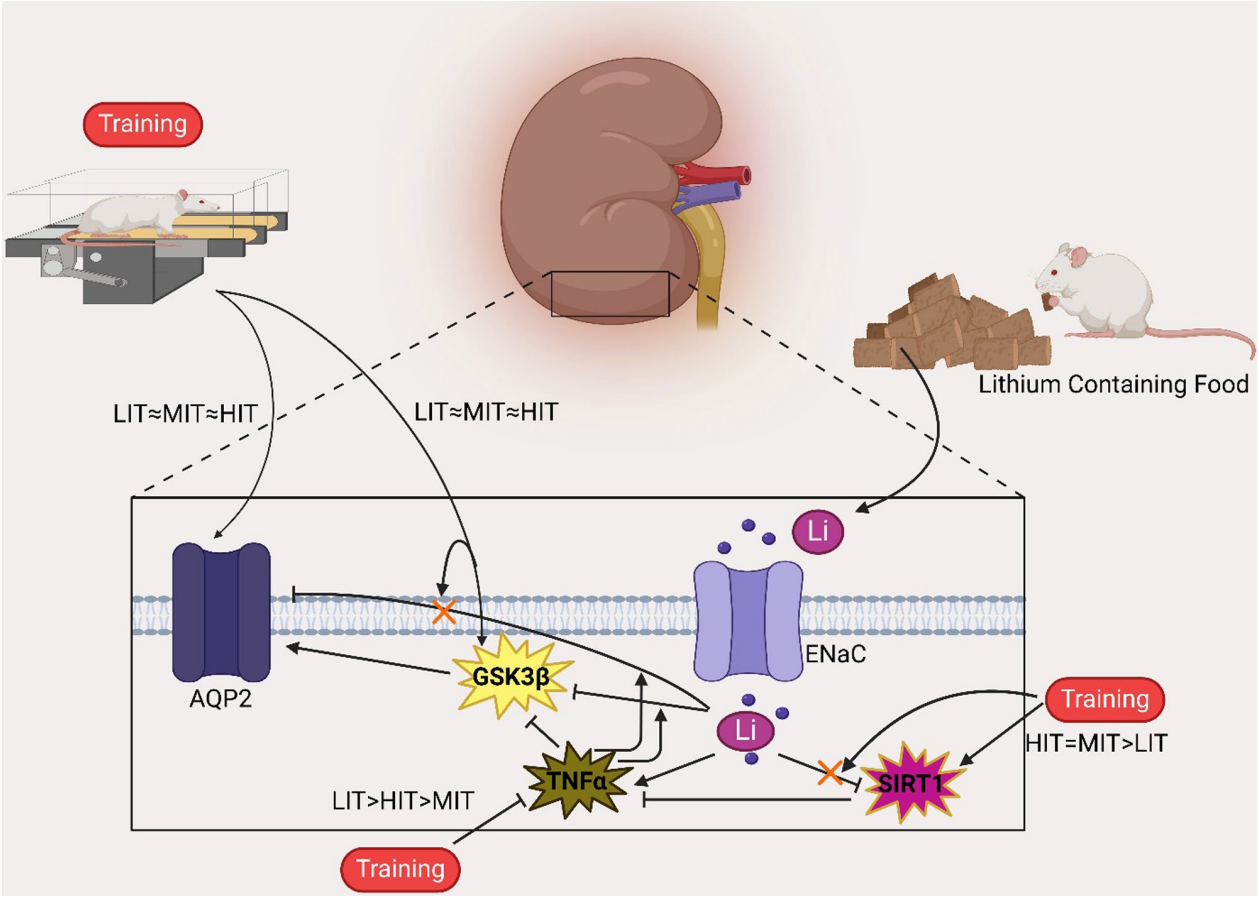
*Correspondence:
Mohammad Amin Rajizadeh
aminrajizadeh@yahoo.com

Full list of author information is available at the end of the article

Clinical trial number Not applicable.

Keywords Lithium-induced nephropathy, Endurance training, Exercise intensity, Glomerular filtration rate, Inflammation, Aquaporin 2, GSK-3β, SIRT1

Graphical Abstract



Introduction

Lithium is the first-line remediation for mood stabilization in bipolar patients [1]. Due to long-term administration, this drug has many irreversible harmful effects [2]. Diabetes insipidus is one of the known side effects of lithium consumption [3]. 15% of patients taking lithium experience a significant decrease in glomerular filtration rate (GFR), which is a key aspect of lithium-induced nephrotoxicity [3, 4]. In individuals treated with lithium, the decline in GFR is a gradual process, requiring more than 20 years to lead to end-stage renal disease (ESRD) [3]. The mechanism of lithium-induced nephrotoxicity involves the targeting of Glycogen synthase kinase 3-beta (GSK-3β) in the adult kidney, leading to apoptosis and proliferation inhibition [5]. Inflammation is another probable mechanism of lithium-induced nephrotoxicity through increasing the serum levels of TNF-α and IL-1β [6, 7]. Sirtuin 1 (SIRT1), an oxidized nicotinamide adenine dinucleotide-dependent protein deacetylase, has a protective role in AKI (acute kidney injury) [8]. In the kidney, SIRT1 is widely expressed in tubular cells and podocytes. SIRT1 exerts renal protective effects by deacetylating and regulating transcriptional factors like p53 and NFκB, contributing to kidney health [9, 10].

Aquaporins are a family of water channels found in biological membranes. There are 13 isoforms in human tissues, among which aquaporin 2 (AQP2) is expressed in the principal cells of the collecting ducts. AQP2 is crucial for regulating the permeability of the collecting ducts and maintaining fluid balance. The relocalization of AQP2 toward the apical membrane to reabsorb water is dependent on antidiuretic hormone (ADH) [11]. Several studies have shown that exercise can reduce mortality risk and enhance the metabolism of renal fatty acids [12, 13]. Aerobic exercise has demonstrated protection against kidney damage caused by cisplatin toxicity and

renal ischemia in rats by reducing inflammatory cytokines and oxidative stress [14]. However, the impact of varying exercise intensities on preventing renal disorders remains uncertain. A study found that moderate exercise notably reduces inflammation in mice with Lupus Nephritis [15], while Ishikawa's research in 2012 indicated that low-intensity exercise can slow the progression of early diabetic nephropathy [16]. Further exploration is necessary to determine the optimal exercise intensity and duration for enhancing kidney health. Understanding the mechanistic impact of exercise on renal function could lead to personalized exercise recommendations for individuals at risk of kidney disease. This study aimed to examine the effects of exercise at various intensities on lithium-induced nephropathy, considering the unclear precise mechanisms of chronic lithium consumption on the kidney and unclear mechanisms of effects of exercise on kidney diseases, which could be associated with exercise intensity. The investigation focused on assessing alterations in AQP2 and GSK3β to explore their potential protective effects of exercise in improving GFR. Additionally, we evaluated inflammation and SIRT1 to elucidate their roles as mechanisms through which exercise may mitigate renal injury induced by chronic lithium consumption, thereby providing insights into how exercise intensity influences kidney health."

Material and methods

Animals, grouping, and lithium-induced acute renal injury model

This study included 35 male Wistar rats weighing 200–250 g ($n=7$). Animals were purchased from the Kerman University of Medical Sciences animal farm and kept under standard conditions (23 ± 2 °C, relative humidity 40–45%, light/dark period 12 h). The animals had free access to water and food during the research period. All experiments were approved by the ethics committee of Kerman University of Medical Sciences (Ethics No: IR.KMU.AEC.1402.013). The animals were randomly divided into five groups: 1- Control group (CTL): the animals did not receive any special intervention during the 8 weeks of the study and had a normal diet. 2- Lithium group: the animals received lithium for one week at 40 mmol/kg of dry food weight and then continued until 8 weeks at a dose of 60 mmol/kg [17]. 3- Lithium group + low-intensity exercise (LIT): The animals received lithium according to the mentioned doses and ran on a low-intensity treadmill during the 8 weeks. 4- Lithium group + exercise with medium intensity (MIT): animals received lithium during the 8 weeks of the study, exercised on the treadmill with moderate intensity. 5- Lithium group + high-intensity exercise (HIT): the animals of this group received lithium and ran on the treadmill with high intensity during the 8 weeks of the study. To prepare lithium-containing food and ensure its uniform distribution in the food, the required amount of lithium was added to the water according to the mentioned dose. Then, the animal food was turned into a paste by mixing it with water containing lithium; then, it was turned into dry pellets. The duration of exercise was 8 weeks. One day after the last exercise session, the animals were placed in metabolic cages individually for 24 h to collect urine samples. Then, the animals were euthanized with a high dose of ketamine (100 mg/kg) and xylazine (80 mg/kg), and their blood and kidney samples were collected.

Exercise protocol

In the familiarization phase, the rats were trained on the treadmill at 15 m/min for 15 min for two weeks. The Vmax was measured to calculate the maximal oxygen consumption (VO2max). At first, rats performed an incremental test for obtaining the Vmax (sedentary male rats; $y=29.3x+2.1$; $y=$VO2max, $x=$Vmax-m/s). The incremental test was initiated with a 10 m/min warm-up that gradually increased (3 m/min) until exhaustion [18]. After the incremental test, the lactate levels were measured using a lactometer (Lactate Scout Company/Code: 37, Germany), and values above 6 mmol/L were considered high-intensity [19]. Then, VO2 max was calculated. Three types of treadmill exercise training protocols were designed for three different groups of animals based on the Vmax: low intensity (LIT: 35–45% of Vmax), moderate intensity (MIT: 65–70% of Vmax), and high intensity (HIT: above 80% of Vmax). Increasing load with increasing speed and checking every two weeks of Vmax were done. The training course was performed for 8 weeks, 5 days a week, for about 30 min with the same distance in all training groups per session (Table 1) [20]. To apply the stress caused by the device, the control group and lithium

Table 1 Exercise training protocol

Weeks	1,2	3	4	5	6	7	8
HIT Time (minute)	15	14	13	13	13	13	13
HIT Speed (m/min)	18	22	25	28	31	32	33
MIT Time (minute)	19	18	17	17	17	18	18
MIT Speed (m/min)	14	17	19	21	23	23	24
LIT Time (minute)	30	28	27	26	25	26	27
LIT Speed (m/min)	9	11	12	14	16	16	16

users were placed on the treadmill without doing exercise [21].

Sampling

To collect urine and calculate GFR, the animals were placed individually in a metabolic cage for 24 h after the last exercise session (to prevent the acute effect of exercise). At the end of the research, the animals were sacrificed with an intraperitoneal injection of a lethal dose of Ketamine (100 mg/kg) and Xylazine (80 mg/kg), and the left kidney was immediately frozen in liquid nitrogen and stored in a -80 °C freezer for measuring biochemical indices and molecular studies.

Glomerular filtration rate (GFR) and Fractional excretion sodium (FENa) calculation

The glomerular filtration rate was calculated via creatinine (Cr) clearance using the following formula:

$$GFR = \frac{\mathrm{UCr} \times \mathrm{V}^{\circ}}{\mathrm{PCr}}$$

UCr: urinary creatinine concentration (mg/dl), PCr: plasma creatinine concentration (mg/dl), and V°: urine volume (µl/min). Cr clearance presented as microliters/minute/mg kidney weight (µl/min/mgKW) [22].

Also, the FENa was calculated based on the following formula: (P_{Na}: Plasma sodium concentration, U_{Na}: Urine Sodium concentration, PCr: plasma creatinine concentration, UCr: urine creatinine concentration) [23].

$$FENa\% = \frac{\mathrm{UNa} \times \mathrm{PCr}}{\mathrm{PNa} \times \mathrm{UCr}}$$

Biochemical evaluations

To measure the amounts of TNF-α (DuoSet Co, Cat No: DY510-05), IL-10 (DuoSet Co, Cat No: DY522-05), and SIRT1 (CUSABIO Co, Cat No:CSB-EL021339RA) in the kidney tissue, 100 mg of frozen tissue was used, it was taken out of the freezing state at room temperature and cooled with phosphate buffer solution. Homogenized on ice, then centrifuged for 20 min at 13,000 rpm, and the supernatant was measured using the corresponding ELISA kits [24].The urine and serum levels of creatinine were measured by standard kits (Pars Azmoon, Tehran, Iran) using an autoanalyzer (Selectra-XL, Vital Science, Netherlands). The urine and serum sodium levels was measured by flame photometry (Corning, Halstead, Essex, UK).

Western blotting

The renal tissue was homogenized in ice-cold lysis buffer and incubated for 30 min. The samples were centrifuged at 12,000 x g, 4 °C for 10 min, and their protein concentration was determined using the Bradford method. Proteins were separated by size using SDS-PAGE and then transferred onto a polyvinylidene fluoride (PVDF) membrane. The PVDF membrane was incubated in the blocker solution overnight at 4 °C. In the next step, the PVDF membranes were incubated with related antibodies (GSK3β (Santa Cruze, sc-81462) and AQP2 (Santa Cruz, sc-515770) for 3 h at room temperature. After being washed three times with Tris-buffered saline with 0.1% Tween 20 (TBST) (5 min each time), the PVDF membrane was incubated with horseradish peroxidase (HRP)-conjugated goat anti-mouse IgG (SC-516102) for 1 h at room temperature. After washing with TBST, enhanced chemiluminescence (Thermo Fisher Scientific, Inc.) was used to observe the protein bands in a dark room. Beta actin (sc-47778) was used as housekeeping control, and the protein band density was quantified using Image J software.

Statistical analysis

Prism version 8 software was used for statistical analyses. The normality of the data was checked with the Shapiro-Wilk test. One-way analysis of variance and Tukey's post hoc test were used to compare the groups in normally distributed data, and Kruskal Wallis followed by Mann Whitney post hoc test for non-normal distributed data. The data are expressed as mean ± SEM and the difference is considered significant at $P < 0.05$.

Results

The effects of exercise on serum lithium, and body weight following renal injury

Serum lithium was measured to confirm the effect of chronic lithium intake. Our findings revealed that 8 weeks of lithium consumption increased serum lithium compared to the control group. All intensities of training reduced serum lithium compared to the lithium group significantly ($P < 0.05$) (Fig. 1 A). All groups had no significant difference in body weight (Fig. 1 B).

The effects of exercise on serum creatinine,urine creatinine, GFR, and FENa% following renal injury

Our findings revealed that lithium increased serum Cr while reducing urinary Cr ($P < 0.001$, $P < 0.05$, respectively). HIT training reduced serum Cr and MIT training increased urinary Cr compared to the lithium group significantly ($P < 0.05$) (Fig. 2A and B). Also, lithium reduced Cr clearance and increased FENa% compared to healthy animals. However, high-intensity training could increase Cr clearance compared to the lithium group ($P < 0.01$); all intensities of training could reduce FENa% (Fig. 2C and D).

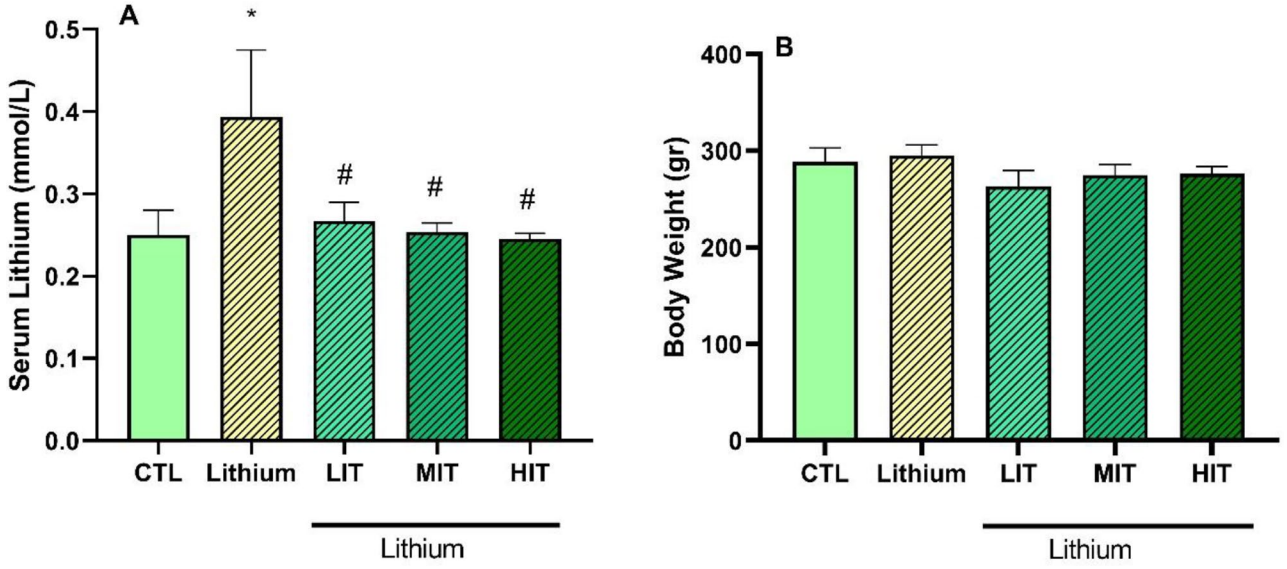


Fig. 1 The effects of different training intensities on serum lithium (**A**) and body weight (**B**) ($n=7$). LIT: Low-intensity training, MIT: Medium intensity training and HIT: High-intensity training. Data is presented as Mean ± SEM.* $P<0.05$ & ** $P<0.01$ & *** $P<0.001$ vs. CTL# $P<0.05$, ## $P<0.01$ & ### $P<0.001$ vs. Lithium. One-way ANOVA test was used for data analysis

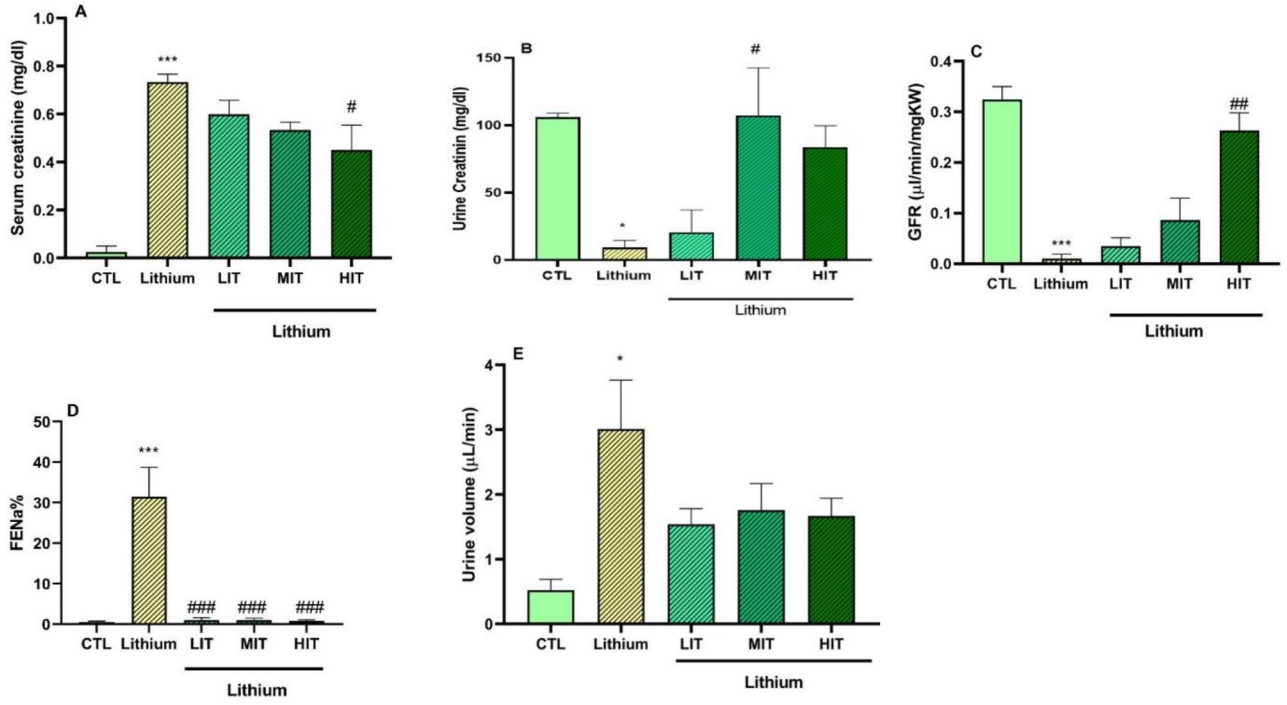


Fig. 2 The effects of different training intensities on serum Cr (**A**), urinary Cr (**B**), GFR (**C**), FENa (%) (**D**) and urine volume (**E**) ($n=7$). LIT: Low-intensity training, MIT: Medium intensity training and HIT: High-intensity training. Data is presented as Mean ± SEM.* $P<0.05$ vs. CTL# $P<0.05$ vs. Lithium. A one-way ANOVA test was used for data analysis

The impacts of exercise on inflammation following renal injury

Our results showed that lithium increased the level of TNF-α in the kidney tissue compared to the healthy rats ($P<0.001$). At the same time, all intensities of exercise training diminished the level of TNF-α compared to the lithium group ($P<0.01$ for LIT & $P<0.05$ for HIT). On the other hand, based on our findings, the level of IL10 was reduced following lithium consumption in the kidney tissue compared to the healthy animals ($P<0.05$). All exercise intensities increased this anti-inflammatory

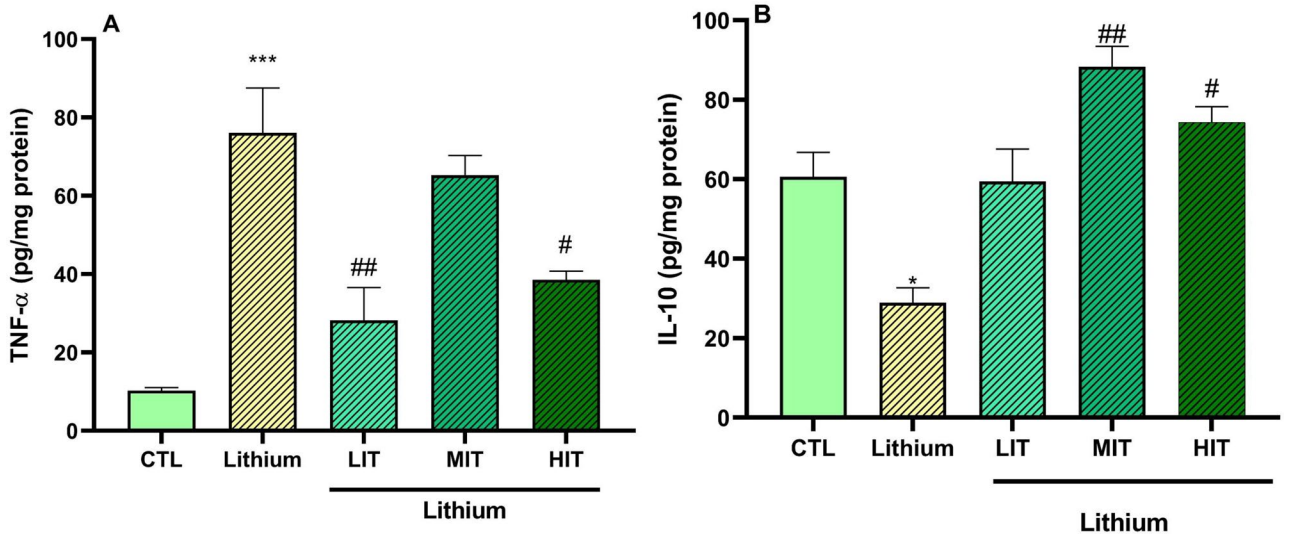


Fig. 3 The effects of different training intensities on inflammatory cytokines ($n=4$). LIT: Low-intensity training, MIT: Medium intensity training, and HIT: High-intensity training. Data are presented as Mean ± SEM.* $P<0.05$ & *** $P<0.001$ vs. CTL. # $P<0.05$ & ## $P<0.01$ vs. Lithium. A one-way ANOVA test was used for data analysis

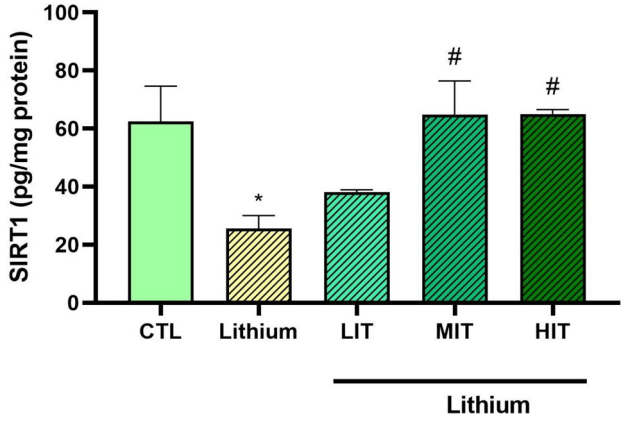


Fig. 4 The effects of different training intensities on SIRT1 levels ($n=4$). LIT: Low-intensity training, MIT: Medium intensity training and HIT: High-intensity training. Data are presented as Mean ± SEM.* $P<0.05$ vs. CTL. # $P<0.05$ vs. Lithium. A one-way ANOVA test was used for data analysis

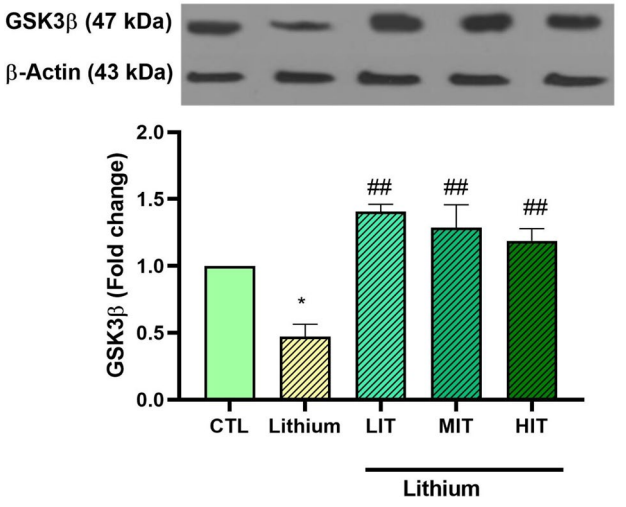


Fig. 5 The effects of different training intensities on the relative density of GSK3β protein expression (normalized to the β-Actin) ($n=4$). LIT: Low-intensity training, MIT: Medium intensity training, and HIT: High-intensity training. Data are presented as Mean ± SEM.* $P<0.05$ vs. CTL. ## $P<0.01$ vs. Lithium. A one-way ANOVA test was used for data analysis

cytokine ($P<0.01$ for MIT & $P<0.05$ for HIT) (Fig. 3 A&B).

The effects of exercise on SIRT1 level following renal injury

Our findings disclosed that lithium consumption significantly diminished the SIRT1 level in the kidney tissue ($P<0.05$). However, MIT and HIT increased SIRT1 levels ($P<0.05$) (Fig. 4).

The impacts of exercise on GSK3β expression following renal injury

Our observations disclosed that lithium consumption diminished the expression of GSK3β compared to the control group ($P<0.01$), while all intensities of exercise increased this expression ($P<0.01$) (Fig. 5).

The effects of exercise on AQP2 expression following renal injury

Our results disclosed that lithium consumption diminished the expression of AQP2 compared to the control group ($P<0.05$). At the same time, all intensities of exercise increased this expression ($P<0.01$ for low intensity & $P<0.05$ for medium and high intensities) (Fig. 6).

Discussion

Many studies have indicated that the intensity of exercise [25], the timing of exercise initiation [26], and the Protocol of exercise [27] can either diminish or improve

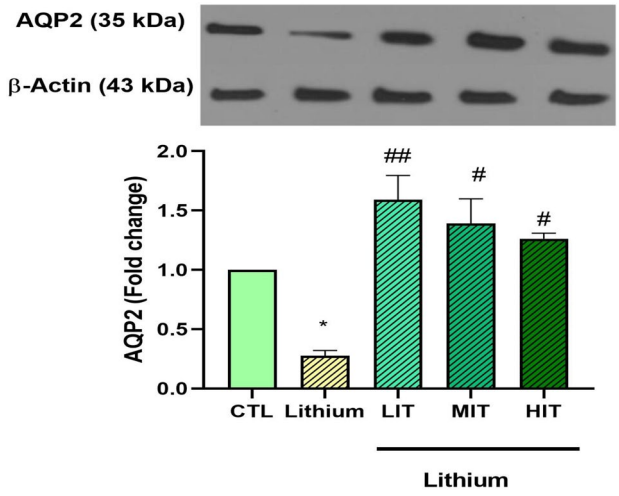


Fig. 6 The effects of different training intensities on the relative density of AQP2 protein expression (normalized to the β-Actin) ($n=4$). LIT: Low-intensity training, MIT: Medium intensity training, and HIT: High-intensity training. Data are presented as Mean ± SEM.* $P<0.05$ vs. CTL. # $P<0.05$ & ## $P<0.01$ vs. Lithium. A one-way ANOVA test was used for data analysis

the effectiveness of exercise [28]. Additionally, previous studies have reported the impact of lithium on kidney function [29, 30]. In this study, we conducted a novel investigation to compare the impacts of various intensities of endurance exercise on lithium-induced nephropathy. We also evaluated the potential effects of exercise on the expression of AQP2 and GSK3β proteins and inflammation in kidney tissue.

Our study found that treatment with lithium for eight weeks led to increase in serum lithium (SLi) levels, polyuria, natriuresis, and kidney damage. This was accompanied by heightened inflammation and decreased SIRT1, GSK3β, and AQP2 expression levels. However, endurance exercise at all intensities (high, moderate, and low) significantly improved the renal impairments caused by lithium and aided in kidney damage recovery. HIT showed the most significant improvement.

Our results also indicated that lithium reduced Cr clearance and increased serum Cr levels, while all exercise intensities restored them, with high-intensity exercise appearing to be the most effective. In line with our results, Leite et al. found that high-intensity exercise was more effective than continuous exercise in reducing inflammation markers in female rats with cisplatin nephrotoxicity [31]. Similarly, Tucker (2012) discovered that high-intensity interval training (HIIT) was more effective than low-intensity exercise at increasing the expression of SOD1 and catalase enzymes in a model of chronic kidney disease (CKD) caused by nephrectomy and ischemia-reperfusion [32]. In contrast, a 2018 study by Espada revealed that high-intensity resistance training (HIIRT) led to early muscle and kidney damage, with significant increases in creatine kinase, myoglobin, SCr, microalbuminuria, and urinary markers of renal tubular damage [33]. On the other hand, a study by Ishikawa in 2012 revealed that moderate and low-intensity exercise improved kidney function in diabetic rats [16]. Serum Cr concentration is affected by.

muscle mass and physical activity; therefore, it is recommended to assess kidney function using serum cystatin C (SCys-C) in individuals engaged in exercise. In contrast, several studies have indicated that these two biomarkers are altered in parallel during exercise training. A study involving young, healthy adults indicated that two exercise protocols (endurance and speed training) had similar effects on SCr and SCys-C levels in both the acute and chronic phases [34]. Moreover, three intensities of exercise training in healthy elderly individuals (some of whom had renal dysfunction, estimated GFR, [eGFR] < 60 mL/min/1.73 m2) did not change SCr or Scyc-C levels, confirming that acute mild to severe exercise training did not show harmful effects on renal function [35]. Another study revealed that GFR estimated based on Cr and Cys-C in CKD patients assessed the renal function similarly at baseline and after 12 months of exercise training [36]. Although exercise is supposed to increase serum Cr, the creatinine lowering effect of exercise remains in these experiments.

In our study, lithium increased FENa and urine volume while reducing the expression of AQP2, GSK3β proteins, and Cr clearance. However, at all three exercise intensities, these parameters improved by lowering serum lithium levels, FENa and urine volume and increasing the expression of AQP2, GSK3β proteins, and Cr clearance, with no significant difference observed between the exercise intensities. The increase in FENa can be explained by greater sodium excretion due to the competitive effect of lithium on reabsorption through ENaC in the distal tubules and a reduction in Cr clearance; both factors contribute to the elevation of FENa. Previous studies have explained the involvement of down-regulation of AQP2 and AQP3 in lithium-induced diabetes insipidus, while sodium transporters were not implicated [17].Similar protective results of exercise training have been observed in other studies. Almeida et al. (2022) investigated how eight weeks of swimming exercise could protect the kidneys of cisplatin-injured mice. They found no significant difference in Nrf2 gene expression at the three exercise intensities [37]. Also, Sari et al. (2024) examined how different levels of exercise affected body weight, body mass index, and kidney damage in mice given fructose. They found that SCr levels were reduced by moderate-intensity training (MIT) but not low- or high-intensity training (LIT, HIT). The authors explained that this difference was related to LIT, which was not adequate in preventing fat accumulation or metabolism impairment in the kidneys. At the same time, HIE induced too much distress

in the animals, preventing renal protection. In spite of renal function improvement, none of the exercise intensities significantly improved the glomerulosclerosis score or interstitial fibrosis [28]. In contrast to Sari et al., HIT improved renal function significantly by reducing SCr and Cr clearance in our study. This discrepancy may stem from variations in exercise type and animal species. Fructose-received mice experienced swimming against a 9% body weight load, which might be stressful for animals, while the rats in our study ran on a treadmill that is less stressful and not life-threatening. Our findings indicated that endurance exercise in all intensities had protective effects against kidney injury induced by chronic lithium consumption. Based on our observations, the possible mechanisms of this renoprotection may involve an increasing SIRT1, an anti-inflammatory cytokine, IL-10 (primarily in MIT and HIT), and a reduction in the pro-inflammatory TNF-α (mostly in LIT and HIT). However, further pharmacological or genetic inhibitory experiments are needed to confirm these results. Additionally, renal function biomarkers such as SCr and Cr clearance improved with HIT. These differences can be explained by complicated factors that regulate renal function, including autonomic nervous system (ANS), hemodynamic condition, autacoids secreted from renal tissue, and renin-angiotensin system (RAS). Literature shows that different exercise regimen activates RAS differently; for instance, moderate-intensity continuous exercise (MICE) reduced serum levels of angiotensin-converting enzyme (ACE), while high-intensity interval exercise (HIIE) increased serum levels of angiotensin-converting enzyme 2 (ACE2). Neither of these two exercise protocols influenced serum levels of angiotensin (Ang) II or Ang 1–7, but urinary Ang 1–7 increased by both [38]. Considering the activation of the protective non-classic arm of RAS by MICE and HIIE, these exercises, especially MICE, are suggested for hypertensive individuals to help control blood pressure. In line with this research, our previous study indicated the cardioprotective effect of MIT compared to LIT or HIT in lithium-treated rats [21]. Moreover, besides activating the RAS, the type and intensity of exercise also affected ANS stimulation. A study found that moderate to high-intensity exercise enhances cardiac control by the ANS [39]. Additionally, an article [40] reviews the effects of different types of exercise on renal diseases. The study suggests that long-term moderate-intensity exercise protocols benefit patients undergoing hemodialysis or renal transplantation. In our study, while different exercise intensities effectively reduced inflammatory markers, renal function improved with HIT.

Despite lithium being the most effective remediation for bipolar disorder, its long-term prescription is accompanied by caution because of side effects, including nephrotoxicity characterized by reduced GFR, polyuria, and natriuresis [29]. One of the mechanisms of lithium-induced kidney damage is inflammation [41]. Our results showed that lithium could increase inflammation by increasing TNF-α and reducing IL10. In agreement with our results, it has been shown that lithium increases kidney inflammation via ROS/NF-κB/NLRP3 pathway activation [30]. Additionally, Erbas et al. demonstrated that lithium increases TNF-α in mouse kidneys [42]. Vian has reported the anti-inflammatory effects of exercise in chronic kidney disease [43], and in numerous other studies involving various tissues, including the kidneys, heart, and lungs [44–46]. Potential mechanisms for the anti-inflammatory effects of exercise include reducing visceral fat mass (by decreasing adipokine release), macrophage infiltration into fat tissue, circulating pro-inflammatory monocytes, toll-like receptor expression, increasing cortisol, adrenaline, fetuin-A levels [28, 47], and regulatory T cells in circulation [44, 45, 48].

Our results also showed that SIRT1 levels decreased following lithium-induced kidney injury. Other studies have also demonstrated reduced SIRT1 levels in various animal models of kidney injury [49–51]. Exercise increased SIRT1 expression in the kidney tissue of experimental diabetic animals [52]. SIRT1 is the most studied isoform of the sirtuin family in the kidney and is widely expressed in tubular cells and podocytes [53]. By regulating various transcription factors for deacetylation, reducing interstitial fibrosis, inhibiting podocyte and tubular cell apoptosis, suppressing inflammation, improving mitochondrial function, and regulating blood pressure, SIRT1 provides renal protective effects [54].Thus, decreased SIRT1 associated with lithium may contribute to the initiation and progression of kidney diseases, whereas increased SIRT1 levels after exercise may mitigate kidney damage.

In our study, although all three intensities (high, moderate, and low) increased the anti-inflammatory cytokines IL-10 and SIRT1, moderate and high-intensity exercise groups were significantly effective. These findings are consistent with previous studies on the anti-inflammatory effects of exercise in various diseases. In Leite et al., three different intensities of aerobic exercise were examined in AKI-induced mice with cisplatin, and high-intensity exercise (HIIT) was more effective than moderate-intensity continuous exercise in reducing kidney TNF-α, IL-1β, IL-6, MCP-1 levels, and macrophage infiltration [31]. Juszczak et al. also demonstrated that moderate-intensity exercise could reduce TNFα, IL-1β, IL-6, and MCP-1 levels in chronic kidney disease induced by obesity in high-fat diet-fed mice by activating the AMPK pathway [55]. Sossdorf et al. (2013) reported that both high- and low-intensity running for six weeks could reduce urea and creatinine levels, improve kidney

function, and decrease inflammatory markers such as IL-6 and IL-10 in sepsis-induced AKI models [56]. However, Ishikawa et al. (2012) found moderate and low-intensity exercise improved renal function in diabetic KK-Ay mice. Both intensities reduced urinary albumin excretion and podocyte numbers, but moderate exercise increased HIF-1α expression, potentially exacerbating renal ischemia. Low-intensity exercise attenuated early diabetic nephropathy progression [16].

The urinary concentration mechanism mediated by ADH is disrupted by lithium treatment [57]. Several mechanisms have been proposed to explain the molecular basis of this effect. Typically, ADH binding to the V2 receptor in collecting duct epithelial cells activates adenylyl cyclase, increases cAMP levels, and stimulates AQP2 expression and localization on the luminal membrane to increase water permeability. Lithium enters the collecting duct epithelial cells via epithelial sodium channels (ENaC), inhibits adenylyl cyclase, reduces cAMP production, and decreases AQP2 expression [58]. Moreover, GSK3β, which mediates ADH function in collecting duct cells, is inhibited by lithium treatment [59].

The inhibition of GSK3β mediated by lithium occurs through direct and indirect mechanisms. The direct inhibitory mechanism involves lithium binding ambiguously to the GSK3β molecule, leading to its inhibition. In contrast, the indirect mechanism entails phosphorylation of a specific site (Serine-9) on the N-terminal of the GSK3β molecule [59]. It has been reported that GSK3β can regulate adenylate cyclase activity, expression, and trafficking of AQP2. Additionally, inhibition of GSK3β has been shown to regulate cyclooxygenase 2 (COX-2) and increase prostaglandin E2 (PGE2) production. COX-2 and PGE2 have been implicated in inhibiting water reabsorption by counteracting ADH function [60].

Moreover, the role of inflammation in altering AQPs expression has been reported in renal diseases. In UUO mice treated with renin inhibitors, AQP2 expression improved by suppressing inflammasomes and activating IL-1β [61]. Another study demonstrated increased AQP2 expression by alleviating diet-induced inflammation in kidney tissue [62]. Natriuresis is another sign of lithium toxicity. In lithium-induced NDI rats, expression of α, β, and γ ENaC subunits decreased [63, 64], which could explain the sodium wasting observed in our results. Consistent with previous studies, our findings demonstrated that lithium intake led to inflammation with increased TNF-α, decreased IL-10, and SIRT1, subsequently reducing GSK3β and AQP2 expression in kidney tissue. Meanwhile, different intensities of endurance training increased the expression of these proteins and facilitated Na^+ excretion while reducing renal inflammation. Thus, exercise may reverse the renal adverse effects of lithium.

It's essential to find non-pharmacological methods to prevent kidney damage caused by lithium. Our study not only explained how lithium can be toxic to the kidneys but also examined how exercise can help reduce its negative effects. However, it's recommended that future studies compare different exercise plans and durations in lithium-induced nephropathy models.

The severity of lithium-induced nephropathy is time-dependent. It was initiated by urine concentration impairment after several weeks of lithium therapy and progressed to chronic kidney disease and ESRD after 10–20 years [1]. Since bipolar disorder usually begins between the ages of 15 and 24, the duration of lithium administration might be more than 30 years, so the development of chronic kidney disease is prevalent in bipolar patients. Although there are some medical treatments, such as amiloride, to reduce lithium nephrotoxicity, finding non-medical treatment to prevent renal injury is valuable.

A sedentary lifestyle is common in bipolar patients [65]. Physical activity was associated with better functioning, quality of life, and reduced depressive symptoms. Moreover, it has been shown that bipolar patients suffer from balance disorders and skeletomuscular impairment in old ages [66, 67]. Therefore, the importance of suggesting suitable exercise training for bipolar patients with possible comorbidity is evident. Our result revealed the beneficial effects of exercise in different intensities, so endurance exercise training could be considered a non-medical or alternative care option in patients treated with lithium following their physical and neuromuscular abilities.

Conclusion

Our findings disclosed that endurance training at low, medium, and high intensities, particularly high-intensity exercise, significantly enhances kidney function. This results in increased GFR, reduced polyuria, decreased sodium excretion, and lower serum Cr levels. The potential mechanisms behind the improvement in GFR and renal injury involve heightened expression of GSK3β and AQP2, elevated levels of SIRT1, and decreased inflammation (Fig. 6).

We recommend further exploration of the long-term adverse effects of lithium treatment on the kidneys. This investigation should consider age, gender, disease duration, and lithium usage. Endurance training with different intensities is suggested to eliminate renal adverse effects of long-term lithium therapy in considering the patients' age and neuromuscular condition.

Limitations

A limitation of this study was the lack of histological examination of kidney tissue. On the other hand, future studies should use genetic and pharmacological inhibitors to investigate the pathways involved further.

Supplementary Information

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Supplementary Material 1

Author contributions

Shadan Saberi: ConceptualizationMohammad Amin Rajizadeh: Investigation and Writing of original draftMohammad Khaksari; Methodology Soheil Aminizadeh: MethodologyAzadeh saber: InvestigationForouzan Rafiei: Investigation and Writing of original draftMohammad Akhbari: Writing of original draft.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

The animals used in the experiments were owned by the Kerman University of Medical Sciences and housed in their animal house. The experiments were carried out according to ARRIVE guidelines and the US National Institutes of Health, with the approval of the Research and Ethics Committee of Kerman University of Medical Sciences (Ethic No. IR.KMU.AEC.1402.013).

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[2]Endocrinology and Metabolism Research Center, Kerman University of Medical Sciences, Kerman, Iran
[3]Department of Physiology and Pharmacology, Afzalipour School of Medicine, and Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[4]Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[5]Department of Medicine, Division of Geriatrics & Gerontology, Emory University School of Medicine, Atlanta, GA, USA

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