The Effects of Two Different Dietary Regimens During Exercise On Outcome of Experimental Acute Kidney Injury

Nazanin Sabet
Kerman University of Medical Sciences

Zahra Soltani (✉ soltaniy@yahoo.com)
Kerman University of Medical Sciences

Mohammad Khaksari
Kerman University of Medical Sciences

Alireza Raji- amirhasani
Kerman University of Medical Sciences

Research

Abstract

Introduction: Acute kidney injury (AKI) is a syndrome characterized by rapid loss of excretory function of kidney. One of the molecules considered in the treatment of renal failure is the silent information regulator (SIRT1). In this study, the effect of two different diets during exercise on AKI was investigated.

Materials and Methods: A number of rats were randomly divided into four groups; control without exercise, control with exercise, exercise + calorie restriction (CR), and exercise + time restriction (TR). Each group was divided into two subgroups of without AKI and with AKI (six rats in each group). Endurance exercise and diets were implemented before AKI. Serum urea and creatinine, urinary albumin, kidney malondialdehyde (MDA), total antioxidant capacity (TAC), transforming growth factor (TGF-β1), and SIRT1 levels, glomerular filtration rate (GFR) and relative kidney weight were measured before and 48 h after AKI induction.

Results: After induction of kidney injury, serum urea and creatinine, urinary albumin, kidney MDA and TGF-β1 levels and relative kidney weight increased in rats with both previous exercise and no previous exercise ($p < 0.001$), while GFR, and kidney TAC and SIRT1 levels decreased ($p < 0.001$). These changes after AKI were less in the group with previous exercise than in the group that had no exercise ($p < 0.001$). The TR diet during exercise caused a less increase in serum urea ($p < 0.001$) and creatinine ($p < 0.05$), and urinary albumin ($p < 0.01$) levels after injury compared to the just exercise group. Also, both CR and TR diets during exercise caused less change in MDA ($p < 0.01$, $p < 0.05$, respectively) and TAC ($p < 0.001$, $p < 0.05$, respectively) levels compared to just exercise group.

Conclusion: The results showed that exercise alone had no effect on preventing function impairment of kidney, oxidative stress, inflammation and also SIRT1 alteration following AKI in athletes, although these indexes were less among those with exercise than those without exercise. However, when the CR and TR diets were implemented during exercise, strong renoprotective effects appeared, and the protective effect of TR diet was greater.

Introduction

Acute kidney injury (AKI) is a complex clinical disorder. It is also a syndrome of sudden loss of excretory function of kidney that is often associated with oliguria and mortality. Despite technological advances that have been made in the treatment of kidney disease, AKI is still associated with poor clinical outcomes (1). Causes of AKI can be pre-renal, intrinsic, and post-renal. Approximately 70% of AKI cases in the society are attributed to pre-renal causes. Decreased arterial blood pressure (for example due to heart failure or sepsis) leads to a decrease in glomerular filtration rate (GFR) (2, 3). Patients with AKI eventually develop chronic kidney disease (CKD). They are also at risk for end-stage kidney disease (ESKD) and premature death (4).

A number of inflammatory mediators are involved in the pathophysiology of kidney injury, including pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), transforming growth factor (TGF-β1),

interleukin-18 (IL-18), interleukin-1 (IL-1) and interleukin-6 (IL-6) (5). TGF-β1 is a member of growth factor family that initiates a variety of pathophysiological processes at the onset of kidney injury, including apoptosis of tubular epithelial cell, lack of intrinsic cell differentiation and extracellular matrix deposition, which are associated with acute deterioration in renal function and fibrosis (6). Some cells, such as macrophages, tubular epithelial cells and myofibroblasts, are able to secrete TGF-β at different stages of the renal fibrosis. Multiple related factors such as oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress and a severe inflammatory response cause destruction of extracellular matrix, loss of kidney structure, impaired cellular homeostasis, and ultimately impaired renal function (7).

One of the molecules suggested as a target in the treatment of many diseases is the silent information regulator (SIRT1), a member of nicotinamide adenine dinucleotide-dependent histone deacetylase that regulates various biological pathways by switching off the chromatin and suppressing transcription. It is in relation to cellular energy metabolism, mitochondrial biogenesis, stress response, apoptosis, inflammation, and fibrosis (8, 9). A collection of evidence suggests that SIRT1 plays a role in protecting cellular stress in kidney disease (10). SIRT1 regulates the activity of several transcription factors that regulate renal cell homeostasis. SIRT1 expression decreases in patients with renal injury (11).

Physical activity and exercise promote health, help to maintain weight, and prevent health problems, vascular diseases and inflammatory diseases (12). Regular muscle exercise has been shown to reduce oxidative stress and increase antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPX) in various organs such as liver, kidney, heart and lungs (13).

Exercise may boost immune function in kidney disease and have anti-inflammatory effects (14). It has been shown that regular and progressive aerobic exercise before AKI decreases the plasma creatinine and plasma levels, severity of tubular injury and saspase3 levels within 48 hours of reperfusion in Wistar rats. Regular aerobic exercise and previous adaptation reduce morphological damage to the kidney in the form of interstitial edema in terms of mononuclear infiltration and loss of tubular brush border cells (15–17). It has been reported that regular exercise before induction of diabetes improves metabolic control of renal function and decreased TGF-β expression in kidney tissue, which is associated with decreased fibronectin expression and a renoprotective effect (18). It has also been reported that previous exercise or preconditioning can reduce damage to renal endothelial cell and improve angiogenesis (19).

Studies have shown that diet manipulation, whether by changing calorie intake amount or food intake time, can lead to delayed onset and progression of disease and also a long and healthy life in most organisms (20). Among dietary interventions, we can point to the classic calorie restriction diet (CR), in which daily caloric intake is normally reduced by 15 to 40% (21), and the time restriction diet (TR), in which daily food intake is limited to 4 to 12 hours per day (22). Neither of the diet has been proven to be superior to the other one. Diets that are associated with reduced energy intake exert their positive effects through weight loss, and reduced metabolism and oxidative damage (23).

CR diet has been shown to improve metabolic health and improve chronic metabolic diseases, such as type 2 diabetes and cardiovascular disorders. CR diet initiates a consistent defense mechanism that

increases resistance to stress. CR diet in particular has been shown to provide strong protection in laboratory models that induce ischemia-reperfusion (IR) injury in the brain, heart, liver and kidney (24). Application of TR before renal injury has been shown to increase resistance to AKI and prevent the progression of interstitial fibrosis and oxidative stress (25).

Exercise, like CR and TR, has been shown to affect health survival and disease recovery (19). There is little evidence that CR along exercise can cause a greater increase in several health indicators (26). Both exercise and CR have been shown to increase SIRT1 expression and ultimately, reduce kidney injury (27, 28).

Athletes who are on the TR diet are able to maintain muscle mass, and reduce body fat and inflammatory markers. The TR diet, with 16 hours of starvation and 8 hours of nutrition, improved health-related biomarkers, reduced fat mass and maintained muscle mass in people who had endurance exercise. This type of diet is used in athletes during the maintenance stages of training that aims to maintain muscle mass while reducing fat mass (29).

It is not clear whether the implementation of these diets in athletes affects their susceptibility towards diseases such as AKI or not. Therefore, in this study, the effects of CR and TR diets during exercise on the renal injury, oxidative stress and inflammation indexes, and SIRT1 in AKI male rates were investigated.

Materials And Methods

Animals

Animal care experiments were performed in accordance with standard ethical guidelines, and every effort was made to minimize animal suffering. All laboratory work was carried out according to the instructions of the Animal Care Committee of Kerman University of Medical Sciences (Ethics Code: IR.KMU.REC.1398.457). Male animals were placed in a cycle of 12 h of darkness and 12 h of light in the animal house of Kerman University of Medical Sciences at 22 to 23 °C, allowing them free access to food and water.

Study groups

Two groups were used in the study to prove the induction of AKI, which included before and after AKI groups without exercise. The rest of the animals in the study had previous exercise, which were divided into three groups of without diet restriction (control), calorie restriction (CR) and time restriction (TR). Each one of these three groups also had two subgroups of before and after AKI (Fig. 1). The study protocol is also shown in Fig. 2.

Study protocols

Implementation of CR and TR diets

To calculate the amount of food given to the CR group, first the amount of food consumed per week in the group that had free access to food was determined and using the average value, the amount of daily food consumption was calculated. Then 60% of the daily intake in the group that had free access to food was calculated and given to the CR group. This regimen was applied for 2 months before induction of AKI in the CR group (21). In the TR group, five hours of free access to food was provided (22, 23).

Exercise protocol

Treadmill exercise was performed for eight weeks (5 days a week) until the day before AKI induction. For the first five days, the exercise was performed for 10 minutes a day at a speed of 20 meters per minute on a flat surface. For the next 5 days, the duration of exercise increased by 10 minutes each day to 60 minutes at a speed of 26 meters per minute without slope. For the rest of experiment time, the speed (26 m/min), duration (60 min), and 0° slope remained constant for eight weeks (30).

Induction of AKI

Two months after the start of the study, the animals in the AKI groups were deprived of water for 24 h and then injected with a single dose of 50% hypertonic glycerol solution (dissolved in saline). The injection was in a way that 8 ml/kg of hypertonic glycerol solution was injected evenly into the muscles of both lower limbs (31). With this method, nephropathy developed rapidly within 24 h of injection. Glycerol generally causes rhabdomyolysis, which eventually leads to myoglobinuria, ischemia, and nephrotoxicity in the kidney (32).

Evaluation of kidney function indexes

Measurement of serum urea and creatinine, and urinary albumin

To measure serum urea and creatinine, before and two days after the induction of AKI, blood samples were collected from the ocular sinus and immediately centrifuged and the serum was isolated. Then the measurements were performed using an analyzer (XL Selectra, Vital Scientific Company, Netherlands Country). Also, 24-hour urine of the animal was collected two days after the induction of AKI and the amount of albumin in the urine was measured using the aforementioned analyzer (21, 31).

Determining the GFR level

The GFR level was calculated using creatinine clearance according to the following formula (20).

$$\text{GFR (ml/ min)} = \frac{\text{urinary creatinine concentration (mg/ dl)} * \text{urine volume in time unit (ml/ min)}}{\text{plasma creatinine concentration (mg/ dl)}}$$

The ratio of kidney weight to body weight

The ratio of kidney weight to body weight is an indicator of hypertrophy. At the end of the study, the animals were killed under anesthesia and their kidneys were removed from the body and weighed. The

weight of the animals was also determined before their death (33).

Evaluation of inflammation and oxidative stress markers, and SIRT1 in kidney tissue

Measurement of malondialdehyde level

Malondialdehyde (MDA), the product of membrane lipid peroxidation, is considered as an oxidant that is measured by thiobarbituric acid (TBA) method. To measure MDA, a reaction mixture containing TBA, sodium dodecyl sulfate (SDS), 20% acetic acid (pH = 3.5) and distilled water were added to the homogenized tissue of kidney. The resulting mixture was heated at 90 °C for 45 minutes and after cooling in room temperature it was centrifuged at 10000g for 10 minutes to obtain a smooth solution. Then the adsorption of the supernatant was recorded at 532 nm. The amount of lipid peroxidation was expressed using the standard curve in micromoles per milligram of tissue (34).

Measurement of total antioxidant capacity

Total antioxidant capacity (TAC) was measured by ferric reducing antioxidant power (FRAP). For this purpose, homogenized samples of kidney tissue were first centrifuged at 10,000 g for 7 minutes. The supernatant was removed from the precipitate and diluted with distilled water for 5 times, and then quickly used to measure antioxidants. To measure the antioxidant activity, FRAP solution including sodium acetate, TPTZ (2, 4, 6-tri-pyridyl-s-3, 6 triazine) and ferric chloride were used. Then, from homogenized diluted samples, distilled water (as a control) and standard solution with predetermined dilutions (ferrous sulfate with concentrations of 125, 250, 500 and 1000 µM) were added to each test tube containing FRAP, and was heated at 37 °C in a hot water bath for 5 min. The absorbance of the samples was measured at wavelength of 593 nm, after removing the tubes from the hot water bath (34).

Measurement of TGF-β1 and SIRT1 levels

TGF-β1 and SIRT1 levels of kidney homogenized tissue were measured by ELISA method (Zellbio, Germany). In this case, the measurement was based on the reaction between the antigen and the antibody, and finally the adsorption was read at 450 nm. After placing the adsorption and concentration of standard solutions in Excel program, the standard curve was prepared. Concentration of the samples was determined based on the adsorption using the standard curve linear equation (35-37).

Statistical analysis

Two-way repeated measures ANOVA and T-test were used to compare quantitative variables between the study groups if the assumptions were observed (data normal distribution). A significant level of 0.05 was considered and statistical analyzes were performed by SPSS22 software.

Results

The effect of exercise and different diets on the kidney function indexes in AKI

Serum urea and creatinine levels increased after AKI, both in the group with previous exercise and in the group without previous exercise compared to before AKI (p <0.001) (Table 1). The percentage of this increase in the exercised group was less than the group that had no exercise (p <0.001) (Table 2). In the exercised groups, the levels of increase in urea after injury in the TR group was less than in the Ctrl and CR groups (p <0.001 and p <0.05, respectively) and the level of creatinine increase was lower in the TR group compared to the Ctrl group (p <0.05). Also, the amount of urea and creatinine after AKI was higher in the TR and CR groups compared to Ctrl group before the injury (p <0.001) (Table 3).

The levels of urinary albumin increased after injury in both exercised and non-exercised groups compared to before injury (p <0.001) (Table 1). The percentage of this increase in the exercised group was less than non-exercised group (p <0.001) (Table 2). Albumin levels after injury in CR and TR groups increased slightly compared to Ctrl group (p <0.05 and p <0.01, respectively). Albumin levels after AKI also increased in CR and TR groups compared to Ctrl group before the injury (p <0.001) (Table 3).

Both in the group with previous exercise and in the group without previous exercise, the GFR decreased after AKI compared to before AKI (p <0.001) (Table 1). The percentage of this reduction in the exercised group was less than the non-exercised group (p <0.001) (Table 2). In the exercise condition, this rate before AKI was lower in CR group compared to Ctrl and TR groups (p <0.05 and p <0.001, respectively). The decrease in GFR level after injury in TR group was less than CR group (P <0.01). GFR levels in CR and TR groups decreased after injury compared to Ctrl group before injury (p <0.001) (Table 3).

The ratio of kidney weight to body weight after injury in both groups with and without previous exercise increased compared to before injury (p <0.001) (Table 1). The percentage of this increase in the exercised group was less than the non-exercised group (p <0.001) (Table 2). In the exercise condition, the ratio of kidney weight to body weight before AKI was higher in the TR group than the Ctrl group (p <0.001). This ratio after the injury was higher in the TR group than in the Ctrl and CR groups (p <0.01 and p <0.05, respectively) (Table 3). The ratio in the TR and CR groups after injury was higher than the Ctrl group before injury (p <0.001) (Table 3).

Table 1
Levels of kidney function indexes following acute kidney injury in non-exercised and exercised groups (n = 6 in each group).

	Experimental groups			
	No Exercise		Exercise	
	Before AKI	After AKI	Before AKI	After AKI
Serum Urea (mg/ dL)	70.83± 3.37	312.66± 10.51 @@@	64± 4.37	172.31± 4.07 ^^^
Serum Creatinine (mg/ dL)	0.45± 0.03	3.38± 0.14 @@@	0.48± 0.1	1.78± 0.1 ^^^
Urinary Albumin (mg/ dL)	0.51±0.17	28.16± 0.80 @@@	0.58± 0.08	21.33± 0.8 ^^^
GFR (ml/ min)	0.52±0.01	0.10±0.007 @@@	0.606± 0.02	0.256± 0.02 ^^^
Kidney Weight/ Body Weight (mg/g)	4.14±0.13	5.91±0.10 @@@	3.9± 0.05	4.06± 0.02 ^^^

Information is represented as mean ± SEM. @@@ $p < 0.001$, versus before AKI in the non-exercised groups. ^^^ $p < 0.001$, versus before AKI in the exercised groups. AKI: Acute kidney injury, GFR: Glomerular filtration rate.

Table 2
Percentage of changes in Kidney function indexes following acute kidney injury in non-exercised and exercised groups (n = 6 in each group).

Parameters	Experimental groups	
	No Exercise	Exercise
Serum Urea (%)	362.26± 8.99	184.15± 11.78 ***
Serum Creatinine (%)	559.21± 55.61	286.54± 9.27 ***
Urinary Albumin (%)	6050 ± 715.42	3800± 382.09 ***
GFR (%)	-79.46± 1.75	-57.11± 4.82 ***
Kidney Weight/ Body Weight (%)	42.75± 0.13	14.31± 0.02 ***

Information is represented as mean ± SEM. *** $p < 0.001$ versus non-exercised group. AKI: Acute kidney injury, GFR: Glomerular filtration rate.

Table 3
The levels of kidney function indexes following AKI in different exercised groups (n = 6 in each group).

Experimental groups						
Before AKI			After AKI			
Ctrl	CR	TR	Ctrl	CR	TR
Serum Urea (mg/ dL)	64± 4.37	78.66± 5.32	57.5± 4.43	172.31±4.07 ^^^	187.66± 3.9 ^^^	158.63± 4.35 $^{\varepsilon\varepsilon\varepsilon, \#, \wedge\wedge\wedge}$
Serum Creatinine (mg/ dL)	0.48± 0.02	0.46± 0.02	0.36± 0.02	1.78± 0.10 ^^^	1.36± 0.13 ^^^	1.16± 0.09 $^{\varepsilon, \wedge\wedge\wedge}$
Urinary Albumin (mg/ dL)	0.58± 0.08	0.324± 0.1	0.27± 0.1	21.33± 0.88 ^^^	15± 0.68 $^{\varepsilon, \wedge\wedge\wedge}$	13.33± 0.49 $^{\varepsilon\varepsilon, \wedge\wedge\wedge}$
GFR (ml/ min)	0.60± 0.02	0.48± 0.01^{a}	0.70± 0.02^{bbb}	0.25± 0.02 ^^^	0.21± 0.01$^{\wedge\wedge\wedge}$	0.30± 0.02 $^{\#\#, \wedge\wedge\wedge}$
Kidney Weight/ Body Weight (mg/g)	3.9± 0.05	4.18± 0.07	4.23± 0.13^{aaa}	4.06± 0.02$^{\wedge\wedge\wedge}$	4.31± 0.12$^{\wedge\wedge\wedge}$	5± 0.11 $^{\varepsilon\varepsilon, \#, \wedge\wedge\wedge}$

Information is represented as mean ± SEM. ^{aaa} p <0.001 versus Ctrl group before AKI. ^{a} p <0.05 versus Ctrl group before AKI. ^{bbb} p <0.001 versus CR group before AKI. $^{\varepsilon\varepsilon\varepsilon}$ p <0.001 versus Ctrl group after AKI. $^{\varepsilon\varepsilon}$ p <0.01 versus Ctrl group after AKI. $^{\varepsilon}$ p <0.05 versus Ctrl group after AKI. $^{\#\#}$ p <0.01 versus CR group after AKI. $^{\#}$ p <0.05 versus CR group after AKI. $^{\wedge\wedge\wedge}$ p <0.001 versus Ctrl group before AKI. AKI: Acute kidney injury, Ctrl: Control, CR: Caloric restriction, GFR: Glomerular filtration rate: TR: Time restriction.

The effect of exercise and different diets on the levels of inflammation and oxidative stress markers, and SIRT1 in the kidney following AKI

MDA levels in the study groups

Kidney tissue MDA levels in the study groups are shown in Fig. 3. An increase in MDA levels after injury compared to before injury appeared in both exercised and non-exercised groups (p <0.001) (Fig. 3A). The percentage of this increase in the exercised group was less than non-exercised group (P<0.001) (Fig. 3B). In the exercise condition, the level of MDA before AKI in the TR group was lower than the Ctrl group (p <0.001). The MDA levels in the CR and TR groups after AKI were lower than the Ctrl group (p <0.05 and p<0.01, respectively) (Fig. 3C). The MDA levels in CR and TR groups after injury showed no difference compared to Ctrl group before injury.

TAC levels in the study groups

Figure 4 shows the levels of kidney tissue TAC in the study groups. After AKI, the levels of TAC decreased in the non-exercised and exercised groups compared to before AKI (p <0.001) (Fig. 4A). The percentage of this decrease in the exercised group was less than non-exercised group (p <0.01) (Fig. 4B). In the exercise condition, the levels of TAC before AKI in CR and TR groups were higher than Ctrl group (p <0.05 and p <0.001, respectively) and this increase in TR group was higher than CR group (p <0.05). The decrease in TAC levels after AKI was less in CR and TR groups than in Ctrl group (p <0.05 and p <0.001, respectively) and this decrease was less in TR group compared to CR group (p <0.01) (Fig. C). Also, no difference was observed in the TAC levels of CR and TR groups after injury compared to Ctrl group before injury.

TGF-β1 levels in the study groups

Kidney tissue TGF-β levels were measured in the study groups (Fig. 5). In both exercised and non-exercised groups, the levels of TGF-β1 increased after injury compared to before injury (p <0.001) (Fig. 5A). This increase in the exercised group was less than the non-exercised group (p <0.001) (Fig. 5B). In the exercise condition, the levels of TGF-β1 before AKI in CR and TR groups were lower than Ctrl group (p <0.001 and p <0.01, respectively) and in CR group was lower than TR group (p <0.01). Also, in the exercise condition, the level of TGF-β1 after injury increased less in CR group than Ctrl and TR groups (p <0.001) (Fig. 5C). No difference in TGF-β1 levels was observed after injury in CR and TR groups compared to Ctrl group before injury.

SIRT1 levels

Kidney tissue SIRT1 levels in the study groups are shown in Fig. 6. The level of SIRT1 decreased after injury compared to before injury (p <0.001) (Fig. A). The percentage of this decrease in the exercised group was less than the non-exercised group (p <0.001) (Fig. B). After injury, the level of SIRT1 was higher in the TR group compared to the Ctrl group (p <0.01) (Fig. C). No difference was observed in the SIRT1 levels of CR and TR groups after injury compared to Ctrl group before injury.

Discussion

In this study, for the first time, the effect of two types of dietary regimen during exercise on AKI outcomes was investigated. Following eight weeks of moderate-intensity endurance exercise along the use of different diets, the following results were obtained:

1) Following AKI, the serum urea and creatinine, and urinary albumin levels increased in the exercised and non-exercised groups, and this increase was less in the exercised rats than in non-exercised ones. Serum urea levels were lower in the exercised group with TR than the exercised group with CR and just exercised group, while urinary albumin was lower in exercised groups with CR and TR diets than just exercised groups. 2) GFR levels decreased after AKI in exercised and non-exercised groups, and this decrease was less in the exercised rats than non-exercised ones. It was also less in the exercised rats on TR diet than in exercised rats on CR diet. 3) The relative weight of the kidney increased after injury in the exercised and non-exercised groups, and this increase was less in the exercised rats than non-exercised ones. 4) The

MDA levels increased and TAC levels decreased following injury in the exercised and non-exercised groups. These changes were less in the exercised groups than the non-exercised groups. They were also less in exercised rats with prescribed regimens than rats that only performed exercise. Also, the level of TAC reduction was lower in the exercised group with TR than in exercised group with CR. 5) Increase in inflammatory factor (TGF-β1) levels following injury in exercised and non-exercised groups showed that the increase was less in the exercised group than the non-exercised group and also, it was less in the exercised group with CR compared to just exercise group and exercised group with TR. 6) Decrease in SIRT1 levels following AKI in exercised and non-exercised groups revealed that the decrease in exercised group was less than the non-exercised group. This decrease was also less in the exercised group with TR after injury than in just exercised group.

Rhabdomyolysis, the leading cause of AKI, is common in athletes and can occur 1 to 10 hours after exercise and resolve after 2 to 10 days (38). Therefore, the effectiveness of exercise as a treatment depends on its duration, intensity and type.

In this study, the effect of TR and CR diets during exercise was investigated. The beneficial effects of these diets depend on many factors including age, physical activity and disease status (39). The TR diet is a form of Islamic fasting (40). A CR diet however, in which daily calorie intake is limited, can also be an intervention for athletes who want to control their body weight and increase their physical function and energy (26). CR in athletes reduces the risk of metabolic disease and mortality (39).

Increased serum urea and creatinine levels following AKI in the present study have also been shown in other AKI models, such as the use of cisplatin (41). Lower increase in the serum urea and creatinine levels in the exercised group compared to non-exercised group has been confirmed in the study of Weslei et al (2019) (42). De lima et al (2019) showed that regular exercise with moderate intensity for four weeks before AKI causes a decrease in serum urea and creatinine levels, and tubular injury (42). In this study, it was shown that TR diet combined with exercise resulted in a lower increase in serum urea and creatinine levels following AKI. Prevention of excessive increase in serum urea and creatinine levels following AKI by the use of TR diet has also been reported (25), which its mechanism of action is still unknown. Therefore, exercise prevents excessive increase in serum urea and creatinine levels after AKI, and when combined with TR diet, its effect is greater. A study showed that TR diet in athletes did not change the renal function indexes including serum urea and creatinine levels (43). The difference in the results could be due to differences in the studied species, and intensity and duration of exercise.

The increase in urinary albumin levels after AKI in the present study has also been confirmed in the study of Palm et al (2004) (44). One possible cause of the increase in urinary albumin is increased kidney injury and tubular damage. Consistent with our result that revealed less increase in urinary albumin after AKI in the group with previous exercise, it has been shown that regular exercise for 10 weeks reduces urinary albumin levels in diabetic rats (45). Also, endurance exercise with moderate intensity for four weeks before induction of diabetes decreases urinary albumin levels after injury (46). There are also contradictory results regarding the effects of exercise on proteinuria, and evidence suggests that the

intensity of exercise is very important in this area. Some studies have shown that high-intensity exercise increases albuminuria in laboratory animals and humans, while moderate-intensity and regular exercise prevents albuminuria / proteinuria in STZ-induced diabetic rats (47–49). Although exercise prevents increase in urinary albumin levels following AKI, when combined with TR and CR diets, its effect is greater. According to the searching that we carried out, no study has been conducted to investigate the effects of these two diets on the reduction of proteinuria to this date.

In the present study, similar to another study (50), GFR decreased following AKI, and this decrease was less in exercised group compared to non-exercised group. It has been shown that performing eight weeks of moderate-intensity endurance exercise before induction of diabetes improves GFR after injury and prevents a large decrease in GFR (54). Toyama et al. (2010) reported that exercise for 12 weeks improves GFR in patients with CKD (55). Although the mechanism by which moderate-intensity exercise improves renal function is not well understood, there is evidence to suggest that better metabolic control, reduced oxidative stress, and increased nitric oxide (NO) production may play a role in this protective process (51, 52). Decreased GFR before injury was observed in the exercised rats on CR diet in the present study. In one study, the CR diet alone reduced GFR by reducing tubular hypertrophy (56). It is possible that the reduction of tubular hypertrophy in the CR diet group caused the decrease in GFR was not compensated in the CR diet group with exercise. The decrease in GFR in the TR diet group during exercise was less than the CR diet group during exercise, which is probably due to compensatory tubular hypertrophy both before and after injury.

Amaral et al., similar to the present study, reported that the relative weight of kidney increased after kidney injury, and eight weeks of moderate-intensity endurance exercise before induction of diabetes prevented the increase in relative weight of the kidney after injury (18). The reason for the increase in relative kidney weight in the TR diet group during exercise, before and after AKI in this study, may be due to the increase in compensatory hypertrophy, which is in contrast with the CR diet group during exercise. In a study, CR diet prevented a relative increase in heart weight associated with aging (51). Therefore, CR with exercise has a more effect on preventing the increase in compensatory renal hypertrophy after AKI.

Therefore, it can be concluded that in the present study, exercise probably decreased renal injury by reducing oxidative stress (49), which is the cause of tubular damage, and by increasing renal NO (48) and proliferation of kidney tissue cells (52) prevented GFR reduction. Also, compensatory hypertrophy in TR group led to less reduction in GFR, increased relative kidney weight, and improved renal function, which could be observed by smaller increase in serum urea and creatinine, and urinary albumin levels. In the TR diet group with exercise, these effects were reinforced and played a more effective role in improving kidney function.

The increase in lipid peroxidation and the decrease in antioxidant defense after AKI in this study are also confirmed by Ibrahim et al (2008), (53). Evidence suggests that exercise before AKI prevents the subsequent increase in oxidative stress (58, 60). Exercise is said to strike a balance between the oxidant and antioxidant systems (54). The findings of Húngaro et al (2020) study are contradictory to the results

of our study, as they reported that moderate-intensity endurance exercise for four weeks before AKI could not prevent oxidative stress (55). The reason for the difference between this study and our study could be the difference in the duration of exercise and the type of animal used in these studies. Walsh et al (2014), similar to the results of present study, reported that dietary restriction prevents the progression of oxidative stress after AKI (56). The protective mechanism of this regimen is still unknown, but it has been shown that this protective effect is probably exerted by an increase in antioxidant factors (64) that prevent DNA oxidative damage induced by kidney injury (57). One study even suggested that a reduction in oxidative stress by CR diet may be due to weight loss. Another study found that exercise did not prevent oxidative stress in brain tissue, but the CR diet prevented the production of ROS products and established a balance between oxidant and antioxidant systems (58). The difference could be due to differences in the type, intensity and duration of exercise, as well as the studied tissue and the study conditions. Wycherley et al (2008) showed that CR with exercise reduced serum MDA, possibly due to weight loss. Reduction of oxidative stress may also be due to reduced insulin resistance and blood pressure following CR diet (59).

Although in this study weight gain was observed during exercise with TR diet, kidney weight loss could have been the cause of reduced oxidative stress in the CR diet. TR has been shown to prevent mitochondrial fragmentation associated with severe mitochondrial dysfunction, overproduction of free radicals, and worsening of AKI. At present, the molecular mechanisms of this effect are unclear, but it is possible that the nuclear factor-erythroid factor 2-related factor 2 (NRF2) and peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α), are both oxidation-sensitive transcriptional regulators, which are activated by nutrient restriction, affect mitochondrial homeostasis and play a role in the beneficial effects of TR (60−62). It seems that the reduction of oxidative stress both before and after AKI in the TR group during exercise may be due to the effect of TR on preventing mitochondrial damage following regulating oxidation-sensitive transcriptional factors, which requires further research.

In the present study, similar to another study, AKI increased the level of TGF-β1 in kidney tissue (63). It has been shown that regular moderate-intensity exercise before induction of diabetes partially reduces the progression of renal fibrosis by significantly reducing advanced glycation end products (AGE), which consequently reduces the production of TGF-β1 in mesangial, fibroblasts and tubular cells (64). The results of Húngaro et al (2020) study contradict the findings of present study, as they reported that moderate-intensity endurance exercise for four weeks before AKI could not prevent inflammation (55). A reason for the increased expression of TGF-β1 is the increased expression of fibronectin and type four collagen following kidney damage, which in turn causes the accumulation of extracellular matrix and the progression of fibrosis. Exercise before induction of injury, reduces the expression of fibronectin and type four collagen in kidney tissue and prevents the progression of fibrosis by reducing TGF-β1 production after AKI (65−67). These effects of exercise in the present study might have caused the level of TGF-β1 after AKI in the exercised group to be less than in the non-exercised group.

In other studies, similar to the present study, it has been reported that dietary restriction prevents the progression of renal fibrosis by reducing TGF-β production after AKI (25, 68). Liu et al (2020) found that

CR diet reduces TGF-β1 and ultimately fibrosis in aging-related kidney disorders (69). The CR-induced protection against fibrosis could be due to reduced oxidative stress, which reduces mitogen-activated protein kinase (MAPK) activity, activator protein-1 (AP-1) regulation, and TGFβ1 expression and signaling (70). Given the effect of CR diet during exercise on oxidative stress in the present study, it is likely that CR during exercise reduces TGFβ1 by reducing oxidative stress.

A decrease in SIRT1 levels in kidney tissue following AKI was observed in this study similar to the study of Zhong et al (2018), (27). Decreased SIRT1 expression is associated with increased nuclear factor kappa B (NF-κB) acetylation. Exercise suppresses NF-κB activity and inflammation by increasing SIRT1 expression in the kidney. In addition, exercise induces mitochondrial complex expression and the release of antioxidant enzymes by improving the activity of SIRT1 enzyme in the kidney (71). Prevention of SIRT1 reduction after AKI by previous exercise may have contributed to the reduction of oxidative stress and TGFβ1 after AKI in the exercised group. Marton and his colleagues showed that in metabolic disorders caused by aging, exercise could not prevent the reduction of SIRT1 in the cerebellum (72), which is contrary to our results. This difference could be due to the age of the animal, duration of exercise and the type of tissue studied. In the present study, an increase in SIRT1 after AKI was observed in the TR group during exercise. In another study, the TR diet restored the circadian rhythm of SIRT1 expression in the liver following metabolic disorders (73).

Therefore, in AKI, due to kidney injury, there is an increase in oxidative stress and inflammation, and also a decrease in renal function indexes and SIRT1 levels, which are less in the presence of exercise. However, with the application of CR and TR diets, especially TR, these changes are reduced in the presence of exercise. Applying the TR regimen before injury prevents structural damage to the kidney and renal function reduction in kidney injury (74). These effects are associated with the response to prevent proliferation of epithelial cells of damaged tubules and suppression of extracellular signal-regulated kinases1 / 2 (ERK1/2) activation in ischemic kidney. The TR diet reduces damage to epithelial cell of proximal tubule, death of tubular cell and activation of ERK1/2 in response to stress (75). The CR improves AKI by increasing autophagy and dealing with reduced renal expression of endothelial nitric oxide synthase (eNOS), and PGC-1a caused by kidney damage. It also reduces acute tubular necrosis, and prevents reduction of renal function during injury (76). But more research is needed in the future to discover the molecular mechanisms of this effects.

Conclusion

Findings of this study showed that regular moderate-intensity exercise before induction of AKI reduces injury, inflammation and oxidative stress following AKI and also leads to less reduction in SIRT1 in those with previous exercise compared to those without exercise. When the two CR and TR regimens are applied to athletes, the renoprotective effects of exercise are greater in AKI, and among these two regimens, the effect of TR regimen is greater.

Abbreviations

AGE: Advanced glycation end products; AKI: Acute Kidney Injury AP-1: Protein Aactivator-1; CKD: Chronic Kidney Disease; CR: Calorie Restriction; ERK1 / 2: Extracellular signal-Regulated Kinases1 / 2; ESKD: End-Stage Kidney Disease; FRAP: Ferric reducing antioxidant power; GFR: Glomerular Filtration Rate; GPx: Glutathione Peroxidase; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-18: Interleukin-18; IR: Ischemia-reperfusion; eNos: endothelial Nitric Oxide Syntheses; MAPK: Mitogen- Activated Protein Kinase; MDA: Malondialdehyde; NF-κB: Nuclear Factor kappa B; NO: Nitric oxide; NRF2: Nuclear factor-erythroid factor 2-related factor 2 ; PGC1α: Peroxisome proliferator-activated receptor Gamma Co-activator 1-α; SIRT1: Silent information regulator1; SOD: Superoxide dismutase; TAC: Total antioxidant capacity; TBA: Thiobarbituric acid; TGF-β: Transforming Growth Factor- β; TNF-α: Tumor Necrosis Factor-α; TPTZ: 2, 4, 6-tri-pyridyl-s-3, 6 triazine; TR: Time restriction

Declarations

Authors' contributions

NS: Collection of data and writing manuscript.

ZS and MK supervised and directed the project, contributed to the data analyses and interpretations, and prepared the manuscript.

AR: Collection of data .

Ethics approval

The study was approved by the Ethical Committee of Kerman University of Medical Sciences with Code of Ethics IR.KMU.REC.1398.457

Consent for publication

Not applicable.

Consent to participate

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

References

1. Lameire N, Van Biesen W, Vanholder R. Acute kidney injury. The Lancet. 2008;372(9653):1863–5.

2. Koza Y. Acute kidney injury: current concepts and new insights. Journal of Injury Violence Research. 2016;8(1):58.

3. Rahman M, Shad F, Smith MC. Acute kidney injury: a guide to diagnosis and management. Am Family Phys. 2012;86(7):631–9.

4. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. American journal of kidney diseases. 2009;53(6):961–73.

5. Misseri R, Meldrum DR, Dagher P, Hile K, Rink RC, Meldrum KK. Unilateral ureteral obstruction induces renal tubular cell production of tumor necrosis factor-α independent of inflammatory cell infiltration. The Journal of urology. 2004;172(4):1595–9.

6. Huynh P, Chai Z. Transforming growth factor β (TGFβ) and related molecules in chronic kidney disease (CKD). Clin Sci. 2019;133(2):287–313.

7. Wen X, Murugan R, Peng Z, Kellum JA. Pathophysiology of acute kidney injury: a new perspective. Cardiorenal Syndromes in Critical Care. 165: Karger Publishers; 2010. p. 39-45.

8. Wątroba M, Szukiewicz D. The role of sirtuins in aging and age-related diseases. Advances in medical sciences. 2016;61(1):52–62.

9. Bazyluk A, Malyszko J, Hryszko T, Zbroch E. State of the art–sirtuin 1 in kidney pathology–clinical relevance. Advances in medical sciences. 2019;64(2):356–64.

10. Wakino S, Hasegawa K, Itoh H. Sirtuin and metabolic kidney disease. Kidney international. 2015;88(4):691–8.

11. Dong Y-j, Liu N, Xiao Z, Sun T, Wu S-h, Sun W-x, et al. Renal protective effect of sirtuin 1. Journal of Diabetes Research. 2014;2014.

12. Moghetti P, Bacchi E, Brangani C, Donà S, Negri C. Metabolic effects of exercise. Sports Endocrinology. 2016;47:44–57.

13. Lemus-Mondaca R, Vega-Gálvez A, Zura-Bravo L, Ah-Hen K. Stevia rebaudiana Bertoni, source of a high-potency natural sweetener: A comprehensive review on the biochemical, nutritional and functional aspects. Food Chem. 2012;132(3):1121–32.

14. Viana JL, Kosmadakis GC, Watson EL, Bevington A, Feehally J, Bishop NC, et al. Evidence for anti-inflammatory effects of exercise in CKD. J Am Soc Nephrol. 2014;25(9):2121–30.

15. Kroshian VM, Sheridan AM, Lieberthal W. Functional and cytoskeletal changes induced by sublethal injury in proximal tubular epithelial cells. American Journal of Physiology-Renal Physiology. 1994;266(1):F21–30.

16. Linkermann A, Chen G, Dong G, Kunzendorf U, Krautwald S, Dong Z. Regulated cell death in AKI. J Am Soc Nephrol. 2014;25(12):2689–701.

17. Haase VH. Mechanisms of hypoxia responses in renal tissue. Journal of the american society of nephrology. 2013;24(4):537–41.

18. Amaral LSdB, Silva FA, Correia VB, Andrade CE, Dutra BA, Oliveira MV, et al. Beneficial effects of previous exercise training on renal changes in streptozotocin-induced diabetic female rats. Experimental biology medicine. 2016;241(4):437–45.

19. Faleiros CM, Francescato HD, Papoti M, Chaves L, Silva CG, Costa RS, et al. Effects of previous physical training on adriamycin nephropathy and its relationship with endothelial lesions and angiogenesis in the renal cortex. Life sciences. 2017;169:43–51.

20. Hall IE, Coca SG, Perazella MA, Eko UU, Luciano RL, Peter PR, et al. Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. Clin J Am Soc Nephrol. 2011;6(12):2740–9.

21. Kume S, Uzu T, Horiike K, Chin-Kanasaki M, Isshiki K, Araki S-i, et al. Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. J Clin Investig. 2010;120(4):1043–55.

22. Cheng C-W, Villani V, Buono R, Wei M, Kumar S, Yilmaz OH, et al. Fasting-mimicking diet promotes Ngn3-driven β-cell regeneration to reverse diabetes. Cell. 2017;168(5):775–88. e12.

23. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science. 2018;362(6416):770–5.

24. Brandhorst S, Harputlugil E, Mitchell JR, Longo VD. Protective effects of short-term dietary restriction in surgical stress and chemotherapy. Ageing Res Rev. 2017;39:68–77.

25. Rojas-Morales P, León-Contreras JC, Granados-Pineda J, Hernández-Pando R, Gonzaga G, Sánchez-Lozada LG, et al. Protection against renal ischemia and reperfusion injury by short-term time-restricted feeding involves the mitochondrial unfolded protein response. Free Radic Biol Med. 2020;154:75–83.

26. Pons V, Riera J, Capó X, Martorell M, Sureda A, Tur JA, et al. Calorie restriction regime enhances physical performance of trained athletes. J Int Soc Sports Nutr. 2018;15(1):1–10.

27. Zhong Y, Lee K, He JC. SIRT1 is a potential drug target for treatment of diabetic kidney disease. Front Endocrinol. 2018;9:624.

28. Liu H-W, Kao H-H, Wu C-H. Exercise training upregulates SIRT1 to attenuate inflammation and metabolic dysfunction in kidney and liver of diabetic db/db mice. Nutrition metabolism. 2019;16(1):1–10.

29. Moro T, Tinsley G, Bianco A, Marcolin G, Pacelli QF, Battaglia G, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. Journal of translational medicine. 2016;14(1):1–10.

30. Soltani N, Soltani Z, Khaksari M, Ebrahimi G, Hajmohammmadi M, Iranpour M. The changes of brain edema and neurological outcome, and the probable mechanisms in diffuse traumatic brain injury induced in rats with the history of exercise. Cellular and molecular neurobiology. 2019:1–13.

31. Zhang Y, Du Y, Yu H, Zhou Y, Ge F. Protective effects of ophiocordyceps lanpingensis on glycerol-induced acute renal failure in mice. Journal of immunology research. 2017;2017.

32. Sun X, Luan Q, Qiu S. Valsartan prevents glycerol-induced acute kidney injury in male albino rats by downregulating TLR4 and NF-κB expression. Int J Biol Macromol. 2018;119:565–71.

33. Zhaleh F, Amiri F, Mohammadzadeh-Vardin M, Bahadori M, Harati MD, Roudkenar MH, et al. Nuclear factor erythroid-2 related factor 2 overexpressed mesenchymal stem cells transplantation, improves renal function, decreases injuries markers and increases repair markers in glycerol-induced Acute kidney injury rats. Iranian journal of basic medical sciences. 2016;19(3):323.

34. Velayutham PK, Adhikary SD, Babu SK, Vedantam R, Korula G, Ramachandran A. Oxidative stress–associated hypertension in surgically induced brain injury patients: Effects of β-blocker and angiotensin-converting enzyme inhibitor. journal of surgical research. 2013;179(1):125–31.

35. Huang XZ, Wen D, Zhang M, Xie Q, Ma L, Guan Y, et al. Sirt1 activation ameliorates renal fibrosis by inhibiting the TGF-β/Smad3 pathway. Journal of cellular biochemistry. 2014;115(5):996–1005.

36. Ka S, Yeh Y, Huang X, Chao T, Hung Y, Yu C, et al. Kidney-targeting Smad7 gene transfer inhibits renal TGF-β/MAD homologue (SMAD) and nuclear factor κB (NF-κB) signalling pathways, and improves diabetic nephropathy in mice. Diabetologia. 2012;55(2):509–19.

37. Velagapudi R, El-Bakoush A, Lepiarz I, Ogunrinade F, Olajide OA. AMPK and SIRT1 activation contribute to inhibition of neuroinflammation by thymoquinone in BV2 microglia. Mol Cell Biochem. 2017;435(1):149–62.

38. Betts JA, Williams C. Short-term recovery from prolonged exercise. Sports Med. 2010;40(11):941–59.

39. Mercken EM, Carboneau BA, Krzysik-Walker SM, de Cabo R. Of mice and men: the benefits of caloric restriction, exercise, and mimetics. Ageing Res Rev. 2012;11(3):390–8.

40. Trabelsi K, El Abed K, Stannard SR, Jammoussi K, Zeghal KM, Hakim A. Effects of fed-versus fasted-state aerobic training during Ramadan on body composition and some metabolic parameters in physically active men. Int J Sport Nutr Exerc Metab. 2012;22(1):11–8.

41. Estrela GR, Wasinski F, Batista RO, Hiyane MI, Felizardo RJ, Cunha F, et al. Caloric restriction is more efficient than physical exercise to protect from cisplatin nephrotoxicity via PPAR-alpha activation. Frontiers in physiology. 2017;8:116.

42. de Lima WV, Visona I, Schor N, Almeida WS. Preconditioning by aerobic exercise reduces acute ischemic renal injury in rats. Physiological reports. 2019;7(14):e14176.

43. Trabelsi K, Stannard SR, Ghlissi Z, Maughan RJ, Kallel C, Jamoussi K, et al. Effect of fed-versus fasted state resistance training during Ramadan on body composition and selected metabolic parameters in bodybuilders. J Int Soc Sports Nutr. 2013;10(1):1–11.

44. Palm F, Ortsäter H, Hansell P, Liss P, Carlsson PO. Differentiating between effects of streptozotocin per se and subsequent hyperglycemia on renal function and metabolism in the streptozotocin-

diabetic rat model. Diab/Metab Res Rev. 2004;20(6):452–9.

45. Somineni HK, Boivin GP, Elased KM. Daily exercise training protects against albuminuria and angiotensin converting enzyme 2 (ACE2) shedding in db/db diabetic mice. J Endocrinol. 2014;221(2):235.

46. Ishikawa Y, Gohda T, Tanimoto M, Omote K, Furukawa M, Yamaguchi S, et al. Effect of exercise on kidney function, oxidative stress, and inflammation in type 2 diabetic KK-Ay mice. Experimental diabetes research. 2012;2012.

47. Albright A, Mahan JD, Ward KM, Sherman WM, Roehrig KL, Kirby TE. Diabetic nephropathy in an aerobically trained rat model of diabetes. Med Sci sports Exerc. 1995;27(9):1270–7.

48. Rodrigues AM, Bergamaschi CT, Araújo RC, Mouro MG, Rosa TS, Higa EM. Effects of training and nitric oxide on diabetic nephropathy progression in type I diabetic rats. Experimental Biology Medicine. 2011;236(10):1180–7.

49. Silva KAdS, Luiz RdS, Rampaso RR, de Abreu NP, Moreira ÉD, Mostarda CT, et al. Previous exercise training has a beneficial effect on renal and cardiovascular function in a model of diabetes. PloS one. 2012;7(11):e48826.

50. Swärd K, Valson F, Ricksten SE. Long-term infusion of atrial natriuretic peptide (ANP) improves renal blood flow and glomerular filtration rate in clinical acute renal failure. Acta anaesthesiologica scandinavica. 2001;45(5):536–42.

51. Yu W, Qin J, Chen C, Fu Y, Wang W. Moderate calorie restriction attenuates age–associated alterations and improves cardiac function by increasing SIRT1 and SIRT3 expression. Mol Med Rep. 2018;18(4):4087–94.

52. Saad RA. Long term exercise preconditioning protects against renal dysfunction after ischemia reperfusion injury in rat kidneys. Journal of American Science. 2014;10(6):154–61.

53. Ibrahim A, Al-Hizab FA, Abushouk AI, Abdel-Daim MM. Nephroprotective effects of benzyl isothiocyanate and resveratrol against cisplatin-induced oxidative stress and inflammation. Front Pharmacol. 2018;9:1268.

54. Ji LL. Antioxidants and oxidative stress in exercise. Proceedings of the Society for experimental Biology and Medicine. 1999;222(3):283-92.

55. Húngaro TGR, Freitas-Lima LC, Gregnani MF, Perilhão MS, Alves-Silva T, Arruda AC, et al. Physical exercise exacerbates acute kidney injury induced by LPS via toll-like receptor 4. Frontiers in physiology. 2020;11:768.

56. Walsh ME, Shi Y, Van Remmen H. The effects of dietary restriction on oxidative stress in rodents. Free Radic Biol Med. 2014;66:88–99.

57. Rojas-Morales P, León-Contreras JC, Aparicio-Trejo OE, Reyes-Ocampo JG, Medina-Campos ON, Jiménez-Osorio AS, et al. Fasting reduces oxidative stress, mitochondrial dysfunction and fibrosis induced by renal ischemia-reperfusion injury. Free Radic Biol Med. 2019;135:60–7.

58. Radák Z, Silye G, Bartha C, Jakus J, Stefanovits-Bányai É, Atalay M, et al. The effects of cocoa supplementation, caloric restriction, and regular exercise, on oxidative stress markers of brain and

memory in the rat model. Food chemical toxicology. 2013;61:36–41.

59. Wycherley T, Brinkworth GD, Noakes M, Buckley J, Clifton P. Effect of caloric restriction with and without exercise training on oxidative stress and endothelial function in obese subjects with type 2 diabetes. Diabetes Obesity Metabolism. 2008;10(11):1062–73.

60. Gureev AP, Shaforostova EA, Popov VN. Regulation of mitochondrial biogenesis as a way for active longevity: interaction between the Nrf2 and PGC-1α signaling pathways. Frontiers in genetics. 2019;10:435.

61. Lettieri Barbato D, Baldelli S, Pagliei B, Aquilano K, Ciriolo MR. Caloric Restriction and the Nutrient-Sensing PGC-1 in Mitochondrial Homeostasis: New Perspectives in Neurodegeneration. International Journal of Cell Biology. 2012;2012.

62. Hine CM, Mitchell JR. NRF2 and the phase II response in acute stress resistance induced by dietary restriction. Journal of clinical & experimental pathology. 2012(4).

63. Sharma K, McGowan TA. TGF-β in diabetic kidney disease: role of novel signaling pathways. Cytokine Growth Factor Rev. 2000;11(1-2):115–23.

64. Boor P, Celec P, Behuliak M, Grančič P, Kebis A, Kukan M, et al. Regular moderate exercise reduces advanced glycation and ameliorates early diabetic nephropathy in obese Zucker rats. Metabolism. 2009;58(11):1669–77.

65. Dixon A, Maric C. 17β-Estradiol attenuates diabetic kidney disease by regulating extracellular matrix and transforming growth factor-β protein expression and signaling. American Journal of Physiology-Renal Physiology. 2007;293(5):F1678-F90.

66. Aparecido Volpini R, Giovanini Alves da Silva C, Silva Costa R, Machado Coimbra T. Effect of enalapril and losartan on the events that precede diabetic nephropathy in rats. Diab/Metab Res Rev. 2003;19(1):43–51.

67. Sharma K, Ziyadeh FN. Renal hypertrophy is associated with upregulation of TGF-beta 1 gene expression in diabetic BB rat and NOD mouse. American Journal of Physiology-Renal Physiology. 1994;267(6):F1094-F01.

68. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science. 1996;273(5271):59–63.

69. Liu J-r, Cai G-y, Ning Y-c, Wang J-c, Lv Y, Guo Y-n, et al. Caloric restriction alleviates aging-related fibrosis of kidney through downregulation of miR-21 in extracellular vesicles. Aging. 2020;12(18):18052.

70. Castello L, Froio T, Cavallini G, Biasi F, Sapino A, Leonarduzzi G, et al. Calorie restriction protects against age-related rat aorta sclerosis. The FASEB journal. 2005;19(13):1863–5.

71. Tang L-X, Wang B, Wu Z-K. Aerobic exercise training alleviates renal injury by interfering with mitochondrial function in type-1 diabetic mice. Medical science monitor: international medical journal of experimental clinical research. 2018;24:9081.

72. Marton O, Koltai E, Nyakas C, Bakonyi T, Zenteno-Savin T, Kumagai S, et al. Aging and exercise affect the level of protein acetylation and SIRT1 activity in cerebellum of male rats. Biogerontology.

2010;11(6):679−86.

73. Ye Y, Xu H, Xie Z, Wang L, Sun Y, Yang H, et al. Time-restricted feeding reduces the detrimental effects of a high-fat diet, possibly by modulating the circadian rhythm of hepatic lipid metabolism and gut microbiota. Frontiers in nutrition. 2020;7:288.

74. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Investig. 2011;121(11):4210−21.

75. Kong T, Liu M, Ji B, Bai B, Cheng B, Wang C. Role of the extracellular signal-regulated kinase 1/2 signaling pathway in ischemia-reperfusion injury. Frontiers in physiology. 2019;10:1038.

76. Lempiäinen J, Finckenberg P, Mervaala E, Sankari S, Levijoki J, Mervaala E. Caloric restriction ameliorates kidney ischaemia/reperfusion injury through PGC-1α−eNOS pathway and enhanced autophagy. Acta Physiol. 2013;208(4):410−21.

Figures
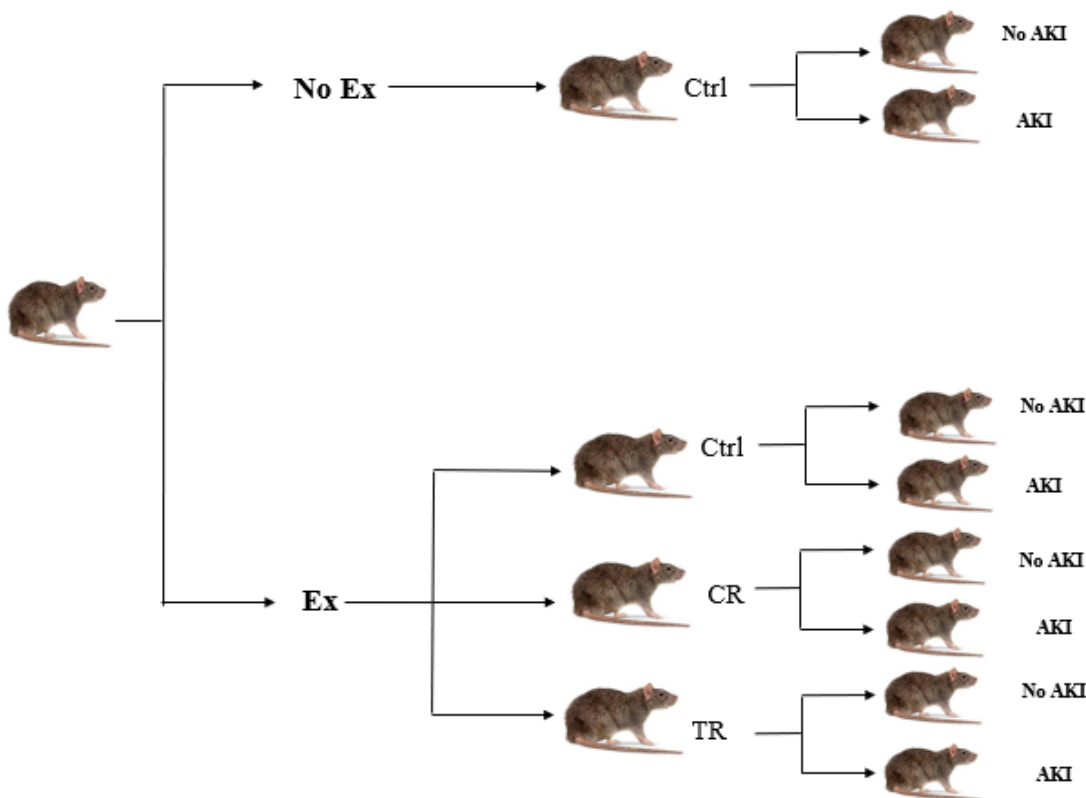
Fig. 1

Figure 1

An overview of the study groups. AKI: Acute kidney injury; CR : Calorie restriction; Ctrl: Control; Ex: Exercise; TR: Time restriction.
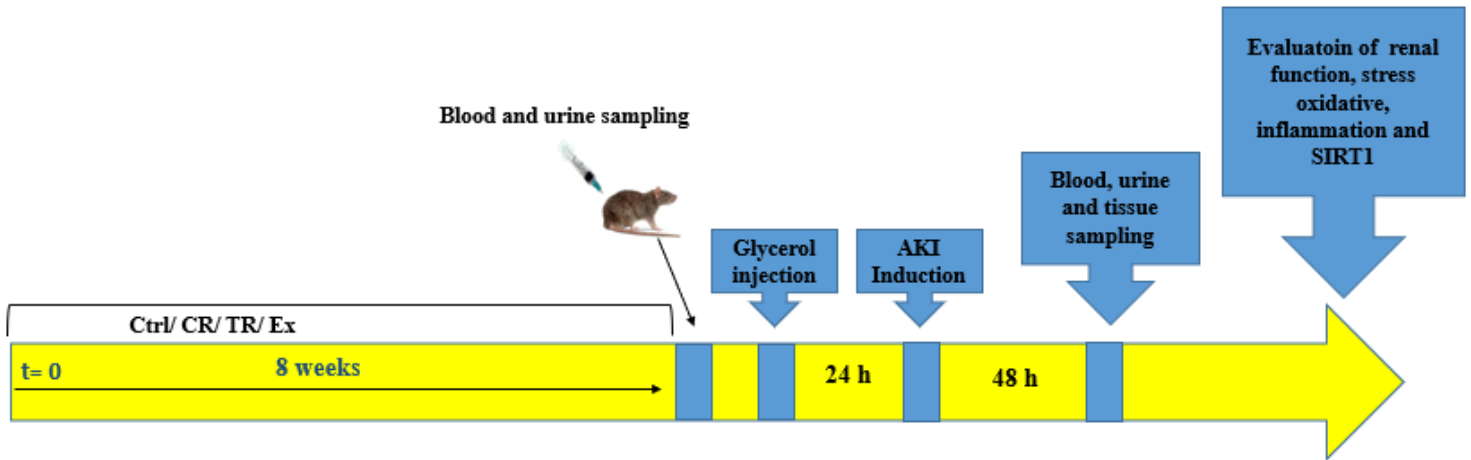
Figure 2

A schematic representation of the experimental protocol. AKI: Acute kidney injury; CR: Calorie restriction; Ctrl: Control; Ex: Exercise; SIRT1: Silent information regulator; TR: Time restriction.
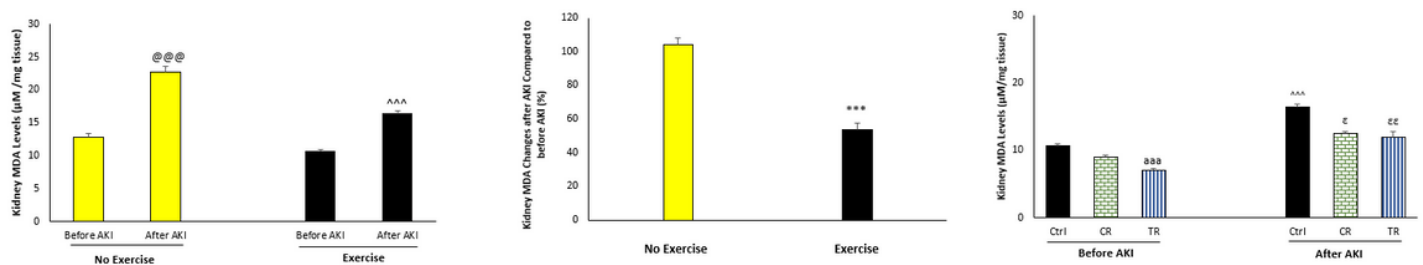

Figure 3

Kidney malondialdehyde (MDA) levels in the study groups (n = 6 in each group). Data are represented as mean ± SEM. A) Kidney MDA levels before and after AKI in non-exercised and exercised groups. @@@ p <0.001 vs. before AKI in the non-exercised groups. ^^^ p <0.001 vs. before AKI in the exercised groups. B) Percentage of kidney MDA changes after AKI in non-exercised and exercised groups. *** p <0.001 vs. non-exercised group. C) Kidney MDA levels in exercised groups. aaa p <0.001 vs. Ctrl group before injury. εε p <0.01 vs. Ctrl group after injury. ε p <0.05 versus Ctrl group after injury. ^^^ p <0.001 vs. Ctrl group before AKI. AKI: Acute kidney injury, Ctrl: Control, CR: Caloric restriction: TR: Time restriction.
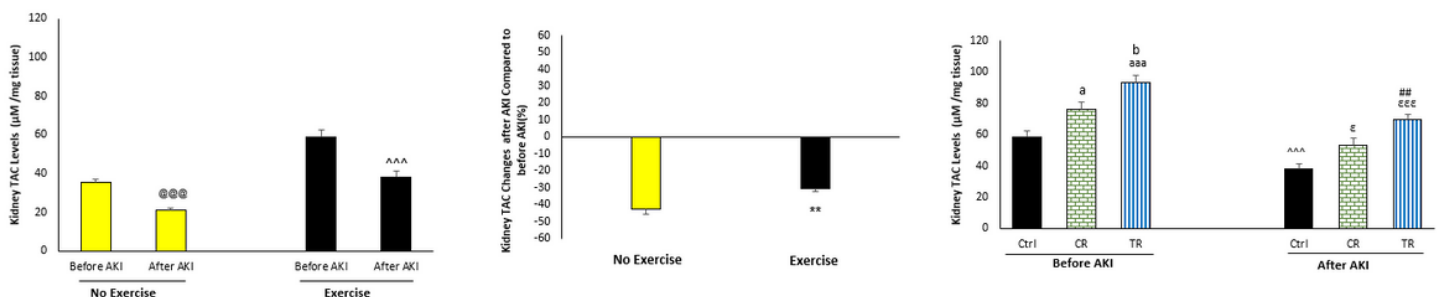
Figure 4

Kidney total antioxidant capacity (TAC) levels in the study groups (n = 6 in each group). Information is represented as mean ± SEM. A) Kidney TAC levels before and after AKI in non-exercised and exercised groups. @@@ p <0.001 vs. before AKI in non-exercised groups. ^^^ p <0.001 vs. before AKI in the non-exercised Kidney tissue groups. B) Percentage of changes in kidney TAC after AKI in non-exercised and exercised groups. ** p <0.01 vs. non-exercised group. C) Kidney TAC levels in exercised groups. aaa p <0.001 vs. Ctrl group before AKI. a p <0.05 vs. Ctrl group before AKI. b p <0.05 vs. CR group before AKI. εεε p <0.001 vs. Ctrl group after AKI. ε p <0.05 vs. Ctrl group after AKI. ## p <0.01 vs. CR group after AKI. ^^^ p <0.001 vs. Ctrl group before AKI. AKI: Acute kidney injury, Ctrl: Control, CR: Caloric restriction: TR: Time restriction.
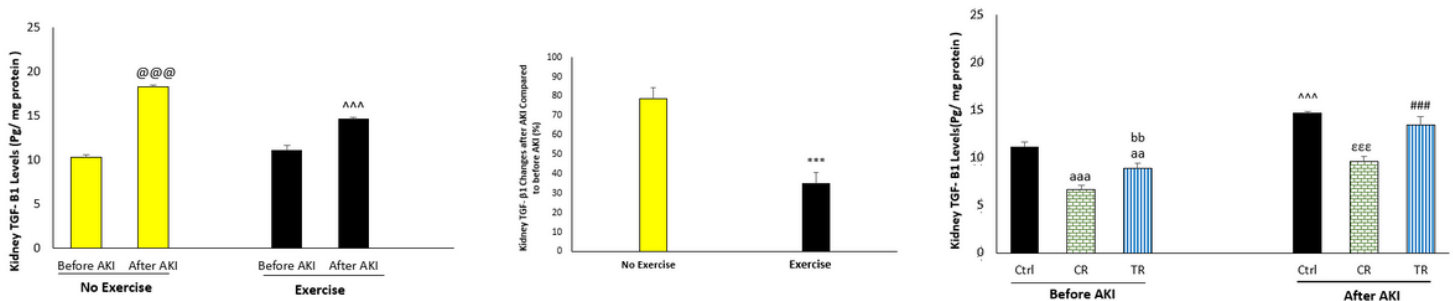

Figure 5

Kidney transforming growth factor (TGF-β1) in the study groups (n = 6 in each group). Data are represented as mean ± SEM. A) Comparison of kidney TGF-β1 levels before and after AKI in non-exercised and exercised groups. @@@ p <0.001 vs. before AKI in the non-exercised groups. ^^^ p <0.001 vs. before AKI in the exercised groups. B) Comparison of changes percentage in kidney TGF- β1 after AKI in non-exercised and exercised groups. *** p <0.001 vs. Ctrl group after AKI. C) Comparison of TGF-β1 levels in exercised groups. aaa p <0.001 vs. Ctrl group before AKI. aa p <0.01 vs. Ctrl group before AKI. bb p <0.01 vs. CR group before injury. εεε p <0.001 vs. Ctrl group after injury. ### p <0.001 vs. CR group after injury. ^^^ p <0.001 vs. Ctrl group before AKI. AKI: Acute kidney injury, Ctrl: Control, CR: Caloric restriction: TR: Time restriction
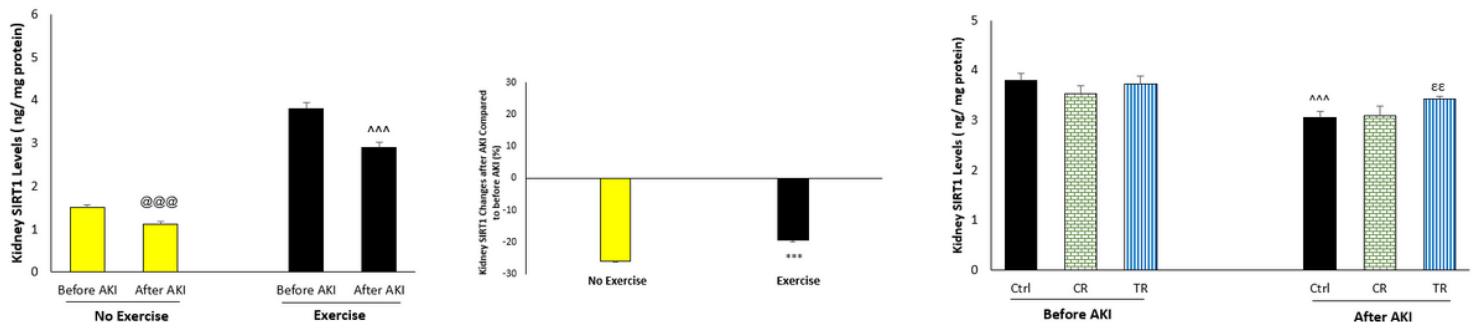

Figure 6

Kidney silent information regulator (SIRT1) levels in the study groups (n = 6 in each group). Data are expressed as mean ± SEM. A) Kidney SIRT1 levels before and after AKI in non-exercised and exercised groups. @@@ p <0.001 vs. before AKI in non-exercised groups. ^^^ p <0.001 vs. before AKI in the exercised groups. B) Percentage of changes in kidney SIRT1 levels after AKI in the non-exercised and exercised groups. *** p <0.001 vs. Ctrl group after AKI. C) Kidney SIRT1 levels in exercised groups. εε p <0.01 vs. Ctrl group after AKI. ^^^ p <0.001 vs. Ctrl group before AKI. AKI: Acute kidney injury, Ctrl: Control, CR: Caloric restriction, TR: Time restriction