



Nonpreventive Role of Aerobic Exercise Against Cisplatin-induced Nephrotoxicity in Female Rats

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ABSTRACT

Background: Cisplatin (CP) is a chemotherapy drug and nephrotoxicity is a major concern for CP therapy. CP-induced nephrotoxicity is gender-dependent, and the effect of aerobic exercise in females has not been reported yet while it has a beneficial effect in males. Hence, this study was designed to determine the protective role of aerobic exercise against CP-induced nephrotoxicity in female rats.

Methods: Twenty-eight adult female rats were divided into four groups. Groups I and II had aerobic exercise on a treadmill for 8 weeks. Then, the exercise protocol was continued for another week in group I and stopped in group II. All animals in these groups received CP (2.5 mg/kg/day; i.p.) for 1-week. Groups III and IV were treated with CP and vehicle, respectively, without exercise. Finally, the animals were sacrificed for biochemical measurements and tissue histopathology investigations.

Results: CP alone without exercise increased serum levels of blood urea nitrogen (BUN) and creatinine (Cr), kidney weight, and kidney tissue damage score (KTDS); while exercise could not attenuate these parameters in female rats. Exercise in females increased the serum levels of BUN and Cr and KTDS and weight loss ($P < 0.05$). Kidney nitrite levels reduce significantly in group I in compared to positive and negative control groups. Exercise also did not have beneficial effects on malondialdehyde levels in plasma and kidney.

Conclusions: Aerobic exercise cannot reduce CP-induced nephrotoxicity in female rats. Increasing the damage in female rats may be related to female sex hormone estrogen or gender differences in renal hemodynamic and renin-angiotensin system activity in the presence of exercise. In general, it is recommended that the females under CP chemotherapy avoid exercising during treatment.

Keywords: Aerobic exercise, cisplatin, female rats, nephrotoxicity

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INTRODUCTION

Cancer is a major cause of morbidity and mortality throughout the world. Chemotherapy is recommended to inhibit tumor cells growth and platinum compounds are categorized as chemotherapeutic agents.^[1,2] Cisplatin (cis-diamminedichloroplatinum) (CP) is a platinum compound that is used to treat various types of

cancers.^[1,3] Despite the antineoplastic effect of CP, its use is limited due to severe side effects such as neurotoxicity,^[4] nausea and vomiting cardiac toxicity, ototoxicity, myelotoxicity, and hemolytic anemia.^[5-7] Nephrotoxicity is a major concern for CP therapy.^[8] CP is the inhibitor of deoxyribonucleic acid synthesis,^[9] and induce tubular damage by various mechanisms including oxidative stress.^[8,10] It is reported that CP-induced nephrotoxicity is ameliorated by free radical scavenging agents such as Vitamin E,^[11] Vitamin C, losartan,^[12,13] gamma-amino butyric acid,^[14] and melatonin.^[15] CP-induced nephrotoxicity is also gender-related.^[16,17] Several studies indicated exercise activity changes antioxidant content.^[18-20] Prolonged exercise activity reduces erythrocyte glutathione peroxidase (GSH-PX) level.^[18] Furthermore, moderate regular exercise for 9 months decreased malondialdehyde (MDA) levels.^[21] It is reported that long-term aerobic exercise increases GSH erythrocyte PX enzyme (GSH) activity and superoxide dismutase activity.^[19] Our previous study indicated that aerobic exercise reduce CP-induced nephrotoxicity with a favorable effect on renal function by reducing lipid peroxidation.^[22] Exercise has been also shown to have a protective effect against CP-induced cell death in the kidney,^[23] and it is suggested that physical exercise before and during chemotherapy could attenuate the side-effects of medications and improve the quality of life for patients.^[23] As mentioned before, gender plays a role in CP-induced nephrotoxicity, and previously we reported that aerobic exercise could attenuate the CP-induced kidney damage in male rats.^[22] However, the effect has not been reported in females. Furthermore, inhibition of tumor cell proliferation by CP chemotherapy is different in male and female patients.^[24] Therefore, this study was designed to investigate the protective effect of aerobic exercise against CP-induced nephrotoxicity in female rats.

METHODS

Experimental protocol

Twenty-eight adult female Wistar rats (weighing 211 ± 7 g) (Animal Centre, Isfahan University of Medical Sciences, Isfahan, Iran) were used. The animals were housed at the room temperature of 23–25°C and 12 h light/12 h dark cycle and free access to water and rat chow. The experimental procedures were in advance approved by the Isfahan University of Medical Sciences Ethics Committee.

The animals were categorized into four groups as described previously.^[22] Groups I (called EX + CP + EX) ($n = 7$) and II (called EX + CP) ($n = 8$) were subjected to aerobic exercise on a treadmill 1 h/day and 5 days/week for 8 weeks. Then, exercise was

continued in group I in the 9th week. The animals in groups III (positive control) ($n = 5$) and IV (negative control) ($n = 8$) did not have exercise during the experiment. In addition, all animals in groups I, II, and III received CP (2.5 mg/kg/day; i.p.) and animals in group IV received saline in the 9th week. The animals in the positive and negative control groups were placed in the apparatus for the same duration of time without running.

Treadmill exercise

The rats were exposed to treadmill exercise as a moderate regular exercise on a motorized rodent treadmill with an inclination of 0% during the study. The animals in groups I and II underwent training adaptation for 7 days (each day 15 min) at 16 m/min. Then, groups I and II received a progressive exercise. During the first 2 weeks, the speed was increased to 20 m/min for 60 min/day for 5 days/week. Then, the speed was raised to 23, 25, and 28 m/min in the second (weeks 3 and 4), third (weeks 5 and 6), and fourth (weeks 7 and 8) 2 weeks, respectively. After endurance training for 8 weeks, group I with reduced aerobic exercise to 23 m/min and group II with stopped aerobic exercise were treated with CP for 1-week. The animals in this study were exposed to moderate exercise. The oxygen consumption in this position was about 65% for the rats.^[25,26]

Measurements and histopathological procedures

At the end of the experiment, the rats were anesthetized with chloral hydrate injection (450 mg/kg; i.p.) to obtain blood samples via heart puncture. Moreover, right and left kidneys and uterus were removed and weighed immediately. After hematoxylin and eosin staining, the left kidney was fixed in 10% formalin solution. The damage was evaluated and scored by a pathologist who was blind to the study protocol. The right kidney was homogenized to obtain supernatant for tissue nitrite measurements. The levels of serum creatinine (Cr) and blood urea nitrogen (BUN) were determined using quantitative diagnostic kits (Pars Azmoon, Iran). The serum and tissue levels of nitrite (stable nitric oxide metabolite) were measured using a colorimetric assay kit (Promega Corporation, USA) that involves Griess reaction. The serum level of MDA was measured by preparing a mixture of trichloroacetic acid (15%) and thiobarbituric acid (0.375%) (Merck). Then, 1 ml of the sample was added to 2 ml prepared the mixture and incubated in the boiling water for 60 min. After cooling, the samples were centrifuged for 10 min and finally the supernatant light absorbance was read at 535 nm.

Statistical analyses

Data were expressed as mean \pm standard error of the mean one-way ANOVA followed by the Tukey posttest was applied to compare the groups in terms of BUN,

Cr, NO, and MDA levels, kidney weight (KW), and bodyweight (BW). To compare the pathology damage score, the Kruskal–Wallis and Mann–Whitney U-test were applied. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of cisplatin and exercise on serum levels of blood urea nitrogen and creatinine, body weight change, kidney weight, and kidney tissue damage score

The serum levels of BUN and Cr significantly increased in groups I to III when compared with the negative control group (sham) ($P < 0.05$). However, these parameters increased non-significantly in the EX + CP + EX group more than that in the EX + CP and CP groups [Figure 1]. This was also observed for kidney tissue damage score (KTDS); as KTDS was significantly higher than that in the positive control group ($P < 0.05$) [Figures 1 and 2]. On the contrary, BW decreased significantly in groups I

to III in comparison with the sham group ($P < 0.05$). In addition, the BW changes in group II was less than group I ($P < 0.05$) [Figure 1]. KW increased significantly in all the CP-treated groups when compared with the sham group ($P < 0.05$) [Figure 1].

Effect of cisplatin and exercise on serum and kidney nitrite

No significant difference was observed among the groups with regard to the serum level of nitrite. The kidney level of nitrite reduced significantly in EX + CP + EX group when compared with the positive and negative control groups ($P < 0.05$) [Figure 3]. The serum levels of MDA significantly increased in the EX + CP + EX and EX + CP groups when compared with the negative and positive control groups ($P < 0.05$).

DISCUSSION

Previously, we reported the beneficial effect of aerobic exercise against CP-induced nephrotoxicity in male

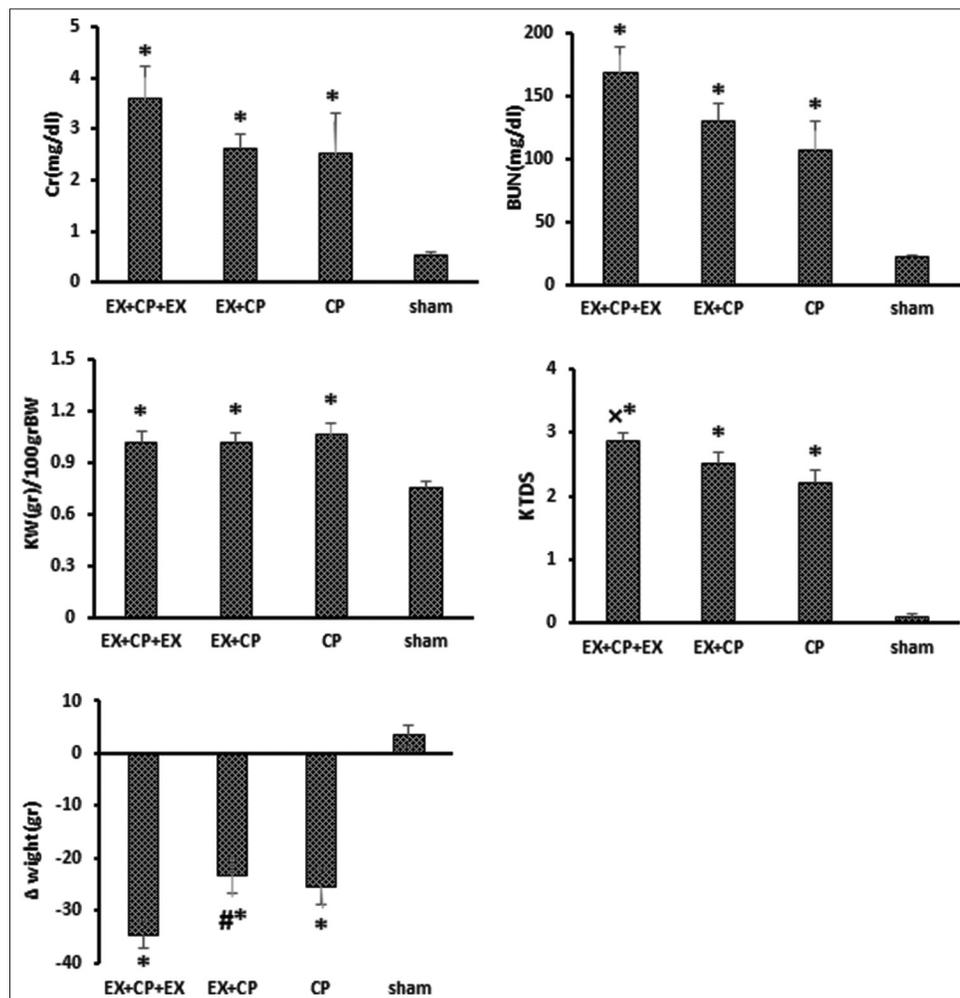


Figure 1: Serum levels of blood urea nitrogen and creatinine, kidney weight, body weight change (Δ BW), kidney tissue damage score *indicates significant difference from the negative control (sham) group and #indicates significant difference from the EX + cisplatin (CP) + EX group. *indicates significant difference from the positive control (CP) group ($P < 0.05$)

rats.^[22] In the current study, female rats were subjected to treadmill exercise and CP therapy simultaneously to find the role of exercise in females. Our results were in agreement with previous studies in CP alone treated groups.^[27-32] Histopathological examination has shown 50–75% of tubular degeneration due to CP administration^[33] by the mechanisms such as oxidative stress and apoptosis.^[10,34,35] Our study indicated that exercise did not protect the kidney against CP-induced nephrotoxicity. This finding is in contrast to the findings of our previous study on male rats.^[22] Moderate regular exercise before or simultaneously with CP therapy has a

protective effect against CP-induced nephrotoxicity in the male rats.^[22] In our study, exercise increased the serum MDA level in groups I and II. A study has indicated the high intensity of exercise increased MDA in skeletal muscle^[36] as well as, exhaustive maximal exercise-induced free radical generation while short periods of submaximal exercise may inhibit it and lipid peroxidation.^[37] CP is known as a drug that causes endothelial dysfunction and decreases endothelial NO synthase (eNOS).^[38] On the other hand, it enhances NO production by the inducible isoform of NO synthase.^[39] In our study, CP alone treated group did not show a significant difference in nitrite levels in compared to the negative control group. Alteration of NO production due to CP influences male rat more than female rat.^[40] A study indicated mild, regular aerobic endurance exercise increased NO production in elderly woman^[41] but the result of this study indicated reduction of nitrite in EX + CP + EX group. Maybe reduction of nitrite in female rat under the combination of CP and exercise was related to increase endothelial dysfunction in the female rat and reduced NO production by eNOS. Our data indicated BW decreased in groups I, II, and III when compared with the negative control group. This reduction was higher in EX + CP + EX group than other CP treated groups. CP reduced BW by induced gastrointestinal disturbance.^[42] Furthermore, physical activity decreased BW.^[43-45] It was reported that administration of CP increased KW, which is directly related to kidney injury.^[46] This is while several studies indicated that increase in the levels of biochemistry markers such as BUN or Cr after CP

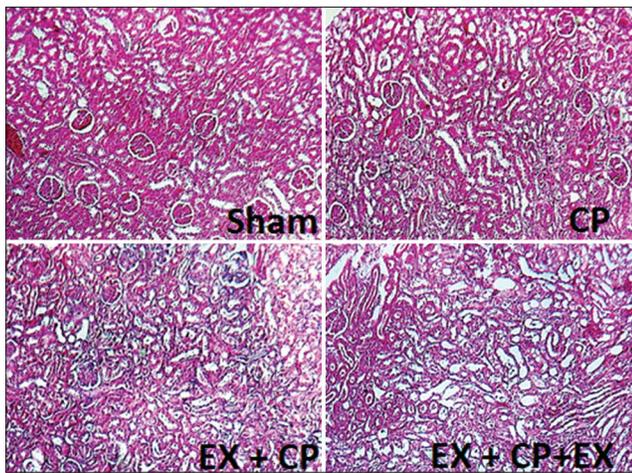


Figure 2: The images of kidney tissue with H and E staining to examine tissue damage in four experimental groups. The images were presented at $\times 100$

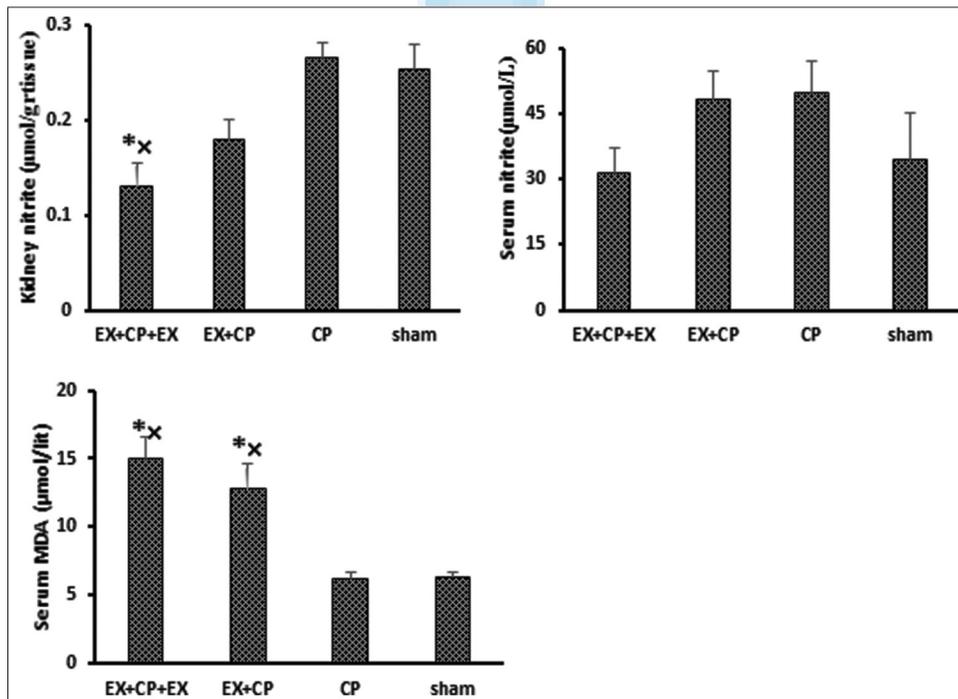


Figure 3: Serum levels of nitrite and malondialdehyde, and kidney tissue level of nitrite. *indicates significant difference from the negative control (sham) group, *indicates significant difference from the positive control (cisplatin) group ($P < 0.05$)

therapy is higher in males.^[16,17] Nevertheless, when CP is co-administrated with another compound, contradictory results are achieved in males and females. For example L-arginine, losartan, and vitamin E have protective effects against CP-induced nephrotoxicity in male rats, but these agents did not have ameliorative effects on CP-induced nephrotoxicity in female rats.^[11,47,48] Inhibition of tumor cell proliferation is different in male and female patients under CP chemotherapy.^[24] Males have higher respiratory exchange ratios (mean 0.94 vs. 0.87), higher muscle glycogen utilization (by 25%), and higher urea nitrogen excretion (by 30%) than the females.^[49] Furthermore, there is a high basal level of vasodilator prostaglandins in renal medulla of female rats that is affected by blood flow autoregulation in this area, and medullary flow in female rats is partially influenced by endogenous angiotensin (AT).^[50] Moreover, physical activity affects the sensitivity of the renin-angiotensin system (RAS).^[51,52] There is a gender difference in RAS activity.^[53-55] Losartan, as an AT II receptor I blocker, has higher protective effects against CP-induced nephrotoxicity in males.^[47] A study indicated despite a parallel fitness in males and females, development of metabolic responses are different in incremental exercise. These gender differences may be related to body mass because of a positive correlation between body mass and enhancement of systemic oxygen consumption in males and females.^[56] This may be also related to male and female sex hormones. Several studies indicated estrogen abolish the protective effect of Vitamins E and C, losartan, and erythropoietin against CP-induced nephrotoxicity in female rats.^[31,57,58] This is while testosterone administration reduces CP-induced nephrotoxicity in male rats.^[59]

CONCLUSIONS

Aerobic exercise cannot reduce CP-induced nephrotoxicity in female rats. Increasing the damage in female rats may be related to the female sex hormone, estrogen or gender differences in renal hemodynamic and RAS activity in the presence of exercise. In general, it is recommended that the females under CP chemotherapy avoid exercise during the treatment.

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