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# Does exercise training attenuate cisplatin nephrotoxicity?

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**ABSTRACT**

Cisplatin (CP), a medication originating from the platinum has been used for solid cancers' treatment in the last decade. CP is associated with numerous side effects as well. One of the side effects is nephrotoxicity. There are some types of procedure which can attenuate harmful effects of the drug, and the effectiveness of physical activity has been a controversial topic. It is well established that physical activity has positive effects on chronic kidney disease (CKD). The exercise training can modulate CP induced muscle wasting both in males and females. Although exercise training may have protective effect on renal function and the related risk factors, it cannot attenuate the renal injury resulted from CP therapy in females. The exercise training may improve interleukin 6 and heme oxygenase-1, reduces the production of CD4+T cell cytokines from the kidney, which play a major role in adaptive immune response. The present mini-review considered the effect of exercise training accompanied by the CP treatment.

Mini Review

*Implication for health policy/practice/research/medical education:*
Cisplatin (CP), is one of the most prevalence and effective medications applied to treat numerous cancer. Recently, researches have focued on the attenuation of CP therapy risk factors, which one of these adjusters is exercise training.
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## Introduction

Cis-diamminedichloroplatinum (II), cisplatinum, or cisplatin (CP), is one of the most prevalence and effective medications applied to treat various cancer such as carcinoma, germ cell tumor, sarcoma, as well as lymphoma. The function is connected to DNA binding, causing DNA damages and inhibition of DNA synthesis and mitosis (1). Unfortunately, CP has numerous toxicological effects including, hepatotoxicity, cardiotoxicity, nephrotoxicity, ototoxicity and gastrotoxicity (2). Nephrotoxicity is more common compared to the other side effects, while the kidney accumulates a greater amount of CP in comparison with the other organs. The most concentrated site in the kidney is epithelial cells of renal proximal tubules which is five times of the CP plasma levels (3). CP impairs renal function via mechanisms such as tubular epithelial cell toxicity which causes necrosis and apoptosis. Vasoconstriction in the renal microvasculature by this drug reduces the renal blood flow subsequently, and shedding pro-inflammatory substances like tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-gamma), interleukin-6 (IL-6) and caspase, which cause leukocytes infiltration in kidney eventually (4-6). The important manifestations of CP nephrotoxicity are non-oliguria acute renal failure, hypomagnesemia, Fanconi syndrome, and anemia(7). The diagnostic criteria for CP nephrotoxicity would be RIFLE (Risk, Injury, Failure, Loss, and End-Stage Renal Failure) and AKIN (Acute Kidney Injury Network) according to serum level of creatinine and urine output. Pharmaceutical approaches to prevent nephrotoxicity are prescribing a lower dose of CP and administration of full isotonic saline for hydration

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before and after CP intake (8).

## Exercise training and kidney

It is reported that physical activity resulted from regular exercise induces physical and psychological benefits, which prevents or delays various chronic diseases, such as metabolic, endocrine, cardiovascular, hepatic, neuronal, cancer, and gestational diseases (9). In biological view, the probable mechanisms of regular physical activity comprise, (I) playing in the role of buffer versus stress based disorders, (II) enhancing physiological responses and neuroendocrine reactions to physical or psychosocial stressors, (III) improving the anti-inflammatory capability, (IV) optimizing neuroplasticity and expression of growth factors (10).

Greenwood and colleagues investigated the outcomes of 12 months of physical training on renal function and found that exercise-based rehabilitation might be a kidney-protective therapy in patients with chronic kidney disease (CKD) (11). Albumin/creatinine ratio is one of the renal function biomarkers, since it has been shown that increased television watching and inactivity were accompanied by increased albuminuria and reduced glomerular filtration rate (GFR) (12, 13). A study on 256 CKD patients by Robinson-Cohen et al showed a reduction of GFR about 9.6% and 6.2% in sedentary and active patients per year respectively. Hence, increasing the time of physical activity is matched for a lower reduction in estimated GFR (eGFR). Therefore, every 60 minutes of physical activity is accompanied by a further 0.5% reduction in eGFR (14).

A recent study showed that muscle atrophy is related to the raised levels of muscle RING-finger protein-1 (MuRF1) and atrogin-1 (as the biomarkers of muscle atrophy) in mice (15). Exercise leads to synthesize the muscle proteins by improving the affirmative effects of the protein kinase B/mammalian target of rapamycin/p70 ribosomal S6 protein kinase (Akt/mTOR/p70S6K) pathway (15). It was found that aerobic exercise significantly attenuated the side effects of CP such as upregulation of atrogin-1 and MuRF1 in mice quadriceps and gastrocnemius muscles (15). Furthermore, the declined AKT-p70S6 kinases, and phosphorylation of FOXO3a resulted from CP treatment were considerably recovered via treadmill exercise training in the mentioned muscles (15). Moreover, myostatin (Mstn) gene expression, up-regulated by CP treatment, attenuated by aerobic exercise as well (16-18). It has been proved that voluntary wheel running (VWR) during the process of treatment can attenuate body weight loss by 50%, retain lean body mass, and muscle strength (15).

## Exercise training during CP-therapy and nephrotoxicity modulation

It has been reported that physical exercise modulates inflammatory effects on human bodies via targeting immune cells, endothelial cells, adipose tissues and muscle tissues (19). Miyagi and colleagues realized that aerobic exercise decreases kidney cell apoptosis induced by CP (20). Furthermore exercise training reduces the expression of TNF and IL-10 in renal tissue and serum, and also increases renal expression of IL-6 and heme oxygenase-1 (HO-1) (20). It is well established that HO-1 has a cytoprotective effect on several pathophysiological states namely AKI-induced nephrotoxicity (21). Furthermore, aerobic exercise contributes to the reduction of CP-induced AKI by enhancing the immune cells via decreasing the CD4+T (T helper) cell activation (22). Alternations in creatinine level in the serum and Kim-1 levels in the kidney shows that physical activity can modulate renal function impairment induced by CP. Figure 1 illustrates an overview of destructive effects of CP-therapy on the kidney, and how aerobic exercise can attenuate the injuries resulted from AKI induced by CP (22).

Francescato et al examined the effect of exercise in CP-induced renal injury (23). They found that levels of serum creatinine, potassium, and sodium fractional excretion were higher in the sedentary rats treated with CP. Sedentary rats cured with CP were associated with increased tubulointerstitial lesion and macrophage number, declined endothelial cells, and raised vascular endothelium growth factor, vimentin, and smooth muscle alpha-actin expression in renal outer medulla. They also found an increase of renal IL-1β and monocyte chemoattractant protein-1 expression and transforming growth factor-beta in comparison with control group. The alternations were moderated in trained rats due to increasing the expression of phospho-eNOS and stromal cell-derived factor (SDF)-1alpha and the renal level of tissue nitric oxide (NO) (23).

Investigating the role of exercise against CP-induced nephrotoxicity in female rats, reported that exercise

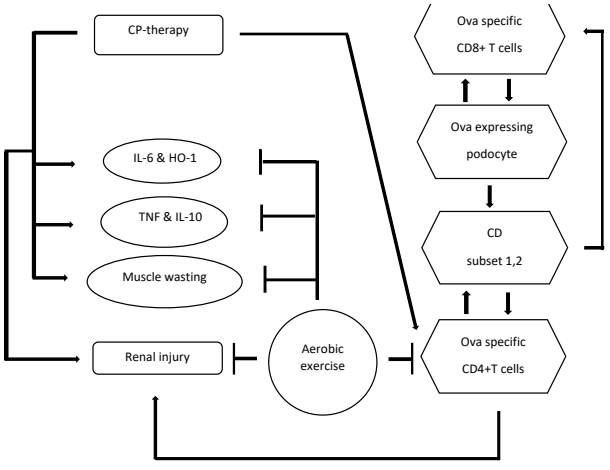


**Figure 1.** The overall view of beneficial effects of aerobic exercise on renal injuries resulted from CP-therapy.

cannot attenuate renal lesion since the possible mechanisms perhaps are associated with estrogen, female sex hormones, or gender related differences in renal hemodynamic and also renin/angiotensin system activity (24).

It is also found that aerobic exercise can modulate biomarkers related to acute kidney injury resulted from CP therapy such as the levels of blood urea nitrogen, serum creatinine, malondialdehyde, and kidney nitrite levels (25). The considerable point was the better renal function in the group in which the exercise was interrupted before CP therapy (25).

Physical exercise coupled with caloric restriction as the two non-pharmacological actions reduce CP nephrotoxicity, and in comparing these two methods and their effects on CP nephrotoxicity, Gabriel et al reported that both methods reduced serum creatinine level (26). However, tubular necrosis and tissue damage induced by CP in caloric restriction group showed a significant decrease compared to the exercise group. Their findings suggested that that physical activity along with caloric restriction decreased serum levels of IL-1β and TNFα, whereas there were not any differences between groups in their renal levels. In addition, the levels of IL-6, MCP-1 and IL-10 did not show significant differences between the two groups. Apoptotic activity was not different between the two groups of physical exercise and caloric restriction groups, however the expression of TNFR2 (tumor necrosis factor receptor 2) protein and caspase-3 as the main effector of apoptotic was remarkably decreased in caloric restriction group. Peroxisome proliferator-activated receptor alpha (PPAR-alpha), is a nuclear receptor protein encoded by the PPARA gene in humans and activated by energy deprivation. It is necessary for the ketogenesis process, a key adaptive reaction to long-running fasting. It has been shown that physical exercise as well as caloric restriction both exert their effects through this factor. The study found that the effects of caloric restriction on this factor and its related genes were greater than physical exercise. Therefore, by this mechanism it exerts its protective effects on CP-induced kidney damage(26).

## Conclusion

CP therapy is one of the most effective treatments against solid cancers despite various side effects. A variety of studies have focused on the attenuation of CP therapy risk factors recently, which one of these adjusters is exercise training.

1. Aerobic exercise during treatment can modulate CP-induced muscle wasting.
2. Aerobic exercise can modulate CP-induced AKI by improving IL-6 and HO-1 that declines inflammation, and it also reduces the production of CD4+T cells cytokines from kidneys draining lymph nodes.
3. Aerobic exercise does not have protective effects against nephrotoxicity, and cannot attenuate CP-therapy risk factors in females.

## Authors' contribution

MK, MRK, MN, MM and TS designed, conducted, supervised the first draft of article and participated in the writing and editing the paper.

## Conflicts of interest

None to be declared.

## Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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