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Protective Effects of Long-term High-intensity Interval Training on Cisplatin-induced Renal Injury in Male Rats

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ABSTRACT

Background: Cisplatin is a potent chemotherapeutic agent whose clinical use is limited by acute nephrotoxicity. This study aimed to evaluate the impact of high-intensity interval training (HIIT) on renal function and histology in cisplatin-treated rats.

Materials and Methods: Thirty-two male Sprague-Dawley rats were assigned to four groups (n=8): Healthy control (HC): No intervention; cisplatin control (CC): Received cisplatin only (single intraperitoneal injection, 5 mg/kg); exercise control (Ex): Underwent 8-week HIIT protocol only (treadmill running), cisplatin+exercise (Cis+Ex): Received cisplatin + 8-week HIIT protocol. Nephrotoxicity was induced by a single intraperitoneal cisplatin injection (5 mg/kg). Serum creatinine and urea were measured, and kidney tissues were analyzed using stereological methods.

Results: Cisplatin administration significantly increased serum creatinine (CC: 1.28±0.11 mg/dL vs HC: 0.45±0.08 mg/dL, P=0.001) and urea (CC: 112.5±8.4 mg/dL vs HC: 45.3±5.1 mg/dL, P=0.001). HIIT in cisplatin-treated rats significantly reduced these levels (creatinine: C-HIIT: 0.68±0.09 mg/dL vs CC, P=0.016; urea: C-HIIT: 58.7±6.9 mg/dL vs CC, P=0.005). Stereological analysis revealed cisplatin-induced increases in kidney volume (P=0.003), glomerular volume (p=0.039), and cortical volume (P=0.02), which were significantly attenuated by HIIT (P<0.05 for all).

Conclusion: An 8-week HIIT protocol significantly ameliorated cisplatin-induced renal dysfunction and histological damage in rats. These findings highlight the potential of HIIT as a non-pharmacological strategy to mitigate chemotherapy-related nephrotoxicity.

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Introduction

Platinum-based chemotherapeutic agents are widely used in cancer treatment [1]. Among them, cisplatin—formally known as cis-diamminedichloroplatinum (II)—plays a critical role as an adjuvant therapy following radiotherapy [2]. It is one of the most commonly used anticancer drugs, effective against a broad spectrum of malignancies, including ovarian, head and neck, lung, and testicular cancers, as well as tumors resistant to conventional regimens [3]. The antitumor properties of cisplatin were first demonstrated in animal studies conducted in 1969 [4]. Cisplatin's primary mechanism of action involves interference with DNA purine bases, resulting in DNA-protein and DNA-DNA cross-links [5]. After passive diffusion across the plasma membrane and hydrolysis, its chlorine atoms are replaced, increasing its reactivity and enabling DNA binding. This interaction inhibits cancer cell proliferation, damages DNA, and disrupts cellular transport systems, ultimately leading to apoptosis or necrosis [6]. Despite its clinical efficacy, cisplatin is associated with several adverse effects, including nephrotoxicity, hepatotoxicity, neurotoxicity, and weight loss due to muscle and fat depletion [7]. Among these, nephrotoxicity is the most significant dose-limiting side effect, primarily affecting the renal tubules and glomeruli [7]. Exposure of renal tubular cells to cisplatin activates complex signaling pathways that lead to cell injury and death. It forms covalent bonds with kidney macromolecules, triggering acute kidney injury [8]. Although the exact mechanisms are not fully understood, inflammation is widely recognized as a key contributor. In vitro studies have shown that cisplatin induces reactive oxygen species (ROS) and stimulates the release of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and monocyte chemoattractant protein-1 (MCP-1), which activate intrinsic and extrinsic apoptotic pathways, DNA degradation, and lipid peroxidation [9].

Damage to the proximal and distal tubules, along with morphological and functional impairments, reduces the reabsorptive capacity of tubular cells. This leads to decreased glomerular filtration rate (GFR), increased proteinuria, and elevated biomarkers of renal failure, such as serum creatinine and blood urea nitrogen (BUN). Numerous studies have confirmed that cisplatin nephrotoxicity primarily targets the tubules and glomeruli, especially the proximal tubules. A single dose can cause extensive tubulointerstitial damage, reduced GFR, and elevated serum creatinine in both humans [10] and laboratory animals [11]. Histopathological findings include acute cellular necrosis, particularly in the proximal tubules, along with apoptosis and interstitial tissue damage [12]. Despite the high incidence of renal toxicity, cisplatin remains a cornerstone of chemotherapy due to its potent antitumor effects [4]. Strategies to mitigate its toxicity are essential to allow for higher therapeutic doses. One promising approach is physical exercise [13]. As a non-pharmacological intervention, exercise can be implemented immediately after cancer diagnosis and throughout treatment [14]. It has been shown to enhance immune function and reduce complications associated with diseases, such as obesity, diabetes, cardiovascular disorders, and cancer [15]. Moreover, exercise can alleviate chemotherapy-related side effects [16]. Recent studies suggest that exercise may protect against cisplatin-induced renal injury [13]. For instance, Leite et al. reported that high-intensity interval training (HIIT) reduced serum creatinine and BUN levels in cisplatin-treated rats [17]. Similarly, Amaral et al. found that combined aerobic and resistance training improved kidney function and glycemic control in patients with diabetic nephropathy [18]. Additionally, regular exercise has been shown to prevent the accumulation of free radicals and reduce oxidative stress compared to sedentary individuals [19]. However, few studies have examined the structural effects of exercise on kidney tissue in cisplatin-treated subjects using rigorous stereological methods. Therefore, the present study aimed to investigate the impact of an 8-week HIIT protocol on serum creatinine and urea levels, as well as stereological parameters of kidney tissue in male rats exposed to cisplatin.

Materials and Methods

Study design and animals

This experimental study used 32 male Sprague-Dawley rats (10 weeks old, 200–250 g) obtained from the Pasteur Institute. The sample size was determined using G*Power software, version 3.1 for a one-way ANOVA, with an effect size of 0.78, $\alpha=0.05$, and power $(1-\beta)=0.95$, resulting in a total of 32 rats (n=8 per group). Animals were housed in polycarbonate cages under controlled conditions (temperature: 22±2 °C, humidity: 55%, 12:12 light-dark cycle) with ad libitum access to food and water. After a one-week acclimatization period, the rats were randomly assigned to one of four groups:

- Healthy control (HC): No exercise, no cisplatin.
- Cisplatin control (CC): Cisplatin injection, no exercise.

- HIIT-only (HIIT): HIIT protocol, no cisplatin.

- Cisplatin + HIIT (C-HIIT): Cisplatin injection followed by the HIIT protocol.

Cisplatin injection protocol

To induce nephrotoxicity, rats in the CC and C-HIIT groups were fasted for 12 hours and then received a single intraperitoneal injection of cisplatin (Sobhan Oncology Co., Iran) at a dose of 5 mg/kg body weight, diluted in normal saline [20]. The HIIT protocol commenced one week after cisplatin administration.

HIIT protocol

The HIIT protocol, adapted from previously validated regimens for rodents [17, 20], was conducted over eight weeks on a motorized treadmill. The program commenced with a one-week acclimatization phase, during which rats walked daily for 10 to 15 minutes at a speed of 8 m/min. This was followed by a structured overload phase spanning week two to four. On alternating days, the training regimen varied: on odd days, the animals performed two to six intervals of three-minute high-intensity running at 40 m/min, each interspersed with one-minute active recovery periods at 16 m/min. Conversely, on even days, the protocol consisted of three to twenty intervals of thirty-second high-intensity running at a higher speed of 54 m/min, with thirty-second active recovery periods at 16 m/min. For the subsequent maintenance phase from weeks five to eight, the structure of the overload phase was maintained. Throughout the program, the number of intervals was progressively increased based on the animals' tolerance, which was determined by their willingness to run without external prodding, and no electrical stimulation was applied. Every training session was preceded by a five-minute warm-up at 16 m/min and concluded with a five-minute cool-down at gradually decreasing speeds, with training conducted six days per week [17, 20].

Stereological analysis

Twenty-four hours after the final training session, the left kidney from each rat was harvested, weighed, and fixed in 10% formalin. A systematic uniform random sampling method was used. The kidney was cut into 2 mm thick slices. Every other slice was embedded in paraffin, and sections of 5 µm and 20 µm thickness were cut using a microtome. The 5 µm sections were stained with Hematoxylin and Eosin (H&E) for general histology. Stereological analysis was performed using the Cavalieri principle for volume estimation and point-counting methods [21]. A microscope (Olympus BX51) equipped with a live video camera and connected to a computer running Stereology Software (Stereologer, Systems Planning and Analysis Inc.) was used. A point grid was superimposed on the live images at various magnifications (4x for total kidney and cortex/medulla, 40x for glomeruli and tubules). The volume density (Vv) of a structure was estimated using the Equation 1:

1. $Vv=P(structure) / P(reference)$,

where P is the number of points hitting the structure or the reference space (e.g. cortex). The absolute volume was calculated by multiplying Vv by the reference volume. For glomerular volume, the physical dissector method was applied using the 5 µm and 20 µm sections. A minimum of 100-150 fields and 8-10 sections per kidney were analyzed to achieve a coefficient of error of less than 0.05.

Sample collection and biochemical analysis

Following kidney harvest, blood samples (5 mL) were collected via cardiac puncture under anesthesia (overdose of ketamine 90 mg/kg and xylazine 10 mg/kg). Serum was separated by centrifugation at 3500 rpm for 10 minutes and stored at -70 °C. Serum creatinine and urea levels were measured using commercial kinetic colorimetric assay kits (Creatinine: Pars Azmoon Co., Iran, Cat. No. 12001; Urea: Pars Azmoon Co., Iran) according to the manufacturer's instructions on an autoanalyzer (Hitachi 917).

Statistical analysis

Data normality was confirmed using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used to compare groups, followed by Tukey's HSD post-hoc test for pairwise comparisons. Results are presented as Mean±SD. Statistical analyses were performed using SPSS software, version 26, and significance was set at $P<0.05$.

Results

Body and kidney weight

No statistically significant differences were observed in the mean body weight of rats across groups at the beginning or the end of the study ($P>0.05$) (Table 1). There were no significant differences in absolute kidney weight or kidney-to-body weight ratio among the

Table 1. Mean body weight in experimental groups (n=8 per group)

Group	Mean±SD	
	Week 1 (g)	Week 8 (g)
HC	221.27±2.2	273.25±1.7
CC	223.44±5.7	310.14±2.4
HIIT only	276.13±4.8	320.3±1.7
Cisplatin + HIIT	216.10±3.6	332.41±5.9

Table 2. Kidney weight, relative weight, and length (n=8 per group)

Group	Mean±SD		
	Kidney Weight (g)	Kidney/Body Weight (%)	Kidney Length (cm)
HC	0.982±0.14	0.45±0.08	1.70±0.15
CC	1.2±0.31	0.539±0.14	1.53±0.14
HIIT only	1.082±0.15	0.391±0.04	1.01±0.16
Cisplatin + HIIT	1.03±0.21	0.476±0.1	1.44±0.14

Abbreviations: HC: Healthy control; CC: Cisplatin control; HIIT: HIIT-only; C-HIIT: Cisplatin + HIIT.

groups. However, kidney length was significantly different (P=0.015), with the post-hoc test indicating a significant difference between the CC and HIIT-only groups (P=0.011) (Table 2).

Stereological findings

Microscopic examination revealed normal kidney architecture in the HC and HIIT groups. The CC group showed significant histological damage, including glomerular swelling, tubular dilation, and interstitial expansion. The quantitative stereological data are presented in

Table 3. Stereological and biochemical parameters across experimental groups (n=8 per group)

Variables	Mean±SD					
	HC	CC	HIIT	C-HIIT	ANOVA P	Post-hoc P (Sig. Comparisons)
Kidney volume (mm^3)	707.06±15.24	781.33±14.54*	692.3±10.13	755.45±14.89**	0.002	CC vs HC: 0.003*; C-HIIT vs CC: 0.03**
Cortex volume (mm^3)	542.38±40.24	589.96±9.53*	531.43±16.2	569.87±12.11**	0.02	CC vs HC: 0.02*; C-HIIT vs CC: 0.04**
Medulla volume (mm^3)	165.41±7.43	160.33±23.78	161.01±3.21	160.09±29.36	0.89	N/S
Glomerular volume (mm^3)	21.22±3.55	26.31±2.33*	19.86±2.45	23.03±3.13**	0.03	CC vs HC: 0.039*; C-HIIT vs CC: 0.033**
Serum creatinine (mg/dL)	0.45±0.08	1.28±0.11*	0.48±0.07	0.68±0.09**	0.001	CC vs HC: 0.001*; C-HIIT vs CC: 0.016**
Serum urea (mg/dL)	45.3±5.1	112.5±8.4*	48.1±6.2	58.7±6.9**	0.001	CC vs HC: 0.001*; C-HIIT vs CC: 0.005**

Abbreviations: N/S: Not significant; HC: Healthy control; CC: Cisplatin control; HIIT: HIIT-only; C-HIIT: Cisplatin + HIIT.
*Significant difference vs HC, **Significant difference vs CC.

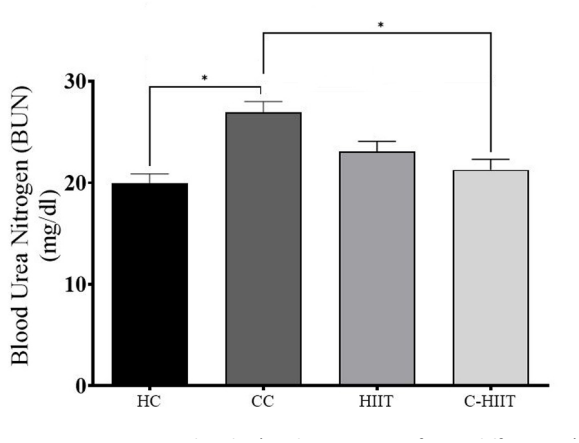

Figure 1. Serum BUN levels
*Significantly difference (P<0.05).

Table 3. Cisplatin administration significantly increased total kidney volume, cortex volume, and glomerular volume compared to the HC group (P=0.003, P=0.02, and P=0.039, respectively). HIIT intervention in the C-HIIT group significantly attenuated these changes, reducing total kidney volume, cortex volume, and glomerular volume compared to the CC group (P=0.03, P=0.04, and P=0.033, respectively). No significant differences were found in medulla volume, proximal or distal tubule volumes, or tubule lengths among the groups (P>0.05).

Serum urea and creatinine levels

One-way ANOVA revealed significant differences in serum urea (P=0.001) and creatinine (P=0.001) levels among the groups. Tukey's post-hoc test showed that cisplatin injection significantly increased serum urea by 148% and creatinine by 184% compared to the HC group (P=0.001 for both). HIIT intervention in the C-HIIT group significantly reduced these levels by 48% for urea and 47% for creatinine compared to the CC group (P=0.005 and P=0.016, respectively). There was no significant difference in these parameters between the C-HIIT and HC groups (P>0.05), indicating a near-complete restoration of renal function (Table 3, Figures 1 and 2).

Discussion

The primary finding of this study is that an 8-week HIIT regimen significantly mitigated cisplatin-induced nephrotoxicity in rats, as evidenced by improved renal function tests and attenuated histological damage. Cisplatin administration led to a profound decline in renal function, marked by ~184% and ~148% increases in serum creatinine and urea, respectively, and significant

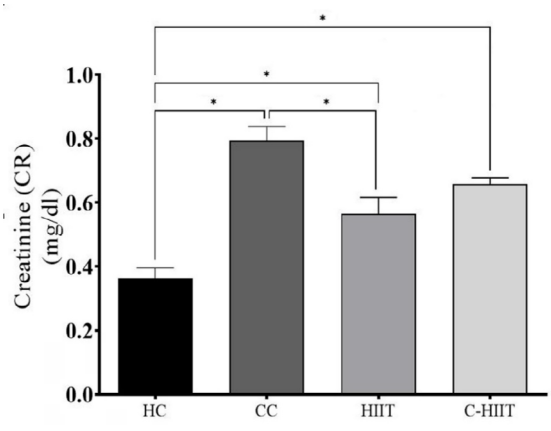

Figure 2. Serum creatinine (CR) levels
*Significantly difference (P<0.05).

increases in kidney, cortical, and glomerular volumes. HIIT intervention effectively reversed these changes, normalizing functional biomarkers and preserving renal microstructure.

Our findings on cisplatin-induced toxicity are consistent with a large body of literature. Altındağ et al. similarly reported elevated serum creatinine, urea, and glomerular volume following cisplatin administration [12]. The swelling of kidney structures is a hallmark of acute injury, driven by inflammatory cell infiltration, edema, and tubular cell necrosis [23]. The efficacy of HIIT in counteracting these effects aligns with the growing evidence for exercise as a renoprotective strategy. Leite et al. demonstrated that HIIT was superior to continuous training in reducing inflammatory markers (TNF-α, IL-6) and renal functional biomarkers in a similar model [17]. Our study extends these findings by providing robust stereological evidence that HIIT also preserves renal histoarchitecture.

The biological mechanisms through which HIIT confers protection are likely multifactorial, involving antioxidative, anti-inflammatory, and anti-apoptotic pathways. Cisplatin nephrotoxicity is primarily mediated by oxidative stress and inflammation [9, 23]. Exercise training is a powerful modulator of redox status, upregulating endogenous antioxidant defense systems, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [19]. By enhancing antioxidant capacity, HIIT may quench the excess ROS generated by cisplatin, thereby reducing lipid peroxidation and DNA damage in renal cells. Furthermore, as shown by Miyagi et al., aerobic exercise can reduce the renal expression of pro-inflammatory cytokines, like TNF-α and upregulate cytoprotective proteins, like heme oxygenase-1 (HO-1) [13]. The reduction in glomerular and interstitial swelling observed in our C-HIIT group strongly suggests a dampening of the inflammatory response.

Another potential mechanism is the modulation of apoptosis. Cisplatin activates both intrinsic and extrinsic apoptotic pathways in renal tubular cells [9]. Exercise has been shown to inhibit apoptosis in various tissues, potentially through the regulation of Bcl-2 family proteins and caspase activity [34]. The improved integrity of tubular epithelia in the C-HIIT group, as seen in our stereological analysis, may be a consequence of reduced apoptotic cell death. While our study did not measure these molecular markers directly, the functional and structural improvements provide a strong rationale for future mechanistic investigations.

It is also worth considering the hemodynamic effects of exercise. Acute exercise induces transient renal vasoconstriction, but chronic training improves overall cardiovascular health and may lead to better long-term regulation of renal blood flow and the renin-angiotensin system [33, 36]. This improved hemodynamic profile could reduce the renal accumulation of cisplatin and mitigate ischemic injury.

When compared to other training modalities, our results support the particular efficacy of HIIT. Parastesh et al. found HIIT to be more effective than moderate-intensity continuous training (MICT) in mitigating cisplatin toxicity, possibly due to superior stimulation of antioxidant and anti-inflammatory pathways [20]. The intense bursts of activity in HIIT may create a more potent hormetic stress, triggering stronger adaptive responses than continuous, submaximal exercise.

Conclusion

In conclusion, an 8-week HIIT protocol effectively ameliorated cisplatin-induced renal injury in rats, significantly improving serum creatinine and urea levels and preserving kidney morphology. These findings underscore the potential of structured exercise as a safe, non-pharmacological adjuvant strategy to protect against chemotherapy-induced nephrotoxicity.

Study limitations and future directions

This study has several limitations. First, we did not assess oxidative stress or inflammatory markers, which would have provided deeper insight into the underlying mechanisms. Second, we only evaluated one exercise protocol (HIIT); comparative studies with resistance or continuous aerobic training are needed. Third, the single-dose animal model may not fully replicate the clinical scenario of repeated cisplatin cycles in human patients. Future research should focus on: 1) Elucidating the molecular mechanisms of HIIT-induced protection through 'omics' technologies; 2) Conducting clinical trials to validate these findings in cancer patients undergoing cisplatin-based chemotherapy; and 3) Exploring the optimal timing, type, and intensity of exercise for maximum renoprotection without interfering with the anti-tumor efficacy of cisplatin.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Arak University of Medical Sciences, Arak, Iran (Code: IR.ARAKU.REC.1402.022). All procedures involving laboratory animals adhered to the principles outlined by the Committee for the Control and Supervision of Experiments on Animals (CPCSEA), ensuring responsible and humane treatment throughout the study. Euthanasia was performed using an overdose of ketamine and xylazine, an approved method.

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Authors contribution

All authors were equally involved in the conceptualization and design of the study, data acquisition and analysis, interpretation of findings, and preparation of the manuscript. Each author reviewed and approved the final version for submission.

Conflict of interest

The authors declared are no conflict of interest.

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