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The Role of Moderate-intensity Continuous Exercise in Reducing Liver Enzyme Levels and Lipid Dysregulation in Platinol-induced Rats

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ABSTRACT

Background: Platinum-based chemotherapy, a cornerstone in cancer treatment, can induce hepatotoxicity. Exercise can mitigate adverse effects of chemotherapy, including liver damage. This study aimed to investigate the protective effects of moderate-intensity continuous training (MICT) on liver function and lipid metabolism in rats induced with Platinol.

Materials and Methods: Twenty-four male Sprague-Dawley rats were randomly divided into four groups: A healthy control group, a platinol-injected control group, a MICT group, and a platinol-injected group with MICT. Serum liver enzymes alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST) and lipid profiles were measured after 10 weeks of training or platinol injection.

Results: MICT significantly reduced serum levels of AST, ALT and ALP in platinol-induced rats, comparable to healthy controls. Additionally, MICT improved lipid profiles by reducing cholesterol, triglycerides, and low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol (HDL).

Conclusion: MICT may be a promising intervention to mitigate platinum-induced liver toxicity and dyslipidemia. Further research is warranted to explore the potential clinical implications of these findings for cancer patients undergoing chemotherapy.

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Introduction

Drug-induced liver injury (DILI) is a significant public health concern characterized by hepatic damage caused by medications or their metabolites. Given the liver's pivotal role in detoxification, metabolism, and bile production, DILI can have severe consequences, ranging from mild symptoms to life-threatening conditions. The incidence of DILI has been steadily increasing, with approximately 20 new cases per 100000 inhabitants reported annually [1]. The widespread use of prescription and over-the-counter medications, particularly non-steroidal anti-inflammatory drugs and antibiotics, is a primary contributor to this rise. Older individuals, due to their higher medication use and age-related physiological changes, are at an elevated risk of experiencing DILI [2]. The clinical manifestations of DILI are diverse, encompassing symptoms such as fatigue, jaundice, abdominal pain, nausea, and loss of appetite. In severe cases, DILI can lead to liver failure, necessitating urgent medical intervention. Several factors contribute to the development of DILI, including drug toxicity, drug metabolism, genetic susceptibility, underlying liver conditions, and drug interactions [3]. Elevated levels of hepatic enzymes, including alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), are commonly used as diagnostic indicators of liver tissue damage. Numerous studies have demonstrated a strong correlation between the plasma concentrations of these enzymes and the severity of hepatic dysfunction [4].

Chemotherapy, a cornerstone in cancer treatment, involves cytotoxic drugs to eradicate malignant cells. While highly effective in numerous cases, chemotherapy can also induce significant adverse effects, including hepatotoxicity. Platinum-based chemotherapy, a mainstay in the treatment of various cancers, is mainly associated with liver damage. The accumulation of platinum metabolites within the liver can exacerbate hepatotoxicity, even at lower doses [5]. Individual variations in metabolism, genetic factors and underlying health conditions can further influence the severity and spectrum of side effects experienced by patients [6].

Regular physical activity has been shown to benefit overall health and well-being, including in cancer patients. Exercise has been demonstrated to reduce cancer mortality and recurrence risk [7, 8]. Additionally, exercise can mitigate the harmful side effects of cancer treatments, such as fatigue and reduced quality of life [9]. Previous studies have explored the potential of exercise to protect against chemotherapy-induced liver damage in animal models [10, 11, 12]. These studies have found that exercise can reduce hepatic enzyme levels, improve antioxidant status, and decrease oxidative stress, which are important factors in preventing liver injury. While substantial evidence supports the protective effects of exercise on overall health and its potential to mitigate chemotherapy-induced liver damage, a significant gap remains in understanding the specific mechanisms by which moderate-intensity continuous training (MICT) influences liver enzymes and lipid profiles in the context of platinum-based chemotherapy. Most existing studies have focused on general exercise benefits or high-intensity training, leaving a need for detailed investigation into moderate-intensity regimens. Additionally, the interaction between exercise-induced changes at the cellular level and the hepatotoxic effects of platinum compounds like platinol has not been thoroughly explored. This study aims to fill these gaps by examining the effects of a moderate continuous exercise regimen on liver function and lipid metabolism in a rat model induced with Platinol, providing insights that could inform clinical practices and therapeutic strategies for cancer patients undergoing chemotherapy.

Materials and Methods

This experimental study aims to evaluate the protective effect of moderate-intensity continuous exercise on liver enzymes and lipid profiles in platinol-induced rats. Twenty-four adult sprague-dawley rats, weighing approximately 220 g, were housed in a controlled environment at the Arak University of Medical Sciences, Arak City, Iran. The environment was maintained at a constant temperature of 23 ˚C with a 12-hour light/dark cycle. Rats had unrestricted access to food and water. To minimize stress and ensure their adaptation to the new environment, a one-week acclimatization period was implemented before the start of the experiment. Subsequently, the rats were randomly divided into 4 groups: A healthy control group, a platinol-injected control group, MICT healthy group, platinol and MICT (P-MICT) group.

Exercise training

A standardized MICT protocol was implemented for 10 weeks. The training modality employed a 5-channel treadmill (TRD19, Pishro Andisheh Sanat Company) to ensure precise control over exercise intensity (speed) and duration. This level of control is essential for maintaining consistency and accuracy throughout the training program. Rats assigned to the exercise group participat-

ed in training sessions five days per week for the entire 10-week period. The training protocol was meticulously designed and comprised three phases: familiarization, overload and maintenance. During the familiarization phase (week 1), the rats were acclimatized to the treadmill environment and the exercise routine. During this phase, the exercise intensity was gradually increased to minimize potential stress or injury. Rats began with low-intensity walking exercises at a speed of 8 m/min for 10-15 minutes daily. The overload phase (weeks 2-4) aimed to progressively challenge the cardiorespiratory and musculoskeletal systems of the rats, thereby promoting physiological adaptations and enhancing their overall fitness level. The training intensity was systematically increased throughout this phase. Rats began with running at a moderate speed of 27 m/min for 20 minutes, gradually extending to 60 minutes or four weeks. The maintenance and stabilization phase (weeks 5-10) aimed to consolidate the fitness gains achieved during the overload phase and ensure long-term maintenance of these improvements. Rats continued to perform MICT training at a constant speed of 27 m/min for a sustained duration of 60 minutes, five days per week, for the remaining six weeks. To optimize training effectiveness and minimize the risk of injury, each session incorporated a structured warm-up (5 minutes at a speed of 16 m/min) followed by a cool-down period (5 minutes at 16 m/min, gradually decreasing to a minimum). This structured approach ensured the safety and well-being of the animals throughout the training program [13, 14].

Platinum injection

To induce hepatic toxicity, rats were fasted for 12 hours prior to receiving an intraperitoneal injection of platinol solution (Sobhan Oncology Pharmaceutical Company, Iran). Platinol, a widely used chemotherapeutic agent, was administered at a 5.5 mg/kg dose, diluted in normal saline. This dose was carefully selected based on previous studies to ensure the induction of liver toxicity without causing excessive mortality [15]. The MICT protocol was initiated one week following the injection, allowing sufficient time for the cisplatin to exert its toxic effects on the liver tissue. This delayed initiation of MICT was also intended to minimize any potential interference of the training regimen on the absorption and distribution of Platinol.

Blood collection and serum separation

Subjects were anesthetized with diethyl ether 48 hours following the final training session. Blood samples were subsequently collected from the left ventricle of the animal hearts. Centrifugation of the blood samples at 3000 rpm for 10 minutes facilitated serum isolation. The extracted serums were initially stored in liquid nitrogen at -196 ˚C and transferred to -80 ˚C for long-term preservation until experimentation. A photometric microplate reader (Elizarider) model MR4+ was employed to measure serum liver enzyme levels. Serum concentrations of ALP, ALT, AST, triglycerides (TG), total cholesterol (TC) and high-density lipoprotein (HDL) were determined enzymatically using commercially available kits (Pars Azmoun Co., Tehran, Iran). These measurements were conducted using a spectrophotometer (JENWAY 6505, European Union). Low-density lipoprotein (LDL) was calculated using the Friedwald formula.

Statistical data analysis

Data were analyzed using SPSS software, version 26. The Shapiro-Wilk test was conducted to verify the normality of the data distribution. Levene's test was employed to assess the homogeneity of variances. After confirming these assumptions, a one-way analysis of variance (ANOVA) was performed to determine significant differences among groups. The Tukey HSD post hoc test was applied to identify specific pairwise differences between groups at a significance level of $P<0.05$.

Results

Table 1 presents the Mean±SD of the measurement variables for the groups.

Liver enzymes

To assess the impact of MICT on liver function, we measured serum levels of AST, ALT and ALP.

AST

One-way ANOVA revealed significant differences in AST levels among the study groups ($F_{(3, 20)}=14.894$, $P=0.001$). Post hoc Tukey HSD tests indicated that the platinol control group exhibited significantly elevated AST levels compared to the healthy control group ($P=0.001$). MICT significantly reduced AST levels in the platinol group with moderate continuous training (P-MICT) compared to the platinol control ($P=0.004$). However, there were no significant differences in AST levels between the platinol group with MICT and the healthy control and healthy MICT groups ($P=0.221$ and $P=0.967$, respectively).

Table 1. Serum lipid profile and liver enzymes of rats in different study groups

Groups	Mean±SD						
	ALT (mg/dL)	AST (mg/dL)	ALP (mg/dL)	Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
HC	67.32±2.13	141.10±22.6	284.16±58.47	64.38±3.63	95.16±22.64	11.83±1.9	34.83±1.9
PC	92.71±10.17	299.33±93.17	370.66±25.54	76.65±7.1	137.83±8.08	16.16±3.31	27.20±4.12
MICT	64.33±3.32	127.83±17.92	257.66±38.96	57.71±4.29	86.83±19.91	10.33±1.21	32.88±2.39
P-MICT	74.83±12.51	185.10±22.46	270.16±45.43	60.91±5.31	105.66±10.67	9.5±3.27	31.61±1.5

Abbreviations: HC: Healthy control; PC: Platinol-injected control; MICT: Moderate-intensity continuous training; P-MICT: Platinol and moderate-intensity continuous training; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

ALT

Similar to AST, significant differences were observed in ALT levels among the study groups ($F_{(3, 20)}$=11.901, P=0.001). The platinol control group displayed significantly elevated ALT levels compared to the healthy control group (P=0.001). MICT significantly reduced ALT levels in the platinol group with MICT compared to the platinol control (P=0.014). Notably, the P-MICT showed no significant difference in ALT levels compared to the healthy control and healthy MICT groups (P=0.195 and P=0.911, respectively).

ALP

One-way ANOVA revealed significant differences in ALP levels among the study groups ($F_{(3, 20)}$=8.206, P=0.001). The platinol control group exhibited significantly elevated ALP levels compared to the healthy control group (P=0.013). MICT significantly reduced ALP levels in the platinol group with MICT compared to the platinol control (P=0.004). Notably, the P-MICT showed no significant difference in ALP levels compared to the healthy control and healthy MICT groups (P=0.959 and P=0.723, respectively).

These findings demonstrate that MICT effectively improves liver function in patients with platinol-induced liver injury. MICT significantly reduces AST, ALT and ALP levels, restoring liver enzyme levels to healthy control levels.

Lipid profile

To assess the impact of MICT on lipid metabolism, we analyzed serum cholesterol, triglyceride, LDL and HDL levels.

Cholesterol

One-way ANOVA revealed significant differences in serum cholesterol levels among the study groups ($F_{(3, 20)}$=14.931, P=0.001). Post hoc Tukey HSD tests indicated that the platinol control group exhibited significantly higher cholesterol levels than the healthy control group (P=0.003). Conversely, MICT significantly reduced cholesterol levels in the platinol group with MICT compared to the platinol control (P=0.001). Notably, this reduction eliminated significant differences compared to the healthy control and healthy MICT groups (P=0.668 and P=0.719, respectively).

Triglycerides

Like cholesterol, serum triglyceride levels differed significantly among the study groups ($F_{(3, 20)}$=11.013, P=0.001). The platinol control group displayed significantly elevated triglyceride levels compared to the healthy control group (P=0.002). MICT effectively lowered triglyceride levels in the platinol group with MICT compared to the platinol control (P=0.015). Importantly, this improvement showed no significant differences between the platinol group with MICT and the healthy control and healthy MICT groups (P=0.692 and P=0.229, respectively).

LDL

Serum LDL levels also varied significantly among the study groups ($F_{(3, 20)}$=7.854, P=0.01). Post hoc Tukey HSD test indicated that the platinol control group had significantly higher LDL levels than the healthy control group (P=0.001). MICT significantly reduced LDL levels in the platinol group with MICT compared to the platinol control (P=0.001). This reduction was sufficient to eliminate significant differences compared to the healthy control and healthy MICT groups (P=0.423 and P=0.944, respectively).

HDL

One-way ANOVA revealed significant differences in serum HDL levels among the study groups ($F_{(3, 20)}$=9.597, P=0.001). The platinol control group exhibited significantly lower HDL levels than the healthy control group (P=0.001). MICT significantly increased HDL levels in the platinol group with MICT compared to the platinol control (P=0.034). Importantly, this improvement showed no significant differences between the platinol group with MICT and the healthy control and healthy MICT groups (P=0.827 and P=0.562, respectively).

These findings demonstrate that MICT effectively improves lipid profiles in patients with platinol-induced dyslipidemia. MICT significantly reduces cholesterol, triglyceride and LDL levels while increasing HDL levels, thereby restoring lipid profiles to levels comparable to those of healthy controls.

Discussion

This study demonstrated that MICT significantly reduced serum levels of AST, ALT and ALP in platinol-induced rats, bringing them close to levels seen in healthy controls. MICT also improves lipid profiles by decreasing cholesterol, TG and LDL cholesterol while increasing HDL cholesterol. In line with the findings of our study, Ye et al. investigated the association of health-related physical fitness with liver function. In this study, indicators related to the physical fitness of 330 students were measured, and the relationship between these indicators and liver function was evaluated. This study showed a positive relationship between high physical fitness and optimal liver function [16]. Shephard and Johnson explored the liver's response to acute and chronic physical activity. Their findings highlight that regular, moderate exercise improves liver health. Conversely, insufficient habitual activity can lead to negative functional changes. Highly prolonged competitive exercise can also be harmful, particularly under harsh conditions [17]. Loprinzi and VanWagner investigated the impact of physical activity on survival rates among individuals with liver disease. Their research demonstrates that even modest increases in moderate-to-vigorous physical activity can provide survival benefits for those with a self-reported liver condition. They found that moderate-to-vigorous physical activity is inversely related to all-cause mortality among these individuals and this relationship holds regardless of alcohol use or hepatitis C status [18].

Platinol, or cisplatin, is a chemotherapy drug that can cause liver toxicity. The exact mechanisms underlying this toxicity are complex but involve several key factors. platinol can directly damage hepatocytes (liver cells) through apoptosis. This process involves the activation of cellular pathways that lead to cell death [19]. Platinol can induce oxidative stress in the liver, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. ROS can damage cellular components, including DNA, proteins, and lipids.

Additionally, platinol can trigger an inflammatory response in the liver, activating immune cells and releasing inflammatory mediators [20, 21]. Chronic inflammation can contribute to liver damage and dysfunction. Platinol can interfere with bile flow from the liver, leading to cholestasis. This condition can build up bile in the liver, leading to inflammation and damage. Furthermore, platinol can damage the mitochondria, the energy-producing organelles within cells, leading to mitochondrial dysfunction, cellular stress, and death [22].Genetic factors also influence a person's susceptibility to platinol-induced liver toxicity; some individuals may have genetic variations that make them more prone to liver damage. Compounding these effects, pre-existing liver conditions or concurrent medications can exacerbate platinol's liver toxicity [23]. Physical activity and exercise training have emerged as promising interventions for preventing and managing liver diseases. The mechanisms behind these benefits are multifaceted, involving several key pathways. Exercise-induced increases in energy expenditure contribute to weight loss and reduced hepatic steatosis [24]. Enhanced insulin sensitivity from physical activity decreases hepatic glucose production and lipid accumulation [24]. Additionally, exercise promotes fatty acid oxidation, reducing the accumulation of TG within the liver. Regular physical activity increases the number and function of mitochondria in liver cells, improving metabolic efficiency and reducing oxidative stress. Exercise-induced autophagy helps remove damaged organelles and proteins, promoting liver cell health and regeneration. Physical activity reduces inflammation by modulating the expression of inflammatory cytokines and chemokines. Exercise stimulates the production of endogenous antioxidants, protecting liver cells from oxidative damage [17].

Furthermore, exercise influences the secretion of adipokines, such as adiponectin and leptin, which benefit liver health. Physical activity also increases growth hormone levels, promoting liver regeneration and improving metabolic function. Emerging evidence suggests that exercise

may positively influence the gut-liver axis, where changes in the gut microbiota due to physical activity can lead to improved liver health through metabolic and immune system interactions. Lastly, regular physical activity has been associated with improved vascular function, which enhances blood flow to the liver, further supporting its detoxification processes and nutrient delivery [25, 26].

Platinol, or cisplatin, increases total cholesterol, TG and LDL levels. In some cases, it may also reduce HDL levels [27]. The exact mechanisms underlying platinol-induced changes in lipid profile are complex and multifaceted. However, several potential mechanisms have been proposed. Firstly, platinol can directly affect the liver, leading to alterations in the synthesis, breakdown, and secretion of lipids. This condition can result in increased production of cholesterol and TG and decreased clearance of LDL. The liver's lipid homeostasis disruption significantly contributes to these changes [28]. Secondly, platinol-induced damage to other organs, such as the kidneys or gastrointestinal tract, can indirectly affect lipid metabolism. For example, kidney damage can lead to alterations in electrolyte balance and hormonal factors involved in lipid regulation. The kidneys play a crucial role in maintaining lipid balance, and their impairment can have systemic effects on lipid profiles. Moreover, platinol may influence the secretion of hormones involved in lipid metabolism, such as thyroid hormones, cortisol, and sex hormones. These hormonal changes can contribute to alterations in lipid profiles. For instance, changes in thyroid hormone levels can significantly impact lipid metabolism, while cortisol and sex hormones can influence lipid synthesis and breakdown [29, 30]. Additionally, platinol-induced oxidative stress and inflammation can further exacerbate lipid dysregulation. Producing ROS and the subsequent oxidative damage can disrupt normal cellular processes involved in lipid metabolism. Inflammation can also influence lipid metabolism by altering the expression and activity of key enzymes involved in lipid synthesis and degradation [31, 32]. Lastly, genetic factors may also influence an individual's susceptibility to platinol-induced lipid changes. Some individuals may have genetic variations that make them more prone to lipid dysregulation when exposed to platinol. Understanding these genetic factors can help identify those at higher risk and guide personalized treatment approaches [33].

A significant body of research has demonstrated the beneficial effects of exercise on lipid profiles, including reductions in LDL, TG and total cholesterol, as well as increases in HDL. Exercise-induced increases in energy expenditure contribute to weight loss and reduced body fat mass, which are associated with improved lipid profiles [34]. Regular physical activity enhances insulin sensitivity, leading to reduced hepatic glucose production and increased glucose uptake by peripheral tissues. This condition can result in decreased hepatic lipid synthesis and improved lipid clearance. Furthermore, exercise stimulates the breakdown of fatty acids for energy, reducing the accumulation of TG in the liver and adipose tissue [34]. Chronic inflammation is linked to dyslipidemia, and exercise can mitigate inflammation by modulating the production of inflammatory cytokines and chemokines. Exercise enhances endothelial function, which is crucial in regulating lipid metabolism. Improved endothelial function can increase LDL cholesterol clearance and reduce LDL oxidation [35]. Exercise can also influence the secretion of hormones involved in lipid metabolism, such as adiponectin, leptin, and growth hormone, which can benefit lipid profiles. For instance, exercise can lower triglyceride levels by increasing energy expenditure, improving insulin sensitivity, and stimulating fatty acid oxidation [36]. Physical activity is associated with increased HDL cholesterol levels. HDL cholesterol plays a critical role in reverse cholesterol transport, removing excess cholesterol from the tissues and transporting it to the liver for excretion. While exercise may not directly lower LDL cholesterol levels as significantly as some medications, it can still benefit by improving endothelial function and reducing inflammation [37].

Conclusion

This study provides compelling evidence that MICT can significantly mitigate the adverse effects of platinol-induced liver toxicity and dyslipidemia in rats. The findings demonstrate that MICT effectively reduces serum levels of liver enzymes and improves lipid profiles by lowering cholesterol, TG and LDL and increasing HDL cholesterol. These results suggest that exercise may be a promising intervention to protect the liver from chemotherapy's harmful effects and improve overall metabolic health in cancer patients. Further research is warranted to elucidate the specific mechanisms underlying the protective effects of MICT on liver function and lipid metabolism in platinum-based chemotherapy. Additionally, studies investigating the optimal exercise regimen, including intensity, duration and frequency, are necessary to maximize the benefits in human patients. If these findings are replicated in clinical trials, MICT could be integrated into the standard care for cancer patients undergoing chemotherapy to improve their quality of life and overall prognosis.

Study limitations

This study has several limitations that should be considered when interpreting the findings. The study included a relatively small sample of rats. A larger sample size would have increased the study's statistical power and strengthened the findings' generalizability. While rat models are commonly used to study DILI and the effects of exercise, they may not fully replicate the complex physiological and pharmacological responses observed in humans. Therefore, the findings may not directly translate to human patients. The study used a single dose of platinol to induce liver toxicity. However, human patients often receive multiple doses of chemotherapy over an extended period, which may lead to different patterns of liver injury and response to exercise. Further research is needed to elucidate the specific pathways through which exercise exerts its beneficial effects.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Arak University of Medical Sciences, Arak Iran (Code: IR.ARAKMU.REC.1401.014). The committee for control and supervision of experiments on animals (CPCSEA) guidelines were followed to ensure compliance with ethical standards in animal studies.

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Authors contribution's

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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