Research in Molecular Medicine

Effects of HIIT on Lipid Profile and Body Weight in Radiotherapy Rats

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Citation Parastesh M, Aria B, Torkashvand Z, Sadeghian Shahi AH. Effects of HIIT on Lipid Profile and Body Weight in Radiotherapy Rats. Research in Molecular Medicine. 2024; 12(3):67-74. https://doi.org/10.32598/rmm.12.2.1352.2

https://doi.org/10.32598/rmm.12.2.1352.2

Article Type:
Research Paper

Article info:
Received: 13 May 2024
Revised: 28 May 2024
Accepted: 10 Aug 2024

Keywords:
Dyslipidemia, High-intensity interval training (HIIT), Radiotherapy (RT), Lipid profile

ABSTRACT

Background: Dyslipidemia, marked by abnormal levels of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG), is a key risk factor for cardiovascular diseases. Radiotherapy (RT), while effective in cancer treatment, may induce adverse metabolic effects, including dyslipidemia. High-intensity interval training (HIIT) has shown potential in improving lipid metabolism. This study investigated the effects of HIIT on lipid profiles and body weight in rats undergoing RT.

Materials and Methods: This study was an experimental, randomized controlled trial conducted over 10 weeks. Twenty-four male Wistar rats (aged 8 weeks) were randomly divided into four groups (n=6 per group): Control, HIIT, RT, and HIIT + RT. The HIIT protocol consisted of 6 sessions per week on a treadmill, including familiarization (week 1), progressive overload (weeks 2–4), and stabilization phases (weeks 5–10). RT was administered as a single 11 Gy dose using a linear accelerator. Blood samples were collected post-intervention, and lipid profiles (TG, TC, LDL, and HDL) were analyzed using enzymatic assays and a spectrophotometer. Data were analyzed by SPSS software,version 26 using one-way ANOVA and Bonferroni post-hoc test; significance was set at $P<0.05$.

Results: Compared to controls, RT significantly increased TC (69.3±3.1 mg/dL vs 59.5±6.3 mg/dL, P=0.002), LDL (14.3±1.2 mg/dL vs 11.5±1 mg/dL, P=0.001), and TG (83.7±3.5 mg/dL vs 75.7±6.3 mg/dL, P=0.13) while decreasing HDL (21.7±1.4 mg/dL vs 30±3.3 mg/dL, P=0.001). HIIT significantly improved all parameters compared to RT alone: TC (52.0±2.8 mg/dL vs 69.3±3.1 mg/dL, P<0.001), LDL (9.5±1 mg/dL vs 14.3±1.2 mg/dL, P<0.001), TG (50.7±6.3 mg/dL vs 83.7±3.5 mg/dL, P<0.001), and HDL (36±3 mg/dL vs 21.7±1.4 mg/dL, P<0.001). No significant weight changes occurred (270.4±28.7 g vs 274±18.7 g, P=0.65). HIIT may counteract RT-induced dyslipidemia.

Conclusion: These findings suggest that HIIT may counteract RT-induced dyslipidemia, highlighting its potential as a therapeutic intervention. Further studies are needed to validate these results and explore underlying mechanisms.

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Introduction

Lipid profile disorders, also known as dyslipidemia, involve abnormal changes in blood lipid levels, including total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). These disorders play a significant role in increasing the risk of cardiovascular diseases, such as atherosclerosis, myocardial infarction, and stroke [1]. Elevated levels of LDL and TG, along with reduced HDL levels, are associated with the accumulation of fatty plaques in arterial walls, which can lead to arterial narrowing and reduced blood flow to vital organs [2, 3]. Furthermore, lipoproteins, which are complexes of lipids and proteins, play a crucial role in lipid metabolism and their transport in the bloodstream. In the context of cancer, lipoproteins can influence tumor growth and progression. Some studies have suggested that high levels of LDL may be associated with an increased risk of cancer, as LDL can provide the necessary lipids for the growth and proliferation of cancer cells. On the other hand, HDL may have protective effects against cancer by aiding in the removal of excess cholesterol from cells and preventing lipid accumulation in tumors. Overall, the balance between different types of lipoproteins and their role in lipid metabolism can influence cancer progression [4].

The management of these disorders through lifestyle modifications, such as a healthy diet, regular physical activity, and, when necessary, the use of lipid-lowering medications, can significantly reduce cardiovascular risks and improve overall health [5, 6]. Among these interventions, exercise, as a non-pharmacological, cost-effective, and accessible approach, plays a vital role in improving metabolic health and weight management [7]. Among various types of exercise, high-intensity interval training (HIIT) has garnered considerable attention from researchers and professionals due to its rapid and profound effects on metabolism. HIIT involves short periods of intense activity followed by periods of rest or low-intensity activity. Numerous studies have demonstrated that HIIT can improve lipid profiles (including reductions in TG, TC, and LDL, as well as increases in HDL), enhance insulin sensitivity, and aid in weight loss. These effects are likely mediated through mechanisms, such as increased fat oxidation, improved mitochondrial function, and reduced systemic inflammation [8, 9].

Radiotherapy (RT), as one of the primary methods for cancer treatment, utilizes ionizing radiation to destroy cancer cells and inhibit tumor growth. Although the primary goal of RT is to control and treat cancer, recent studies suggest that this method may also have metabolic side effects, including impacts on blood lipid profiles [10]. RT can lead to changes in blood lipid levels. These changes may result from the effects of radiation on lipid metabolism or alterations in liver function [11, 12]. However, few studies have been conducted in this area. Therefore, a more detailed investigation into the effects of RT on lipid profiles is warranted. Given the positive effects of HIIT on lipid metabolism and body weight, the question arises as to whether combining HIIT with RT can mitigate the adverse metabolic effects of RT. To address this question, the use of animal models, particularly rats, is invaluable due to their physiological and metabolic similarities to humans. Rats are widely used in medical and exercise science research because they allow for precise control of experimental variables and the examination of molecular and cellular mechanisms [13]. This study aimed to investigate the effects of HIIT on the lipid profile (including TG, TC, LDL, and HDL) and body weight in rats undergoing RT.

Materials and Methods

Study design and methodology

This study was designed as a controlled experiment to investigate the combined effects of RT and HIIT on lipid profile and body weight in an animal model. A total of 24 adult male Wistar rats, with an average weight of 205±54 grams and aged 8 weeks, were selected as the study subjects. The animals were randomly divided into four groups: Control group (n=6): No exercise or RT intervention; HIIT group (n=6): Receiving only the HIIT program; RT group (n=6): Receiving only RT; combined group (RT + HIIT, n=6): Receiving both RT and HIIT.

Environmental conditions included a controlled temperature of 22±2 ˚C, free access to water and food, and a 12-hour light/dark cycle.

RT protocol

For RT administration, the rats were first anesthetized via an intraperitoneal injection of ketamine (60-90 mg/kg) and xylazine (6-10 mg/kg). The animals were then placed on a 1 cm-thick plexiglass sheet positioned on a 2 cm-thick base. This setup created an effective point of measurement (MPP) of 3 cm between the radiation source and the rats. The distance from the radiation source to the plexiglass sheet was set at 1 meter [14]. A radiation dose of 11 Gy was selected and administered using a linear accelerator (Elekta Compact 6-MV, China)

with x-ray photon beams at the RT Center of Khansari Hospital in Arak. This dose was chosen based on previous studies to achieve measurable biological effects.

HIIT protocol

The HIIT program was designed to last 10 weeks, with 6 training sessions per week. The program was divided into three main phases: 1) Familiarization phase (week 1): Rats walked on a treadmill daily for 10-15 minutes at a speed of 8 m/min to acclimate to the exercise conditions. 2) Progressive overload phase (weeks 2-4): Rats performed 2 to 6 intervals of 3 minutes at a speed of 40 m/min, and on even days, they performed 3 to 20 intervals of 30 seconds at a speed of 54 m/min. 3) Stabilization phase (weeks 5-10): Rats underwent the HIIT program for 6 weeks. Between exercise intervals, active rest at a speed of 16 m/min for 1 minute was included. Each training session began with a 5-minute warm-up and ended with a 5-minute cool-down at a speed of 16 m/min [15].

Lipid profile assessment

Twenty-four hours after the last training session, 5 mL of blood was collected from all rats via the tail vein. After clotting, the blood samples were centrifuged at 3500 rpm for 10 minutes to separate the serum. The serum samples were stored at -70 ˚C to prevent biological degradation. Serum concentrations of TG (TG), TC, and HDL were measured using commercial kits (Pars Azmun, Tehran, Iran) and enzymatic methods. Measurements were performed using a spectrophotometer (JENWAY 6505, EU). LDL concentrations were calculated using the Friedewald formula [16].

Statistical analysis

Data were analyzed using SPSS, software, version 26. The normality of the data distribution was first assessed using the Shapiro-Wilk test. Given the normal distribution of the data, one-way ANOVA was used to compare means between groups. In cases of significant differences, the Bonferroni post-hoc test was used for pairwise comparisons. A significance level of $P<0.05$ was considered for all tests.

Results

The comparison of blood parameters and body weight among the four study groups revealed significant changes. As shown in Table 1, the groups were homogeneous in terms of initial weight ($P>0.98$) and showed no significant differences in final body weight ($P=0.65$).

Table 2 demonstrates that RT alone significantly increased TC ($P=0.002$), LDL ($P=0.001$), and decreased HDL ($P<0.001$) levels compared to the control group. In contrast, HIIT significantly improved the lipid profile, with the HIIT+RT group showing marked reductions in Tg ($P<0.001$), TC ($P<0.001$), and LDL ($P<0.001$) levels, along with increased HDL levels ($P<0.001$) compared to RT alone.

The statistical comparisons presented in Table 3 indicate that significant differences existed between the HIIT and control groups for all lipid parameters except TG levels ($P=0.13$). The combination of HIIT with RT completely counteracted RT's negative effects on lipid profile (all $P<0.001$). No significant differences were observed between the HIIT and HIIT+RT groups ($P>0.05$ for all parameters).

These findings suggest that HIIT may serve as an effective intervention to mitigate RT-induced metabolic disturbances.

Discussion

The findings of the present study indicate that RT leads to unfavorable changes in the lipid profile. However, 8 weeks of HIIT resulted in a significant reduction in TG, total TC, and LDL levels, as well as an increase in HDL levels in rats. Nevertheless, no significant changes in body weight were observed. Wolny-Rokicka et al. demonstrated that RT in prostate cancer patients increases TC, LDL, and TG levels while decreasing HDL levels [12]. Regarding the effects of HIIT on the lipid profile, Liu et al. showed that 3 weeks of HIIT improved the lipid profile in patients with type 2 diabetes [8]. Similarly, Ghodssi et al. reported that HIIT reduced TG, TC, and LDL levels while increasing HDL levels in inactive women [9].

RT, as one of the primary methods for cancer treatment, utilizes ionizing radiation to destroy cancer cells and inhibit tumor growth. Although the primary goal of RT is to control and treat cancer, recent studies suggest that this method may also have metabolic side effects [11, 12]. The increase in TC, TG, and LDL, along with a decrease in HDL levels following RT, may result from complex mechanisms involving direct and indirect effects of ionizing radiation on lipid metabolism and related biological systems. Ionizing radiation may impair liver function, which plays a central role in lipid metabo-

Table 1. Baseline weight of experimental groups

Group	No.	Mean±SD		Radiation Dose
		Initial Weight (g)	Final Weight (g)	
Control	6	205±12	283±6	-
HIIT	6	208±10	274.8±5	-
RT	6	207±11	274±18.7	11 Gy
HIIT + RT	6	206±13	270.4±28.7	11 Gy

Table 2. Lipid profile outcomes (mg/dL)

Group	Mean±SD			
	LDL	HDL	TG	TC
Control	11.5±1	30±3.3	75.7±6.3	59.5±6.3
HIIT	8.7±1*	37.5±4.5*	53.2±5.8*	47.3±2.6*
RT	14.3±1.2*	21.7±1.4*	83.7±3.5*	69.3±3.1*
HIIT + RT	9.5±1*	36±3*	50.7±6.3*	52±2.8*

Abbreviations: LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; TC: Total cholesterol.
*Statistically significant difference ($P<0.05$) compared to the control group.

lism. The liver is responsible for cholesterol synthesis, TG production, and the regulation of lipoprotein levels. RT may reduce the activity of liver enzymes, such as lipoprotein lipase (LPL), which plays a key role in the breakdown of TG and the formation of HDL [17]. Additionally, radiation may reduce the expression or function of LDL receptors in the liver, which are responsible for the uptake of LDL from the bloodstream and the reduction of its levels. Dysfunction of these receptors leads to the accumulation of LDL in the blood and an increase in TC levels [18].

Systemic inflammation and oxidative stress induced by RT can also affect lipid metabolism. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), may increase the production of VLDL in the liver, which is a precursor to LDL. Oxidative stress caused by free radicals can lead to the oxidation of LDL, resulting in the formation of oxidized LDL (ox-LDL). This form of LDL is more atherogenic and contributes to an increased risk of cardiovascular diseases [19, 20]. Furthermore, inflammation and oxidative stress caused by RT can increase the degradation of HDL and reduce its levels in the blood [21]. Changes in the gut microbiome may also

Table 3. Comparison of the groups regarding their lipid profile

Comparison	TG (mg/dL)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Weight (g)
HIIT vs control	0.001	0.001	0.001	0.004	0.35
RT vs control	0.13	0.002	0.001	0.001	0.82
HIIT+RT vs RT	0.001	0.001	0.001	0.001	0.78
HIIT+RT vs HIIT	0.62	0.34	0.28	0.58	0.91

Abbreviations: LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; TC: Total cholesterol; HIIT: High-intensity interval training; RT: Radiotherapy.

influence lipid metabolism. Ionizing radiation may alter the composition and function of the gut microbiome, which can affect the absorption of fats and cholesterol from the intestine, leading to increased levels of TG and LDL [22].

The reduction in TG levels in rats undergoing HIIT and RT is likely due to increased fat oxidation and improved insulin sensitivity. HIIT activates key enzymes, such as LPL, and enhances mitochondrial activity, leading to greater breakdown of TG and the use of fatty acids as an energy source. LPL is an enzyme that plays a primary role in the breakdown of TG into fatty acids and glycerol. Increased activity of this enzyme results in greater TG breakdown in adipose and muscle tissues, and the released fatty acids are used as an energy source [23, 24]. Additionally, HIIT increases mitochondrial activity in muscle cells. Mitochondria are responsible for fatty acid oxidation and energy production. The increase in mitochondrial number and function due to HIIT enhances the body's ability to use fats as fuel, thereby reducing blood TG levels [25]. HIIT also plays a significant role in reducing blood TG levels by improving insulin sensitivity. Insulin resistance is a major factor in elevated TG levels, as it reduces the body's ability to use glucose and increases fat storage. HIIT enhances glucose uptake by muscles and reduces insulin resistance, thereby helping to lower triglyceride levels. Improved insulin sensitivity also reduces the activity of enzymes involved in TG synthesis in the liver [26].

The reduction in TC and LDL levels is likely due to increased activity of enzymes involved in cholesterol metabolism and increased LDL receptors in the liver. HMG-CoA reductase is an enzyme that plays a central role in cholesterol synthesis in the liver. Increased activity of this enzyme leads to reduced internal cholesterol production and, consequently, lower levels of TC and LDL in the blood [27]. HIIT may reduce TC and LDL levels by decreasing the activity of HMG-CoA reductase (involved in cholesterol synthesis) and increasing the activity of LDL-degrading enzymes, such as LPL [28]. Additionally, HIIT may increase the activity of other enzymes, such as LPL and cholesterol esterase, which are involved in the breakdown and removal of LDL from the bloodstream. These enzymes help break down LDL and use it as an energy source [23, 24]. HIIT also increases the expression of LDL receptors in the liver, which helps reduce LDL levels in the blood. LDL receptors in the liver are responsible for the uptake and removal of LDL from the bloodstream. An increase in the number of these receptors enhances LDL uptake by the liver and reduces its levels in the blood. This mechanism is one of the primary ways through which HIIT can improve the lipid profile [29].

The increase in HDL levels is likely due to increased production of apolipoprotein A-I (ApoA-I), the main component of HDL, and increased activity of enzymes involved in HDL metabolism, such as lecithin-cholesterol acyltransferase (LCAT). ApoA-I is the primary component of HDL and plays a key role in its formation and function [30]. HIIT may increase the synthesis of ApoA-I by upregulating genes associated with its production in the liver. Increased levels of ApoA-I lead to greater HDL formation and improved function in transporting cholesterol from peripheral tissues to the liver (reverse cholesterol transport) [30]. HIIT may also increase HDL levels by enhancing the activity of key enzymes in HDL metabolism, such as LCAT. LCAT is an enzyme that plays a central role in the esterification of free cholesterol in HDL, converting immature HDL into mature HDL. Increased activity of this enzyme enhances HDL's efficiency in cholesterol transport and improves the lipid profile [31]. HIIT also increases HDL levels by improving insulin sensitivity and reducing systemic inflammation. Insulin resistance and chronic inflammation are major factors in reduced HDL levels. HIIT enhances glucose uptake by muscles and reduces insulin resistance, thereby improving lipid metabolism and increasing HDL levels [26].

Despite significant improvements in the lipid profile (reduction in TG, TC, and LDL, and an increase in HDL levels), no significant changes in body weight were observed in the rats. The 8-week HIIT program may not have been sufficient to induce significant changes in body weight, especially if the rats were in a state of energy balance. Changes in body weight typically occur gradually over time, and longer intervention periods may be required to observe significant changes. HIIT may reduce body fat and increase muscle mass, but these changes may not be reflected in total body weight. In other words, fat loss and muscle gain may offset each other, keeping overall weight stable. HIIT improves body composition by increasing fat oxidation and stimulating protein synthesis in muscles without causing significant changes in total body weight [32, 33].

Conclusion

The findings of this study suggest that combining 8 weeks of HIIT with RT can have positive effects on the lipid profile of rats undergoing RT. These effects are likely mediated through metabolic and molecular mechanisms related to lipid breakdown and synthesis. However, the lack of significant changes in body weight may be due to the study's duration or the interplay between exercise and RT on body composition. To better under-

stand these mechanisms and their long-term effects, further studies with longer intervention periods and human samples are recommended.

Study limitations

This research has several limitations that must be taken into account when interpreting the results. The limited number of rats in each group (n=6) may reduce the statistical power of the study and limit the generalizability of the results. Although the rats had access to standard food and water, precise control of dietary intake (e.g. calorie intake or nutrient composition) was not implemented, which could influence the study outcomes. While this study examined changes in the lipid profile, the precise molecular and cellular mechanisms underlying these changes were not fully explored. Further studies at the molecular level are necessary to better understand these mechanisms. The 11 Gy dose of RT used in this study may be sufficient to induce significant changes in the lipid profile, but the effects of different radiation doses on lipid profiles and body weight were not investigated. Although no significant changes in body weight were observed, changes in body composition (e.g. fat loss and muscle gain) were not assessed. These changes may not be reflected in total body weight but could impact metabolic health.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted in full compliance with ethical guidelines for the use of laboratory animals and was approved by the Ethics Committee of Arak University of Medical Sciences, Arak, Iran (Code: IR.ARAKMU.REC.1401.015). All efforts were made to minimize pain and suffering in the animals and to adhere to international standards for animal research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contribution's

All authors made equal contributions to the study's conception and design, data collection and analysis, interpretation of the findings, and manuscript preparation. Each author reviewed and approved the final version of the manuscript before submission.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors would like to extend their sincere gratitude to all individuals who contributed to the successful completion of this research.

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