The Effect of High-Intensity Interval Training and High-Fat Diet on Serum Concentration of Uncoupling Protein 1 (UCP1) and Cardiovascular Risk Factors in Girls with Overweight and Obesity

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Abstract

Introduction: High-fat diets and physical exercise are associated with increased expression of genes involved in the metabolism and browning of adipose tissue; however, their molecular mechanisms are not fully understood. In the present study, the effect of high-intensity interval training (HIIT) over a period of a ketogenic diet (KD) on serum levels of uncoupling protein 1(UCP1), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC) in females with overweight and obesity were investigated. **Materials and Methods:** In this quasi-experimental study with pre- and post-test design, 16 inactive females with overweight and obesity (BMI>25 kg.m-2, aged 18-24 years) were randomly divided into two groups of eight individuals (KD+HIIT: Experimental group or KD: Control group) and participated in a six-week experimental period (KD: 70% fat, 20% protein and 10% carbohydrate; HIIT: 4×4 min running with an intensity of 85-95% of maximal heart rate, three 45-min sessions per week). Blood samples were collected and analyzed 48 h before and after the experimental period. The data were analyzed using ANCOVA and paired-samples t-tests at the 95% confidence level. **Results:** From pre-test to post-test, KD+HIIT was associated with a significant increase in UCP1 (P=0.007) and HDL (P<0.001) and a significant decrease in LDL (P=0.001) and TC (P=0.009), whereas KD led to a significant increase in HDL (P<0.001) and a significant decrease in LDL (P=0.002). After controlling for pre-test effects, the levels of UCP1 (P=0.006) and HDL (P<0.001) in experimental group in post-test were significantly higher than in KD group, whereas differences in LDL (P=0.486) and TC (P=0.665) levels were not statistically significant (P>0.05). **Conclusion:** Combining HIIT with a KD is more effective than KD alone in activating the browning pathways of adipose tissue and improving blood lipid profile, which can be used to manage overweight and prevent the cardiovascular consequences of obesity.

Keywords: Brown Adipose Tissue; High-Intensity Interval Training; High-Fat Diet; Obesity Management; Uncoupling Protein 1

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Introduction

Overweight and obesity are due to genetic predisposition combined with a sedentary lifestyle and excessive calorie intake, and are related to the development of non-communicable diseases (NCDs) such as cardiovascular disease, type 2 diabetes, cancers (*i.e.*, colon, female breast, endometrium, kidney, and esophagus), and increase the rate of mortality (1). Adipose tissue regulates metabolism, but its accumulation may have negative consequences including abdominal obesity and high levels of serum triglycerides, low-density lipoprotein (LDL), cholesterol, blood pressure, and blood sugar, which together form the metabolic syndrome (2). Mammals, including humans, have two types of adipose tissue that control the body's energy metabolism: white adipose tissue (WAT), which stores energy in the form of triglycerides; and brown adipose tissue (BAT) for thermogenesis in response to chronic cold and diet (3, 4). BAT thermogenesis is dependent on β-adrenoceptor-mediated lipolysis activation and subsequent reduction of fatty acids through *Uncoupling Protein 1* (UCP1), which disperses large amounts of chemical energy in the form of heat (5). The expression of UCP1 in the mitochondrial membrane of BAT causes oxidation of ATP-producing substrates, thereby generating heat (6).

The functions of BAT in weight control and prevention of metabolic disorders such as insulin resistance and diabetes have drawn the attention of researchers to the BAT activation mechanisms (7). Studies have shown that certain stimuli, such as chronic cold and β-adrenergic stimulation, are effective in browning brown fat-like cells in the WAT of rodents (8, 9). Brown-like fat cells, also called brite or beige fats, have lesser UCP1 gene expression compared to BAT cells, but are highly inducible in response to appropriate stimulation, leading to mitochondrial respiration and high energy expenditure, similar to what happens in brown fat cells (10, 11). In brown adipocytes, activation of protein kinase A (PKA) leads to the activation of mitogen-activated protein kinase P38 (MAPK) and two important substrates, activating transcription factor 2 (ATF-2) and peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α). PGC-1α contributes to UCP1 transcription and BAT thermogenesis by activating peroxisome proliferator-activated receptor gamma (PPARγ) (12). PGC-1α also contributes to irisin secretion via expression of the fibronectin type III domain containing 5 (FNDC5) (13, 14).

Diet-based interventions are among the most effective strategies for weight management in obese and overweight population (2). Studies in animal models have shown that high-fat diets are effective in increasing UCP1 expression in BAT (12, 15, 16). The KD is a high-fat diet (often between 70 and 90%), limited in protein and very low in carbohydrates. In KD, ketone bodies produced in the liver act as an alternative energy source and compensate for the limited access to glucose (17). Under normal conditions (without a KD or long periods of fasting), the amount of circulating ketone bodies (especially β-hydroxybutyrate) is very low (less than 3 $mmol.L^{-1}$). However, during physiological ketosis induced by a KD, ketonemia can reach 7-8 $mmol.L^{-1}$ without significant changes in the blood pH (18). In a healthy population, the amount of circulating ketone bodies does not exceed 8 $mmol.L^{-1}$, because the central nervous system effectively uses these molecules as an energy source instead of glucose (19). In previous studies, a 1.5- to 3-fold increase in mitochondrial proteins of BAT, including PGC1-α, and expression of the UCP1 gene have been reported in response to a KD (20). The main concern regarding the use of KDs is their effects on blood lipids in individuals with overweight and obese. It is widely believed that a low-carbohydrate, high-protein, and high-fat diet boosts cardiovascular risk factors by increasing the LDL and triglyceride levels. However, recent studies have shown that reducing carbohydrates can be effective in increasing the level of HDL and decreasing the level of TCand blood triglycerides (21, 22). In addition, KDs increase the size and volume of LDL particles; however, they reduce the atherogenic properties of LDL, which lessen the risk of cardiovascular disease (23). Furthermore, KD can play a inhibiting role in the synthesis of endogenous cholesterol. The major enzyme in cholesterol biosynthesis is 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG CoA reductase), which is activated by insulin, meaning that the increase in blood glucose due to the consumption of carbohydrates, and thus the production of insulin, leads to increased synthesis of endogenous cholesterol. Consequently, reducing carbohydrates in the diet along with proper cholesterol intake leads to inhibition of cholesterol biosynthesis (22).

On the other hand, the use of physical activity, exercise, and sports and in general an active lifestyle, are another effective strategy in managing obesity. Physical exercise improves lipid profile (24, 25), reduces glucose intolerance (26), reduces insulin resistance (27), and improves metabolic syndrome and its components (28). In addition, high levels of cardiorespiratory fitness reduce the negative effects of obesity on mortality (29). At the present, molecular mechanisms underlying beneficial effects of exercise-based interventions are not fully understood. One proposed mechanism is the possible role of irisin (a type of myokin with autocrine and paracrine effects) in the effects of exercise on fat metabolism, BAT activation, and browning of beige fat cells in WAT, which may prevent obesity by increasing basal metabolism and calorie consumption (14, 30). The secretion of irisin is dependent on the contraction of skeletal muscle fibers; therefore, in physical exercise, PGC-1α-induced expression increases and breaks down the FNDC5 membrane protein, and irisin is produced in muscle fibers (30). Inside the cell, irisin stimulates glucose uptake into skeletal muscle cells by increasing the phosphorylation of adenosine monophosphate-activated protein kinase α2 (AMPKα2), thus activating p38MAPK, which results in the transfer of glucose transporter type 4(GLUT4) from the peripheral region to the plasma membrane (30). By circulating irisin to adipose tissue, expression of the UCP1 gene is increased in beige cells of WAT, which are preferentially more sensitive to the polypeptide hormone irisin than in BAT cells, and leads to browning of WAT (14).

Based on the above evidence, recent studies have focused on combining diet and exercise programs to identify effective intervention strategies for obesity management. Studies in animal models have provided evidence that the combination of a high-fat diet and exercise may increase the expression of adipose tissue UCP1 gene by increasing PGC1-α and irisin (31-35). In these studies, the maximum portion of fat in the diet varied between 30 and 50%, which cannot be considered as KDs. Furthermore, existing studies have focused on the individual effects of physical exercise or a KD, which does not provide comprehensive insight into the effectiveness of combined diet

and exercise interventions in human models. Therefore, this study aimed to determine the effect of HIIT over a period of KD on the serum levels of UCP1 and blood lipid profile in overweight and obese girls aged 18-24 years.

Materials and Methods

Study design

This research was a pre- and post-test quasi-experimental study with no follow-up, aimed to determine the effect of HIIT over a six-week KD on the serum levels of UCP1, LDL, HDL, and TC). The study included two groups: KD+HIIT (experimental group) and KD (control group). The dependent variables were measured immediately before (pre-test) and after a six-week (post-test) intervention. This study was approved by the Department of Sport Physiology, at Alzahra University, and ethical approval was obtained from the Research Ethics Committee of the Institute of Physical Education and Sport Sciences, Alzahra University, Tehran, Iran (Code: IR.SSRI.REC.1399.467).

Participants

The participants were inactive female students in the age range of 18-24 years enrolled in undergraduate programs at Alzahra University in the academic year of 2019-2020. The required sample size was determined to be 16 individuals using the G*Power software (version 3.1) considering the effect size reported in the literature and the characteristics of the present study (effect size F=0.4, α error probability=0.05, power=0.80, number of groups=2, number of measurements=2, correlation among repeated measures=0.5, Nonsphericity correction ε=1). The inclusion criteria were: 1) lack of regular exercise in the past six months; 2) BMI>25 $kg.m^{-2}$; 3) no specific disease and no use of medication; 4) no physical injury; and 5) written informed consent. The exclusion criteria were as follows: 1) absence more than once from training sessions or non-observance of diet; 2) injury during the interventions; 3) dissuasion from participation in the study; and 4) resistant to ketosis throughout the experimental period. The sampling was conducted based on a research call at the beginning of the second semester of the academic year. After identifying potential individuals and conducting preliminary evaluations, 16 participants agreed to participate in the study and signed an informed consent form. Then the participants were randomly assigned to one of two groups (KD+HIIT or KD). A lottery draw was used for randomization, in which, participants' names were written on a separate card and placed in a bag in a random order. Then, the drawn cards with odd sequence were assigned to the experimental group (KD+HIIT) and even sequence to the control group (KD).

Experimental Intervention

A six-week period of KD for both groups and HIIT only for the experimental group were studied as described below.

Ketogenic diet: The diet was prescribed and controlled based on the studies conducted by Greene *et al.* (36) and Vargas *et al.* (37). The diet composition was based on the carbohydrate intake ratio (70% fat, 20% protein, and 10% carbohydrates); however, the total calories consumed were free. Required advice about nutritional resources and suggested daily meal plans were provided to all participants to help them adhere to KD at the beginning of the study. The plans were provided to meet micronutrient needs, with particular attention paid to sodium intake; however, no individual meals were provided to the participants. The list of foods that were encouraged to eat included unprocessed foods consisting of green leafy vegetables, raw nuts and seeds, eggs, animal meat, and vegetable oils such as avocado, coconut, and olive. The participants and the researcheres communicated through social networks (*i.e.*, Telegram, WhatsApp and Skype) and in person in the gym, and their diets were monitored using a self-report meal checklist. The diet was used cyclically, and the participants followed a normal diet one day each week. The amount and percentage of macronutrients in each meal were analyzed using nutrition software available on smartphones (i.e., Nutrition Fact). The keto check rapid colorimetric test was performed every two weeks to check whether participants actually followed KD and entered ketosis (36, 37).

High-intensity interval training: The HIIT protocol designed based on the recent evidence-based guidelines (38, 39). The experimental group performed three 45-min sessions of HIIT per week (4×4 min running on a treadmill with an intensity of 85-95% of the maximal heart rate and a 3-min active recovery at 50-60% of the maximal heart rate between intervals). The training intensity was 85% of the maximal heart rate in the first two weeks, 90% in the second two weeks, and 95% in the third two weeks. Each workout session began and ended with a warm-up and cool-down protocol (*i.e.*, walking, jogging, and dynamic stretching) for 10 min. In total, 18 sessions of 45 minutes (three sessions per week, for six weeks) were performed during the experimental period.

Laboratory Measurements

Two blood samplings were conducted 48 h before and after the experimental period between 8 and 9 am in a licensed laboratory. The participants were asked not to eat for 12 h before the sample collection. For sampling, 5 ml of blood was collected by an experienced laboratory technician from the vein of the left hand in a sitting position. Blood samples were then centrifuged at 3000 rpm for 10 min at 4°C, and the resulting

Table 1. Individual characteristics of the groups and total sample

Characteristics	Groups		Total Sample (*N*=16)	Groups Comparison	
	KD+HIIT (*n*=8)	KD (*n*=8)		*t*	*p*
Age (yr)	21.44 (0.75)	21.25 (0.53)	21.34 (0.94)	1.11	0.212
Height (cm)	164.53 (5.02)	162.80 (4.34)	163.66 (5.27)	0.82	0.136
Weight (kg)	82.30 (7.28)	79.40 (7.25)	80.85 (7.51)	0.58	0.106
Body Mass Index (kg.m^{-2})	30.40 (2.16)	29.96 (2.09)	30.19 (2.34)	0.63	0.114

Values presented as M±SD; the P-values for the Levene's tests are greater than 0.05 in all comparisons; KD=Ketogenic Diet; HIIT=High-Intensity Interval Training

Table 2. Descriptive statistics of the variables by group and measurement and results of within-group and between-group (pre-test) comparisons

Variables	Groups	Measurements		Within-Group Changes				Groups Comparison in Pre-Test	
		Pre-Test	Post-Test	$\Delta M_{Pre-Post}$	%Δ	*t*	*P*	*t*	*p*
UCP1 (mmol.L^{-1})	**KD+HIIT**	2.11 (0.23)	2.65 (0.47)	- 0.54	25.47 ↑	-3.77	0.007 **	0.87	0.399
	KD	2.01 (0.24	1.87 (0.39)	0.14	6.71 ↓	0.96	0.368		
LDL (mg.dL^{-1})	**KD+HIIT**	166.63 (11.03	133.64 (22.03)	32.99	19.80 ↓	5.99	0.001 ***	1.82	0.090
	KD	153.72 (16.72	130.38 (11.15)	23.35	15.19 ↓	4.69	0.002 **		
HDL (mg.dL^{-1})	**KD+HIIT**	11.95 (1.01	18.82 (1.63)	-6.87	57.46 ↑	-8.67	<0.001 ***	2.03	0.062
	KD	10.87 (1.10	13.96 (1.43)	-3.09	28.36 ↑	-7.36	<0.001 ***		
TC (mg.dL^{-1})	**KD+HIIT**	165.55 (17.63	137.19 (13.28)	28.36	17.13 ↓	3.59	0.009**	1.83	0.089
	KD	146.32 (23.93	133.56 (20.19)	12.76	8.72 ↓	2.15	0.069		

Table 3. Summary of ANCOVA results to compare groups in the post-test

Variables	Source of Effect	Statistics		
		F	*p*	η_P^2
UCP1	**Pre-Test**	2.84	0.116	0.179
	Group	10.89	0.006 **	0.456
Low-Density Lipoprotein	**Pre-Test**	6.47	0.024 *	0.332
	Group	0.51	0.486	0.038
High-Density Lipoprotein	**Pre-Test**	0.09	0766	0.007
	Group	27.31	< 0.001 ***	0.677
Total Cholesterol	**Pre-Test**	3.84	0.072	0.228
	Group	0.20	0.665	0.015

*$P\leq0.05$, **$P\leq0.01$, ***$P\leq0.001$

serum was stored at -24°C. For biochemical analysis, serum UCP1 and blood lipid profiles were measured using ELISA and enzyme colorimetric assay, respectively. It should be mentioned that all the laboratory costs were free for the participants and all expenses were covered by the researchers.

Data Analysis

Before analysis, normality and homogeneity of variance assumptions for all data were checked using the Shapiro-Wilk and Levene's tests, respectively. Initially, independent-*t*-tests samples were used to compare individual characteristics and variables between the groups in the pre-test. Due to the proximity of *P*-values to the significance level of 0.05, the data were analyzed using two methods: a series of 2 *time* (pre-test/post-test)× 2 *group* (KD+HIIT/KD) mixed analysis of variance and a series of analysis of covariance (ANCOVA; pre-test levels were considered as covariates). In addition, paired- *t*-tests samples were used to examine within-group changes. Data were analyzed using the IBM SPSS software (version 24), at the significance level of 0.05.

Results

Table 1 shows the mean and standard deviation of individual characteristics of the groups and total sample. The independent- *t*-test samples showed that the groups were homogeneous in terms of age (*P*=0.212), height (*P*=0.136), weight (*P*=0.106), and body mass index (*P*=0.114). Before the main analysis, the Shapiro-Wilk test showed that the variables data in the groups in the pre-test and post-test were normally distributed (*P*>0.05). Levin's test also revealed that the variances of data between the two groups in both pre-test and post-test were equal (*P*>0.05). Table 2 shows the descriptive statistics of UCP1 level and blood lipid profile (LDL, HDL, and TC) by group and measurement and the results of within-group and between-group (pre-test) comparisons.

As shown in Table 2, the results showed that there were no significant differences in the levels of UCP1 (*P*=0.399), LDL (*P*=0.090), HDL (*P*=0.062), or TC (*P*=0.089) between the two groups in pre-test. The results of within-group comparisons (Table 2) and ANCOVAs (Table 3) revealed that the level of UCP1 from pre-test to post-test in control group did not change significantly despite a decrease of 6.71% (*P*=0.368), but in experimental group increased significantly by 25.47% (*P*=0.007), so that in post-test, the level of UCP1 in experimental group was higher than in control group (*P*=0.006). In contrast, LDL level significantly decreased from pre-test to post-test in control groupby 15.19% (*P*=0.002) and in experimental group by 19.80% (*P*=0.001), so that in post-test, no significant difference was observed between the LDL levels of the groups (*P*=0.486). The HDL level also significantly increased from pre- test to post-test

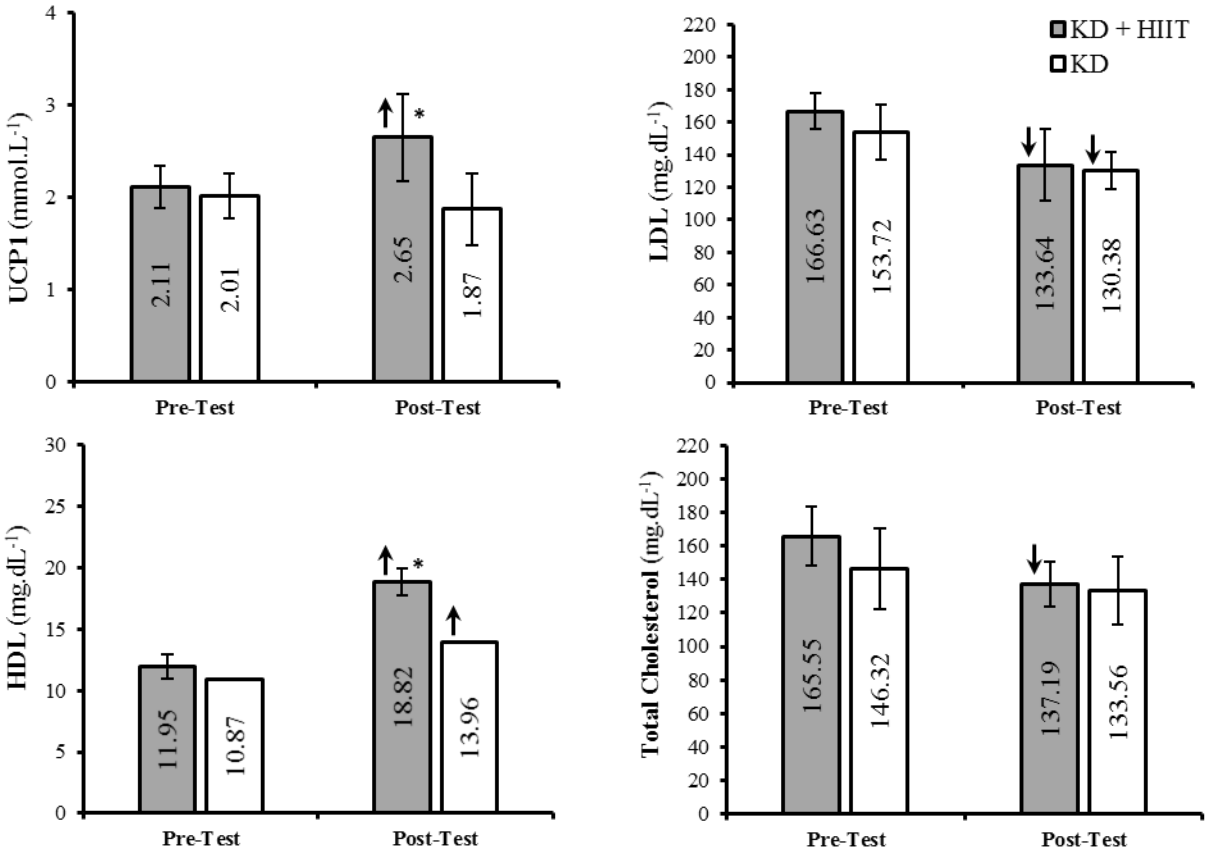

Figure 1. Mean and standard deviation of serum UCP1 concentration and blood lipid profile (LDL, HDL, and total cholesterol) by group and measurement. ↑ Significant increase from pre-test to post-test;↓ Significant decrease from pre-test to post-test; * Significant between-group difference in post-test. KD=Ketogenic Diet; HIIT=High-Intensity Interval Training; UCP1=Uncoupling Protein 1; LDL=Low-Density Lipoprotein; HDL=High-Density Lipoprotein.

in control groupby 28.36% (P<0.001) and in experimental group by 57.46% (P<0.001), so that in post-test, HDL level in experimental group was higher than in control group(P<0.001). Finally, the TC level from pre-test to post-test in control groupdid not change significantly, despite a decrease of 8.72% (P=0.069), but in experimental group, it decreased significantly by 28.36% (P<0.001); however, no significant difference was observed between the TC levels of the groups in post-test (P=0.665). The descriptive statistics and results of these comparisons are shown in Figure 1.

Discussion

This study examined the effect of HIIT over a period of KD on the serum levels of UCP1 and blood lipid profile among inactive girls with overweight and obesity. The findings on UCP1 showed that there was a significant difference between the effects of interventions: KD did not change UCP1 level, but HIIT over the six-week KD effectively increased UCP1 level. The effect size (η_p^2) for the effect of group on UCP1 was 0.456, meaning that 45.6% of the observed variance in post-test was explained by the intervention, which indicated a large effect for HIIT. These findings were confirmed by within-group comparisons.The level of UCP1 decreased significantly from pre-test to post-test in Control group by 6.71% but increased by 25.47% in the combined condition.

Existing evidence on the effects of combining a KD with physical exercise, especially in human models, is limited. In one of these studies, Rocha-Rodrigues et al. (40) showed that moderate-intensity continuous training (50-60% of maximal oxygen consumption) in combination with a standard diet (35% fat) increased the levels of UCP1 and FNDC5, but in combination with a high-fat diet, did not alter UCP1 levels study, which is inconsistent with the findings of the present study. However, other studies have shown that physical exercise in combined with a high-fat diet is associated with increased UCP1 levels. Khalafi *et al.* (41) showed that moderate-intensity continuous training (65-70% of maximal oxygen consumption) in combination with a high-fat diet (60% fat) increased UCP1 concentrations compared to mice fed a

low-fat (10% fat) or high-fat (60% fat, 20% carbohydrate, and 20% protein) diet alone, which was consistent with the findings of the present study (41). The main difference between these studies and the present study is the proportion of fat in the high-fat diet.

A KD is a low-carbohydrate, high-fat diet that is planned based on dietary characteristics (macronutrient ratio) and physiological changes (ketosis). The major ketone bodies (acetate, acetone, and β-hydroxybutyrate) are produced in the liver under low-carbohydrate conditions and act as alternative energy sources for peripheral tissues such as skeletal muscle, brain, and heart (42). To achieve ketosis through a KD, carbohydrate intake should be reduced to a maximum of 50 g per day or 10% of the total daily caloric intake, while protein intake should be moderate (approximately 1.2 to 1.5 g for per kg of body weight per day), and the rest of energy should be provided from fats (70-90%) (43). Under normal conditions (without a KD or long periods of fasting), the amount of circulating ketone bodies (especially β-hydroxybutyrate) is very low (less than 3 mmol.L-1). However, during physiological ketosis induced by a ketogenic diet, ketonemia can increase to 7-8 mmol.L-1 without significant changes in the blood pH (18). The process of ketogenesis begins with the lipolysis of fatty acids into free fatty acids, which are then transferred from the fat cells to the liver cells and oxidized to acetyl CoA. Under low glucose conditions, acetyl CoA accumulates and is then converted to acetoacetate by the enzyme thiolase. In the next step, β-hydroxy-β-methylglutaryl CoA (HMG CoA) is synthesized from acetoacetyl CoA, which is catalyzed by HMG CoA synthase. HMG CoA is then reconstituted with acetoacetate and acetate with HMG CoA lyase. Acetoacetate can further convert to acetone via β-hydroxybutyrate hydrogenase to form 3-β-hydroxybutyrate or via non-enzymatic decarboxylation. Acetone is no longer used and is excreted through the urine or exhalationin the lungs. Simultaneously, acetoacetateand 3-β-hydroxybutyrate circulate in the blood stream and reach non-liver tissues. Ketolysis must occur to obtain energy from ketone bodies. During ketolysis, acetoacetate and 3-β-hydroxybutyrate converted to acetyl-CoA by succinyl-CoA. Acetyl-CoA passes through the Krebs cycle and is oxidized by the formation of twenty-two ATPs per molecule. Ketolysis occurs more in non-hepatocytes, because although the liver is the major producer of ketones, the lack of 3-ketoacid CoA transferase limits the ability of the liver to use them (44). A 1.5- to 3-fold increase has been reported in BAT mitochondrial proteins, including UCP1 gene expression, due to consumption of a KD (20). Therefore, in the present study, we hypothesized that a ketogenic diet is associated with an increase in serum levels of UCP1. However, the results showed that a six-week KD resulted in a 6.71% reduction in serum levels of UCP1. In contrast, increased levels of UCP1 after combining KD with HIIT showed that a combination of nutritional and exercise interventions was more effective in browning of BAT.

The findings on blood lipid profile showed that there were significant improvements in the levels of LDL (19.80%), HDL (57.46%), and TC (17.13%) in the combined condition, as well as significant improvements in the levels of LDL (15.19%) and HDL (28.36%) in KD alone. Combining a KD with HIIT was found to be more effective in improving HDL levels than a KD alone; however, no significant difference was observed in the effectiveness of LDL and TC between the two types of interventions. The effect size (ηp2) for the effect of group on HDL was 0.677, which showed that HIIT had a large effect on HDL levels and 67.7% of the observed variance for HDL in post-test was resulted from the intervention. Total cholesterol is the sum of LDL and HDL cholesterol and is often measured in milligrams per deciliter of blood or millimoles per liter of blood. Approximately 75% of blood cholesterol is carried as LDL cholesterol, and the higher the level of LDL in the blood, the higher is the risk of coronary heart disease. LDL above 160 mg.dL-1 are correlated with a high risk of coronary heart diseases in susceptible individuals, and levels below 100 mg.dL-1 have low risk, but levels above 200 mg.dL-1 are known as high-risk cholesterol levels (45). In the present study, the mean LDL levels of KD+HIIT and Control groups in pre-test were 166.63 and 153.72 mg.dL-1, respectively, which were at risk for coronary heart diseases, but after the intervention, these values decreased to 133.64 and 130.38 mg.dL-1, indicating that the interventions have reduced the cardiovascular risk factors. Although, in the present study, there was no significant difference between the effectiveness of the two interventions in reducing LDL levels, but due to more favorable changes in HDL, it can be concluded that combining a KD with HIIT was more effective in improving blood lipid profile and reducing cardiovascular risk factors in girls with overweight and obesity. Extensive studies have been conducted on the effects of different types of physical exercise and KD on blood lipid profile. Review of these studies have indicated the effectiveness of exercise- and KD-based interventions in improving the blood lipid profile (24, 25), which is supported by the findings of the present study.

Further studies are required to identify the most effective strategy for managing overweight and obesity. Researchers should examine the effects of combining KDs with endurance, resistance, and hybrid training (a combination of endurance and resistance training) on the browning pathways of adipose tissue. In addition, the effects of combining KDs with

continuous training at different intensities on the browning pathways of adipose tissue should be compared. Finally, due to gender differences in adipose tissue composition and muscle adaptations to exercise, it is recommended that a similar study performed in males with overweight and obesity.

Conclusion

The combination of HIIT and KD was more effective than the KD alone in activating adipose tissue browning pathways and improving blood lipid profile; especially in increasing the serum level of UCP1 and HDL. In addition, the effectiveness of both intervention strategies in reducing LDL and TC was similar. Based on these findings, nutrition and exercise professionals, as well as individuals with overweight and obesity, are suggested to use HIIT accompanied by a KD for at least six weeks, for overweight management and prevention of cardiovascular complications of obesity.

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Ethical approval

The research was conducted with regard to the ethical principles (Ethic Code: IR.SSRI.REC.1401.1601).

Conflict of interest

None.

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Authors' contributions

All authors made substantial contributions to the conception, design, analysis, and interpretation of data.

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