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Effects of short-term aerobic, resistance and combined exercises on the lipid profiles and quality of life in overweight individuals with moderate hemophilia A: A randomized controlled trial

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Abstract

Background: Overweight is related to increased risks of cardiovascular diseases and dyslipidemia, and reduced quality of life (QOL). Exercise training improves QOL and modifies cardiovascular risk factors and lipid profile. The present study was conducted to compare three types of exercise in terms of their short term effects on QOL and lipid profile in overweight individuals with moderate hemophilia A (IWMHA).

Methods: This study was a randomized, controlled, assessor-blinded trial (IRCT20180128038541N1). Sixty IWMHA with a body mass index (BMI) of 25-30 kg/ m2 and a mean age of 35-55 years were randomly assigned to four groups of 15, namely aerobic training (AT), resistance training (RT), combined training (CT) and control. The intervention groups participated in 45-minute exercises three days a week for six weeks. The 36-item short-form health survey (SF-36) was used to measure QOL. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), waist-to-hip ratio (WHR), and waist circumference (WC) were measured before and after six weeks of training. For the data analysis using SPSS version 20, the ANCOVA was used to determine the differences among the four groups.

Results: A significant decrease was observed in the intervention groups compared to the control group in terms of weight, BMI, LDL-C, TC, WHR, and WC ($p<0.05$). Significant increase was observed in HDL-C and SF-36 subscales in the intervention groups compared to the control group ($p<0.001$). There was no significant difference among the intervention groups ($p>0.05$). In comparison with the control group, more significant improvement was observed in the TC, TG, LDL-C, HDL-L, and SF-36 subscales in the CT group compared to the RT and AT groups.

Conclusion: CT was the most effective training method in improving lipid profile and QOL in overweight IWMHA.

Keywords: Hemophilia A, Overweight, Lipid Profile, Combined Training, Quality of Life

Conflicts of Interest: None declared
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Introduction

As an X-linked bleeding disorder, hemophilia A is associated with coagulation factor VIII deficiency (1). An in-

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↑What is "already known" in this topic:
Cardiovascular risk factors such as obesity have become increasingly prevalent in IWH, and weight control can cause more effective conservation of normal joint function and improved quality of life. Exercise training is the best primary and secondary prevention of chronic diseases, especially CVD, obesity, and lipid disorders in different ages.

→What this article adds:
In overweight patients with moderate hemophilia A, all types of exercise can decrease the LDL-C, TC, TG, and increase HDL-C and quality of life. Combination of aerobic and resistance training has the most significant desirable changes in lipid profile and quality of life and thus can be used for disorders associated with sedentary lifestyle in IWH.

crease from 30 to 60-70 years has been reported in the life expectancy of individuals with hemophilia (IWH) in developed countries (2). Thus, age-related complications, especially cardiovascula r risk factors such as obesity, have become increasingly prevalent in IWH (3). Hemophilia causes a negative perception of the quality of life (QOL) due to diminished independence, pain, and fear of the future (4). Restricted physical activity because of fear of bleeding also reduces QOL in IWH (4). Given the pathophysiological synergy between hemophilia and obesity, controlling weight in IWH can more effectively conserve a normal joint function and improve QOL. Obesity disrupts physical activity and increases the frequency of bleeding and the administration of factor VIII in hemophiliacs (5). Overweightness thus has an indirect role in the poor QOL experienced by IWH (4). Research suggests body mass index (BMI) is positively correlated to total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), and negatively correlated with high-density lipoprotein cholesterol (HDL-C) (6). This correlation between BMI and the levels of lipoproteins, especially LDL-C, is a significant contributing risk factor of cardiovascular disease (CVD) in obese individuals (7). High levels of TC and LDL-C have also been well documented to play a vital role in developing arteriosclerosis and coronary artery disease (8). Research suggests that exercise training is the best primary and secondary prevention of chronic diseases, especially CVD, obesity, and lipid disorders in men and women of different ages (9). Aerobic training (AT) and resistance training (RT) are both recommended as significant therapeutic modalities to modify cardiovascular risk factors (10). Combined training (CT) is defined as a combination of simultaneous AT and RT programs in a regular exercise routine (10). Exercise training may increase the risk of injury, particularly re-bleeding in IWH. Exercise training improves joint function in IWH by increasing their muscle function, muscle strength, and joint stability (10).

Decreased levels of LDL-C, TC, and TG and increased levels of HDL-C were reported after resistance, aerobic, and combined exercises in the literature (11-19). To the best of the authors' knowledge, exercise training has not been compared yet in terms of their effect on lipid profile in IWH. The present research was therefore performed to investigate the effect of six weeks of aerobic, resistance, and combined training on QOL and the serum levels of TC, TG, LDL-C, and HDL-C in overweight IWMHA.

Methods

Study design and sampling

This study was a randomized controlled trial. The study was registered in the Iranian Registry of Clinical Trials (IRCT20180128038541N1). Written informed consent forms were signed by all the participants. This study was conducted by a team of specialists with 15-20 years of clinical and research experience of IWH. After examination by the hemophilia specialists and physiotherapists familiar with the treatment of IWH, all volunteers were allowed to participate in the study if they met the inclusion criteria. The eligible candidates comprised non-smoking IWMHA aged 35-55 years with no history of an inhibitor, a BMI of 25-30 kg/ m^2, a total hemophilia joint health score (HJHS) of at most ten without diabetes mellitus, hepatitis B or C, human immunodeficiency virus (HIV) and factor VIII prophylaxis before and during the treatment protocol and under musculoskeletal assessments in the Iranian Comprehensive Hemophilia Care Center (ICHCC). The exclusion criteria consisted of clinical symptoms of active bleeding, uncontrolled hypertension, i.e., a systolic blood pressure (SBP) of over 140 mmHg and diastolic blood pressure (DBP) of over 100 mmHg, and performing regular physical activities within the previous six months. Sports facility in Tarbiat Modares University was employed for the exercises from March 30th and May 31st, 2018. Given the mean ± standard deviation of TC between the combined and control groups after the intervention in a study by Azarbayjani et al. (13), and considering 95% confidence interval and 80% study power, the sample size was determined as 15 participants in each group. According to Figure 1, all the participants were randomly assigned to four groups, namely AT, RT, CT, and control. Randomization was performed by an external observer using closed envelopes in blocks of eight, in each block two persons were randomly assigned to one of the groups. The laboratory technicians and the person in charge of marker measurements were blinded to the grouping. In contrast, the physiotherapist in charge of therapeutic exercises, who was to complete the joint health questionnaire, was not blinded to the grouping.

Exercise protocols

The participants completed eighteen 45-minute training sessions three times a week, every other day, within six weeks. Based on the findings of a previously-conducted study, the intervention duration was considered six weeks to prevent potential complications (20). Before beginning the exercise protocol, the RT group was assigned a 10-repetition maximum (10RM) for resistance exercises (RE), and a 1-repetition maximum (1RM) was determined using 10RM=75% 1RM (20). The number of repetitions of RE was ten repetitions per odd weeks and twelve repetitions per even weeks. Resistance was fixed at 65% of 1RM in the first two weeks, 70% of 1RM in the second two weeks, and 75% of 1RM in the third (10). Twelve repetitions of every exercise were performed in the 2nd, 4th and, 6th weeks and ten repetitions in the 1st, 3rd and, 5th. Ten-second breaks were considered between the repetitions and 1-2 minute breaks between the muscle group exercises (Fig. 2). Free weights, barbells, and dumbbells were employed to perform RE, including the squat, the chest press, the shoulder press, the leg press, calf raise, the knee flexion, and the leg extension. Moreover, exercises for the lower and upper extremities were bilaterally performed. In all the sessions, core exercises first performed in all the sessions were followed by upper and lower limb exercises (21, 22). RE was designed based on ACSM's (American College of Sports Medicine) recommendation (large before small muscle group exercises, and multiple-joint exercises before single-joint exercises), and taking into account musculoskeletal bleeding pattern in PWH

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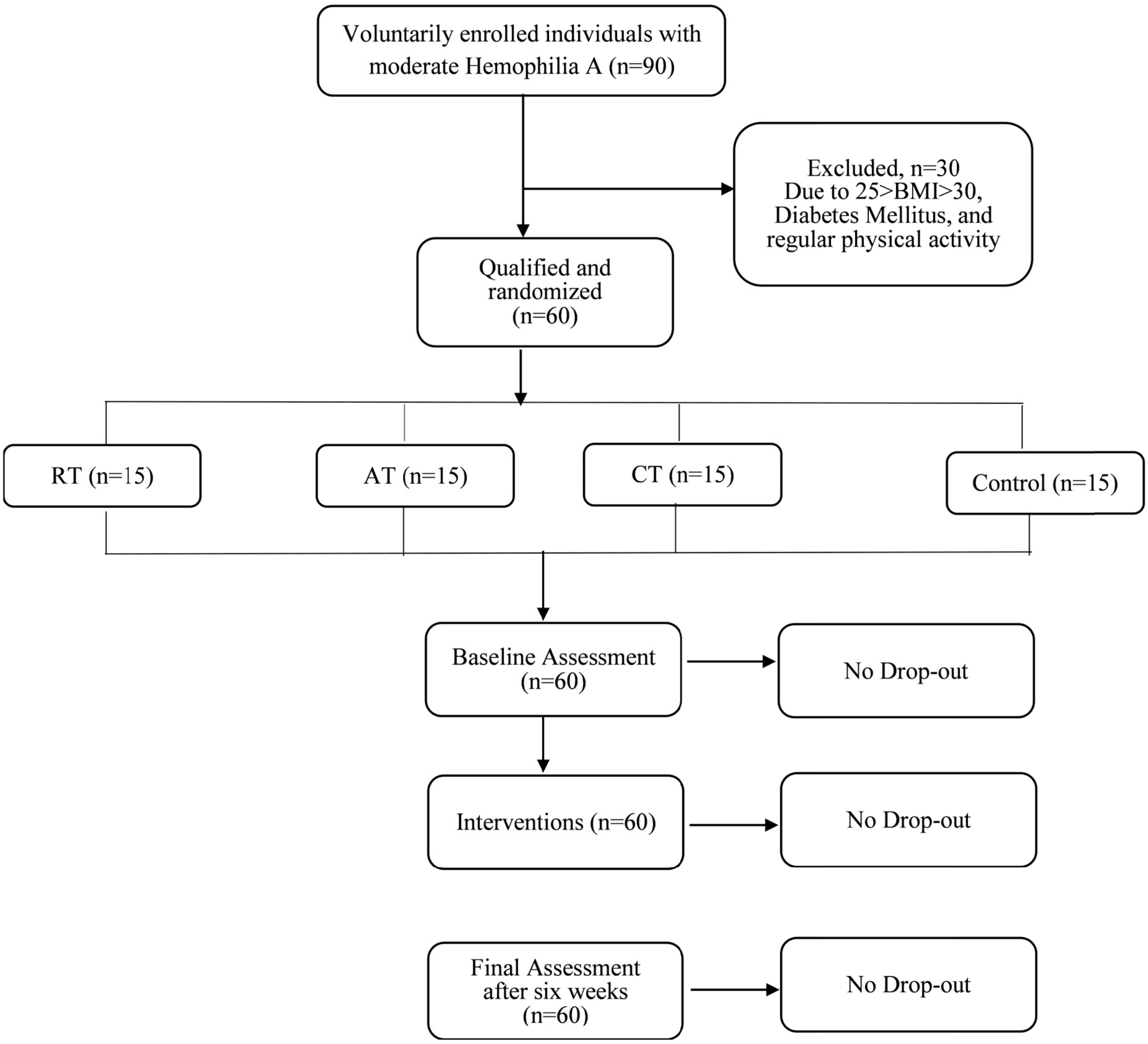

Fig. 1. The study design and the flow of participants. bmi, body mass index; rt, resistance training; at, aerobic training; ct, combined training

(10). During each training session, the participants were asked to perform ten minutes of global and segmentary stretching (as warm up) before starting the exercise protocol (10, 20). The participants in the AT group performed a 20-minute aerobic treadmill exercise and ergometer cycling for 20 minutes with a two-minute rest in between. The 220-age equation was used to adjust the aerobic exercise intensity at 65% of maximum heart rate (MHR) during the first two weeks, 70% of MHR during the second two weeks and 75% during the third (10, 23). Every step respectively involved a warm-up, exercising at a constant workload, and a cool-down. The aerobic exercise comprised a 5-minute warm-up followed by a 12-minute exercise and a 3-minute cool-down (Fig. 3). The participants in the CT group first performed aerobic exercises for 20 to 25 minutes, took a two-minute break, and then performed resistance training for 20 minutes. Although the intensity of RE was the same in both the CT group and the RT group, the CT group performed six repetitions of every exercise in the 2nd, 4th , and 6th weeks of training and five repetitions in the 1st, 3rd , and 5th weeks. Every session of aerobic exercise included eleven minutes of aerobic treadmill exercises followed by eleven minutes of ergometer cycling. After warming up for three minutes, the participants underwent a six-minute training followed by a 2-minute cool-down (Fig. 4).

Physical activity evaluation

Hemophilia Activity List (HAL), with 42 items in 7 domains, was used to assess the physical activity of IWH. Each topic describes hardship caused by hemophilia over the past month. Higher scores indicate better functional status (24). Control and intervention groups were asked to maintain their routine physical activity and diet during the study (10, 25). Upon the completion of the six-week intervention, a belated one-month intervention was performed in the control group, which was not followed by any tests.

Joint health status

The HJHS 2.1 with a total score of 124 was used to assess the joint health status in each participant, with higher scores denoting worse joint health (26).

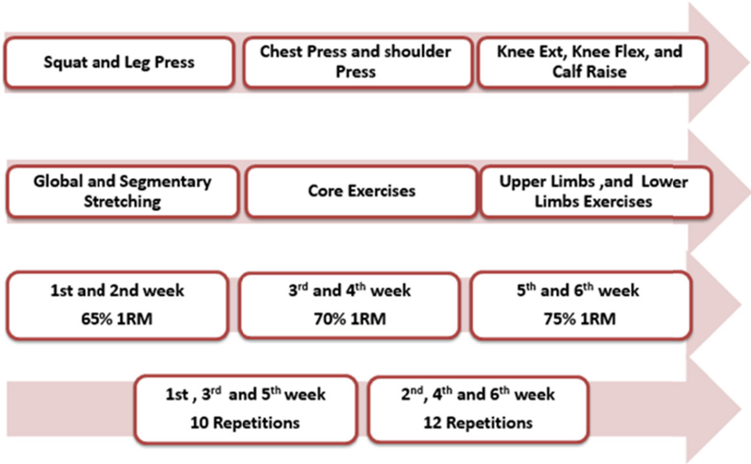

Fig. 2. The exercise protocol in the resistance training group. 1RM, One Repetition Maximum

Fig. 3. The exercise protocol in the aerobic training group. MHR, Maximum Heart Rate

Fig. 4. The exercise protocol in the combined training group

Body fat assessment and anthropometric measurement

At the end of the expiration, a tape measure was used to measure waist circumference (WC) in the thinnest part of the body (10). Also, for measuring the hip circumference (HC), the level of maximal protrusion of the gluteal muscles was selected (27).

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Blood pressure assessment

SBP and DBP were measured by blood pressure monitor (Omron, BP7250, Japan) in a sitting position after at least 10 minutes of rest before starting exercises and 30 minutes after the end of the training from the left brachial artery, and a mean of the three measurements was obtained (14).

QOL Assessment

The SF-36 was used to assess QOL before and six weeks after the intervention. It includes eight domains and 36 items that measured bodily pain (BP), social functioning (SF), physical functioning (PF), general health (GH), role physical (RP), mental health (MH), vitality (VT), and role emotional (RE). The physical component score (PCS) subscale comprised the GH, BP, RP, and PF subscales, and the general subscale of the mental component score (MCS) comprised the RE, VT, SF, and MH subscales. A higher score indicated higher levels of QOL (4).

Lipid profiles analysis

Following 24 h before the first training session and 48 h after its last session, fasting blood collection was performed between 8 to 9 AM (13). All blood samples were stored immediately at -80°C before analysis. The serum concentration of HDL, LDL, TG, and TC were measured before and after the six weeks by a photometric method using Pars Azmoon kits, Iran, in the ICHCC laboratory, Tehran, Iran.

Statistical analyses

The Kolmogorov-Smirnov test was used to confirm the distribution of the data follows a normal one. Furthermore, the differences among the four groups were determined using the univariate analyses of covariance (ANCOVA) and the discrepancies between the data with significant interaction effects using the Bonferroni post hoc test. The treatment group was considered the constant; the pre-intervention value was taken as the covariate and the post-intervention value of the same variable as the dependent variable. All the analyses were performed in IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). Furthermore, effect sizes measured using the Cohen d. P<0.05 was set as the level of statistical significance.

Results

Anthropometric and hemodynamic parameters changes

The demographic details of the participants are presented in Table 1. A significant decrease was observed in the RT, AT, and CT groups compared to the control group in terms of weight, BMI, WHR, WC, SBP, and DBP ($p<0.05$) (Table 2). There was no significant difference among the intervention groups ($p>0.05$).

Changes in the total HJHS

There was no musculoskeletal bleeding in the intervention groups. The total HJHS was significantly reduced in the RT, AT, and CT groups compared to the control group through the six weeks intervention ($p\leq 0.001$) (Table 2). There was no significant difference among the intervention groups ($p>0.05$).

HAL sum score changes

A significant increase was observed in the HAL sum score in all the intervention groups compared to the control group after six weeks of intervention ($p\leq 0.001$) (Table 2). There was no significant difference among the intervention groups ($p>0.05$).

Changes in SF-36 subscales

The study groups were not significantly different in terms of eight subscales of the SF-36 at baseline ($p>0.05$). The total SF-36 score, MCS, PCS, MH, RE, SF, VT, GH, BP, and PF were significantly increased through the six-week intervention in the RT, AT, and CT groups compared to the control group ($p\leq 0.001$) (Table 3). No significant difference was observed among the intervention groups ($p>0.05$).

Lipid profile changes

A significant increase in HDL-C was also observed in the AT, RT and CT groups compared to the control group after six weeks ($p<0.001$) (Table 4). A significant decrease was observed in the LDL-C and TC in the AT, RT, and CT groups compared to the control group ($p<0.05$).

Table 1. Subject characteristics at baseline

Characteristic	RT (n=15)	AT (n=15)	CT (n=15)	CON (n=15)	p
Age(yr)	46.87 (4.27)	46.2 (5.59)	46 (6.07)	46.07 (4.68)	0.967
Height (m)	1.76 (0.03)	1.76 (0.03)	1.77(0.04)	1.76 (0.04)	0.863
Weight (kg)	85.13 (5.46)	86.33 (4.68)	87.73 (7.83)	87.07 (4.23)	0.865
BMI (kg/m^2)	27.82 (1.08)	27.74 (1.12)	28.01 (1.31)	27.85 (1.05)	0.931
Factor VIII activity (IUdL^{-1})	3.77 (0.74)	4 (0.830	3.92 (0.84)	3.82 (0.66)	0.856
Total HJHS Scores	6.2 (1.2)	5.93 (1.03)	7.06 (1.86)	6.46 (1.4)	0.165
HAL (Sum Score)	171.6 (4.04)	171.4 (3.41)	169.7(4.58)	172.66 (6.11)	0.391
Total SF-36	76.7 (6.6)	77.8 (8.2)	75.2 (4.7)	78.5 (6.5)	0.570
HDL-C(mg/dL)	39.66 (2.35)	41.13 (2.58)	40.46 (3.94)	40.6 (3.22)	0.872
LDL-C(mg/dL)	119.06 (16.34)	117.73 (13.6)	122.93 (15.88)	116.86 (14.40	0.949
TC(mg/dL)	168.2 (17.1)	173.33 (8.85)	172.53 (37.07)	176 (25.96)	0.906
TG(mg/dL)	149.13 (45.8)	135.4 (36.8)	155.2 (44.61)	146.2 (49.23)	0.973

Data are expressed as the mean ± standard deviation.
RT, resistance training; AT, aerobic training; CT, combined training; CON, control; BMI, Body Mass Index; HJHS, Hemophilia Joint Health Score, HAL; Hemophilia Activity List; SF-36, Short- Form 36; HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides

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Table 2. Anthropometric parameters, blood pressure, Total HJHS and HAL sum score before and after six weeks of training

Variable	RT group				AT group				CT group				CON group	
	Pre	Post	P	Cohen d	Pre	Post	P	Cohen d	Pre	Post	P	Cohen d	Pre	Post
Weight (kg)	86.13 (5.46)	85.2 (5.37)†	≤ 0.001	0.17	86.33 (4.68)	85.33 (4.92)†	≤ 0.001	0.2	87.73 (7.83)	86.13 (7.13)†	≤ 0.001	0.21	87.07 (4.23)	87.47 (4.06)
BMI (kg/m^2)	27.82 (1.08)	27.56 (1.04)†	0.007	0.24	27.74 (1.12)	27.43 (1.22)†	0.001	0.26	28.01 (1.31)	27.48 (1.11)†	≤ 0.001	0.43	27.85 (1.05)	27.99 (1.15)
WHR	0.932 (0.039)	0.928 (0.36)†	0.006	0.17	0.928 (0.561)	0.925 (0.61)†	0.020	0.005	0.932 (0.048)	0.928 (0.047)†	0.004	0.09	0.944 (0.039)	0.948 (0.039)
WC (Cm)	100.3 (7.48)	99.9 (7.43)†	0.010	0.05	99.16 (7.7)	98.1 (7.83)†	0.048	0.13	97.6 (9.06)	97.1 (9.09) †	0.005	0.05	100.66 (7.48)	101.06 (7.54)
HC (Cm)	106.86 (7.26)	106.8 (7.33)	0.91	0.008	106.53 (5.53)	106.53 (5.53)	1	0	104.33 (5.2)	104.33 (5.2)	1	0	106.26 (5.07)	106.26 (5.07)
SBP (mm)	130.26 (6.1)	122 (6.96)†	≤ 0.001	1.26	131.13 (4.73)	120.7 (8.46)†	≤ 0.001	1.52	130.46 (7.65)	120.6 (7.9)†	≤ 0.001	1.26	125.53 (7.63)	127.73 (6.54)
DBP(mm)	82.2 (6.39)	76.6 (5.92)†	≤ 0.001	0.91	83.53 (5.61)	77.2 (6.32)†	≤ 0.001	1.06	83.3 (4.59)	72.86 (5.33)†	≤ 0.001	2.1	79.33 (5.42)	82.2 (4.79)
Total HJHS	6.2 (1.2)	3.86 (1.3)†	≤ 0.001	1.32	5.93 (1.03)	4.1 (1.8)†	≤ 0.001	1.25	7.06 (1.86)	4.2 (1.26)†	≤ 0.001	1.81	6.46 (1.4)	7.6 (1.99)
HALsum score	171.6 (4.04)	204.6 (4.7)†	≤ 0.001	7.3	171.4 (3.41)	198.8 (5.36)†	≤ 0.001	6.1	169.7 (4.58)	211.4 (4.53)†	≤ 0.001	9.16	172.66 (6.11)	172.8 (3.9)

Data are expressed as the mean ± standard deviation.
RT, resistance training; AT, aerobic training; CT, combined training; CON, control; BMI, Body mass index; WHR, waist to hip ratio fat mass ; WC, Waist circumference ; HC, hip circumference, SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HJHS, Hemophilia Joint Health Score; HAL; Hemophilia Activity List. †Significant difference related to the control group.

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Table 3. SF-36 subscales before and after six weeks of training

Variable	RT group				AT group				CT group				CON group	
	Pre	Post	P	Cohen d	Pre	Post	P	Cohen d	Pre	Post	P	Cohen d	Pre	Post
PF	75.73 (6.49)	85.6 (4.5)†	≤0.001	1.75	77.26 (5.4)	85.9 (4.5)†	≤0.001	1.73	73.8 (8.8)	85.8 (8.3)†	≤0.001	1.4	79.2 (6.8)	77.9 (6.5)
RP	80 (6.8)	90.1 (6.03)†	≤0.001	1.72	76.65 (8)	85.3 (6.5)†	≤0.001	1.18	80.6 (7.3)	92.3 (5.8)†	≤0.001	1.84	82.5 (5.8)	78.4 (8.7)
BP	77.2 (6.79)	90 (7.58)†	≤0.001	1.78	77.5 (6.5)	82.5 (6.2)†	≤0.001	0.8	78.03 (4.2)	92.6 (5.9)†	≤0.001	2.84	80.8 (7)	78.3 (7.1)
GH	76.67 (10)	83.75 (7.42)†	≤0.001	0.8	77.9 (8.2)	81.8 (7)†	≤0.001	0.51	78.02 (6.9)	87 (5.4)†	≤0.001	1.45	81.1 (9.9)	77.9 (9.1)
VT	72.3 (8.6)	84.8 (6.5)†	≤0.001	1.64	77.6 (8.4)	85.2 (6.3)†	≤0.001	1.02	78 (9.6)	90 (7)†	≤0.001	1.42	78.8 (8.9)	77.6 (8)
SF	77.86 (8.6)	86.1(5.9)†	≤0.001	1.11	75.6 (7.2)	82.5 (6.2)†	≤0.001	1.02	80.6 (12)	91.5 (7.6)†	≤0.001	1.08	78.9 (8)	77.7 (8.5)
RE	81.05 (7.57)	90.3 (6.7)†	≤0.001	1.29	77.4 (9.5)	84.6 (8.6)†	≤0.001	0.79	81.7 (10)	91.4 (7.3)†	≤0.001	1.1	82.9 (7.9)	81.9 (8.15)
MH	74.8 (6.7)	82.8 (4.5)†	≤0.001	1.4	77.2 (6.5)	84 (6.7)†	≤0.001	1.03	79.8 (10)	88.8 (7.2)†	≤0.001	1.03	78.6 (6.6)	75.7 (5.9)
PCS	77.4 (3.9)	87.3 (2.8)†	≤0.001	2.92	78.12 (2.67)	85.2 (2.8)†	≤0.001	2.93	77.6 (3.06)	89.4 (2.9)†	≤0.001	3.26	80.9 (3.3)	78.1 (3.3)
MCS	76.5 (5.6)	86 (4.2)†	≤0.001	1.92	76.97 (4.7)	84 (4.42)†	≤0.001	1.54	80 (5.5)	90.6 (4.4)†	≤0.001	2.12	79.8 (2.72)	78.25 (2.97)
Total SF-36	76.7 (6.6)	87 (4.9)†	≤0.001	1.77	77.8 (8.2)	86.6 (8.4)†	≤0.001	1.06	75.2 (4.7)	89.8 (4.8)†	≤0.001	3.07	78.5 (6.5)	76.7 (6)

Data are expressed as the mean ± standard deviation.

RT, resistance training; AT, aerobic training; CT, combined training; CON, control; PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health; PCS, Physical Component Score; MCS, Mental Component Score

†Significant difference related to the control group.

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Table 4. Lipid profiles before and after six weeks of training

Variable	RT group				AT group				CT group				CON group	
	Pre	Post	P	Cohen d	Pre	Post	P	Cohen d	Pre	Post	P	Cohen d	Pre	Post
HDL-C (mg/dL)	39.66 (2.35)	41.46 (2.5)†	0.001	0.74	41.13 (2.58)	42.33 (2.35)†	0.002	0.48	40.46 (3.94)	42.8 (3.76)†	≤0.001	0.6	40.6 (3.22)	39.2 (3.48)
LDL-C (mg/dL)	119.06 (16.34)	116.4 (15.98)†	0.010	0.16	117.73 (13.6)	115.13 (13.2)†	0.009	0.19	122.93 (15.88)	117.4 (15.09)†	≤0.001	0.35	116.86 (14.4)	119.46 (13.82)
TC (mg/dL)	168.2 (17.1)	165 (17.01)†	0.009	0.18	173.33 (38.8)	168.5 (36.6)†	≤0.001	0.12	172.53 (37.07)	166.6 (37.25)†	≤0.001	0.15	176 (25.96)	176.86 (25.74)
TG (mg/dL)	149.13 (45.8)	146.33 (45.38)	0.070	0.06	135.4 (36.8)	132.6 (35.9)†	0.030	0.07	155.2 (44.61)	147.6 (37.51)†	≤0.001	0.18	146.2 (49.23)	149.46 (49.81)

RT, resistance training; AT, aerobic training; CT, combined training; CON, control; HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides,
†Significant difference related to the control group.

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A significant decrease was also observed in the TG in the CT and AT groups compared to the control group ($p<0.001$). No significant differences were observed among the intervention groups ($p>0.05$).

Comparing the mean differences among the four groups

There was no significant difference among the intervention groups ($p>0.05$). The decrease observed in the mean differences in the total HJHS, WC, WHR, BMI, TC, LDL-C, weight, and TG was significant in the CT group compared to the RT and AT groups. In comparison with the control group, more significant improvement was observed in the PCS, MCS, HAL sum score, and HDL-C in the CT group compared to the RT and AT groups (Table 5).

Table 5. Mean differences comparison among the intervention groups with the control group after six weeks of training

Variable	Group	MD	SE	95% CI
Weight				
	RT	-1.38†	0.32	-2.26 to -0.49
	AT	-1.43†	0.32	-2.32 to -0.55
	CT	-1.96†	0.32	-2.84 to -1.08
BMI				
	RT	-0.39†	0.11	-0.71 to -0.8
	AT	-0.46†	0.11	-0.77 to -0.14
	CT	-0.66†	0.11	-0.98 to -0.34
WHR				
	RT	-0.008†	0.002	-0.015 to -0.002
	AT	-0.007†	0.002	-0.014 to -0.00
	CT	-0.009†	0.002	-0.015 to -0.002
WC				
	RT	-0.79†	0.24	-1.45 to -0.14
	AT	-0.66†	0.24	-1.32 to -0.004
	CT	-0.86†	0.24	-1.52 to -0.19
Total HJHS	RT	-3.52†	0.44	-4.7 to -2.3
	AT	-3.05†	0.44	-4.26 to -1.83
	CT	-3.86†	0.44	-5.08 to -2.64
HAL Sum Score	RT	32.5†	1.19	29.23 to 35.77
	AT	26.4†	1.19	23.57 to 30.1
	CT	40.6†	1.22	37.31 to 43.99
PCS				
	RT	11.43†	0.81	9.2 to 13.66
	AT	8.78†	0.79	6.6 to 10.9
	CT	13.36†	0.8	11.15 to 15.57
MCS				
	RT	10.2†	0.75	8.1 to 12.16
	AT	7.95†	0.74	5.9 to 9.9
	CT	12.23†	0.72	10.23 to 14.2
HDL-C				
	RT	2.99†	0.71	1.03 to 4.95
	AT	2.71†	0.71	0.76 to 4.67
	CT	3.7†	0.71	1.75 to 5.65
LDL-C	RT	-5.09†	1.53	-9.3 to -0.89
	AT	-5.13†	1.53	-9.33 to -0.93
	CT	-7.67†	1.55	-11.91 to -3.42
TC	RT	-4.29†	1.27	-7.79 to -0.79
	AT	-5.74†	1.27	-9.23 to -2.25
	CT	-6.9†	1.27	-10.38 to -3.41
TG	RT	-5.91	2.28	-12.15 to 0.32
	AT	-6.62†	2.3	-12.88 to - 0.35
	CT	-10.4†	2.28	-16.66 to-4.14

RT, resistance training; AT, aerobic training; CT, combined training; BMI, Body mass index; WHR, waist to hip ratio; WC, Waist circumference ; HJHS, Hemophilia Joint Health Score; HAL, Hemophilia Activity List; PCS, Physical Component Score; MCS, Mental Component Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglyceride; MD, Mean Difference; SE, Standard Error; CI, Confidence Interval for difference, †The mean difference is significant at the 0.05 level.

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Discussion

The most important finding of this study was a further decrease in LDL-C, TC, and TG and a further increase in the QOL and HDL-C in the CT group compared to the RT and AT groups. Given that no similar studies have been yet conducted on modifying lipid profile using exercise training in IWH, and therefore little information was available for determining the training protocol, this preliminary study was conducted to adapt a training program compatible with musculoskeletal conditions of IWH.

Anthropometric measures

Significant decrease was observed after six weeks in BMI, WHR, WC, and weight in the CT, RT, and AT groups compared to the control group. Despite the short duration of the study, the designed protocol of the exercises was effective in reducing body weight and improving anthropometric parameters in addition to being safe and not causing musculoskeletal bleeding in the IWH. The tendency for reduction in WHR and WC in the CT, RT and AT groups and a tendency for an increase in WHR and WC in the control group suggest the preventive and improving effect of AT, RT, and CT for modifying the cardiovascular risk factors in the over-weighted IWH. Henrad et al. (28) measured a high mean factor VIII recovery in inactive IWH suffering over weight, and high BMI, and fat mass index. Given the reductions in weight and BMI in all three types of exercise and its further reduction in the CT group, the present study revealed the potential role of these exercises in improving homeostasis and normalization of factor VIII recovery in IWH. The factor VIII dose is determined by body weight. Therefore, weight control can reduce factor VIII consumption and treatment costs (28). In line with a previous study in overweight and obese subjects (29), the present study confirmed that combined exercises are the more beneficial training approach for improving cardiorespiratory fitness and reducing body weight compared to AT and RT in people suffering from moderate hemophilia A. Thus, CT is recommended to be prescribed for alleviating cardiovascular risk factors and reducing adiposity in obese or overweight IWH.

Hemophilia activity list sum and hemophilia joint health score

More significant improvements were also observed in the HAL sum score and total HJHS in the CT group compared to in the RT and AT groups. According to Biere-Rafi et al. (30), lower (worse) HAL sum scores in obese IWH compared to that in normal-weight subjects goes back to the lower limb impaired function.

Quality of Life

An study showed that those IWHs, who receive prophylaxis, have a better QOL in terms of BP, PF, GH, and MH than those who receive the factor on demand (31). Exercises enhance self-confidence, social adaptations, insight, and healthy body image and help with overcoming disabilities, health problems, and displaying abilities (32). In this study, we administered a prophylactic injection of factor VIII to motivate the patients to participate in exercise training, which had a positive psychological effect on their QOL. It should be noted that the control group also received a prophylactic dose, but their QOL was reduced despite the injection. The present study pioneered the investigation of the effect of AT, RT, and CT on QOL in overweight IWMHA using the SF-36. After six weeks, significant increases were observed in MCS and PCS in all three exercise groups compared to the controls. The improvement observed in the CT group was more significant than in the RT and AT groups. The results of a recent study on the QOL of Greek adults with hemophilia using SF-36 showed that IWH had a lower QOL in all SF-36 subscales, mainly RP, BP, and GH than the healthy population (33). A score difference above minimally important difference (MID) is considered as clinically significant. MIDs were also reported for MCS (3) and PCS (2-3) (34). The present study found variations in PCS and MCS in the AT, RT, and CT groups to be different by over eight points, suggesting the decisive role of exercise training in improving the QOL of clinically-overweight IWH. Due to the high cost of coagulation factors, attention to safe, non-pharmaceutical, complementary therapies that have no side effects, such as exercise training, is essential in improving the QOL of these patients.

Blood pressure and lipid profile measures

Recent reviews and meta-analyses have found aerobic and resistance exercises to significantly reduce blood pressure by approximately 3-4 mmHg in terms of SBP and DBP (14). In the present study, SBP and DBP decreased in all the training groups. HDL-C is a significant, consistent, and independent predictor of CVD. LDL-C can be protected against oxidative damage by HDL-C, which prevents the production of oxidized LDL-C. In the US, the risk of coronary artery disease was increased by 2-3% through a decrease of 1 mg/dl in HDL-C (35). In line with previous studies, the present study reported an increase in HDL-C in all the training groups (9, 11, 15). Banz et al. (36) reported a 13% increase in HDL-C following 40 minutes of AT on a skiing-style exercise machine at 85% of HR_{max} three times a week.

The risk of atherosclerosis can increase by the accumulation of mild-to-moderate concentrations (2-10 mmol/l) of TG on arterial walls (15). The present research found a more significant decrease in TG in the CT group compared to the control group. Lemura et al.(15) reported significant reductions in TG and increases in HDL-C after 30 minutes of AT at 70-75% of HR_{max} three times a week progressed by a 45-minutes exercise at 85% of HR_{max} four times a week for a total of eight weeks.

The risk of heart diseases can be increased by LDL-C that transports cholesterol to different body cells and leaves its excess on artery walls (11). In a study, the incidence of major vascular events is decreased by approximately 5% by a decrease of one mmol/l in LDL concentrations (37). The present study found significant reductions in LDL-C in the CT, AT, and RT groups compared to the controls. As a combination of lipids, TC is used for generating energy through exercises with specific dura-

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tion and intensity. Elevated TC is a significant risk factor for CVD (37). In our study, the most significant reduction in TC was observed in the CT group compared to the controls. Ha and So (17) investigated a combination of 30 minutes AT at 60-80% of HR_{max} with 30 minutes of RT at 12-15 RM for 12 weeks in 16 participants aged 20-26 years. They reported improvements in lipid profile during the exercise along with reductions in TC, LDL-C, and TG, although the changes were statistically insignificant compared to the corresponding figures in the control group. Tokudome et al. (19) reported a significant reduction of 8% in TG, a significant increase of 3.5% in HDL-C, and no significant changes in LDL and TC in older Japanese adults after twelve weeks of home-based combined RT and walking.

Increasing the activity of lipoprotein lipase (LPL) in mobilizing fatty tissues and converting them to free fatty acids for energy generation and reductions in hepatic TG synthase constitute the main mechanisms contributing to improving lipid profiles after strength-endurance exercises (38). The present findings showed that well-designed and supervised CT can influence the levels of blood lipid profiles, most especially HDL-C. The current data suggest that, compared to aerobic or resistance exercise individually, the burden of cardiovascular risk factors can be more significantly reduced in at-risk middle-aged IWH through simultaneous aerobic and resistance training. The main limitations of the present study included a short duration of exercise protocols and a small sample. Another limitation of the study was that the study participants were not blind. Other limitations included failure to control sleep, nutrition, mental status, and physical activity after training sessions. Due to the high cost of coagulation factors and difficulty travelling to the exercise investigation unit, it was not possible to follow up on the study variables. Furthermore, we had limitations in increased weight of dumbbells, barbells, and weights; and increased intensity of aerobic exercise due to patients' low tolerance level and increased risk of spontaneous musculoskeletal bleeding. The effect of aerobic, resistance, and combined exercises needs to be investigated on lipid profiles of IWH with Factor VIII inhibitors, as well.

Conclusion

The main clinical finding of the present research was the desirable changes in the blood lipid profile and QOL in IWH using all types of exercise. More importantly, the most significant changes were induced in all blood lipid parameters by CT. Therefore, CT may be recommended as a possibly effective therapeutic modality to improve QOL and prevent cardiovascular complications in PWH.

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Conflict of Interests

The authors declare that they have no competing interests.

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