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Effects of aerobic versus resistance training on serum fetuin-A, fetuin-B, and fibroblast growth factor-21 levels in male diabetic patients

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The aim of this study was to compare the effects of 8 weeks of aerobic versus resistance training programs on serum fetuin-A, fetuin-B, and fibroblast growth factor-21 (FGF-21) levels in males with type 2 diabetes mellitus. Participants ($n = 34$) were randomly assigned to a resistance training group (RTG; $n = 12$), an aerobic training group (ATG; $n = 11$), or a control group ($n = 11$). The ATG completed 30–45 min of aerobic running training at 65%–75% of the maximum heart rate. The RTG completed three sets of 10 repetitions maximum of leg press, bench press, knee extension, seated cable row, knee flexion, military press, and calf rise. Blood samples were taken before and after the training period to assess dependent variables. After 8 weeks, both the ATG and the RTG reduced fetuin-A ($p < 0.05$) and fetuin-B ($p < 0.05$), but increased FGF-21 ($p < 0.05$). Moreover, the RTG showed greater decrease than the ATG in fetuin-A (−18.3% vs. −7.9%), fetuin-B (−29.2% vs. −11.45%), and a lower increase in FGF-21 (42.2% vs. 25.1%), respectively. Aerobic and resistance exercise training significantly decreased serum fetuin-A, and fetuin-B, and increased FGF-21 levels in males with type 2 diabetes mellitus. However, more significant alterations in serum factors were observed from resistance training. Thus, resistance training may be considered a more suitable training strategy.

Keywords: exercise training, hepatokines, insulin, glucose, type 2 diabetes

Introduction

Diabetes is a group of metabolic disorders characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both (6). Type 2 diabetes mellitus (T2DM) is a common type of diabetes, represents a major global public health threat, and is an important contributor to the predicted decline in life expectancy (15). T2DM is strongly associated with visceral obesity and insulin resistance representing a global health problem in recent decades (15). T2DM may cause dysfunctions of various organs such as the heart and the peripheral blood vessels (30) including microvascular complications such as retinopathy and nephropathy and macrovascular complications such as coronary artery disease and stroke, with increased risk of premature death (30). In addition, the hepatic function could be impaired via T2DM (30). Moreover, the liver plays an important role in glucose metabolism (33).

Several hepatic plasma proteins may be involved in the regulation of insulin sensitivity including fetuin-A, fetuin-B, and fibroblast growth factor-21 (FGF-21) (33). Fetuin-A is a

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hepatic secretory glycoprotein, and it is a natural inhibitor of the insulin receptor tyrosine kinase in the liver (22, 35). Fetuin-B is another type of hepatokine, reducing glucose uptake catalyzed by insulin (22, 35). Moreover, fetuin-A and fetuin-B impaired insulin secretions from beta cells, reduced insulin sensitivity, and may have an important role in the pathogenesis of T2DM (22). In addition, some studies suggest that high levels of circulating fetuins are in line with insulin resistance and subclinical inflammation resulting in T2DM (22, 32, 36).

In addition to fetuins, FGF-21 is a protein that has been implicated in the regulation of lipid and glucose metabolism (33). In fact, FGF-21 may be a major regulator of glucose and lipid homeostasis and obesity (16). In humans, FGF-21 was shown to increase glucose uptake and based on these observations, FGF-21 has been proposed as a potential therapeutic agent for T2DM (13). Overall, it appears that there are relationships between circulating hepatokines and other metabolic variables, such as blood sugar, HbA1c, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and insulin sensitivity in diabetes (13, 16, 25, 33).

Physical activity and structured exercise training are the foundation of therapy for T2DM. Evidence for the benefits of exercise training is obtained from studies showing that active individuals had less symptoms of T2DM including lower fasting blood sugar (FBS), LDL, homeostatic model assessment of insulin resistance (HOMA-IR), triglyceride, and cholesterol (6, 15). The American Diabetes Association recommends at least 150 min weekly aerobic exercise to improve glycemic control and cardiovascular risk factors in patients with T2DM (34). In recent years, resistance training has become a familiar form of training to improve physical fitness and prevent injuries (2). It appears that resistance training may be useful to increase the number of glucose transporter (GLUT) protein, to increase total muscle mass, and to increase the number of insulin receptors in the muscle fiber (2). The American College of Sport Medicine recommends at least three resistance training sessions a week, targeting all major groups for 3 sets of 10 repetitions maximum with moderate intensity to reduce the risk of T2DM (37, 38).

Several studies have focused on the effects of resistance and aerobic training on some variables of T2DM (2, 4, 6, 8, 15, 19, 34) but the effects on hepatokines are controversial, and the effects of resistance training are unclear.

Different forms of exercise training induced different exercise adaptations. Aerobic exercise increased skeletal muscle capitalization and blood flow, muscular GLUT4 levels, hexokinase, and glycogen synthase activities (2). On the contrary, resistance training improved muscular strength (force-generating capacity), endurance, and power and body composition, and decreased the risk of cardiovascular disease (29). The aim of this study was to examine the effects of 8-week resistance and aerobic training on plasma concentration of fetuin-A, fetuin-B, FGF-21, and other relevant variables in men with T2DM.

Materials and Methods

Subjects

Initially, 39 diabetic men volunteered to participate in this study. To be included in the final analyses, subjects were required to complete all the training sessions and attend all assessment sessions. As a result of these requirements, five subjects were excluded from the study. Thus, 34 men were included in the final analyses. The three final groups were: resistance training group (RTG; $n = 12$), aerobic training group (ATG; $n = 11$), and control

Table I. Subjects' characteristics (mean ± SD)

	RTG ($n = 12$)	ATG ($n = 11$)	CG ($n = 11$)
Age (years)	52.4 ± 1.8	52.4 ± 1.5	53.0 ± 1.1
Height (cm)	171.6 ± 5.8	175.2 ± 5.5	172.9 ± 5.3
Body mass (kg)	92.1 ± 8.6	100.2 ± 14.7	97.8 ± 10.9
BMI (kg/m^2)	31.2 ± 1.2	32.4 ± 3.3	32.6 ± 2.9
Body fat (%)	27.1 ± 1.6	32.4 ± 4.7	30.1 ± 3.3
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	29.0 ± 3.6	30.1 ± 3.5	29.5 ± 5.0

SD: standard deviation; RTG: resistance training group; ATG: aerobic training group; CG: control group; BMI: body mass index

group (CG; $n = 11$; Table I). The inclusion criteria were: men with established T2DM for at least 5 years duration, sedentary lifestyle; HbA1c level ≥ 6.5%, body mass index (BMI) > 30 kg/m^2; FBS > 126 mg/dl (e.g., between 150 and 200 mg/dl); 45–55 years of age; no history of musculoskeletal injury or any orthopedic problems affecting the ability to train; no intake of any food supplements with suggested effects on the results 6 months before initiation of the study and throughout the study period; and no history of serious cerebrovascular or cardiovascular diseases, retinopathy, and nephropathy restricting physical activity. The participants were informed about the experimental procedures and signed informed consent and filled in medical history forms in adherence with the human guidelines, ethics committee, and the Declaration of Helsinki.

Study design

A week before the initiation of the training period, all participants reported to the laboratory for the familiarization with training and testing procedures. During this session, the subject's initial characteristics such as age, height, body mass, and percent body fat were measured. One day later, upper and lower body strength was assessed using 10 repetition maximum (10RM) of bench press and leg press exercises. Moreover, VO_{2max} was assessed to determine aerobic capacity of the subjects. The men performed an 8-week training program and blood was drawn before and after the training session. All tests were administered in the same order or time of day before and after training intervention and recorded by the same investigators. Participants were instructed to maintain their regular physical activity and diet throughout the duration of the study.

Measurements

Anthropometric measures. Height was measured using a wall-mounted stadiometer (Seca 222, Terre Haute, IN, USA) recorded to the nearest 0.5 cm, body mass was measured to the nearest 0.1 kg using a digital scale (Tanita, BC-418MA, Tokyo, Japan), and BMI was calculated (kg/m^2). Skinfold thicknesses were obtained using Harpenden Skinfold Caliper (Baty International, West Sussex, UK) at the chest, abdomen, and thigh following the procedures previously described (14). A three-site skinfold equation was used to estimate percent body fat using Jackson and Pollock method (21).

Strength assessment. Upper and lower body strength was assessed using a series of 10RM tests with free weights for bench press and 45° leg press (Nebula Fitness, Inc., Versailles, OH, USA). Specifically, all subjects performed a warm-up with a light resistance. The resistance was then increased with the subjects performing only 10 repetitions (26). Coaches were present to provide verbal encouragement and ensure safety.

Aerobic capacity. The Balke treadmill test was used as a clinical test to determine VO_{2max} in T2DM patients. The subjects walked on a treadmill to exhaustion and the time was measured to estimate VO_{2max} using this formula: $VO_{2max} = 1.444\ (\text{time}) + 14.99$ (17).

Blood sampling and analyses. Blood samples were drawn (10 ml) from the antecubital vein into plain evacuated test tubes at rest between 8:30 and 9:00 a.m. before and after the training to evaluate FBS, HbA1c, HDL, LDL, insulin, cholesterol, triglyceride, fetuin-A, fetuin-B, and FGF-21. The blood was allowed to clot at room temperature for 30 min and centrifuged at $3600 \times g$ for 10 min. The serum layer was removed and frozen at –60 °C in multiple aliquots for further analyses.

Measurements of serum cholesterol, HDL, LDL, and triglyceride were carried out in a photometric end point method using Pars Azmoon® enzyme kits, in auto-analyzer (Hitachi®, model 704, 902 made in Japan). HbA1c levels were measured using a HPLC method (Hitachi®). The glucose level was determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Diaplus Company, USA) and insulin level was measured by a radioimmunoassay. Insulin resistance index (HOMA-IR) was calculated according to the formula (31): HOMA-IR = (fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5). The fetuin-A, fetuin-B, and FGF-21 levels were measured using commercial ELISA kits (ZellBio GmbH Veltlinerweg 29, 89075, Ulm, Germany). The coefficient of variation for the measurements was less than 5%.

Training program. To standardize training procedures, 2 weeks of orientation took place including three sessions in which the methods and techniques were demonstrated. The subjects were involved in a 10-week training protocol including 2 weeks for the familiarization with the training and 8 weeks for the main training. The resistance training program consisted of the following exercises: leg press, bench press, knee extension, seated cable row, knee flexion, military press, and calf rise, 3 days a week for 8 weeks. The subjects performed three sets of 10RM with 1.5-min rest between sets and 2-min rest between exercises. The loads were increased, if the prescribed number of repetitions was reached. Each resistance training session lasted for 60 min, including 10 min of warm-up (e.g., jogging, stretching, and ballistic exercises), 45 min of main training, and 5 min of cool down (e.g., stretching exercises). The aerobic training program included running at 75%–85% of maximum heart rate (HR_{max}), which was calculated using the Karvonen formula (24), for 30–45 min per day, 3 days a week for 8 weeks. Each training session started with a warm-up and finished with a cool down. The exercise intensity was controlled by the coaches, using a heart rate monitor (Polar S610i heart rate monitor, FIN, 90440, Finland), ensuring that HR was between 75% and 85% of HR_{max} throughout the trial. The training sessions were performed at the University and were supervised by the coaches. The CG did not perform any exercise and continued their regular sedentary life. In training sessions, the subjects were under direct supervision and were instructed how to perform each exercise by a certified strength and conditioning specialist.

Statistical analyses

All values are presented as mean ± standard deviation. Pre- and post-values for the dependent variables were analyzed to determine if the distributions were normal using the Shapiro–Wilk

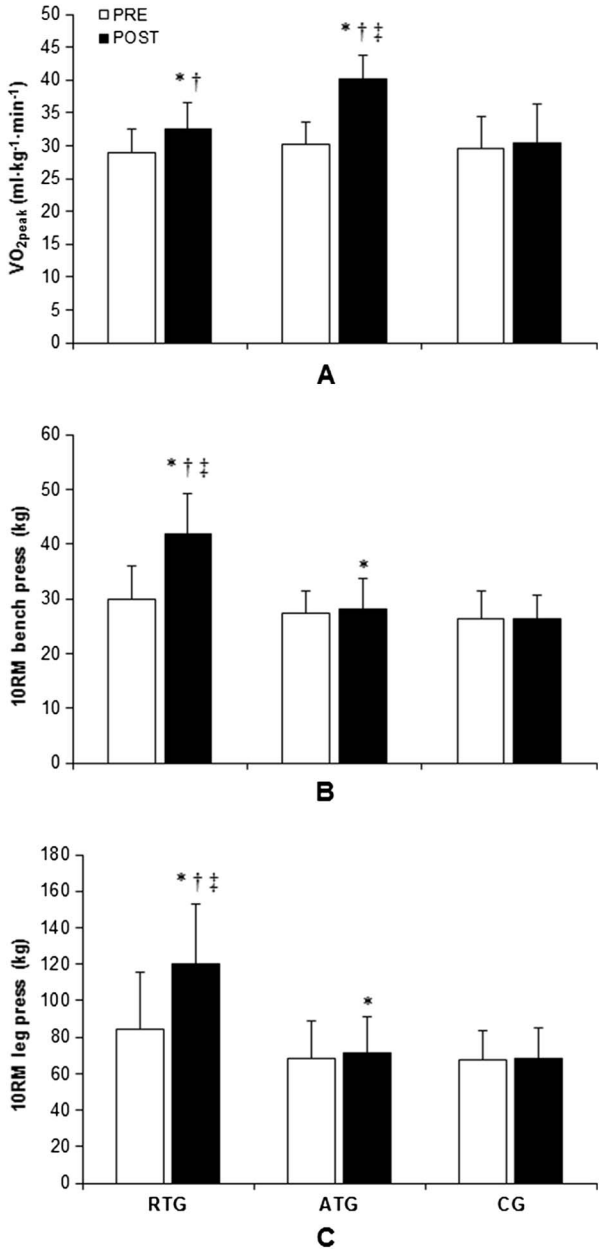

Fig. 1. Changes in strength performance and aerobic capacity in all groups (mean ± SD). RTG: resistance training group; ATG: aerobic training group; CG: control group. *Significant differences compared to the pretraining value ($p < 0.05$). †Significant differences compared to CG ($p < 0.05$). ‡Significant differences between training groups ($p < 0.05$)

normality test. Differences in all variables were analyzed using 3 (Group) × 2 (Time) repeated measures analysis of variance. When a significant F value was achieved across time or ages, Bonferroni post-hoc procedures were performed to locate the pairs. Regarding pretest differences, analyses of covariance were used to test for differences between groups for the dependent variable values. For each measure, a percent change (Δ changes) score was calculated [(post 8 weeks − baseline/(baseline × 100)]. Statistical significance was set at $\alpha \leq 0.05$.

Results

No significant changes in dependent variables were observed for the CG after 8 weeks ($p > 0.05$).

Both training groups increased the bench press (RTG, from 30 ± 6 to 41.7 ± 7.5 kg, Δ 39%; ATG, from 27.3 ± 4.1 to 28.2 ± 5.6 kg, Δ 3.2%) and leg press performance (RTG, from 84.2 ± 31.5 to 120 ± 32.8 kg, Δ 42.5%; ATG, from 68.2 ± 20.9 to 71.4 ± 20.1 kg, Δ 4.7%) ($p < 0.05$), and only the RTG achieved a significant increase in comparison to the CG in these tests ($p < 0.05$). In addition, differences were found between the RTG and the ATG in strength performance indicating greater adaptive responses to training for the RTG ($p < 0.05$; Fig. 1A, B).

Both training groups improved the VO_{2max} (RTG, from 29 ± 3.6 to 32.5 ± 4 $ml \cdot kg^{-1} \cdot min^{-1}$, Δ 12%; ATG, from 30.1 ± 3.5 to 40.1 ± 3.6 $ml \cdot kg^{-1} \cdot min^{-1}$, Δ 33.2%; $p < 0.05$), and both achieved a greater increase compared to the CG in this test ($p < 0.05$). In addition, differences were found between the ATG and the RTG in aerobic capacity indicating significant adaptation to training for the ATG ($p < 0.05$; Fig. 1C).

Both training groups decreased ($p < 0.05$) their blood variables in the FBS (RTG: 28.5% and ART: 20.8%), HbA1c (RTG: 11.5% and ART: 6.6%), insulin (RTG: 5.8% and ART: 4.5%), cholesterol (RTG: 14.2% and ART: 18.2%), triglyceride (RTG: 12.7% and ART: 17.7%), LDL (RTG: 10.8% and ART: 11.5%), HOMA-IR (RTG: 27.7% and ART: 24.3%), fetuin-A (RTG: 18.3% and ART: 7.9%), and fetuin-B (RTG: 29.2% and ART: 11.4%) after training, and both achieved significant differences compared to the CG in these tests ($p < 0.05$). The RTG had greater training effects in FBS, HbA1c, fetuin-A, and fetuin-B in comparison with the ATG ($p < 0.05$), whereas the ATG had greater training effects in cholesterol and triglyceride in comparison with the RTG ($p < 0.05$; Table II).

Table II. Changes in variables for the all groups

		RTG ($n = 12$)		**ATG ($n = 11$)**		**CG ($n = 11$)**
		Mean ± SD		**Mean ± SD**		**Mean ± SD**
FBS (mg/dl)	Pre	174.2 ± 7.3		172.7 ± 8.8		168.3 ± 7
	Post	129.2 ± 7.5	*†‡	136.7 ± 4.8	*†	160.4 ± 11.4
	Δ%	−25.8		−20.8		−4.7
HbA1c (%)	Pre	7.8 ± 1.1		7.5 ± 1.2		7.2 ± 1.6
	Post	6.9 ± 0.8	*†‡	7 ± 1.2	*†	7.2 ± 1.7
	Δ%	−11.5		−6.6		0
Insulin (mU/L)	Pre	8.6 ± 0.2		8.7 ± 0.2		8.8 ± 0.2
	Post	8.1 ± 0.2	*†	8.3 ± 0.2	*†	8.7 ± 0.2
	Δ%	−5.8		−4.5		−1.1
Cholesterol (mg/dl)	Pre	187.8 ± 20		193.6 ± 12.9		184.5 ± 18.9
	Post	161 ± 20.7	*†	158.2 ± 17.8	*†‡	180.8 ± 17
	Δ%	−14.2		−18.2		−2

(Continued)

Table II. Changes in variables for the all groups *(Continued)*

		RTG ($n = 12$)		ATG ($n = 11$)		CG ($n = 11$)
		Mean ± SD		**Mean ± SD**		**Mean ± SD**
Triglyceride (mg/dl)	Pre	216.6 ± 29.2		199.2 ± 12.3		184.6 ± 37.5
	Post	188.9 ± 30.1	*†	163.9 ± 17.5	*†‡	183.5 ± 35.6
	Δ%	−12.7		−17.7		−0.6
HDL (mg/dl)	Pre	32.9 ± 6.9		34.9 ± 6.3		35.5 ± 7
	Post	39.9 ± 7.1	*†	42.8 ± 7.6	*†	35 ± 6.3
	Δ%	21.2		22.6		−0.1
LDL (mg/dl)	Pre	102.6 ± 10.1		101.5 ± 6.7		100 ± 8.1
	Post	91.5 ± 9.3	*†	89.8 ± 5.4	*†	98.5 ± 8.2
	Δ%	−10.8		−11.5		−1.5
HOMA-IR	Pre	3.6 ± 0.3		3.7 ± 0.4		3.5 ± 0.6
	Post	2.6 ± 0.2	*†	2.8 ± 0.3	*†	3.3 ± 0.6
	Δ%	−27.7		−24.3		−5.7
Fetuin-A (mg/L)	Pre	405.9 ± 7.7		417.3 ± 6.4		433.4 ± 10.5
	Post	331.3 ± 10.7	*†‡	384.4 ± 7.1	*†	433.5 ± 10.6
	Δ%	−18.3		−7.9		0.02
Fetuin-B (ng/L)	Pre	275.3 ± 3		285.2 ± 4.3		284.7 ± 3.3
	Post	194.7 ± 5.2	*†‡	252.7 ± 4.9	*†	275.3 ± 4.8
	Δ%	−29.2		−11.4		−3.3
FGF-21 (pg/ml)	Pre	144.5 ± 3.1		137.8 ± 2.7		132.2 ± 5.5
	Post	250.1 ± 6.7	*†‡	184 ± 4.6	*†	128.2 ± 1.9
	Δ%	42.2		25.1		−3.0

RTG: resistance training group; ATG: aerobic training group; CG: control group; SD: standard deviation; FBS: fasting blood sugar; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; FGF-21: fibroblast growth factor-21.
*Significant differences compared to the pretraining value ($p < 0.05$).
†Significant differences compared to CG ($p < 0.05$).
‡Significant differences between training groups ($p < 0.05$)

Both training groups increased HDL (RTG: 21.2% and ART: 22.6%) and FGF-21 (RTG: 42.2% and ART: 25.1%; $p < 0.05$), and both achieved greater increase compared to the CG ($p < 0.05$). In addition, differences were found between the RTG and the ATG in FGF-21, which indicated greater adaptive responses to training for the RTG ($p < 0.05$; Table II).

Discussion

This study suggests that 8 weeks of resistance and aerobic training induced significant increases in strength performance, aerobic capacity, HDL, and FGF-21, and significant decreases in FBS, HbA1c, insulin, cholesterol, triglyceride, LDL, HOMA-IR, fetuin-A, and fetuin-B in T2DM men. Moreover, the RTG showed greater changes than the ATG in strength, FBS, HbA1c, fetuin-A, fetuin-B, and FGF-21, whereas the ATG indicated greater changes than RTG in aerobic capacity, cholesterol, and triglyceride.

In this study, subjects in the RTG and the ATG improved their strength performance in 10RM leg press (42.5% vs. 4.7%) and bench press (39% vs. 3.2%) tests after 8 weeks of training, and in comparison with the CG. Moreover, the RTG indicated significant differences compared to the ATG in strength performance. Several studies have reported the positive transfer of resistance training to improve strength performance (1, 10), which is in line with our findings. We also found that ATG improved strength performance that confirms the effects of exercise training on strength gains. For this study, the possible explanation for the enhancement of strength performance could be due to increasing motor neuron excitability, increasing motor unit firing frequency, and increasing in efferent motor drive following both strength and aerobic training with greater effects via resistance training (1).

Both groups improved aerobic capacity (VO_{2max}) after 8 weeks of training and these changes were statistically significant compared to the CG. The ATG (33.2%) also indicated more changes than the RTG (12%) after the 8-week training period. There are few resistance and aerobic training studies that have reported different findings. Alam et al. (3) reported significant increases in VO_{2max} after a 6-month exercise program. Cauza et al. (9) observed improvements in VO_{2peak} after aerobic training, whereas no such changes were seen in resistance training in people with T2DM. In addition, other researchers did not find changes in aerobic capacity in a short-term comparison study of resistance training with non-exercising control subjects (29). We found improved aerobic capacity, which supports the findings of previous studies and indicates that the intensity and duration of the training were sufficient to induce the required physiological improvements with greater effects for the ATG. According to these reports, the possible explanation to greater changes for the ATG could be due to increased muscle fiber capillary density, increase of hexokinase enzyme activity, improved environmental diffusion slope, and expression of (GLUT4) after aerobic exercise (2, 18, 33). However, we did not measure these variables directly.

There were significant decreases in FBS, HbA1c, insulin, and HOMA-IR in the RTG and the ATG after 8 weeks of training. In addition, the changes in FBS and HbA1c were greater for the RTG compared to the ATG. These findings confirm those of previous studies that found increase in insulin sensitivity and decrease in blood sugar after training (28, 40). There were different mechanisms for the increases in insulin sensitivity and management of blood glucose after resistance and aerobic training (20). It appears that aerobic training increased post-receptor insulin signaling, increased GLUT protein and mRNA, increased activity of glycogen syntheses and hexokinase, increased muscle glucose delivery, and induced changes in muscle composition (5, 11, 12). Although the effects of resistance training on glucose homeostasis and insulin sensitivity are similar to aerobic training (17), the resistance training leads to increases in the protein content of GLUT4, insulin receptors, glycogen synthase, and protein kinase B. Regarding greater changes in FBS and HbA1c for the RTG, it seems that resistance training could be an optimum training modality to manage the symptoms of T2DM by increasing insulin sensitivity (11, 40). However, further studies

are required to confirm this in different populations and investigate the mechanism(s) responsible for these changes.

In this study, both resistance and aerobic training caused a significant decrease in cholesterol (−14.2% and −18.2%), triglyceride (−12.7% and −17.7%), and LDL (−10.8% and −11.5%), whereas HDL increased significantly for both the RTG (21.2%) and ATG (22.6%). In addition, changes in cholesterol and triglyceride were greater for the ATG compared to the RTG after 8 weeks of training. These results are inconsistent with the findings of Sigal et al. (39) and Castanada et al. (8), reporting no significant changes in lipid profile after training. In agreement with our findings, Kelly and Kelly (23) in a meta-analysis concluded that exercise training is a modality to reduce LDL levels. In addition, the findings of Balducci et al. (7) who demonstrated a significant reduction in cholesterol, LDL, and triglycerides are in line with our findings. Arora et al. (6) indicated the effectiveness of both aerobic and resistance training with the superiority of resistance exercise on the management of cholesterols and triglycerides, which is not in line with our findings because we found the superiority of aerobic exercise training on cholesterol and triglyceride responses to training. Thus, it can be concluded that changes in lipid profile in response to exercise training might be related to training intensity, duration, frequency, and study population (26). The possible mechanism to manage the lipid profile after training could be due to increasing fatty acid transfer, increasing oxidative mitochondrial enzymes, and other carriers such as carnitine palmitoyltransferase (6, 8, 15).

Eight weeks of aerobic and resistance training changed serum fetuin-A, fetuin-B, and FGF-21 concentrations, with superior effects via resistance training (Table II). Very few resistance and aerobic-training studies that have investigated changes in hepatokines have also reported conflicting results (16, 22, 25, 27, 33, 36). Reduction in serum concentration of fetuin-A and fetuin-B is in line with reduction of blood glucose and insulin resistance in T2DM. In fact, fetuin-A and fetuin-B levels were associated with more than a twofold increased risk of type 2 diabetes and some symptoms of T2DM (35). Furthermore, some researchers have reported that high levels of circulating fetuins are in line with insulin resistance and subclinical inflammation resulting in T2DM (32, 35, 36). In addition to fetuins, FGF-21 plays an important role in regulation of glucose and lipid homeostasis. On the other hand, FGF-21 could increase glucose uptake with upregulation of GLUT4 potentially representing a therapeutic agent for type 2 diabetes. Overall, exercise training altered some sign symptoms of T2DM such as FBS, HbA1c, HOMA-IR, LDL, and hepatokines (fetuin-A, fetuin-B, and FGF-21) via upregulation of natural inhibitor of the insulin receptor tyrosine kinase in the liver, insulin sensitivity, GLUT-4, GLUT protein and mRNA, activity of glycogen syntheses and hexokinase, muscle glucose delivery, and changes in muscle composition (13, 16, 25, 37).

In summary, our findings support the benefits of physical training in T2DM patients. Aerobic and resistance training induce positive effects in the prevention or management of symptoms of T2DM and hepatokines. The greater improvement of variables such as FBS, HbA1c, fetuin-A, fetuin-B, and FGF-21 seems to be best with resistance training for managing the T2DM. The significant additive adaptations in the RTG suggest that this type of exercise may be preferable for diabetic patients and this type of exercise training may be emphasized.

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HA designed the study. AK and HA prepared the manuscript. AK and MK gathered data and searched the literature. AK analyzed data. All authors read and approved the final version of the manuscript.

Conflict of interest

All authors declare no conflict of interest.

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