International Journal of Diabetes in Developing Countries (April–June 2025) 45(2):472–479
https://doi.org/10.1007/s13410-024-01343-3

ORIGINAL ARTICLE

The effect of 8 weeks of endurance and resistance exercises on the serum levels of FGF23 and s-Klotho in type 2 diabetic women

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Received: 29 October 2022 / Accepted: 22 April 2024 / Published online: 19 May 2024
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Abstract

Background It has been reported that exercise could improve diabetes via the VitD-FGF23-sKlotho axis.

Objective We evaluated the effects of 8 weeks of endurance and resistance training on serum levels of fibroblast growth factor 23 (FGF23), soluble klotho (s-Klotho), 1,25-dihydroxyvitamin D (VitD), and diabetes biomarkers in overweight/obese postmenopausal type 2 diabetic (T2DM) women.

Methods Thirty overweight/obese postmenopausal women with T2DM were randomly divided into three groups, including endurance exercise (3 days/week of walking and jogging), resistance exercise (60 min weight resistance training 3 days/week), and control groups (no physical activity and dietary change). Before and after the 8-week training, serum levels of FGF23, s-Klotho, VitD, blood sugar, lipid profile, and hemoglobin A1c (HbA1c) as well as anthropometric, physiological, and cardiac characteristics were evaluated.

Results The endurance or resistance training did not significantly change the anthropometric and cardiac parameters ($p > 0.05$), and only fat percent, resting heart rate, and systolic blood pressure levels were significantly decreased after the endurance exercise ($p < 0.05$). Both endurance and training exercises could improve serum levels of insulin and glucose. The serum levels of FGF23 and s-Klotho were significantly increased in the endurance and resistance groups ($p < 0.05$), while no significant change was found in the VitD levels.

Conclusion Physical exercises, especially the endurance feature of the training modality, could increase serum FGF23 and s-Klotho levels and decrease FBG and HbA1c levels in postmenopausal T2DM women which might be a sign of improvement in glucose metabolism through regulation of VitD-FGF23-s-klotho axis.

Keywords FGF23 · Insulin · Klotho · Exercise · Physical Activity · Menopause

Introduction

Diabetes mellitus is one of the most common metabolic disorders affecting more than 415 million people worldwide [1]. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of patients with diabetes [1]. Different cellular and molecular factors have been introduced as potential players in T2DM pathogenesis such as klotho and fibroblast growth factor 23 (FGF-23) [2].

Klotho, a single-unit membrane protein, binds to the FGF-23 as a co-receptor to maintain endocrine system homeostasis [3]. Klotho is associated with FGF-23, and insulin-like growth factor 1 (IGF-1) is involved in the regulation of energy metabolism and insulin resistance [4]. It has been demonstrated that a reduction in the serum level of soluble klotho (s-Klotho) could cause metabolic diseases such as T2DM [4]. In vitro studies indicated that s-klotho could inhibit the auto-phosphorylation of insulin

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and IGF-1 receptors. Moreover, mice with deficient klotho showed hypoglycemia and hypo-insulinemia with elevated insulin sensitivity [5]. Recently, clinical studies demonstrated that higher serum levels of FGF23 were also associated with an increased risk of metabolic disorders and mortality in T2DM patients [6]. In addition, studies reported that 1,25-dihydroxy-vitamin D (VitD) deficiency is associated with the development of T2DM [7]. Since FGF23 regulates VitD production as well as klotho expression [8], the VitD-FGF23-sKlotho axis might play an important role in the development of T2DM [2, 9].

Besides the genetic factors, a sedentary lifestyle and obesity are also risk factors for T2DM [10]. In contrast, physical exercise is an important non-pharmacological intervention to take care of T2DM patients' health. Previous studies documented that aerobic exercise could improve blood levels of s-Klotho [11, 12], and consequently inflammation [13] and endothelial dysfunction [12]. Furthermore, it has been shown that concurrent exercise increased s-Klotho, but not serum FGF23 in patients with end-stage renal failure [14].

Considering the well-known beneficial influences of both endurance and resistance exercises on T2DM and its complications by regulation of the VitD-FGF23-sKlotho axis, in this study, we investigated the effects of 8 weeks of moderate-intensity endurance as well as resistance training on serum levels of FGF23, sKlotho, vitamin D, diabetes biomarkers (fasting blood sugar and hemoglobin A1c (HbA1c)), and physiological parameters in overweight/obese postmenopausal type 2 diabetic (T2DM) women.

Materials and methods

Study design

This randomized controlled trial study was conducted according to the guidelines of the Declaration of Helsinki, and all the procedure was approved by the Ethical Committee of Urmia University. Moreover, written informed consent was obtained from all participants before entering the study. In terms of sample size, we took into consideration three factors and recruited 30 participants: (a) the sample sizes of previous studies examining the impact of exercise on klotho levels [15, 16] [11], (b) calculations derived from the following formula for randomized control trials (RCT) as advised by Charan et al. [17], assuming a type one error of 5% ($Z\alpha/2 = 1.96$) and power of 80% ($Z\beta = 0.84$).

$$n = \frac{2 \times SD^2 \times (Z_{\alpha/2} + Z_{\beta})^2}{d^2}$$

Thirty overweight/obese postmenopausal women with T2DM were recruited and randomly divided into three groups based on the exercise type: (1) endurance exercise ($n = 10$), (2) resistance exercise ($n = 10$), and (3) control ($n = 10$) groups. The inclusion criteria for this study were (1) women aged 50–60 years old who had passed their menopause at least 5 years ago, (2) overweight or obese women with body mass index (BMI) ≥ 25 kg/m^2, (3) having fasting blood glucose of > 126 mg/dl, (4) having serum levels of hemoglobin A1c (HbA1c) $\geq 6/4$ mg/dl, (5) having 2-h postprandial blood glucose > 200 mg/dl, (6) having a history of T2DM for more than 1 year, (7) taking metformin alone as the medication with a dose of 500–1000 mg /day, and (8) no history of regular exercise. Moreover, we excluded patients who had hormone therapy (e.g., insulin injection) and smoking for at least 6 months before the study and patients who had other chronic diseases such as cardiovascular diseases (CVDs), pulmonary diseases, cerebrovascular diseases, fatty liver disease, bone disorders, diabetic deformities, and diabetic nephropathy. By the end of the study, two women from each group were unable to complete the study due to irregular participation in exercise protocol, car accident–related trauma, or absence of blood sampling at week 8.

Exercise protocols

Assessment of physical activity and energy expenditure was expressed in terms of metabolic equivalent of tasks (METs) in all participants.

Endurance exercise was performed 3 days/week (180–190 min per week) at 70–75% of each individual's maximal heart rate reserve (HRmaxR) as walking and jogging training for 8 weeks in the endurance group. In the first week, this group performed moderate-intensity endurance exercise training intervention at 50–60% of HRmaxR. During the second week, the exercise intensity was increased to 60–70% of HRmaxR. In the last 6 weeks, participants were trained at 70–75% of HRmaxR. Each training session included 10 min of prior warm-up and 5 min of cooling down (active-recovery) on a treadmill at an ambient temperature of 26–28 °C and relative humidity of 47%. During the exercise, the heart rate of participants was recorded using a heart rate monitor (Polar Pacer, T415C, Finland) to control the intensity of the exercise. All exercise sessions were performed between 09:00 and 10:00 A.M., and participants were supervised by an exercise physiologist.

Resistance exercise training was also performed for 8 weeks, and the training was adjusted based on the one-repetition maximum (1-RM) of each participant which is the maximum amount of weight that the participant could lift for one repetition. The 1-RM test was conducted using Brzyski's method to determine maximal strength in each resistance training. The training was a warm up—resistance exercise training program—cool down with 50–60% 1-RM (the first week for preparatory training), 60–70% 1-RM (the second week), and 70–75% 1-RM (6 weeks) individually in the gym

for three sessions per week in the morning (between 09:00 and 10:00 A.M.). Resistance training intervention included 60-min weight resistance training exercises consisting of nine stations (1—leg extension, 2—leg curl, 3—chest press, 4—leg press, 5—seated cable row, 6—Lat pull down behind the neck, 7—cable crunch, 8—dumbbell biceps curl first 2.5 up to 5 kg, and 9—dumbbell triceps curl first 2.5 up to 5 kg, respectively), and each session involved three sets of eight to nine repetitions at 70–75% of 1-RM. The resting time between sets and stations was 10 s. The warm-up for resistance training was performed as 10 min of walking and jogging on a treadmill.

The control group continued their normal sedentary lifestyle and dietary habits with no physical activity during the study.

Measurements

Physiological characteristics Weight, BMI, resting heart rate, body fat percentage, waist circumference or hip circumference, and/or waist-to-hip ratio (WHR) were evaluated in all participants at baseline.

Dietary intake assessment Dietary recall data was assessed via a 24-h dietary recall record to control participants' diet (Bailey et al., 2009) at baseline and after the 8-week training. The participants were requested to maintain their normal diet during the 8 weeks and were instructed to consume a diet as similar as possible on each sampling day. Nutrition analysis software was used for nutrition and dietary data (Nutrition data proTM v1.1, StarApps Co, USA).

Serum markers Five milliliters of fasting blood sample was collected from all participants at baseline and 48 h after the 8-week training. After isolation of serum, levels of FGF23 (Bioassay technology-FGF23, E4142Hu, China), s-Klotho (Bioassay Technology-Klotho, E4142Hu, China), and VitD (ParsTest-Vitamin D, Iran) were evaluated by commercial enzyme-linked immunosorbent assay (ELISA) kits using Elisa reader (EpoccH2, Iran). Moreover, levels of insulin, cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood glucose (FBG), and HbA1c were measured by standard automated laboratory techniques (AutoAnalyzer, Biotecnica BT-1500, Italy).

Statistical analysis

The statistical software program SPSS (SPSS Co, Chicago IL, version 23) was used for the data analyses. All data are expressed as means ± standard deviation (SD) and checked for normality using Kolmogorov–Smirnov and homogenize of variances (Levene's test) tests. Paired samples *t* test was employed to evaluate the difference between baseline and after 8-week training in each group. The ANOVA test following the Tukey post hoc test was used to compare data among three groups. The significance level was considered at a $p < 0.05$.

Results

Anthropometric characteristics

There was no significant difference in age, menopause age, BMI, waist circumference, hip circumference, waist-to-hip ratio (WHR), and fat percentage among the endurance, resistance, and control groups at baseline ($p > 0.05$, Table 1). Moreover, 8-week endurance or resistance training did not

Table 1 Anthropometric characteristics of study groups before and after an 8-week exercise training

		Endurance group ($n = 10$)	Resistance group ($n = 10$)	Control group ($n = 10$)
Age (year)		55.12 ± 2.85	58.12 ± 3.18	55.75 ± 3.61
Menopause age (year)		7.5 ± 3.2	12.0 ± 8.7	8.66 ± 1.52
BMI (kg/m^2)	Before	32.98 ± 4.26	31.13 ± 3.44	31.18 ± 4.75
	After	30.31 ± 3.77	30.16 ± 3.79	31.55 ± 4.84
Waist circumference (cm)	Before	95.75 ± 5.72	94.5 ± 7.80	94.37 ± 6.92
	After	93.62 ± 5.73	90.50 ± 7.21	93.25 ± 5.52
Hip circumference (cm)	Before	109.87 ± 9.43	109.12 ± 7.96	107.12 ± 9.37
	After	106.37 ± 10.09	107.62 ± 7.30	108.75 ± 11.07
WHR (cm)	Before	0.87 ± 0.07	0.84 ± 0.02	0.88 ± 0.08
	After	0.88 ± 0.09	0.83 ± 0.03	0.86 ± 0.09
Fat percentage (%)	Before	40.70 ± 3.27	39.38 ± 4.83	40.41 ± 6.96
	After	37.07 ± 3.75*$	37.89 ± 4.45	39.11 ± 7.92

Values are presented as mean ± SD; before, baseline levels before the exercise training; after, 48 h after 8-week training

BMI body mass index; *WHR* waist-to-hip ratio

*Significant difference ($p < 0.05$) between before and after exercise in each group; $significant difference ($p < 0.05$) with the control group

significantly change the anthropometric factors in the related groups ($p > 0.05$) except fat percent percentage that significantly reduced after endurance exercise ($p < 0.05$).

Physiological and cardiac characteristics

Physiological and cardiac parameters before and after an 8-week exercise training in the endurance, resistance, and control groups are listed in Table 2. Our results showed no significant difference in VO2max, resting heart rate, SBP, DBP, and METs among the groups at the baseline level. Furthermore, no significant results were obtained when we compared these factors before and after the training course in each group; however, resting heart rate and SBP levels were significantly decreased after the endurance exercise ($p < 0.05$, Table 2).

Dietary intake

Dietary intake parameters including total energy intake (TEI), fat, carbohydrate, and protein were not significantly different among groups before the training course and after 8 weeks of training ($p > 0.05$, Table 3).

Biochemical markers

As shown in Table 4, there was no significant difference in the lipid profile of participants at the baseline level ($p > 0.05$). However, we found that both endurance and resistance exercises for 8 weeks could significantly decrease serum levels of cholesterol, TG, and LDL and also significantly increased HDL levels. Moreover, levels of all these factors in the endurance group were significantly different from the control group after the training course ($p < 0.05$). Whereas, the results showed that only TG levels were significantly different between the control and resistance groups after the 8-week training ($p < 0.05$).

Interestingly, both endurance and training exercises for 8 weeks could significantly improve serum levels of insulin and FBG ($p < 0.05$, Table 4). Moreover, endurance exercise had a significant effect on serum levels of HbA1c; this effect was not observed in the resistance group. Our results showed that the endurance exercise had more effect on levels of FBG compared to the resistance exercise (Table 4).

After an 8-week training, serum levels of FGF23 and s-Klotho were significantly increased in the endurance

Table 2 Physiological and cardiac characteristics of study groups before and after an 8-week exercise training

		Endurance group ($n = 10$)	Resistance group ($n = 10$)	Control group ($n = 10$)
VO_2max (ml/kg/min)	Before	32.22 ± 2.73	31.23 ± 3.02	30.43 ± 2.25
	After	37.85 ± 5.49	33.20 ± 5.36	31.01 ± 1.65
Resting heart rate (b/min)	Before	80.0 ± 9.43	82.70 ± 8.11	81.50 ± 6.86
	After	71.0 ± 6.12*$	76.41 ± 9.04	80.10 ± 7.28
SBP (mmHg)	Before	134.0 ± 15.16	136.66 ± 8.16	132.75 ± 12.25
	After	121.5 ± 13.20*$	130.42 ± 9.33	135.68 ± 10.18
DBP (mmHg)	Before	91.0 ± 11.40	92.0 ± 3.1	90.0 ± 3.46
	After	82.0 ± 9.56	87.1 ± 5.2	89.2 ± 6.23

Values are presented as mean ± SD

VO_2max maximal oxygen consumption, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MET* metabolic equivalent of task

*Significant difference ($p < 0.05$) between before and after exercise in each group; $significant difference ($p < 0.05$) with the control group

Table 3 Comparison of the dietary intake at baseline and after 8-week training among study groups

		Endurance group ($n = 10$)	Resistance group ($n = 10$)	Control group ($n = 10$)
Total energy intake (kcal/d)	Before	2121.35 ± 453.59	1927.35 ± 339.39	1943.93 ± 412.57
	After	2146.10 ± 458.31	1949.80 ± 285.64	1942.46 ± 386.86
Fat (g)	Before	96.74 ± 24.31	98.38 ± 39.59	80.19 ± 38.88
	After	92.90 ± 15.22	93.53 ± 35.88	80.42 ± 37.41
Carbohydrate (g)	Before	201.74 ± 65.69	167.21 ± 91.07	146.37 ± 71.21
	After	201.10 ± 63.72	151.80 ± 60.67	141.50 ± 63.13
Protein (g)	Before	65.53 ± 27.05	75.80 ± 25.39	85.07 ± 27.05
	After	57.63 ± 15.26	76.60 ± 25.10	80.91 ± 27.01

Values are presented as mean ± SD. Before, baseline levels before the exercise training; After, 48 h after 8-week training. No significant difference ($p < 0.05$) was found among the groups or in each group before and after 8-week training

Table 4 Biochemical characteristics of study groups before and after an 8-week exercise training

		Endurance group ($n=10$)	Resistance group ($n=10$)	Control group ($n=10$)
Cholesterol (mg/dl)	Before	190.13 ± 37.77	192.0 ± 43.07	188.5 ± 39.34
	After	147.75 ± 22.72*$	166.13 ± 38.70*	190.37 ± 27.47
Triglyceride (mg/dl)	Before	262.0 ± 26.13	263.62 ± 29.76	262.75 ± 54.88
	After	193.10 ± 28.74*$	220.75 ± 30.54*$	263.88 ± 53.51
LDL (mg/dl)	Before	100.06 ± 19.88	101.05 ± 22.67	103.62 ± 29.09
	After	80.59 ± 14.65*$	86.24 ± 23.22*	104.84 ± 27.31
HDL (mg/dl)	Before	38.27 ± 7.89	38.96 ± 13.72	37.87 ± 16.81
	After	53.46 ± 13.02*$	50.05 ± 13.63*	37.63 ± 16.31
Insulin (IU/ml)	Before	18.00 ± 2.13	17.75 ± 3.10	17.87 ± 2.10
	After	12.12 ± 1.24*$	13.62 ± 2.44*,$	17.75 ± 2.49
FBG (mg/dl)	Before	218.37 ± 28.59	221.25 ± 22.75	219.88 ± 29.92
	After	136.75 ± 24.2*$	173.88 ± 8.27*#$	218.0 ± 28.25
HbA1c (mg/dl)	Before	8.58 ± 0.86	8.7 ± 0.94	8.46 ± 0.73
	After	7.8 ± 0.66*	8.22 ± 1.06	8.48 ± 0.67
FGF23 (pg/ml)	Before	150.75 ± 4.16	156.88 ± 7.58	155.0 ± 9.19
	After	178.38 ± 12.70*$	169.25 ± 11.61*$	152.75 ± 8.61
s-Klotho (ng/ml)	Before	1.46 ± 0.14	1.47 ± 0.16	1.48 ± 0.19
	After	1.83 ± 0.18*$	1.79 ± 0.14*$	1.42 ± 0.10
VitD (pmol/l)	Before	34.89 ± 3.45	34.41 ± 4.58	34.22 ± 3.45
	After	34.47 ± 2.63	33.94 ± 2.28	34.37 ± 2.36

Values are presented as mean ± SD. Before, baseline levels before the exercise training; After, 48 h after 8-week training

LDL low-density lipoprotein, *HDL* high-density lipoprotein, *FBG* fasting blood glucose, *HbA1c* hemoglobin A1c, *FGF23* fibroblast growth factor 23, *s-Klotho* soluble klotho, *VitD* 1,25-dihydroxyvitamin D

*Significant difference ($p<0.05$) between before and after exercise in each group; #significant difference ($p<0.05$) with the endurance group; $significant difference ($p<0.05$) with the control group

and resistance groups ($p<0.05$, Table 4), while no significant change was found in the VitD levels. The levels of FGF23 and s-Klotho were significantly higher in both exercise groups compared to the control group after the training course ($p<0.05$, Table 4).

Considering the obtained results showing significant effect of the 8-week intervention on FGF23, s-Klotho, FBG, and HbA1c levels, further statistical analyses were conducted to find possible association among these serum factors (Table 5). We found significant positive correlations between FGF23 and s-Klotho before ($r=0.425$, $p=0.031$) and after ($r=0.683$, $p<0.001$) the intervention. Moreover, serum levels of FBG had negative correlations with s-Klotho ($r=-0.377$, $p=0.048$) before and with s-Klotho ($r=-0.727$, $p<0.001$) and FGF23 ($r=-0.646$, $p<0.001$) after the 8-week intervention. The FGF23 also had significant positive correlations with insulin before and after the intervention. We also observed a significant correlation between s-Klotho and insulin after the 8-week intervention ($r=0.507$ and $p=0.004$).

Discussion

The VitD-FGF23-sKlotho axis is impaired in diabetic patients, exacerbating cardiac and kidney complications [2, 9]. On the other hand, it has been well-documented that physical exercise can improve diabetes-related issues [10]. Therefore, in this study, we investigated the effects of 8 weeks of endurance and resistance exercises on serum levels of FGF23, s-Klotho, and VitD, as well as lipid and carbohydrate profiles in overweight/obese postmenopausal T2DM women.

We found that an 8-week endurance or resistance training could not significantly improve the anthropometric indicators. Previous studies also showed mixed results regarding the beneficial effects of exercise on anthropometric characteristics. In this regard, some studies showed that exercise could effectively reduce obesity parameters [18, 19]. However, in line with our study, several reports confirmed a lack of significant improvement in the anthropometric indices after short-time exercise [20, 21]. No

Table 5 Correlation among serum factors at before and after the 8-week interventions

		FGF23	s-Klotho	FBG	HbA1c	Insulin
Before ($n=30$)	**VitD**	$r=0.089$ $p=0.641$	$r=0.006$ $p=0.973$	$r=-0.106$ $p=0.578$	$r=-0.037$ $p=0.846$	$r=0.217$ $p=0.250$
	FGF23	-	**$r=0.425$** **$p=0.031$**	$r=-0.087$ $p=0.646$	$r=-0.084$ $p=0.659$	**$r=0.474$** **$p=0.008$**
	s-Klotho	-	-	**$r=-0.377$** **$p=0.048$**	$r=-0.318$ $p=0.087$	$r=0.217$ $p=0.250$
	FBG	-	-	-	**$r=0.359$** **$p=0.044$**	$r=-0.122$ $p=0.522$
	HbA1c	-	-	-	-	$r=-0.213$ $p=0.259$
After ($n=30$)	**VitD**	$r=0.191$ $p=0.313$	$r=0.246$ $p=0.190$	$r=-0.150$ $p=0.430$	$r=-0.212$ $p=0.351$	$r=0.244$ $p=0.193$
	FGF23	-	**$r=0.683$** **$p<0.001$**	**$r=-0.646$** **$p<0.001$**	$r=-0.190$ $p=0.315$	**$r=0.594$** **$p=0.001$**
	s-Klotho	-	-	**$r=-0.727$** **$p<0.001$**	$r=-0.077$ $p=0.687$	**$r=0.507$** **$p=0.004$**
	FBG	-	-	-	**$r=0.304$** **$p=0.050$**	$r=-0.331$ $p=0.074$
	HbA1c	-	-	-	-	$r=-0.173$ $p=0.360$

VitD 1,25-dihydroxyvitamin D, *FGF23* fibroblast growth factor 23, *s-Klotho* soluble klotho, *FBG* fasting blood glucose, *HbA1c* hemoglobin A1c

significant change in the anthropometric parameters could be due to the short time of the exercise. Rica et al. [22] have also reported that 8-week water-based exercise did not affect the obesity parameters in obese older women. It seems a long-term follow-up is required to obtain a significant result. Moreover, the second reason for these findings could be a lack of control over the participants' dietary intake. In this regard, Alrushud et al. [23] documented that exercise with dietary restriction can result in satisfactory improvement of obesity parameters.

Our results demonstrated that both endurance and resistance exercises could significantly improve the lipid profiles of participants. However, the effect of endurance exercise was stronger than the resistance exercises on serum lipid parameters. The beneficial effects of physical activities on lipid metabolism and consequently blood lipid profile have been well-documented in previous studies [24, 25]. In consistence with our findings, Banz et al. [26] demonstrated that 10 weeks of endurance exercise but not resistance training could improve HDL levels in obese individuals. This group suggested that endurance training with high intensity is more effective than resistance exercise. Research has shown that resistance exercise can effectively enhance lipid profiles by reducing body fat mass, a process that typically requires a substantial length of time [27]. Given the duration of our intervention, coupled with the insignificant difference in fat percentage following resistance exercise in our study, the relatively low beneficial impact on lipid profiles from this exercise type when compared to endurance exercise can be understood. Additionally, it has been reported that the stimulation of beta-adrenergic receptors is a key factor in increasing lipolysis, which in turn elevates blood cholesterol, TG, and LDL levels [28]. Conversely, it has been found that endurance exercise reduces the activation of these receptors, thereby improving blood lipid profiles [29].

We found that 8-week endurance and resistance exercises could increase serum levels of FGF23 and s-klotho. These findings were consistent with the results of the Middelbeek et al.'s [11] study that reported an elevation in the klotho concentration after 2 weeks of moderate-intensity cycle ergometer exercise in sedentary men. In addition, Matsubara et al. [16] demonstrated that 12 weeks of moderate-intensity endurance exercise training increased plasma klotho concentration in healthy postmenopausal women. It is possible that elevation in serum s-Klotho following the exercise could be due to an increase in peroxisome proliferator-activated receptors (PPARs) and a decrease in angiotensin II type I receptor (AT1R) signaling pathways [30]. Fakhrpour et al. [14] also showed that 16 weeks of concurrent aerobic and resistance intervention increased circulating klotho in maintenance hemodialysis patients. However, this group did not observe a significant change in the circulating levels of FGF23 after the exercise [14]. Keshavarzi et al. [31] also found no significant change in the serum levels of FGF23 after 12 weeks of aerobic exercise in hypertensive elderly women which is inconsistent with our findings. The inconsistency might be due to the type of exercise, the intervention period, and the study population status.

In line with Jorge et al.'s [32] study, we indicated that both endurance and resistance exercises could improve glucose metabolism, insulin resistance, and diabetes risk factors. On the other hand, studies have shown that improvement in glucose metabolism is associated with better regulation of the VitD-FGF23-s-Klotho axis [2, 9]. In support of this mechanism, the current study also demonstrated an increase in the levels of both FGF23 and s-Klotho. Moreover, we found significant positive correlation between FGF23 and s-Klotho before and after the intervention. On the other hand, the serum levels of FBG had negative correlations with s-Klotho (before and after) and FGF23 (after). The FGF23 also had significant positive correlations with insulin before and after the intervention. Although we did not observe a significant increase in the serum levels of VitD; it might be due to the relatively short-term (8-week) intervention, obesity, and diabetes of participants as well as being in the postmenopausal period. It can be hypothesized that exercise-induced FGF23 could promote several mechanisms such as improvement in (1) calcium-phosphate homeostasis and renal calcium reabsorption [33, 34], (2) glucose metabolism and insulin resistance [6], and (3) cardiac function and blood pressure [33] and thereby modulate diabetes complications. However, it should be mentioned that information about the association of exercise with the VitD-FGF23-s-klotho axis and the role of glucose metabolism in this signaling is very limited, and further investigations are required to clarify the exact underlying mechanism(s). Nevertheless, previous studies mentioned the association of FGF23 with impaired glucose metabolism and increased risk of diabetes [6, 34]. Our study had several limitations which should be considered in future studies including relatively short-time intervention, lack of diet restriction, and also no molecular evaluation of the potential mechanisms in the effect of exercise on the VitD-FGF23-s-klotho axis.

Conclusion

In conclusion, we found that both endurance and resistance exercises could increase serum FGF23 and s-Klotho levels and decrease FBG and HbA1c levels in postmenopausal diabetic women which might be a sign of improvement in glucose metabolism through regulation of VitD-FGF23-s-klotho axis.

Acknowledgements We would like to thank all participants in this study.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Niloufar Ghadamyari, Mohammad Reza Zolfaghari, Javad Tolouei Azar, and Amir Fattahi. The first draft of the manuscript was written by Amir Fattahi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Most of the data available within the article and more data available on request due to privacy/ethical restrictions.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of Urmia University.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication None.

Conflict of interests The authors declare no competing interests.

References

1. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. The Lancet. 2017;389(10085):2239–51.
2. Berezin AE, Berezin AA. Impaired function of fibroblast growth factor 23/Klotho protein axis in prediabetes and diabetes mellitus: promising predictor of cardiovascular risk. Diabetes Metab Syndr. 2019;13(4):2549–56.
3. Wang Y, Sun Z. Antiaging gene klotho regulates endothelin-1 levels and endothelin receptor subtype B expression in kidneys of spontaneously hypertensive rats. J Hypertens. 2014;32(8):1629–36.
4. Razzaque MS. The role of klotho in energy metabolism. Nat Rev Endocrinol. 2012;8(10):579–87.
5. Klotho K-O M. Pflugers Arch. 2010;459(2):333–43.
6. Yeung SM, Bakker SJ, Laverman GD, De Borst MH. Fibroblast growth factor 23 and adverse clinical outcomes in type 2 diabetes: a bitter-sweet symphony. Curr Diab Rep. 2020;20(10):1–9.
7. Holick MF. Nutrition: D-iabetes and D-eath D-efying vitamin D. Nat Rev Endocrinol. 2012;8(7):388–90.
8. Quarles LD. Role of FGF23 in vitamin D and phosphate metabolism: implications in chronic kidney disease. Exp Cell Res. 2012;318(9):1040–8.
9. Haussler MR, Whitfield GK, Kaneko I, Forster R, Saini R, Hsieh J-C, Haussler CA, Jurutka PW. The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis. Rev Endocr Metab Disord. 2012;13(1):57–69.
10. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2020;16(10):545–55.
11. Middelbeek RJ, Motiani P, Brandt N, Nigro P, Zheng J, Virtanen KA, Kalliokoski KK, Hannukainen JC, Goodyear LJ. Exercise intensity regulates cytokine and klotho responses in men. Nutr Diabetes. 2021;11(1):1–11.
12. Saghiv MS, Sira DB, Goldhammer E, Sagiv M. The effects of aerobic and anaerobic exercises on circulating soluble-Klotho and IGF-I in young and elderly adults and in CAD patients. J Circ Biomarkers. 2017;6:1849454417733388.
13. Kuro-O M. The klotho proteins in health and disease. Nat Rev Nephrol. 2019;15(1):27–44.
14. Fakhrpour R, Khosroshahi HHT, Ebrahim K, Ahmadizad S, Abbasnejad M, Abbasi MM, Ghanbari A, Yaghoobi SF. Effect of sixteen weeks combined training on FGF-23, klotho, and Fetuin-A

levels in patients on maintenance hemodialysis. Iran J Kidney Dis. 2020;14(3):212.
15. King KE, Mccormick JJ, Notley SR, Fujii N, Kenny GP. Serum klotho concentrations in young and older men during prolonged exercise in temperate and hot conditions. Curr Aging Sci. 2022;15(2):180–5.
16. Matsubara T, Miyaki A, Akazawa N, Choi Y, Ra S-G, Tanahashi K, Kumagai H, Oikawa S, Maeda S. Aerobic exercise training increases plasma klotho levels and reduces arterial stiffness in postmenopausal women. Am J Physiology-Heart Circ Physiol. 2014;306(3):H348–55.
17. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121–6.
18. Alizadeh Z, Younespour S, RajabianTabesh M, Haghravan S. Comparison between the effect of 6 weeks of morning or evening aerobic exercise on appetite and anthropometric indices: a randomized controlled trial. Clin Obes. 2017;7(3):157–65.
19. Kim K-B, Kim K, Kim C, Kang S-J, Kim HJ, Yoon S, Shin Y-A. Effects of exercise on the body composition and lipid profile of individuals with obesity: a systematic review and meta-analysis. J Obes Metabol Syndrome. 2019;28(4):278.
20. Tomljanović M, Spasić M, Gabrilo G, Uljević O, Foretić N. Effects of five weeks of functional vs. traditional resistance training on anthropometric and motor performance variables. Kinesiology. 2011;43(2):145–54.
21. Bocalini DS, Serra AJ, Rica RL, Dos Santos L. Repercussions of training and detraining by water-based exercise on functional fitness and quality of life: a short-term follow-up in healthy older women. Clinics. 2010;65(12):1305–9.
22. Rica RL, Carneiro RMM, Serra AJ, Rodriguez D, Pontes Junior FL, Bocalini DS. Effects of water-based exercise in obese older women: impact of short-term follow-up study on anthropometric, functional fitness and quality of life parameters. Geriatr Gerontol Int. 2013;13(1):209–14.
23. Alrushud AS, Rushton AB, Kanavaki AM, Greig CA. Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: a systematic review and mixed method data synthesis. BMJ Open. 2017;7(6): e014537.
24. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med. 2014;44(2):211–21.
25. Doewes RI, Gharibian G, Zaman BA, and Akhavan-Sigari R. An updated systematic review on the effects of aerobic exercise on human blood lipid profile. Curr Probl Cardiol. 2022:101108.
26. Banz WJ, Maher MA, Thompson WG, Bassett DR, Moore W, Ashraf M, Keefer DJ, Zemel MB. Effects of resistance versus aerobic training on coronary artery disease risk factors. Exp Biol Med. 2003;228(4):434–40.
27. Perez-Gomez J, Vicente-Rodríguez G, Royo IA, Martínez-Redondo D, Foncillas JP, Moreno LA, Díez-Sánchez C, Casajús JA. Effect of endurance and resistance training on regional fat mass and lipid profile. Nutr Hosp. 2013;28(2):340–6.
28. Arner P, Langin D. Lipolysis in lipid turnover, cancer cachexia, and obesity-induced insulin resistance. Trends Endocrinol Metab. 2014;25(5):255–62.
29. Mahdirejei TA, Razi M, Barari A, Farzanegi P, Mahdirejei HA, Shahrestani Z, Ahmadi M. A comparative study of the effects of endurance and resistance exercise training on PON1 and lipid profile levels in obese men. Sport Sciences for Health. 2015;11:263–70.
30. Ciampone S, Borges R, De Lima IP, Mesquita FF, Cambiucci EC, Gontijo JA. Long-term exercise attenuates blood pressure responsiveness and modulates kidney angiotensin II signalling and urinary sodium excretion in SHR. J Renin Angiotensin Aldosterone Syst. 2011;12(4):394–403.
31. Keshavarzi Z, Daryanoosh F, KooshkiJahromi M, Mohammadi M. The effect of 12 weeks of aerobic exercise on plasma levels of fibroblast growth factor 23, angiotensin converting enzyme and left ventricular hypertrophy in hypertensive elderly women. SSU J. 2017;25(3):222–9.
32. Jorge MLMP, De Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz ALD, Resende ES, Ropelle ER, Carvalheira JB, Espindola FS. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. Metabolism. 2011;60(9):1244–52.
33. Andrukhova O, Slavic S, Smorodchenko A, Zeitz U, Shalhoub V, Lanske B, Pohl EE, Erben RG. FGF 23 regulates renal sodium handling and blood pressure. EMBO Mol Med. 2014;6(6):744–59.
34. Vervloet M. Renal and extrarenal effects of fibroblast growth factor 23. Nat Rev Nephrol. 2019;15(2):109–20.

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