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Original Article

The impact of exercise on serum irisin, osteocalcin, and adiponectin levels and on glycolipid metabolism in patients with type 2 diabetes

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Abstract: Objective: This study aimed to investigate the impact of a 12-week moderate-intensity exercise intervention on the serum Irisin, osteocalcin (OC), and adiponectin (ADP) levels and their relationships with glycolipid metabolism, islet β-cell function, and insulin resistance status in patients with type 2 diabetes (T2DM). Methods: 60 patients with T2DM were randomly assigned to an exercise group (EG, n=30) and a control group (CG, n=30). 20 age-matched healthy individuals were recruited for a normal control group (NCG). The T2DM EG underwent a regular exercise intervention for 12 weeks. Their pre- and post-training anthropometric and biochemical indicators and their serum irisin, OC, and ADP levels were determined. Results: the baseline irisin and ADP levels in the T2DM groups were lower than they were in the NCG (P<0.05). The post-training irisin and ADP levels in the T2DM EG were significantly increased (P<0.05), and there were no changes in the OC levels (P>0.05). The BMI, HbA1C, FPG, 2 h PBG, HOMA2-%B, and HOMA2-IR levels were significantly improved compared with their pre-training levels and with the T2DM CG's levels (P<0.05). A correlation analysis showed that the serum OC levels were negatively correlated with the FPG, 2 h PBG, and HOMA2-IR levels in the T2DM patients and positively correlated with the serum ADP and irisin levels (P<0.05). The serum irisin level was negatively correlated with the 2 h PBG level and positively correlated with the serum ADP level (P<0.05). The OC change rate was positively correlated with the FCP and HOMA2-IR change rates (P<0.05). The irisin change rate was negatively correlated with the FPG and HOMA2-IR change rates and positively correlated with the ADP change rate (P<0.05). Conclusion: Regular exercise results in an improvement of the serum irisin and ADP levels, the systemic metabolic markers, the islet β-cell function, and insulin resistance in patients with T2DM.

Keywords: Exercise, type 2 diabetes, irisin, osteocalcin, adiponectin, glycolipid metabolism

Introduction

Type 2 diabetes (T2DM) is a group of systemic metabolic diseases characterized by insulin resistance and relatively insufficient insulin secretions and accounts for more than 90% of all types of diabetes [1]. As one of the classic "five carriages" for the prevention and treatment of T2DM, exercise therapy is attracting more and more attention for its specific accessibility, cost-effectiveness, and universality. It has been shown to reduce blood glucose and lipid levels, body mass index and insulin resistance and to improve islet cell function in T2DM patients [2]. However, a detailed mechanism that links physical activity to T2DM remains unclear.

In recent years, some cytokines such as myokine irisin, osteokine osteocalcin (OC), adipokine adiponectin (ADP), have been closely related to diabetes and metabolic diseases. Studies have found that the cytokines as exercise-induced hormonal mediators act on the whole body and play an important role in regulating glycolipid metabolism and insulin resistance. However, there are still many controversies about the relationship between changes in cytokine levels and physical exercise, or even their potential interaction.

To date, most research subjects have been mainly healthy young, overweight, or obese people. T2DM patients are rarely recruited in ran-

domized controlled trials. Therefore, this study set out to investigate the effects of physical exercise on the serum irisin, OC, and ADP levels and their correlation with the cytokine levels and the metabolic indicators in T2DM patients. It aims to explore the possible mechanism behind exercise therapy and to provide a more reliable theoretical basis for personalized exercise programs.

Materials and methods

Participants

From March 2017 to October 2017, 74 eligible T2DM patients were recruited from the Department of Endocrinology of the First Affiliated Hospital of Kunming Medical University. They were randomly assigned into two groups: the T2DM exercise group (EG, n=36) and the T2DM control group (CG, n=38). 14 subjects failed to complete the study (6 in the EG and 8 in the CG) and were excluded from the final analysis. Each group included 16 males and 14 females respectively. 20 age-matched, healthy individuals were recruited for the normal control group (NCG, n=20), including 10 males and 10 females. This study was approved by the Ethical Committee of the First Affiliated Hospital of Kunming Medical University. A written informed consent was obtained from each participant.

Inclusion criteria: Patients who met the diagnostic criteria for T2DM released by the WHO in 1999. The diagnostic criteria for T2DM are defined as: a fasting plasma glucose concentration of 126 mg/dl (7 mmol/L) or higher, or a 2-hour postprandial plasma glucose concentration of 200 mg/dl (11.1 mmol/L) or higher measured at 2 different times.

Exclusion criteria: Patients with severe acute and chronic complications of diabetes and exercise contraindications, such as ketosis, frequent hypoglycemia, diabetic nephropathy with renal failure, proliferative retinopathy as well as severe myocardial ischemia, uncontrolled arrhythmia, asthma attacks after exercise, a history of stroke, severe hypertension (BP≥160/100 mmHg) or other diseases unsuitable for physical activity, patients with a high fasting blood glucose level (>16.7 mmol/L), patients who are pregnant, patients who suffer from amenorrhea (duration <1 year), patients with a history of fractures (<1 year), a history of beta blocker and calcium or vitamin D drug use, and patients who exercised regularly in the past 6 months (>2 times/week, at least 20 minutes each time).

Anthropometric and indicators measurements

The participants were evaluated before and after a 12-week exercise intervention. Their anthropometric measurements were recorded to calculate their body mass indexes (BMI) and their waist-to-hip ratios (WHR). Peripheral blood was drawn from the elbow vein in the morning (after 8-12 h fasting) to determine their fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting C-peptide (FCP), and fasting insulin (FINS) levels. The patients' two-hour postprandial blood glucose (2 h PBG) levels were measured at two hours after a meal (steamed bread). Also, a fasting blood sample of 3-4 mls was collected for serum separation by centrifugation (3000 rpm, 10 min). The serum was then collected and stored at -80°C for a subsequent analysis. The concentrations of the serum irisin, osteocalcin (OC), and adiponectin (ADP) were determined using enzyme-linked immunosorbent assays (ELISA). The ELISA reagents were provided by Andy Gene Biotechnology Co., LTD [catalogue number: irisin (AD0008Hu), OC (AD-11834Hu), ADP (AD8763Hu)]. The β-cell function (HOMA2-%B) and insulin resistance (HOMA2-IR) indexes were calculated using The HOMA2 Calculator© The University of Oxford 2013 (http://www.dtu.ox.ac.uk) by inputting the of FBG and FCP values.

Exercise protocol

The patients in both groups were routinely treated with glucose-lowering drugs in combination with conventional diet control. The T2DM control group (CG) and the normal control group (NCG) maintained their original lifestyles. Meanwhile, the T2DM exercise group (EG) performed an exercise program 3-5 times a week for 12 weeks.

Exercise guidance: Regular diabetes education and health care were given to all the patients after their enrollment. Specifically, the EG group underwent one-on-one guidance in the

Table 1. A comparison of the three groups of participants before the exercise intervention

Parameter	T2DM EG	T2DM CG	NCG	*P* value
Age (years)	47.73±7.36	45.20±8.82	43.20±7.96	0.148
BMI (kg/m^2)	24.64±2.94*	25.25±2.18*	22.17±1.40	<0.001
HbA1C (%)	10.52±2.20*	9.61±2.13*	5.60±0.32	<0.001
FPG (mmol/L)	9.49±2.66*	9.26±2.87*	4.68±0.35	<0.001
TC (mmol/L)	4.56±1.06*	4.57±0.82*	3.99±0.43	0.036
LDL-C (mmol/L)	3.01±0.82*	2.97±0.70*	2.35±0.45	0.003
TG (mmol/L)	2.06 (1.47, 2.46)*	2.31 (1.90, 3.76)*	1.02 (0.86, 1.39)	<0.001
HDL-C (mmol/L)	0.85 (0.71, 1.09)*	0.94 (0.82, 1.07)*	1.34 (1.23, 1.45)	<0.001
OC (ng/L)	201.84 (105.25, 264.25)	194.67 (78.58, 323.50)	204.17 (180.33, 313.67)	0.473
ADP (μg/L)	100.00 (86.63, 139.63)*	109.50 (85.25, 129.13)*	180.00 (126.50, 250.75)	<0.001
Irisin (pg/mL)	16.98 (14.55, 26.86)*	19.07 (15.62, 23.79)*	37.44 (23.16, 50.15)	<0.001

*Significantly different compared to the normal control group, $P<0.05$.

exercise program, including learning the correct pulse rate counting method, undergoing behavioral counselling, and recording exercise repetitions on a log sheet on training days. According to their ages, sports hobbies, and physical conditions, the trainers helped the participants develop a personalized exercise program, for example, brisk walking, aerobics gymnastics, swimming, cycling, Tai Chi, equipment training, etc.

Exercise program: After a week of exercise preadaptation, the participants continued to maintain a moderate activity intensity, which was measured using self-testing their radial artery pulse rates, using the simple method (calculated as 170-age) to approximately evaluate 60% of the maximum oxygen consumption. In this manner no less than 30 minutes of exercise (including a 3-minute warm-up and cool-down) at the target pulse rate was performed once a day or every other day for 12 weeks. In other words, the total active aerobic activity time was at least 150 minutes per week. The combined resistance exercise (standing, squat, sit-ups, equipment exercises) was also considered but not enforced.

Statistical analysis

All the data were analyzed using SPSS 23.0 statistical software. The normal distribution data were expressed as the mean ± standard deviation. One-way ANOVA was used for the comparisons among multiple groups. The homogeneity of variance with LSD-t method and the heterogeneity of variance with Tamhane's method were used for the pairwise comparisons. Two independent samples t-tests were used for the comparisons between two groups. Paired t-tests were used to compare the differences before and after the intervention. The median (P25%, P75%) was used for the skewed distribution data. Kruskal-Wallis tests were used in the comparison among groups, and Mann-Whitney tests were used for the comparisons between two groups. Wilcoxon signed-rank tests were conducted for the comparisons before and after the intervention. The correlation analysis was performed using Spearman's rank correlation coefficient. Statistical significance was set to $P<0.05$.

Results

The comparison of the three groups of patients before the exercise intervention

A total of 80 individuals were recruited for this study. The descriptive statistics of these individuals are provided in **Table 1**. Before the exercise intervention, there were some differences in BMI, HbA1c, FPG, TC, LDL-C, TG, HDL-C, irisin, and ADP among the three groups ($P<0.05$), which were taken for the further comparisons between two groups. There were no significant differences between the two T2DM groups at the baseline ($P>0.05$), but the above-mentioned variables were significant when each T2DM group was compared with the normal control group ($P<0.05$) (**Table 1**).

A comparison of the T2DM exercise group and the T2DM control group before and after the exercise intervention

As shown in **Table 2**, it was apparent that the BMI, HbA1C, FPG, 2 h PBG, and HOMA2-IR lev-

els significantly decreased in the T2DM exercise group compared with the T2DM control group, but the HOMA2-%B, ADP, and irisin levels significantly increased after the exercise intervention (P<0.05). For the T2DM exercise group, except for the FINS, TC, and serum OC levels (P>0.05), there were significant differences in the other measured indicators before and after the exercise intervention (P<0.05). Only the HbA1C and 2 h PBG levels presented significant changes in the T2DM control group (P<0.05), but the other indicators did not show any differences before and after the exercise intervention (P>0.05).

A comparison of the three groups of patients after the exercise intervention

The irisin and ADP levels in the two T2DM groups were lower than they were in the normal control group (P<0.05) at the baseline level. There was marked growth of the irisin and ADP levels in the T2DM exercise group compared to the T2DM control group after the 12-week exercise intervention (P<0.05) (**Figure 1**). The post-training data indicate that the OC, ADP, irisin, and LDL-C levels in the T2DM exercise group did not differ from the levels in the normal control group (P>0.05), but the levels in the T2DM control group were significantly different when compared to the normal control group (P<0.05). We found no significant differences in TC among the three groups after the exercise intervention (P>0.05).

A correlation analysis between the irisin, OC, and ADP levels and their change rates with the clinical variables

A Spearman's correlation analysis was used to investigate the correlation between the concentrations of serum Irisin, OC, and ADP with the metabolic indicators in the T2DM patients. The results suggested a weak negative correlation between the OC and FPG levels and the 2 h PBG and HOMA2-IR levels (R=-0.273, -0.335, -0.281, P<0.05). The OC level was positively correlated with the ADP and irisin levels (R= 0.515, 0.317, P<0.05). The circulating irisin showed a significant positive correlation with ADP (R=0.459, P<0.001) (see **Figure 2A**), but a weak negative correlation with 2 h PBG (R= -0.264, P<0.05).

As shown in **Figure 2B**, the serum irisin change rate was negatively weakly-correlated with the FPG and HOMA2-IR change rates (R=-0.285, -0.350, P<0.05) and positively correlated with the ADP change rate (R=0.329, P<0.05) before and after the intervention. In addition, the serum OC change rate was positively correlated with the FCP and HOMA2-IR change rates (R=0.278, 0.304, P<0.05).

Discussion

The effects of regular exercise on glycolipid metabolism

In this study, compared with the T2DM control group, there were significant decreases in the FPG, 2 h PBG, and HbA1c levels in the T2DM EG following the 12-week exercise intervention. It seems that the exercise intervention was able to achieve better glucose control, which is consistent with previous studies [3, 4]. However, no significant reduction in the blood lipids in the T2DM exercise group was observed when compared with the T2DM control group. It is possible that blood lipid changes are largely affected by diet, or that regular exercise has only little or a slow effect on lipid metabolism. Moreover, regular moderate-intensity exercise also showed a remarkable comprehensive effect on the physical indicators like WHR and BMI. Due to an increased consumption of excessive body fat, exercise is beneficial for preventing obesity and T2DM. Currently, how exercise regulates the glycolipid metabolism in T2DM patients is not yet fully understood. Our study revealed that the post-training HOMA2-%B and HOMA2-IR levels were significantly improved, as seen in earlier studies [5]. A possible explanation for this might be that exercise can increase the expression of the glucose transporter 4 (GLUT4) protein in muscle and promote its translocation to cell membranes, resulting in an enhancement of glucose uptake and transport [6]. Another reason might be that exercise can enrich skeletal muscle cells with mitochondria and activate mitochondrial oxidase to improve glucose oxidation [7]. Hence, weakened glucotoxicity may be conducive to the protection and recovery of the residual islet β-cell function.

The effects of regular exercise on cytokines

Irisin: Previous studies found that irisin can up-regulate UCP-1 expression and increase mito-

Table 2. Comparison between T2DM exercise group and T2DM control group before and after exercise intervention [mean ± SD, M (P25%, P75%)]

Parameter	T2DM exercise group (EG)		*P* value (Pre vs. Post)	T2DM control group (CG)		*P* value (Pre vs. Post)	*P* value (EG vs. CG)
	Pre	Post		Pre	Post		
BMI (kg/m^2)	24.64±2.94	23.86±2.69*,#	<0.001	25.25±2.18	25.16±2.21	0.606	0.046
WHR	0.92±0.04	0.90±0.04*	0.001	0.92±0.03	0.91±0.03	0.257	0.356
HbA1C (%)	10.52±2.20	6.57±0.75*,#	<0.001	9.61±2.13	7.71±1.38*	<0.001	<0.001
FPG (mmol/L)	9.49±2.66	6.19±1.06*,#	<0.001	9.26±2.87	8.54±2.32	0.098	<0.001
2 h PBG (mmol/L)	13.77±3.77	7.90±1.87*,#	<0.001	12.81±3.48	10.01±2.84*	0.001	0.001
FCP (ng/mL)	1.56±0.37	1.45±0.33*	0.049	1.53±0.30	1.53±0.21	0.964	0.257
FINS (uIU/mL)	9.85±2.50	9.97±2.86	0.837	10.77±2.93	11.43±4.04	0.314	0.110
TC (mmol/L)	4.56±1.06	4.20±0.72	0.063	4.57±0.82	4.49±0.94	0.670	0.187
LDL-C (mmol/L)	3.01±0.82	2.67±0.58*	0.029	2.97±0.70	2.82±0.73	0.354	0.377
TG (mmol/L)	2.06 (1.47, 2.46)	1.66 (1.23, 1.99)*	0.009	2.31 (1.90, 3.76)	1.95 (1.26, 2.85)	0.185	0.139
HDL-C (mmol/L)	0.85 (0.71, 1.09)	0.99 (0.86, 1.22)*	<0.001	0.94 (0.82, 1.07)	1.04 (0.84, 1.21)	0.073	0.487
OC (ng/L)	201.84 (105.25, 264.25)	146.67 (102.17, 255.00)	0.141	194.67 (78.58, 323.50)	138.67 (68.67, 271.50)	0.441	0.492
ADP (μg/L)	100.00 (86.63, 139.63)	153.00 (101.88, 197.38)*,#	<0.001	109.50 (85.25, 129.13)	107.50 (87.00, 155.00)	0.364	0.029
Irisin (pg/mL)	16.98 (14.55, 26.86)	33.53 (18.04, 42.28)*,#	<0.001	19.07 (15.62, 23.79)	17.46 (15.15, 23.23)	0.716	0.001
HOMA2-%B	30.45 (23.13, 56.03)	69.00 (54.38, 84.23)*,#	<0.001	37.85 (24.60, 53.25)	41.60 (27.50, 55.30)	0.237	<0.001
HOMA2-IR	1.33 (1.12, 1.67)	1.06 (1.02, 1.27)*,#	<0.001	1.28 (1.16, 1.62)	1.26 (1.17, 1.49)	0.577	0.001

*Difference between pre- and post-training within group, $P<0.05$. #Difference between T2DM EG and T2DM CG post-training, $P<0.05$.

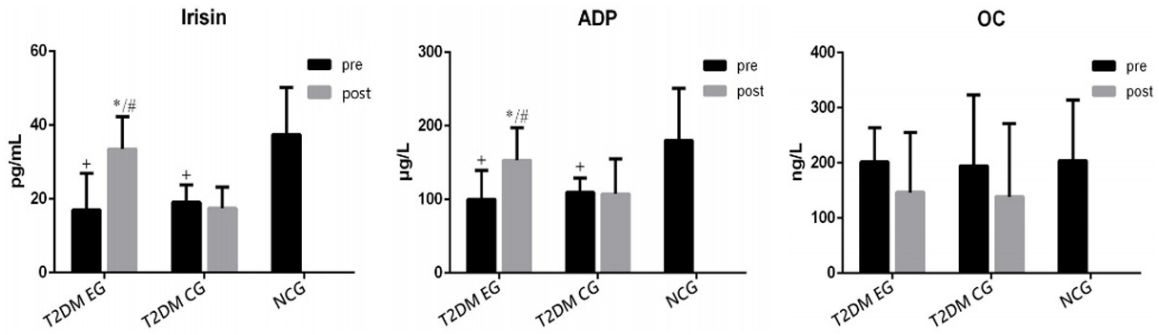

Figure 1. Comparison of the circulating irisin, ADP and OC levels in in the T2DM EG, T2DM CG, and NCG pre- and post-training: The irisin and ADP levels in the two T2DM groups were lower than they were in the NCG (P<0.05) at baseline. There was marked growth of the irisin and ADP levels in the T2DM EG compared to the T2DM CG after the 12-week exercise intervention (P<0.05). +: Difference compared to the NCG, *P*<0.05. *: Difference between the pre- and post-training within the group, *P*<0.05. #: Difference between the T2DM EG and the T2DM CG post-training, *P*<0.05.

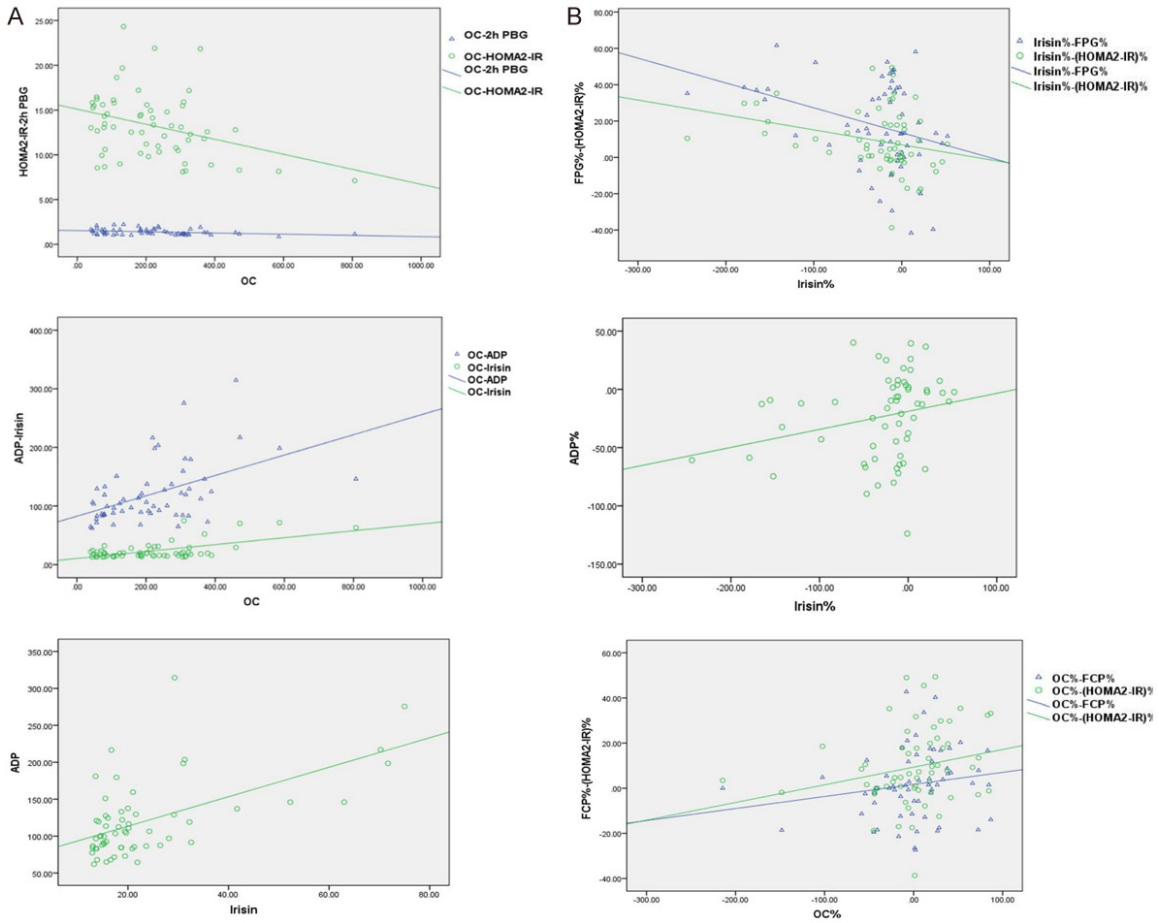

Figure 2. A. The correlations between the baseline serum OC, irisin, and clinical variables: the baseline OC was negatively correlated with the 2 h PBG and HOMA2-IR levels (R=-0.335, -0.281, P<0.05) and positively correlated with the ADP and irisin levels (R=0.515, 0.317, P<0.05). The baseline irisin level was positively correlated with the ADP level (R=0.459, P<0.001). B. Correlation between the change rate of serum OC and irisin and the change rate of the clinical variables: the change rate of the serum irisin was negatively weakly-correlated with the change rates of FPG and HOMA2-IR (R=-0.285, -0.350, P<0.05) and positively correlated with the ADP change rate (R=0.329, P<0.05) pre- and post-training. The change rate of the serum OC was positively correlated with the change rates of FCP and HOMA2-IR (R=0.278, 0.304, P<0.05).

chondrial biosynthesis, thereby inducing the browning and thermogenesis of white adipose tissue [8]. It is well established that the level of circulating irisin is lower in patients with T2-DM [9], which is consistent with our result. It seems presumably due to the fact that the expression of PGC1-α in T2DM is often impaired to some extent, leading to a decline in irisin. In this study, a weak negative correlation existed between irisin and 2 h PBG, suggesting that irisin may exert its effects on the regulation of glucose metabolism. In contrast, some studies have observed higher levels of plasma irisin in obese individuals [10]. It is probable that some irisin may be produced by adipocytes in the developing phase of irisin resistance. Although irisin is known as an exercise-induced myokine, there are still many contradictions. Our data showed an increased circulating irisin level after exercise, similar to one study in China [11]. There is some evidence that exercise stimulation can activate multiple pathways, including calcineurin A (cnA), calmodulin-dependent protein kinase (CaMK), p38 mitogen-activated protein kinases (p38 MAPK), and activated protein kinase (AMPK), to up-regulate the expression of PGC1-α and irisin in need of energy metabolism [12, 13]. Interestingly, changes in the irisin level are likely related to the exercise mode or intensity. Further studies focusing on T2DM patients are therefore necessary to investigate the possible link between irisin and exercise.

Osteocalcin: Abnormal bone metabolism is a common complication of diabetes characterized by lower serum osteocalcin [14]. From our data no difference in the baseline serum OC was found between the T2DM patients and healthy individuals. OC may be susceptible to age, gender, course of the disease, menopausal status, or other unclear factors. Additionally, our results showed a negative correlation between baseline OC and FPG, 2 h PBG, and HOMA2-IR. In this regard, it is possible that OC positively exerts its effects mainly by way of circulating undercarboxylated OC (ucOC) [15]. UcOC can not only directly stimulate insulin synthesis and secretion using islet β-cells, but it can also promote the expressions of ADP and PGC1-α, resulting in an improvement in glucose metabolism and insulin sensitivity [16]. Nevertheless, no significant correlation was found between OC and FINS, FCP, and HOMA2-%B, perhaps owing to the interference of the administered insulin and insulin sensitizer. Our findings indicated there was no significant difference in OC pre-and post-training ($P>0.05$), consistent with the results of *Colleluori et al.* [17]. We speculated that moderate-intensity exercise did not reach the stimulated threshold of OC. Given the complexity of the mechanism, some researchers support the idea that acute exercise can increase the serum ucOC and OC to meet the energy needs of muscle fiber in adaptive exercise [18]. There is another opinion that exercise is associated with an increase in bone turnover against weight loss-induced bone loss [19]. Our current study was limited by the absence of a bone mineral density test so the relationships among exercise and bone and glycolipid metabolism remain to be explored.

Adiponectin: Adiponectin (ADP) is secreted by adipocytes and plays an pivotal role in energy metabolism, anti-inflammation and anti-atherosclerosis [20]. We found that the baseline serum ADP was significantly lower in the T2DM group than in the normal control group ($P<0.05$), in accord with earlier studies [21]. It is thought that hyperglycemia and hyperlipidemia may affect the differentiation and maturation of 3T3-L1 preadipocytes, leading to a decrease in ADP [22]. Our study found no correlation between ADP and the glycolipid metabolic indicators. Considering that most of the patients enrolled in this study were overweight (BMI≥24 kg/m^2) but not obese (BMI≥28 kg/m^2), this may weaken the individual difference in ADP. In addition, the relatively small sample size may be another reason for the negative result. In this study, it was found that the serum ADP levels in the T2DM exercise group were significantly higher than the levels in the T2DM control group after exercise ($P<0.05$), similar to the results observed earlier [23]. Despite this, some studies have failed to show any impact of exercise on ADP in the obese population [24]. Presumably, adiponectin is closely related to exercise, but its changes only occur when exercise reaches a certain threshold that initiates fat hydrolysis. Being limited to the assessment of the body fat rate and fat distribution, this study lacks the evidence needed to prove the association between ADP and fat change.

The interactions between irisin, osteocalcin and adiponectin

Irisin, osteocalcin, and adiponectin, deemed as the circulating energy hormones, are closely

related to the metabolic process of exercise. Significantly, a positive correlation was found among them ($P<0.05$). These findings suggested that irisin, OC, and ADP may exert synergetic effects in improving diabetes and metabolic diseases. To our knowledge, AMPK has been found to be a key regulator of metabolism in cells and the whole body. *Hou et al.* found that serum irisin can up-regulate the heme oxygenase-1/ADP axis and activate the AMPK signaling pathway, thereby protecting cardiovascular function [25]. In vitro experiments showed that irisin can directly induce osteoblast differentiation and inhibit osteoclast activity and is potentially involved in OC secretions [26]. Furthermore, osteoblasts can also express ADP and its receptors, which make it possible for ADP to participate in bone metabolism. The changes in ADP and OC in our study were not consistent after exercise, possibly due to the complex effects of the BMD changes. In short, the interaction and mechanism of cytokines need to be further explored.

Conclusion

In general, patients with T2DM also often have changes in cytokines. This study has shown that a 12-week moderate-intensity regular exercise intervention was effective at improving the glycolipid and physical indicators, the insulin resistance and islet β-cell function, along with the higher levels of serum irisin and ADP in T2DM patients. There were still some conflicting results in the cytokines pre- and post-training, possibly related to the study population, exercise program or experimental methods. Overall, this study has provided an important new insight for diabetes exercise therapy and serves as a springboard for future in-depth research.

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Disclosure of conflict of interest

None.

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