Exercise ameliorates the FGF21–adiponectin axis impairment in diet-induced obese mice

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Abstract

Objective: The protective effects of exercise against glucose dysmetabolism have been generally reported. However, the mechanism by which exercise improves glucose homeostasis remains poorly understood. The FGF21–adiponectin axis participates in the regulation of glucose metabolism. Elevated levels of FGF21 and decreased levels of adiponectin in obesity indicate FGF21–adiponectin axis dysfunction. Hence, we investigated whether exercise could improve the FGF21–adiponectin axis impairment and ameliorate disturbed glucose metabolism in diet-induced obese mice.

Methods: Eight-week-old C57BL/6J mice were randomly assigned to three groups: low-fat diet control group, high-fat diet group and high-fat diet plus exercise group. Glucose metabolic parameters, the ability of FGF21 to induce adiponectin, FGF21 receptors and co-receptor levels and adipose tissue inflammation were evaluated after 12 weeks of intervention.

Results: Exercise training led to reduced levels of fasting blood glucose and insulin, improved glucose tolerance and better insulin sensitivity in high-fat diet-induced obese mice. Although serum FGF21 levels were not significantly changed, both total and high-molecular-weight adiponectin concentrations were markedly enhanced by exercise. Importantly, exercise protected against high-fat diet-induced impaired ability of FGF21 to stimulate adiponectin secretion. FGF21 co-receptor, β-klotho, as well as receptors, FGFR1 and FGFR2, were upregulated by exercise. We also found that exercise inhibited adipose tissue inflammation, which may contribute to the improvement in the FGF21–adiponectin axis impairment.

Conclusions: Our data indicate exercise protects against high-fat diet-induced FGF21–adiponectin axis impairment, and may thereby exert beneficial effects on glucose metabolism.

Introduction

The prevalence of diabetes is growing rapidly around the world. An estimated 415 million people aged 20–79 years suffered from diabetes in 2015 and it is predicted that the number of people with diabetes aged 20–79 years will rise to 642 million by 2040 (1). Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all diabetes cases (2). Promising targets to improve glucose homeostasis are of particular interest.

Fibroblast growth factor 21 (FGF21), a member of the fibroblast growth factor superfamily, has attracted increasing attention in recent years for its role in regulating glucose and lipid metabolism.
During the consumption of a ketogenic diet or a high-fat diet, FGF21-knockout mice develop more insulin resistance and show more disorganized liver lipid metabolism compared to their WT littermate controls (3, 4, 5). On the other hand, replenishment of FGF21 can reduce obesity, improve insulin sensitivity and increase glucose clearance (5, 6). FGF21 exerts its biological actions through binding to FGFR receptors (FGFRs) and an essential co-receptor, β-klotho (7), forming the FGF21 receptor complex.

FGF21 is produced predominantly in the liver (4, 8). Adipose tissue is a primary target of FGF21 action. Adipose tissue-specific FGFR1 or β-klotho knockout abolishes FGF21 effects on glucose and energy regulation (9, 10). Adiponectin, an insulin-sensitizing adipokine, has been shown as an effector of FGF21. Both acute and chronic FGF21 treatment increase the secretion and expression of adiponectin partly through PPARγ (11). FGF21 significantly reverses the tumor necrosis factor α (TNFα)-induced impairment in adiponectin secretion (12). Furthermore, adiponectin deficiency abrogates the benefits of FGF21 on glucose and lipid control (11). A growing body of studies provide convincing evidence demonstrating that the FGF21–adiponectin axis plays an important role in regulating glucose homeostasis through the crosstalk between the liver and adipose tissue (11, 12, 13).

The beneficial effects of exercise on glucose homeostasis are well documented (14), and exercise has been shown to reduce adipogenesis, alleviate adipose tissue inflammation and improve the disturbed pattern of adipokine secretion (15, 16). Studies have shown that exercise affects serum levels of FGF21 and increases circulating adiponectin concentrations (16, 17, 18). However, no one has addressed the question whether exercise had an impact on the FGF21–adiponectin axis. Given that the FGF21–adiponectin axis exerts protective effects on glucose homeostasis, we speculated the FGF21–adiponectin axis may play a crucial role in exercise-related benefits on glucose metabolism. The aim of our present study was to investigate whether exercise could alleviate the FGF21–adiponectin axis impairment and ameliorate glucose metabolism and insulin resistance in diet-induced obese mice.

Materials and methods

Animals and diet

Eight-week-old male C57BL/6J mice were randomly divided into a low-fat diet control group (LFD, n=24), a high-fat diet group (HFD, n=24) and a high-fat diet plus exercise group (HFD+EXE, n=24). The mice from LFD group received a low-fat diet containing 10% kcal from fat (D12450J, Research Diets Inc.). Both the HFD mice and the HFD+EXE mice were fed a high-fat diet containing 60% kcal from fat (D12492, Research Diets Inc.) for 12 weeks. At the same time, mice in HFD+EXE group were subjected to exercise training. All animals were kept under 12 h light–darkness cycles at 22–24°C, with free access to food and water. Body weight was recorded weekly. Two days after the final training session, mice were subjected to FGF21-induced adiponectin examination or killed for collection of serum, liver and adipose tissue under anesthesia (sodium pentobarbital 50μg/g). All procedures were approved by the Institutional Animal Care and Use Committee of Guangzhou Sport University (2018DWLL-003).

Exercise protocol

The HFD+EXE mice were trained on a treadmill at 0% grade 5 days per week for 12 weeks. Five minutes of warm up at 6 m/min, 20 min of main exercise at 10 m/min, and 5 min of cool down at 6 m/min were performed during the first week for adaptation. From the 2nd week to the 12th week, 5 min of warm up at 6 m/min, 50 min of main exercise at 12 m/min (75% maximum oxygen consumption) (19), and 5 min of cool down at 6 m/min were performed.

Blood analysis

Triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) were measured in serum by commercial kits (BioSino Biotechnology Company, Ltd., Beijing, China). Serum insulin (Alpco Diagnostics, Salem, NH, USA), total and high-molecular-weight (HMW) adiponectin (Alpco Diagnostics) and FGF21 (R&D Systems) were determined using commercial ELISA kit according to the manufacturer’s instructions.

FGF21-induced adiponectin examination

To analyze the effects of acute FGF21 intervention on adiponectin secretion, the mice were intraperitoneally administered saline or 2μg/g (11) of recombinant human FGF21 (PeproTech Inc., Rocky Hill, NJ, USA). After a 2-h fast, mice were killed. Serum was collected for total and HMW adiponectin determination.

Oral glucose tolerance test (OGTT)

OGTT was performed after 10 weeks of diet and exercise intervention. Following overnight fasting, mice were

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given a glucose load (1 mg/g) orally. Blood sample was collected from the tail vein at various time points (0, 15, 30, 60, 90, 120 min) for glucose determination using the Accu-Chek Performa glucometer (Roche).

**Insulin tolerance test (ITT)**

ITT was performed after 10 weeks of diet and exercise intervention. After a 3-h fast, mice received an intraperitoneal injection of diluted human insulin (Actrapid, Novo Nordisk) at a dose of 0.75 IU/kg. Tail vein blood glucose was measured with a glucometer at 0, 15, 30, 60, 90, 120 min after injection.

**Homeostatic model assessment for insulin resistance (HOMA-IR) calculation**

HOMA-IR was calculated to assess the insulin resistance, using the formula: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mIU/L)/22.5 (20).

**Quantitative real-time PCR**

Total RNA was extracted from epididymal white adipose tissue (WAT) and liver with TRIzol Reagent (Invitrogen). Quantitative PCR was carried out on the Applied Biosystems 7000 sequence detection system with the primers shown in Supplementary Table 1 (see section on supplementary data given at the end of this article). Calculations were done using a comparative method ($2^{-ΔΔCt}$) and normalized to β-actin as housekeeping genes.

**Immunohistochemistry analysis**

For F4/80 staining, epididymal WAT samples were fixed in 4% paraformaldehyde solution for 24 h, embedded in paraffin. After deparaffinized and rehydrated, the WAT sections were stained with F4/80 antibody (Santa Cruz Biotechnology), and then revealed by DAB (Vector Laboratories).

**Statistical analysis**

All data were expressed as mean ± S.E.M. values. Statistical significance between two groups was evaluated by two-tailed Student's t-test, and for more than two groups by one-way ANOVA. All analyses were performed using SPSS 20.0. Differences with a P value less than 0.05 were considered to be significant.

**Results**

**Exercise reduces HFD-induced adiposity and hyperlipidemia**

Compared with mice in the LFD group, HFD-fed mice became obese, indicated by greater weight gain as well as significant increase in epididymal and subcutaneous fat weight. Twelve weeks of exercise training showed remarkable improvement in obesity caused by HFD. The body weight and adipose tissue fat weight in the HFD + EXE group were significantly lower than those in the HFD group. Serum TG, TC and LDL-C levels were significantly increased in HFD mice. Exercise ameliorated HFD-induced hyperlipemia (Table 1).

**Exercise protects against deranged glucose homeostasis under a HFD challenge**

Fasting blood glucose and insulin levels were significantly increased in HFD-fed mice. Exercise training protected

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**Table 1** Metabolic parameters of male C57BL/6J mice received a low-fat diet (LFD), a high-fat diet (HFD) or a high-fat diet plus exercise training (HFD + EXE).

<table>
<thead>
<tr>
<th>Metabolic parameters</th>
<th>LFD</th>
<th>HFD</th>
<th>LFD + EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial body weight (g)</td>
<td>$20.5 \pm 0.4$</td>
<td>$20.1 \pm 0.4$</td>
<td>$20.3 \pm 0.4$</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>$26.0 \pm 0.8$</td>
<td>$38.5 \pm 1.2^a$</td>
<td>$27.9 \pm 0.4^b$</td>
</tr>
<tr>
<td>Body weight gain (g)</td>
<td>$5.5 \pm 0.4$</td>
<td>$18.4 \pm 0.8^a$</td>
<td>$7.6 \pm 0.2^{ab}$</td>
</tr>
<tr>
<td>Epididymal fat weight (g)</td>
<td>$0.27 \pm 0.03$</td>
<td>$2.04 \pm 0.14^a$</td>
<td>$0.55 \pm 0.04^b$</td>
</tr>
<tr>
<td>Epididymal fat/body weight ratio (%)</td>
<td>$1.00 \pm 0.09$</td>
<td>$5.26 \pm 0.23^a$</td>
<td>$1.94 \pm 0.11^{ab}$</td>
</tr>
<tr>
<td>Subcutaneous fat weight (g)</td>
<td>$0.24 \pm 0.04$</td>
<td>$1.78 \pm 0.16^a$</td>
<td>$0.49 \pm 0.04^b$</td>
</tr>
<tr>
<td>Subcutaneous fat/body weight ratio (%)</td>
<td>$0.94 \pm 0.15$</td>
<td>$4.63 \pm 0.38^a$</td>
<td>$1.78 \pm 0.16^b$</td>
</tr>
<tr>
<td>Serum metabolites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>$0.36 \pm 0.03$</td>
<td>$0.57 \pm 0.06^a$</td>
<td>$0.38 \pm 0.03^b$</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>$2.36 \pm 0.08$</td>
<td>$3.40 \pm 0.15^a$</td>
<td>$2.84 \pm 0.11^{ab}$</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>$0.17 \pm 0.02$</td>
<td>$0.27 \pm 0.03^a$</td>
<td>$0.19 \pm 0.01^b$</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>$2.13 \pm 0.14$</td>
<td>$2.55 \pm 0.19$</td>
<td>$2.29 \pm 0.17$</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. n = 10 per group.

$^aP < 0.05$ for difference from LFD; $^bP < 0.05$ for difference from HFD.
against HFD-induced hyperglycemia and hyperinsulinemia (Fig. 1A and B). HOMA-IR indicating insulin resistance caused by HFD was ameliorated in HFD + EXE mice (Fig. 1C). The protective effects of exercise against insulin resistance were further confirmed by ITT. Compared with the HFD mice, the HFD + EXE mice showed reduced blood glucose excursion and area under the curve (AUC) analysis during ITT (Fig. 1D and E). Tolerance to the oral glucose challenge was also improved by exercise training (Fig. 1F and G).

**Exercise does not lead to a significant increase in circulating FGF21 concentrations but enhances adiponectin levels in HFD-fed mice**

To evaluate the effects of exercise on the FGF21–adiponectin axis, we set out to detect the levels of FGF21 and adiponectin. Compared with the LFD feeding, the HFD feeding resulted in a significant increase in FGF21 levels (Fig. 2A, B and C). Although FGF21 mRNA expression in WAT was slightly enhanced by exercise, no significant difference in serum levels and hepatic mRNA expression of FGF21 was observed between the HFD and HFD + EXE mice (Fig. 2A, B and C). Compared to LFD mice, HFD mice exhibited lower levels of adiponectin. Exercise enhanced both total and HMW adiponectin concentrations. Adiponectin mRNA expression in adipose tissue was also markedly elevated by exercise (Fig. 2D, E and F).

**Exercise ameliorates HFD-induced impaired ability of FGF21 to stimulate adiponectin secretion**

Administration of FGF21 led to a rapid and dramatic increase in both total and HMW adiponectin secretion. This response is impaired by HFD feeding (Fig. 3A, B, C and D). In LFD mice, FGF21 administration increased circulating levels of total and HMW adiponectin by 74% and 138%, respectively. However, in HFD mice, FGF21 stimulation only enhanced total and HMW adiponectin by 36% and 83%, respectively. We observed a 51% increase in total adiponectin concentrations and a 147% elevation in HMW adiponectin secretion upon FGF21 stimulation in HFD + EXE mice (Fig. 3B and D), indicating that exercise protects against HFD-induced reduction of FGF21-mediated adiponectin secretion.

**Exercise increases β-klotho and FGFRs expression in WAT**

The biological function of FGF21 is mediated by its receptors and an essential co-receptor, β-klotho (7). We assessed β-klotho and FGFRs mRNA expression in WAT. HFD mice showed significantly lower mRNA expression of β-klotho, FGFR1, FGFR2 and FGFR3 than LFD mice (Fig. 4A, B, C and D). Compared with HFD mice, β-klotho mRNA levels were increased by 2.5-fold in HFD + EXE mice and FGFR1, the most abundant receptor in WAT, was enhanced by 83% (Fig. 4A and B). Exercise also significantly increased FGFR2 mRNA expression in WAT.
No difference was observed in the FGFR4 mRNA expression among the three groups (Fig. 4E).

**Exercise reduces HFD-induced inflammation in WAT**

Studies have suggested that inflammation contributes to the impairment of FGF21 action. (21, 22). We examined whether exercise alleviated inflammation in WAT. F4/80, an established marker of mature macrophages, was detected. Exercise reduced HFD-induced accumulation of adipose macrophages, suggested by decreased formation of crown-like structures (defined as F4/80-positive cells surrounding a degenerating adipocyte (23)) and a significant reduction in F4/80 mRNA levels (Fig. 5A and B). HFD feeding increased the expression of proinflammatory cytokines TNFα, IL-1β, IL-6 and MCP-1, which was largely prevented by exercise training (Fig. 5B).

**Discussion**

Multiple studies have demonstrated that exercise improves glucose metabolism effectively. Exercise training ameliorates blood glucose concentrations, glycated hemoglobin (HbA1c) levels, hyperinsulinemia, hyperlipemia, blood pressure and mortality in patients with T2DM (24, 25). Various mechanisms including stimulation of glucose uptake in skeletal muscle, enhancement of insulin sensitivity, reduction in hepatic gluconeogenesis and improvement of pancreatic beta-cell function are involved in exercise-elicited improvement of glucose homeostasis (26, 27). Our results also showed clearly that 12 weeks of exercise effectively protected against HFD-induced obesity, hyperglycemia, impaired glucose tolerance and insulin resistance. The mechanism underlying the benefits of exercise on glucose metabolism is still imperfectly understood. The present study demonstrated that instead of increase FGF21 levels, exercise sensitizes FGF21 action to induce adiponectin in adipose tissues. This interesting finding increases our understanding of how exercise exert its protective effects against glucose dysregulation.

FGF21, firstly identified in embryonic mouse embryo in 2000 (28), is expressed predominantly by the liver (8, 28). FGF21 exerts its biological function as an important metabolic regulator. Since FGF21-elicited glucose uptake on 3T3-L1 adipocytes was reported by Alexei Kharitonenkov in 2005 (6), the effects of FGF21 on glucose metabolism have been gradually revealed. FGF21 treatment significantly reduced blood glucose, enhanced insulin sensitivity and improved glucose clearance in obese animals (6, 29). Loss- and gain-of-function experiments
further demonstrated that FGF21 played a crucial role in maintain glucose homeostasis (6, 30). FGF21 has been suggested as an exercise-induced hormone-like factor. Only a single bout of acute exercise increases circulating FGF21 (17, 31, 32). The exercise-induced FGF21 response is regulated by enhanced glucagon-to-insulin ratio during exercise (32). However, long-term effects of exercise on FGF21 regulation remains inconclusive. FGF21 was decreased after 12 weeks of combined aerobic and resistance training in obese women (33), whereas no change was detected after a 8-week endurance training in obese men (34). In the present study, we did not observe any significant difference in the circulating levels of FGF21 between the HFD and HFD + EXE mice after 12 weeks of aerobic exercise. The role of exercise in FGF21 regulation may depend on exercise type, exercise mode, exercise intensity, intervention duration and even characteristics of trial subjects.

Adiponectin, a well-known adipokine, is produced almost exclusively by adipocytes (35) and exhibits anti-diabetic properties. Serum adiponectin levels are decreased in patient with obesity and T2DM, and in the general population, low circulating adiponectin levels are associated with increased risk of T2DM (36). Administration of adiponectin to diabetic animals corrected glucose disturbance (37). In blood, adiponectin exists as three main forms: HMW, middle molecular weight hexameric (MMW) and low-weight trimer (LMW) (38). The HMW adiponectin has been considered as the most biologically active isoform and improve insulin sensitivity and glucose uptake (39, 40). Our results showed that aerobic exercise increased adiponectin, especially HWM adiponectin in HFD-fed mice. This improvement may account for exercise-induced glucose metabolic benefit.

Although the major production site is different, there are many functional similarities between FGF21 and adiponectin. Researchers hypothesized that a link may exist between these two hormones. As expected, the FGF21–adiponectin axis has been demonstrated. It has been demonstrated in humans that FGF21 analogue LY2405319 increases adiponectin in a dose-dependent manner (41), and FGF21 stimulates both total and HMW
adiponectin secretion (12). Adiponectin acts as a mediator of the beneficial metabolic effects of FGF21 (11). The FGF21–adiponectin axis participates in the regulation of diverse biological processes, including glucose and lipid metabolism. It is worthwhile to note that disturbed FGF21–adiponectin function is observed in chronic metabolic disease such as obesity and diabetes, suggested by elevated FGF21 levels and reduced adiponectin levels (13) and is further demonstrated by our current study showing that the ability of FGF21 to induce total and HMW adiponectin was impaired in diet-induced obese mice. Amelioration of the FGF21–adiponectin axis dysfunction may be a promising target for the prevention and treatment of obesity and T2DM.

Exercise alleviates insulin resistance and improves glucose homeostasis. These effects are primarily attributed to adaptations in skeletal muscle (27). However growing evidence shows that besides skeletal muscle, many other tissues such as liver and adipose tissue are involved in exercise-induced benefits in glucose homeostasis (42, 43). The FGF21–adiponectin axis facilitates liver-to-adipose tissue communication and plays a crucial role in glucose and lipid metabolism regulation. To explore the effects of exercise training on the FGF21–adiponecin axis, we started with analysis of FGF21 and adiponectin levels. Exercise did not alter serum FGF21 levels but significantly elevated circulating concentrations of total and HMW adiponectin, and led to a marked increase in adiponectin mRNA levels. A recent study found exercise-elicted adiponectin elevation was mediated by FGF21 (44). We conclude that the increase adiponectin levels observed in our study may due to the enhancement of endogenous FGF21 function to induce adiponectin. It was reported that a single bolus of exogenous FGF21 could stimulate adiponectin secretion (11). We further examined the ability of exogenous FGF21 to induce adiponectin. Our current study showed that exercise significantly alleviated the HFD-induced impairment of FGF21 to stimulate total adiponectin. More impressively, HFD-elicted impaired ability of FGF21 to induce HMW adiponectin, the most biologically active adiponectin isoform, was completely restored by exercise training. Our current data indicated that exercise enhanced the levels of FGF21-induced adiponectin, particularly the HMW isoform in HFD-induced obese mice. The molecular mechanisms for FGF21-elicted adiponectin secretion remain imperfectly understood. PPARγ has been suggested to play an important role in FGF21-induced adiponectin (11). Further work is needed to investigate whether PPARγ takes part in the exercise-elicited enhanced function of FGF21 to induce adiponectin.

FGF21 levels are increased significantly in humans and animals with obesity or diabetes (45), while the physiologic action of FGF21 such as glucose-lowering and nonesterified fatty acid (NEFA)-lowing effect is attenuated, indicating reduced FGF21 sensitivity (46). Decreased expression of FGF21 co-receptor β-klotho and FGFRs may contribute to the impaired FGF21 sensitivity in obesity (46). In the present study we found that β-klotho as well as FGFR1 and FGFR2 were upregulated by exercise in diet-induced obese mice. However, serum levels of FGF21 were not significantly changed by exercise training. These results imply that the exercise-induced improvement in the FGF21–adiponectin axis may be through the upregulation of FGF21 sensitivity, rather than FGF21 expression itself.

The precise molecular mechanism responsible for the FGF21–adiponectin axis dysfunction is not clearly determined. The impaired FGF21–adiponectin axis is a manifestation of adipose tissue dysfunction, which is considered to be related to inflammation (47). Proinflammatory cytokines such as TNFs and IL-1β inhibit β-klotho expression and impair FGF21 action (21, 22). In the present study, we found that exercise training ameliorated the FGF21–adiponectin axis impairment, with concomitant inhibition of inflammation in adipose tissue. However, whether exercise alleviates the FGF21–adiponectin axis dysfunction through the reduction of inflammation in adipose tissue needs further research.

In summary, our current data demonstrate that exercise training inhibits adipose tissue inflammation and leads to liver-to-adipose tissue communication via improving the FGF21–adiponecin axis impairment, which seems to be plausible mechanism for exercise-related benefits in glucose homeostasis and insulin resistance. A recent study by Leiluo Geng et al. also identified that exercise increased β-klotho and FGFR1 in adipose tissue and protected against HFD-induced FGF21 resistance (44). More impressively, they found that adipose β-klotho-deficient mice were resistant to exercise-mediated metabolic benefits and showed lower levels of exercise-induced adiponectin, further indicating that the FGF21–adiponectin axis serves as a crucial mediator of exercise-induced metabolic improvement.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EC-19-0034.
Declarations of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
Liangming Li designed the research; Wenqi Yang, Ling Liu, jinbao Chen, Qinghua Han, Melfang Huang, Xuan Tan, Qiuyue Liu, Qiang Pan, Lu Zhang and Xiaojuan Lei performed the research; Yuan Wei, Chunlu Fang, Fu Zhou analyzed data; Liangming Li and Wenqi Yang wrote the paper.

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