Whole body vibration remodels skeletal muscle via autophagy and energy metabolism in diabetic mice

SHANSHAN AN, DAHAO WANG, XUE MA and CHANG LIU

First Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning 121000, P.R. China

Received September 4, 2020; Accepted March 8, 2022

DOI: 10.3892/mmr.2022.12698

Abstract. Hyperglycemia occurs due to a defect in insulin secretion or impaired biological functions, or both. The long-term hyperglycemia during diabetes causes chronic damage and dysfunction of various tissues. Whole body vibration (WBV) has significant effects on lipid and glucose metabolism and endocrine and motor systems. In order to explore the effects of WBV on skeletal muscle, mice trained for 12 weeks with WBV (15 Hz, 30 min) were used as experimental subjects and their skeletal muscle morphology under the pathological state of diabetes was observed. In addition, the blood lipids, blood glucose, gastrocnemius muscle glycogen and mRNA and protein levels of autophagy and glucose metabolism biomarkers were compared among the three groups of mice via western blot and RT-qPCR. The results showed that WBV can significantly reshape skeletal muscle morphology and upregulate high density lipoprotein. The expression of glucose-6-phosphatase (G6P), Beclin1 and Atg7 in the gastrocnemius muscle of the WBV group was significantly increased. Therefore, it can be concluded that WBV promotes skeletal muscle remodeling in diabetic mice. The present study confirmed that WBV can attenuate the development of diabetes melitus (DM) and lead to lower level low density lipoprotein in the blood. In addition, G6P level plays an important role in WBV-treated DM model and may be used to monitor the effect of WBV in patients. The findings of the present study may provide a new molecular basis for WBV to play a therapeutic role in the treatment of diabetes and may have potential clinical applications in the future.

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by high blood sugar (1). Hyperglycemia occurs due to a defect in insulin secretion or impaired biological effects, or both. The long-term hyperglycemia during diabetes causes chronic damage and dysfunction of various tissues, particularly the eyes, kidneys, heart, blood vessels, muscle and nerves (2). The development of diabetes is a complicated process, including lipid infiltration, glucose metabolism disorder, autophagy imbalance and inflammatory response (3). Therefore, targeting the aforementioned mechanisms is an effective strategy to delay the development of complications of diabetes.

Whole body vibration (WBV) is a new physical exercise method to improve athletic ability (4,5). Compared with traditional exercise methods, inactive patients need less WBV and have higher compliance (6). WBV is widely used in warm-up of athletes and rehabilitation training for patients. Previous study has found that WBV can improve metabolic levels in diabetic rats (7). The complex relationship between autophagy and energy metabolism has attracted wide interest and has been extensively studied. In the present study, the relationships that enable autophagy to control or regulate energy metabolism and allow metabolic pathways to regulate autophagy in a diabetic state were examined. Specifically, the association between autophagy and energy homeostasis from glycolysis, fatty acid metabolism and amino acid metabolism was studied. However, its further molecular mechanism has not yet been elucidated. Therefore, it was hypothesized that WBV can attenuate the development of DM and lead to lower level of low density lipoprotein (LDL) in the blood.

In the present study, a mouse model of diabetes was established and trained with WBV (15 Hz, 30 min) for 12 weeks to explore the possible muscle protection mechanism of WBV for the treatment of diabetes. The findings of the present study may provide a new molecular basis for WBV to play a therapeutic role in the treatment of diabetes and may have potential clinical applications in the future.

Materials and methods

Animals. A total of 36 C57BL/6 mice were bred at the Experimental Animal Center of Jinzhou Medical University (Jinzhou, China). The present study was approved (approval no. 2020008) by the Ethics Committee of Jinzhou Medical University (Jinzhou, China). The mice were housed under controlled pathogenic (SPF) conditions in a temperature-controlled (22˚C) and humidity-controlled (55-65%)

Correspondence to: Professor Chang Liu, First Affiliated Hospital of Jinzhou Medical University, 2 Renmin Street, Jinzhou, Liaoning 121000, P.R. China
E-mail: liuchang1971mei@163.com

Key words: whole body vibration, autophagy, energy metabolism, diabetes

light-dark cycle (12/12-h). Access to food and water was provided *ad libitum*. A total of 12 male mice (8 weeks of age, 20-23 g) were fed normally, and 24 male mice of the same age were fed with high-fat diet (0.15% cholesterol) for 8 weeks and injected with streptozocin (200 mg/kg; sigmaaldrich.cn/CN/zh/product/sigma/s0130.) under the aforementioned conditions. After blood glucose levels reached 11.1 mmol/l, mice fed with high-fat diet were randomly divided into 2 groups. The WBV group was trained on a LD-P vertical vibration testing machine (China Guangdong Central Vibration Machinery Co., Ltd., frequency 15 Hz, acceleration 0.68 g, amplitude 2 mm) for 30 min per day. Vibration intervention took place from Monday to Saturday, with Sunday as a rest day. The training session started at 9:00 AM and lasted 12 weeks. Then, the mice of each group were weighed after 12 h of fasting, and blood samples were collected and examined. At the end of the experiment, mice were euthanized by intraperitoneal injection of sodium pentobarbital (100 mg/kg). Death was confirmed from respiratory and cardiac arrest without response to external stimuli.

Blood biochemical analysis. After WBV for 12 weeks, blood samples were collected from the venous system, the serum was separated at 3,000 rpm (956 g) for 15 min at 4˚C and stored at -80˚C until analysis. Triglycerides (TG; cat. no. A110-1-1), total cholesterol (TC; cat. no. A111-1-1), high density lipoprotein cholesterol (HDL; cat. no. A112-1-1) and LDL cholesterol (cat. no. A113-1-1) were detected by commercially available kits (Nanjing Jiancheng Bioengineering Institute).

HE staining. The 10-μm frozen (-80˚C) gastrocnemius sections were dried at room temperature for 30 min and immersed into hematoxylin for 6 min; then the slides were rinsed with running water for 10 sec. The sections were incubated in HCl/95% alcohol (1:50) solution for 5 sec. After washing with running water for 25 min, the slides were stained with eosin with 1 min and then fixed with neutral balsam after dehydration via 75, 95 and 100% alcohol with 3 min and soaked in xylene for transparency for 5 min at room temperature. The sections were observed under a light microscope.

Western blot analysis. Gastrocnemius tissues were chopped into small chunks with fine scissors and then dissolved in RIPA lysis buffer (Beyotime Institute of Biotechnology). The final protein concentration was quantified by BCA Protein Kit (Beyotime Institute of Biotechnology), with bovine serum albumin (BSA, Sigma) as protein standard. The same amount (20 μg) of protein samples was added into polyacrylamide gels (12%). The samples were subjected to SDS-PAGE and transferred to a PVDF membrane, then blocked with 1% BSA in TBST (0.05% Tween-20) at room temperature for 2 h. Then, the membranes were incubated with the primary antibodies at 4˚C overnight. Following the primary incubation, membranes were incubated with the secondary antibodies [Horseradish peroxidase labeled goat anti rabbit IgG antibody (1:5,000; cat. no. SA00001-2) and goat anti mouse IgG antibody (1:5,000, no. SA00001-1); both ProteinTech Group, Inc; diluted with 0.5% BSA in TBST] at room temperature for 2 h. The protein bands were visualized using ChemiDoc-ItTMTS2Imager (Analytik Jena AG) and protein expression was quantified using ImageJ software (National Institutes of Health). Anti-G6P (1:1,000; cat. no. ab133964), anti-Beclin1 (1:1,000, ab207612), Atg7 (1:1,000, ab133528), AKT (1:1,000, ab179463), P-AKT (1:1,000, ab192623), MTOR (1:1,000, ab134903), P-MTOR (1:1,000, ab109268), PI3K (1:1,000, ab191606) and P-PI3K (1:1,000, ab278545) were used as the primary antibodies, with glyceraldehyde-3-phosphate dehydrogenase (cat. no. HC301; Beijing Transgen Biotech Co., Ltd.) as the internal reference.

Reverse transcription-quantitative (RT-q)PCR. After the mice were euthanized by excessive anesthetic, a gastrocnemius tissue was received for RT-qPCR. According to the manufacturer's protocol (Promega Corporation), total RNA extracts were obtained using TRIzol® Reagent (Ambion; Thermo Fisher Scientific, Inc.), and 5 μg of total RNA was used to synthesize cDNA (Promega Corporation). RT-qPCR was performed using SYBR-Green. cDNA samples were amplified on a 7500 fast RT-PCR system (Applied Biosystems) under the following thermocycling conditions: 95˚C for 3 min, followed by 40 cycles of 95˚C for 15 sec and 60˚C for 45 sec. The relative expression levels of the target genes were normalized to those of the housekeeping gene ribosomal protein S18 (RPS18) and the target genes from the experimental group were compared with the corresponding target genes from the control group using the $2^{-\Delta\Delta Cq}$ method. The following oligonucleotide primers were used: G6P forward, 5'-CCTTTGGGTAGCTGTGATTGGA-3' and reverse, 5'-GGCACGGAAGTGTTGCTGTAGTAG-3'; FAS forward, 5'-GTGCTTGCTGGCTCACAGTTA-3' and reverse, 5'-GGTTGGTGTACCCCCATTCA-3'; SREBP-1c forward, 5'-GCATCTTCTTGTGCAGTGCC-3' and reverse, 5'-TACGGCCAAATCCGTTCACA-3'; Beclin1 forward, 5'-AAAGAGTGGAAGATGTCCGGC-3' and reverse, 5'-CAGCTGCTTCTCACCCTTGTA-3'; Atg7 forward, 5'-GCCAGGTACTCCTGAGCTGT-3' and reverse, 5'-GGTCTTACCCTGCTCCATCA-3'; and RPS18 forward, 5'-GCAATTATTCCCCATGAAG-3' and reverse, 5'-GGCCTCACTAAACCATCCAA-3'. The amount of RPS18 in samples was used to normalize the mRNA content (the RNA level was expressed relative to that of the corresponding control).

Statistical analysis. Statistical analysis was performed using Prism 5 software (GraphPad Software, Inc.). $P<0.05$ was considered to indicate a statistically significant difference. Paired Student's t-test and one-way ANOVA followed by post hoc Tukey's test were used to compare 2 and >2 groups, respectively. Data are presented as the mean ± SD of at least three independent experiments. Each data point in the figures represents one sample from one mouse. The numbers of animals used in each experiment are indicated in the figure legends.

Results

Effect of WBV on blood glucose and blood lipid in DM mice. Previous studies have shown that in mouse models, exercise training [such as swimming (8) and running wheels (9)] decreases as injuries develop. To investigate the effects of WBV on gastrocnemius, mice were trained with WBV for 12 weeks, and examined in 0, 2, 4, 6, 8, 10 and 12 weeks after feeding and blood sugar reached 11.1 mmol/l. In the present

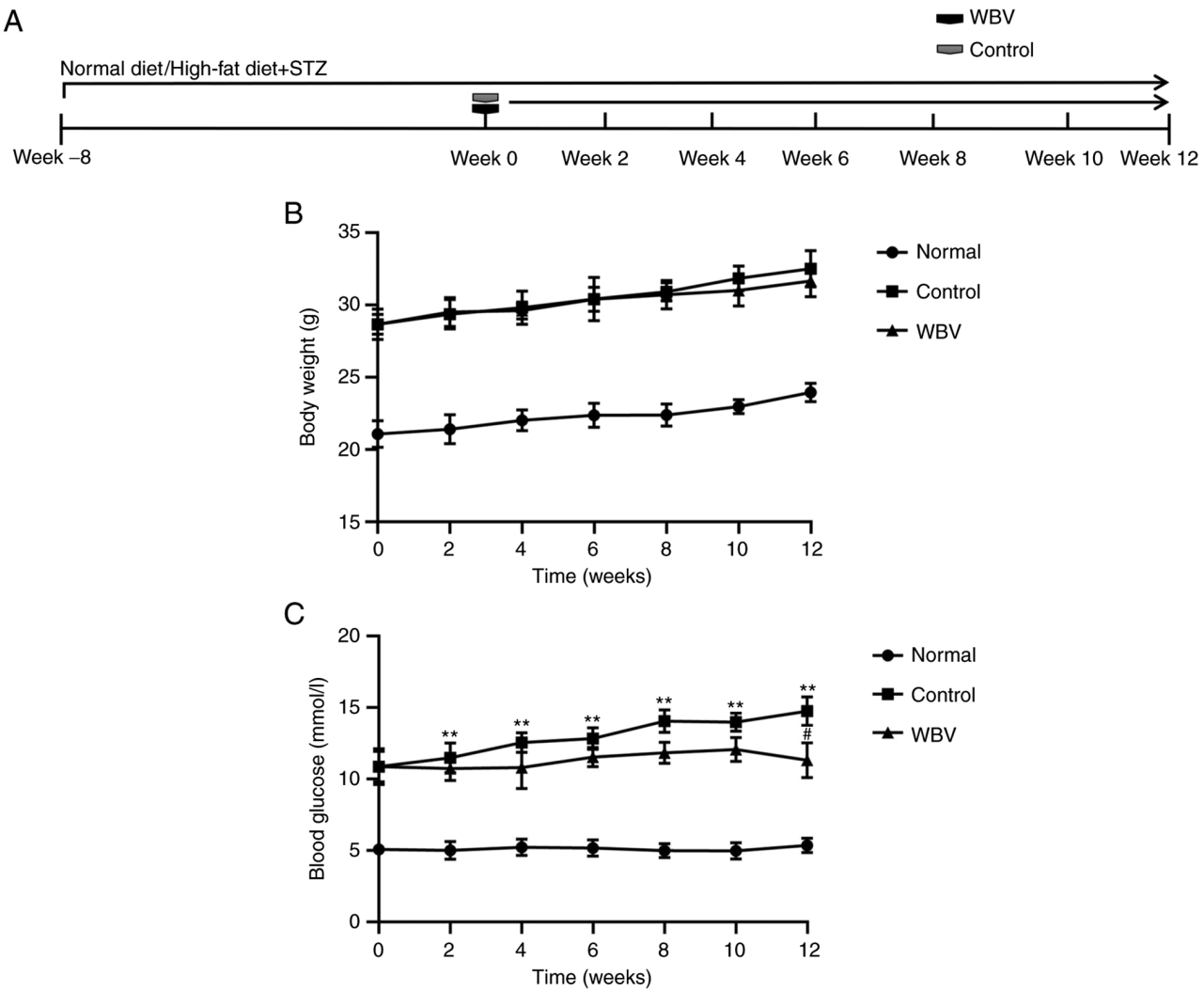

Figure 1. Physiological conditions of the three groups of mice. (A) Timing of body weight and blood glucose measurements in different treatment mice. (B) Body weight was measured before the intervention and at the 2, 4, 6, 8, 10 and 12 weeks after the intervention. (C) Levels of blood glucose were evaluated before the intervention and at the 2, 4, 6, 8, 10 and 12 weeks after the intervention (n=5 animals/group). **P<0.01 vs. Normal; $^{\#}$P<0.05 vs. Control. WBV, whole body vibration; STZ, streptozocin.

study, the weight of diabetic mice was significantly higher than that of normal mice, while there was no significant difference in weight between the control and WBV groups (Fig. 1B). As revealed in Fig. 1C, a significant decrease in blood glucose levels was observed after 12 weeks of WBV treatment compared with the control group. Regarding blood lipids, WBV had no significant effect on TC and TG concentrations in mice (Fig. 2B); however, the level of LDL was significantly reduced in the WBV group, and the level of HDL was significantly increased in the WBV group (Fig. 2B). Reductions in blood glucose and lipoprotein indicated that WBV has an effect on diabetes in mice after 12 weeks (Figs. 1A and 2A).

Effect of WBV on muscle reshaping in DM mice. In order to explore whether chronic WBV training can remodel skeletal muscle in diabetic mice, the cross-sectional area of skeletal muscle was examined using H&E staining (Fig. 3A). The cross-sectional area of skeletal muscle was measured to compare the difference between the control and WBV groups. It was revealed that the skeletal muscle area of the control group is smaller than that of the WBV group (Fig. 3B). In addition, skeletal muscle morphology showed that WBV training significantly reduced the progression of DM complications (Fig. 3C). Therefore, long-term WBV training can delay the development of complications in diabetic mice.

Effect of WBV to metabolism in DM mice. Skeletal muscle remodeling in the WBV group indicated that long-term intervention of WBV promotes the basic physiological processes of skeletal muscle. Skeletal muscle glucose metabolism (10,11) and lipid metabolism (12,13) play an important role in the complications of DM. Among them, G6P is an important rate-limiting enzyme of the glycolysis pathway (14) and Fas is an important rate-limiting enzyme of fatty acid metabolism (15). Therefore, the mRNA and protein expression of G6P was evaluated in three groups of mouse skeletal muscle (Fig. 4A). As demonstrated in Fig. 4B-D, G6P mRNA and protein expression significantly increased after WBV treatment compared with the control group. SREBP-1c mRNA significantly decreased after WBV treatment in DM mice, FAS mRNA level had indifferent in WBV and control groups

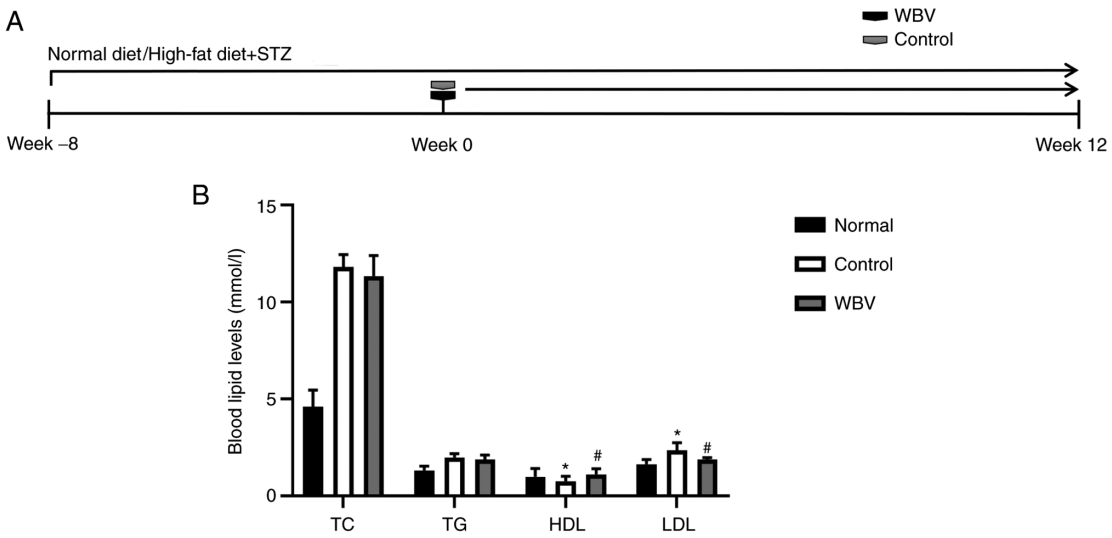

Figure 2. Fat metabolism in mice in different treatment groups by lipoprotein. (A) The timing of fat measurements in different treatment mice. (B) After the intervention, TC, TG, HDL and LDL levels were used to assess lipid metabolism in the three groups of mice at 12 weeks after the intervention (n=5 animals/group). *P<0.05 vs. Normal; #P<0.05 vs. Control. WBV, whole body vibration; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein.

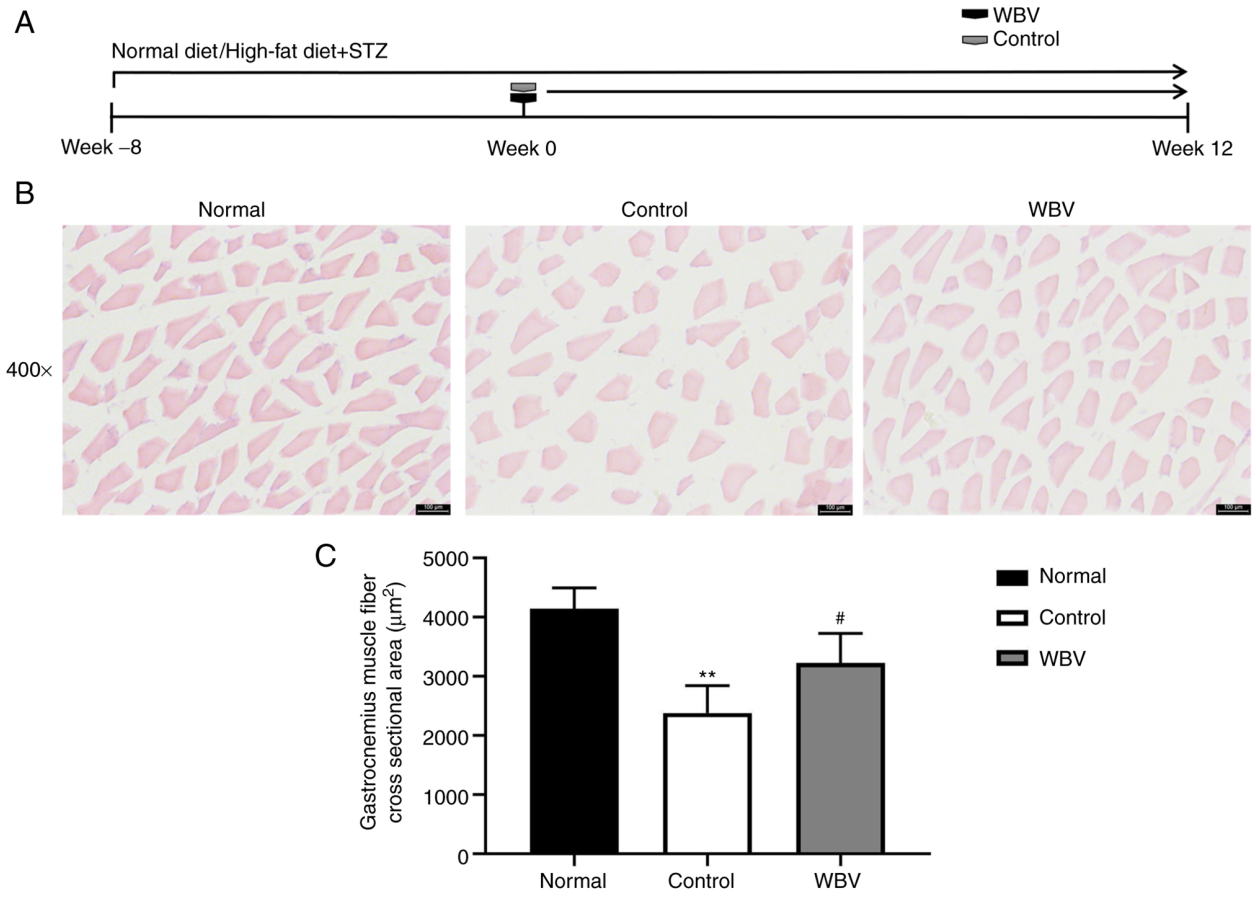

Figure 3. Morphology in mice in different treatment groups by lipoprotein. (A) Timing of HE staining in different treatment mice. Gastrocnemius muscle morphology in mice in different treatment groups by HE staining. (B and C) At 12 weeks post-intervention, the gastrocnemius muscle morphology of the three treatment groups was evaluated by HE staining (magnification, x400). Scale bar, 100 μm (n=3 animals/group). **P<0.01 vs. Normal; #P<0.05 vs. Control. WBV, whole body vibration.

(Fig. 4E and F). The aforementioned results indicated that long-term WBV can influence glucose and lipid metabolism of skeletal muscle.

Effect of WBV to autophagy in DM mice. Previous studies showed that autophagy can promote skeletal muscle recovery in disease (16,17). In order to confirm whether WBV promotes

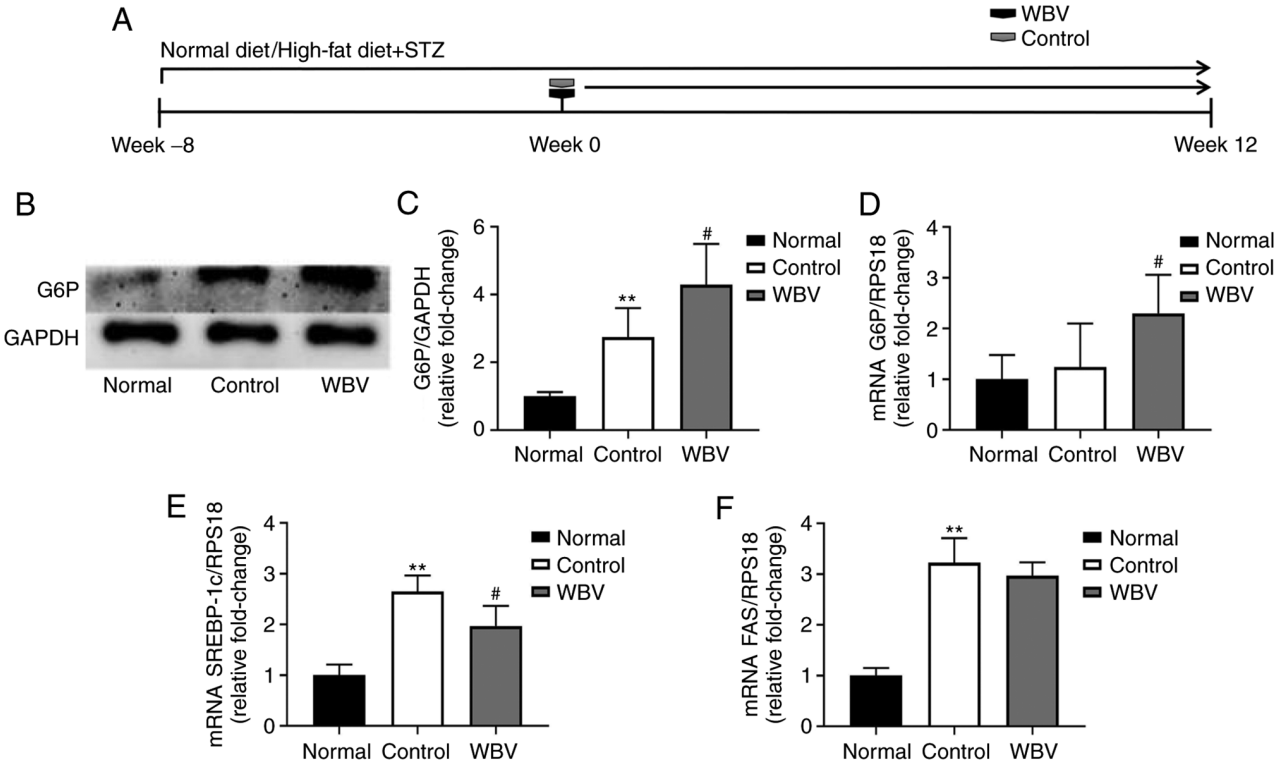

Figure 4. Effect of WBV on the energy metabolism of gastrocnemius muscle in diabetic mice. (A) Timing of western blot in different treatment mice. Following intervention, the effect of WBV on the energy metabolism of gastrocnemius muscle in diabetic mice was detected using western blot and RT-qPCR at the 12th week. (B and C) Western blot analysis of G6P of the three treatment groups. (D-F) mRNA levels of (D) G6P, (E) SREBP-1c and (F) FAS were determined by RT-qPCR (n=3 animals/group). **P<0.01 vs. Normal; $^{\#}$P<0.05 vs. Control. RT-qPCR, reverse transcription-quantitative PCR; G6P, glucose 6-phosphatase; WBV, whole body vibration.

skeletal muscle remodeling through autophagy, western blot analysis was performed (Fig. 5A). The results revealed that the expression of autophagy-specific proteins Beclin1 and Atg7 was increased in the WBV group compared with the control group (Fig. 5B-D). In addition, the aforementioned results were validated using RT-qPCR (Fig. 5E and F). Next, to further investigate whether or not WBV could affect autophagy-specific signaling pathways *in vivo*. We found that the administration of WBV decreased the level of p-AKT, P-MTOR and P-PI3K via using western blot (Fig. 6A-6B). In summary, long-term WBV can increase autophagy, thereby promoting skeletal muscle remodeling.

Discussion

In the present study, it was evaluated whether WBV can promote skeletal muscle remodeling in diabetes. Mice administered high-fat diet for 8 weeks showed skeletal muscle contraction. The 12-week vibration training significantly increased the cross-sectional area, autophagy and glucose metabolism of skeletal muscle in DM mice, while significantly reducing serum LDL. These results indicated that long-term WBV can delay DM concurrency. The disease progresses with low levels of lipoproteins and high levels of autophagy.

DM is a chronic inflammatory disease (2). Oxidative stress not only plays a key role in the formation of initial lesions, but also plays a key role in the progression and instability of lesions (2,18,19). In the complication stage, abnormal blood glucose and accumulation of blood glucose in skeletal muscle lead to oxidative stress (20). In the present study, vibrational motion did not significantly reduce TC in DM mice, although previous study has shown that WBV significantly reduced elevated levels of TC and TG in obese mice (4). In addition, lipoprotein levels were examined and it was found that WBV significantly decreased LDL in DM mice. Numerous studies have confirmed that prolonged or high-intensity exercise causes oxidative damage to large molecules in blood and skeletal muscle (19,20).

Skeletal muscle is the main tissue for glucose uptake by insulin in the body and plays an important role in glucose metabolism balance, particularly in patients with diabetes (21,22). Skeletal muscle contraction involves multiple regulatory steps in glucose metabolism, of which glucose glycolysis is considered a rate-limiting step (3). G6P is a carrier of rate-limiting enzymes in the glucose glycolysis pathway of the cell. G6P exists in various tissues and cells of the human body. It stimulates glucose metabolism by regulating the rate of glucose breakdown under the signal of insulin (14). Previous research has found that exercise training may affect glucose metabolism by increasing the glycoprotein content of myoblasts and increasing the transport and use of glucose by myoblasts (21). Moreover, a previous study demonstrated that the activation of autophagy during exercise may increase the positive regulation of skeletal muscle utilization (23). A previous study demonstrated that the effects of exercise on glucose transport depend on autophagy through studies of lateral femoral muscles of mice, cultured rat toe extensors and L6 muscle tubules (24).

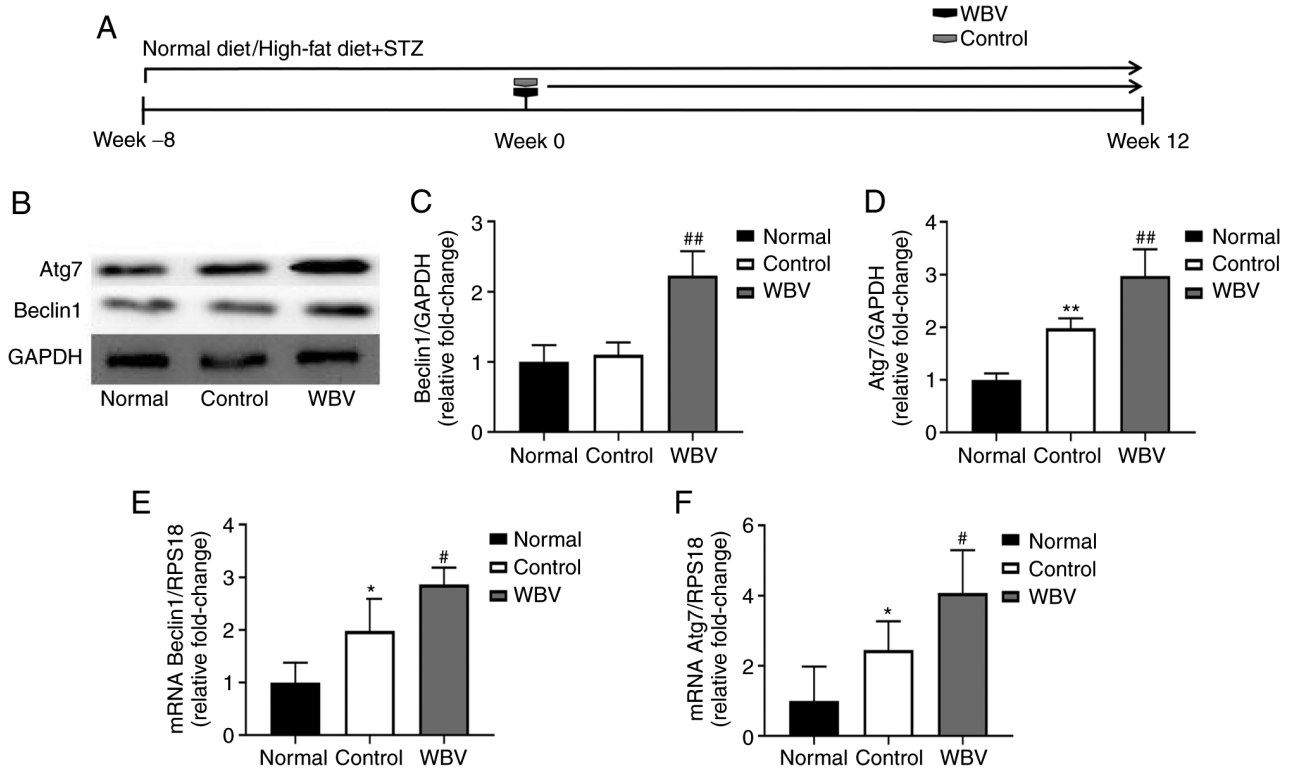

Figure 5. Effect of WBV on the autophagy of gastrocnemius muscle in diabetic mice. (A) Timing of western blot in different treatment mice. After the intervention, the effect of whole-body vibration on the autophagy of gastrocnemius muscle in diabetic mice was detected using western blot analysis and RT-qPCR at the 12th week (B-D). The protein expression levels of Atg1 and Beclin1 were determined by western blot analysis. (E and F) mRNA levels of (E) Beclin1 and (F) Atg7 were determined using RT-qPCR (n=3 animals/group). *P<0.05, **P<0.01 vs. Normal; $^{\#}$P<0.05, $^{\#\#}$P<0.01 vs. Control. RT-qPCR, reverse transcription-quantitative PCR; WBV, whole body vibration.

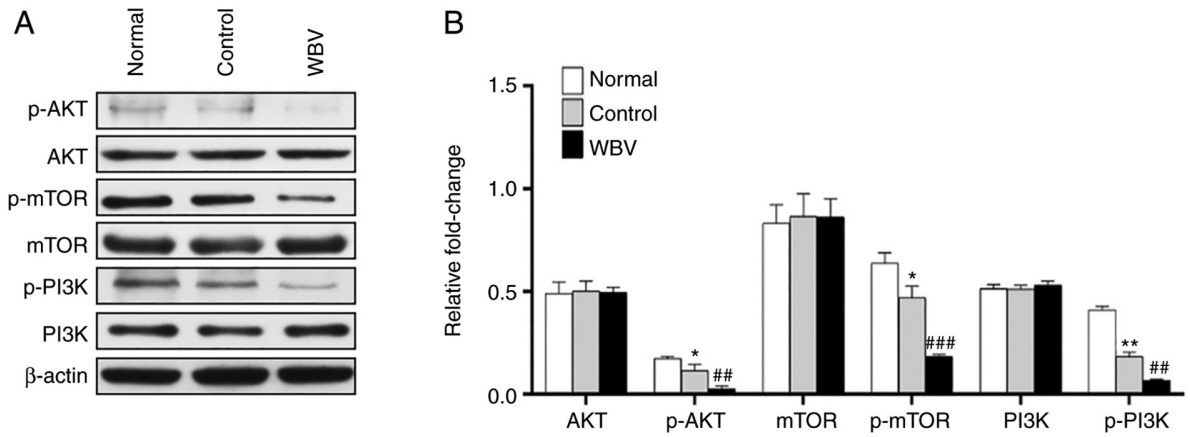

Figure 6. Effect of WBV on the PI3K/Akt pathway of gastrocnemius muscle in diabetic mice. After the intervention, the effect of WBV on the PI3K/Akt pathway of gastrocnemius muscle in diabetic mice was detected using (A) western blot at the 12th week. (B) PI3K/Akt pathway-related proteins expressions in three groups (n=3 animals/group). *P<0.05, **P<0.01 vs. Normal; $^{\#\#}$P<0.01, $^{\#\#\#}$P<0.001 vs. Control. WBV, whole body vibration; p-, phosphorylated.

Autophagy is a conservative catabolic process. When cells are in a hungry environment, autophagy can reuse long-lived proteins and organelles as nutrients (16). Genes and proteins involved in autophagy have been identified in yeast. These genes are called ATGs, which control autophagy formation through two ubiquitin like systems Atg12/5 and Atg7/Atg8 (17). There are similar genes and proteins in human. The transformation of LC3 (Atg8) from lc3i to lc3ii represents autophagy (17). The signal of autophagy is regulated by the mTOR pathway (25). Through the PI3K/Akt pathway (25), p70S6 kinase and eIF2α kinase activate the mTOR pathway, while beclin-1 (Atg6) regulates autophagy process through the class III PI3K pathway (26). Recent studies (16,17) have revealed that autophagy plays an important role in maintaining the metabolic balance of skeletal muscle cells under certain pathological conditions (atrophy of skeletal muscle caused by heart failure and hyperglycemia), but the specific mechanism remains to be explored. Autophagy is a lysosome-dependent catabolic process. Both extracellular and intracellular components are phagocytosed by autophagosomes and degraded into simple

molecules such as monosaccharides, fatty acids and amino acids. These molecules can then be further used to produce ATP through catabolic reactions and/or provide the basis for the synthesis of essential proteins. Therefore, it is considered that autophagy is a key and fine-tuned process for maintaining energy homeostasis, particularly in diseases (25). The complex relationship between autophagy and energy metabolism has attracted wide interest and has been extensively studied. In the present study, the relationships that enable autophagy to control or regulate energy metabolism and allow metabolic pathways to regulate autophagy in a diabetic state were investigated. Specifically, the association between autophagy and energy homeostasis from glycolysis, fatty acid metabolism, and amino acid metabolism was studied. Understanding the role of autophagy in energy homeostasis can help in improved understanding of how autophagy determines skeletal muscle fate through energy metabolism in diabetic mice.

The present study confirmed that WBV can attenuate the development of DM and lead to lower level of LDL in the blood. In addition, G6P level plays an important role in WBV-treated DM model and may be used to monitor the effect of WBV in patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SA designed and performed the experiments, analyzed the data and wrote the manuscript. DW performed the staining and western blot experiments and analyzed data. XM performed the PCR experiments. CL supervised the study, designed the experiments, interpreted data and wrote the manuscript. SA, DW, XM and CL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. 2020008) by the Ethics Committee of Jinzhou Medical University (Jinzhou, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wei H, Hu Q, Wu J, Yao C, Xu L, Xing F, Zhao X, Yu S, Wang X and Chen G: Molecular mechanism of the increased tissue uptake of trivalent inorganic arsenic in mice with type 1 diabetes mellitus. Biochem Biophys Res Commun 504: 393-399, 2018.
2. Rampogu S, Rampogu and Lemuel M: Network based approach in the establishment of the relationship between type 2 diabetes mellitus and its complications at the molecular level coupled with molecular docking mechanism. Biomed Res Int 2016: 6068437, 2016.
3. Maegawa H and Kashiwagi A: Molecular mechanism and clinical impact of insulin resistance in type 2 diabetes mellitus. Nihon Rinsho 57: 539-544, 1999.
4. Lai CC, Tu YK, Wang TG, Huang YT and Chien KL: Effects of resistance training, endurance training and whole-body vibration on lean body mass, muscle strength and physical performance in older people: A systematic review and network meta-analysis. Age Ageing 47: 367-373, 2018.
5. Sierra-Guzmán R, Jiménez-Diaz F, Ramírez C, Esteban P and Abián-Vicén J: Whole-body-vibration training and balance in recreational athletes with chronic ankle instability. J Athl Train 53: 355-363, 2018.
6. Sierra-Guzmán R, Jiménez JF, Ramírez C, Esteban P and Abián-Vicén J: Effects of synchronous whole body vibration training on a soft, unstable surface in athletes with chronic ankle instability. Int J Sports Med 38: 447-455, 2017.
7. Liu Y, Liu C, Lu ML, Tang FT, Hou XW, Yang J and Liu T: Vibration exercise decreases insulin resistance and modulates the insulin signaling pathway in a type 2 diabetic rat model. Int J Clin Exp Med 8: 13136-13144, 2015.
8. Szostak J, Miguet-Alfonsi C, Berthelot A and Laurant P: Training-induced anti-atherosclerotic effects are associated with increased vascular PPARgamma expression in apolipoprotein E-deficient mice. Acta Physiol (Oxf) 216: 221-230, 2016.
9. Shing CM, Fassett RG, Peake JM and Coombes JS: Voluntary exercise decreases atherosclerosis in nephrectomised ApoE knockout mice. PLoS One 10: e0120287, 2015.
10. Zhao C, Yang C, Wai STC, Zhang Y, P Portillo M, Paoli P, Wu Y, San Cheang W, Liu B, Carpéné C, *et al*: Regulation of glucose metabolism by bioactive phytochemicals for the management of type 2 diabetes mellitus. Crit Rev Food Sci Nutr 59: 830-847, 2019.
11. Wu H, Deng X, Shi Y, Su Y, Wei J and Duan H: PGC-1α, glucose metabolism and type 2 diabetes mellitus. J Endocrinol 229: R99-R115, 2016.
12. Yoo JS and Lee SJ: A meta-analysis of the effects of exercise programs on glucose and lipid metabolism and cardiac function in patients with type II diabetes mellitus. Taehan Kanho Hakhoe Chi 35: 546-554, 2005 (In Korean).
13. Iizuka Y, Murase T and Iizuka Y: Abnormalities in lipid metabolism associated with diabetes mellitus. Nihon Rinsho 55 (Suppl): S603-S608, 1997.
14. Kundu BK, Zhong M, Sen S, Davogustto G, Keller SR and Taegtmeyer H: Remodeling of glucose metabolism precedes pressure overload-induced left ventricular hypertrophy: review of a hypothesis. Cardiology 130: 211-220, 2015.
15. Herrera E and Desoye G: Maternal and fetal lipid metabolism under normal and gestational diabetic conditions. Horm Mol Biol Clin Investig 26: 109-127, 2016.
16. Jiao J and Demontis F: Skeletal muscle autophagy and its role in sarcopenia and organismal aging. Curr Opin Pharmacol 34: 1-6, 2017.
17. Lee DE, Bareja A, Bartlett DB and White JP: Autophagy as a therapeutic target to enhance aged muscle regeneration. Cells 8: 183, 2019.
18. Oguntibeju OO: Type 2 diabetes mellitus, oxidative stress and inflammation: Examining the links. Int J Physiol Pathophysiol Pharmacol 11: 45-63, 2019.
19. Annunziata G, Barrea L, Ciampaglia R, Cicala C, Arnone A, Savastano S, Nabavi SM, Tenore GC and Novellino E: Arctium lappa contributes to the management of type 2 diabetes mellitus by regulating glucose homeostasis and improving oxidative stress: A critical review of in vitro and in vivo animal-based studies. Phytother Res 33: 2213-2220, 2019.
20. Ighodaro OM: Molecular pathways associated with oxidative stress in diabetes mellitus. Biomed Pharmacother 108: 656-662, 2018.
21. Teng S and Huang P: The effect of type 2 diabetes mellitus and obesity on muscle progenitor cell function. Stem Cell Res Ther 10: 103, 2019.

22. Sala D and Zorzano A: Differential control of muscle mass in type 1 and type 2 diabetes mellitus. Cell Mol Life Sci 72: 3803-3817, 2015.
23. Tam BT and Siu PM: Autophagic cellular responses to physical exercise in skeletal muscle. Sports Med 44: 625-640, 2014.
24. Chen HC, Bandyopadhyay G, Sajan MP, Kanoh Y, Standaert M, Farese RV Jr and Farese RV: Activation of the ERK pathway and atypical protein kinase C isoforms in exercise- and aminoimidazole-4-carboxamide-1-beta-D-riboside (AICAR)-stimulated glucose transport. J Biol Chem 277: 23554-23562, 2002.
25. Wu YT, Tan HL, Huang Q, Ong CN and Shen HM: Activation of the PI3K-Akt-mTOR signaling pathway promotes necrotic cell death via suppression of autophagy. Autophagy 5: 824-834, 2009.
26. Furuya N, Yu J, Byfield M, Pattingre S and Levine B: The evolutionarily conserved domain of Beclin 1 is required for Vps34 binding, autophagy and tumor suppressor function. Autophagy 1: 46-52, 2005.