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Original Article

Swimming exercise reversed the loss of grip strength, muscle cross-sectional area and trabecular bone volume among type 1 diabetic rats independent of insulin therapy

Xinlu Li[1], Yiqun Xiao[1], Yuming Zheng[1], Yurui Ye[1], Chenyi Dong[1], Yihan Zhu[1], Yuxuan Du[1], Ren Cai[2], Zun Wang[1], Jiajia Qian[1]

[1]*Rehabilitation Therapy Department, The Acupuncture and Moxibustion School of Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China;* [2]*The Sports Department of Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China*

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Abstract: Background: This study was designed to test the therapeutic effect of swimming exercise on grip strength, muscle cross-section of quadriceps, and trabecular bone volume of the femur among STZ-induced type 1 diabetic rats, independent of insulin therapy. Methods: Sprague-Dawley rats were divided into three groups: control group (CON), diabetes mellitus group (DM), and diabetes mellitus plus exercise group (DM+EX). Type 1 Diabetes was established with intraperitoneal injection of streptozotocin (50 mg/kg body weight). The DM+EX group received progressive swimming exercise five days a week for 12 weeks. Results: Both the DM and DM+Ex groups displayed hyperglycemia, with no statistically significant difference in blood glucose levels observed between these two groups. Compared to the control group (CON), the DM group demonstrated significant reductions in grip strength and quadriceps cross-sectional area ($P<0.05$), which was reversed by swimming exercise ($P<0.05$). Micro-CT analysis of the femoral bone revealed that the DM group had significantly lower BV/TV and Tb.N, compared with the CON group ($P<0.05$), while exhibiting a significant increase in trabecular spacing (Tb.Sp). In contrast, the DM+Ex group showed significant increases in BV/TV ($P<0.01$) and Tb.N ($P<0.01$) compared to the DM group, along with a significant decrease in Tb.Sp ($P<0.001$). Conclusion: Swimming exercise may reverse the loss of grip strength, muscle cross-sectional area, and trabecular bone volume in STZ-induced type 1 diabetic rats - independent of insulin therapy.

Keywords: Swimming exercise, grip strength, muscle cross-sectional area, trabecular bone volume, diabetes

Introduction

Type 1 diabetes mellitus (T1DM) is a significant global health burden, with an estimated 9.15 million individuals affected worldwide in 2024, including 599,000 Chinese people across all age groups living with the condition [1]. This chronic metabolic disorder results in multiple organ damage, such as the cardiovascular system, kidneys, retina, skeletal muscles, and bones, posing serious threats to overall health. Among the negative changes of muscular and skeletal mass, including loss of mass and decline in strength, common complications for type 1 diabetes lead to weakness, fragility, and immobilization. The notably elevated prevalence of osteoporosis and sarcopenia among diabetic populations underscores the critical necessity for implementing multifaceted therapeutic interventions to improve muscle and bone health during the treatment of diabetes mellitus.

Exercise training has been recognized as a basic intervention method to address this issue. Extensive research has demonstrated that exercise training exerts a profound therapeutic effect on enhancing both muscular and skeletal tissue properties [2]. Regarding the training methods, resistance training is often the first choice for strengthening muscular and bone tissue [3]. However, several clinical con-

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straints limit its widespread application in diabetic populations. Specifically, achieving positive regulatory effects on general bone and muscle tissue typically necessitates high-volume resistance training involving multiple joint movements, which presents significant challenges for individuals with diabetes. Furthermore, diabetic patients often exhibit reduced exercise tolerance, making it difficult to complete sufficient training due to accelerated fatigue onset. Additionally, resistance training carries inherent risks of musculoskeletal injury stemming from improper technique or excessive loading. In contrast, swimming emerges as a safer alternative exercise modality. The buoyancy effect during aquatic activities substantially reduces biomechanical stress on weight-bearing joints, thereby mitigating injury risk while maintaining therapeutic benefits. According to a recent study, swimming could produce greater benefits on cortical and trabecular bone than other aerobic exercises like incline treadmill activity [4]. Another study showed that eight weeks of swimming training could effectively potentiate the recovery of femoral neck strength among STZ-induced diabetic rats under insulin therapy [5]. Other studies have documented the positive regulatory effect of swimming on muscle properties among diabetic subjects [6, 7]. Therefore, swimming may become an alternative exercise training modality to counteract muscle and bone loss in diabetes. However, the majority of prior studies have predominantly focused on type 2 diabetes (T2D), wherein exercise training has demonstrated significant regulatory effects on blood glucose levels. This predominant focus on T2D creates a knowledge gap regarding the direct protective effect of swimming exercise on muscular tissue under chronic and severe hyperglycemic conditions. Furthermore, the impact of swimming on bone parameters in type 1 diabetes mellitus (T1DM) remains largely unexplored. In summary, the direct regulatory effects of swimming exercise on both muscle and bone volume in T1DM subjects remain unclear. It remains uncertain whether swimming exercise can be employed as a preventive measure against secondary muscle and bone alterations in T1DM under hyperglycemic conditions.

This study was designed to determine whether swimming exercise alone could enhance muscle and bone tissue volume in T1DM rats. We hypothesized that swimming exercise would directly and concurrently improve grip strength, muscle cross-sectional area of the quadriceps, and bone volume of the femur in streptozotocin (STZ)-induced T1DM rats, independent of insulin therapy.

Materials and methods

Animals and groups

Nine male Sprague-Dawley rats (body weight: 220-250 g; 6-7 weeks in age) were randomly divided into three groups (n=3, in each group): normal control group (CON), diabetes mellitus group (DM), and diabetes mellitus with exercise group (DM+EX). All the rats were housed in groups of three per cage at the Animal Experimental Institute of Nanjing University of Chinese Medicine (Nanjing, China) under controlled environmental conditions: at a constant temperature of 22±2°C, humidity 50%-60%, free diet, and 12-h light/dark cycle. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. To minimize environmental stress, animals were acclimatized for one week prior to experimental commencement. Streptozotocin (STZ; Sigma-Aldrich, USA) was dissolved in ice-cold sodium citrate buffer (pH 7.4) to maintain solution stability. After a 12-hour fasting period with ad libitum access to water, diabetes was induced via intraperitoneal injection of STZ (50 mg/kg body weight). Rats with fasting blood glucose (FBG) level ≥16.7 mmol/L at 72 h after STZ administration were considered successfully diabetic.

Swimming intervention

One week after the successful establishment of the diabetic model, rats in the DM+EX group underwent supervised aerobic swimming training for 12 weeks (5 sessions/week) in a temperature-controlled environment (23-25°C). The exercise regimen was conducted in a cylindrical tank with a diameter of 100 cm and a height of 80 cm. The water depth during training was maintained at 55 cm. In the first week, animals in the DM+EX group exercised for 15 minutes per session. From the 2nd week to the 11th week, the training time gradually increased. (Increased by 5 minutes every two weeks). In the last week, the training time was increased to 45 minutes per session.

Blood glucose and body weight records

The blood glucose at the tip of the tail of the rat was measured with a blood glucose meter (Yuwell-580, Jiangsu Yuyue Medical Equipment & Supply Co., Ltd., Danyang, Jiangsu Province) at 10 a.m. every Monday. Then, the rats were put on a digital scale to record body weight (accuracy ± 0.1 g).

Grip strength test

The four-limb grip strength test was employed to evaluate the muscular strength of rats. Upon completion of the 12-week training protocol, grip strength measurements were conducted using a Grip Strength Meter (Model YLS-13A, Jinan Yiyan Technology Development Co., Ltd.), with each assessment repeated three times per animal. The mean value from these triplicate measurements was recorded as the representative limb grip strength for each rat. During testing, animals were gently positioned on a metallic mesh grid and encouraged to grasp the grid with all four limbs. They were pulled by the tail with increasing force until the grasp of all four limbs was eventually lost. Each measurement cycle required 4-5 seconds to complete, with a standardized 1-minute rest interval between consecutive trials. The mean grip strength (in grams) across the three measurements was subsequently normalized to body weight using the formula: grip strength (g)/body weight (g) × 100, expressed as g/100 g body weight. All data are presented as mean ± standard deviation (SD).

Micro-computed tomography (Micro-CT) examination of the femur

At the end of the experimental period, all rats were euthanized with sodium pentobarbital (100 mg/kg) to ensure minimal pain or distress. Their right femur bones were removed, and the femur bones were placed into EP tubes, which were filled with 70% ethanol. After that, the samples were labeled and preserved in a 4°C refrigerator. Then, they were scanned by the micro-CT system at 90 kV, 88 μA with 10 μm isotropic voxels and a 0.5 mm aluminum filter (Quantum GX, PerkinElmer, USA) to detect the proportion of bone tissue (BV/TV) and bone microstructure, including trabecular number (Tb.N), trabecular thickness (Tb.Th), and trabecular separation (Tb.Sp). The region of interest for trabecular analysis was the distal metaphysis (starting 1 mm proximal to the distal growth plate; length 1-2 mm). Cortical analysis was performed at the mid-diaphysis (a 0.5-1 mm section at the midshaft). A global threshold, chosen from the gray-scale histogram, was used to segment the bone from non-bone tissue consistently across all samples.

HE staining

The quadriceps muscle, femur bone, and kidney were initially fixed in 10% (w/v) buffered formaldehyde solution. Following fixation, femur bones underwent decalcification in 10% EDTA solution (pH 7.4) at room temperature for 3-7 days, with solution replacement performed every 48 hours. Subsequently, decalcified bone samples were processed through a standard protocol including dehydration in graded ethanol solutions, clearing in xylene, paraffin embedding, and sectioning at 5 μm thickness. Muscle and bone tissues were directly processed for paraffin embedding without decalcification. All sections were then stained with hematoxylin and eosin (HE) using a commercially available staining kit (Solarbio, Beijing, China) according to the manufacturer's instructions. For morphometric analysis, the muscle cross-sectional area (CSA) was quantified from five randomly selected fields that were evenly distributed across the entire muscle cross-section. All identifiable fibers within each field were segmented and analyzed using ImageJ 2.0.0 software (Fiji 1.54f, 2024).

Statistical analysis

Statistical analyses were performed using GraphPad Prism software (version 10.0, USA). All the data were presented as mean ± standard deviation (SD). A one-way ANOVA (and nonparametric or mixed) followed by Tukey's post-hoc test was utilized to assess differences between the CON, DM and DM+EX groups. A two-tailed $P<0.05$ was considered to be statistically significant.

Results

Baseline characteristics of rats across groups

The initial body weight and fasting blood glucose of the rats in different groups are summarized in **Table 1**. One-way ANOVA revealed no

Table 1. Initial body weight (g) and blood glucose (mmol/L)

	CON (n=3)	DM (n=3)	DM+EX (n=3)	*p*-value
Body weight (g)	297.3±10.0	289.2±12.0	294.5±11.0	0.63
Blood glucose (mmol/L)	5.8±1.0	5.6±1.1	5.7±0.9	0.96

Data are presented as mean ± SD. *p*-values were calculated using one-way ANOVA.

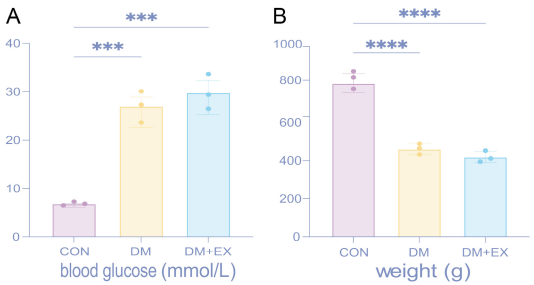

Figure 1. Comparison of the blood glucose levels and body weight in each group (n=3). The blood glucose (A) of the nine rats and their body weight (B). *P<0.05; **P<0.01; and ***P<0.001.

statistically significant differences in initial body weight or fasting blood glucose among the CON, DM and DM+EX groups (P>0.05 for all variables; **Table 1**), indicating comparable baseline conditions prior to interventions.

Swimming exercise failed to affect blood glucose and body weight in diabetic rats

Twelve weeks post-intervention, the CON group demonstrated an average blood glucose level of 7.629 mmol/L. In contrast, both the DM and DM+EX groups exhibited significantly elevated blood glucose levels (**Figure 1A**; P<0.001). No significant difference in blood glucose levels was observed between the DM and DM+EX groups (**Figure 1A**; P>0.05). Regarding body weight (**Figure 1B**), the average weight of rats in the CON group was 783.3 g. Both the DM and DM+EX groups showed significantly lower body weights compared to the CON group (P<0.0001), with no significant difference detected between these two groups (P>0.05).

Swimming exercise significantly reversed the decline in grip strength and quadriceps cross-sectional area in diabetic rats

Compared with the CON group, the grip strength of rats in the DM group was significantly reduced by 27.1% (P<0.01). In the DM+EX group, the grip strength and the normalized grip strength were increased by 5% and 27.6% when compared with the DM group (**Figure 2A**, **2B**; P<0.05; P<0.01). The HE staining of the quadriceps in the CON group revealed polygonal muscle fibers that were tightly connected and showed no signs of atrophy. In contrast, the muscle fibers from the DM and DM+EX groups displayed an oval shape and varied in size (**Figure 2D**, **2E**). The mean of muscle cross-sectional area was significantly diminished in the DM, which was significantly increased by 20% in DM+EX (P<0.05; **Figure 2C**).

Swimming exercise significantly reversed the loss of the femur trabecular bone volume in diabetic rats

Compared to the CON group, the DM group exhibited a reduction in trabecular thickness and an increase in trabecular spacing as manifested by significantly lower BV/TV and Tb.N, as well as higher Tb.Sp in the Micro-CT examination (**Figure 3A**, **3B**). Swimming exercise significantly improved the microstructure of the femur bones in DM rats. The BV/TV went up from 29.35% in the DM group to 55.31% in the DM+EX group (P<0.01; **Figure 3C**). Additionally, the DM+EX group exhibited a 0.42 (1/mm) increase in Tb.N and a 0.41 mm decrease in Tb.Sp compared to the DM group (**Figure 3D**, **3F**). However, no significant difference in Tb.Th was found between the DM group and the DM+EX group (**Figure 3E**). These microstructural findings were further corroborated by histological analysis using hematoxylin and eosin (HE) staining of femoral bone sections (**Figure 3G**).

Renal morphological changes across groups

Given that secondary kidney injury is common in diabetic patients and closely linked to bone and muscle mass, we also performed HE staining of kidney tissues in this study. The DM group showed vacuolation and amyloid casts in renal tubules, which appeared less pronounced in the DM+Ex group (Supplementary Figure 1).

Discussion

The current study demonstrated that swimming exercise alone, without insulin therapy,

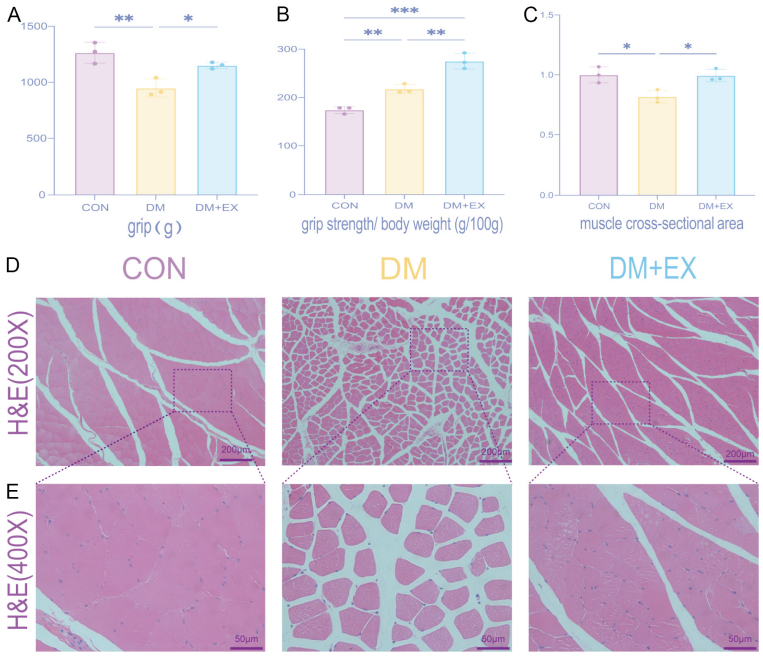

Figure 2. Comparison of the skeletal muscle parameters in each group (n=3). The swimming exercise effect on grip strength (A), the normalized grip strength (B), the HE staining of muscle cross-section area at ×200 (D) and ×400 (E) magnification, and the data are presented as mean ± SD (C). *P<0.05; **P<0.01; and ***P<0.001.

may significantly reverse the decline in grip strength, the loss of muscle cross-sectional area of quadriceps, and the decrease in trabecular bone volume of the femur among STZ-induced type 1 diabetic rats without significant alteration of hyperglycemia.

The loss of bone and muscle mass represents a prevalent and clinically significant complication of diabetes mellitus, substantially elevating the risk of osteoporosis and sarcopenia in affected individuals [8]. Recent studies have discovered that these two conditions exhibit a biomechanically interdependent relationship due to the intricate mechanical and endocrine coupling between muscle and bone tissues [9-12]. Furthermore, emerging evidence has revealed that both skeletal and muscular tissues possess endocrine functions, whereby their pathological deterioration can further impair glucose metabolism through altered secretion of myokines and osteokines [13, 14]. Therefore, the loss of muscle and bone tissue after type 1 diabetes deserves attention.

In this study, we first evaluated the efficacy of a 12-week swimming intervention in mitigating grip strength decline and quadriceps muscle cross-sectional area reduction in streptozotocin (STZ)-induced type 1 diabetic rats in the absence of insulin therapy. Our findings demonstrate that swimming exercise effectively reverses both grip strength impairment and muscle volume loss in type 1 diabetic rats, independent of glycemic control. The beneficial effects of exercise on muscle fiber composition and metabolic regulation have been well documented in prior studies. For instance, McBey et al [15] demonstrated that combined aerobic/resistance training with insulin therapy enhances overall muscle fiber content and increases type I fiber proportion. Similarly, Rahmati [16] reported that treadmill training elevates gastrocnemius muscle fiber cross-sectional area in STZ-induced diabetic rats, while Sammut et al. [17] found that resistance training reduces glycogen content in the white gastrocnemius muscle of type 1 diabetic female rats. Additionally, emerging evidence suggests that swimming may delay age-related sarcopenia [18, 19]. Compared to these prior studies, our results provide novel evidence that swimming exercise could exert a protective effect on muscle tissue against hyperglycemia-induced damage, further supporting the therapeutic potential of swimming exercise in preserving muscle strength and volume among diabetic populations.

This study further investigated the impact of swimming exercise on bone volume in type 1 diabetic mellitus (T1DM) rats. Bone tissue morphology was systematically evaluated using both hematoxylin-eosin (HE) staining and micro-computed tomography (micro-CT) in the current study. The experimental results revealed a significant loss of trabecular bone volume in diabetic rats, which was substantially ameliorated by swimming intervention, as manifested by significantly higher BV/TV and Tb.N, as well as significantly lower Tb.Sp in the DM+Ex group when compared with the DM group. In prior studies, the effects of swimming on bone volume in T1DM rats have been less explored.

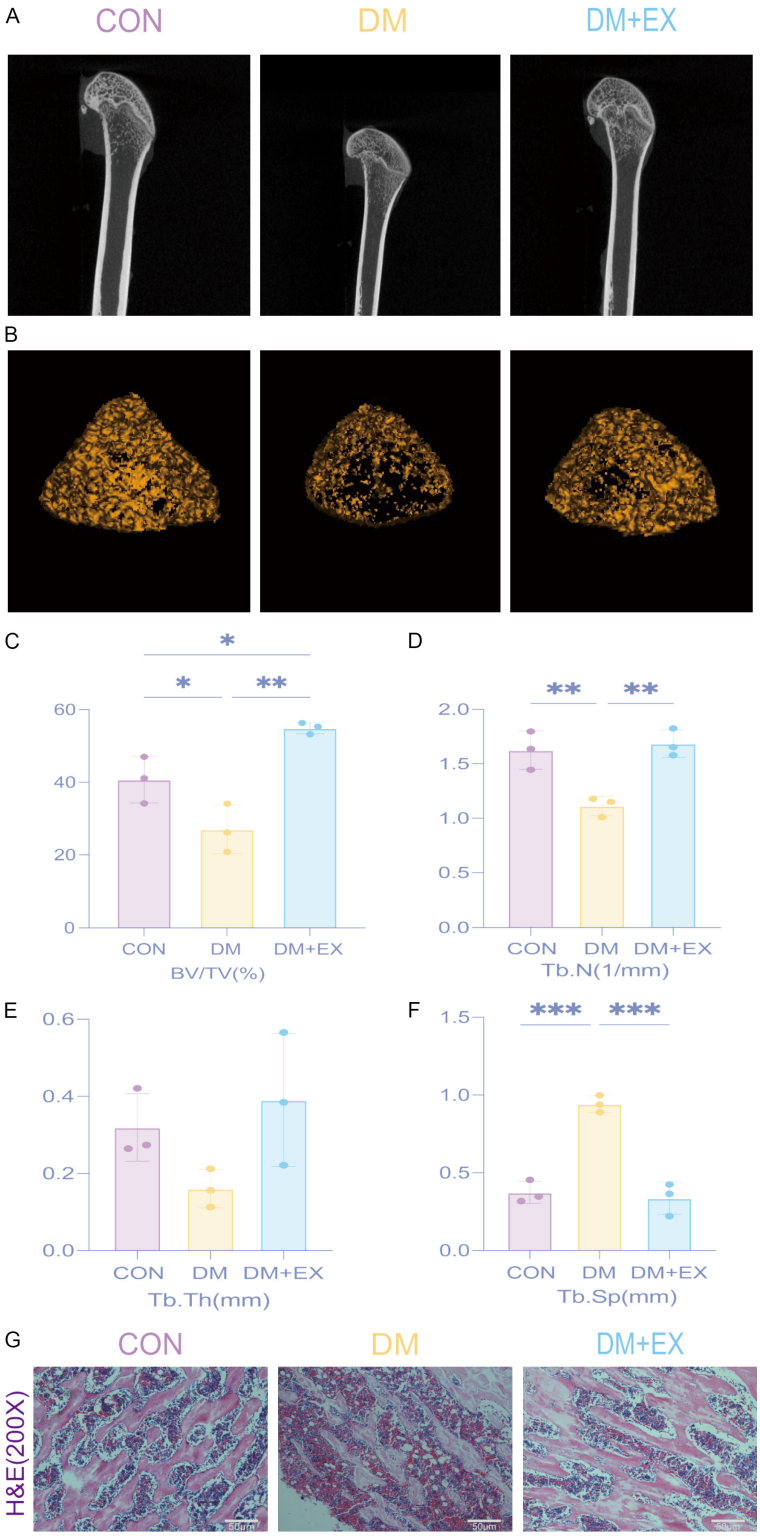

Figure 3. Comparison of the bone parameter in each group (n=3). Comparison of the femur micro-CT (A, B) and the data of microstructure (C-F), the HE staining of the femur (G; ×200). *P<0.05; **P<0.01; and ***P<0.001.

One study demonstrated that eight weeks of swimming training enhanced the recovery of femoral neck strength in young rats with severe streptozotocin (STZ)-induced diabetes [5]. However, since insulin therapy was co-administered in this study, it is difficult to ascertain the direct protective role of swimming alone. Another study demonstrated that six weeks of swimming exercise effectively mitigated reductions in tibial length, total area, and bone mineral content in T1DM rats without insulin therapy [20], although this study lacked direct trabecular bone volume assessment through HE staining or micro-CT. Our experimental results provide novel, direct evidence supporting swimming's beneficial role in preventing trabecular bone volume decline under hyperglycemic conditions. Given that trabecular bone is a critical determinant of bone quality, and its loss is strongly associated with increased fragility fracture risk - a common complication in T1DM [21, 22] - swimming's protective effect on trabecular bone volume suggests its potential as a therapeutic strategy to improve bone health in diabetic populations. It is important to note that, unlike its well-established benefits for muscle mass regulation, swimming's osteogenic potential remains controversial [23-26]. Some studies report elevated bone turnover rates in swimmers compared to sedentary controls [23], while others suggest swimming may be less effective than weight-bearing activities in promoting bone formation [26], with some even indicating lower bone density in swimmers [27]. These discrepancies may stem from variations in study design, subject characteristics, and outcome measures. Besides, the controversy over the efficacy of swim-

ming in regulating bone tissue may largely be attributed to swimming's characteristic low-impact, non-weight-bearing nature. However, given that high-impact exercises are often unsuitable for diabetic patients, our findings regarding swimming's protective effect on trabecular bone volume in T1DM models may hold significant clinical relevance.

The novel finding of our study was that swimming exercise exerted protective effects on grip strength, muscle cross-sectional area, and trabecular bone volume in type 1 diabetic rats without altering blood glucose levels. These results suggest that swimming may directly influence bone and muscle tissue in type 1 diabetes. The lack of significant impact on blood glucose levels can be attributed to the underlying pathophysiology of type 1 diabetes mellitus, which is primarily characterized by insulin deficiency due to pancreatic beta-cell dysfunction rather than insulin resistance. Consequently, exercise training - which predominantly exerts beneficial effects by improving insulin sensitivity - would not be expected to significantly alter blood glucose levels in this context. This aligns with the findings of a prior study [28], which similarly reported no significant effect of exercise on blood glucose regulation in type 1 diabetic rats. Collectively, these observations imply that swimming may exert its beneficial effects on bone and muscle through mechanisms independent of blood glucose modulation. Future research should focus on elucidating the underlying molecular pathways mediating these effects.

Our study also has several limitations. First of all, the sample size per group was quite small. Secondly, the outcome measurements were simple and incomplete. Future studies should incorporate muscular weight measurements to determine whether observed increases in cross-sectional area correspond to actual gains in muscle mass. Additionally, comprehensive evaluation of muscle mass could be enhanced through methods such as DXA examination and pathological staining techniques, including MHC immunohistochemistry or immunofluorescence staining. Furthermore, the study focused exclusively on the quadriceps muscle, which was selected due to its relevance to swimming exercise, potentially limiting the generalizability of the findings. Future research should evaluate multiple muscle groups following swimming exercise. In terms of bone assessment, only trabecular bone volume was measured using micro-CT examination. Future studies should also investigate cortical bone changes after swimming exercise in type 1 diabetic rats. Other methodological shortcomings include the absence of food intake evaluation and the lack of a control group undergoing swimming exercise, which could be included in future investigations. Despite these limitations, our study represents the first to demonstrate that swimming exercise alone may exert significant protective effects on grip strength, muscle cross-sectional area, and trabecular bone volume in type 1 diabetic rats. These preliminary findings may serve as a foundation for establishing swimming as a secondary preventive measure against osteoporosis and sarcopenia in diabetic populations.

Conclusions

This current study demonstrated that twelve weeks of swimming exercise significantly reversed the decline in grip strength, prevented loss of quadriceps muscle cross-sectional area, and mitigated reductions in femoral trabecular bone volume in STZ-induced type 1 diabetic rats, indicating the protective effect of swimming on bone and muscle mass under deteriorating hyperglycemic conditions.

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Disclosure of conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abbreviations

STZ, streptozotocin; CON, control group; DM, diabetes mellitus; DM+EX, diabetes mellitus plus exercise group; FBG, fasting blood glucose; Micro-CT, micro-computed tomography; BV/TV, bone volume fraction; Tb.N, trabecular

number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; HE, hematoxylin-eosin; T1DM, type 1 diabetes mellitus; T2D, type 2 diabetes; ANOVA, analysis of variance; SD, standard deviation; IL-15, interleukin-15; DXA, dual energy X-ray absorptiometry.

Address correspondence to: Ren Cai, The Sports Department of Nanjing University of Chinese Medicine, Qi Xia District, Xianlin Road 138th, Nanjing 210023, Jiangsu, China. E-mail: 070007@njucm.edu.cn; Zun Wang and Jiajia Qian, Rehabilitation Therapy Department, The Acupuncture and Moxibustion School of Nanjing University of Chinese Medicine, Qi Xia District, Xianlin Road 138th, Nanjing 210023, Jiangsu, China. E-mail: wangzun270996@njucm.edu.cn (ZW); 270724@njucm.edu.cn (JJQ)

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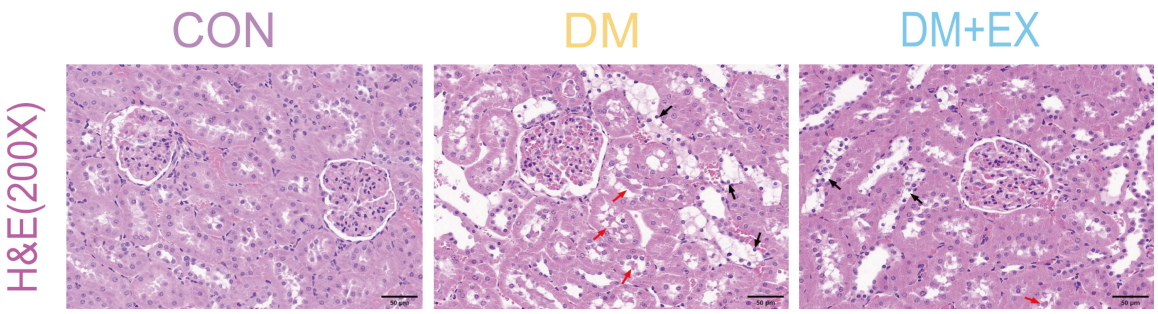

Supplementary Figure 1. Comparison of the kidney pathology in each group (n=3). The HE stained kidney tissues (×200; black arrows: vacuolation; red arrows: amyloid casts).