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Pilot Study on the Effects of Aerobic and Resistance Exercise on Glucose Metabolism and Gut Microbiota in Older Adults with Type 2 Diabetes Mellitus

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Abstract: BACKGROUND: Physical exercise has a regulatory effect on intestinal flora and glucose metabolism, but the effect of aerobic combined resistance exercise on intestinal flora and glucose metabolism in patients with T2DM is unclear, so this paper will investigate the effect of aerobic combined resistance exercise on glucose metabolism and intestinal flora in patients with T2DM. **METHODS:** Twelve patients with T2DM were recruited, 4 were shed, and 8 were finally available, and aerobic combined Resistance exercise intervention was carried out on the patients for a period of 6 weeks, 3 times per week, and fasting blood and fecal samples were collected from the subjects before and after the intervention, and glucose metabolism indexes were detected on the blood samples, and intestinal flora was detected on the fecal samples, and the changes in glucose metabolism indexes and intestinal flora indexes of the patients with type 2 diabetes mellitus were compared before and after the intervention Results. **RESULTS:** (1) GSP in blood indexes was significantly reduced (t=9.07, P<0.05), FINS (t=0.84, P=0.43) and FBG (t=0.72, P=0.50) did not change significantly, but decreased compared with pre-intervention; (2) Alpha diversity analysis showed that the diversity of intestinal flora communities (Shannon index) and community richness (Chao index) did not change significantly (P = 0.4165/P = 0.1019) but increased, and community coverage (Coverage index) decreased significantly (P < 0.05). (3) Venn diagrams showed a relative increase in the number of intestinal flora species by 58, and a decrease in the abundance of Actinobacteria phylum, Anaplasma phylum, Aspergillus phylum, and Clostridium phylum in the intestinal flora by 2.75%, 4.69%, 6.86%, 1.37%, respectively. The abundance of the thick-walled phylum increased by 15.62%, with a significant increase in the abundance of Agathobacter in the thick-walled phylum (P<0.05).**CONCLUSIONS:** Aerobic combined with Resistance exercise intervention has a significant improvement effect on GSP in T2DM patients, and can increase the number of beneficial flora in the intestine and enhance the stability of intestinal flora, the study also found that with the decrease of FINS Agathobacter increased, this class of genera and sugar metabolism related indexes were significantly negatively correlated, which is for the future physical activity intervention in patients with T2DM study has an This is an important reference value for future research on physical exercise intervention in T2DM patients.

Keywords: Aerobic combined resistance exercise; type 2 diabetes mellitus; gut flora; glucose metabolism; intervention; effect

1. Introduction

In recent years, Approximately 415 million individuals globally are affected by diabetes mellitus, of which about 2/3 of T2DM patients are not properly treated and the severity of the disease has increa sed [1]. The number of adult diabetic patients in China is as high as 125 million, of which 90% are T2D M [2], and T2DM has become an important problem in the field of public health in China [3].With Chi na's rapid economic growth and the enhancement of living standards, there has been an increased con sumption of high-sugar and high-fat diets[4], along with an increase in the proportion of individuals e ngaged in mental work, has led to sedentary behaviors and other unhealthy habits[5]. Consequently, t he prevalence of chronic diseases, such as diabetes, has steadily risen[6]. According to a national surve y in 2007, the prevalence of diabetes in China was 9.7%, with an estimated 92.4 million adults sufferin g from the disease[7]. In 2010, a survey conducted by the Chinese Center for Disease Control and Prev ention and the Endocrinology Branch of the Chinese Medical Association on the prevalence of diabete s among individuals aged 18 and older revealed a prevalence rate of 9.7%[8]. From 2015 to 2017, the pr evalence of diabetes among adults in China was 11.2%[9]. The "Guideline for the Prevention and Treat ment of Type 2 Diabetes in China (2020 Edition)" pointed out that the prevalence of diabetes in China c ontinues to rise, with a significant increase in the prevalence rate among obese and overweight individ uals[10]. The prevention and treatment of type 2 diabetes mellitus have become urgent healthcare issu es in China[11].

The gut microbiome is a complex and important micro-ecosystem in the human body[12]. It is a r elatively open system containing a large number of bacteria, along with a small amount of fungi and v iruses[13]. The abundance, diversity, and evenness of the gut microbiome are key indicators reflecting its composition[14]. Gut microorganisms play crucial roles in regulating human metabolism, maintain ing gut barrier function, and modulating the immune system[15]. When the balance of the gut microbi ome is disrupted, it can lead to the occurrence of various diseases[16]. According to the Human Micro biome Project, the major microbial phyla in the human gut include Bacteroidetes[17], Firmicutes[18], a nd Proteobacteria[19]. The gut microbiome of individuals with type 2 diabetes mellitus (T2DM) is ofte n disrupted[20]. A study utilizing 16S ribosomal RNA (rRNA) gene sequencing found that the fecal mi crobiota of individuals with T2DM exhibits moderate dysbiosis, marked by a reduction in beneficial b acteria and an increase in opportunistic pathogens[21].It can be seen that T2DM is closely associated w ith glucose metabolism indicators.

The treatment methods for T2DM include dietary therapy, physical exercise[21], blood glucose monitoring, medication, and diabetes health education[22].The treatment methods for type 2 diabetes mellitus (T2DM) inclu de dietary therapy, physical exercise, blood glucose monitoring, medication, and diabetes health education[23]. Among these, medication and dietary therapy remain primary treatment options for T2DM[24]. In recent years, p hysical exercise rehabilitation has been increasingly used in the intervention and treatment of diabetes, as it can e ffectively lower blood glucose and lipid levels in patients[25]. Additionally, maintaining good physical exercise habits plays an important role in preventing diabetes[26]. The most commonly used forms of physical exercise fo r treating diabetes include aerobic physical exercise[27], resistance training[28], high-intensity interval training[2 9], and other combined physical exercise forms such as Tai Chi, Baduanjin, and Wuqinxi[30,31]. Currently, aero bic combined resistance physical exercise interventions for type 2 diabetes mellitus are beginning to be promoted in countries around the world, such as the United States [32], Canada [33], Austria [34], and Italy [35].A random ized pilot study showed that patients with T2DM who performed more than 150 minutes of aerobic and resistance exercise per week had a nearly 1% reduction in glycated hemoglobin [36]. In another study of older adults T2DM patients, sustained resistance physical activity significantly reduced insulin sensitivity and FPG and significantly improved abdominal fat accumulation [37].A randomized controlled study on T2DM patients also demonstrated that a combination of aerobic and resistance exercise was more effective than either aerobic or resistance exercise alone [38]. Aerobic exercise combined with resistance training is currently considered the most effective form of physical activity for the treatment of diabetes, offering greater benefits than either exercise modality alone [39]. Therefore, the present study aimed to investigate the effects of combining aerobic and resistance exercise on glucose metabolism and the gut microbiome in patients with type 2 diabetes mellitus.

Physical exercise guidelines for patients with type 2 diabetes suggest that 120-150 minutes of physical activity per week significantly improve glycemic markers, as evidenced by two randomized trials [40,41]. A meta-analysis revealed that just one week of aerobic training can enhance systemic insulin sensitivity in patients with type 2 diabetes [42]. Two clinical trials have demonstrated that moderate to high-intensity aerobic combined with resistance training (three sets, three times per week) yields beneficial outcomes in older adults patients with type 2 diabetes [43,44]. A meta-analysis of guidelines for aerobic and resistance exercise in patients with type 2 diabetes states that at least 150 minutes per week of moderate-intensity aerobic exercise (50-70% of maximal heart rate) and/or 90 minutes per week of vigorous aerobic exercise (over 70% of maximal heart rate) is recommended[45]. Additionally, patients with type 2 diabetes should engage in resistance training more than three times a week, targeting all major muscle groups with 3-4 sets of 8-15 repetitions per set (8-15 RM)[46,47]. In this study, the exercise program was designed in strict adherence to these guidelines, ensuring that the intensity, duration, and frequency of physical activity were in line with recommended standards for patients with type 2 diabetes.

2. Materials and Methods

2. 1 Study Design

2.1.1Experimental Design

Considering the small sample size , the before-after study in the same patient was conducted.

2.1.2 Place of Experimental Completion

This experiment was completed by a team of teachers and Ph.D students majoring in kinesiology from the School of Physical Education, Southwest University. The physical exercise was conducted in the Lab of Sports Rehabilitation of Southwest University and the testing of all indicators was completed in the Hospital of Chongqing Municipality.

2.1.3 Experiment Completion Time

This experiment took a total of approximately six months to complete from December 2020 to May 2021, from recruitment of subjects to the end of the experiment.

2.1.4 Study Participants

This experiment recruited subjects who had a strong desire to participate in this physical exercise intervention. After the subjects were recruited, they were instructed to complete the following questionnaires based on their individual conditions: the "Basic Information Questionnaire for Patients with Type 2 Diabetes Mellitus," the "International Physical Activity Questionnaire," and the "Physical Exercise Risk Screening Form." The collection and entry of questionnaire information was carried out by the same experimental staff. The subjects were screened by the same researcher strictly accordance with the criteria for inclusion and exclusion. After identifying the subjects, the current physical exercise intervention experiment was conducted after ensuring that the subjects were motivated by their own volition and had no relevant physical exercise risk, and then the informed consent form were signed. After the preparatory work was completed, the pre-test was used to adjust and improve the shortcomings in the experimental design, while avoiding the physical exercise risk and preventing the physical exercise load from being too large or too small.

The subjects of this experiment were older adults patients with type 2 diabetes mellitus (T2DM) aged 60 to 69 years. Due to the challenges in recruiting older adults patients with chronic conditions, the primary aim of the study was to explore the preliminary effects and mechanisms of T2DM in this population, with the goal of providing a data foundation and research direction for future experiments involving larger sample sizes. Therefore, the small sample size was within the scope of the study.A total of 12 volunteers were recruited for the physical exercise intervention experiment. Due to scheduling conflicts, 4 participants dropped out, leaving 8 participants in the final analysis. The basic information of the subjects, including age, height, weight, fasting blood glucose, fasting insulin, glycated serum protein, duration of illness, and medication use, was recorded. The baseline data of the subjects were generally consistent, as shown in Table 1. The data of T2DM patients before the aerobic and resistance exercise intervention were labeled as Group AeA, and the data after the intervention were labeled as Group AeB.Inclusion criteria:1. older adults patients aged 60-69 years; 2. Diagnosed with type 2 diabetes mellitus (T2DM); 3. No severe diabetic complications and stable condition over the past year; 4. No regular physical exercise routine; 5. Willingness to participate in the physical exercise program; 6. No exercise contraindications or hidden risks.Exclusion criteria:1. T2DM patients with severe physical exercise contraindications, such as coronary heart disease, cancer, or stroke; 2. Patients with severe diabetic complications, such as diabetic nephropathy, diabetic neuropathy, retinopathy, diabetic foot, or lower limb vascular disease; 3. T2DM patients with movement disorders, such as joint or bone diseases; 4. Participants who withdrew from the study midway; 5. Patients with severe mental illness who are unable to perform combined aerobic and resistance exercise（Table 1）.

The study was approved by the Ethics Committee of the School of Physical Education and Sports at Southwestern University (SWU-ETF-2023-07-17-011). Participants voluntarily signed an informed consent form after being thoroughly briefed and understanding the relevant information.

Table 1. Basic information about the subject.

Form	Value
Number of persons	Male（n=3）, Female（n=5）
Age	66.38±7.55
Height	159.75±6.12
Weight	59.2±8.68
FPG（mmol/L）	9.18±2.51
FINS（μU/ml）	17.36±28.44
GSP（mmol/ml）	2.45.±0.07
Length of illness	7.98±2.82
Medications	Biguanides, Glargine, Premixed insulin

Note:FPG stands for fasting plasma glucose.FINS stands for fasting insulin.GSP stands for Glycosylated serum protein.

2.1.5 Intervention design

Aerobic plus resistance training program: aerobic physical exercises through the elastic band, the elasticity of the band size of 10, 15, 20 pounds (according to the subject's own situation to choose).Total duration of single physical exercises intervention totaling 30 minutes, including 5 minutes before and after the physical exercise of the warm-up and relaxation activities, the formal exercise for 30 minutes.

Aerobic combined resistance exercise consisted of a total of 6 movements involving all large muscle groups throughout the body, 4 sets per day (approximately 20 minutes), 15 repetitions per set for each movement; heart rate was monitored by heart rate bands (GymSmart Smart Exercise Detection Device) to ensure that the subject's heart rate was maintained at between 50% and 70% HRmax throughout the entire physical exercise program (HRmax=220-age).

Physical exercise period: a total duration of 6 weeks; physical exercise frequency: 3 times per week; physical exercise intensity: 11-15 RPE, 50%-70% HRmax; the specific physical exercise program is shown in Table 2.

Table 2. Aerobic Combined Resistance Physical Exercise Program.

Training movements and sequences	Training volume	Main training area	Rhythm of Movement
1. Deep squats/biceps curls	15 reps x 4 sets	Leg , arm muscles	The contractions were explosively fast during centripetal movements and held for 2-3 seconds of slow contractions during centrifugal movements.
2. Elastic Band Clip Chest		Pectoralis major, anterior deltoids, triceps	
3. Squat/rocket shoulder press		Quadriceps, biceps, glutes, deltoids	
4. Lateral raises with hands		middle deltoid	
5. Prone rowing/hard pulling		Back, hip and leg muscles	
6. Lunge arm extension		Leg muscles, triceps brachii	

Height, weight, body composition and other physical indicators: Inbody 720 Body Composition Tester manufactured by BIOSPACE Company was used. Blood indexes: the subjects went to the hospital for blood collection, and the blood samples were processed by the same inspector in the Laboratory Department using Eppendorf Centrifuge5424R, the fasting insulin was measured by ChemiLuminescence (CL), the fasting glucose was measured by Glucose Oxidase (Glucose Determination Kit), and the glycated serum protein was measured by Glycated Serum Protein Assay (GSPA). （Fasting insulin was measured by ChemiLuminescence (CL), fasting glucose was measured by Glucose Oxidase method (Glucose Assay Kit), and glycated serum protein was measured by Glycated Serum Protein Assay Kit/NBT method. Physical exercise intervention equipment: elastic bands (Suzhou Joinfit Jieyingfei equipment, 10, 15, 20 pounds); rope skipping device (Li Ning); heart rate belt (GymSmart intelligent physical exercise detection equipment).

2.1.6 Procedure

One week before the physical exercise intervention: centralized training for the subjects, including introducing the basic information of the physical exercise intervention experiment, explaining the process and precautions of the physical exercise intervention, explaining the methods of blood and fecal sample collection, filling out questionnaires (Basic Information Questionnaire for Patients with Type 2 Diabetes Mellitus, International Physical Activity Scale, and the Physical exercise Risk Screening Scale), the informed consent form, the safety responsibility form, and other related contents; Three days before the physical exercise intervention: Acclimatization training was organized daily to determine the appropriate physical exercise load for the subjects, and baseline data were collected from the subjects on the third day, and fasting blood and stool sample collection was organized. During the physical exercise intervention, 5 minutes of preparatory activities (moving joints, marching in place) were performed before physical exercise, 20 minutes of formal physical exercise (6 aerobic physical exercises combined with resistance exercises, 1 minute rest between each exercise, 15 repetitions of each physical exercise x 4 sets, 1 minute rest between each set), and 5 minutes of relaxation (stretching of the physical exercising muscles) were performed after physical exercise. The testers reminded the subjects of the physical exercise rhythm and posture according to their individual conditions, and the testers monitored the subjects' heart rate in real time according to the heart rate belt, and asked the subjects about their condition immediately between and at the end of each set of movements (using the RPE scale, see Appendix A for details); after the physical exercise intervention: the data and samples were collected in the same way as the baseline data collection method (We organized the collection of blood and stool samples from the subjects in the early morning following the day of the exercise intervention). The specific experimental flow is shown in Figure 1. The questionnaires are detailed in Appendices B, C and D.(Since subjects' fitness and muscular endurance subsequently increased with continued training, the intervention was conducted using a progressive loading intervention model, with 10 lbs. of elastic bands at weeks 1-2, 15 lbs. of elastic bands at weeks 3-4, and 20 lbs. of elastic bands at weeks 5-6).

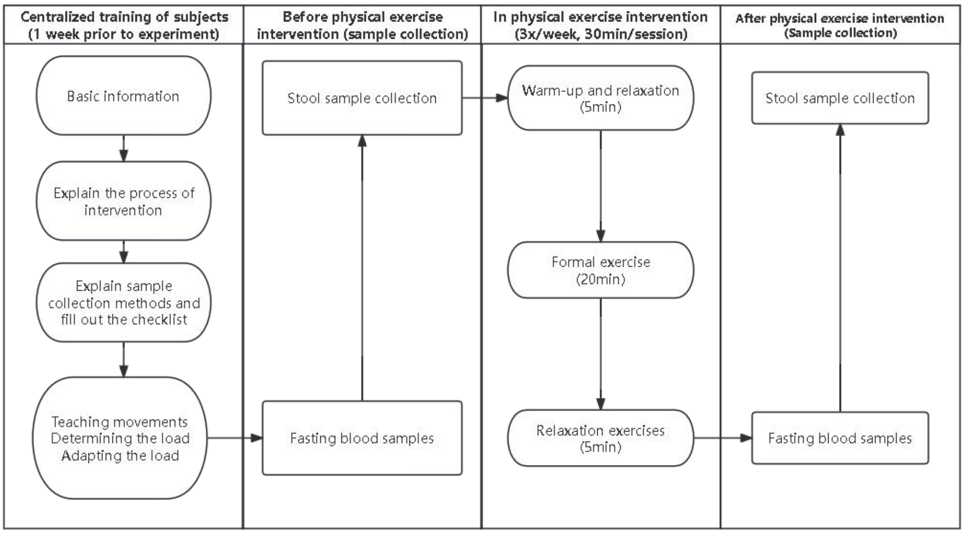

Figure 1. Experimental flow chart.

2.2 Main Observational Indicators

2.2.1 Blood Indicators

Before the physical exercise intervention and after six weeks of aerobic and resistance exercise, fasting venous blood was collected from all participants in the early morning. The samples were processed using an Eppendorf high-speed refrigerated centrifuge (Centrifuge 5424R). Fasting insulin levels were measured using the chemiluminescence (CL) method, fasting blood glucose levels were assessed using the glucose oxidase method (glucose assay kit), and glycated serum protein was measured using a glycated serum protein detection kit with the NBT method[48].

2.2.2 Intestinal Flora Indicators

The stool samples collected from patients before and after six weeks of combined aerobic and resistance exercise intervention were sent to Majorbio Bio-Pharm Technology Co., Ltd. The gut microbiome genome was extracted for 16S rDNA amplicon sequencing and SMRT Bell library construction. Operational Taxonomic Unit (OTU) analysis was performed using PacBio's SMRT analysis software, with species annotation based on the PacBio sequencing platform. The sequencing utilized Single Molecule Real-Time (SMRT) technology[49]. Marker genes were analyzed, and after filtering the Circular Consensus Sequencing (CCS) sequences, Optimization-CCS was used for OTU clustering. The species composition and abundance were analyzed, along with alpha diversity, beta diversity, and within-group significant species difference analysis, to explore species composition differences among the samples[50].

2.3 Statistical Analysis

The sequencing and analysis of gut microbiome genomes from patient stool samples were performed using the Majorbio Cloud Platform. This study primarily analyzed the diversity, richness, evenness, and coverage of the microbiome through alpha diversity. Venn diagrams were used to assess changes in the number of microbiome species. Significant difference tests were applied to identify microbiota with notable changes. Correlation heatmaps were created to explore the relationship between gut microbiota and glucose metabolism indicators. Data processing and analysis before and after the intervention were carried out using SPSS 25.0 software. Data are presented as mean ± standard deviation (X±SD). Paired sample t-tests were used to analyze glucose metabolism indicators, Welch's t-test was employed for alpha diversity of the gut microbiome, and the Wilcoxon signed-rank test was used to analyze significant changes in characteristic microbiota. Spearman's correlation analysis was performed to assess the correlation between microbiota and glucose metabolism indicators. Statistical significance was set at $P < 0.05$. The statistical methods used in this study have been reviewed and approved by biostatistics experts at Southwest University.

3. Results

3.1. Effects of Aerobic Combined with Resistance Exercise Intervention on Glucose Metabolism in Patients with Type 2 Diabetes Mellitus

Glycemic metabolic indexes, including fasting insulin (FINS), fasting blood glucose (FBG), and glycated serum protein (GSP), were statistically analyzed in patients with type 2 diabetes before and after the aerobic combined with resistance exercise interventions. The specific results are presented in Table 3.

Table 3. Glycemic metabolism in patients before and after aerobic combined resistance_exercise intervention.

Norm	Preintervention	Postintervention	t	*p*	*d*
FINS（μU/ml）	17.36±28.44	15.88±24.22	0.84	0.43	0.056
FPG（mmol/L）	9.81±2.51	8.71±3.30	0.72	0.50	0.375
GSP（mmol/ml）	2.45±0.07	2.00±0.10	9.07	0.00	5.214

Note:FPG stands for fasting plasma glucose. FINS stands for fasting insulin. GSP stands for Glycosylated serum protein.

The results of the paired sample t-test analysis indicated that after six weeks of combined aerobic and resistance exercise intervention, glycated serum protein levels in type 2 diabetes patients significantly decreased ($P < 0.05$). However, no significant changes were observed in fasting insulin and fasting blood glucose levels ($P > 0.05$), although both showed a slight decrease compared to pre-intervention levels.

3.2. The Effect of Aerobic Combined with Resistance Exercise Intervention on the Intestinal Flora of Patients with Type 2 Diabetes Mellitus

3.2.1. Alpha Diversity Analysis of Intestinal Flora

Alpha diversity analysis was conducted on the number of gut microbiota OTUs in type 2 diabetes patients before and after the combined aerobic and resistance exercise intervention. Community diversity was represented by the Shannon index, richness by the Chao index, and coverage by the Coverage index[52]. The specific findings are as follows:

After six weeks of combined aerobic and resistance exercise intervention, the Shannon index of gut microbiota diversity in type 2 diabetes patients increased from 3.0809 to 3.4104, indicating an upward trend. However, Welch's t-test results showed that these changes were not statistically significant (P > 0.05) (Figure 2).

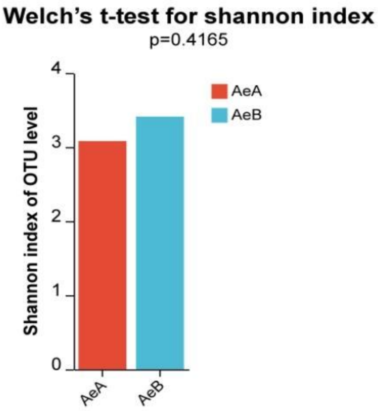

Figure 2. Community diversity of intestinal flora in patients before and after aerobic combined resistance physical exercise intervention.

3.2.2. Intestinal Flora Community Richness Analysis

After six weeks of combined aerobic and resistance exercise intervention, the Chao index of gut microbiota richness in type 2 diabetes patients increased from 306.83 to 401.55, demonstrating an upward trend. However, Welch's t-test results indicated that this change was not statistically significant (P > 0.05) (Figure 3).

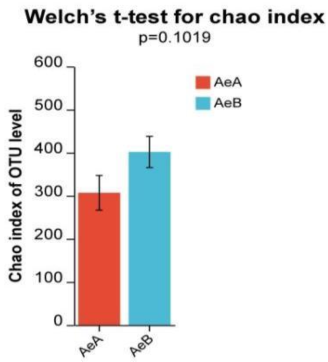

Figure 3. Intestinal flora community richness in patients before and after aerobic combined resistance physical exercise intervention.

3.2.3. Analysis of Intestinal Flora Community Coverage

After six weeks of combined aerobic and resistance exercise intervention, the Coverage index of gut microbiota in type 2 diabetes patients decreased from 0.998 to 0.99691, indicating a downward trend. Welch's t-test results showed that this change was statistically significant ($P < 0.05$) (Figure 4).

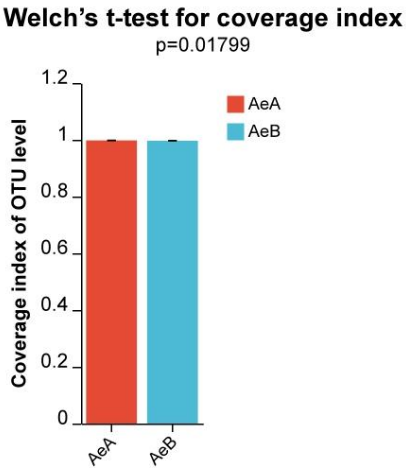

Figure 4. Gut flora communty coverage in patients before and after aerobic combined resistance physical exercise intervention.

3.2.4. Analysis of the Number of Intestinal Flora

The Venn diagram was used to count the number of shared and unique species in the gut microbiota samples of type 2 diabetes patients, visually presenting the similarities and differences in species composition before and after the combined aerobic and resistance exercise intervention[53].

In the overlapping area of the two groups, 653 OTUs were shared, indicating that the physical exercise did not affect this portion of the microbiota. After six weeks of combined aerobic and resistance exercise intervention, 76 species were reduced, and 134 species were added, showing an overall increasing trend in the total number of species among the eight patients. The top five shared microbial species between the two groups were OTU224, OTU943, OTU487, OTU698, and OTU497. The first two belong to the genera Faecalibacterium and Bifidobacterium longum, while the latter three belong to the family Lachnospiraceae. Further analysis revealed that these five OTUs were present in all samples, ruling out the possibility that any of these OTUs existed only in individual samples by chance. These microbial species warrant further exploration and discussion(Figure 5).

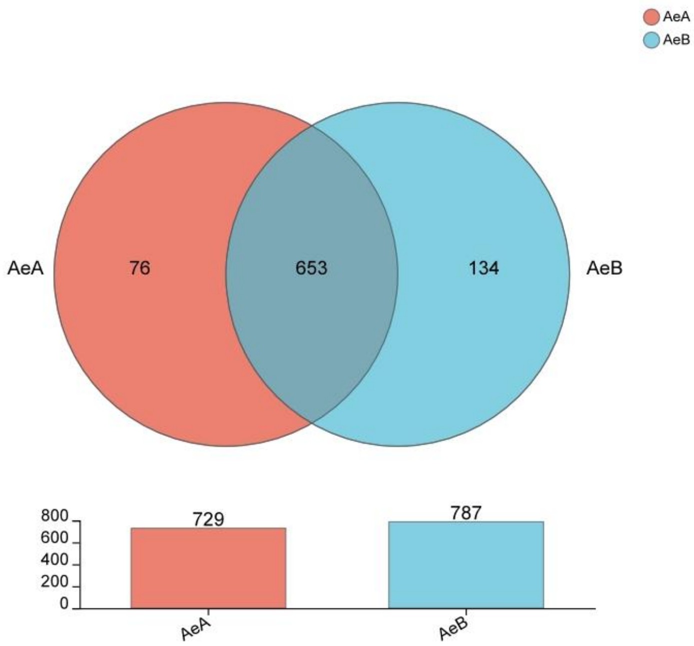

Figure 5. Venn diagram of the number of intestinal flora in patients before and after aerobic combined resistance exercise intervention.

3.2.5. Analysis of Relative Abundance of Gut Flora Before and After Aerobic Combined Resistance Exercise Intervention

The top five phyla in terms of relative abundance were Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria, and Fusobacteria. After six weeks of combined aerobic and resistance exercise intervention, the relative abundance of Firmicutes in T2DM patients increased from 64.23% to 79.85%, while the relative abundance of Actinobacteria decreased from 12.1% to 9.35%, Bacteroidetes decreased from 12.42% to 7.73%, Proteobacteria decreased from 8.48% to 1.62%, and Fusobacteria decreased from 2.5% to 1.13%. This indicates that after the combined aerobic and resistance exercise intervention, the relative abundance of Firmicutes increased, while the relative abundance of the other four phyla decreased in the gut microbiota of type 2 diabetes patients (Figure 6).

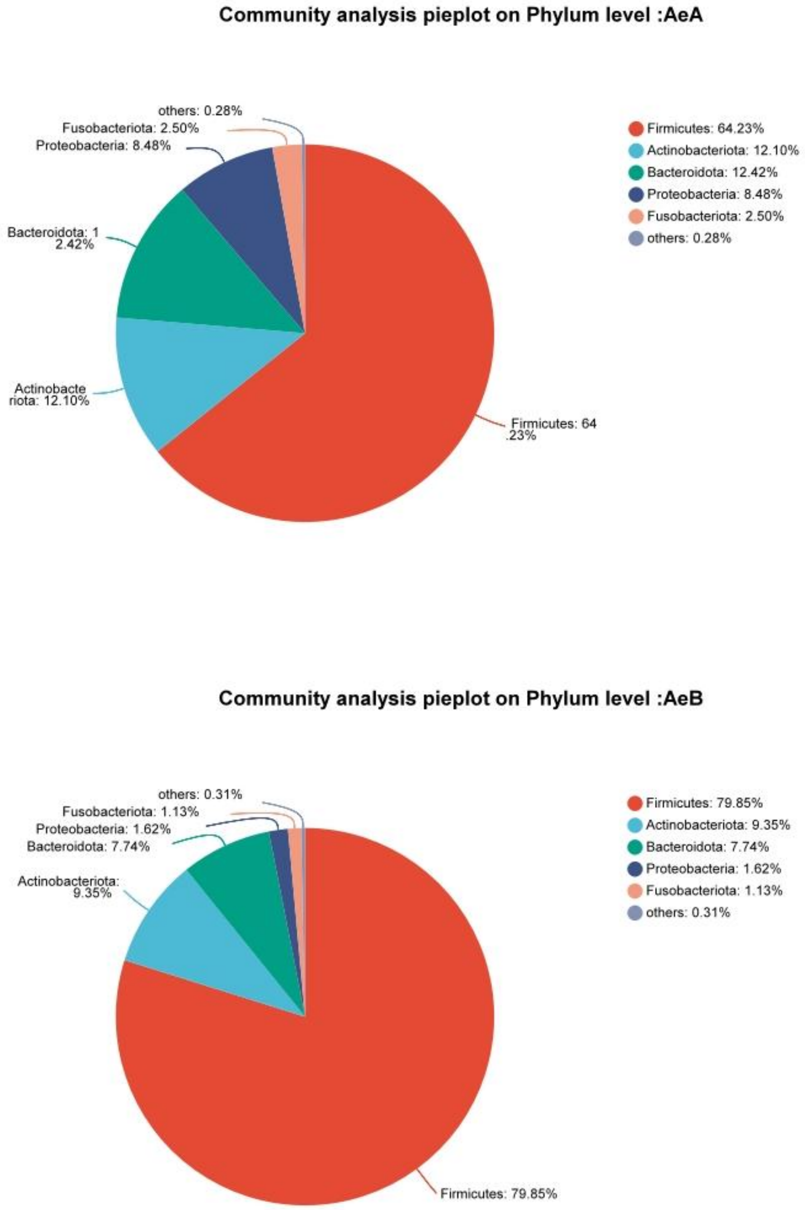

Figure 6. Comparison of relative abundance of intestinal flora in patients before and after aerobic combined resistance exercise intervention.

3.2.6. Significance Analysis of Differences in Gut Flora Before and After Aerobic Combined Resistance Exercise Intervention

The Wilcoxon signed-rank test results showed that after six weeks of combined aerobic and resistance exercise intervention, the relative abundance of Firmicutes in the gut microbiota of type 2 diabetes patients significantly increased ($P = 0.03$). Specifically, the abundance of Agathobacter, which belongs to the Firmicutes phylum, significantly increased. This increase is one of the reasons for the overall significant rise in the abundance of Firmicutes[54,55]. No significant changes were observed in the other phyla(Figure 7).

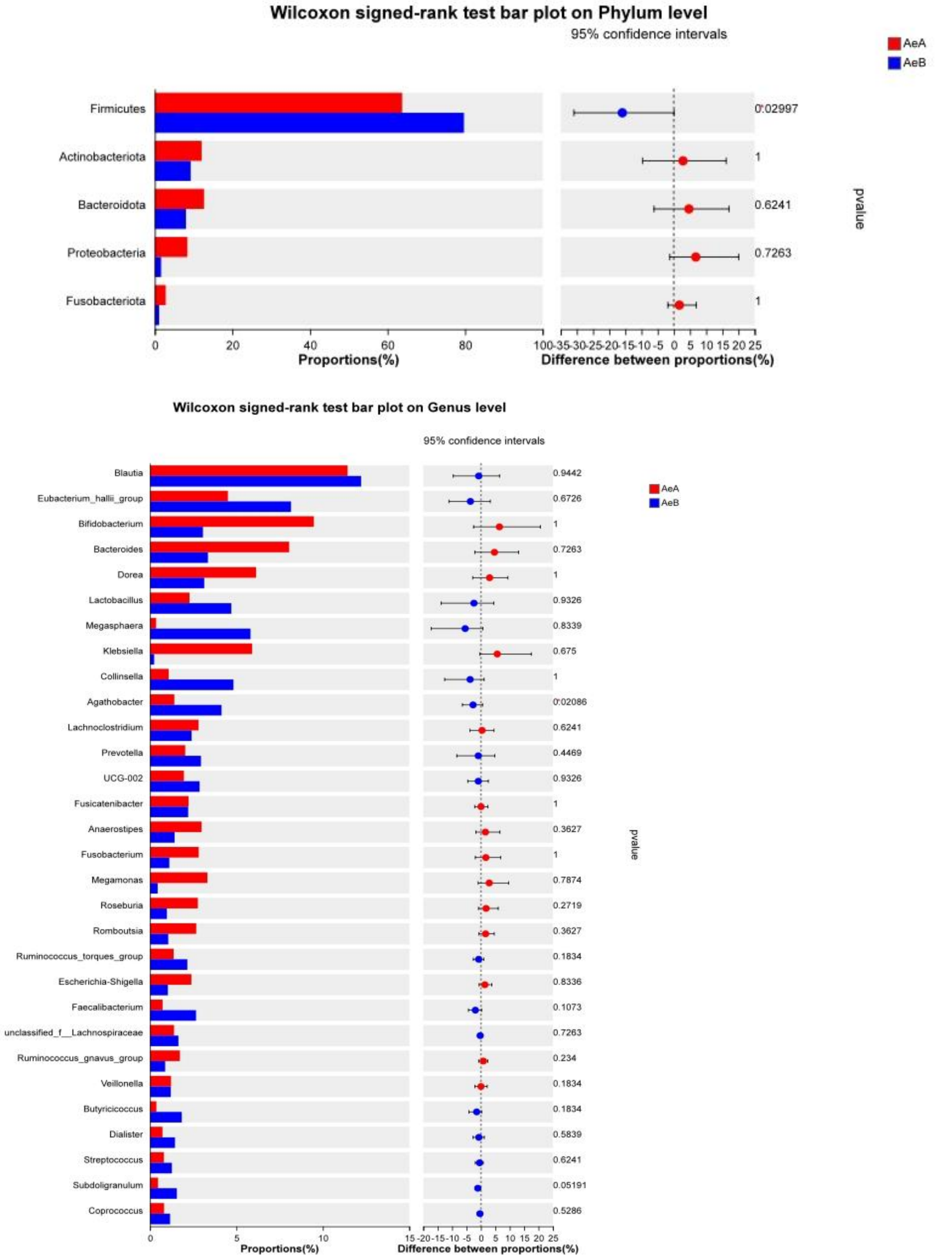

Figure 7. Significant changes in intestinal flora of patients before and after aerobic combined resistance exercise intervention.

The correlation heatmap was used to analyze the Pearson correlation coefficients between glucose metabolism indicators and gut microbiota in type 2 diabetes patients. The colors in the heatmap represent the strength of the correlation, with darker colors indicating stronger correlations and lighter colors indicating weaker correlations[56]. After six weeks of combined aerobic and resistance exercise intervention, the gut microbiota at the genus level exhibited a significant negative correlation with fasting insulin in Agathobacter ($\rho = -0.75$), Roseburia ($\rho = -0.58$), and Bacteroides ($\rho = -0.51$). In contrast, Dorea ($\rho = 0.52$) and Anaerostipes ($\rho = 0.47$) showed a significant positive correlation with fasting insulin. No significant correlations were observed between highly abundant genera and glycated serum protein. Furthermore, Holdemanella (ρ = 0.41), an unnamed genus in the *Ruminococcaceae* family (ρ = 0.59), and Blautia (ρ = 0.46) were significantly positively correlated with fasting blood glucose, while Lactobacillus (ρ = -0.50) exhibited a significant negative correlation with fasting blood glucose (Figure 8).

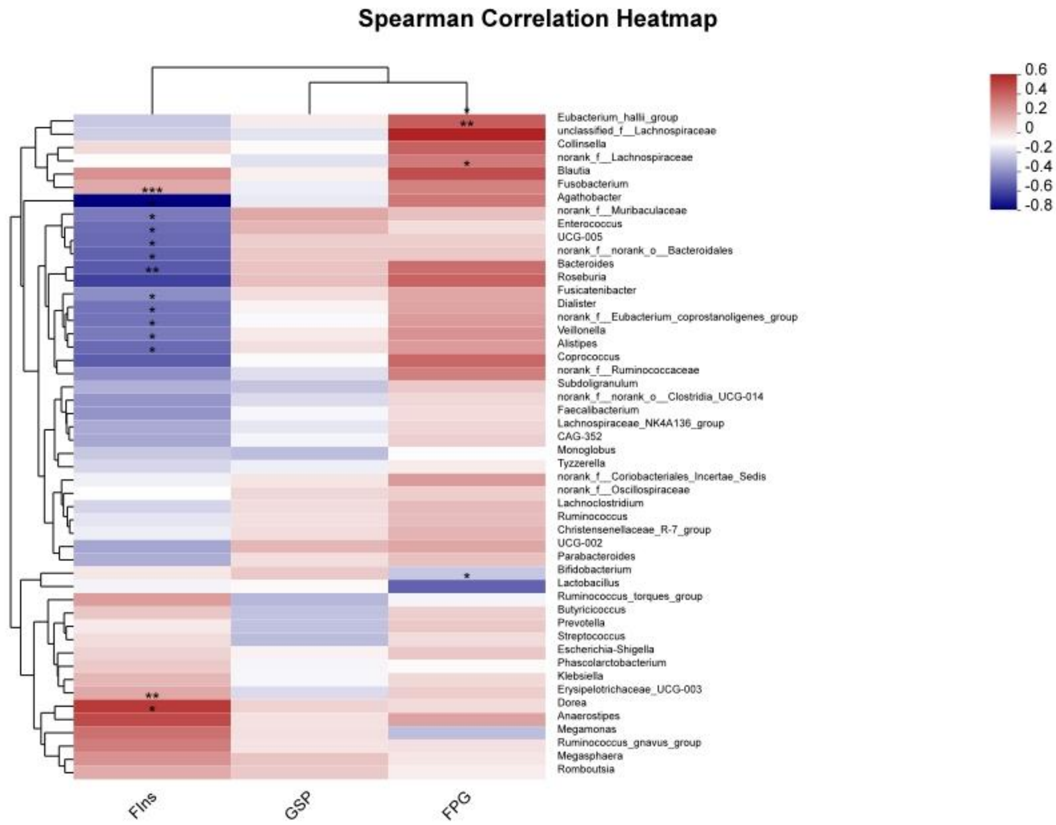

Figure 8. Heatmap of the correlation between gut flora and glucose metabolism before and after aerobic combined resistance exercise intervention.

4. Discussion

The study revealed that a 6-week aerobic and resistance exercise program significantly reduced glycated serum protein levels in individuals with type 2 diabetes mellitus. While fasting blood glucose levels showed no statistically significant change, a decreasing trend was observed. Similarly, fasting insulin levels did not show a marked difference but also exhibited a downward tendency. In terms of gut microbiota, there was no notable alteration in community diversity or richness, although both demonstrated a slight increasing trend. Conversely, the community coverage of intestinal flora significantly declined. The number of microbial strains increased, with a significant rise in the relative abundance of the Firmicutes phylum, whereas the relative abundance of Proteobacteria, Actinobacteria, Verrucomicrobia, and Clostridia decreased. Notably, Agathobacter abundance increased significantly post-intervention and was negatively correlated with the observed reduction in fasting insulin levels.

4.1. Effects of Aerobic Combined with Resistance Exercise on Glucose Metabolism in Patients with Type 2 Diabetes Mellitus

Glycated serum proteins (GSP) are ketoamine compounds resulting from the attachment of glucose to serum proteins. Due to their shorter half-life and faster turnover compared to glycated hemoglobin, GSP measurements provide insight into recent glycemic control in diabetic patients [57]. Our study observed a significant reduction in GSP levels among type 2 diabetes mellitus (T2DM) patients following six weeks of combined aerobic and resistance exercise. This aligns with findings from a randomized controlled trial involving 31 T2DM patients, which also reported a notable decrease in GSP levels after a similar intervention [58]. The six-week aerobic and resistance exercise intervention did not produce significant changes in fasting blood glucose levels, although a downward trend was evident. Previous research suggests that longer interventions may yield better outcomes, as 12 weeks of aerobic exercise significantly lowered fasting blood glucose levels in diabetic rats [59] and T2DM patients [60]. These findings imply that a six-week duration may be insufficient for substantial improvement in fasting glucose levels and that extending the intervention period could enhance efficacy. Similarly, the exercise intervention showed no significant effect on fasting insulin levels, despite a slight decreasing trend. Studies have demonstrated that a 12-week aerobic exercise program can significantly reduce fasting insulin levels in diabetic individuals [61]. Furthermore, resistance training has been found to outperform aerobic exercise in improving fasting insulin levels and insulin resistance [62,63]. This contrast suggests that longer, combined aerobic and resistance exercise regimens may be more effective in improving fasting insulin levels among T2DM patients.

4.2. Effect of Aerobic Combined with Resistance Exercise on the Alpha Diversity of Intestinal Flora in Patients with Type 2 Diabetes Mellitus

The precise mechanisms by which exercise influences gut microbiota remain unclear. Some studies suggest that metabolic disorders in T2DM can slow gastrointestinal peristalsis, leading to prolonged intestinal transit time [64]. It has been observed that shorter intestinal transit times promote the colonization of bacteria with faster replication rates, such as SCFA-producing microbes like *Ruminococcus* and *Bacteroides* spp., while being less favorable for other bacterial colonization [65]. Additionally, exercise may alter intestinal pH, with studies indicating that a decrease in pH supports the growth of beneficial bacteria such as *Lactobacillus* [66]. This evidence points to the potential role of exercise in modifying gut flora composition by regulating the intestinal environment, thereby promoting the colonization of probiotics and providing long-term health benefits.Microbiome diversity serves as an indicator of overall health, with higher microbial diversity positively correlated with better health outcomes. Visualization studies of gut flora have demonstrated this association [67]. Compared to healthy individuals, T2DM patients exhibit lower Alpha diversity in gut microbiota, with measures such as richness (Chao index), diversity (Simpson index), and evenness (Shannon index) significantly reduced [68,69]. This highlights the link between microbiome diversity and health.In the present study, a six-week intervention combining aerobic and resistance exercise in T2DM patients did not lead to significant changes in gut microbiota diversity or richness, though both showed an upward trend. However, a significant reduction in gut microbiota coverage was observed. These findings align with an eight-week study on mice with T2DM, where aerobic and resistance exercise significantly enhanced gut microbiota diversity [70], as well as a 12-week intervention in T2DM patients that yielded similar results [71]. Both studies, involving longer durations, suggest that extended periods of combined aerobic and resistance exercise may exert a more pronounced positive impact on gut microbiota diversity in T2DM patients.

4.3. Effect of Aerobic Combined with Resistance Exercise on the Number Composition of Intestinal Flora Species in Patients with Type 2 Diabetes Mellitus

In general, a higher abundance and evenness of gut microbiota are associated with greater stability in the gut microbiome structure [72]. In this study, a Venn diagram revealed that after six weeks of combined aerobic and resistance exercise in patients with type 2 diabetes, the number of gut microbiota species increased, suggesting improved microbiome stability. The relative abundance of Firmicutes significantly rose, while Bacteroidetes, Actinobacteria, Proteobacteria, and Fusobacteria showed decreased relative abundances.Similar findings have been reported in previous studies. For instance, a six-week physical exercise intervention in mice led to an increase in Firmicutes and a decrease in Bacteroidetes [73]. Additionally, a study on high-intensity training in wrestlers found a significant reduction in *Bifidobacterium breve*, a member of the Actinobacteria phylum [74]. Other research has shown that aerobic exercise can lower the abundance of Proteobacteria, Verrucomicrobia, Bacteroides, and *Faecalibacterium* in mice [75]. Furthermore, a 12-week exercise intervention in type 2 diabetes patients reduced Acidobacteria abundance across multiple taxonomic levels, including phylum, class, order, family, and genus [76].The findings of this study align with most of these previous studies, indicating that different types, intensities, and durations of exercise can have distinct effects on the relative abundance of gut microbiota in individuals with type 2 diabetes.

4.4. Analysis of the Correlation between Glucose Metabolism and Intestinal Flora in Patients with Type 2 Diabetes Mellitus Before and After Aerobic Combined resistance Exercise Intervention

Following the combined aerobic and resistance exercise intervention, the abundance of *Agathobacter* significantly increased and exhibited a negative correlation with fasting insulin levels. This finding suggests that such exercise can influence *Agathobacter* abundance, contributing to the regulation of fasting insulin and improved glucose metabolism in patients. Previous studies have reported that *Agathobacter* is more abundant in individuals with normal blood glucose levels compared to those with prediabetes, highlighting its enrichment in the normal glucose group [77].Moreover, *Agathobacter* has been negatively linked to several health conditions, including internal damp-heat syndrome [78], colorectal cancer [79], and psoriasis [80]. These observations imply that aerobic and resistance exercise interventions not only enhance *Agathobacter* abundance but may also help reduce the risk of these associated diseases, further underscoring the potential health benefits of such exercise regimens.

5. Conclusions

In conclusion, a 6-week intervention combining aerobic and resistance exercise showed a trend toward improved glycemic regulatory markers and an increase in gut microbiota diversity and abundance. Increased microbial species may contribute to improved gut microbiota stability in patients with type 2 diabetes. Notably, the significant increase in Agathobacter abundance was negatively correlated with fasting insulin levels, indicating a possible relationship between physical activity and glucose metabolism. However, the study used a pre-post design with no control group, so the observed changes could not be fully attributed to the intervention. Factors such as natural variation, external influences and spontaneous improvement may have influenced the results. The results of these studies indicate the potential benefits of exercise interventions, but these results need to be interpreted with caution. Future studies should prioritize the inclusion of a control group to establish a clearer causal relationship. In addition, rigorous randomized controlled trials (RCTs) with large sample sizes are needed to investigate the specific effects of different exercise types, intensities, and durations on glucose metabolism and gut microbiota composition. These studies would improve our understanding of the health status of people with type 2 diabetes and contribute to improving their health.

6. Shortcomings of the study and future perspectives

The strength of this study lies in the combination of aerobic and resistance exercise as an intervention to assess the effects on glucose metabolism and gut microbiota in patients with T2DM. The results of this study highlight improvements in both areas and provide valuable insights for future research. As an exploratory preliminary study, the primary objective of this study was to assess the initial effects and potential mechanisms of this intervention in patients with T2DM. The small sample size is consistent with the purpose of this study, which is to provide basic data and guide future large-scale studies. A before-and-after experimental design was chosen for this study to directly assess the combined effects of aerobic and resistance exercise, while also recognizing that the lack of a control group limited our ability to draw clear causal inferences. Nevertheless, this study has laid the groundwork for planning and evaluating the results of future randomized controlled trials (RCTs). Future studies will address these limitations and improve the generalizability and external validity of the findings by expanding the sample size, examining various forms of exercise intervention, and extending the exercise cycle. Inclusion of a control group in subsequent studies would further improve the accuracy of causal inferences and provide stronger evidence on the effectiveness of the intervention.

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Conflicts of Interest: Declare a conflict of interest or state “Author declares no conflict of interest”.

Appendix A：

Rating of Physical Perception Scale (RPE)

Rating of Physical Perception Scale (RPE Scale): a valid method of projecting the intensity of exercise load s using subjective sensations, which can be referred to the RPE to control the intensity of exercise.

Borg Scoring	Level of exertion for perception
6	Very, very light
7	
8	
9	very light

10	
11	light
12	
13	A little hard.
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

Note: Exercise intensity settings for aerobic exercise should be controlled for a self-perceived exertion rating in the range of 11-14 points.

Appendix B:

Basic Information Questionnaire for People with Type 2 Diabetes

Name: Age: Phone:

1. How long have you been diagnosed with type 2 diabetes mellitus (e.g., fasting blood glucose ≥7.0mmol/L on two consecutive occasions, blood glucose ≥11.1mmol/L at the time of glycemic load 2, or have been diagnosed at the hospital)?
O1 Not yet diagnosed O2 1 years or less O3 1-3 years O4 3-5 years O5 5 years or more

2. In the past month, the number of times you had unstable blood glucose (fasting blood glucose is not 6.1~7.0mmoVL, two hours after meal blood tree is not 7.2~8.8mmol/L) is:
O1 did not occur O2 1 O3 2 O4 3 and above O5 do not remember

3. Is your condition stabilized within one year without diabetic acute metabolic disorders (such as diabetic ketoacidosis, lactic acidosis, insulin overdose, etc.)?
O1 yes O2 no

4. Do you have serious chronic complications of diabetes?
Diabetic nephropathy O1 yes O2 no
Retinopathy O1 yes O2 no
Diabetic neuropathy O1 yes O2 no
Diabetic lower extremity vasculopathy O1 yes O2 no
Diabetic foot O1 yes O2 no

5. Do you also suffer from other chronic diseases?
O1 no O2 yes
Hypertension O1 yes O2 no
Coronary heart disease O1 yes O2 no

Stroke O1 yes O2 no
Hyperlipidemia O1 yes O2 no
Tumor O1 yes O2 no
Other (specify):

6. Do you have any bone and joint diseases (such as back and back, knee joints, acid joints, etc.) that are not suitable for exercise?
O1 no O2 yes

7. Do you control your blood sugar by injecting glucose-lowering drugs such as insulin/ or taking glucose-lowering drugs?
O1 No
O2 Yes (please continue to fill in multiple choice questions)
Current treatment: Oral hypoglycemic drugs No Yes (if yes, please select the type of oral drug)
①biguanides ②a-glucosidase inhibitors ③sulfonylureas glinides ④thiazolidinediones ⑤DPP-IV insulinNo Yes (if yes, please select insulin type)
Current therapy: short-acting insulin intermediate-acting insulin premixed insulin Rapid-acting insulin analogs Long-acting insulin analogs
Dose of insulin__/day
GLP-1:O1 no O2 yes Dose__/day
Apart from hypoglycemic drugs, are there any other medications that need to be taken for a long period of time?
O1No O2Yes (please specify the name of the medication and its effects):
____________.

8. How many cigarettes do you usually smoke in a week? (counting even one puff)
O1 Never smoked O2 1-10 cigarettes O3 11-20 cigarettes O4 21 and above

9. Have you consumed alcohol in the last month?
O1 No O2 Yes

10. How many days a week do you usually drink alcohol?
O 0 days O 1 days O 2 days O 3 days O 4 days O 5 days O 6 days O 7 days

11. Are you able to control your eating habits in line with the recommendations for diabetes?
O1 Yes O2 No

12. Is it possible to ensure that there are less than 2 absences during the experiment?
O1 yes O2 no

Appendix C:
IPAQ Short Questionnaire

1. In the last 7 days, how many days did you do strenuous physical activity? Such as lifting heavy objects, digging, aerobics or fast biking?
Per week__day.
□ No related sports activities → skip to question 3

2. How much time do you usually spend on strenuous physical activity on one of these days?
Daily _____ hours _____ minutes
□ The mouth does not know or is not sure

3. In the last 7 days, how many days have you done moderate physical activity, such as lifting light objects, bicycling at your usual speed, or playing double tennis? Please do not include walking.
Per week__day
□ No moderate physical activity → skip to question 5

4. How much time do you usually spend on moderate physical activity on one of these days? Every day _____ hours ____ minutes
□ don't know or aren't sure

5. How many days are walking and at least 10 minutes at a time?
Per week__day
□ No walking → skip to question 7

6. How much time do you usually spend on walking on one of these days?
Every day ____ hours ____ minutes
□ don't know or aren't sure

7. During the last seven days, how much time on weekdays did you spend sitting?
Every day ____ hours ____ minutes
□ don't know or aren't sure

Appendix D:
ACSM Exercise Risk Screening Expert Questionnaire

Check the appropriate box depending on the health of the individual

Step 1 Symptoms and signs
□ Exertional chest discomfort
□ Unexplained dyspnea
□ Vertigo, syncope, blackouts
□Ankle edema
□ Discomfort from a strong, rapid or irregular heartbeat □ Burning or "cramp-like" sensation in the lower extremities when walking short distances □ Known heart murmur

If any condition is checked in the Symptoms column, stop the questioning and the subject should be medically screened before starting or resuming exercise - the subject may also require medical supervision (using equipment and in the presence of a medical professional). If no symptoms are checked, continue with steps 2 and 3.

Step 2 Current Activities
Does the subject engage in planned, systematic physical activity at least 3 days/week, 30 min/day, moderate intensity - for at least 3 months - Yes□ No□

Step 3
Medical Condition
Whether the subject has had or is having an
□ Cardiac arrest
□ Cardiac surgery, cardiac catheterization, coronary angioplasty oral pacemaker, implantable cardiac defibrillator, arrhythmia
□ Cardiac dissociative membrane disease
□ Heart failure
□ Heart transplantation
□ Congenital heart disease
□ Diabetes mellitus
□ Kidney disease

Assessment of steps 2 and 3

If nothing in step 3 is checked, no medical screening is required.
If “Yes” is checked in Step 2 and any of the conditions in Step 3 are checked, subjects may continue low to moderate intensity exercise without medical screening, or medical screening is recommended for higher intensity exercise.
If “No” is checked in Step 2 and any of the conditions in Step 3 are checked, medical screening is recommended. Subjects may also require medical supervision (use of equipment and presence of a medical professional)

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