Effects of different aerobic exercise training on glycemia in patients with type 2 diabetes
A protocol for systematic review and meta analysis

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Abstract
Background: Type 2 diabetes is an emergent worldwide health crisis, and rates are growing globally. Aerobic exercise is an essential measure for patients with diabetes, which has the advantages of flexible time and low cost. Aerobic exercise is a popular method to reduce blood glucose. Due to the lack of randomized trials to compare the effects of various aerobic exercises, it is difficult to judge the relative efficacy. Therefore, we intend to conduct a network meta-analysis to evaluate these aerobic exercises.

Methods: According to the retrieval strategies, randomized controlled trials on different aerobic exercise training will be obtained from China National Knowledge Infrastructure, WanFang, SinoMed, PubMed, Web of Science, EMBASE, and Cochrane Library, regardless of publication date or language. Studies were screened based on inclusion and exclusion criteria, and the Cochrane risk bias assessment tool will be used to evaluate the quality of the literature. The network meta-analysis will be performed in Markov Chain Monte Carlo method and carried out with Stata14 and OpenBUGS software. Ultimately, the evidentiary grade for the results will be evaluated.

Results: Eighteen literatures with a total of 1134 patients were included for the meta-analysis. In glycemia assessment, Tennis (standard mean difference = 3.59, credible interval 1.52, 5.65), had significantly better effects than the named control group. Tennis (standard mean difference = 3.50, credible interval 1.05, 5.59), had significantly better effects than the named Taiji group.

Conclusion: All together, these results suggest that tennis may be the best way to improve blood glucose in patients with type 2 diabetes. This study may provide an excellent resource for future control glycemia and may also serve as a springboard for creative undertakings as yet unknown.

Abbreviations: A = normal activity, B = Baduanjin formation, C = walking at constant speed, D = Taijiquan, E = jogging, F = Taijiquan + Baduanjin, G = social dance, H = Tai Chi kneading ball, I = tennis, J = brisk walking + table tennis, RCTs = clinical randomized controlled trials, SMD = standard mean difference, SUCRA = surface under the cumulative ranking curve.

Keywords: aerobic exercise training, mesh meta-analysis, type 2 diabetes

1. Introduction

Type 2 diabetes is an emergent worldwide health crisis, and rates are growing globally.[1–3] More than 500 million people in 45 countries worldwide are effected by diabetes, in 2018. By 2045, an estimated 629 million people will have this lifelong chronic diseases.[5] It was estimated that 114 million adults were living with diabetes in 2017, which is expected to rise to 120 million by 2045 in china.[6] Type 2 diabetes mellitus (T2DM) increases the risk of cardiovascular disease, neuropathy, nephropathy, retinopathy, and microvascular complications. Moreover, it has been reported that the risk of heart disease among diabetic patients is 2- to 4-fold higher compared with normal subjects.[7]

In the word, disability caused by type 2 diabetes is increasing.[8] In 2017, diabetes has become the fourth leading cause of disability globally.[9] In addition, the economic burden of diabetes is also huge. The global cost of diabetes is $1.31 trillion, accounting for 1.8% of global GDP.[10] Therefore, fighting diabetes mellitus has become an urgent challenge.

T2DM is a metabolic disorder characterized by hyperglycemia and a chronic and progressive metabolic state characterized by hyperglycemia.[11] Insulin damage, insulin resistance in peripheral tissues, or a combination of the 2 are the most common
pathophysiological causes of T2DM. In addition, the plasma levels of adipokines and resistin in patients with type 2 diabetes may be increased, which may also increase impaired glucose tolerance and insulin resistance. The American Diabetes Association recommends 2 types of exercise mode for individuals with diabetes, which includes strengthening exercises and aerobic exercises. Aerobic exercise is the basis of the treatment of type 2 diabetes, and it is an indispensable part of the comprehensive treatment of type 2 diabetes.

Aerobic exercise refers to repeated and continuous exercise of large muscle groups, including walking, cycling, jogging, and swimming. The study found that regular aerobic exercise can not only reduce glycosylated hemoglobin, improve cardiopulmonary function, enhance lipid oxidation, increase aerobic fitness ability, promote liver glucose metabolism, but also reduce the mortality of diabetes. In addition, aerobic exercise also has economic benefits, simple, unrestricted, and other advantages.

Early aerobic exercise is very necessary for patients with type 2 diabetes. However, there are many types of aerobic exercise styles in T2DM, and little attention has been paid to the ranking of aerobic exercise effectiveness. Network meta-analysis (NMA) is a new method that employs Bayesian statistical theory. Although aerobic exercise, such as Taijiquan, jogging, and swimming, is generally believed to be beneficial to patients with type 2 diabetes, the above interventions are hardly measurable. To address this question, Bayesian NMA enables a comprehensive analysis through integrating all direct and indirect evidence to compare various interventions. In the mesh meta-analysis, the accuracy of effect estimation is improved than that of traditional meta-analysis, which allows the estimation of direct and indirect therapeutic effects. Therefore, the main purpose of this study is to find out the best aerobic exercise mode for patients with type 2 diabetes by summarizing and analyzing the existing evidence.

2. Methods
The literature search of the NMA is based on the expanded statement of preferred reporting items for systematic review and meta-analysis systematic evaluation report, including the NMA of health interventions. The retrieval strategy was formulated by 2 authors according to the research purpose. Without the limitation of year and language, a detailed search method of PubMed, Cochrane, and Web of Science was made by using medical subject words (mesh), text words, and Boolean logic operators Science, EMBASE, HowNet, Wanfang, etc. Taking PubMed as an example, the retrieval strategy is shown in Table 1. The retrieval time is from the database establishment to September 2020. The keywords are as follows: walking, brisk walking, jogging, swimming, cycling, Taijiquan, Baduanjin, etc. These terms use the operator “and” to combine with type 2 diabetes, noninsulin dependent diabetes, and T2DM.

2.1. Objectives and registration
This systematic review will aim to evaluate the effectiveness of aerobic exercise in reducing fasting blood glucose. Our protocol has been registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY). The registration number was INPLASY202130055 (DOI:10.37766/inplasy2021.3.0055).

2.2. Ethics and communication plan
Our article is a secondary study, which does not involve the recruitment of patients, data collection, and ethical considerations. We will publish the results of NMA in the form of journal papers or conference papers.

2.3. Qualification and exclusion criteria qualification criteria
Participants: adult patients with T2DM. The diagnostic criteria of T2DM were consistent with those of the American Diabetes Association or Chinese Diabetes Association. Interventions: participate in at least 1 aerobic exercise, such as walking, jogging, swimming, cycling, Taijiquan, Baduanjin. Comparison: routine life or other activities. Results: the main outcome was glycemia in patients with type 2 diabetes. Study design: randomized controlled trials (RCTs) were conducted in adults with T2DM. The exclusion criteria were as follows:
(1) animal experiments;
(2) non-RCTs, reviews or meta-analysis;

| Table 1 |
|---|
| Retrieval strategy of PubMed. |
| #1 |
| “Diabetes Mellitus, Type 2” [MeSH] OR “Diabetes Mellitus, Noninsulin-Dependent” [Title/Abstract] |
| OR “Diabetes Mellitus, Non Insulin Dependent” [Title/Abstract] |
| OR “Non-insulin-Dependent Diabetes Mellitus” [Title/Abstract] OR “Diabetes Mellitus, Type II” [Title/Abstract] |
| OR “Diabetes Mellitus, Noninsulin Dependent” [Title/Abstract] OR “Diabetes Mellitus, Maturity-Onset” [Title/Abstract] |
| OR “Diabetes Mellitus, Maturity Onset” [Title/Abstract] OR “Diabetes Mellitus, Slow-Onset” [Title/Abstract] |
| OR “Slowl-Onset Diabetes Mellitus” [Title/Abstract] OR “Type 2 Diabetes Mellitus” [Title/Abstract] |
| OR “Noninsulin-dependent Diabetes Mellitus” [Title/Abstract] OR “Type 2 Diabetes” [Title/Abstract] |
| OR “Noninsulin dependent Diabetes Mellitus” [Title/Abstract] OR “Maturity-Onset Diabetes” [Title/Abstract] |
| OR “Diabetes, Type 2” [Title/Abstract] OR “Diabetes Mellitus, Adult-Onset” [Title/Abstract] |
| OR “Adult-Onset Diabetes Mellitus” [Title/Abstract] OR “Diabetes Mellitus, Non Insulin Dependent” [Title/Abstract] |
| Training, Resistance” [Title/Abstract] OR “Walking” [Title/Abstract] OR “Ambulation” [Title/Abstract] |
| OR “Jogging” [Title/Abstract] OR “Bicycling” [Title/Abstract] OR “Taiji boxing” [Title/Abstract] |
| OR “Aerobic exercise” OR “Physical Activity” [Title/Abstract] |
| OR “Exercise, Isometric” OR “Exercise, Isometric” [Title/Abstract] OR “Exercise, Aerobic” [Title/Abstract] |
| OR “Aerobic Exercise” OR “Aerobic Exercises” [Title/Abstract] OR “Exercises, Aerobic” [Title/Abstract] |
| #2 |
| Randomized controlled trial [Title/Abstract] OR Controlled clinical trial [Title/Abstract]. |
| #3 |
| #1 AND #2 AND #3 |
(3) incomplete information in published articles, which only presented in abstract form;
(4) other forms of exercise other than aerobic exercise.

2.4. Study selection and data extraction
As shown in Figure 1, the study selection will be divided into 2 steps and completed by 2 researchers (Xianhuang Li and Liping Liu). According to the criteria of Cochrane,[23] an extraction table was established to extract information related to the study, including author information, study design, intervention measures, participant characteristics, outcome measurement, intervention duration, and other required information. If the data is not clear or there is objection to the data information, contact the author to verify and supplement the data. If there is any problem in the extraction process, the problem can be solved through consultation or consulting experts.

2.5. Deviation risk assessment
Two reviewers independently assessed and classified the included articles according to Cochrane Handbook,[26] and classified them according to the established criteria (Xianhuang Li, Liping Liu). Finally, the study was divided into high risk, low risk, and uncertainty according to the allocation concealment, whether the subjects and researchers were blind, and whether they were random. In case of any disagreement or disagreement between the 2 reviewers in the process of evaluation, the 2 reviewers shall negotiate or consult experts (Ying Li, Xianhuang Li).

2.6. Statistical analysis
Bayesian NMA can summarize a variety of treatment measures, thus allowing maximum flexibility to use complex models and produce relatively scientific explanations in terms of causality.[27] Bayesian NMA integrates direct evidence and indirect evidence into an interconnected network through prior distribution, so as to compare different aerobic exercise modes.

The network diagram serves as a simple summary description to reveal all available evidence for each treatment evidence.[20] The network diagram is generated by Stata 14.0 (Stata Corp, College Station, TX). As the presence of effect sizes refer to continuous outcome, standard mean differences (SMDs) were calculated for each comparison using group (relevant) means and standard deviations from individual studies.[28] We compared the clinical and methodological characteristics of all included studies in order to ensure sufficient similarity between different intervention comparisons, so as to provide effective indirect inference.[29]

In the Bayesian framework, the parameters are estimated by the restricted maximum likelihood method.[30] We use Bayesian random effect model to integrate direct and indirect estimation by forming a connection network and comparing different aerobic exercise modes. We also use multivariate meta-analysis method.

Figure 1. PRISMA flow chart. PRISMA = preferred reporting items for systematic review and meta-analysis.
| Inclusion study | Publication time (yr) | Sample size | Experimental group | Interventions | Control group | Intervention time | Outcome indicators |
|-----------------|-----------------------|-------------|--------------------|---------------|---------------|------------------|-------------------|
| Lin Qin         | 2016                  | 30          | 30                 | Brisk walking + table tennis: keep the heart rate between 120 and 140/min, exercise for about 1.5 h each time, that is, 30 min of walking, 1 h of table tennis practice, 4 times a week. | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 16 weeks (4 times a week) | ① |
| Qingwen Li      | 2016                  | 30          | 30                 | Baduanjin formation: Each time 45–50 min, 2 sets of continuous play, the interval between 5 min, including preparation activities and exercise after finishing activities, each 5 min, 5 times a week, by professional teachers to guide and lead the exercise to complete, for 12 consecutive weeks | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 12 weeks (3 times a week) | ①② |
| Yunchuan Wu     | 2015                  | 20          | 20                 | Walking at a constant speed: walk twice a day for 30 min at a pace of 80–100 times/min for more than 5 d a week, | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 3 months | ①② |
| Yuxiang Guan    | 2012                  | 40          | 40                 | Baduanjin: once a day, about 1 h each time | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 4 months | ①②③ |
| Zhibin Li       | 2012                  | 50 vs 43    | 44                 | Baduanjin: the exercise time was 30 min/group, and 1 group was completed every day Taijiquan: training time 30 min a day | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 9 months | ①②④⑥ |
| Yuanyaun Lian   | 2019                  | 39          | 40                 | Brisk walking: walk at a constant speed for 50–80 min every day and maintain the speed of 50–70 m/min. Once a day in the morning and once in the evening, at least 5 d a week | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 6 months | ①③ |
| Tongtong Gao    | 2019                  | 20 vs 30    | 10                 | Brisk walking: vigorous walking: about 30 min each time, that is, based on the average daily activity, 20% aerobic fast walking steps (60 m/min speed or above) were increased. The average speed of aerobic walking was 5000 steps/D in the first 2 wk, and 6000 steps/D during the test period. The steps were recorded with a pedometer once a week. Baduanjin: at least 4 times a week, take moderate intensity training at 10 a.m. or 1 h after dinner, about 30 min each time | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 12 weeks | ①④⑤⑥ |
| Lan Pu          | 2020                  | 20          | 29                 | Jogging: exercise time, 2 times/day, 30 min after lunch and dinner, jogging for 30–60 min. It is better to keep the heart rate within 100 beats/min and to exercise for more than 30 min | Routine activities (no exercise intervention and no other regular exercise activities during the period) | 3 months | ①⑤⑥ |
| Ping Wang       | 2009                  | 28          | 26                 | Taijiquan: equivalent to 50%–60% of the maximum oxygen uptake or 70%–80% of the maximum heart rate (HRmax) as the target | Social dance: exercise 5–7 times a week, lasting 30–50 min each time | 6 months | ①②④⑤ (continued) |
| Inclusion study       | Publication time (yr) | Sample size | Experimental group | Control group | Interventions                                                                                                                                  | Intervention time | Outcome indicators |
|----------------------|-----------------------|-------------|--------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------|
| Han Yang             | 2019                  | 56          | 56                 |               | Baduanjin: 2 times a day, lasting for 20 min each time, and persisting in exercise for more than 5 d a week, mainly low-intensity exercise. | 6 months          | ①②③               |
| Xiaobingli           | 2013                  | 30          | 30                 |               | Taijiqun: the setting of the bull’s-eye rate, more than 1 time more than 5 min                                                                 | 8 weeks           | ①③                 |
| Deliang Wei          | 2012                  | 26          | 26                 |               | Taijiqun: warm up for 5 min at 15:00–16:00 every day, Music practice 36 Taiji Softball for 40 min, and then relax for 15 min              | 12 weeks          | ①②                 |
| Weishan Xue          | 2012                  | 39          | 30                 |               | More than 15 min of target exercise, each time more than 60 min                                                                                | 4 months          | ①②                 |
| Chuying Zhang        | 2002                  | 42          | 40                 |               | Constant speed walking: 50–80 min, walk at a constant speed of 50–80 m/min every day, move joints for 5–10 min before exercise, relax for 5–10 min after exercise, control it at 50%–60% of the maximum aerobic exercise, and control the heart rate below 110 beats/min, twice a day | 6 months (5 times a week) | ①②③               |
| Danwen Wang          | 2017                  | 48          | 46                 |               | Taijiqun + Baduanjin: 3 times a week (after breakfast) Taijiqun fitness for 30 min, (1 h after dinner) Baduanjin fitness for 15 min. Practice 1–2 times in the morning and evening every day. The time should be consistent with the concentrated practice time, and each time should be more than 30 min. | 6 months          | ①②④               |
| Bin Li               | 2005                  | 23          | 22                 |               | Jogging: the total time of each time is 60 min, with the heart rate reaching 60% of the maximum heart rate as the standard, each cycle at least 10 min | 12 weeks (3 times a week) | ①②                 |

① Glycemia; ② postprandial blood glucose; ③ glycosylated hemoglobin; ④ triglyceride; ⑤ high density lipoprotein.
to compare. In order to simulate the accurate estimation of statistical patterns, 3 parallel Markov chains were initially established with randomly selected states. Each chain generates 50,000 iterations. Due to the aging period, the first 20,000 iterations are discarded to ensure the minimum deviation of the initial value when the chain reaches its target distribution. The surface under the cumulative ranking curve (SUCRA) is represented as a simple statistical cumulative ranking probability graph, which is used to rank each intervention. The higher the SUCRA value is, the greater the possibility of a specific treatment being at the top or high efficiency, while 0 is the treatment that is definitely the worst. We use the “node splitting” technology to explore whether there will be potential source inconsistency in our network. By comparing the direct evidence and indirect evidence from the whole network (P > 0.05 indicates consistency generation), subgroup analysis is conducted if there is inconsistency. The above analysis was performed using “STATA14” (64 bit version) and OPENBUGES.

3. Results

A total of 5973 records were obtained. The title and abstract screening revealed 205 potentially qualified articles, of which 987 were repetitive and 4986 covered unique RCTs. Based on the full-text examination, 157 records were preliminarily consistent with the study: 33 including inconsistent intervention measures, 55 research reports with inconsistent outcome indicators, 34 were not RCTs, 15 studies were missing data, and 20 studies did not determine the control group. Finally, only 16 articles were considered qualified and contributed to our final NMA. The studies, which consisted of 1134 participants, provided sufficient data from the database establishment year to 2020. The basic characteristics of the included literature are shown in Table 2.

We conducted a global model test and a local inconsistency test for the articles. The degree of inconsistency in all studies was very small (P > 0.005). Depending on the distribution of the funnel in this publication, the distribution of these points is symmetric.

As shown in Figure 2, conduct network diagram display and study the situation of each arm. Each process has its own unique node, and its size depends on the number of contributions they make to the entire network. We describe 16 comparisons in the type 2 diabetes group in the NMA. Baduanjin Exercise (n = 195) was the most frequent intervention, followed by constant speed walking (n = 99) and Taijiquan group (n = 99). Jogging group (n = 43), social dance group (n = 26), Taijiquan and Baduanjin group (n = 48), Taiji softball group (n = 26), tennis group (n = 30), vigorous walking and table tennis group (n = 30). Relative effect sizes of efficacy at postintervention according to NMA.

Considering the efficacy of each intervention from baseline to the end of it, Tennis group was statistically significant superior to Routine activities group and Tai ji quan group (SMD = 3.59, credible interval 1.52, 5.65, (SMD = 3.50, credible interval 1.05, 5.95). (shown in Fig. 3). A SUCRA line was drawn to rank the hierarchy of each aerobic exercise (shown in Fig. 4), which
indicated that Tennis got the highest probability (SUCRA = 98.4%) in reducing glycemia compared with the other 9 active interventions, although walking + table tennis (SUCRA = 87.3%) also got a remarkable ranking among the 10 treatments. Following by Taiji Soft ball (SUCRA = 63.5%), jogging SUCRA (60.5%), Baduanjin (SUCRA = 54.6%), Taijiquan + Ba duan jin (SUCRA = 36.4%), constant walking (SUCRA = 35.6%), Taijiquan (SUCRA = 17.0%), and routine activities (SUCRA = 10.5%) got an inferior ranking.

4. Discussion
Despite some progress in the diagnosis and treatment of diabetes, patients with type 2 diabetes remain a major public health burden worldwide. Exercise is an essential measure for patients with diabetes, which has the advantages of flexible time and low cost. In this study, we conducted a meta-analysis of RCTs published so far. The results obtained in the league table show that only tennis and Taijiquan are 3.50 (1.05, 5.95), tennis and regular activities are 3.59 (1.52, 5.65), only 2 groups of data have difference. Taijiquan belongs to low-intensity exercise, and its peak exercise intensity only reaches about 45% of the maximum heart rate, so the metabolism of glucose and lipid in physiological function is weak.[51] According to Colberg et al.[52] type 2 diabetic patients use the most blood glucose during moderate or above intensity exercise, and the energy supply of myoglycogen oxidation is relatively less, thus reducing the blood glucose of patients with type 2 diabetes. Tennis belongs to moderate intensity exercise. Its physiological energy supply is mainly supplied by glycogen and supplemented by fat. It is superior to Taijiquan and routine activities in reducing glycemia.

In our study, we reviewed the effects of different aerobic exercise interventions on blood glucose in patients with type 2 diabetes. SUCRA analysis showed that tennis (98.4%) was the most effective intervention to reduce glycemia in patients with type 2 diabetes, followed by vigorous walking + table tennis (87.3%), Taiji soft ball (63.5%), jogging (60.5%), Baduanjin (54.6%), Taijiquan + Baduanjin (36.4%), social dance (36.3%), constant walking (35.6%), Taijiquan (17.0%), and routine activities (10.5%). Our research results are different from those of Ye Xinxin.[53] In our research results, tennis is the best exercise measure to reduce glycemia in patients with type 2 diabetes, and tennis exercise mainly relies on muscle contraction and relaxation. Muscle contraction and relaxation can improve the tissue demand for sugar and improve the level of glucose metabolism. Long time exercise can not only promote the decomposition of glycosylated hemoglobin, but also improve the oxygen carrying level of blood, providing a good basis for the utilization of sugar.[54] Brisk walking + table tennis cloud sports is only tennis, walking belongs to the lower limb movement, table tennis belongs to the upper limb movement, the combination of the 2 can achieve the whole body balanced movement.[57] Long...
time but monotonous exercise can shorten the exercise time. Walking and table tennis are the combination of 2 aerobic exercises, which can avoid such defects and increase the exercise time.

To sum up, our network meta analysis shows that tennis is the best exercise intervention for patients with type 2 diabetes, while routine activities (without regular activities) are the least effective intervention. Our study may provide strong evidence to show which exercise intervention is the best intervention to reduce blood glucose in patients with type 2 diabetes. However, our study is limited, which makes it difficult to draw conclusions from our NMA.

5. Limitations

In view of the following limitations, we should carefully explain this study. First, this study contains a limited number of experiments. First, there are only a few RCT studies on tennis, brisk walking, brisk walking, and table tennis in the literature. Second, for diabetes, other outcome indicators are less involved. Third, the quality of several studies, such as lack of blindness in subject participation, personnel or external evaluators, or not using randomized grouping, may threaten the effectiveness of our study. For various reasons, so many aerobic exercise measures are not the result of RCTs, so the evidence based on aerobic exercise is limited, which makes it difficult to draw conclusions from our NMA.

Author contributions

Conceptualization: Ying Li, Runmin Li, Dongying Li. Data curation: Ying Li, Xinhuan Li, Liping Liu. Formal analysis: Ying Li and Runmin Li. Methodology: Dongying Li and Jianting Zhu. Software: Runmin Li, Liping Liu, Jianting Zhu. Supervision: Dongying Li, Xinhuan Li. Writing – original draft: Ying Li and Runmin Li. Writing – review & editing: Dongying Li.

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