

Effect of acupuncture on insulin signalling pathway and mitochondrial AMPK pathway in animal model of type 2 diabetes mellitus: A systematic evaluation and meta-analysis

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Luo, F¹; Chen, HH²; Feng, JJ³; Li, ZX⁴; Ye, JN⁵; Su, CG⁶; Zhang, FR⁷; Zhu, J⁸.**Corresponding author:**

Zhu Jun

zhujuntcm@163.com

Author Affiliation:

Chengdu university of traditional Chinese medicine.

ADMINISTRATIVE INFORMATION**Support** - Natural Science Foundation of Sichuan Province (22NSFSC0166); Project of Sichuan Provincial Science and Technology Department (2023YFS0323).**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2023110086**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 November 2023 and was last updated on 22 November 2023.**INTRODUCTION**

Review question / Objective Participant type (P): all animal studies on T2DM were considered irrespective of species, sex, age in months or model method, site of sampling, criteria for modelling success (fasting glucose \geq 7.0 mmol/ml, postprandial glucose \geq 11.1 mmol/ml, or \geq 11.1 mmol/L after two hours of the OGTT [20]), provided that measurements were made of insulin signalling pathway factors (the main purpose of which is to regulate the insulin signalling pathway) and mitochondrial AMPK signalling pathway factors. Non-animal type 2 diabetes studies were excluded.

Intervention type (I): the intervention group was treated with acupuncture for T2DM, and there were no restrictions on the method of intervention, duration of intervention, duration of intervention sessions, or site of needling. If there were multiple

acupuncture groups, the group with high stimulation intensity and significant reduction in blood glucose values was selected for analysis. .

Comparison type (C): the model group was modelled only, without any treatment.

Outcome type (O):(1) Main outcome markers: glycemic indexes (including random blood glucose (FBG), postprandial blood glucose (PBG), and oral glucose tolerance (OGTT)); insulin indexes (including serum insulin (INS), insulin sensitivity index (ISI), and insulin resistance index (HOMA-IR)); and factors of insulin signalling pathway (including IRS-1, P-IRS-1, IRS-1 mRNA, IRS-2, GLUT 4, GLUT 4 mRNA, PI3K, AKT, p-AKT) and cytokines of the AMPK pathway (including AMPK, P-AMPK, SIRT1, PGC-1 α , NRF1, TFAM) and; (2) secondary outcome indices: body weight, water intake, urine intake, food intake; Lipid factors (including TC, TG, LDL-C, HDL, FFA, HDL-C). No restriction on the site of testing.

Study type (S): randomised controlled trials of all acupuncture interventions in T2DM animal trials. Clinical studies, systematic evaluations, conference reports, and scientific and technical results were excluded. No restriction on country and language to ensure comprehensiveness of the study.

Condition being studied Type 2 diabetes mellitus (T2DM) has become one of the most serious and fastest-growing diseases of the 21st century, with persistent chronic hyperglycaemia and severe complications leading to reduced quality of life. The World Health Organisation predicts that there will be 439 million people with diabetes globally in 2030, placing a huge burden on the world economy.

METHODS

Participant or population Animal model of type 2 diabetes mellitus.

Intervention Only acupuncture and moxibustion.

Comparator The type 2 diabetes mellitus model group was modelled only without any treatment.

Study designs to be included All study of acupuncture on insulin signalling pathway and mitochondrial AMPK pathway in animal model of type 2 diabetes mellitus.

Eligibility criteria Studies in which non-acupuncture interventions or acupuncture was not the primary intervention were excluded.

Information sources Pubmed, Scopus, Embase, Cochrane Library, Web of Science (include Ovide Medline), Wan Fang, CNKI and VIP.

Main outcome(s) Fasting blood glucose, postprandial blood glucose, area of decline in oral glucose tolerance, serum insulin, insulin sensitivity index, insulin resistance index; factors of the insulin signalling pathway (including IRS-1, P-IRS-1, IRS-1 mRNA, IRS-2, GLUT 4, GLUT 4 mRNA, PI3K, AKT, p-AKT) and cytokines of the AMPK pathway (including AMPK, P-AMPK, SIRT1, PGC-1 α , NRF1, TFAM) were extracted from the literature included in the study.

Quality assessment / Risk of bias analysis Quality assessment: Modified from the 10 entries in the Collaborative Methods for the Analysis and

Review of Experimental Research Animal Data (CAMARADES) checklist, with a total score of 10. Risk of bias analysis: We included data on the difference in FBG before and after acupuncture in the study, and applied the Begg test and Egger test to measure the publication bias of the study, and when the result was $P < 0.05$, it indicated that the study might have a publication bias.

Strategy of data synthesis Meta-analysis was performed using RevMan 5.4 and Stata 17.0. All data were continuous variables and standard deviation \pm mean ($X \pm SD$) was used as an indicator of effect size, and the confidence interval CI for all tests was 95%, when $P < 0.05$ was considered statistically significant.

Subgroup analysis Data such as body weight and water intake differed between mice and rats, and data such as blood glucose, lipids, and insulin differed between transgenic and non-transgenic animal models; therefore, all subgroup analyses were performed to avoid excessive heterogeneity.

Sensitivity analysis Sensitivity analysis Firstly, RevMan was used to exclude data one by one to look for studies with excessive risk of bias, if the difference in I^2 was large after exclusion of a study, the reasons for its excessive heterogeneity were discussed individually, and if there was no change in I^2 then Stata was used to carry out a sensitivity analysis Sensitivity analysis was carried out to assess the stability of the results.

Country(ies) involved China.

Keywords type 2 diabetes mellitus, acupuncture, animal models, IRS-1, AMPK pathway, mitochondria pathways, meta-analysis.

Contributions of each author

Author 1 - Luo Fang.
 Author 2 - Chen han-han.
 Author 3 - Feng Jun-Jie.
 Author 4 - Li Zhuo-Xuan.
 Author 5 - Ye Jiang-Nan.
 Author 6 - Su Cheng-Guo.
 Author 7 - Zhang Fu-Rong.
 Author 8 - Zhu Jun.