Zhang et al. Diabetology & Metabolic Syndrome (2024) 16:255
https://doi.org/10.1186/s13098-024-01489-4

Diabetology & Metabolic Syndrome

RESEARCH

Open Access

Acupuncture-assisted lifestyle intervention improve the metabolic status and spontaneous brain activity of type 2 diabetes Mellitus patients: a randomized, clinical trial

Zhitian Zhang[1†], Kaixuan Bao[2†], Jiaojiao Liu[1†], Chunfei Jiang[3], Chunyan Ji[4], Jiawei Han[2,5], Guo Zhou[2], Xiaoyu Liu[6], Tiemin Liu[1,2,7,8,9], Jian Gao[4*], Xiangyu Wang[3,10*] and Hongmei Yan[1,11,12*]

Abstract

Background Aggressive weight management in patients with type 2 diabetes mellitus has demonstrated numerous metabolic advantages, however, existing therapies for weight control have not reached satisfactory results. This study aimed to evaluate the efficacy and safety of acupuncture in the weight management of type 2 diabetes mellitus (T2DM) patients by using a randomized, sham-controlled clinical trial design.

Methods In this single-blind randomized clinical trial, 102 overweight adult T2DM patients were randomized into two groups. The control group receives diet, exercise, and sham acupuncture intervention, whereas the acupuncture group receives diet and exercise and acupuncture intervention, both for 1 month. Body weight and other anthropometric and laboratory indices were assessed at baseline and endpoint, meanwhile, the body fat content and spontaneous brain activity were measured by functional magnetic resonance imaging(fMRI)as the exploratory outcomes.

Results No significant difference was observed between the studied parameters at the baseline. The body weight and BMI were significantly reduced both in the control and acupuncture groups after intervention, without statistical

†Zhitian Zhang, Kaixuan Bao and Jiaojiao Liu contributed equally to this work.

†Hongmei Yan, Xiangyu Wang, and Jian Gao should be considered the joint senior author.

*Correspondence:
Jian Gao
gao.jian@zs-hospital.sh.cn
Xiangyu Wang
wang.xiangyu@zs-hospital.sh.cn
Hongmei Yan
yan.hongmei@zs-hospital.sh.cn

Full list of author information is available at the end of the article

difference between the two groups. What's interesting is that compared to the control, the acupuncture group displayed a greater improvement in central fat tissue. It notes that the acupuncture group achieved significant liver fat content reduction than the sham acupuncture group. At the same time, the spontaneous brain activity in the occipital lobe and parietal lobe significantly increased in the acupuncture group.

Conclusion One month of acupuncture treatment preferentially improved ectopic fat deposition and was accompanied by changes in brain activity compared with the control group, even before significant changes in total body weight had occurred. further studies of longer duration are necessary for validation.

Trial registration : The protocol of this clinical trial is registered at the Acupuncture-Moxibustion Clinical Trial Registry (AMCTR, http://www.acmctr.org/, No. AMCTR-IOR-20000341).

Keywords Acupuncture, Overweight, Obesity, Liver Fat Content, Functional magnetic resonance imaging (fMRI)

Background

Epidemiological studies indicate consistent increases in the prevalence of diabetes worldwide. According to the International Diabetes Federation, around 536.6 million people have diabetes mellitus [1], and this number is projected to be 783.2 million by 2045 [2]. At the same time, the obesity rate has increased rapidly in the past nearly 50 years, by 2016, over 9.6 hundred million (~39%) adults were overweight or obese [3]. The co-prevalence and additional abundant studies indicate the strong links between diabetes and obesity. Existing theory hypothesized that the accumulation of lipids in the liver and other ectopic sites leads to insulin resistance and insulin secretion deficiency, thereby resulting in high blood glucose [4]. Clinical and pathophysiological studies provide pieces of evidence that weight loss, especially the reduction of ectopic fat normalizes blood glucose levels [5], which indicates that remission of type 2 diabetes mellitus (T2DM) can be achieved via weight management.

The fundamental cause of being overweight is the imbalance between the consumption and expenditure of calories. It's thought interactions of genetic predisposition, lifestyle, and environmental factors contribute to the disorder in energy metabolism, but the potential mechanisms underlying obesity remain unclear [6]. Currently, dietary restriction, physical exercise, chemical agents, and bariatric surgery are applied as conventional therapies to treat obesity [7], in which, lifestyle modification is often the first line of treatment for obesity, but also followed by minimal resultant weight loss [8]. The potential gastrointestinal adverse side effects and invasiveness greatly limit the use of anti-obesity drugs and surgery, respectively [9, 10]. Thus, alternative therapies are urgently needed to improve metabolism balance and weight management.

Existing studies indicate that acupuncture, a crucial medical therapy of traditional Chinese medicine, is efficacious in weight management [11, 12]. Referred obese individuals often experience side effects such as lean mass loss and weight regain after discontinuing exercise following lifestyle modifications [13, 14], the combination of lifestyle modification and acupuncture may be more helpful than any one approach in isolation [15, 16]. Previous systematic reviews have illustrated the positive effect of combined acupuncture on weight management [17, 18]. However, the conclusion should be interpreted with caution due to the high heterogeneity of the included trials, especially, since a large part of the trials were conducted with female volunteers and part of them did not strictly set the control group, which could lead to the overestimation of the acupuncture effect due to placebo effect [19].

To validate the effectiveness and safety of the combination of acupuncture, exercise, and calorie restriction (CR) in improving the metabolic status of T2DM patients, we conducted this randomized clinical trial using a combination of sham acupuncture, exercise, and CR as a control. Furthermore, referring to the evidence that the experimental mechanism of acupuncture on obesity focuses on central nervous systems [20, 21] and adipose tissue [22, 23], the alterations in spontaneous brain activity are assessed using resting-state functional magnetic resonance imaging (rs-fMRI), meanwhile, bioelectrical impedance analysis and magnetic resonance imaging derived proton-density-fat-fraction (MRI-PDFF) were performed to analysis peripheral adipose tissue content. These advanced techniques promise to provide more evidence of the potential mechanisms involved.

Materials and methods

Study design

This trial is registered in Acupuncture-Moxibustion Clinical Trial Registry, (AMCTR, http://www.acmctr.org/, No. AMCTR-IOR-20000341). It follows the principles of the Declaration of Helsinki and the Good Clinical Practice Guideline. This study was reported following the Consolidated Standards of Reporting Trials (CONSORT) [24] and STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [25] reporting guidelines. It has been reviewed and approved by the medical ethical committee of Zhongshan Hospital, Fudan University (Approved No. B2019-310R). Before randomization, all participants were requested to sign a written informed consent to decide whether they were willing to participate in this trial. They were informed of the details of the study and all the benefits and risks of participating in this trial.

Participants

All participants were diagnosed with T2DM, and referred by a doctor. Diagnosis of the T2DM was performed as presenting 1 or more of the following: (1) fasting plasma glucose (FPG) ≥ 7.0 mmol/L, (2) 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L, (3) random plasma glucose ≥ 11.1 mmol/L. Referring to the Guidelines for Prevention and Control of Overweight and Obesity in Chinese Adults [26], overweight or obesity was defined as body mass index (BMI) ≥ 24 kg/m^2 or ≥ 28 kg/m^2. Other inclusion criteria were age, from 18 to 70 years old, and voluntary informed consent. The exclusion criteria included pregnancy and lactation; long-term courses of hormone drugs or weight loss supplements, severe organic diseases, such as advanced tumor, cardiac, hepatic, renal, or mental diseases; and unfit to receive treatment of acupuncture. After eligibility, informed consent was obtained from the participants and then confirmed.

The sample size calculation was based on the primary outcome. According to our pilot study, the mean reduction of body weight by a combination of exercise and acupuncture was 4.2 kg, with a standard deviation (SD) of 1.5 kg. To yield an 80%-statistical power with a two-sided significance level of 0.05, 36 participants per group were needed. Furthermore, assuming a dropout rate of 10%, meanwhile, referring to the requirement from higher authority (every group contains ≥ 50 participants), a total of 120 participants were determined.

Randomization and blindings

Qualified participants were randomly assigned by a computer-generated list to the acupuncture or control (sham acupuncture) group according to a ratio of 1:1. An independent mathematician used R 4.0 to generate a randomized sequence according to the order of participant enrollment, and a third party concealed the allocation sequence in sealed opaque envelopes. The acupuncturist will be made aware of group assignments prior to treatment. Throughout the study, participants, data collection staff, and data analysts will remain blinded to the treatment assignments. Additionally, participants will receive their treatments in separate rooms or at different times to prevent communication between them, and the acupuncturist will not disclose any information about the treatment programs to the participants. In the data summary stage, the three separation principles of researcher, operator, and statistician will be implemented. The control group followed a CR diet and engaged in exercise and sham acupuncture, while the acupuncture group received the diet guideline and engaged in exercise and acupuncture interventions.

Intervention

Diet protocol

The CR intervention was designed to reduce body weight via decreasing dietary consumption, meanwhile improving eating habits. All participants were prescribed a balanced diet that provided an energy deficit of 500 kcal per day, with a macronutrient distribution within the range of 45–60 energy percent (E%) carbohydrate, 15–20 E% protein, and 20–35 E% fat (<7 E% saturated fat). The dietitian would provide individualized recommendations and recipes based on the qualitative evaluation of food diaries daily.

Exercise protocol

The exercise intervention was designed to increase energy expenditure and reduce lean mass loss to improve body composition via combining aerobic and resistance exercises [27, 28]. All participants take exercise five times weekly, including three times aerobic and two times resistance exercise. The exercise was approximately 30–40 min, followed by a sequence of static stretching exercises (~ 20 min) designed to improve flexibility. The types of aerobic exercise included brisk walking, jogging, cycling, swimming, and Taiji. The resistance training consists of a sequence exercise for upper-extremity and lower-extremity exercises, including shoulder presses, push-ups, dumbbell front raise, plank, squats, and glute bridge. Participants exercised at approximately 65% of their peak heart rate, which was gradually increased to 70 to 85% to reach the criteria of moderate-intensity exercise. The exercise is conducted under the distance instruction and supervision of a fitness instructor.

Acupuncture protocol

According to the theory of channels of Traditional Chinese Medicine, the following acupoints of Foot Yang Ming stomach channel were chosen refer to previous systematic reviews and consultations with specialists [23, 29]: Renying (ST9, level with the tip of and 1.5 cun lateral to the laryngeal prominence), Shuitu (ST10, 1 cun down from ST9, on the anterior border of sternocleidomastoideus muscle), Liangmen (ST21, 4 cun above the midline of the umbilicus, 2 cun lateral to the anterior midline of the abdomen), Tianshu (ST25, 2 cun lateral to the midline of the umbilicus), Guilai (ST29, 4 cun below the midline of the umbilicus, 2 cun lateral to the anterior midline of the abdomen), Zusanli (ST36, 3 cun below the lateral depression of patellar ligament, one finger width lateral from the anterior crest of the tibia), Fenglung (ST40, 8 cun superior to the tip of the external malleolus, two finger width lateral from the anterior crest of the tibia), Neiting (ST44, Proximal to the web margin between the 2nd and 3rd toes, at the junction posterior to the toe web of the red and white skin).

The acupuncture was completed by a professional acupuncturist with a Chinese medicine practitioner license from the Ministry of Health of the People's Republic of China. In the authentic acupuncture group, each point was penetrated with disposable acupuncture needles (45 mm in length and 0.3 mm in diameter, Suzhou Medical Appliance Factory, Jiangsu Province, China) approximately 30 to 40 mm into the skin. The needles in ST25, ST29, ST36, and ST40 were connected to an electro-stimulator (G6805-2 A, Shanghai Huayi Medicinal Instruments Co., Ltd, Shanghai, China), producing electrical stimulation with a continuous 1 Hz wave for 10 min. In the sham acupuncture group, the needles were penetrated only 2–3 mm into the skin, and the needles in ST25, ST29, ST36, and ST40 were connected to the electro-stimulator without electrical stimulation. The needles were left for 30 min. The procedure was carried out once every 2 days, 15 times in total.

Outcomes measurement

Primary outcome measure

The primary outcome was the change in body weight after treatment.

Secondary outcome measure

Secondary outcomes included the change in BMI, waist-to-hip ratio (WHR), FPG, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and body fat content. The complete body measurements and scheduled laboratory tests were conducted before and after the intervention.

rs-fMRI outcome measures

The MRI experiment was performed using a 3.0 Tesla MR device (Discovery MR750, GE Healthcare, Wisconsin, USA), which is equipped with an 8-channel phased array head coil. The rs-fMRI data were acquired using an echo-planner imaging sequence with the following parameters: repetition time (TR) = 986 ms; echo time (TE) = 30 ms; flip angle (FA) = 52°; voxel size = 2.2 × 2.2 mm; field of view (FOV) = 220 × 220 mm^2; slice thickness = 2.5 mm, 78 axial slice. Subsequently, high-resolution 3-Dimensional T1-weighted images were acquired using a whole-brain sagittal spoiled gradient echo (TR = 8.26 ms; TE = 3.24 ms; FA = 8°; voxel size = 0.8 × 0.8 × 0.8 mm; FOV = 256 × 256 mm, and 256 sagittal slices). During the MRI scan, participants were instructed to close their eyes but to remain awake.

MRI-PDFF outcome measures

The acquisition was performed during a single breath-hold of 21 s. PDFF, and water fraction, were acquired automatically via iterative decomposition of water and fat with echo asymmetry and least squares estimation quantification. The parameters were listed as follows: TR = 6.4 ms, TE = Min Full, FA = 3°, matrix size = 160 × 160; FOV = 35 × 24 cm; bandwidth = 111.11 kHz, 24 axial slices with 10 mm slice gap. Quantitative analysis of PDFF was completed by a senior radiologist blinded to the subjects' information. For the quantification of fat content, three regions of interest (ROI) with 150 mm^2 in the area were placed at different locations in every interested organ, including the liver, pancreas, and psoas, avoiding the adjacent structures and the main vessel, and the average of the three ROIs was considered as the result of MRI-PDFF.

Data and statistical analysis

MRI data analysis

The MRI data were pre-processed using the DPABI toolbox v8.0 (www.rfmri.org) on the Matlab R2019a platform. This process mainly contained 6 steps: (1) DICOM format conversion, (2) removing the first ten scan volumes, (3) section timing correction, (4) correction of head movement, (5) spatial standardization, and (6) spatial smoothing. The images were spatially normalized into the standard Montreal Neurological Institute (MNI) template with a resampling voxel size of 3 × 3 × 3 mm^3. Temporal bandpass filtrating (0.01–0.1 Hz) was performed to reduce the effect of low-frequency drifts and high-frequency noise.

Analysis of fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo) analysis was performed using the DPARSF software in the DPABI toolbox. After spatial standardization, the linear tendency of the preprocessed data was removed by the linear regression method. To obtain individual fALFF values, the fast Fourier transform of each voxel signal of the time series in the whole brain image was performed and converted into the square root of the frequency domain power spectrum. In this study, fALFF was obtained as the division of the average square root of the power spectrum at each voxel across 0.01–0.1 Hz by the whole frequency range observed in the signal. Individual ReHo maps were generated by calculating Kendall's coefficient of concordance (KCC) of the time series of every 27 neighboring voxels. Then the ReHo value was divided by the global mean KCC value in each subject for further statistical analysis. 2 × 2 repeated-measures ANOVA analysis of variance with intervention (control versus acupuncture) and time point (baseline versus follow-up) was performed to assess between-group differently of rs-fMRI activity. The regions with significant changes in the fALFF and ReHo values were considered as uncorrected $p < 0.005$ with cluster-extent ≥ 10 voxels.

Clinical data analysis

All clinical statistical analyses were performed in R 4.0. The primary outcome, change in body weight, was evaluated by repeated-measures analysis of variance. Baseline differences between groups and other outcome variables were assessed by Student's *t*-test, Mann–Whitney U-test, or Chi-square test according to the data characteristics. The paired *t*-test between before and after interventions was performed with a paired samples *t*-test or Wilcoxon signed-rank test. Data were presented in mean values with an SD or as a number with a percentage. Significance was defined as a two-tailed value of 0.05.

Results

Baseline characteristics

From November 2020 to December 2022, 118 eligible individuals were recruited and randomized. Finally, 102 participants completed the intervention. The reasons for withdrawal included time conflict ($n=6$), travel ($n=3$), undesired efficacy ($n=1$), and Covid-19 ($n=6$). Figure 1 presents the participant flowchart. The baseline characteristics of the included participants are presented in Table 1. No significant difference between the two groups.

Changes in body weight and blood glucose

As shown in Table 1, five weeks of treatment reduced 0.89 ± 1.94 kg ($p=0.003$) body weight of the acupuncture group, while it was 1.03 kg ± 1.79 kg ($p<0.001$) in the sham control. Similarly, the mean reduction of BMI after treatment is 0.31 ± 0.71 kg/m^2 ($p=0.008$) and 0.4 ± 0.64 kg/m^2 ($p<0.001$) in the acupuncture and sham acupuncture groups, respectively. However, there is neither significance on reduction of body weight ($p=0.763$) or BMI ($p=0.558$) between acupuncture and sham acupuncture groups. In blood glucose, the fasting plasma blood glucose significantly reduces both in the acupuncture (-0.44 ± 1.46 mmol/L, $p=0.015$) and sham acupuncture (-0.37 ± 1.46 mmol/L, $p=0.037$) groups, however, the 2 h postprandial blood glucose (-1.38 ± 2.80 mmol/L, $p=0.001$) and HbA1c (-0.18 ± 0.43 mmol/L, $p=0.01$) only decrease in the acupuncture group, which might indicate the potential benefit on blood glucose control of acupuncture treatment.

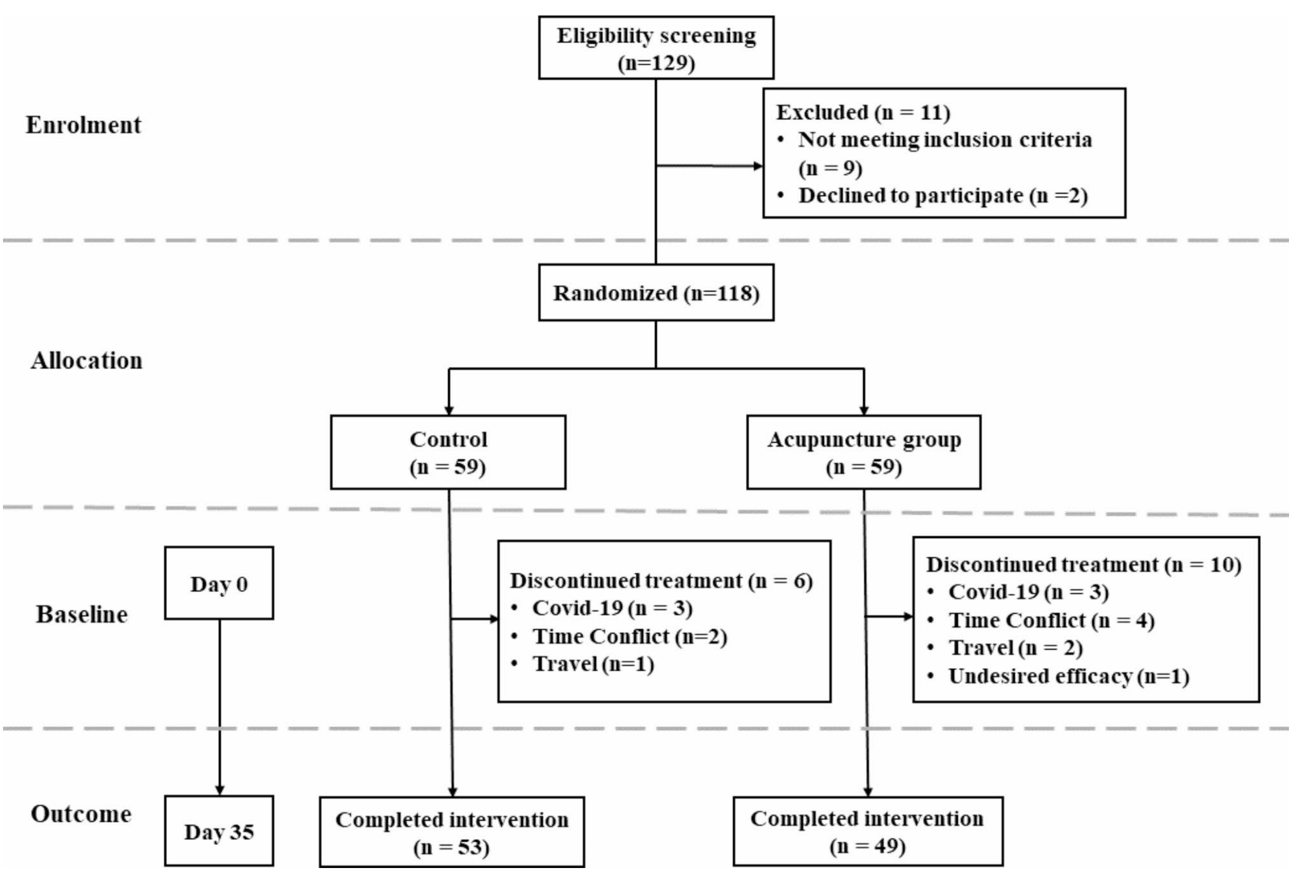

Fig. 1 The flow of participants

Table 1 Baseline and change of anthropometric and laboratory indices

Variables	Acupuncture group ($n=49$)				Control group ($n=53$)				*p*	
	Before treatment	After treatment	*End Point - Baseline*	*p*	Before treatment	After treatment	*End Point - Baseline*	*p*	Baseline	*End Point –Baseline*
Body Weight (kg)	80.43 (11.37)	79.54 (11.10)	-0.89 (1.94)	0.003	80.52 (12.37)	79.49 (12.50)	-1.03 (1.79)	< 0.001	0.92	0.763
BMI (kg/m^2)	29.15 (3.03)	28.84 (2.98)	-0.31 (0.71)	0.008	29.55 (3.01)	29.16 (3.09)	-0.40 (0.64)	< 0.001	0.514	0.558
Waistline (cm)	99.35 (9.04)	97.22 (8.59)	-2.12 (3.68)	< 0.001	99.49 (7.61)	97.13 (8.51)	-2.36 (2.85)	< 0.001	0.912	0.322
Hipline (cm)	104.84 (7.21)	103.63 (6.59)	-1.21 (3.81)	0.031	104.44 (6.83)	103.61 (6.67)	-0.83 (3.86)	0.023	0.859	0.674
WHR	0.95 (0.06)	0.94 (0.06)	-0.01 (0.04)	0.191	0.95 (0.06)	0.94 (0.06)	-0.02 (0.04)	0.003	0.671	0.311
FPG (mmol/L)	7.37 (1.96)	6.92 (2.02)	-0.44 (1.46)	0.015	7.72 (2.03)	7.36 (2.18)	-0.37 (1.52)	0.037	0.177	0.881
2 h PG (mmol/L)	14.13 (4.43)	12.75 (4.10)	-1.38 (2.80)	0.001	14.25 (3.29)	13.30 (3.91)	-0.95 (3.34)	0.103	0.58	0.293
HbA1c (%)	6.87 (1.12)	6.68 (0.97)	-0.18 (0.43)	0.01	7.12 (1.16)	6.96 (1.13)	-0.17 (0.52)	0.064	0.148	0.409
TC (mmol/L)	4.87 (0.95)	4.96 (0.93)	0.09 (0.62)	0.259	5.16 (1.00)	5.09 (1.02)	-0.07 (0.81)	0.559	0.077	0.235
TG (mmol/L)	2.17 (1.22)	1.90 (1.08)	-0.26 (0.68)	0.018	2.42 (1.30)	2.19 (1.07)	-0.24 (1.16)	0.12	0.227	0.842
HDL-c (mmol/L)	1.21 (0.31)	1.20 (0.28)	-0.02 (0.15)	0.684	1.14 (0.25)	1.13 (0.23)	-0.01 (0.15)	0.804	0.32	0.677
LDL-c (mmol/L)	2.70 (0.81)	2.92 (0.78)	0.22 (0.64)	0.015	3.00 (0.75)	2.98 (0.82)	0.00 (0.68)	1	0.015	0.064
ALT (U/L)	36.26 (31.01)	33.14 (28.04)	-3.12 (19.50)	0.065	34.51 (16.34)	32.21 (24.55)	-2.3 (24.87)	0.004	0.298	0.323
AST (U/L)	26.58 (15.89)	25.08 (14.25)	-1.5 (8.64)	0.284	25.67 (13.20)	24.79 (12.52)	-0.88 (12.86)	0.041	0.927	0.51
ALP (U/L)	76.98 (22.90)	72.78 (19.74)	-4.70 (8.43)	0.002	74.47 (22.06)	70.83 (18.22)	-3.64 (12.43)	0.043	0.568	0.43
GGT (U/L)	38.94 (23.95)	34.00 (23.82)	-4.94 (11.02)	< 0.001	42.29 (35.51)	40.13 (48.90)	-2.16 (21.45)	0.006	0.936	0.586
BUN (mmol/L)	5.08 (1.21)	5.21 (1.31)	0.13 (1.01)	0.359	5.31 (1.11)	5.37 (1.33)	0.06 (1.17)	0.906	0.466	0.675
Scr (umol/L)	67.77 (18.26)	68.33 (19.30)	0.56 (5.39)	0.438	67.86 (14.87)	67.37 (14.50)	-0.49 (4.65)	0.974	0.809	0.542
SUA (umol/L)	357.38 (77.65)	365.16 (96.18)	7.78 (64.29)	0.931	366.75 (82.59)	372.15 (88.40)	5.40 (88.14)	0.496	0.513	0.652

Data are in mean (SD) values. BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; 2 h PG, 2-h plasma glucose; HbA1c, glycated hemoglobin (A1C); TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; BUN, blood urea nitrogen; Scr, Blood urea nitrogen; SUA, serum uric acid

Change of body adipose tissue

Based on voluntariness, the bioelectrical impedance analysis and MRI-PDFF were conducted to investigate the effect of acupuncture intervention on fat tissue at baseline and end-point on 74 participants (39 in the control group and 35 in the acupuncture group). As shown in Table 2, fat content, including psoas fat (-1.35±3.66%, $p=0.049$), body fat (-0.99±1.63%, $p=0.004$), and visceral fat area (-6.23±9.06 cm^2, $p=0.001$) significantly decrease in the acupuncture group after intervention. Meanwhile, the liver fat content reduced both in the acupuncture group (-3.31±3.68%, $p<0.001$) and the control group (-0.99±2.84%, $p=0.032$). What is noteworthy is that the liver fat content of the acupuncture group decreases larger ($p=0.038$, Table 2), almost 20% lower than baseline.

Rs-fMRI activity alterations

The rs-fMRI examination is conducted based on the principle of voluntariness, occurring one day before the intervention officially begins and one day after its completion. To evaluate the impact of acupuncture intervention on rs-fMRI activity, a 2×2 repeated-measures ANOVA analysis of variance was conducted. Before the intervention,

Table 2 Baseline and change of body composition and adipose tissue

Variables	Acupuncture group ($n=35$)				Control group ($n=39$)				p	
	Before treatment	After treatment	*End Point - Baseline*	p	Before treatment	After treatment	*End Point - Baseline*	p	Baseline	*End Point –Baseline*
Liver Fat Composition (%)	16.29 (7.65)	12.98 (6.26)	-3.31 (3.68)	< 0.001	16.64 (7.45)	15.65 (7.39)	-0.99 (2.84)	0.032	0.918	0.038
Pancreatic Fat Composition (%)	10.45 (5.03)	10.35 (4.45)	-0.10 (3.86)	0.412	12.14 (5.75)	11.52 (5.30)	-0.62 (4.44)	0.295	0.279	0.463
Psoas Fat Composition (%)	8.73 (4.50)	7.38 (3.66)	-1.35 (3.66)	0.049	7.66 (4.25)	7.57 (5.51)	-0.08 (4.79)	0.758	0.709	0.092
Body Fat Percentage (%)	29.14 (6.53)	27.68 (6.18)	-1.28 (1.63)	0.004	28.89 (5.16)	28.77 (5.55)	-0.12 (1.74)	0.505	0.540	0.058
Visceral Fat Area (cm^2)	142.95 (38.14)	134.00 (37.68)	-8.95 (9.06)	0.001	137.61 (30.24)	137.12 (32.69)	-0.49 (12.34)	0.326	0.660	0.076
Body Water Percentage (%)	36.28 (6.22)	36.63 (5.97)	0.35 (0.80)	0.336	37.93 (7.68)	36.98 (7.35)	-0.95 (1.49)	0.537	0.430	0.281
Skeletal Muscle Mass (kg)	27.25 (5.12)	27.56 (4.91)	0.31 (0.69)	0.347	28.57 (6.27)	27.86 (5.98)	-0.71 (1.20)	0.875	0.443	0.544

Data are in mean (SD) value

no significant differences were observed between the control and acupuncture groups. However, as shown in Fig. 2A; Table 3, the acupuncture groups showed significantly increased fALFF in the left medial occipital gyrus (MOG_L, $p=0.047$), and right calcarine cortex ($p=0.018$) compared to the controls. In ReHo analysis, bilateral cuneus ($p=0.034$), and right inferior parietal lobule (IPL_R, $p=0.016$) significantly increased in the acupuncture group (Fig. 2B; Table 3).

Safety assessment

No abnormalities were reported in vital signs or laboratory tests. Two participants in the sham acupuncture group and three participants in the acupuncture group have minor abdominal hematomas. Relief was achieved without treatment. No other adverse events (AEs) were documented.

Discussion

To the best of our knowledge, this is the first randomized clinical trial focused on the effect of acupuncture-assisted treatment on weight management of overweight T2DM patients. Using sham acupuncture as a control ensures that the observed physiological changes can be attributed specifically to the acupoint effect. The short-term acupuncture-assisted weight management was not superior to sham control. However, it is noted that a one-month acupuncture treatment significantly decreases the liver fat content in overweight patients with T2DM. This finding suggests potential benefits of acupuncture in reducing ectopic fat accumulation. Further studies are required to validate and explore the role of acupuncture in fat metabolism.

In the one-month treatment, significant body weight reduction and improvement in blood glucose management in both groups are observed, which agrees with the existing research that exercise [30] and calorie restriction [31] have positive effects on weight control and blood glucose management. Although there was no significant difference in the degree of weight loss between the two groups, the acupuncture group experienced a greater reduction in weight. This may be due to the small sample size or the short duration of the intervention, which might not be sufficient to show a significant difference between the two groups. Interestingly, compared to sham acupuncture, acupuncture treatment significantly decreases the ectopic fat accumulation, especially in liver. Existing studies illustrate liver fat as the most rapidly mobilized ectopic fat stored during weight loss interventions [32, 33], which might indicate the role of liver fat content as a sensitive indicator of metabolic status. Referring to its crucial role as a therapeutical target tissue for T2DM [34], the specific role of liver fat in the improvement of metabolic status [35], and the potential mechanism underlying acupuncture's efficacy warrant further investigation. Highlighting liver fat content as an acupuncture target has been a trigger for subsequent clinical trials. (Chinese Clinical Trial Registry, CHICTR, http://www.chictr.org.cn/, No. ChiCTR2400083721).

In previous studies, the brain attracted lots of attention as the primary target organ of acupuncture [36, 37]. Differential analysis of fALFF and ReHo revealed that spontaneous activity primarily enhanced brain area mainly in the occipital lobe (MOG_L, right calcarine cortex, and bilateral cuneus) and parietal lobe (inferior parietal lobule) in the acupuncture group. Existed studies have demonstrated significantly decreased ALFF and ReHo values in the occipital lobe and parietal lobe among patients with T2D [38], which are correlated with impaired neurocognitive performance [38, 39]. The partially restored

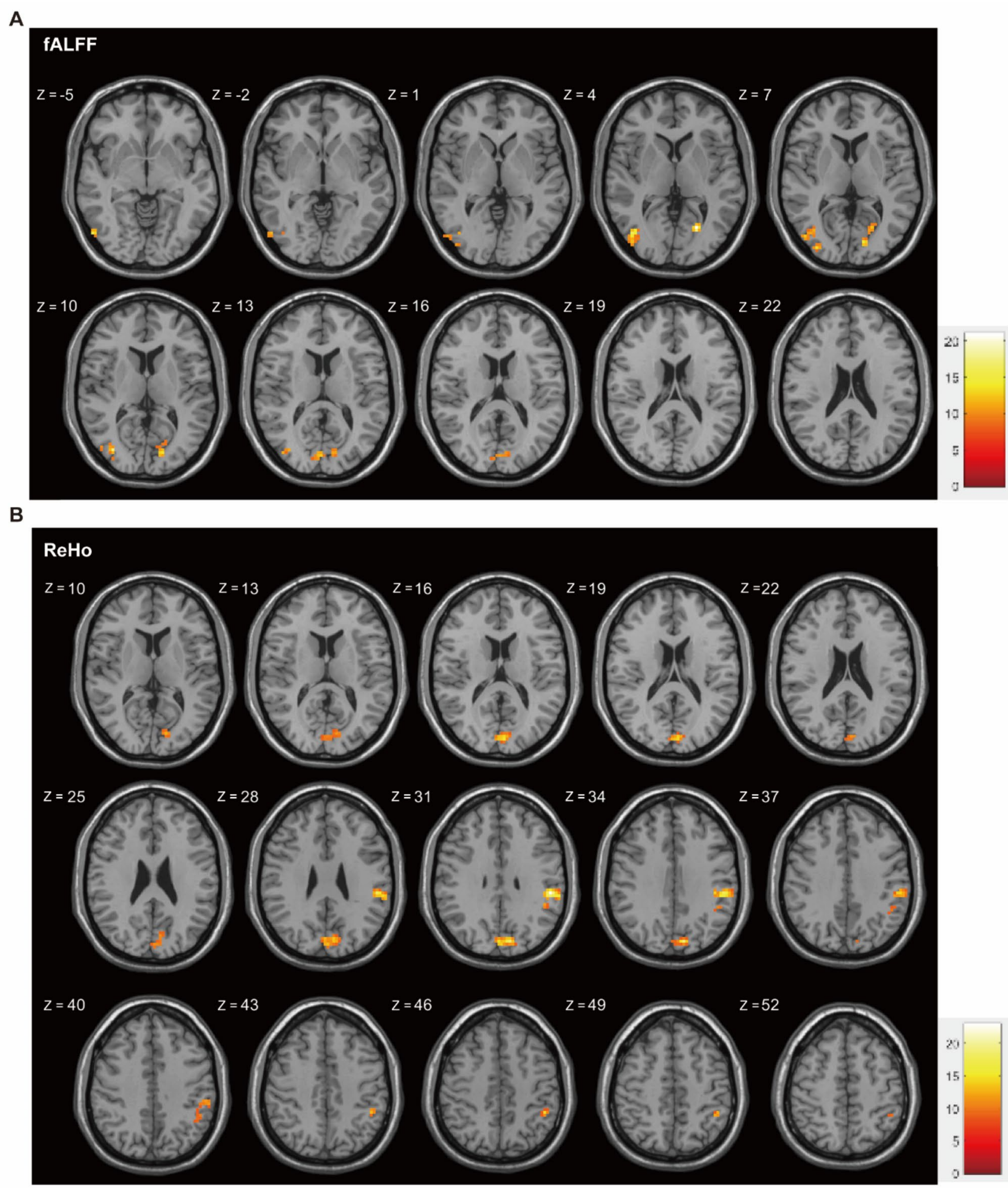

Fig. 2 Difference in whole brain (**A**) fALFF, and (**B**) ReHo using 2 × 2 repeated-measures ANOVA analysis of variance between acupuncture and control group ($p < 0.05$, Bonferroni corrected). Color scale denotes the t value. *z*, Montreal Neurological Institute coordinates; Left in picture is left in the brain

Table 3 Differences in fALFF and ReHo values between the acupuncture and control groups ($p < 0.05$)

		MNI coordinates				
Brain Region	**BA**	**x**	**y**	**z**	**Cluster Size**	**Peak t Score***
fALFF difference						
L middle occipital gyrus	18	21	-66	3	56	20.79
R calcarine cortex	30	-36	-78	12	67	17.12
ReHo difference						
Cuneus	19	51	-30	30	113	22.60
R IPL	40	9	-81	33	130	18.64

Comparisons were performed at $p<0.05$, corrected for multiple comparisons. BA, Brodmann area; IPL, inferior parietal lobule; L, left; R, right; MNI, Montreal Neurological Institute; x, y, z, coordinates of primary peak locations in the MNI space. *Positive t score: acupuncture group > control

activity in the cognition-related brain area following acupuncture suggests the potential therapeutic effects of acupuncture against cognitive disorders induced by T2DM. However, the exploration of brain activity alterations in metabolic diseases is still in its early stages. The role of the brain in mediating the impact of acupuncture on metabolic status remains elusive and requires further investigation. Therefore, the significant brain activity observed after acupuncture treatment in this paper should be regarded as a descriptive result that can provide a reference for future studies.

Although previous studies have been trying to identify potential participants and molecular pathways involved in the effects of acupuncture on promoting fat reduction [40, 41] and improving cognitive impairment [42], further experimentation is needed to elucidate the specific mechanisms. Additionally, comprehensively understanding the complex interaction between acupoints and physiological responses remains a significant challenge in unraveling the underlying mechanism of acupuncture and evaluating optimal clinical parameters.

Our study has several limitations. First, due to the limited financial support and labor, the treatment lasted for only one month, the more significant result might be obtained through a long-term intervention. Besides, longer-term follow-ups are required to understand the full benefits of these interventions on health outcomes. Second, this study focuses on the weight management of T2DM patients, some of them receiving constant drug therapy to control blood glucose. Although, the differential analysis on drug use between the two groups did not display significance, and the result of excluding drug users agrees with the no-exclude result, which partially eliminates the worry about the physiological effect of drug use, the possible drug use-induced bias on the result of interventions still worth attention. Third, this study takes superficial needling as a sham acupuncture method, which is not a real placebo. This procedure still needed to penetrate the skin of the acupoint shallowly which can cause needle sensation. Therefore, the acupuncture-induced physiological alterations are strictly due to the acupoint effect. Thus, the control procedure should be improved and well-designed in future trials to obtain a comprehensive understanding of the effectiveness of acupuncture. In light of the issues above, future studies will be designed with a longer intervention duration and a larger number of participants. Besides, investigation into these potential mechanisms will contribute to the development of therapeutic strategies aimed at improving metabolic status.

In summary, the short-term acupuncture-assisted weight management was not superior to sham control. However, it is noteworthy that acupuncture intervention significantly reduced ectopic fat accumulation, especially in the liver. Besides, the rs-fMRI analysis revealed potential spontaneous brain activity associated with acupuncture. Both efficacy and safety profiles indicated that acupuncture could be used as a supplement therapy for managing metabolic status.

Abbreviations

2-h PG	2-h plasma glucose
AMCTR	Acupuncture-Moxibustion Clinical Trial Registry
BMI	Body mass index
CONSORT	Consolidated Standards of Reporting Trials
CR	Calorie restriction
fALFF	Fractional amplitude of low-frequency fluctuation
FPG	Fasting plasma glucose
KCC	Kendall's coefficient of concordance
MNI	Montreal Neurological Institute
MRI-PDFF	Magnetic resonance imaging derived proton-density-fat-fraction
OGTT	Oral glucose tolerance test
ReHo	Regional homogeneity
ROI	Regions of interest
rs-fMRI	Resting-state functional magnetic resonance imaging
SD	standard deviation
STRICTA	STandards for Reporting Interventions in Clinical Trials of Acupuncture
T2DM	type 2 diabetes mellitus
WHR	Waist-to-hip ratio

Acknowledgements
The authors gratefully acknowledge the hospital staff for their excellent facilities and support. We also thank the Guangzhou Nanda Fite Medical Health Technology Co., Ltd. for support in diet and exercise intervention.

Author contributions
H.Y., X.W., and J.G. designed the experimental plan. X.W., Z.Z., C.J. (Chunfei Jiang), C.J. (Chunyan Ji), and J.H. performed the experiments. K.B., J.L., G.Z., and X.L. analyzed the data. K.B. and J.L. drafted the manuscript and incorporated

edits and comments from H.Y., X.W., J.G., T.L., and all other authors. Each author accepted the submitted version of the paper and made contributions to it.

Funding
This research was funded by Natural Science Foundation of Shanghai (21ZR141320), Shanghai Municipal Health Commission [ZY(2018–2020)-FWTX-301], the Guidance Project from Shanghai Science and Technology Commission (19401931100), Fudan Zhangjiang Clinical Medicine Innovation Fund Project (KP7202117), the National Key R&D Program of China (2019YFA0801900, 2018YFA0800300), National Natural Science Foundation of China (No. 92357304, No. 92249302), Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (ZYYCXTD-D-202001), Shanghai Frontiers Science Research Base of Exercise and Metabolic Health, Aculty Resources Project of College of Life Sciences, Inner Mongolia University (2022 – 102).

Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the medical ethical committee of Zhongshan Hospital, Fudan University (Approved No. B2019-310R). Every member of the study endorsed an informed consent form. Every procedure used in this investigation complied with the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai 200032, China
[2]Human Phenome Institute, Fudan University, Shanghai 201203, China
[3]Department of traditional Chinese medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China
[4]Department of Nutrition, Zhongshan Hospital, Fudan University, Shanghai 200032, China
[5]Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai 201203, China
[6]Department of Endocrinology and Metabolism, Huashan Hospital, Fudan University, Shanghai 200040, China
[7]State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai 200438, China
[8]Shanghai Key Laboratory of Metabolic Remodeling and Health, Institute of Metabolism & Integrative Biology, Fudan University, Shanghai 200433, China
[9]School of Life Sciences, Inner Mongolia University, Hohhot 010020, Inner Mongolia, China
[10]Fudan Zhangjiang Institute, Shanghai 201203, China
[11]Fudan Institute for Metabolic Diseases, Shanghai 200032, China
[12]Department of Endocrinology and Metabolism, Wusong Branch of Zhongshan Hospital, Fudan University, Shanghai 200940, China

Received: 5 July 2024 / Accepted: 17 October 2024
Published online: 28 October 2024

References

1. Chivese T, Hoegfeldt CA, Werfalli M, Yuen L, Sun H, Karuranga S, Li N, Gupta A, Immanuel J, Divakar H, et al. IDF Diabetes Atlas: the prevalence of pre-existing diabetes in pregnancy - A systematic reviewand meta-analysis of studies published during 2010–2020. Diabetes Res Clin Pract. 2022;183:109049.
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
3. Obesity. and overweight https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
4. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. J Intern Med. 2021;289(6):754–70.
5. Taylor R, Al-Mrabeh A, Sattar N. Understanding the mechanisms of reversal of type 2 diabetes. Lancet Diabetes Endocrinol. 2019;7(9):726–36.
6. Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, Kushner RF, Daniels SR, Wadden TA, Tsai AG, et al. The science of obesity management: an endocrine Society Scientific Statement. Endocr Rev. 2018;39(2):79–132.
7. Durrer Schutz D, Busetto L, Dicker D, Farpour-Lambert N, Pryke R, Toplak H, Widmer D, Yumuk V, Schutz Y. European practical and patient-centred guidelines for adult obesity management in primary care. Obes Facts. 2019;12(1):40–66.
8. Du F, Virtue A, Wang H, Yang XF. Metabolomic analyses for atherosclerosis, diabetes, and obesity. Biomark Res. 2013;1(1):17.
9. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S. Association of Pharmacological Treatments for Obesity with Weight Loss and adverse events: a systematic review and Meta-analysis. JAMA. 2016;315(22):2424–34.
10. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. Nat Rev Gastroenterol Hepatol. 2017;14(3):160–9.
11. Kim SY, Shin IS, Park YJ. Effect of acupuncture and intervention types on weight loss: a systematic review and meta-analysis. Obes Rev. 2018;19(11):1585–96.
12. Zhong YM, Luo XC, Chen Y, Lai DL, Lu WT, Shang YN, Zhang LL, Zhou HY. Acupuncture versus sham acupuncture for simple obesity: a systematic review and meta-analysis. Postgrad Med J. 2020;96(1134):221–7.
13. Björntorp P. Physical training in the treatment of obesity. Int J Obes. 1978;2(2):149–56.
14. Gwinup G. Effect of Exercise alone on the weight of obese women. Arch Intern Med. 1975;135(5):676–80.
15. Nourshahi M, Ahmadizad S, Nikbakht H, Heidarnia MA, Ernst E. The effects of triple therapy (acupuncture, diet and exercise) on body weight: a randomized, clinical trial. Int J Obes. 2009;33(5):583–7.
16. Shafshak TS. Electroacupuncture and Exercise in Body Weight reduction and their application in rehabilitating patients with knee osteoarthritis. Am J Chin Med. 1995;23(01):15–25.
17. Kim SY, Shin IS, Park YJ. Comparative effectiveness of a low-calorie diet combined with acupuncture, cognitive behavioral therapy, meal replacements, or exercise for obesity over different intervention periods: a systematic review and network meta-analysis. Front Endocrinol (Lausanne). 2022;13:772478.
18. Wang L, Yu CC, Li J, Tian Q, Du YJ. Mechanism of action of acupuncture in obesity: a perspective from the Hypothalamus. Front Endocrinol (Lausanne). 2021;12:632324.
19. Pariente J, White P, Frackowiak RS, Lewith G. Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture. NeuroImage. 2005;25(4):1161–7.
20. He Y, von Deneen KM, Li G, Jing B, Zhou Y, Zhang K, Zhang Y, Ren Y. Electroacupuncture enhances resting-state functional connectivity between dorsal caudate and precuneus and decreases associated leptin levels in overweight/obese subjects. Brain Imaging Behav. 2022;16(1):445–54.
21. Lips MA, Wijngaarden MA, van der Grond J, van Buchem MA, de Groot GH, Rombouts SA, Pijl H, Veer IM. Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. Am J Clin Nutr. 2014;100(2):524–31.
22. Mannerås L, Jonsdottir IH, Holmäng A, Lönn M, Stener-Victorin E. Low-frequency electro-acupuncture and physical exercise improve metabolic disturbances and modulate gene expression in adipose tissue in rats with dihydrotestosterone-induced polycystic ovary syndrome. Endocrinology. 2008;149(7):3559–68.
23. Lu M, Yu Z, Li Q, Gong M, An L, Xu T, Yuan M, Liang C, Yu Z, Xu B. Electroacupuncture Stimulation regulates adipose lipolysis via Catecholamine Signaling mediated by NLRP3 suppression in obese rats. Front Endocrinol (Lausanne). 2021;12:773127.
24. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med. 2008;148(4):295–309.
25. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, Moher D. Revised STandards for reporting interventions in clinical trials

of acupuncture (STRICTA): extending the CONSORT statement. J Evid Based Med. 2010;3(3):140–55.
26. Chen C, Lu FC. The guidelines for prevention and control of overweight and obesity in Chinese adults. Biomed Environ Sci. 2004;17 Suppl:1–36.
27. Waters DL, Aguirre L, Gurney B, Sinacore DR, Fowler K, Gregori G, Armamento-Villareal R, Qualls C, Villareal DT. Effect of Aerobic or Resistance Exercise, or both, on intermuscular and visceral Fat and Physical and metabolic function in older adults with obesity while dieting. J Gerontol Biol Sci Med Sci. 2022;77(1):131–9.
28. Luan X, Tian X, Zhang H, Huang R, Li N, Chen P, Wang R. Exercise as a prescription for patients with various diseases. J Sport Health Sci. 2019;8(5):422–41.
29. Wen J, Chen X, Yang Y, Liu J, Li E, Liu J, Zhou Z, Wu W, He K. Acupuncture medical therapy and its underlying mechanisms: a systematic review. Am J Chin Med. 2021;49(1):1–23.
30. Yao T, Wang H, Lin K, Wang R, Guo S, Chen P, Wu H, Liu T, Wang R. Exercise-induced microbial changes in preventing type 2 diabetes. Sci China Life Sci 2023.
31. Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, Aribisala B, Caslake M, Taylor R. Very low-calorie Diet and 6 months of Weight Stability in Type 2 diabetes: pathophysiological changes in responders and nonresponders. Diabetes Care. 2016;39(5):808–15.
32. Gaborit B, Ancel P, Abdullah AE, Maurice F, Abdesselam I, Calen A, Soghomonian A, Houssays M, Varlet I, Eisinger M, et al. Effect of empagliflozin on ectopic fat stores and myocardial energetics in type 2 diabetes: the EMPACEF study. Cardiovasc Diabetol. 2021;20(1):57.
33. Kahl S, Gancheva S, Straßburger K, Herder C, Machann J, Katsuyama H, Kabisch S, Henkel E, Kopf S, Lagerpusch M, et al. Empagliflozin effectively lowers Liver Fat Content in Well-controlled type 2 diabetes: a Randomized, Double-Blind, phase 4, placebo-controlled trial. Diabetes Care. 2020;43(2):298–305.
34. Jayedi A, Soltani S, Motlagh SZ, Emadi A, Shahinfar H, Moosavi H, Shab-Bidar S. Anthropometric and adiposity indicators and risk of type 2 diabetes: systematic review and dose-response meta-analysis of cohort studies. BMJ. 2022;376:e067516.
35. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, Peters C, Barnes AC, Aribisala BS, Hollingsworth KG, Mathers JC, Sattar N, Lean MEJ: Remission of Human Type 2 Diabetes Requires Decrease in Liver and Pancreas Fat Content but Is Dependent upon Capacity for β Cell Recovery. *Cell Metab* 2018, 28(4):547–556.e543.
36. Asamoto S, Takeshige C. Activation of the satiety center by auricular acupuncture point stimulation. Brain Res Bull. 1992;29(2):157–64.
37. Shu Q, Chen L, Wu S, Li J, Liu J, Xiao L, Chen R, Liang F. Acupuncture targeting SIRT1 in the Hypothalamic Arcuate Nucleus can improve obesity in High-Fat-Diet-Induced rats with insulin resistance via an anorectic effect. Obes Facts. 2020;13(1):40–57.
38. Cui Y, Jiao Y, Chen Y-C, Wang K, Gao B, Wen S, Ju S, Teng G-J. Altered spontaneous brain activity in type 2 diabetes: a resting-state functional MRI study. Diabetes. 2014;63(2):749–60.
39. Chen Y-C, Jiao Y, Cui Y, Shang S-A, Ding J, Feng Y, Song W, Ju S-H, Teng G-J. Aberrant brain functional connectivity related to Insulin Resistance in type 2 diabetes: a resting-state fMRI study. Diabetes Care. 2014;37(6):1689–96.
40. Lu SF, Tang YX, Zhang T, Fu SP, Hong H, Cheng Y, Xu HX, Jing XY, Yu ML, Zhu BM. Electroacupuncture reduces Body Weight by regulating Fat Browning-related proteins of adipose tissue in HFD-Induced obese mice. Front Psychiatry. 2019;10:353.
41. Xia X, Xie Y, Gong Y, Zhan M, He Y, Liang X, Jin Y, Yang Y, Ding W. Electroacupuncture promoted intestinal defensins and rescued the dysbiotic cecal microbiota of high-fat diet-induced obese mice. Life Sci. 2022;309:120961.
42. Ge X, Wang L, Cui Q, Yan H, Wang Z, Ye S, Zhang Q, Fei A. Electroacupuncture improves cognitive impairment in diabetic cognitive dysfunction rats by regulating the mitochondrial autophagy pathway. J Physiological Sci. 2022;72(1):29.

Publisher's note