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Immediate fasting blood glucose response to electroacupuncture of ST36 versus CV12 in patients with type 2 diabetes mellitus: randomized controlled trial

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary Background. Electroacupuncture (EA) is one of the main alternative or complementary therapies used to treat diabetic symptoms, but the immediate hypoglycemic effect of EA at one acupoint only has not been studied in type 2 diabetes mellitus (T2DM) patients.

Objectives. This study aimed to investigate the immediate response of fasting blood glucose (FBG) to EA at ST36 (Zusanli) versus CV12 (Zhongwan) acupoints in T2DM patients.

Material and methods. With a body mass index < 30 kg/m², one hundred T2DM men 40–73 years of age were randomly divided into four groups: a real EA of CV12 group, placebo-controlled EA of CV12 group, real EA of ST36 group and placebo-controlled EA of ST36 group. All groups – containing 25 T2DM men – received one session of a 30-minute 2-Hz EA. Pre- and post-FBG levels were evaluated for every patient within each group.

Results. The only group that showed a significant reduction of FBG was the real EA of CV12 group ($p < 0.05$) while the placebo-controlled EA of CV12, real EA of ST36 and placebo-controlled EA of ST36 groups did not reveal any significant FBG decline ($p > 0.05$) in men with T2DM.

Conclusions. A 30-minute 2-Hz real EA of CV12 produced a highly significant decrease of FBG levels in T2DM men.

Key words: blood glucose, electroacupuncture, type 2 diabetes mellitus, randomized controlled trial.

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Background

In 2019, there were 8.9 million registered diabetic adults 20–70 years of age in Egypt, which represents the 9th country with the highest documented number of diabetic patients worldwide. The 2013-estimated prevalence of diabetes mellitus (DM) was 7.5 million, and in 2035, it is expected to be 13.1 million [1].

DM is a group of metabolic disorders defined as hyperglycemia originating from defects in the secretion or action of insulin or both [2]. Besides the general positive effects of exercise on the psychological and physical sense of wellbeing in many patients [3], exercise is considered one of the therapeutic procedures for controlling/regulating plasma glucose levels in type 2 diabetes mellitus (T2DM) patients, in addition to hypoglycemic medications and different diet regimens [4].

Besides the long-term need for exercise to control T2DM-associated hyperglycemia [5], available hypoglycemic drugs are efficacious, but many pharmacological hypoglycemic agents can lead to serious complications and side effects [4]. Recently, with rapid medical advancement, complementary or alternative therapies have seen more attention from many patients due to the absence of complications and/or side effects, in addition to the hopeful results in the short- and long-term management of T2DM symptoms [6].

In Traditional Chinese Medicine (TCM), acupoint therapy, alone and/or combined with western medicine, is considered a main treatment for DM and/or its complications, with lower-reported rates of side effects than with the sole use of western medicine. Acupoint therapy is a treatment conducted through the meridians and acupoints utilizing one of the following: acupuncture, injection of acupoint, moxibustion, acupressure and external application [7].

For 2000 years, with positive evidence-based clinical effects in human and animal studies [8], alternative therapies have been used safely with no complications [9, 10] for T2DM treatment with different techniques of needle acupuncture stimulation [8]. Electroacupuncture (EA), a recent used clinical technique for needle stimulation, other than traditional manual hand stimulation, is a non-invasive technique [11] that uses a charge of electricity to enforce needle stimulation inserted into the selected meridians and points of acupuncture [12]. As it utilizes an electrical current that passes through the inserted acupuncture needles into single or multiple acupoints, EA is said to be a strong hypoglycemic treatment modality in patients with T2DM [13].

Based on the meridian theory, the Zusanli or Stomach 36 (ST36) acupoint, located at the stomach meridian under the knee within the tibialis anterior muscle [14], is commonly used as a general acupuncture acupoint to relieve symptoms of DM [7], restore the normal aliment of gastrointestinal functions, re-



cover a general sense of well-being [15], refresh the functions of internal organs, including the pancreas [16], energize physical activities and cure the diseases [4].

Based on Korean medicine, the Zhongwan or Conception Vessel acupoint 12 (CV12) (located on the wall of abdomen) is a treatment point for disorders of the digestive organs, including the pancreas [17]. Studies have reported a significant hypoglycemic effect of manual acupuncture at a single acupoint with one needle inserted at CV12 [18] and ST36 [19] in T2DM patients.

Despite the evidence-based hypoglycemic effect of single-acupoint laserpuncture at BL 20 [20] and EA at GB 26 [21], ST36 [4] and CV12 [7] in diabetic rats, no published data at present – to our knowledge – has investigated the hypoglycemic effect of EA at ST36 or CV12 in T2DM patients.

With recommendations to investigate the immediate response of fasting blood glucose (FBG) to a 30-minute single-acupoint EA at ST36 [19] or CV12 [18], this study was the first aimed at making a comparison between the immediate FBG response to a 30-minute EA at CV12 versus ST36 in T2DM men.

Material and methods

In addition to a signature obtained from all patients on the consent form for participation in the study, this randomized placebo-controlled prospective study followed the recommendations of the Helsinki Declaration. Under number P.T.REC/012/002919, the Local Scientific Ethical Committee for Human Research, Faculty of Physical Therapy, Cairo University, approved the carrying out of this study. Under identification number PACTR202010486385289, the trial was also registered with the Pan-African Clinical Trials Registry (PACTR).

Sample size

The number of patients was determined according to a pilot study on 20 patients with T2DM and G*Power (version 3.1.9.2) (Franz Faul, Uni Kiel, Germany). The calculation depended upon the F-test, power at 85% and type I error at 5%, and the effect size of FBG was (0.32). The proper minimum sample size for this study was 92 patients.

Participants

With a body mass index (BMI) < 30 kg/m² and a FBG > 126 mg/dl, one hundred T2DM men 40–73 years of age were randomly selected from the DM outpatient clinics of Cairo University, Om El-Masryeen, and Meetghamr General Hospitals during the period from 18 October to 30 November 2020.

Via a physician, patients with respiratory, renal, hepatic and cardiac disorders were excluded. Besides smokers and those with addictions, patients with hypertension, a cardiac pacemaker, malignancy, active dermatological infection, mental disorders and a history of admission with any type of complementary therapies within the last 3 months were also rejected from participation in this study.

The patients were divided into one of the four following groups (every group contained 25 men): group 1 (real-EA of CV12 group), group 2 (placebo-controlled EA of CV12 group), group 3 (real-EA of ST36 group), group 4 (placebo-controlled EA of ST36 group).

Figure 1 presents the consort flow diagram of the study. Utilizing a computer-generated randomized block list, a physiotherapy assistant – blinded to the trial protocol and not involved in any part of the treatment or assessment – divided the patients to one of the treatment groups.

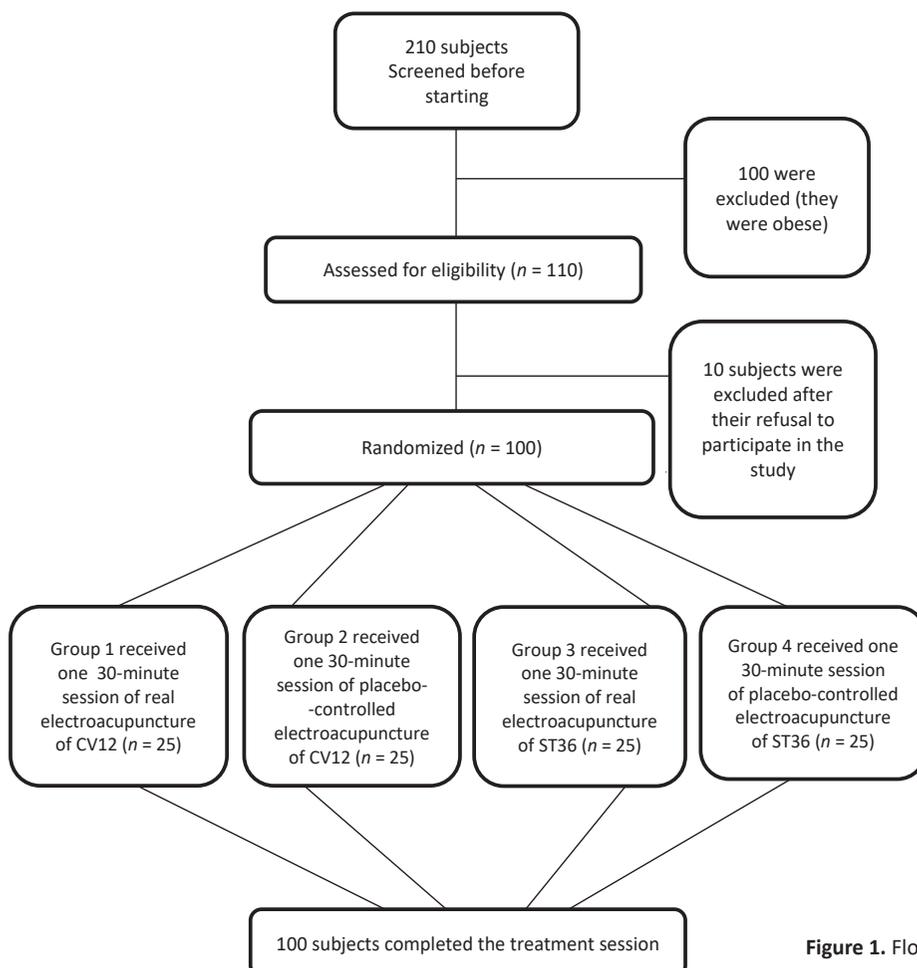


Figure 1. Flow chart of study participants

Interventions

Group 1

After insertion of the needle at the CV12 acupoint, which was located on the median anterior line of the upper abdomen, 4 cun (breadth of the thumb) proximal to the umbilical center [22], the *de qi* sensation was confirmed by all patients of this group via the manipulation of the needle into the CV12 acupoint; the needle then was connected to the EA device.

Group 2

Where there was no known acupoint at this area, the needle was placed one cun lateral to the CV12 acupoint in the right abdominal side in this group; the needle was then connected to the EA device.

Group 3

After insertion of the needle at the ST36 acupoint, which was located one cun lateral to the lower border of the tuberosity of tibia [23], the *de qi* sensation was confirmed by all patients of this group via the manipulation of the needle into the ST36 acupoint; the needle was then connected to the EA device.

Group 4

Where there was no known acupoint at this area, the needle was placed at the midline connecting the patellar apex and the tuberosity of tibia in this group; the needle was then connected to the EA device.

A sterile single-use stainless-steel acupuncture needle (CE 0197, made in China, with a size 0.25 x 25 cm) was inserted perpendicularly with a 0.5-cun depth into the detected point in each group. In every patient within each group, the positive pole of the EA device (inter-TENS 668, made in Egypt) was connected to the needle, and the reference (negative) pole was fixed with a bandage one centimeter proximal to the needled point [23]. All patients within each group received only one session of 30-minute 2-Hz EA between 8 am to 9 am.

With overnight fasting, FBG was measured immediately before and after the session with every patient in all groups using a blood glucose meter (On Call Plus, made in China).

Statistical analysis

The collected data was handled using version 18 of the SPSS program (Chicago, SPSS Inc. IBM Corp.). After verification with the Kolmogorov–Smirnov normality test, the normal distribution of all data was confirmed. All baseline and post-treatment data among groups was treated using the one-way ANOVA test. To test the significant changes between pre- and post-FBG values within each group, multiple pairwise comparisons by a post hoc test was used. The significance value was determined at $p < 0.05$.

Results

Regarding the baseline data (Age and BMI), Table 1 presents a non-significant difference among the four groups ($p > 0.05$). tPost Post The post hoc test (Table 2) revealed a significant difference between pre- and post-treatment at G1 as $p < 0.0001$, while the other groups did not show any significant difference. Partial Eta Square was used to determine the effect size between groups post-treatment and found a large difference: $\eta^2 = 0.29$ (Table 2).

Discussion

The present study found a highly significant immediate decline of FBG after one session of a 30-minute real CV12-EA, while the placebo-controlled CV12-EA, real ST36-EA and placebo-controlled ST36-EA did not produce the same effect in T2DM men.

There is little literature that explains the mechanism of an immediate significant FBG drop after a 30-minute real-EA session at CV12, but studies on diabetic animal models justified this drop due to the increased production of endogenous β -endorphin [4] and pancreatic opioid peptides [24] that promote insulin production and sensitivity [4].

Stimulation of the real acupoints is guaranteed to produce a higher hypoglycemic effect than needle stimulation of adjacent non-acupoints [4]. Based on TCM, when a specific acupoint is needled, the effect of treatment occurs on the corresponding body part [25]. Greater insulin sensitivity is encouraged by the closest location of CV12 to the pancreas rather than the furthest location from the pancreas – ST36 (located in the upper anterolateral lower leg) [26].

The study was supported by Chang et al. [26], who found a non-significant hypoglycemic effect after a 30-minute EA session at bilateral ST36 in rats with induced DM. Non-significant changes within the placebo group [18] supported the present results, especially after a significant decrease of random blood glucose in the group that received one session of a 30-minute manually-acupunctured CV12 in T2DM patients. In accordance with the present results, another study revealed a non-significant reduction of FBG after 30-minute 2-Hz EA of bilateral ST36 in patients with DM-complicated gastric dysrhythmia [27].

Mohanty et al. [28] have contradicted the results of this study, as the 20-minute manual real-CV12 needling produced a mild non-significant hypoglycemia may be due to the very small number of participated healthy volunteers ($n = 18$). 30-minute bilateral manual needling at ST36 also produced a more effective significant reduction of random blood glucose levels in T2DM patients than the placebo group [19].

Table 1. Baseline data among groups using the One-Way ANOVA test

	G1	G2	G3	G4	F	p
Age (years)	53.64 ± 8.05	54.28 ± 8.23	55.32 ± 8.84	52.64 ± 8.25	0.45	0.72 ^a
BMI (kg/m ²)	28.46 ± 1.22	27.62 ± 1.53	28.06 ± 1.37	27.80 ± 1.34	1.74	0.16 ^a

G – group, BMI – Body Mass Index, kg – kilogram, m – meter, p -value significance was set at < 0.05 , ^a no significant difference between the four groups.

Table 2. Comparison between pre- and post-FBG within each group by post hoc test and between groups by One-Way ANOVA

Outcome	G1	G2	G3	G4	P	F	η^2
FBG (mg/dL)							
Pre-treatment	140 ± 11.87	139.24 ± 9.41	138.84 ± 8.63	139.64 ± 10.52	0.98 ^a	0.06	
Post-treatment	124.92 ± 8.49	138.04 ± 9.44	137.44 ± 8.78	139.52 ± 10.16	0.0001 ^b	13.38	0.29
p -value (within group)	0.0001 ^b	0.42 ^a	0.35 ^a	0.94 ^a			
% of improvement	10.7%	0.86%	1%	0.08%			

G – group, FBG – fasting blood glucose, mg – milligram, dL – deciliter, p -value significance was set < 0.05 , ^a non-significance difference, ^b significance difference, Partial Eta Square – effect size (small > 0.01 , medium > 0.06 , large > 0.14).

In opposition to the results of this study, in normal rats, EA with a frequency of 2 Hz at the ST36 produced a greater hypoglycemic response than stimulation at the CV12 acupoint [29]. A 15 Hz bilateral EA of ST36 improved prednisolone-induced insulin resistance and activity in male rats via the enhanced recovered expression of signal proteins of insulin in addition to the decreased levels of plasma-free fatty acids [13].

Limitations of the study

The absence of a follow-up, lack of female inclusion and the large number of diabetic patients in each group are the main limitations of this study.

Conclusions

A 30-minute 2-Hz electroacupuncture of CV12 – within the limitations of this study – produced a highly significant decline of FBG levels in men with T2DM.

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Conflicts of interest: The authors declare no conflicts of interest.

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