The effect of electroacupuncture at the MA-IC 3 endocrine ear acupoint on fasting blood glucose levels in type 2 diabetes mellitus patients

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Abstract. The management of diabetes mellitus (DM) involves education, nutritional intervention, and physical exercise, in addition to pharmacological interventions, with the long-term goal of preventing complications through the control of blood glucose levels. Several studies have shown that acupuncture, both conventional acupuncture and electroacupuncture, is useful for lowering blood glucose levels in patients with DM. This study aimed to determine the additional effect of electroacupuncture at the MA-IC 3 Endocrine ear acupoint on fasting blood glucose levels in patients with Type 2 DM who were receiving oral hypoglycemic agents at Banjar General Hospital. In this randomized controlled study, fifty-four study participants who were being treated with oral antidiabetics were allocated into two groups, receiving either electroacupuncture (EA) at the MA-IC 3 ear acupoint with dense disperse wave for 30 minutes or acupuncture at the same point and for the same duration but without EA (No EA). Fasting blood glucose levels were measured before and after the intervention. In Group A (EA), the mean fasting blood glucose (FBG) level decreased from 157.26±24.485 to 142.59±26.771 (p < 0.05), whereas in Group B (No EA), the mean FBG decreased from 149.67±21.485 to 148.74±21.326 (p < 0.05). The difference in the amount of FBG decrease between Group A (EA) and Group B (No EA) was statistically significant (p < 0.05). EA at the MA-IC 3 Endocrine lowers FBG levels to a greater degree than acupuncture with no EA in patients with type 2 DM.

1. Introduction
Diabetes mellitus (DM) is a group of clinical problems characterized by an absolute or relative deficiency in the production or action of insulin, which results in hyperglycemia [1]. Various epidemiological studies have shown the increasing incidence and prevalence of type 2 DM in various parts of the world. The WHO predicts a large increase in the number of diabetics for years to come. The WHO predicts that in Indonesia, there will be an increase in the number of patients from 8.4 million in 2000 to about 21.3 million in 2030 [2]. The pathophysiology of type 2 DM is based on insulin resistance, regulatory disorders of liver glucose production, and decreased pancreatic beta cell function, resulting in the decreased secretion of insulin [3]. In patients with insulin resistance, the disruption of blood glucose level regulation occurs despite normal or elevated insulin levels because the reduced expression of insulin receptors on the cell surface results in relative insulin deficiency and ultimately pancreatic beta cell exhaustion [4].
During DM management, the short-term the goal is to eliminate the symptoms of DM and maintain the patient’s comfort and health. In the long term, the goal is to prevent complications, such as macroangiopathy, microangiopathy, and neuropathy, and ultimately reduce morbidity and mortality associated with DM [1,2]. The potential ability of acupuncture to decrease blood glucose levels and normalize endocrine function, especially in patients with type 2 DM, has been discussed [5,6]. Ear acupuncture is a diagnostic and therapy system based on the normalization of body dysfunction through the stimulation of ear acupoints [7]. In traditional Chinese medicine (TCM), all organs of the body are represented in the outer ear [8]. Electroacupuncture (EA) is any diagnostic or therapeutic procedure that is based on the science of acupuncture but uses electrical stimulants [9]. Electroacupuncture with a frequency of 2 Hz stimulates the release of enkephalin, β-endorphin and endomorphin, while EA at a frequency of 100 Hz stimulates the release of dinorphine. The combination of these two frequencies will stimulate the release of all four of these opioid peptides [10]. Various existing studies have used the acupuncture points of the body for DM therapy. In Indonesia, acupuncture research on DM has been performed using the acupuncture points of the body, but no studies have used ear acupuncture alone or attempted to determine the effects of EA at a particular point. In this study, we explored the effect of EA at the MA-IC 3 Endocrine ear acupoint on fasting blood glucose (FBG) levels in patients with type 2 DM.

2. Materials and Methods
The study protocol was approved by the Ethics Committee of Medical Faculty Universitas Indonesia and the Subcommittee on Medical Ethics of Banjar General Hospital. Participants who took part in this study agreed to participate on a voluntary basis and provided written consent. The research design chosen for this research project was the randomized clinical trial, and the research was performed at the Polyclinic of Internal Medicine of Banjar General Hospital. The inclusion criteria for the research subjects were as follows: (a) Patients with type 2 DM who had been diagnosed for 1-5 years; (B) male and female patients aged 40-70 years; (C) receiving standard oral hypoglycemic agent (OHA) therapy: glibenclamide 1 x 5 mg, Metformin 3 x 500 mg or Glucobay 3 x 50 mg; (D) not receiving insulin therapy; (E) fasting blood glucose (FBG) levels ≥130 mg up to ≤200 mg; (F) Body Mass Index (BMI) ≥23 to ≤30; (G) willing to sign informed consent; and (H) willing to continue with the research until completion according to the research schedule. The exclusion criteria were as follows: (a) female patients with positive pregnancy urine test results; (B) patients with a History of heart disease or hypertension; (C) patients using cardiac pacemakers; and (D) patients with contraindications for acupuncture, for example, skin infections, ear injuries or cauliflower ear. The subjects were randomly allocated into two groups, Group A (EA = electroacupuncture) and Group B (without EA = without electroacupuncture). Blood glucose measurements were performed using capillary blood and the GCU Easy Touch blood glucose meter. Electroacupuncture was performed using a KWD - 808 I electrical stimulator.

In all subjects, the procedures were conducted after a minimum of 10 hours of fasting, from 10 PM to 8 AM. The initial FBG level was measured before each procedure at 8 AM. While the patient was in the supine position, needle puncture was performed, at the right and left MA-IC 3 Endocrine ear acupoints until the sensation of puncture was felt. In the EA group, an electrostimulator was mounted on the right and left MA-IC 3 Endocrine ear acupuncture points with a dense disperse wave type at an intensity level that was comfortable for the subject for 30 minutes. In the No EA Group, the same electrostimulator was mounted in the same manner but was not powered on. In the EA group, after 30 minutes, the electrostimulator was powered off and removed, the needle was taken off, and the post-intervention FBG level was measured. The results of this study were assessed by comparing the FBG levels before and after acupuncture in each group and the extent of the difference in FBG reduction between the groups. Differences with p-values of <0.05 were considered statistically significant. Subjects were monitored for toxicities related to vagal/parasympathetic nerve stimulation, which include nausea, dizziness, loss of vision, excessive sweating, cold sensation, fatigue, and loss of
3. Results and Discussion

3.1 Results
This study included 54 patients with type 2 DM who met the inclusion criteria. These subjects were divided randomly into two groups, namely Group A (EA) and Group B (non-EA), each consisting of 27 research subjects. All participants completed the study intervention according to the protocol. There were no significant differences regarding the basic characteristics of the subjects in both groups (Table 1), i.e., age (Group A 55.19 ± 8.195 vs group B 56.15 ± 7.518, p = 0.655), sex (Group A male 15 people vs Group B twelve people, p = 0.414), education level (Group A undergraduate 33.3% vs Group B junior high school and senior high school 25.9%, p = 0.175), job history (Group A number of pensioners and civil servants was equal respectively 29.6% vs Group B civil servants 33.3%, p = 0.992), BMI (Group A 26.059 ± 2.8072 vs Group B 24.859 ± 2.0123, p = 0.077), and initial FBG levels (Group A 157.26 ± 24.485 vs Group B 149.67 ± 21.485, p = 0.231). Statistically significant reductions in FBG levels were observed in both the EA and non-EA groups after the intervention (Table 1). This reduction was more marked in the group receiving EA (initial FBG levels 157.26 ± 24.485 g/dL and final FBG levels 142.59 ± 26.771 g/dL, p < 0.05) than in the No EA group (initial FBG 149.67 ± 21.485 and final FBG 148.74 ± 21.326, p < 0.05).

Table 1. Comparison of mean FBG levels before and after intervention in groups A and B

| Group          | Initial FBG (mean ± SD) | Final FBG (mean ± SD) | p-value |
|---------------|-------------------------|-----------------------|---------|
| EA            | 157.26 ± 24.485         | 142.59 ± 26.771       | 0.000*  |
| Without EA    | 149.67 ± 21.485         | 148.74 ± 21.326       | 0.003*  |

* T-Test

The comparison between the two groups showed a statistically significant difference between mean reduction of FBG levels in subjects in the EA Group as compared with the No EA Group (14.67 ± 10.845 in EA vs 0.93 ± 1.466 in No EA, p < 0.05). The acupuncture intervention, with and without EA, was well-tolerated by the study participants. We did not observe any adverse effects due to either needle puncture or electrostimulation in our study participants.

3.2 Discussion
In this randomized controlled study, we explored the effect of electroacupuncture (EA) on fasting blood glucose (FBG) levels in patients with type 2 diabetes mellitus who were undergoing pharmacological treatment with oral hypoglycemic agents. Based on the results of this research, it was demonstrated that acupuncture at the MA-IC 3 Endocrine ear acupoint decreases FBG levels in patients with type 2 diabetes. The results of a comparison of the initial and final mean FBG concentrations in Group A and Group B showed significant differences (p < 0.05) in each group. In addition, the amounts of FBG decrease between Group A and Group B were also significantly different (p < 0.05), with the effect of ear acupuncture on FBG decrease being strengthened by electrostimulation. Studies using only ear acupuncture in DM patients are still rare, especially in Indonesia. Most studies of DM patients use body acupuncture or a combination of body acupuncture and ear acupuncture. Therefore, this study is a preliminary study that aims to determine the effect of puncture at the MA-IC 3 Endocrine ear acupoint in patients with type 2 DM.

An experimental study of rabbits using ear acupuncture at the MA-SC 6 Pancreas, MA-IC 3 Endocrine, MA-AH 7 Sympathetic, MA-IC 1 Lung, MA-IC Stomach, and MA-SC Kidney acupoints showed a significant decrease in FBG levels and an increase in insulin secretion. This ear acupuncture stimulates the auricular branch of the vagus fiber, resulting in decreased blood sugar and increased consciousness, as well as possible acupuncture-related complications, including bruising or bleeding in the puncture site and vaso-vagal response.
insulin secretion [11]. Several experimental studies on the use of electro acupuncture (EA) in mice with DM have shown that EA had an effect on plasma glucose levels by increasing insulin production and improving insulin sensitivity through the induction of endogenous β-endorphin secretion [12]. β-endorphins induce insulin secretion through the activation of opioid receptors in pancreatic beta cells, and β-endorphins also affect paracrine control in insulin secretion [13]. This was proven in an experimental study conducted by Chang et al. (1999) in mice with DM using an EA frequency of 15 Hz at the CV 12 Zhongwan point for 30 minutes [14] and in another study performed by Lin et al. (2002) in mice with DM using an EA frequency of 2 Hz at the CV 12 Zhongwan point for 30 minutes, both of which resulted in a decrease in plasma glucose levels and an increase in insulin secretion due to an increase in plasma β-endorphins [13].

Other experimental studies have used the ST 36 Zusanli point and an EA frequency of 15 Hz in mice with DM, including a study performed by Lee et al. (2010) in which EA for 30 minutes resulted in significantly decreased plasma glucose levels. In that study, hypoglycemia occurred due to the stimulation of the parasympathetic nerve, i.e., cholinergic nerve fibers that trigger acetylcholine secretion [12]. This study was continued by Lee et al. (2011), who applied EA for 60 minutes. By the 30th minute, EA had resulted in a decrease in plasma glucose levels, and by the 60th minute, EA had resulted in the increased expression of IRS-1 and AKT-2 proteins. These results show that EA has an effect other than the decreasing of plasma glucose levels through cholinergic nerve stimulation; it can also induce the regulation of the IRS-1 and AKT-2 insulin signaling proteins, which leads to increased insulin sensitivity [15]. In Lin et al.’s (2009) study, mice with DM received EA at a frequency of 15 Hz for 60 minutes at the ST 36 Zusanli point. The results revealed that EA can improve insulin resistance due to improvements in the expression of the IRS-1 and GLUT4 insulin signaling proteins, which increase insulin activity [16].

Insulin resistance and abnormal insulin secretion are the main causes of type 2 DM. Type 2 DM is characterized by three pathophysiological disorders: insulin secretion disorder, peripheral resistance and excessive liver glucose production [17]. Ear acupuncture is the stimulation of acupuncture points in the outer ear. Ear acupuncture may be used as a single therapy or in combination with acupuncture of the body [8]. Ear acupuncture as a form of therapy is originating in China around 500 BC. It was then redeveloped by Nogier, a French doctor. In 1957, Nogier proposed that the earlobe represents the fetus at the end of the pregnancy in a head-down position (an inverted fetus) [18]. The mechanism of ear acupuncture is achieved through reticular formation (RF) and the sympathetic and parasympathetic nervous systems [7]. Puncture stimulation is transmitted to the thalamus ventroposterior nucleus and then projected onto the cerebral cortex. Puncture stimulation will then reach the hypothalamus and activate the arcuateus and pituitary nuclei to secrete β-endorphins into the blood and cerebrospinal fluid [19-21]. These β-endorphins can induce insulin secretion through the activation of opioid receptors in pancreatic beta cells, and β-endorphins also affect paracrine hormone control in insulin secretion [13]. In addition, the MA-IC 3 Endocrine ear acupoint is connected to the vagus rami auricularis anterior nerve [20]. This vagus nerve is also connected to the internal organs, so the puncture stimulus can activate the pancreatic beta cells to secrete insulin [11]. Parasympathetic nerve stimulation through the cholinergic nerve fibers will trigger the secretion of acetylcholine, which stimulates insulin release, affects pancreatic beta-cell receptors [9], and triggers the release of proteins that play a role in insulin signaling, such as insulin-like growth factor [12]. These mechanisms can increase insulin secretion by increasing insulin sensitivity and lowering insulin resistance. The absence of both acupuncture-related and vagal-stimulation-related toxicity in our study is encouraging. In addition to proving the bidirectional nature of acupuncture’s mechanism, which means that it can adjust to the body’s homeostatic conditions, acupuncture also provides a potential benefit as compared to the escalation of conventional drug therapy, which has its own potential side effects, namely hypoglycemia, weight gain, nausea, bloating, and flatulence [1,2].
4. Conclusion

Ear acupuncture (EA) is a potentially safe and effective component of the management of patients with diabetes mellitus.

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