Effect of electroacupuncture combined with medical treatment on insulin resistance (HOMA-IR) of patients with metabolic syndrome

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Abstract. Metabolic syndrome is a complex disorder defined by a cluster of interconnected factors that increase the risk of cardiovascular diseases and diabetes mellitus type 2. Insulin resistance and central obesity are considered to be significant factors and underlying causes of metabolic syndrome; therefore, a reduction in insulin resistance is an important clinical goal. Studies have concluded that acupuncture can improve insulin sensitivity because it is effective against metabolic disturbances. A single-blind randomized controlled trial was conducted involving 50 patients who were randomly allocated into two groups: the electroacupuncture with medication group (n = 25) and sham electroacupuncture with medication group (n = 25). Electroacupuncture therapy was given twice a week for 10 times at points CV12 Zhongwan, CV4 Guanyuan, ST25 Tianshu, ST36 Zusanli, ST40 Fenglong, SP6 Sanyinjiao, and MA-IC3 Endocrine. Fasting blood glucose and fasting insulin serum levels were assessed according to the homeostasis model assessment of insulin resistance (HOMA-IR) as the primary outcome. There was a statistically significant difference in HOMA-IR changes between the electroacupuncture with medication group and sham electroacupuncture with medication group (−1.66 ± 2.187 and −0.29 ± 2.388, respectively; p = 0.044). Electroacupuncture with medical treatment effectively decreased insulin resistance of patients with metabolic syndrome.

1. Introduction

Metabolic syndrome is a combination of cardiovascular disease risk factors that include diabetes or increase in plasma glucose levels, central obesity, increase in cholesterol, and increase in blood pressure [1]. Metabolic syndrome, also known as the insulin resistance syndrome, has become a major medical problem worldwide [2]. It is estimated that approximately 20%–25% of the adult population worldwide suffers from metabolic syndrome and has a two-times greater risk of death and a three-times greater risk of suffered from heart attacks or stroke than that of individuals without metabolic syndrome. Moreover, individuals with metabolic syndrome have a five-times greater risk of developing type 2 diabetes mellitus [1].

Insulin resistance is the main pathogenesis of metabolic syndrome and may indirectly increase the occurrence of cardiovascular disease through disturbances in the glucose and lipid metabolism, hypertension, and proinflammatory conditions [3]. Therefore, some researchers also refer to metabolic syndrome as insulin resistance syndrome. Decreasing insulin resistance, which can be measured according to the homeostasis model assessment of insulin resistance (HOMA-IR) formula, is an...
important clinical therapy objective. The HOMA-IR scores are obtained from fasting blood glucose and fasting insulin examination results [4,5].

The management of metabolic syndrome includes pharmacological and non-pharmacological therapies. The two groups of medications available today, which provide immediate effects on insulin resistance, are biguanides and thiazolidinediones (TZDs). However, pharmacological therapy has limitations with respect to the side effects of medications, cost, and patient compliance. For biguanides, the most frequently encountered side effect is the presence of gastrointestinal symptoms (diarrhea, discomfort in the stomach, and anorexia). The most commonly seen side effects in TZDs is the presence of edema, weight gain, mood swings, depression, nausea, and dizziness when the medication is stopped. For a therapy to be effective, an integrated management of metabolic syndrome is needed to prevent cardiovascular complications [6].

Acupuncture is a part of traditional Chinese medicine that has been practiced for a long time for the prevention and cure of many diseases. There are many methods of acupuncture; one type, called electroacupuncture (EA), uses electrical stimulations at acupuncture points [7]. Some studies have concluded that EA can increase insulin sensitivity to effectively overcome metabolic disturbances, such as hyperglycemia, obesity, hyperphagia, dyslipidemia, inflammation, changes in the sympathetic nervous system activity, and insulin signal disturbances related to the pathogenesis of insulin resistance [6,8].

Presently, there has been an increase in the clinical evidence of the efficacy of acupuncture for the treatment of insulin resistance [8]. However, clinical research on acupuncture in insulin resistance therapy still has limitations with respect to the adequacy of the number of samples and control [6]. Moreover, research on the effect of acupuncture therapy on insulin resistance has never been conducted in Indonesia. This study aims to assess the effect of the combination of EA with medication on insulin resistance (HOMA-IR scores) in patients with metabolic syndrome.

2. Methods

This was a single-blind randomized controlled clinical trial involving patients with metabolic syndrome who met the inclusion criteria. This study was conducted with an approval from the Health Research Ethics Committee of Faculty of Medicine, Universitas Indonesia-dr.Cipto Mangunkusumo Hospital (No: 460/UN2.F1/ETIK/2017). The study was conducted at the Internal Disease Clinic of Kembangan District Hospital, West Jakarta from May 2017 to June 2017. The research subjects were 50 patients who were randomly divided according to a random computerized table into two groups: the control group and treatment group. Each group comprised 25 research subjects, and two subjects were eliminated (one from the control group and one from the treatment group).

The inclusion criteria of this study were patients diagnosed by internists as having metabolic syndrome based on the NCEP ATP III Asia modification criteria, aged 30–59 years, willing to sign an informed consent form, and willing to participate and continue until the end of the research. The exclusion criteria were patients with a history of heart or cerebrovascular disease; pregnant; had contraindications for acupuncture therapy, such as medical emergencies, malignancies, disturbances in blood clotting, and infection in the acupuncture points; had contraindications for EA therapy, such as using a pacemaker, heart rhythm disturbances, subjects with fasting blood glucose levels >250 mg/dL or undergoing insulin therapy, and subjects with acute diabetes complications, such as hypoglycemia, infection, and hyperosmolar nonketotic state.

The external results of this experiment were the HOMA-IR scores calculated from the fasting blood glucose and fasting insulin examination results. The initial examinations included blood pressure, body weight, and height, which were conducted by paramedics. Anamnesis, physical examination, and therapy were conducted by internists. The patients were then consulted to the Nutrition Clinic to obtain a diet plan based on their condition. Blood was obtained from the subjects twice, before the start of EA/sham EA treatment and after 10x EA treatment. Blood samples were taken by analysts of the Kembangan Laboratory. The fasting blood glucose examination was also performed at the Kembangan District Laboratory, whereas the fasting insulin examination was performed at the dr. Cipto Mangunkusumo Hospital Laboratory. Then, the patients underwent EA or sham EA therapy.
The treatment group patients received acupuncture at points CV12 Zhongwan, CV4 Guanyuan, ST25 Tianshu, ST36 Zusanli, ST40 Fenglong, and SP6 Sanyinjiao. Then, the patients were connected to an electrostimulator (SDZ-V brand) with a dense-disperse wave at a frequency of 3/15 Hz for 20 minutes with light intensity. It was ensured that the patient was comfortable during this treatment. The electrostimulator connected to the ear point MA-IC3 Endocrine used a continuous wave at a frequency of 2 Hz and light intensity for 20 minutes. The control group received treatment at the same acupuncture points, but the needles did not penetrate the skin and the electrostimulator was not activated.

The data obtained in this research was processed by the statistical program SPSS 20. A normality test was performed using the Shapiro–Wilk test. The numeric data with normal distribution are presented as mean scores and standard deviations, and the non-normally distributed data were presented as medians and ranges. The statistical analyses of fasting blood glucose levels, fasting insulin levels, and HOMA-IR before and after 10× EA therapy in each group were performed using the paired t test if the data were normally distributed or the Wilcoxon test if the data were not normally distributed. The statistical analysis of the difference in the HOMA-IR scores between the two groups was performed using the unpaired t test if the data were normally distributed or the Mann–Whitney test if the data were not normally distributed. If the comparative hypothesis test resulted in p < α (p < 0.05), it can be concluded that there was a significant statistical difference between the variables.

3. Results

| Variable            | Treatment Group | Control Group | p     |
|---------------------|-----------------|---------------|-------|
| Sex                 | Male            | 4 (16.0)      | 4 (16.0) | 1.000** |
|                     | Female          | 21 (84.0)     | 21 (84.0) |       |
| Age (years)         | 46.92 ± 8.698   | 50.44 ± 6.07  | 0.104* |
| Weight (kg)         | 68.62 ± 7.322   | 68.40 ± 13.796|       |
| Body Mass Index     | 27.91 ± 3.264   | 28.57 ± 5.303 | 0.603* |
| Systolic BP (mmHg)  | 120 (100–160)   | 130 (100–170) | 0.700* |
| Diastolic BP (mmHg) | 80 (70–100)     | 80 (70–100)   | 0.384* |
| Initial Fasting Blood| 131 (83–250)    | 126 (90–250)  | 0.587* |
| Glucose Level (mg/dL) | 10.65         | 13.27         | 0.410* |
| (μIU/mL)            | (4.63–34.86)    | (2.73–20.40)  |       |
| HOMA-IR             | 3.11            | 3.67          | 0.869* |
|                     | (0.96–19.30)    | (1.15–10.11)  |       |

*Mann–Whitney **Chi-square

Table 1 showed characteristic of the research subjects. The Mann–Whitney test showed that there was no significant difference between the two groups with respect to the systolic blood pressure variable (p = 0.700) and diastolic blood pressure (p = 0.384). The Mann–Whitney test showed that there was no significant difference between the two groups with respect to the fasting blood glucose level variable (p = 0.587), fasting insulin level (p = 0.410), and HOMA-IR (p = 0.869). Based on the data obtained, the two groups could be compared because there were no statistically significant differences (p > 0.005) in the basic characteristics between the two groups. Then, a statistical analysis of the HOMA-IR scores from the results of the fasting blood glucose and fasting insulin levels was performed.
Table 2. Comparison of the median fasting blood glucose levels before and after treatment.

| Subject          | Before       | After        | p       |
|------------------|--------------|--------------|---------|
| Treatment Group  | 131 (83–250) | 118.5 (85.0–264.0) | 0.004*  |
| Control Group    | 126 (90–250) | 117.5 (95.0–201.0) | 0.637*  |

*Wilcoxon

There was a statistically significant difference between the median fasting blood glucose levels before and after electroacupuncture therapy in the treatment group (p = 0.004). However, there was no significant difference in the control group (p = 0.637). These results were obtained based on the Wilcoxon test (see Table 2).

Table 3. Comparison of the median fasting insulin levels before and after treatment.

| Subject          | Before       | After        | p       |
|------------------|--------------|--------------|---------|
| Treatment Group  | 10.65 (4.63–34.86) | 9.93 (2.87–24.32) | 0.017*  |
| Control Group    | 13.27 (2.73–20.40) | 11.29 (3.06–32.53) | 0.199*  |

*Wilcoxon

The Wilcoxon test (see Table 3) showed that there was a statistically significant difference between the median fasting insulin levels before and after EA therapy in the treatment group (p = 0.017). However, there was no significant difference in these levels in the control group (p = 0.199).

Table 4. Comparison of the median HOMA-IR scores before and after treatment.

| Subject          | Before       | After        | p       |
|------------------|--------------|--------------|---------|
| Treatment Group  | 3.11 (0.96–19.30) | 2.63 (0.61–15.60) | 0.001*  |
| Control Group    | 3.67 (1.15–10.11) | 3.38 (0.81–9.54) | 0.376*  |

*Wilcoxon

The Wilcoxon test (see Table 4) showed that there was a statistically significant difference in the median HOMA-IR scores before and after EA therapy in the treatment group (p = 0.001). However, there was no significant difference in the median HOMA-IR scores in the control group (p = 0.376).

Table 5. Comparison of the change in the HOMA-IR scores between the groups.

| Variable | Treatment Group | Control Group | p       |
|----------|-----------------|---------------|---------|
| HOMA-IR  | −1.66 ± 2.187   | −0.29 ± 2.388 | 0.044*  |

*Independent samples t test

According to the Mann–Whitney test, there was no significant difference in the changes in fasting blood glucose levels (p = 0.071) and fasting insulin levels (p = 0.174) between the two groups. The independent samples t test showed that there was a significant difference in the mean change in the HOMA-IR scores (p = 0.044) between the two groups (see Table 5).

4. Discussion

This is the first acupuncture study in Indonesia to use the EA technique to assess insulin resistance in patients with metabolic syndrome. The EA technique was chosen over manual acupuncture because it has several advantages. Generally, EA produces more intensive, effective, and comfortable stimulation than that obtained by manual acupuncture. Electric stimulations from EA also can be accurately measured; therefore, it is frequently used in clinical studies [9].
The selection of the acupuncture points in this study was based on previous studies which proved that these acupuncture points were effective in reducing insulin resistance. Among those was the study by Lin TR et al [10] in which EA at the acupuncture point ST36 Zusanli reduced insulin resistance. There were significant changes in the free fatty acid plasma levels in rats and the HOMA-IR scores as well as a decrease in glucose tolerance. Liang F et al [4] studied the effect of low-frequency EA on improving the sensitivity of insulin in obese rats through the activation of sirtuin 1 (SIRT1)/proliferator-activated receptor coactivator-1α (PGC-1α) in skeletal muscles. EA was applied to the acupuncture points ST36 and CV4 at a frequency of 3 Hz and intensity of 0.5–0.8 mA. In diabetic rats, EA increased insulin sensitivity, decreased free fatty acid levels, and increased the expression of SIRT1 in skeletal muscles and expression of the genes that produce peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), nuclear respiratory factor 1, and acyl-CoA oxidase, thereby improving insulin signals.

In this study, the metabolic syndrome criteria varied between the subjects; the subjects had to fulfill three out of five criteria (central obesity, increase in triglycerides, low fasting blood glucose levels, hypertension, and disturbances in glucose tolerance/diabetes mellitus). The main parameter measured in this study was the HOMA-IR score, which is the most frequently used test for insulin resistance; it was obtained from the fasting blood glucose and fasting insulin examination results. Therefore, the levels of fasting blood glucose and fasting insulin were also measured in this study. There was a statistically significant difference in the median levels of fasting blood glucose before and after therapy in the treatment group. The median blood glucose levels were normal according to WHO and were considered to be controlled according to the Consensus on Management and Prevention of Diabetes Mellitus Type 2 [11]. The results of the fasting blood glucose test showed that a combination of EA therapy and medications was better than combination sham EA therapy and medications because although the subjects in the control group showed a decrease in the median fasting blood glucose levels, the difference was not statistically significantly.

There was little variation in the medications administered (oral hypoglycemic medication). Overall, subjects received a combination of medications (metformin with glimepiride/gliquidone/glibenclamide/acycarbose). Although there were more subjects who received the combination therapy in the control group than in the treatment group, the median decrease in fasting blood glucose levels was greater in the treatment group.

The change in fasting insulin levels did not differ from that in fasting blood glucose levels. There was a significant difference between the median fasting insulin levels before and after therapy in the treatment group. A decrease in the insulin levels was also observed in the control group but it was not statistically significant. These results showed that a combination of EA and medications was more effective in decreasing the levels of fasting insulin than sham electroacupuncture therapy and medications.

The HOMA-IR median scores before and after EA therapy in the treatment group were statistically significantly different. The HOMA-IR score after therapy was <2.77, and this indicated insulin sensitivity. The comparison of the change in the HOMA-IR scores showed that there was a statistically significant difference between the two groups (mean change in the treatment group. These results showed that EA therapy with medications led to a greater decrease in insulin resistance than that obtained by sham EA therapy with medications in patients with metabolic syndrome.

The results were slightly different from those obtained in a study by El-Mekawy HS et al. which evaluated the effect of a combination of laser puncture and diet training on metabolic syndrome in 28 postmenopausal women. Laser puncture was applied at the acupuncture points CV4 Guanyuan, CV9 Shuifen, C12 Zhongwan, ST25 Tianshu, ST26 Zusanli, SP6 Sanyinjiao, and ST40 Fenglong for 2 minutes/point, three times a week for 12 weeks [12]. Both groups showed significant decreases in the anthropometry and metabolic parameters. However, greater decreases in waist circumference (p = 0.001), hip circumference (p = 0.001), cholesterol (p = 0.04), and insulin levels (p = 0.043) were shown in the laser puncture group than those shown in the control group. The decrease in the HOMA-IR scores was greater in the laser puncture group, but the difference was not statistically significant (p = 0.260). The fasting blood glucose level was lower in the laser puncture group, but the difference was not statistically significant (p = 0.679).
Girouzjaei A et al. compared the effect of metformin monotherapy with the combination of acupuncture therapy and metformin on weight loss and insulin sensitivity in 39 diabetic patients [13]. The acupuncture points selected were ST25 Tianshu, SP15 Daheng, ST28 Shuidao, CV12 Zhongwan, CV6 Qihai, CV9 Shuifen, LI4 Hegu, LI11 Quchi, ST36 Zusanli, and SP6 Sanyinjiao. The ear points selected were the Stomach, Shenmen, Endocrine, Spleen, and Hunger points. EA at a frequency of 15 Hz and an intensity of 10 mA was used for 30 minutes every other day for 3 weeks. The results showed that a combination of metformin and acupuncture therapy significantly reduced weight and decreased body mass index, fasting blood glucose, fasting insulin, HOMA score, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, adiponectin, glucagon-like peptide 1, resistin, serotonin, free fatty acid, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and ceramide.

The mechanism of EA in decreasing insulin resistance is related to the central effect of acupuncture and is enhanced by low-intensity EA electric stimulation at a frequency of 2 Hz at the point CV12 Zhongwan, which stimulates the excretion of β-endorphins that increase the secretion of insulin that in turn decreases plasma glucose levels. The hypoglycemic effect of EA at a frequency of 2 Hz at the point ST36 is also mediated by serotonin [6]. The serotonin produced in β pancreas cells increases insulin secretion and proliferation of β pancreas cells [14].

Insulin resistance is characterized by a decrease in the activation of Akt by PI3K, which is stimulated by insulin. EA can modulate the expression of genes involved in signal transduction, cell cycle, metabolism, stress response, and DNA repair. Low-to-moderate intensity electric stimulation influences signal transduction and activates PI3K/Akt, which increases insulin sensitivity and fat metabolism. EA at a frequency of 15 Hz at the ST36 bilateral point increases the expression of signaling insulin proteins (IRS1, GLUT4) in insulin-resistant rats [15]. Low-frequency EA also improves insulin sensitivity through SIRT1 regulation and peroxisome proliferator-activated receptor coactivator-1α (PGC-1α) in skeletal muscle [6]. Additionally, EA also increases insulin sensitivity by increasing the expression of adiponectin, which decreases under insulin-resistant conditions [6]. Adiponectin decreases free fatty acid synthesis, decreases inflammation by suppressing the excretion of TNF-α and modulation of PPAR-γ, and increases beta oxidation of mitochondria by the activation of the cyclic AMP-dependent protein kinase pathway [16].

Obesity, insulin resistance, and type 2 diabetes are closely related to chronic inflammation, which is characterized by an excessive production of proinflammatory cytokines. Acupuncture has anti-inflammatory effects that are mediated by the stimulation of the vagus nerve and significantly modulates the excretion of anti-inflammatory cytokines (such as IL-10 and IL-13), decreases proinflammatory cytokines (such as TNF-α, IL-1, IL-6 and IL-8), and reduces the expression of leptin from adipose tissues related to insulin resistance, obesity, and inflammation [6,17]. Recent studies have provided clinical evidence showing that acupuncture stimulation sends signals to the vagus nerve and mediates anti-inflammatory responses in the lymph node [18]. Nucleus tractus solitarius (NTS) in the vagus nerve can activate the receptor α7 nicotinic acetylcholine of the macrophages in the lymph through-lymph adrenergic input to T-cells, resulting in a cholinergic anti-inflammatory response. Acupuncture stimulation at the point ST36 Zusanli will be responded by the purinergic and dopaminergic receptors in the dorsal vagal complex, which then induces c-Fos protein signal in the NTS, resulting in the reduction of TNF-α signals in the lymph [19]. Besides body acupuncture, ear acupuncture is also closely related to NTS because the ear lobe is innervated by the auricular branch of the vagus nerve [20].

This study showed that there was a statistically significant reduction in the HOMA-IR scores, which indicated an improvement in insulin sensitivity. A decrease in insulin resistance (HOMA-IR score) is expected to control blood glucose, blood pressure, waist circumference, body weight, and the lipid profile of patients with metabolic syndrome and, therefore, decrease the risks of type 2 diabetes, cardiovascular diseases, and complications of type 2 diabetes.

The only side effect observed in this study was hematomas in four study subjects at the acupuncture points. The hematoma disappeared within 1 week. Worse side effects, such as infection and fainting, were not observed. Therefore, we concluded that EA is a safe therapy and can potentially be combined with medication to decrease the risk of cardiovascular disease and diabetes.
A limitation of this study was the difference in metabolic syndrome criteria among the subjects; therefore, further analysis to assess the difference in the effect of the combination of EA and medication on the HOMA-IR score in patients with metabolic syndrome with or without hypertension, obesity, and diabetes could not be performed. A second limitation was the short study period, which meant that long-term observation could not be performed.

5. Conclusions
This study showed that there was a statistically significant difference in the effects on insulin resistance (HOMA-IR score) in patients with metabolic syndrome between the combination of EA therapy with medication and sham electroacupuncture therapy with medication. The change in HOMA-IR score in the treatment group was $-1.66 \pm 2.187$ and that in the control group was $-0.29 \pm 2.388$ ($p = 0.044$). Electroacupuncture with medical treatment effectively decreased insulin resistance of patients with metabolic syndrome.

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