

Study of the Effect of High-Voltage Low-Frequency Electrotherapy on Type 2 Diabetes in an *in Vivo* Model

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Abstract

The study investigates the impact of high-voltage low-frequency electrotherapy on glucose levels and hematological parameters in an *in vivo* model of type 2 diabetes. The results demonstrate a significant reduction in glucose increases during glucose tolerance tests (GTT) and suggest potential mechanisms, including improved insulin sensitivity and reduced inflammation. Hematological analysis indicates no adverse effects of electrotherapy on healthy or diabetic mice. This study supports the potential of high-voltage low-frequency electrotherapy as an adjunctive treatment for type 2 diabetes, warranting further research into its mechanisms and long-term effects.

Keywords

Type 2 Diabetes, *In Vivo* Model, High-Voltage Electrotherapy, Glucose Tolerance Test (GTT), Hematological Analysis

1. Introduction

The treatment of type 2 diabetes (T2D) requires an effective integrative approach utilizing all advancements in medicine. One of the methods increasingly being used in diabetes treatment is electrotherapy, which involves exposing patients to various modalities of electric fields. Results from various preclinical and clinical studies suggest that the use of electrotherapy in T2D can lead to normalization of glucose levels, wound healing, and alleviation or reduction of diabetic neuropathic pain [1]-[11]. Existing methods for treating diabetes, including medication and lifestyle changes, do not always provide sufficient glucose control. Innovative methods, such as high-voltage low-frequency electrotherapy, could complement

or improve current treatment approaches.

Aim of the Study

The aim of this study is to evaluate the effectiveness of high-voltage low-frequency electrotherapy, which influences the body with an electrostatic field changing polarity according to a set program, in influencing blood glucose levels in mice with type 2 diabetes. The main hypotheses include:

- High-voltage electrotherapy reduces the increase in blood glucose levels during the glucose tolerance test (GTT).
- High-voltage electrotherapy positively affects hematological parameters in diabetic mice.
- High-voltage electrotherapy does not negatively impact hematological parameters in healthy mice.

2. Methods and Experimental Design

2.1. Technology of High-Voltage Low-Frequency Electrotherapy

This study utilized high-voltage low-frequency therapy using the stationary electrotherapy devices Healectrics (model S02). The therapy operates based on the application of high-voltage direct current (30 - 50 kV), with a polarity change frequency of up to 1 Hz. In this experiment, a frequency of ~0.2 Hz was used. To ensure effective therapy and safety, the subject undergoing therapy must be electrically isolated from other large conductive objects. For instance, when treating humans, the subject sits on a chair made of dielectric materials. Similarly, when treating animals, they are placed in a plastic cage on a dielectric stand at least 5 cm above a conductive surface, and other conductive objects should also be maintained at a distance of at least 5 cm. This method differs from previously considered electrotherapy techniques by inducing polarization effects throughout the subject's body, thereby increasing the body potential to a level of 30 - 50 kV. This saturation of the body with ions begins to dissipate into the air, and microcurrents arise in the patient's body.

2.2. Experimental Animals

Streptozotocin (STZ)-induced diabetes in ICR mice is often used to model diabetes mellitus and its complications, as well as other pathologies [12]. The study used 24 ICR mice, aged 8 - 12 weeks. The animals were kept under standard conditions with controlled lighting and had ad libitum access to food and water.

2.3. Induction of Diabetes

A model of type 2 diabetes was induced in mice by intravenous administration of nicotinamide (120 mg/kg) and intraperitoneal administration of streptozotocin (65 mg/kg). Nicotinamide was injected intravenously at a dose of 120 mg/kg, with the volume determined individually for each animal based on their body weight.

Fifteen minutes later, streptozotocin in citrate buffer (pH 4.5) was injected intraperitoneally at a dose of 65 mg/kg, with the volume determined individually for each animal based on their body weight. Before the administration of streptozotocin, the animals were fasted for 4 hours. A glucose tolerance test was conducted to confirm diabetes.

2.4. Groups and Housing Conditions

The animals were divided into four groups of six mice each:

- Group 1: Diabetes, no electrotherapy.
- Group 2: Diabetes, high-voltage low-frequency electrotherapy.
- Group 3: Healthy mice, no electrotherapy.
- Group 4: Healthy mice, high-voltage low-frequency electrotherapy.

Animals with no signs of health problems were selected for the experiment. Animals were distributed into groups using the randomization principle, using the glucose level in the GTT on day 0 of the study as a criterion.

2.5. Study Design

The first day of electrotherapy was considered day 1 of the study. Animals in Groups 2 and 4 were subjected to electrotherapy three times a day for 30 minutes over 2 weeks (with a technical break on day 9). Electrotherapy was conducted by placing the animals in individual cages without metal parts. A conductive plate (electrode) was placed under the bedding at the bottom of the cage, to which a high-voltage electric field of approximately ~30 - 50 kV was applied. Every 5 seconds, the polarity of the field was reversed (the field was turned off for 1 second and then applied again with the opposite polarity).

2.6. Glucose Tolerance Test (GTT)

The GTT was conducted on days 15 and 22 of the study. Animals were fasted for 4 hours before the test, after which they were given glucose intragastrically (2 g/kg). Blood glucose levels were measured before glucose administration and at 30, 60, 90, and 120 minutes after administration.

2.7. Hematological Analysis

Blood for hematological analysis was collected from the tail vein. The following parameters were determined: Red blood cell count (RBC), hemoglobin level (Hb), hematocrit (HCT), white blood cell count (WBC), lymphocyte count (LYM#, LYM%), monocyte count (MON#, MON%), granulocyte count (GRA#, GRA%), mean corpuscular hemoglobin content (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cell distribution width—coefficient of variation (RDW), red blood cell distribution width—standard deviation (RDWSD), platelet count (PLT), mean platelet volume (MPV), platelet crit (PCT), platelet distribution width—coefficient of variation (PDW). Statistically significant differences and near statistically significant differences for

pematocrit (HCT), hemoglobin (HGB), leukocytes, and lymphocyte levels were determined.

2.8. Statistical Analysis

Data were analyzed using the t-test for independent samples. The significance level was set at $P < 0.05$.

3. Discussion

3.1. Glucose Tolerance Test (GTT)

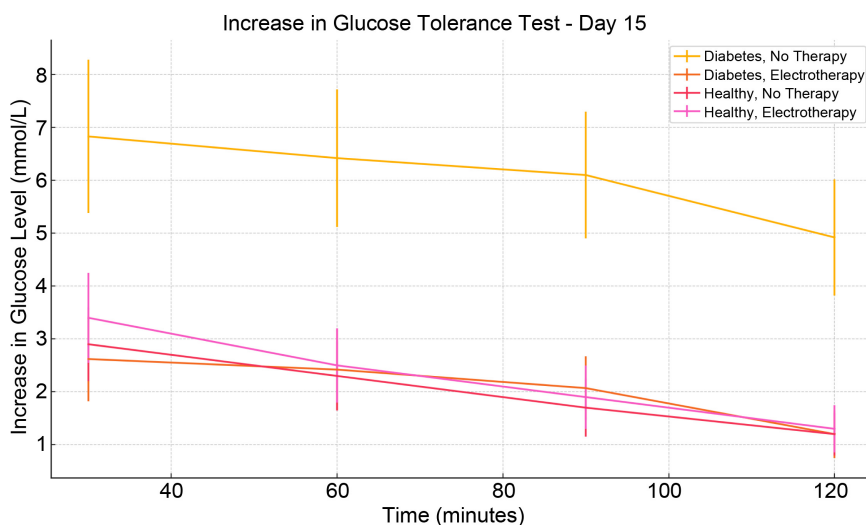
The results of the GTT indicate that two weeks of high-voltage low-frequency electrotherapy significantly reduce the increase in blood glucose levels in diabetic mice. On day 15, the increase in glucose levels post-load in the group receiving electrotherapy (Group 2) was significantly lower compared to the group without therapy (Group 1) (**Table 1, Graph 1**). Significant differences were observed at all time points (30, 60, 90, and 120 minutes) with p-values < 0.05 . On day 22, the effect was also significant (**Table 2, Graph 2**), indicating a sustained effect of high-voltage electrotherapy even a week after its completion. These data suggest that the therapy may have a long-term impact on reducing the increase in glucose levels during the GTT.

Table 1. Glucose Tolerance Test (GTT) on Day 15 (increase in glucose level, mean \pm standard deviation).

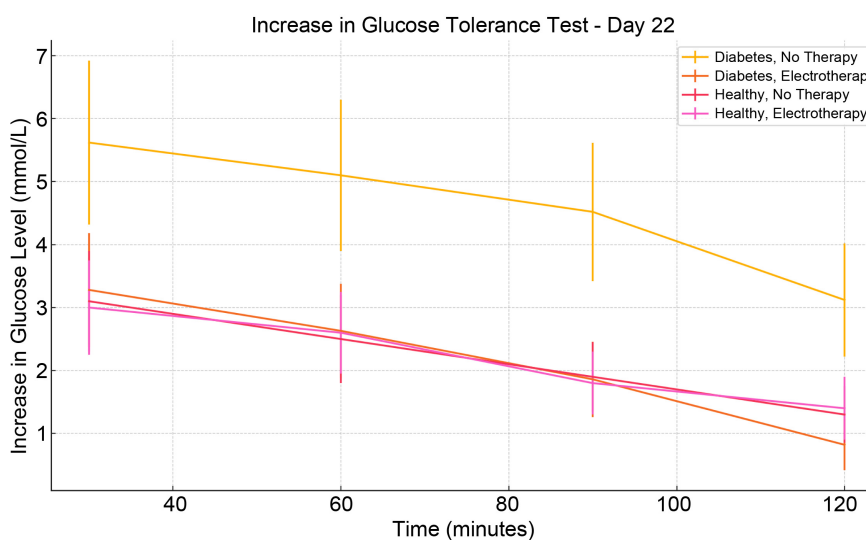
Group	30 min	60 min	90 min	120 min
Diabetes, No Therapy	6.83 \pm 1.45	6.42 \pm 1.30	6.10 \pm 1.20	4.92 \pm 1.10
Diabetes, Electrotherapy	2.62 \pm 0.80	2.42 \pm 0.75	2.07 \pm 0.60	1.20 \pm 0.45
Healthy, No Therapy	2.90 \pm 0.70	2.30 \pm 0.65	1.70 \pm 0.55	1.20 \pm 0.40
Healthy, Electrotherapy	3.40 \pm 0.85	2.50 \pm 0.70	1.90 \pm 0.60	1.30 \pm 0.45

Table 2. Glucose Tolerance Test (GTT) on Day 22 (increase in glucose level, mean \pm standard deviation).

Group	30 min	60 min	90 min	120 min
Diabetes, No Therapy	5.62 \pm 1.30	5.10 \pm 1.20	4.52 \pm 1.10	3.12 \pm 0.90
Diabetes, Electrotherapy	3.28 \pm 0.90	2.63 \pm 0.75	1.86 \pm 0.60	0.82 \pm 0.40
Healthy, No Therapy	3.10 \pm 0.80	2.50 \pm 0.70	1.90 \pm 0.55	1.30 \pm 0.45
Healthy, Electrotherapy	3.00 \pm 0.75	2.60 \pm 0.65	1.80 \pm 0.50	1.40 \pm 0.50



Graph 1. Increase in Glucose Tolerance Test (GTT) on Day 15 (increase in glucose level, mean \pm standard deviation for each group).



Graph 2. Increase in Glucose Tolerance Test (GTT) on Day 22 (increase in glucose level, mean \pm standard deviation for each group).

The reduction in the increase in glucose levels during the GTT is an important indicator suggesting a decrease in insulin resistance. This improvement in the body's ability to utilize glucose post-load is usually associated with increased insulin sensitivity. Improved insulin sensitivity allows cells to more efficiently take up glucose from the blood, reducing overall glucose levels after meals or loads. The reduction in the increase in glucose levels may also indicate improved overall metabolic regulation and a reduction in risks associated with hyperglycemia, such as vascular diseases and organ damage.

3.2. Hematological Analysis

Let's analyze the indicators where significant differences were identified (**Table 3**).

Mice in Group 1 showed a statistically significant decrease in hematocrit compared to the intact Group 3 ($P < 0.05$). In Group 2, the decrease in hematocrit compared to Group 3 was not statistically significant. Diabetes causes a significant decrease in hematocrit, which may be associated with the development of anemia commonly seen in diabetic patients. This decrease may be related to various factors such as chronic inflammation and deterioration of the vascular and hematopoietic systems. The fact that mice in Group 2 (diabetes + electrotherapy) showed a less pronounced decrease in hematocrit compared to mice in Group 1 (diabetes without electrotherapy) may indicate a potential protective effect of high-voltage electrotherapy on the hematopoietic system.

Table 3. Extract from hematological analysis (Leukocytes, Lymphocytes, Granulocytes, Hemoglobin, Hematocrit).

Group	Leukocytes ($10^9/L$)	Lymphocytes ($10^9/L$)	Granulocytes ($10^9/L$)	Hemoglobin (HGB) (g/L)	Hematocrit (HCT) (L/L)
Diabetes, No Therapy	3.4 ± 0.7	2.7 ± 0.7	0.5 ± 0.1	137 ± 4	0.407 ± 0.017
Diabetes, Electrotherapy	3.4 ± 0.8	2.5 ± 0.6	0.6 ± 0.2	141 ± 6	0.419 ± 0.020
Healthy, No Therapy	2.9 ± 0.6	2.2 ± 0.6	0.5 ± 0.1	144 ± 4	0.439 ± 0.016
Healthy, Electrotherapy	3.4 ± 1.7	2.6 ± 1.5	0.6 ± 0.2	144 ± 8	0.431 ± 0.026

Healthy mice in Group 4 exposed to high-voltage electrotherapy showed a significant increase in leukocytes, lymphocytes, and granulocytes compared to the intact Group 3 (more than 20%). This may indicate an immunomodulatory effect of electrotherapy. Despite the observed increase, the data are not statistically significant, which may indicate that the differences are caused by random factors or individual variations among animals. However, it could be an important indicator of potential immunomodulatory effects of electrotherapy. Additional studies with larger samples are needed to better understand the impact of electrotherapy on the immune system.

Comparing Group 3 (no diabetes, no electrotherapy) and Group 4 (no diabetes + electrotherapy), the animals in Group 4 did not show other deviations in blood composition compared to the intact Group 3. This indicates that electrotherapy does not have a negative impact on the hematological parameters of healthy animals, confirming the safety of high-voltage electrotherapy for healthy animals.

Comparing Group 1 (diabetes, no electrotherapy) and Group 2 (diabetes + electrotherapy), the diabetic animals in Group 2 did not show other deviations in blood composition compared to the diabetic group without electrotherapy. This indicates that high-voltage electrotherapy does not worsen hematological parameters

in diabetic mice, confirming the safety of high-voltage electrotherapy for diabetic animals.

3.3. Hypotheses of Mechanisms of High-Voltage Therapy

1) Improvement of Insulin Resistance

- **Stimulation of Receptors:** High-voltage therapy may improve the sensitivity of insulin receptors on cell surfaces, enhancing the efficiency of insulin in reducing blood glucose levels.
- **Increase of Glucose Transporters:** It may stimulate the expression of glucose transporters (e.g., GLUT4), improving glucose uptake by muscle and adipose tissue.

2) Reduction of Inflammation

- **Anti-Inflammatory Effect:** Electrotherapy may reduce the level of systemic inflammation often associated with insulin resistance. Reducing inflammation can improve insulin function and prevent a significant decrease in hematocrit.

3) Regulation of the Nervous System

- **Stimulation of Nerve Pathways:** Electrotherapy may influence the autonomic nervous system, improving the regulation of glucose homeostasis through central mechanisms.

4) Improvement of Blood Circulation and Microcirculation

- Electrotherapy can improve blood flow and microcirculation in tissues, contributing to more efficient delivery of glucose and insulin to target cells. It can also promote better tissue oxygenation and nutrient supply, reducing the negative impact of diabetes on erythropoiesis (red blood cell formation) and leading to a less pronounced decrease in hematocrit.

5) Stimulation of Regenerative Processes

- Electrotherapy may stimulate regenerative processes in the body, promoting the restoration of normal levels of red blood cells and consequently hematocrit.

4. Conclusion

The study results demonstrate that high-voltage electrotherapy can significantly reduce the increase in blood glucose levels during the GTT and potentially improve insulin resistance in diabetic mice. Electrotherapy also shows a possible immunomodulatory effect and does not negatively impact hematological parameters. These findings support the potential of high-voltage electrotherapy as an adjunctive treatment for diabetes, warranting further research into its mechanisms and long-term effects. Future research should focus on long-term observation of metabolic and hematological parameters, combined treatment approaches, and the potential immunomodulatory effects of high-voltage electrotherapy.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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