

# Effects of pulsed electromagnetic fields on lipid peroxidation and antioxidant levels in blood and liver of diabetic rats

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## ABSTRACT

**Objective:** The present study investigated the protective effects of a pulsed electromagnetic field (PEMF) in a rat model of diabetes by analyzing oxidative/nitrosative stress parameters.

**Methods:** Rats were randomly divided into four groups of eight each: a control group, a sham PEMF group, a diabetes group, and a diabetes+PEMF group. Diabetes was induced in the sham PEMF, diabetes, and diabetes+PEMF groups by treatment with 50 mg/kg streptozotocin (STZ). Rats in the sham PEMF group were treated identically, without running the instrument. Following the development of diabetes, rats in the diabetes+PEMF group were treated with PEMF for 60 min/day for 4 weeks.

**Results:** Levels of oxidants, such as malondialdehyde (MDA), nitric oxide (NO), and myeloperoxidase (MPO), and antioxidants, such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT), were measured in blood and liver tissue samples. MPO, MDA, and NO levels were significantly higher, and SOD levels significantly lower, in the sham PEMF and diabetes groups than in the control group ( $p < 0.05$  each), whereas the levels of all these four (i.e.: MPO, MDA, NO, and SOD) in the diabetes+PEMF group were close to those in the control group. GSH levels were significantly lower in the sham PEMF, diabetes, and diabetes+PEMF groups than in the control group ( $p < 0.05$  each), whereas CAT levels were similar in all the four groups.

**Conclusion:** Results indicate that PEMF affects MDA, NO, MPO, SOD, and GSH levels and regulates diabetes-associated damage by reducing oxidative stress and increasing the levels of antioxidants. PEMF may be a non-invasive treatment option for diabetes and associated complications.

**Keywords:** Antioxidants, diabetes, free radicals, oxidative stress, pulsed electromagnetic fields

## INTRODUCTION

Levels of antioxidants in individuals with diabetes increase initially as a response to increases in reactive oxygen species (ROS) and later decrease due to reactions between free radicals and antioxidants. As the disease progresses, antioxidant mechanisms can be damaged in parallel to tissue damage, reducing antioxidant levels. Generalization should be avoided, however, due to increases in vitamin E levels due to hyperlipidemia and increases in ferritin levels due to inflammation (1).

The effects of antioxidants in organs are dependent on tissue physiology. Enzymatic antioxidants are more effective within cells, whereas non-enzymatic antioxidants have a greater effect in the extracellular environment. Vitamin E,  $\beta$ -carotene, and coenzyme-Q have effects on cell membranes (2).

Under normal conditions, the physiological levels and reactivity of free oxygen radicals are finely balanced by detoxification mechanisms, especially by antioxidant defense systems. Recent

studies on oxidant-antioxidant equilibria have focused on the enzyme superoxide dismutase (SOD), which represents the first step in the reactions of catalase (CAT). Lipid peroxidation is measured most frequently using the malondialdehyde assays (MDA-TBARS) reaction and by measuring the levels of the oxidative stress marker nitric oxide (NO) and the inflammation marker myeloperoxidase (MPO) (3). CAT activity is high in the liver and kidneys but is much lower in connective tissues. CAT catalytically detoxifies  $H_2O_2$  by converting it into water and molecular oxygen (4). Glutathione (GSH), a tripeptide consisting of glutamic acid, cysteine, and glycine, is a major intracellular antioxidant due to the thiol group on the cysteine residue. GSH directly interacts with superoxide, hydroxyl radicals, and hydrogen peroxide, keeping-SH groups in proteins in a reduced state (5). GSH constitutes the first defense system within the cell, as it leads to the dismutation of superoxide radicals. It also prevents lipid peroxidation and atherosclerosis development (6). MPO, an enzyme derived from neutrophils, plays a role in the pathogenesis of atherosclerosis by oxidizing apolipoprotein

teins and making high-density lipoprotein (HDL) pathogenic (7). Lipid peroxidation primarily affects the cell membrane, as well as damaging other cellular components via the production of reactive aldehydes. The concentration of malondialdehyde (MDA), which is produced by peroxidation of polyunsaturated fatty acids, shows a good correlation with the degree of lipid peroxidation (8).

Diabetes is a condition that is both caused by and results in oxidative stress. The pathogenesis and clinical manifestations of diabetes are heterogeneous. This chronic condition is characterized by a lack of insulin secretion from pancreatic beta cells, resulting in hyperglycemia due to insulin resistance or dysregulated insulin secretion and affecting carbohydrate, lipid, and protein metabolism. Oxidative stress in diabetes starts with increased intracellular and extracellular glucose levels and increases with glucose auto-oxidation, protein glycosylation, and formation of glycosylation end-products, which in turn lead to complications (6).

The effects of static and pulsed electromagnetic fields (PEMF) in the treatment of chronic pain and other biological problems have not yet been determined precisely. Nevertheless, electromagnetic field therapy has been shown to be effective in the treatment of rheumatic diseases, delayed union fractures, and ischemic disorders of the lower extremities. Moreover, electromagnetic field therapy has shown promising effects in multiple sclerosis, peripheral facial paralysis, craniofacial pain, spasticity, and degenerative diseases of the retina (9), as well as having positive effects on blood glucose and calcium levels, the latter of which affects insulin secretion in diabetes (10). Low-frequency PEMF application had significant benefits in the treatment of resistant peripheral neuropathic pain, as well as reductions in subjective symptoms, and increases in nerve conduction functions and quality of life (11).

This study evaluated the antioxidant effects of PEMF in a rat model of streptozotocin (STZ) induced diabetes by analyzing the oxidants, NO and MPO, and the antioxidants, CAT, SOD, GSH, and thiol-SH, in blood and tissue samples.

## METHODS

The study protocol was approved by the Experimental Animals Ethics Committee of the Gaziantep University School of Medicine (number 28.05.2012/18).

### Animals

Thirty-two male Wistar rats, mean weight  $200 \pm 50$  g (range, 180–220 g), were maintained at  $21^\circ\text{C} \pm 2^\circ\text{C}$ , 55%–60% humidity, and 12:12 dark:light cycles. The animals were fed standard rat chow, and any rat in poor health condition was excluded from the study.

### Groups

Following an adaptation period, the rats were randomly divided into four groups of eight each: a control group, a sham PEMF group, a diabetes group, and a diabetes+PEMF group. Diabetes was induced by intraperitoneal injection of a single dose of 50 mg/kg STZ (2-deoxy-2-[(methylnitrosoamino)carbonyl]amino-D-glucopyranose; Sigma 308-5003) dissolved in citrate buffer (pH 4.5). Animals in the control group were intraperitoneally injected with 0.09% NaCl solution. Seventy-two hours after STZ treatment, blood samples were collected from the tail of each rat, and blood glucose levels were measured. Concentrations over 300 mg/dl were considered diabetic.

### Exposure System

PEMF application was performed at the Gaziantep University Medical Faculty Biophysics Laboratory. PEMF was obtained from a Helmholtz coil pair (Ilfa; Adana, Turkey), fed with a power supply that could be programmed with an internal PIC-16F877A microprocessor. This power supply was developed for application of PEMF at various frequencies (0–100 Hz), amplitudes (0–10 mT), and durations (0–2500  $\mu\text{s}$ ). The PEMF instrument consisted of two parallel 60-cm Helmholtz bobbins placed 30 cm apart.

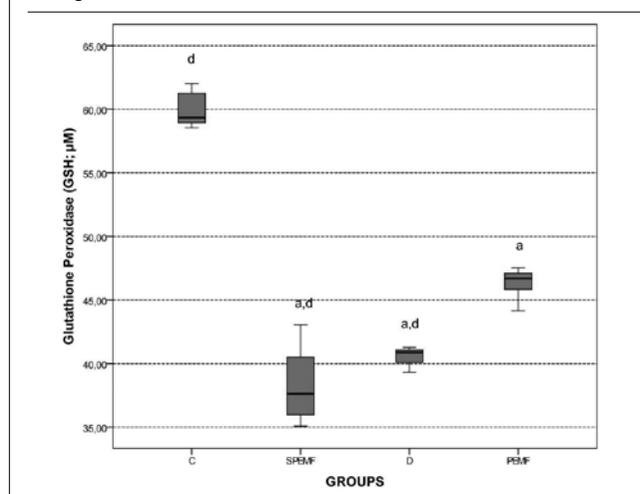
Helmholtz bobbins were placed in a  $90^\circ 90^\circ 50$  cm<sup>3</sup> Faraday cage to prevent any potential effects of EMF from the surrounding environment. A  $30^\circ 30^\circ 25$  cm<sup>3</sup> Plexiglas box was placed in the middle of the straight magnetic field, which was created between the upright coils. During each application, a maximum of eight rats were placed in the PEMF system at the same time. To keep other animals from the magnetic field, a  $3 \times 2$  m<sup>2</sup> grounded sheet of metal was used. The bobbins were connected to the programmed power supply, and magnetic field application was performed automatically. Prior to each application, a hall-effect probe-bound Teslameter (Sypris Model 6010; F.W. Bell, Orlando, FL, USA) was used to control the strength of the magnetic field between the coils (preferably 1.5 mT). Temperature was maintained at  $21^\circ \pm 2^\circ\text{C}$  with an air conditioner.

All treatments were performed during the same time period (9:00–11:00), and all animals were exposed to the same environmental conditions. Rats in the sham PEMF group were treated identically to those exposed to PEMF but without running the instrument.

The eight rats in the diabetes+PEMF group were placed in the PEMF system after confirmation of diabetes (glucose > 300 mg/dL). The rats were exposed to PEMF by applying a consecutive pulse train at four different frequencies (1, 10, 20, and 40 Hz) in three series. The transition period of each pulse train was four minutes, followed by one minute of rest. Each series was performed for 20 min, for a total of 60 min/day. Times were

Figure 1. The average GSH levels in experimental and control groups (mean±SD).

GSH: glutathione; SD: standard deviation



controlled using a digital timer. PEMF applications lasted for 4 weeks.

#### Biochemical Measurements

At the end of the experiment, the rats were anesthetized by the intraperitoneal injection of a mixture of 50 mg/kg ketamine-HCl (Ketalar) and 10 mg/kg xylazine-HCl (Rompun) and sacrificed by decapitation. All dissections were performed under sterile conditions. Half of each liver tissue sample was stored in 10% neutral-buffered formalin for pathological examination, and the rest at -85°C for biochemical assays.

Blood samples were transferred into anticoagulant-free tubes, incubated at room temperature for 30 min, and centrifuged at 1000 g at 4°C for 10 min to obtain serum samples, which were stored at -85°C. Blood samples in heparin-containing tubes were also centrifuged at 1000 g at 4°C for 10 min. Plasma samples were separated, and erythrocyte bags were prepared, aliquoted, and stored at -85°C until analysis.

#### Measurements of NO, MPO, MDA, GSH, CAT, and SOD

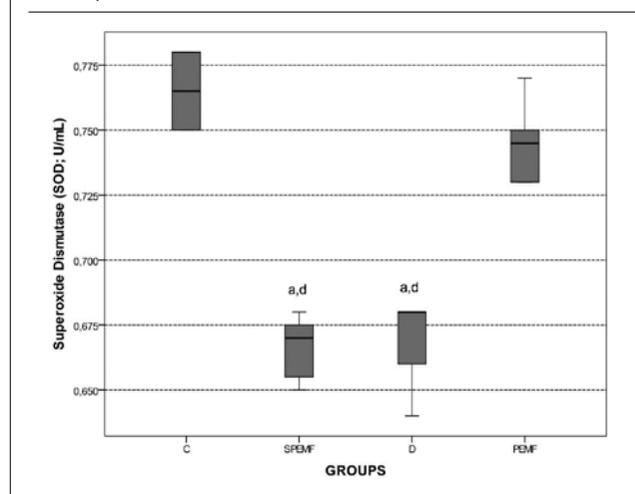
NO levels were measured using nitrate/nitrite colorimetric assay kits (Cayman, #780001), with results expressed as micromoles. MPO was measured by ELISA (Immunodiagnosis, #REF K 6631B), with results expressed as ng/mL. MDA (Cayman, #10009055), GSH (Cayman, #703002), and CAT (Cayman, #707002) levels were also measured colorimetrically, with results expressed as micromoles. SOD levels were also measured colorimetrically (Cayman #706002), with results expressed as U/mL.

#### Statistical Analysis

Statistical Package for the Social Sciences statistical software (SPSS version 17, 2009, SPSS Inc.; Chicago, IL, USA) was used for data analysis. One-way ANOVA test was used to determine the significance levels among the groups.

Figure 2. The average SOD levels in experimental and control groups (mean±SD).

SOD: superoxide dismutase; SD: standard deviation



## RESULTS

Glutathione levels were significantly lower in the sham PEMF, diabetes, and diabetes+PEMF groups than in the control group ( $p < 0.001$ ), but the decreases in the sham PEMF and diabetes groups were greater. There was no significant difference between these two groups (Figure 1). Mean SOD level was significantly and equally lower in the sham PEMF and diabetes groups than in the control group ( $p < 0.001$ ) but was as high in the diabetes+PEMF group as in the control group (Figure 2). CAT levels were similar in the four groups (Figure 3). Similar to SOD, NO levels were significantly and equally higher in the sham PEMF and diabetes groups than in the control group ( $p < 0.01$ ) but were similar in the diabetes+PEMF and control groups (Figure 4). MDA levels were also significantly and equally higher in the sham PEMF and diabetes groups than in the control group ( $p < 0.001$ ) but were similar in the diabetes+PEMF and control groups (Figure 5). Compared with the control group, MPO levels were significantly higher in the sham PEMF ( $p < 0.001$ ) and diabetes ( $p < 0.01$ ) groups but were similar in the diabetes+PEMF and control groups. MPO levels did not differ significantly in the diabetes and diabetes+PEMF groups but differed significantly in the sham PEMF and diabetes+PEMF groups (Figure 6) (Table 1).

## DISCUSSION

Magnetic field treatment has been shown to be successful in patients with non-union fractures, osteoporosis, tendinitis, chronic ulcers, and musculoskeletal disorders, due to its effects on mineralization, collagen formation, and endochondral ossification, as well as its non-invasive nature and low cost. Moreover, it has been shown effective in stroke, insomnia, depression, bowel diseases, diabetes, and circulation disorders. Magnetic field treatment has shown positive effects in patients with diabetes, by affecting levels of blood glucose

Figure 3. The average CAT levels in experimental and control groups (mean±SD).

CAT: catalase; SD: standard deviation

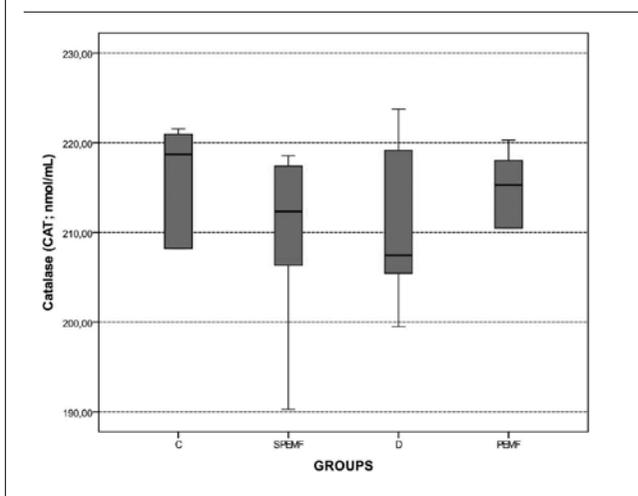


Figure 5. The average MDA levels in experimental and control groups (mean±SD).

MDA: malondialdehyde; SD: standard deviation

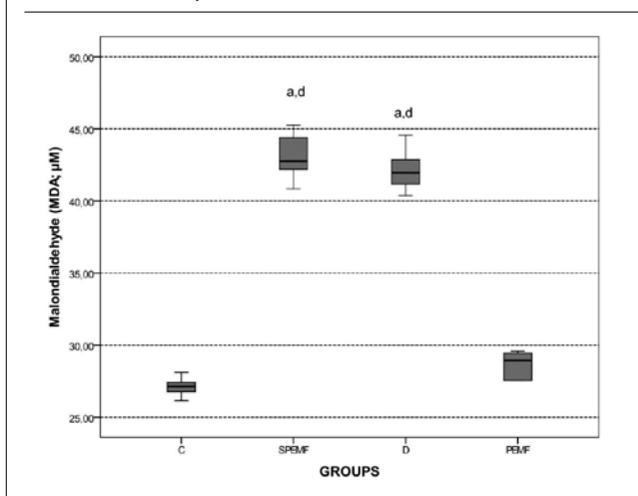


Figure 4. The average NO levels in experimental and control groups (mean±SD).

NO: nitric oxide; SD: standard deviation

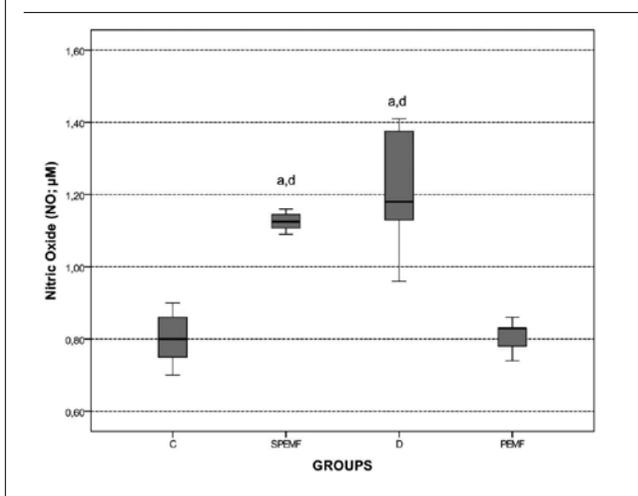
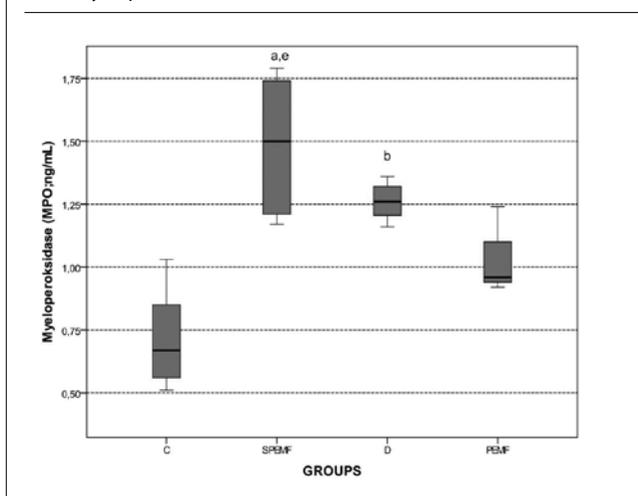


Figure 6. The average MPO levels in experimental and control groups (mean±SD).

MPO: myeloperoxidase; SD: standard deviation



and calcium, the latter of which affects insulin secretion. In addition, magnetic field treatment can affect angiogenesis, neuronal protein synthesis, synaptic neurotransmitters, and axoplasmic transport, resulting in positive outcomes in patients with diabetic neuropathy (11, 12).

Culture of insulin-secreting beta cells in a 60 Hz–5 mT magnetic field resulted in increased cell numbers and insulin secretion, suggesting a possibility for transplantation of beta cells (13). PEMF involving a pulse train of 1, 10, 20, 40 Hz, and 1.5 mT in rats with STZ-induced diabetes had no effect on reduced body weight due to STZ but reduced blood glucose levels (14). Assessment of the effects of exposure of rats to 10-Hz square waves (1.8–3.8 mT) or 40 Hz sinusoidal (1.3–2.7 mT) magnetic fields on pancreatic structure and function showed that, after application for 14 days, glucose concentrations decreased in

both groups, whereas insulin concentrations increased. However, long-term exposure can lead to adaptive changes in hormone levels. This mechanism may be responsible, at least in part, for the effect of magnetic fields on calcium ions in beta cells. Changes were greater, and reversibility lower, with square than with sinusoidal waves (15). A comparison of 10 Hz and 100 Hz PEMF soon after *diabetic* peripheral neuropathy treatment showed that the lower frequency was more effective (16). Low-frequency PEMF was effective in treating resistant peripheral neuropathic pain, as well as in reducing subjective symptoms, increasing nerve conduction, and enhancing quality of life (17).

Although studies have examined the effects of low-frequency PEMF on diabetes and its associated complications, as well as on other diseases, the present work investigated the effects of PEMF

**Table 1.** NO, MPO, CAT, GSH, SOD, and MDA levels in the four experimental groups of rats (mean±SD)

	Control group	Sham PEMF group	Diabetes group	Diabetes+PEMF group
NO	0.8±0.081	1.13±0.027 <sup>a,d</sup>	1.19±0.18 <sup>a,d</sup>	0.81±0.05
MPO	0.72±0.22	1.47±0.28 <sup>a,e</sup>	1.26±0.07 <sup>b</sup>	1.03±0.14
CAT	217.62±5.54	207.55±11.94	210.65±10.38	215.87±3.67
GSH	60.02±1.53 <sup>d</sup>	38.12±2.98 <sup>a,d</sup>	40.53±0.82 <sup>a,d</sup>	46.26±1.34 <sup>a</sup>
SOD	0.76±0.013	0.67±0.01 <sup>a,d</sup>	0.66±0.09 <sup>a,d</sup>	0.75±0.015
MDA	27.1±0.73	42.8±1.72 <sup>a,d</sup>	42.52±1.54 <sup>a,d</sup>	28.9±0.81

All results reported as mean±SD.

PEMF: Pulsed Electromagnetic Field; NO: nitric oxide; MPO: myeloperoxidase; CAT: catalase; GSH: Glutathione; SOD: superoxide dismutase; MDA: Malondialdehyde

<sup>a</sup>p<0.001, <sup>b</sup>p<0.01, <sup>c</sup>p<0.05 compared with the control group.

<sup>d</sup>p<0.001, <sup>e</sup>p<0.01, <sup>f</sup>p<0.05 compared with the diabetes+PEMF group

on oxidative stress and antioxidant mechanisms in diabetes. Similar to a study showing that PEMF using a pulse train (1,10, 20, 40 Hz, and 1.5 mT) had no effect on reduced body weight due to STZ, but did reduce blood glucose levels (10), our study found that PEMF had no effect on decreased body weight due to STZ administration.

Certain diseases, such as diabetes, have been linked to increased NO production (18). In diabetes, glycosylated proteins donate electrons to oxygen in the presence of Cu and Fe, generating ROS, inactivating enzymes, and increasing the activation of transcription factor nuclear factor kappa B (NF-κB), thus enhancing NO levels. Increases in superoxide (O<sub>2</sub><sup>-</sup>) radicals and NO lead to the formation of the more reactive peroxynitrite radical (6). We found that mean NO levels were significantly higher in sham PEMF and diabetic rats than in control rats C (p<0.01) but were significantly lower in diabetes+PEMF rats than in diabetic rats.

Superoxide dismutase activity in diabetes has been shown to decrease (19), remain unchanged (20), and even increase (21). Increased O<sub>2</sub> production leads to an initial increase in SOD activity, whereas glycosylation of the enzyme and/or hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) accumulation decreases SOD activity. SOD activity was found to be lower due to increased lipid peroxidation in types 1 and 2 diabetes than in controls (22). This study found that SOD activity was significantly lower in diabetic and sham PEMF-treated than in control rats (p<0.001).

Biochemical changes in patients with diabetes were assessed by comparing MDA, SOD, CAT, NO, and GSH levels. Compared with controls, SOD and CAT activities were reduced, MDA and NO levels were increased, and GSH levels significantly reduced

in diabetic patients. Oxidative stress plays a major role in protein glycosylation in diabetes and in the formation of advanced glycosylation end-products (23). Hyperglycemia was shown to increase oxidative stress, with the inequilibrium between antioxidants and oxidants increasing lipid peroxidation, leading to diabetic complications (24). An assessment of 40 female and 40 male patients with diabetes showed that MDA levels were increased and GSH levels reduced. We found that MDA levels were significantly higher in sham PEMF-treated and diabetic rats than in control rats (p<0.001) but were similar in the sham PEMF and diabetic groups.

The liver and kidneys are exposed to various endogenous and exogenous oxidants, increasing oxidative stress. Administration of carbon tetrachloride (CCl<sub>4</sub>) to mice enhanced MDA and MPO levels in liver and kidney tissues while reducing GSH-Px and CAT activities (25). In contrast, vitamin C and/or N-acetylcysteine (NAC) reduced oxidative damage in the liver and kidneys, whereas melatonin and NAC treatment increased antioxidant enzyme levels. MPO is derived from neutrophils and plays a role in the pathogenesis of atherosclerosis. MPO exerts its effects by oxidizing apolipoproteins and has been shown to add nitrate to the main lipoprotein of HDL, Apo-A1, making HDL proatherogenic. MPO levels have been associated with the risk of coronary artery disease (CAD) (7). Generally, MPO levels are increased in patients with diabetes and its complications. We found that, compared with control rats, MPO activity was significantly higher in sham PEMF-treated (p<0.001) and diabetic (p<0.01) rats but was similar in control and diabetes+PEMF-treated rats. Moreover, MPO levels did not differ significantly in diabetic- and diabetes+PEMF-treated rats but did differ significantly in diabetes+PEMF and sham PEMF-treated animals (p<0.05).

Glutathione plays a role in antioxidant defense, decreasing in the presence of oxidants and delaying wound healing (26). Studies on patients with diabetes have shown a decrease in erythrocyte GSH levels and increased erythrocyte lipid peroxidation. Hepatic GSH levels were normal or mildly decreased, whereas GSH peroxidase activity was lower (27). Similarly, we found that GSH levels were lower in sham PEMF-treated and diabetic rats than in control rats (p<0.001).

Catalase activity is high in liver and kidneys but considerably lower in connective tissues. In addition, higher CAT activity has been reported in diabetic kidneys due to a protective mechanism (28). However, kidney CAT activity was found to be lower in an STZ-induced experimental diabetes model than in control animals (29). We found that CAT activity in liver homogenates was somewhat lower in diabetic- and sham PEMF-treated rats than in control rats, but the differences were not statistically significant.

Superoxide dismutase, CAT, and GSH-Px levels have been found to be lower and MDA levels higher in inflamed than in non-inflamed tissues. However, PEMF treatment was found to enhance SOD, CAT, and GSH-Px activities and reduced MDA levels (30). Similarly, we found that MDA and SOD levels were higher in STZ-treated diabetic rats but were reduced in these rats by PEMF treatment ( $p < 0.001$ ). In contrast, GSH levels were significantly lower in diabetic-, sham PEMF-, and diabetes+PEMF-treated rats than in control rats ( $p < 0.001$ ), whereas CAT levels were similar in the four groups.

## CONCLUSION

In conclusion, this study investigated the antioxidant effects of PEMF in a rat model of diabetes. PEMF altered the levels of MDA, NO, MPO, SOD, and GSH, suggesting that it regulates diabetes-associated damage. PEMF exerts these effects by reducing oxidative stress and increasing antioxidant levels. These findings suggest that PEMF may become a widespread non-invasive treatment option for diabetes and its complications.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Gaziantep University Animal Experiments Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - H.G., C.D.; Design - H.G., C.D.; Supervision - Can Demirel; Resource - H.G., C.D.; Materials - H.G., C.D.; Data Collection and/or Processing - H.G., C.D., M.A., M.T.; Analysis and/or Interpretation - H.G., C.D., M.A., M.T.; Literature Search - H.G., C.D.; Writing - H.G., C.D.; Critical Reviews - C.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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**How to cite:**

Gözen H, Demirel C, Akan M, Tarakçioğlu M. Effects of pulsed electromagnetic fields on lipid peroxidation and antioxidant levels in blood and liver of diabetic rats. *Eur J Ther* 2017; 23: 152–8.