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Authors

B. Rose[1], M. Lankisch[1], C. Herder[1], K. Röhrig[1], K. Kempf[1], S. Labrenz[1], J. Hänsler[2], W. Koenig[3], L. Heinemann[2], S. Martin[1]

Affiliations

[1] Institute for Clinical Diabetes Research, German Diabetes Center, Leibniz Center at Heinrich-Heine-University, Duesseldorf, Germany
[2] Profil Institute for Metabolic Research, Neuss, Germany
[3] Department of Internal Medicine II-Cardiology, University of Ulm Medical Center, Ulm, Germany

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Correspondence
B. Rose
Institute for Clinical Diabetes Research
German Diabetes Center
Leibniz Center at
Heinrich-Heine-University
Auf'm Hennekamp 65
40225 Duesseldorf
Germany
Tel.: +49/211/338 25 75
Fax: +49/211/338 25 92
bettina.rose@ddz.uni-duesseldorf.de

Abstract

Physical activity improves insulin sensitivity and metabolic control in patients with type 2 diabetes. Moreover, regular exercise can reduce systemic levels of immune markers associated with diabetes development. As patients with physical impairments are not able to exercise sufficiently, the aim of this study was to investigate whether high-frequency external muscle stimulation (hfEMS) improves metabolic and immunologic parameters in patients with type 2 diabetes and might therefore serve as complementary lifestyle therapy. Sixteen patients (12 men/4 women, age 57 ± 11 years (mean ± SD); BMI 34.5 ± 5.2 kg/m^2; HbA1c 7.4 ± 1.1 %) on oral antihyperglycaemic therapy were enrolled in this study. After a run-in phase of 2 weeks, every patient received an hfEMS device (HITOP 191, gbo-Medizintechnik AG, Rimbach/Germany) for daily treatment of femoral musculature for 6 weeks. Thereafter, patients were followed up for additional 4 weeks without hfEMS treatment. At each visit, clinical parameters were assessed and blood samples were drawn for metabolic and immunologic parameters. Immune markers (cytokines, chemokines, adipokines and acute-phase proteins) representative for the different arms of the immune system were analysed. hfEMS treatment resulted in significant reductions of body weight (−1.2 kg [−2.7 kg; −0.5 kg]; $p < 0.05$; median [25th percentile; 75th percentile]), BMI (−0.4 kg/m^2 [−0.8 kg/m^2; −0.1 kg/m^2]; $p < 0.05$) and HbA1c (−0.4 % [−0.9 %; −0.1 %]; $p < 0.05$) which were sustained during the follow-up period. Systemic levels of IL-18 tended to be increased after hfEMS treatment (171 vs. 149 pg/ml; $p = 0.06$), while all other immune markers remained virtually unchanged. Treatment with hfEMS in this first proof-of-principle study has beneficial effects on body weight and improves glycaemic control in patients with type 2 diabetes, which may be associated with changes in subclinical inflammation. Taken together, hfEMS might represent an additional treatment option for patients with type 2 diabetes not being able to exercise.

Introduction

Lack of physical activity and increased caloric intake are the main risk factors for the development of obesity and the induction of insulin resistance in peripheral tissues, especially in muscle tissue. Nowadays, insulin resistance in combination with impaired insulin secretion are thought to be the major causes of type 2 diabetes. But in contrast to insulin secretion, peripheral insulin resistance can be modified by lifestyle interventions consisting of dietary changes and increased physical activity (Houmard et al., 2004; Ross et al., 2000). Thus, lifestyle modifications are included as first-line therapy in newly diagnosed patients with type 2 diabetes into current guidelines (Standards of medical care in diabetes, 2007). Even at later stages of the disease exercise has a major impact on glucose control (Walker et al., 1999; Lindstrom et al., 2003).

But as observed in general practice, the motivation of patients to increase their physical activity is relatively low, and strong efforts have to be made to maintain high exercise levels in patients over a longer time period (Kirk et al., 2003; Krug et al., 1991). Thus, alternative treatment options with comparable effects as voluntary physical activity are of great therapeutic relevance. High-frequency external muscle stimulation (hfEMS) is the percutaneous electrical stimulation of skeletal muscles using frequencies higher than 40 Hz to produce a muscle contraction (Requena et al.,

2005). The method is widely used in orthopaedic rehabilitation, sports medicine and the treatment of peripheral nervous system lesions. It has been shown to be effective in the prevention of muscle atrophy following denervation, in the regain of muscle strength during rehabilitation to shorten rehabilitation time after sport injuries (Hainaut and Duchateau, 1992) and the treatment of symptomatic diabetic polyneuropathy (Reichstein et al., 2005). Hamada et al. could show that short-term EMS acutely increases whole body insulin sensitivity to higher levels than voluntary exercise (Hamada et al., 2004). Taken together, high-frequency EMS might be an additional therapeutic option to include an effective lifestyle-like treatment into the therapeutic regimen of patients with diabetic complications like severe heart disease or diabetic foot syndrome, who are not able to be physically active.

In addition, physical exercise has also an impact on components of the immune system, i.e. cytokines, chemokines and acute-phase proteins (APP), that are associated with type 2 diabetes and prediabetic states (Herder et al., 2005; Muller et al., 2002) and play a crucial role in the development of type 2 diabetes (Kolb and Mandrup-Poulsen, 2005). Acute physical activity is associated with a release of cytokines from the muscle (extensively reviewed in Petersen and Pedersen, 2005; Huang et al., 2007) that may exert anti-inflammatory effects, and indeed regular exercise as well as EMS are associated with reduced production of proinflammatory cytokines (Smith et al., 1999; Karavidas et al., 2006). Thus, physical activity and EMS represent also a causal therapeutic strategy in type 2 diabetes.

Therefore, the aim of our study was to investigate whether the regular use of high-frequency EMS exerts beneficial effects on body weight, glucose control and immune activation and might therefore serve as a novel treatment option in patients with type 2 diabetes.

Materials and Methods

Study population

Patients with type 2 diabetes were eligible for the study if they were aged 18–70 years, had a BMI >27 kg/m^2 and were free of insulin treatment, severe diabetes-related complications or cardiac pacemaker. Sixteen patients (12 men/4 women) were enrolled in this study and gave their written informed consent. The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee at Heinrich-Heine University Duesseldorf.

Study design

After a run-in phase of 2 weeks, every patient received an hfEMS device (HITOP 191, gbo-Medizintechnik AG, Rimbach/Germany) for treatment of the femoral musculature for at least one hour per day over 6 weeks. The hfEMS device generated pulse widths of ≤350 mA, ≤70 V with an initial frequency of 4,096 Hz that were increased over 3 s to 32,768 Hz, held at maximum for 3 s and then downmodulated to the initial frequency. Each patient adjusted the intensity of the electric stimulation to a personally pleasant level that did not produce any pain or discomfort. Duration of daily use was documented in an automatic log file of the hfEMS device to assess patients' compliance. After the treatment phase, patients were followed up for additional 4 weeks without using the hfEMS device to assess the long-term effects. Study site visits took place before and after run-in, treatment and follow-up period (**Fig. 1**). At baseline visit, diabetes history and current medication were assessed and at each visit, anthropometric parameters were documented and blood samples were drawn for the measurement of metabolic and immunologic parameters.

Laboratory and immunological measurements

Blood glucose, HbA1c and serum C-peptide were measured in the central laboratory of the German Diabetes Center using standardised methods. HOMA-IR was calculated using the computer algorithm proposed by Levy et al. based on fasting blood glucose and C-peptide levels (Levy et al., 1998). One additional serum sample was drawn, centrifuged and stored at −80 °C for the analysis of cytokines, chemokines, adipokines and acute-phase proteins. The cytokines tumour necrosis factor (TNF)-α, tumour growth factor (TGF)-β, interleukin (IL)-6, IL-10, the chemokine RANTES and the adipokine adiponectin were analysed using high-sensitive ELISA (R&D Systems, Wiesbaden, Germany). High-sensitive C-reactive protein (hsCRP) was analysed using high-sensitivity latex enhanced nephelometric assay on a BN II analyser (Dade Behring, Marburg, Germany), serum amyloid A (SAA) was also analysed by immunonephelometry (Behring). Serum levels of IL-1α, IL-8, IL-17, IL-18, MCP-1, MIP-1α, MIF and IP-10 were measured by bead-based multiplex technology using a Luminex 100 analyser (Luminex Corporation, Austin, TX, USA) based on a previously published protocol (Herder et al., 2007). Fluorescent xMAP COOH microspheres were purchased from Luminex Corporation. Recombinant protein for IL-8 was obtained from Strathmann Biotec GmbH (Hamburg, Germany), recombinant IL-18 protein and anti-IL-18 antibody pair was purchased from MBL (Nagoya, Japan). All other recombinant proteins and antibody pairs were purchased from R&D Systems. The intra- and interassay coefficients of variation (CV) of quality control test sera were <10% and <20%, respectively.

Statistical analyses

Data are expressed as mean ± SD or median (25th percentile, 75th percentile) as indicated within the figure/table legend. Data were analysed using GraphPad Prism Version 4.03 (GraphPad Software, San Diego, CA, USA). For comparison of medians of paired observations, Wilcoxon signed rank test or Friedman test and an appropriate post test were used, p values ≤0.05 were considered significant.

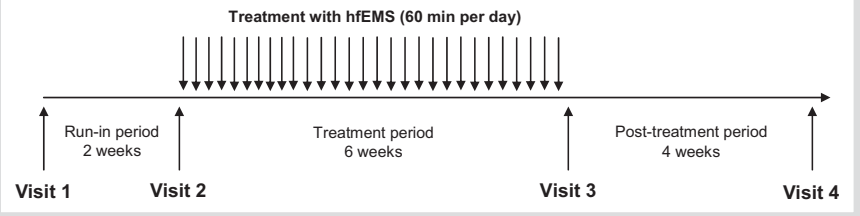

Fig. 1 Study design. After a run-in period of 2 weeks, patients used an hfEMS device daily for 60 min over 6 weeks (treatment period). Thereafter, patients remained without hfEMS treatment during the 4-week post-treatment period.

Results

Reduction of BMI and HbA1c after hfEMS treatment

Study participants had a mean age of 57 ± 11 years and were obese (BMI 34.5 ± 5.2 kg/m^2; waist circumference 116 ± 6 cm). All patients had type 2 diabetes with HbA1c levels of 7.4 ± 1.1 % and an average diabetes duration of 7 ± 5 years (**Table 1**). Oral antidiabetic medication remained unchanged or was reduced due to low blood glucose levels throughout the study, the stability of glycaemic control prior to treatment was verified during the two week run-in phase.

To evaluate the impact of hfEMS therapy on anthropometric and metabolic parameters, the change during the run-in period was calculated and compared with the change during the treatment period. To address whether hfEMS therapy has longer-lasting effects beyond the end of EMS treatment, the difference between the beginning of treatment (visit 2) and the end of study (visit 4) was also analysed. Treatment with high-frequency EMS induced significant reductions in weight (−1.2 kg [−2.7 kg; −0.5 kg]; p < 0.05), BMI (−0.4 kg/m^2 [−0.8 kg/m^2; −0.1 kg/m^2]; p < 0.05) and HbA1c (−0.4 % [−0.9 %; −0.1 %]; p < 0.05) (**Fig. 2**). This reduction was paralleled by a decrease of serum C-peptide levels (−0.5 μg/l; p < 0.05) and HOMA-IR (−0.3; p < 0.05), indicating a reduction of insulin resistance by hfEMS therapy. The observed reduction of weight, BMI, HbA1c and serum C-peptide remained almost stable after the end of hfEMS therapy in the post-treatment period. However, significance was only reached for the reduction in HbA1c (−0.6 %; p < 0.05). Waist circumference was slightly reduced after the hfEMS treatment (−1.3 cm), but this change was not statistically significant, and no changes were observed for fasting blood glucose (data not shown). Taken together, hfEMS therapy reduced body weight and improved metabolic control with possible long-term effects.

Table 1 Baseline characteristics of the study population. Anthropometric, clinical and metabolic baseline variables are given as mean ± SD

age (years)	57.3 ± 11.0
sex (f/m)	4/12
weight (kg)	107.3 ± 15.1
BMI (kg/m^2)	34.5 ± 5.2
waist circumference (cm)	116.0 ± 15.6
hip circumference (cm)	116.2 ± 8.6
HbA1c (%)	7.4 ± 1.1
fasting blood glucose (mg/dl)	159 ± 37
C-peptide (μg/l)	2.8 ± 1.2
diabetes duration (years)	6.8 ± 4.8

Impact of hfEMS treatment on immune markers

To investigate the impact of hfEMS treatment on subclinical inflammation, we analysed the levels of circulating immune markers before and after treatment in all study participants (n = 16) (**Table 2**). As hfEMS treatment has the most pronounced impact on HbA1c levels, an additional exploratory analysis was performed in therapy responders, who were defined as those with a reduction in HbA1c levels of at least 0.1 % after treatment. According to this approach, 12 of 16 patients (75 %) were classified as responders. After hfEMS treatment, systemic levels of the cytokine IL-18 tended to be higher (171 vs. 149 pg/ml; p = 0.06), while levels of other immune parameters and adipokines remained unchanged. This tendency for IL-18 was virtually identical in the responder subgroup (171 vs. 145 pg/ml; p = 0.08). Moreover, a slight reduction of IL-6 levels were observed (1.9 vs. 2.6 pg/ml; p = 0.09). Restricting

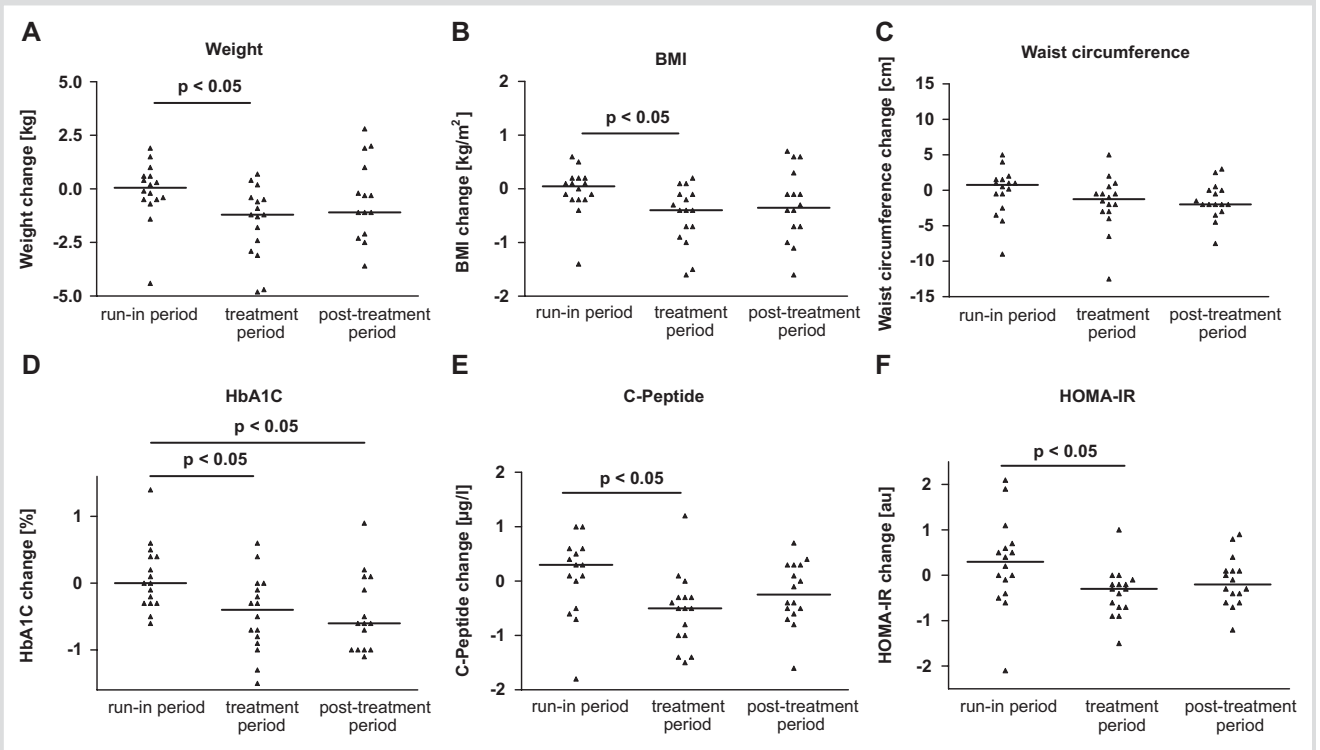

Fig. 2 Differences in anthropometric and metabolic variables before and after hfEMS therapy. The difference of weight (**A**), BMI (**B**), waist circumference (**C**), HbA1c (**D**), serum C-peptide levels (**E**) and HOMA-IR (**F**) were calculated before and after run-in (visit 2–visit 1), treatment period (visit 3–visit 2) and after post-treatment period (visit 4–visit 2). Each symbol represents one individual, the bar indicates the median. Data were analysed using Friedman test for paired observations and Dunn's post test. p-values for comparisons between different time-points are indicated by horizontal lines.

Table 2 Levels of systemic immune parameters before and after hfEMS treatment. The serum levels of immune markers are given as median (25th; 75th percentiles) before (visit 2) and directly after the 6 week hfEMS treatment period (visit 3) in all study participants (n = 16) and in the subgroup of HbA1c-responders (n = 12). Data were analysed using Wilcoxon signed rank test and p-values for the comparison between the two time-points are given

	All study participants (n = 16)			HbA1c responder (n = 12)		
Parameter	**before treatment**	**after treatment**	**p-value**	**before treatment**	**after treatment**	**p-value**
cytokines						
IL-1α [pg/ml]	2.5 (1.5; 3.5)	1.9 (1.5; 5.2)	0.28	2.9 (2.1; 7.9)	3.6 (1.8; 11.7)	0.13
IL-6 [pg/ml]	2.6 (1.4; 3.2)	1.9 (1.4; 2.5)	0.58	**2.6 (1.6; 3.0)**	**1.9 (1.5; 2.1)**	**0.09**
IL-17 [pg/ml]	2.7 (1.8; 3.9)	3.2 (1.2; 6.3)	0.17	3.1 (2.4; 6.1)	4.2 (1.8; 9.2)	0.21
IL-18 [pg/ml]	**149 (121; 191)**	**171 (120; 210)**	**0.06**	**145 (121; 192)**	**171 (127; 210)**	**0.08**
TNF-α [pg/ml]	1.9 (1.3; 2.3)	1.9 (1.1; 2.4)	0.26	2.0 (1.3; 2.5)	2.0 (1.1; 2.5)	0.30
TGF-β [ng/ml]	35.5 (29.3; 41.0)	36.9 (30.6; 43.0)	0.73	35.5 (30.3; 42.6)	36.9 (32.7; 42.3)	0.85
chemokines/adipokines						
IL-8 [pg/ml]	4.5 (1.9; 5.5)	3.8 (1.9; 7.4)	0.45	4.4 (1.9; 5.0)	4.2 (1.8; 7.4)	0.15
IP-10 [pg/ml]	283 (217; 314)	320 (237; 355)	0.54	305 (215; 348)	320 (237; 343)	0.79
MCP-1 [pg/ml]	164 (137; 194)	166 (128; 207)	0.69	166 (118; 219)	181 (132; 208)	0.57
MIF [ng/ml]	10.4 (9.2; 11.6)	9.5 (8.1; 11.7)	0.42	10.4 (9.3; 11.5)	9.2 (8.0; 11.2)	0.27
MIP-1α [pg/ml]	22.4 (12.8; 35.4)	27.3 (17.6; 45.7)	0.33	28.5 (19.0; 49.9)	33.8 (22.5; 51.5)	0.28
RANTES [ng/ml]	23.9 (16.4; 33.0)	24.2 (16.8; 35.8)	0.58	25.2 (17.0; 36.8)	27.1 (14.9; 42.6)	0.73
adiponectin [ng/ml]	5191 (4042; 8662)	5387 (4414; 7830)	0.93	4954 (4042; 6236)	4991 (4414; 6095)	0.68
acute-phase-proteins/leukocyte count						
hsCRP [mg/l]	2.7 (0.8; 4.4)	2.1 (0.9; 5.5)	0.85	3.2 (0.8; 5.3)	2.0 (0.8; 3.6)	0.15
SAA [mg/l]	4.2 (3.0; 7.2)	5.4 (2.2; 9.0)	0.45	4.5 (3.5; 7.8)	4.9 (2.1; 7.6)	0.58
WBC count [per μl]	6250 (5750; 7250)	6400 (5400; 6600)	0.79	6250 (5950; 7350)	6400 (5400; 6450)	0.79

the analysis instead to those who lost at least 1 kg of body weight had no impact on the observed increase of IL-18, but attenuated the patient number further (n=9 out of 16 patients; data not shown).

Discussion

This prospective clinical study showed that a treatment with high-frequency EMS for 6 weeks reduced body weight and improved metabolic control in patients with type 2 diabetes. Moreover, the results remained almost stable in the subsequent weeks indicating that the treatment may also have longer-lasting effects.

hfEMS results in effective muscle contraction and produces less discomfort for the patient than other muscle stimulation methods like transcutaneous electrical nerve stimulation (TENS) using lower stimulation frequencies, which produce only superficial muscle contractions. EMS leads to muscle contraction of large motor units first with synchronous depolarisation and higher firing rates of their motoneurons, resulting in stronger muscle contraction than a voluntary contraction, but also in faster exhaustion and anaerobic metabolism of muscle (Requena et al., 2005). This "reverse-size" recruitment of motor units results in reduced shear forces between muscle fibres preventing discomfort or pain during treatment. Thus, the effect of voluntary isometric contraction can be mimicked by hfEMS treatment, and it is reasonable to hypothesise that comparable mechanisms, i.e. the reduction of insulin resistance, might be involved in mediating the effects of hfEMS on glucose metabolism. The effect on insulin sensitivity by voluntary physical activity is mediated via the increased expression of GLUT-4 on myocytes resulting in elevated glucose uptake and generation of glycogen (Hardin et al., 1995; Kennedy et al., 1999; Christ-Roberts et al., 2004). These effects are observed after acute as well as after chronic exercise, but it is not quite clear whether these effects are independent of an accompanying weight loss (Ross, 2003). An association between change in HbA1c and change in body weight is conceivable. However, we observed no correlation between these two variables after the treatment and therefore did not adjust for change in body weight in our analysis. In line with this, a reduction of insulin resistance measured by HOMA-IR after 6 weeks of treatment with hfEMS was observed, indicating that hfEMS increases insulin sensitivity of peripheral tissues, probably predominantly muscle tissue. This insulin sensitizing effect seems to be more pronounced with EMS treatment than after voluntary exercise (Hamada et al., 2004). Additionally, physical activity can overcome the impaired mitochondrial function observed in patients with type 2 diabetes and increases the amount of mitochondria in muscle of patients with diabetes (Toledo et al., 2007). These improvements are again closely associated with better metabolic control. Thus, hfEMS treatment mimics the beneficial effects of voluntary physical activity.

Despite the reduction of HbA1c fasting glucose levels remained virtually unchanged, suggesting a predominant effect of postprandial levels. Sufficient information from blood glucose diaries were not available and no standardised mixed meal test or oGTT was performed to address this potential effect but should be included in future studies.

Cytokines that are released by muscle tissue directly after exercise (Helge et al., 2003) seem to be related to carbohydrate metabolism of muscle and may induce an anti-inflammatory reaction. It has been shown that regular physical activity reduces the systemic levels of proinflammatory mediators like MCP-1 and IL-8 (Troseid et al., 2004; Kriketos et al., 2004). Although a slight increase of IL-18 levels was observed in our study, while IL-6 levels were reduced after hfEMS treatment at least in HbA1c responders, none of the changes reached statistical significance due to the relatively low sample size. However, it is conceivable that a longer duration of hfEMS treatment resulting in more pronounced weight loss and improvement of metabolic control might also be associated with an attenuation of subclinical inflammation.

To the best of our knowledge, only one study evaluated the effects of external muscle stimulation on metabolic control in patients with type 2 diabetes so far (Poole et al., 2005). They did not found

any improvement in body composition or glucose control. Possible reasons might be the low patient number (four diabetic patients) and the treatment method differing from ours as low-frequency external muscle stimulation was used, which results in only mild muscle contractions. Moreover, no control group was included in this study either, because the selection of an appropriate control group for EMS treatment is challenging and strongly depends on the research question, i.e. placebo treatment to analyse the efficiency of EMS treatment at all or a control treatment (voluntary exercise, isometric training, etc.) to address the equivalency of both treatments. Confounding by effects on the cardiorespiratory system by the control treatment need to be considered further. Thus, we refrained from designing a control group for this first larger proof-of-principle study as Poole et al. also did. Certainly, we cannot exclude a certain effect on glucose control and body weight by participation in the study per se ("study effect"). However, the effect of hfEMS treatment on HbA1c exceeds the effects observed in patients with type 2 diabetes after more than 28 days of participation in pharmacological intervention studies (Gale et al., 2007) indicating that the observed improvement of metabolic control is related to a true treatment effect. Nevertheless the observed improvements need to be evaluated using a larger sample with a carefully designed appropriate control treatment to overcome the limitations of our study.

In conclusion, this study has shown as a proof of principle study that high-frequency EMS has positive effects on body weight and metabolic control and appears to be a promising non-pharmacological additional treatment option for patients with type 2 diabetes.

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Conflict of interest: None.

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