Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Impact of prolonged neuromuscular electrical stimulation on metabolic profile and cognition-related blood parameters in type 2 diabetes: A randomized controlled cross-over trial

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ARTICLE INFO

Article history:
Received 12 January 2018
Received in revised form
2 May 2018
Accepted 17 May 2018
Available online 24 May 2018

Keywords:
Electrical muscle stimulation
Exercise
Metabolism
Brain-derived neurotrophic factor

ABSTRACT

Aims: This study aimed to examine the effect of prolonged neuromuscular electrical stimulation (NMES) on the metabolic profile and cognition-related blood parameters in patients with type 2 diabetes mellitus (T2DM).

Methods: Fourteen patients with T2DM (63.2 ± 3.0 years, 76.1 ± 3.5 kg) participated in a randomized controlled cross-over study, in which 8-week-long NMES interventions were performed on both legs. The NMES training protocol consisted of 40-min sessions, 5 days per week, for 8 weeks. The relative changes in glucose and lipid profiles, and cognition-related blood parameters were evaluated.

Results: NMES training induced significant changes in the fasting glucose concentration ($p < 0.05$) and percent body fat ($p < 0.05$), although there were no significant changes in HbA1c and blood lipid levels ($p \geq 0.05$). The change in plasma brain-derived neurotrophic factor (BDNF) levels was significantly higher in the NMES period than in the control period ($p < 0.05$).

Conclusions: This study showed that an 8-week NMES training program could induce greater changes in the blood glucose concentration, percent body fat, and plasma BDNF levels than the control intervention in patients with T2DM. NMES training might prove to be an alternative exercise method for patients who might have difficulties in performing adequate voluntary exercise.

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https://doi.org/10.1016/j.diabres.2018.05.032
0168-8227/

1. Introduction

Physical activity, along with diet and medication, is considered a cornerstone of type 2 diabetes mellitus (T2DM) treatment. At least 150 min/week of moderate to vigorous physical activities is recommended to patients with T2DM [1], because this might have beneficial effects such as improved glycemic control [2], reduced mortality [3], and reduced risk of diabetic complication development [4]. However, many patients with T2DM are restricted from performing their recommended exercise (e.g., walking or ergometric exercise) because of excessive obesity, orthopedic diseases, or severe diabetic complications.

Neuromuscular electrical stimulation (NMES) is expected to be an alternative exercise method for such patients. NMES has been considered to improve not only muscle strength [5,6] but also glucose metabolism [7,8]. By means of a euglycemic clamp, we have demonstrated that a single bout of NMES more significantly enhanced whole body glucose uptake during and after NMES than voluntary ergometric exercise at the identical oxygen uptake [9,10]. Additionally, we provided the first clinical evidence for the fact that a single bout of NMES could successfully attenuate the postprandial glucose concentration in patients with T2DM [7,8]. These results led us to expect prolonged NMES to be effective in improving glucose and fat metabolism in patients with T2DM.

Furthermore, a single bout of NMES significantly increased blood brain-derived neurotrophic factor (BDNF) levels, to be equivalent to the levels of blood BDNF present during moderate voluntary exercise [11]. BDNF is known as one of the essential mediators, responsible for the beneficial effects of physical activity on cognitive function, as well as insulin-like growth factor-1 (IGF-1) [12,13]. Blood BDNF levels are decreased independent of obesity [14,15], and low levels of blood IGF-1 are positively associated with glucose control in patients with T2DM [16]. Thus, blood BDNF and IGF-1 levels are considered as important blood biomarkers in T2DM because T2DM is one of the independent risk factors for the onset of dementia [17].

However, there are no data, at least to our knowledge, concerning the effects of a prolonged period of NMES training on the metabolic profile and cognition-related blood parameters in patients with T2DM. We hypothesized that prolonged NMES would positively induce significant changes in these parameters, since a single bout of NMES could affect these parameters [7,11]. Accordingly, the purpose of this study was to examine the effect of a prolonged period of NMES training on metabolic parameters, and blood BDNF and IGF-1 levels in patients with T2DM.

2. Subjects, materials and methods

2.1. Participants and informed consent

Outpatients in the Kobe City Medical Center General Hospital with T2DM were recruited. The inclusion criteria were as follows: (1) patients with T2DM, (2) male, (3) $7.0 \geq$ HbA1c $\leq 9.0\%$, (4) permitted to perform additional physical activity by their doctor, (5) performed no physical exercise more than once a week, and (6) possessing the ability to operate the NMES equipment by themselves. The exclusion criteria were as follows: (1) patients treated by exogenous insulin injection, (2) dementia, and (3) inability to undergo any of the study's evaluations. Fourteen men with T2DM (Age: 63.2 ± 3.0 years, Body mass: 76.1 ± 3.5 kg, BMI: 27.0 ± 1.2, HbA1c: 7.7 ± 0.2%, duration of T2DM: 9.6 ± 1.4 years) volunteered to participate in this randomized controlled cross-over study. Eight of fourteen patients had diabetic complications; i.e. retinopathy, nephropathy, and/or neuropathy. All patients were treated by oral hypoglycemic agents such as sulfonylureas (n = 4), glinides (n = 3), thiazolidinediones (n = 2), biguanides (n = 9), alpha-glucosidase inhibitors (n = 3), glucagon-like peptide 1 receptor agonists (n = 1), and dipeptidyl peptidase-4 inhibitors (n = 8). All patients gave informed consent for the study after receiving a detailed oral and written explanation of the purposes, potential benefits, and risks associated with participation. The study was approved by the Ethical Committee of Kobe City Medical Center General Hospital (#14088) and registered at the UMIN Clinical Trials Registry (UMIN000018005).

2.2. Study design

The present clinical study was designed as a randomized controlled cross-over trial to examine the effect of an 8-week NMES training on metabolic parameters, and blood BDNF and IGF-1 levels. After the baseline evaluation, patients were randomly allocated to one of two groups, either first to the NMES and then to the CON groups (Group A) or first to the control (CON) and then to the NMES intervention (NMES) groups (Group B), based on blocked randomization (8 blocks) by their attending doctors. The study durations for CON and NMES periods were of 8 weeks each, and patients' follow-ups were conducted at 8 and 16 weeks for evaluating their condition. Patients were requested to maintain their habits and lifestyle such as food intake and physical activity during both these periods. Additionally, the patients performed 8-week NMES training during the NMES period. At the baseline and after 8- and 16-week periods, body composition, physical activity, energy intake, and metabolic and cognition-related blood parameters were evaluated in all patients. Their attending doctors asked the patients if they experienced the adverse effects of NMES at every visit. The sample size was based on clinical and practical considerations related to cost and patient availability in one hospital.

2.3. NMES intervention

NMES equipment was used for the 8-week-long training period. NMES was applied to gruteal, upper-leg, and lower-leg muscle groups, including the gluteus maximus, quadriceps, hamstrings, hip abductor and adductor muscle groups, and dorsi and plantar flexor muscle groups on each leg. Six silicon-rubber electrode bands were wrapped around the waist, and bilateral distal parts of the thigh and crus were