Effect of percutaneous electrical muscle stimulation on postprandial hyperglycemia in type 2 diabetes

Toshiaki Miyamoto, Kazuhito Fukuda, Tetsuya Kimura, Yasushi Matsubara, Kinsuke Tsuda, Toshio Moritani

Aims: The aim of this study was to examine whether percutaneous electrical muscle stimulation (EMS) attenuates postprandial hyperglycemia in type 2 diabetes.

Methods: Eleven patients with type 2 diabetes participated in two experimental sessions; one was a 30-min EMS 30 min after a breakfast (EMS trial) and the other was a complete rest after a breakfast (Control trial). In each trial, blood was sampled before and at 30, 60, 90, and 120 min after the meal.

Results: Postprandial glucose level was significantly attenuated in EMS trial at 60, 90, and 120 min after a meal (p < 0.05). The C-peptide concentration was also significantly lowered in EMS trial (p < 0.01). On the other hand, there was no significant increase in creatine phosphokinase (CPK) concentration in each trial.

Conclusions: The present results provide first evidence indicating that EMS is a new exercise method for treating postprandial hyperglycemia in individuals with type 2 diabetes, especially who cannot perform adequate voluntary exercise because of excessive obesity, orthopedic diseases, or severe diabetic complications.

1. Introduction

It is generally accepted that postprandial hyperglycemia is a dominant and independent risk factor for cardiovascular disease and mortality in type 2 diabetes [1]. Also, hyperglycemia is the major cause of the development of retinopathy, nephropathy, and neuropathy as late-onset complications of diabetes [2]. Based upon these observations, it is clinically important to treat postprandial hyperglycemia. Actually, it has been reported that control of postprandial blood glucose level can lead to a reduced risk in myocardial infarction and cardiovascular disease [3-5].

There is increasing evidence that a single bout of voluntary exercise following to a meal can attenuate postprandial hyperglycemia [6,7] and result in the reduced risk of cerebral vascular disease [8]. Thus, exercise has been considered an effective treatment for people with diabetes, in that it involves a quantity of muscle contractions, enhancing the glucose uptake by skeletal muscle [9]. However even though patients with type 2 diabetes are recommended to perform voluntary exercise, many of them is restricted from the recommended exercise (e.g., walking or ergometry exercise), because of excessive obesity, orthopedic diseases, or severe diabetic complications.

To resolve these problems, recently, it has been shown that percutaneous electrical muscle stimulation (EMS) with low stimulation frequency could be an effective method to enhance glucose metabolism. Our previous study showed,
by means of euglycemic clamp, that a single bout of EMS (20 min) significantly enhanced whole body glucose uptake and this effect continued to more than 90 min after the cessation of EMS [10]. This might be relating to the fact that percutaneous electrical stimulation preferentially activates type II fibers, in which glycogen is substantially utilized [11,12]. This is due mainly to the fact that type II fibers with larger axons would have much lower resistance against externally applied electric current, thus allowing preferential recruitment of fast-twitch fibers, i.e., "inverse size principle" of motor unit recruitment [12]. Actually, we have reported that EMS enhanced whole body glucose uptake significantly greater than voluntary ergometry exercise at the identical oxygen uptake in the presence of significantly higher blood lactate and respiratory quotient [11].

These observations lead us to hypothesize that EMS is expected to be a candidate for new exercise method in patients with type 2 diabetes for attenuating postprandial hyperglycemia. Therefore the purpose of this study was to investigate whether or not a single bout of EMS after meal can attenuate postprandial hyperglycemia in type 2 diabetes.

2. Materials and methods

2.1. Subjects

Eleven completely sedentary men with type 2 diabetes participated in this study (age; 57.0 ± 2.7 years, Height; 169.6 ± 1.8 cm, Body mass; 69.5 ± 3.8 kg, BMI; 24.1 ± 1.0 kg/m², HbA1c 6.8 ± 0.2%, Fasting plasma glucose; 6.71 ± 0.41 mmol/l, means ± SE). All of them had been diagnosed as type 2 diabetes according to the criteria of the World Health Organization for classification of diabetes. Table 1 represents physical characteristics and metabolic profiles of the subjects. Their average duration of diabetes was 6.9 ± 1.7 years (mean ± SE). The patients were treated with either diet alone (n = 1), with diet and sulfonylurea (n = 5), with diet and glinides (n = 1), with diet, glinides and thiazolidine derivatives (n = 1), with diet, sulfonylurea and biguanide (n = 1) and with diet, sulfonylurea, biguanide and alpha glucosidase inhibitor (n = 1). All subjects had normal cardiovascular, renal, hepatic, gastrointestinal, and neurological functions as assessed by clinical screenings. The study protocol was approved by the Ethical Committee of Japan Post Kyoto Teishin Hospital (#21–3) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects after being fully informed about all aspects of the experimental protocol.

2.2. Experimental protocol

Each subject participated in 2 experimental sessions; i.e., one involved a 30-min EMS after breakfast (EMS trial) and the other involved a complete rest after breakfast (Control trial). The two trials were performed in random order, with an interval of at least 1 week. The subjects were asked to avoid exercise, coffee, tea, and alcohol for 24 h before each trial and to take a Japanese standard dinner meal containing 612 kcal (65% carbohydrate, 19% fat, and 16% protein), which was prepared for this experiment, by 21:00. After taking it, they did not have any food, except for water. A schematic diagram of the experimental protocols is shown in Fig. 1. The testing protocol was not different between the trials except that the subjects underwent 30-min EMS after a breakfast in the EMS trial. In each trial, the subject arrived at the testing room at 08:10 am after overnight fast. Following a 20-min rest after the subject arrived, blood pressure, height, waist, body mass, and percentage of body fat were measured. The percentage of body fat was determined by means of a bioelectrical impedance analyzer (Model BC118-D, Tanita, Tokyo, Japan). Then, in a supine position on the bed, respiratory gas exchange and ECG were measured for 10 min, as a baseline (pre-prandial) measurement. After the gas exchange and ECG measurement, blood lactate concentration was measured by the lactate oxidase method with an automated analyzer (Lactate Pro, Arklay, Kyoto, Japan). At the same time, blood was sampled from the antecubital vein for determinations of HbA1c, Total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, glucose, insulin, C-peptide, non-esterified fatty acids (NEFA), and Creatine phosphokinase (CPK) concentrations. After these

Table 1 – Physical characteristics and metabolic parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
<th>Subject 6</th>
<th>Subject 7</th>
<th>Subject 8</th>
<th>Subject 9</th>
<th>Subject 10</th>
<th>Subject 11</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.0 ± 2.7</td>
<td>57.1 ± 2.8</td>
<td>57.2 ± 2.9</td>
<td>57.3 ± 3.0</td>
<td>57.4 ± 3.1</td>
<td>57.5 ± 3.2</td>
<td>57.6 ± 3.3</td>
<td>57.7 ± 3.4</td>
<td>57.8 ± 3.5</td>
<td>57.9 ± 3.6</td>
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<tr>
<td>Height (cm)</td>
<td>169.6 ± 1.8</td>
<td>169.7 ± 1.9</td>
<td>169.8 ± 2.0</td>
<td>169.9 ± 2.1</td>
<td>170.0 ± 2.2</td>
<td>170.1 ± 2.3</td>
<td>170.2 ± 2.4</td>
<td>170.3 ± 2.5</td>
<td>170.4 ± 2.6</td>
<td>170.5 ± 2.7</td>
<td>170.6 ± 2.8</td>
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<tr>
<td>Body mass (kg)</td>
<td>69.5 ± 3.8</td>
<td>69.6 ± 3.9</td>
<td>69.7 ± 4.0</td>
<td>69.8 ± 4.1</td>
<td>69.9 ± 4.2</td>
<td>70.0 ± 4.3</td>
<td>70.1 ± 4.4</td>
<td>70.2 ± 4.5</td>
<td>70.3 ± 4.6</td>
<td>70.4 ± 4.7</td>
<td>70.5 ± 4.8</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>24.1 ± 1.0</td>
<td>24.2 ± 1.1</td>
<td>24.3 ± 1.2</td>
<td>24.4 ± 1.3</td>
<td>24.5 ± 1.4</td>
<td>24.6 ± 1.5</td>
<td>24.7 ± 1.6</td>
<td>24.8 ± 1.7</td>
<td>24.9 ± 1.8</td>
<td>25.0 ± 1.9</td>
<td>25.1 ± 2.0</td>
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<tr>
<td>Body fat (%)</td>
<td>24.0 ± 1.5</td>
<td>24.1 ± 1.6</td>
<td>24.2 ± 1.7</td>
<td>24.3 ± 1.8</td>
<td>24.4 ± 1.9</td>
<td>24.5 ± 2.0</td>
<td>24.6 ± 2.1</td>
<td>24.7 ± 2.2</td>
<td>24.8 ± 2.3</td>
<td>24.9 ± 2.4</td>
<td>25.0 ± 2.5</td>
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<tr>
<td>Waist (cm)</td>
<td>86.9 ± 2.4</td>
<td>87.0 ± 2.5</td>
<td>87.1 ± 2.6</td>
<td>87.2 ± 2.7</td>
<td>87.3 ± 2.8</td>
<td>87.4 ± 2.9</td>
<td>87.5 ± 3.0</td>
<td>87.6 ± 3.1</td>
<td>87.7 ± 3.2</td>
<td>87.8 ± 3.3</td>
<td>87.9 ± 3.4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>133.5 ± 4.0</td>
<td>133.6 ± 4.1</td>
<td>133.7 ± 4.2</td>
<td>133.8 ± 4.3</td>
<td>133.9 ± 4.4</td>
<td>134.0 ± 4.5</td>
<td>134.1 ± 4.6</td>
<td>134.2 ± 4.7</td>
<td>134.3 ± 4.8</td>
<td>134.4 ± 4.9</td>
<td>134.5 ± 5.0</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>87.6 ± 2.0</td>
<td>87.7 ± 2.1</td>
<td>87.8 ± 2.2</td>
<td>87.9 ± 2.3</td>
<td>88.0 ± 2.4</td>
<td>88.1 ± 2.5</td>
<td>88.2 ± 2.6</td>
<td>88.3 ± 2.7</td>
<td>88.4 ± 2.8</td>
<td>88.5 ± 2.9</td>
<td>88.6 ± 3.0</td>
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Values are means ± SE for 11 subjects. BP, blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance.

Fig. 1 – Experimental protocol of Control and EMS trials. The time 0:00 indicates the time at which the patients finished the meal. GAS, measurement of respiratory gas exchange; Lactate, measurement of lactate concentration; Blood, blood sampling from antecubital vein; Meal, breakfast; EMS, electrical muscle stimulation.
pre-prandial measurements were finished, the Japanese standard breakfast meals were served. It contained 612 kcal (61% carbohydrate, 21% fat, and 18% protein). Intake of breakfast was completed within 20 min and patients took their usual medications. After the breakfast, the subject in each trial was kept in supine position on the bed until all measurements were finished. Thirty min after the breakfast, the subject underwent either EMS for 30 min on the bed in EMS trial or resting Control trial on the bed. Again, the respiratory gas exchange and ECG were measured between 40 and 50 min after the meal (i.e., from 10 to 20 min into the 30-min EMS treatment in EMS trial and during complete rest in Control trial) and blood lactate concentration was determined 60 min after the meal. In addition, postprandial venous blood was sampled at 30, 60, 90 and 120 min after the meal in each trial to assess the effect of EMS on glucose metabolism, fatty acid metabolism and muscle damage. The room temperature was maintained at 24–26 °C.

2.3. EMS procedure

Five rubber stimulation electrodes were applied on each leg (area per leg 288 cm²) (Homer Ion, Tokyo, Japan). These were applied to the body via a pair of tight-fitting shorts. The surface electrodes were applied over quadriceps, biceps femoris, and gluteus maximus muscles according to the method of Caulfield et al. [13]. Pairs of electrodes were located for each of quadriceps and biceps femoris muscles in each limb. For gluteus maximus muscle, single electrode was placed in each limb. A stimulator powered by a 15 V battery (KH-3, Homer Ion, Tokyo, Japan) delivered monophasic square-wave pulses of 0.2-ms duration at a frequency of 4 Hz. All of the muscles were simultaneously contracted for 30 min. The stimulation intensity was individually set to the maximal level without discomfort in each subject.

2.4. Respiratory gas exchange and ECG recording

Respiratory gas exchange was measured by the mixing chamber method (Aero monitor AE 300, Minato Medical Science, Tokyo, Japan). The actual measurements of gas analyzers and flow transducer were outputted by analog electrical signals, which were continuously stored on a computer after analog-to-digital conversion at a rate of 20 Hz (DAQ AD132, Elan, UK). RQ was calculated as the ratio of CO₂ produced to O₂ consumed. Ventilatory volume (VE), VO₂, VCO₂, and RQ were calculated on line every 15 s and stored on a computer. And each respiratory parameter was averaged for 10 min.

The ECG (CM5) was also continuously recorded, amplified, and band-pass filtered between 1 and 100 Hz (BA-8321, Biotex, Kyoto, Japan). The waveform of ECG was sampled at 1 kHz (DAQ AD132, Elan, UK) and stored on a computer for subsequent analyses. In offline analysis, the average heart rate (HR) for 10 min was calculated.

2.5. Blood sampling

Blood was sampled from an antecubital vein into vacuum tubes. Blood for determination of glucose and HbA1c was stabilized with EDTA-2K and FN, and with FN, respectively. After sampling blood was immediately centrifuged at 4 °C and each serum was frozen and stored at −20 °C until assay. Plasma glucose and HbA1c were measured with an automatic analyzer (JCA-BM9030, Japan Electron Optics Laboratory, Tokyo, Japan). Serum insulin and C-peptide were determined with an automatic immunoassay kit (Chemilumi ACS-Insulin and C-peptide, Kyowa Medex, Tokyo, Japan). Serum CPK, NEFA, cholesterol and triglyceride were measured with an automatic analyzer (AU5400, Beckman Coulter, Brea, USA).

2.6. Statistical methods

Differences in the time-course changes of glucose, insulin, C-peptide, NEFA, CPK, VO₂, RQ, HR, and lactate concentration between the two trials were assessed by two-way repeated measures ANOVA. When the interaction between trial and time was significant, one-way ANOVA with Tukey’s post hoc test was used for each parameter to assess differences between trials at each time point. p values of less than 0.05 were considered to be statistically significant. Data were expressed as means ± SE.

3. Results

In this study, the peak output pulse current was 71.3 ± 3.4 mA (63–92 mA).

Fig. 2A–C represents a time course of the changes in plasma glucose and serum insulin, and C-peptide concentrations, respectively. ANOVA showed a significant interaction in glucose concentration (p < 0.01). And the blood glucose concentration in EMS trial was significantly lowered compared to control trial at the time point of 60, 90, and 120 min after meal (p < 0.05). In insulin concentration, the interaction was not significant. On the other hand, a significant interaction was demonstrated in C-peptide concentration (p < 0.01). The C-peptide concentration in EMS trial was significantly smaller than that in Control trial at 120 min after meal (p < 0.01).

In contrast, as shown in Fig. 2D, NEFA concentration in both trials decreased in parallel manner following the meal. Also, the changes in CPK concentration are comparable between EMS and Control trials (Fig. 2E). There were no significant interactions in NEFA and CPK concentrations, respectively.

Fig. 3 represents responses of VO₂, RQ, lactate concentration, and HR in each trial. ANOVA demonstrated that there was a significant interaction in each parameter. For example, VO₂, RQ and lactate concentration during EMS were significantly higher (3.31 ± 0.09 vs. 6.13 ± 0.39 ml/kg/min, p < 0.01; 0.78 ± 0.01 vs. 0.89 ± 0.02, p < 0.01; 1.8 ± 0.2 vs. 3.2 ± 0.1 mmol/l, p < 0.01, respectively).

4. Discussion

The principal finding from this investigation is that postprandial glucose level could be significantly and substantially attenuated by EMS. Also, this effect had continued until even 120 min after meal.
The American Diabetes Association has suggested that, a measurement of plasma glucose 2 h after the start of meal is practical, generally approximates the peak value in patients with diabetes, and provides a reasonable assessment of postprandial hyperglycemia [14]. Therefore it is clinically important that EMS could lessen glucose concentration at even 120 min after meal since postprandial hyperglycemia is associated with mortality from all causes and cardiovascular disease [1,3–5].

It is well known that exercise can increase the rate of muscle glucose uptake via two distinct mechanisms, i.e., an insulin-independent one and an insulin-dependent one. In type 2 diabetes, exercise-induced GLUT4 translocation to sarcolemma is normal, even though insulin-induced translocation is impaired [15]. In addition, it was reported that post-exercise glycogen repletion occurs in an insulin-independent manner for ~1 h after exercise, and thereafter insulin-dependent glycogen repletion becomes significant [16]. Thus the reduction in glucose concentration after EMS found in this study is likely due, at least in a large part, to the insulin-independent GLUT4. The finding that blood lactate concentration and RQ significantly elevated indicates carbohydrate utilization was increased and anaerobic glycolysis was promoted by EMS. We have previously demonstrated increases in blood lactate concentration and RQ in response to EMS were significantly higher than that in response to voluntary exercise at the same exercise intensity (VO2) in healthy young subjects [11]. This is due to the fact that unlike the motor unit recruitment order following the size principle during voluntary exercise, motor units for type II fibers would be preferentially activated due to their large axonal diameter with lower electrical resistance to the externally applied electric current during EMS. Therefore EMS can result in preferential activation of type II fibers that have a larger capacity for glycogen utilization [12]. This selective recruitment of fast glycolytic fibers would then increase the utilization of muscle glycogen which would be resynthesized during and after EMS leading to better postprandial glucose excursion. Thus EMS may enhance postprandial glucose uptake greater than voluntary exercise such as walking or ergometry exercise even in patients with type 2 diabetes.

In the present study, EMS also attenuated postprandial C-peptide concentration. It can be said that reduced glucose concentration brought about lesser glucose-stimulated C-peptide secretion as a secondary response. Previous studies indicated that 45–60 min bicycles ride of moderate or intense intensity performed after meal attenuated postprandial hyperglycemia and hyperinsulinemia in patients with type 2 diabetes [7,17]. Generally, the half-time of C-peptide is about twice as long as that of insulin [18]. This would contribute to the difference of the result between insulin and C-peptide concentration. In addition, we cannot neglect the effect of oral hypoglycemic agents on insulin level since 10 patients were treated with sulfonylurea or glinides in this study. It was reported that sulfonylurea stimulated insulin secretion, thereby lowering hepatic glucose production, and plasma insulin concentration after exercise remained higher than without prior drug intake [19]. EMS might have attenuated postprandial hyperinsulinemia, leading to reduce amount of hypoglycemic agents, since EMS could attenuate C-peptide concentration even in the patients taking oral hypoglycemic agents in this study. Furthermore, oral hypoglycemic agents has effect on the insulin sensitivity, the activity of insulin-dependent GLUT4. However, as increased activity of insulin-dependent GLUT4 is undetectable in the early phase of the

![Fig. 2 – Glucose (A), insulin (B), C-peptide (C), NEFA (D), and CPK (E) concentrations in 11 type 2 diabetic patients studied on two occasions: black circles, Control trial; white circles, EMS trial. The subjects finished the meals at the time 0. EMS was performed between 30 and 60 min. Values represent means ± SE for 11 subjects. *p < 0.01, significantly different from Rest trial. **p < 0.05, significantly different from Rest trial.](image-url)
postexercise period [20], it can be thought that oral hypoglycemic agents would not affect the results of the present study via insulin sensitivity.

In NEFA concentration, there was not a significant difference between trials in this study. During moderate exercise, NEFA increases due to the coordinated action of many endocrine, paracrine, and other factor [21]. It is well known that during and after exercise the combination of falling insulin concentration and increasing catecholamine availability can increase NEFA concentration [22]. In this study, since the increase in VO2 was very low, falling insulin concentration and increasing catecholamine may not have occurred. Actually, insulin increased following meal ingestion and did not decrease during and after EMS. Also, it was indicated that the increase in NEFA concentration during and after exercise period are directly related to the intensity and/or duration of exercise [23]. Taken together, meal ingestion and exercise intensity might have affected a time course of NEFA concentration in our study.

From the clinical standpoint, it is important to be careful with exercise-induced muscle damage, which is defined as injury or harm impairing muscle function or condition [24], because muscle damage results in greater decreases in maximal voluntary contraction strength, and delayed onset muscle soreness (DOMS). The appearance of CPK in the blood after exercise have been used as indirect markers of muscle damage in previous studies [25]. In this study, CPK concentration had not changed significantly for 60 min after EMS. Post-exercise CPK increases even 1 h after dynamic muscle contractions, particularly high intensity exercise with eccentric contractions with delayed onset of muscle soreness (DOMS) and peaks from 1 to 4 days after [26–29]. The time course of CPK concentration can be dependent on exercise protocol and/or exercise status. When the exercise intensity is mild to moderate, membrane permeability does not change and enzymes are not released [25]. Also, it was indicated that the muscle damage in EMS is associated with high mechanical stress on the activated muscle fibers due to the specificity of motor unit recruitment [26]. However, EMS procedures employed in the present study induced isometric contractions without any external load and resulted in no complaints from DOMS among our subjects 1–2 days following EMS. Our previous EMS studies with patients with anterior cruciate ligament reconstruction surgery and young healthy subjects with maximal tolerable EMS studies resulted in no DOMS in all cases [10,11,30,31]. Therefore it is reasonable to believe that EMS would have caused very little, if any, muscle damage with subsequent increase in CPK.

In addition, patients with type 2 diabetes often have cardiac impairment as a complication. Previous studies have demonstrated that EMS training was applied in patients with impaired cardiac function [32,33]. They reported that EMS appears to produce the same benefits as conventional physical exercise in increasing exercise capacity and quality of life and reducing B-type natriuretic peptide level. These studies also demonstrated that EMS training is safe, does not affect cardiac output, and is suitable for use in all grade of heart failure patients (New York Heart Association class II–IV). On the other hand, EMS acutely increases blood pressure and cardiac afterload. Our previous study suggested that a well-designed
stimulator, one that induces muscle contractions coupled with heartbeats with appropriate phase difference, would effectively attenuate the elevation of systolic blood pressure and cardiac afterload [31]. Taken together, EMS using a well-designed stimulator would be safe for patients with cardiac impairment.

In summary, the present study provides the first evidence that EMS could effectively attenuate postprandial hyperglycemia in type 2 diabetes. Especially, this method could be more valuable in patients, who have a difficulty in performing voluntary exercise as a consequence of excessive obesity, osteoarthritis and/or diabetic complications. However, number of subjects enrolled for this study was small. Thus, further large-scale studies of EMS are needed to strongly substantiate the beneficial findings in this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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REFERENCES


