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Acute Effects of Neuromuscular Electrical Stimulation on Blood Glucose and Energy Metabolism in Overweight/Obese Population

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ACUTE EFFECTS OF NEUROMUSCULAR ELECTRICAL STIMULATION ON BLOOD GLUCOSE AND ENERGY METABOLISM IN OVERWEIGHT/OBESE POPULATION

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Dedication

This study is wholeheartedly dedicated to my beloved family, who have been our source of inspiration and gave me strength when I thought of giving up, who continually provide their moral, spiritual, emotional support.

To my mother, thank you for always providing me with unconditional love and support.

To my father, though you never got to see this thesis, you are in every page.

To my brothers for always keeping me in line and staying by my side in support.

To my wife for endless love, support, and encouragement.

To my advisor Dr. Bajpeyi, for providing countless feedback and making my thesis a priority.

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by

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Ali Mossayeb

Abstract

Background: In the perspective of preventing cardiovascular disease and promoting health, weight control and physical activity are the main concerns**.** Electrical stimulation (ES) is an alternate strategy to induce muscle contraction, using electrical impulses. However, effectiveness of ES induced muscle contraction to improve energy expenditure and glucose metabolism is not well examined.

Purpose: To determine the acute effect of ES on whole body energy expenditure and body glucose metabolism in sedentary overweight or obese population

Methods: Sedentary overweight/obese participants (n=8; age: 37.25 ± 6.09 years; BMI= 37.57 ± 2.43 kg/m^2) were included in this study. All participants received bilateral quadriceps ES at maximum tolerable intensity for 30 minutes. Blood glucose metabolism was assessed by RQ and blood lactate level, substrate utilization was measured by indirect calorimetry and body composition was measured by dual X-ray absorptiometry.

Results: Energy expenditure did not change during ES (p=0.19), the mean of blood glucose level during ES significantly decreased compared to baseline (p=0.04), substrate utilization (p=0.17), and blood lactate (p=0.44) did not change compared to the baseline.

Conclusions: Existing evidence suggest that ES can effectively decrease blood glucose level in sedentary overweight or obese population, and it may not effectively improve the energy expenditure. Neuromuscular electrical stimulation (NMES) is a novel alternate strategy to induce muscle contraction, using electrical impulses. However, effectiveness of NMES induced muscle contraction to improve insulin sensitivity and energy expenditure is not clear.

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Introduction

Obesity and diabetes have become major public health issues not only in the United States, but also around the world [1]. Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes, which is caused by insulin resistance in target organs and pancreatic-cell malfunction leading to impairment of insulin action to regulate blood glucose [2]. The number of American's diagnosed with diabetes is more than 34 million (10% of the population) and 90-95% of them have T2DM [3] which is expected to rise to 39.7 million (13% of the population) in 2030, and to 60.6 million (17% of the population) in 2060 [4]. The healthcare burden of diabetes is tremendous as a person with diabetes spends 2.3 times more in medical care expenses compared to someone without diabetes [5]. In 2017, the cost of diagnosed diabetes in the United States was $327 billion, with $237 billion in direct medical costs and $90 billion in lost productivity [5].

Obesity is generally defined as a body mass index (BMI) ≥ 30 kg/m^2 [6]. Individuals in the BMI range of 25 to 30 kg/m^2 are categorized as overweight while a BMI of 40 kg/m^2 and above is considered as morbid obesity [7]. Obesity, also defined as an unusually elevated level of body fat, is a significant risk factor for a variety of chronic diseases, including T2DM, coronary artery disease, hypertension, and certain types of cancer [8-10]. Obesity has roughly tripled globally since 1975 [11]. More than 1.9 billion adults aged 18 and over were overweight worldwide in 2016, with over 650 millions of them being obese [11]. Obesity prevalence in the United States increased from 30.5 % to 42.4 % between 1999 and 2018, with no significant differences between men and women among all individuals or by age group [12]. This disease was responsible for almost 1 million fatalities in 2017, making it the ninth highest cause of death [13].

In Texas, the obesity rate in adults has increased from 21.7% to 34.8% between 2000 to 2021 [14] where 37.9% of the population are Hispanics [12] who are at a greater risk of developing metabolic diseases such as T2DM compared to national average [12]. In 2018, 12.5% of adults in Texas were diagnosed with T2DM whereas prevalence among Hispanic population was 13.1%

[14]. The border region of El Paso, with near 80% Hispanic population, has one of the highest prevalence of obesity (73.5%) compared to other populations [15] and they are at 66% greater risk for developing T2DM [16]. The influence of obesity on T2DM risk has consistently been demonstrated in both cross-sectional [17, 18] and prospective studies [19, 20] that imply people with obesity have higher medical expenses than people within the healthy weight range [21]. Lowering adipose tissue is one of the strategies to lose weight among people with obesity, and is also vital to avoid harmful cardiometabolic co-morbidities [22]. Adipose tissue can be effectively reduced by dietary modification and increasing energy expenditure (e.g. exercise) [23].

Physical activity is defined as bodily movement produced by skeletal muscles that results in energy expenditure [16]. The amount of energy expended as a result of physical activity varies depending on the muscle mass involved, duration, frequency and the intensity at which the activity is performed [24]. Approximately 31% of the world's population at the age of 15 or above engages in insufficient physical activity, which has been linked to the deaths of 3.2 million people each year [25]. Physical inactivity raises the risk of metabolic diseases like obesity and T2DM, and is the world's fourth leading cause of mortality [26]. Only 1 in 4 US adults and 1 in 5 high school students meet the recommended levels of physical activity [27, 28]. Physical activity can reduce the risk of many chronic diseases, including obesity and T2DM, for people of all ages and conditions [29]. While there is no cure for diabetes, weight loss and physical activity have been shown to be effective ways to manage diabetes [30].

Insulin resistance is defined as resistance to the effects of insulin on glucose uptake, metabolism, or storage [31]. Reduced insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle characterize insulin resistance in obesity and T2DM [32]. Glucose uptake in skeletal muscles may occur by insulin dependent or insulin-independent (contraction-induced) mechanisms [33]. Insulin and exercise (contraction-induced) stimulate GLUT4 translocation through distinct signaling mechanisms[34]. Insulin signaling involves rapid phosphorylation of the insulin receptor, insulin receptor substrate-1/2 on tyrosine residues, and the activation of phosphatidylinositol 3-kinase [35, 36]. GLUT4 has been shown to be the primary

transporter responsible for exercise-induced glucose uptake [37]. Exercise can directly activate glucose uptake in skeletal muscle by inducing translocation of GLUT4 to the cell surface via an insulin-independent mechanism (contraction-stimulated glucose transport) [36, 38-41]. Muscle glycogen is an essential fuel for exercise and muscle contraction [42, 43]. During the low intensity exercise (50% maximum VO2max), blood glucose can be used predominantly as a fuel in contracting muscles [44]. Muscle glycogen is resynthesized, both at rest and during low intensity exercise, using blood glucose from accelerated glyconeogenesis [45]. This process is considered to be responsible for the acute effect of exercise on glucose transport with skeletal muscle contraction taking up the majority of glucose [46]. In fact, contraction-stimulated GLUT4 translocation is not impaired in insulin-resistant conditions such as T2DM and obesity [46]. Therefore, following exercise there is an increase in muscle glycogen synthase activity, which is the main pathway of glucose disposal in skeletal muscle [47]. Both acute and chronic exercise can improve glucose metabolism and uptake [48]. It is also well known that muscle contraction from endurance and resistance training improves insulin sensitivity in people of all ages [49-51]. As a result, these insulin-independent and insulin-dependent exercise mechanisms have been widely used to prevent glucose intolerance and enhance glycemic control in people with obesity and T2DM [52].

Prolonged lack of physical activity has been linked to insulin resistance and decreased peripheral glucose absorption [53]. More recently, Mikines et al. [54] and Stuart et al. [55] have demonstrated that physical inactivity caused by bed rest for as little as 7 days of bed rest is associated with a substantial reduction in insulin sensitivity in inactive skeletal muscle without changing the effect of insulin on hepatic glucose production. Furthermore, prolonged physical inactivity has been demonstrated to reduce skeletal muscle oxygen transport capacity [56].

Adherence to physical activity is challenging for those with obesity and T2DM suffering from defects in lipid oxidation capacity, musculoskeletal pain, and peripheral neuropathy that limits their ability to exercise [57-60]. People with obesity have more difficulty with weight-bearing activities like jogging or running, and they are more likely to sustain injuries and develop

pain intolerance [61]. In addition, those with insulin resistance and/or T2DM have a lower physical performance threshold, which pose a physical challenge that prevents them from exercising at the prescribed intensity and duration [62, 63]. Therefore, alternate techniques to induce muscle contraction in individual who are unable to exercise, may be beneficial.

Electrical stimulation (ES) is a practical, non-invasive, cost-effective and innovative method to promote an alternative mode of muscle contraction among individuals who are less likely to engage in conventional physical activity [64]. ES generated muscular contraction has been found to increase glucose uptake in human myotubes and isolated rat skeletal muscle [65, 66]. As a result, the idea of enhancing glucose metabolism and energy expenditure by inducing muscular contraction as an alternative treatment method has piqued the attention of people who are unable to exercise regularly and/or are insulin resistant [67-69]. ES has been widely used in rehabilitation to prevent muscle atrophy and to help individuals with spinal cord or sports injuries regain muscle mass and function [70-73]. However, the effectiveness of ES in enhancing metabolic health has not been thoroughly examined.

ES is an alternate strategy to induce involuntary contraction of skeletal muscle via depolarization of the motor units being stimulated through an electrical current [74-76]. This therapy makes use of random special recruitment, based on the proximity of intramuscular nerve branches to adhesive electrodes [77-79]. These surface electrodes induce muscle contractions similar to when an action potential travels down a motor neuron from the brain initiating the signaling cascade of muscle contraction [80]. ES leads to activation of anaerobic pathways as a source of ATP [81].

Although several animal studies have shown that a single bout of ES can activate both insulin-independent [39-41, 82] and insulin-dependent glucose uptake [49, 83], it has not been investigated whether the acute ES has identical benefits on glucose uptake and energy expenditure in sedentary obese human population.

Literature Review

To date, only a few studies have investigated the effect of ES on blood glucose control and energy expenditure in healthy overweight/obese people who are at high risk of developing T2DM. In the past decade, most of the research regarding the effect of ES on glucose metabolism and/or substrate utilization have been done on individuals with spinal cord injuries (SCI) [84-92] or individuals with T2DM [71, 76, 93-104]. In contrast to four prior studies [76, 84, 88, 105] that found no significant changes in blood glucose following ES intervention, the majority of prior studies reported a significant improvement in glucose metabolism [71, 93, 96, 97, 99, 103, 106-108]. To our knowledge, only three studies have examined the effects of ES on blood glucose metabolism and/or substrate utilization in healthy overweight/obese individuals [105, 109, 110]. Out of these three studies only one study has investigated the acute effect of ES on blood glucose metabolism and substrate utilization [110].

Table 1 describes the population characteristics, methods, and results of the reviewed eight studies that have investigated the acute effects of ES on blood glucose and energy expenditure. The studies have been conducted on healthy individuals (n=4), populations with obesity (n=1), and T2DM (n=3).

Table 1: Characteristics of included studies

Study	Sample size	Study population (Age in years)	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES Intensity	ES Condition	Glucose metabolism outcome	Substrate Utilization outcomes
Hamada et al. 2003	8	Healthy (24.2-25.4)	One session (Acute)	20	20	Limit of 80 mA	CLAMP	GDR: Increased	RER: Increased Lactate: Increased
Hamada et al. 2003(Jan)	8	Healthy (22.8-24)	One session (Acute)	20	20	Limit of 80 mA	CLAMP	GDR: Increased	RER: Increased Lactate: Increased
Jabbour et al. 2014	8	T2DM (39-65)	One session (Acute)	60	8	Max tolerable	OGTT	BG: Decreased	EE: No change
Hsu et al. 2021	40	Healthy (20-63)	One session (Acute)	30	20	Sensory level/ motor threshold /Max tolerable	Postprandial	NA	EE: Increased RER: Increased
Kameda et al. 2010	14	Obese (42.1-47.7)	One session (Acute)	20	4	Max tolerable	Postprandial	BG: Decreased Glucose AUC: Decreased	RQ: No change Lactate: Increased
Chen et al. 2022	9	Healthy (18-65)	One session (Acute)	120	20	Max tolerable	OGTT	BG: No change	EE: Increased RER: Increased
Miyamoto et al. 2011	11	T2DM (54.3-59.7)	One session (Acute)	30	4	Max tolerable	Postprandial	BG: Decreased	RQ: Increased Lactate: Increased
Miyamoto et al. 2014	18	T2DM (47.1-75.8)	One session (Acute)	30	4	Max tolerable	Postprandial	BG: Decreased	RQ: Increased Lactate: Increased

Blood glucose (BG), Energy expenditure (EE), Electrical stimulation (ES), Glucose area under the curve (Glucose AUC), Glucose disposal rate (GDR), Hertz (Hz), Neuromuscular Electrical Stimulation (NMES), Oral glucose tolerance test (OGTT), Respiratory exchange ratio (RER), Respiratory quotient (RQ), Type 2 diabetes mellitus (T2DM),

Acute Effect of ES on Energy Expenditure

Obesity develops as a result of various hereditary and environmental factors including prolonged positive energy balance [111]. As a result, strategies used in the prevention of weight gain and promotion of weight loss manipulate energy balance. Exercise is a well-known strategy to increase energy expenditure [111].

Resting Energy Expenditure (REE) accounts for approximately 60–75% of an individual's daily energy expenditure [112-115]. Slight changes in REE can have a significant influence on body weight management and maintenance [112-115]. Studies investigating an acute bout of resistance [116-118] or aerobic [111, 119] exercise session on energy expenditure have found significant elevations in energy expenditure. To our knowledge, only three studies have reported the energy expenditure during acute ES [96, 120, 121]. Despite being reported to increase energy expenditure in two studies by Chen et al. and Hsu et al. [120, 121], Jabbour et al. did not find any changes in energy expenditure during the stimulation [96]. The acute effect of ES on energy expenditure has not been well explored in an at risk overweight or obese population without T2DM.

Acute Effect of ES on Glucose Metabolism

Prolonged [122-128] and acute [129-132] periods of exercise training have been shown to improve glucose metabolism in individuals with obesity and T2DM. Skeletal muscle is the most metabolically active tissue and is the major site for glucose disposal [133]. Thus, improvements in glucose metabolism are facilitated by increased muscular contraction [134]. Blood flow and circulating glucose concentrations increase when exercise intensity increases, resulting in greater glucose delivery to the working skeletal muscles [135]. Therefore, increased muscle contraction can result in more glucose supply and delivery [136].

Studies on the acute effects of ES on glucose metabolism are limited. Kimuara et al. conducted research on pre-obese and obese Japanese males and reported a significant decrease in blood glucose levels during and immediately after ES [110]. The area under the curve of blood glucose was also significantly lower in the ES group compared with the control group [110]. In

this study a low frequency (4 Hz) and impulse (0.2 μs) of NMES with 20 minutes duration were applied [110]. In two studies by Hamada et al. [106, 107], the glucose disposal rate (GDR) was significantly greater during the hyperinsulinemic-euglycemic clamp in healthy individuals, demonstrating an acute stimulatory effect of ES on glucose uptake in skeletal muscle. Man et al. [108] also discovered a significant reduction in blood glucose levels after ES administration in a healthy population [108]. While in two studies by Hamada et al. [106, 107] young, healthy males, middle-aged females were included in Man et al. study [108] which was the significant variation between two studies by Hamada et al. [106, 107] and the study by Man et al. [108].

Purpose

The primary purpose of this study was to determine the acute effect of ES induced muscle contraction on whole body energy expenditure and substrate utilization in sedentary overweight/obese population.

Hypothesis

We hypothesized that ES-induced muscle contraction enhances energy expenditure and whole-body glucose utilization in individuals who are overweight or obese. In order to examine this hypothesis, we proposed the following specific aims:

Specific Aims

Specific Aim 1: To determine the acute effect of ES on whole body energy expenditure measured by indirect calorimetry.

Specific Aim 2: To determine the effect of ES on whole body glucose metabolism measured by respiratory quotient (RQ), blood glucose level, and blood lactate level measured during electrical stimulation.

Whole body energy expenditure and substrate utilization (RQ) were measured by indirect calorimetry, blood glucose, and blood lactate level during ES via were measured by portable glucose and lactate analyzer and body composition was assessed by dual-energy X-ray absorptiometry.

Methods

Eight overweight/obese Hispanic participants; 6 females and 2 males between the ages of 19 and 65 years old were recruited for this study. Individuals with diagnosed T2DM or significant cardiovascular diseases (CVD), and/or those taking anti-hypertensive, lipid-lowering, or insulin sensitizing medications, smoking, excessive alcohol, pregnant, or those have conditions that confound blood glucose level, or insulin secretion (Table 2) were excluded from the study. Study protocol was approved by the University of Texas at El Paso Institutional Review Board and each participant signed a written informed consent form.

Table 2 Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• 18 ≤ Age ≤ 65 years • 25≤ BMI kg/m^2 • Sedentary/Moderately Active Lifestyle (PAL <1.4) ○ less than 150 minutes per week of voluntary exercise	• Anyone taking anti-hypertensive, lipid-lowering, or insulin sensitizing medications • Smoking • Excessive drinking • Pregnant Women • Unwilling to adhere to the study intervention

BODY MASS INDEX (BMI), PHYSICAL ACTIVITY LEVEL (PAL),

STUDY DESIGN

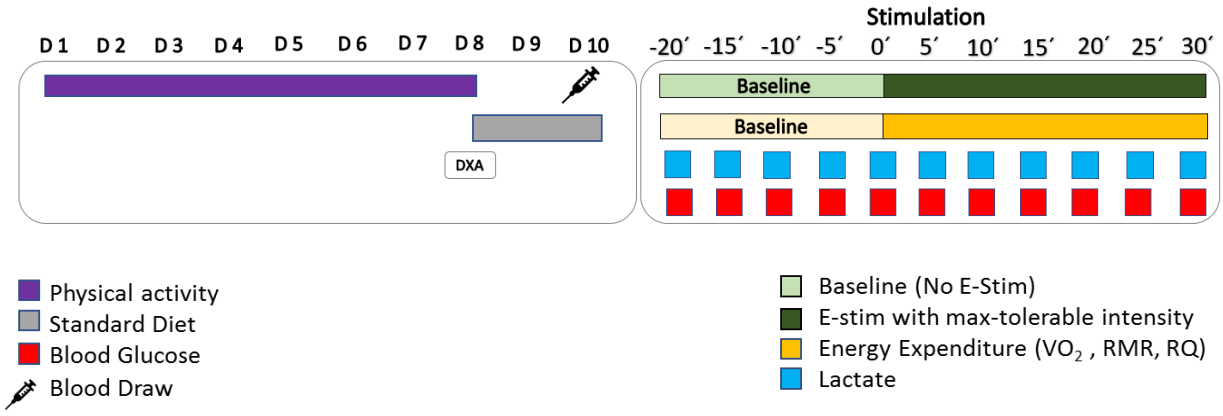


Figure 1 – Experimental protocol of baseline ES trial. The time -20:00 indicates the time at which baseline data was collected and time 0:00 indicates the time of starting stimulation. Day (D), dual-energy X-ray absorptiometry (DXA), Electrical stimulation (E-Stim), Volume oxygen (Vo2), Resting metabolic rate (RMR), Respiratory quotient (RQ)

Figure 1 provides an overview of the study design. If the participants met the basic inclusion criteria based on self-reported age, height, and weight, information about the study, structure of the study, study related procedures, and risks/benefits information were provided to participants prior to signing the consent forms. After providing informed consent the necessary screening measurements (Table 3) to determine any exclusion criteria (Table 2) were undertaken. Participants were then asked to complete a mock ES test to identify the max tolerable ES intensity. Height, weight, and resting blood pressure were measured. If the values met the study's requirements, the participants were given an accelerometer (Figure 1, D1-D8) to determine sedentary lifestyle. Accelerometer data was analyzed to make sure participants met the sedentary physical activity level criteria, defined as less than 60 minutes spent in moderate to vigorous physical activity per week [137].

If participants met the physical activity criteria, then body composition was assessed and a standard diet was provided to control for dietary effects on primary outcome measures after reporting any food allergies (Figure 1, D8). On the day of the experiment electrodes were attached

to all participants. Data were collected for 20 minutes without ES (Baseline, Figure 1, light green bar) immediately followed by 30 minutes of ES (Figure 1, Dark green bar), which the first 10 min used for stabilization of the data and the next 10 min considered as a baseline (Figure 1, light yellow bar). The following 30 min was the data during ES (Figure 1, Dark yellow bar). Blood lactate and blood glucose were measured every 5 minutes during the test (Figure 1, Blue and red bars respectively).

TABLE 3 SCREENING MEASUREMENTS

Measurement	Method
Physical Activity Level	Physical Activity Questionnaire & PAL (Accelerometer data)
Fasting Glucose	Blood Sample via lancet prick/ Analysis via Contour Next Blood Glucose Meter
Lipid Profile (HDL, LDL, Cholesterol)	Laboratory Corporation of America ©
Blood Pressure	Automated Blood Pressure Device
Resting Heart Rate	External Heart Rate Monitor
Body Mass Index (BMI)	Height and Weight Measurements
Medical History	Questionnaire

Physical activity level (PAL), High-density lipoprotein (HDL), Low-density lipoprotein (LDL)

All outcome measures were assessed in two separate visits at baseline and at the intervention day (ES). On the first visit, body composition (DXA, waist circumference) was assessed and the blood was drawn (Figure 1, D10). And on the second visit, the day after two-day diet control, resting metabolic rate (RMR), resting energy expenditure (REE), lactate was measured after an overnight fast (Figure 1, Stimulation Day).

Physical Activity Level

After confirming eligibility, participants were issued with an activity monitor to confirm a sedentary physical activity level to measure the time spent in moderate to vigorous activity. The ActiGraph GT3XP-BTLE 2GB activity monitor (Pensacola, FL) was attached to an elastic belt which the subject wore on the level of the anterior superior iliac crest and wore for 7 consecutive days (5 weekdays and 2 weekend-days) including during sleep times except for during bathing (Figure 1, D1-D8). After the activity monitors were returned, a compliance time of >90% total wear time was confirmed, and physical activity level was quantified to ensure sedentariness.

Dual Energy X-ray Absorptiometry (DXA)

Participants were asked to lie down supine on the scanner table of a GE Medical Systems, Lunar DXA Dual Energy X-ray Absorptiometry (Madison, WI). Participants were instructed to keep their arms close to the body, inside the marked regions with thumbs facing the ceiling and remain as still as possible. Knees and ankles were fastened together to prevent movement and standardize participant positioning. A scanner bar moved in the direction from head to toe of the participant, taking 7-10 minutes depending on the participant's body size. Measurements of total lean mass, total fat mass, bone mineral density (BMD), percent body fat, percent android fat, percent gynoid fat, legs percent fat, legs percent lean, leg fat mass/total fat mass ratio, and visceral adipose tissue volume and mass were obtained (Figure 1, D8).

Dietary Control

Participants were provided with all food for three days prior to ES testing, to control dietary effects on blood glucose and blood profile (Figure 1, D8-Stimulation Day). Meals were designed to comply with the US Department of Agriculture (USDA) 2015-2020 Dietary Guidelines for Americans and individualized to participant preferences/allergies. The standardized diet consisted of macronutrient energy contents of ~55% carbohydrates, ~15% protein, and ~30% fat (<10% of total fat consisting of saturated fat). The Mifflin St. Jour equation was utilized to match participants to their estimated energy requirements. For the duration of the intervention, participants were

encouraged to follow the USDA Dietary Guidelines for Americans (detailed above) and consume an energy balanced diet.

Resting Metabolic Rate and Substrate Utilization

Resting metabolic rate (RMR), and Resting Energy Expenditure (REE) were measured using indirect calorimetry (Parvomedics TrueOne 2400 metabolic cart) with a clear ventilated canopy and dilution pump. Participants were placed into a semi-recumbent position with a hood canopy over their head to obtain measurements of oxygen utilized and carbon dioxide produced, estimating RMR and REE. Participants were fasted for at least 12h and were asked to refrain from caffeine for at least 12 h, light-to-moderate intensity exercise for at least 24h, and moderate-to-heavy intensity exercise for at least 48h. RMR and REE were collected for 20 minutes without NMES and were continued for 30 minutes more simultaneously with ES (Figure 1, Yellow bar). Initially, participants rested in the supine position for 20 minutes period with the hood covering their heads and room dimly lit. The instruction was given to the participants to minimize body movements and to remain awake for the entire measurement.

Lactate Accumulation

Blood lactate was measured from a fingertip using Nova Biomedical Lactate reader prior to stimulation for 20 minutes and during stimulation for 30 minutes, in intervals of 5 minutes.

Electrical Stimulation Protocol

All participants received ES intervention at the University of Texas at El Paso, Metabolism, Nutrition, & Exercise Research (MiNER) laboratory, with the QuadStar® II Digital Multi-Modality Combo Device (TENS-INF-NMS) (BioMedical Life Systems, Vista, CA) and eight 2" x 2" square electrodes (BioMedical Life Systems, Vista, CA). Eight electrodes were placed bilaterally in the proximal location of the quadriceps motor point using anatomical reference points [138-140]. The stimulation device was set to cycled biphasic waveform with pulse duration of 300 μs and frequency set to 50 Hz that is the most common setting of ES among previous studies [81, 84, 109, 141, 142]. Participants received stimulation up to maximum tolerable levels [143].

Statistical Analysis

Results were analyzed using Graph Pad Prism, Version 9.2. One-way ANOVA with repeated measures and Sidak post hoc analysis was used to identify any significant differences among time-points during stimulation. Paired student's T-test was used to compare the baseline and the mean of 30 minutes of stimulation for all comparisons, a $p < 0.05$ was considered significant, and values was presented as means ± Standard Error of Mean (SEM).

Results

Table 4 summarizes the participant's baseline characteristics.

Table 4 Characteristics of subjects

	(n=8)
Demographic variables	
Age (yrs.)	37.25 ± 6.09
Body composition variables	
Height (cm)	165.3 ± 5.13
Weight (kg)	102.4 ± 8.16
Body Mass Index ($kg \cdot m^2$)	37.57 ± 2.43
Waist to Hip ratio	0.85 ± 0.01
Fat Mass (%)	46.68 ± 3.57
Fat Mass (kg)	46.53 ± 5.09
Lean Body Mass (%)	52.18 ± 3.59
Bone Mineral Density (g/cm^2)	1.27 ± 0.09
Hemodynamic	
Resting Heart Rate ($beats \cdot min^{-1}$)	74.0 ± 4.0
Systolic Blood Pressure (mmHg)	113.0 ± 3.0
Diastolic Blood Pressure (mmHg)	73.0 ± 4.0
Blood Variables	
Fasting Blood Glucose (mg/dl)	100.0 ± 2.0
HemoglobinA1c (%)	5.2 ± 0.05

Values are presented as Mean ± SEM

Acute Effect of ES on Energy Expenditure

Figure 2A is a time course of the changes in energy expenditure while resting and during 30 min of ES. There was no significant change in energy expenditure at any time-points compared to baseline (Figure 2A; $p = 0.19$). Mean energy expenditure during ES was also similar compared to pre-stimulation period (Figure 2B; $p = 0.30$).

Figure 2

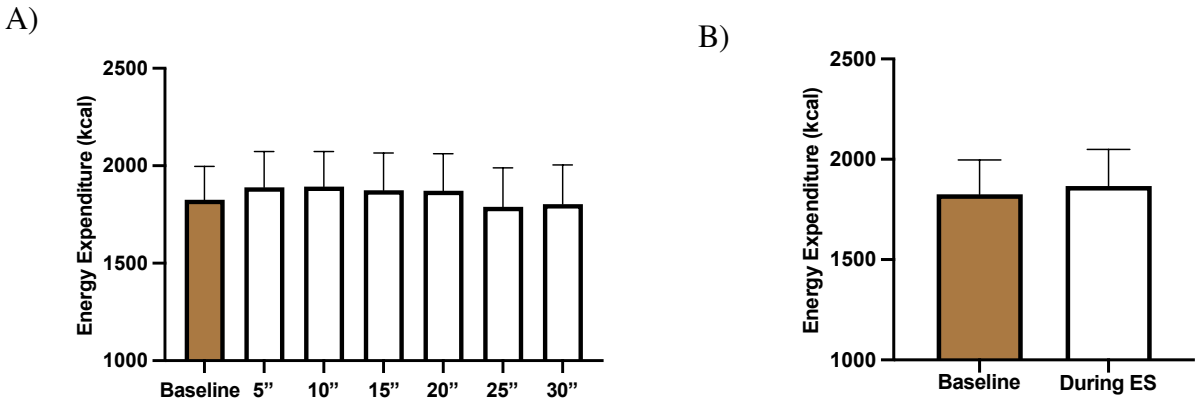


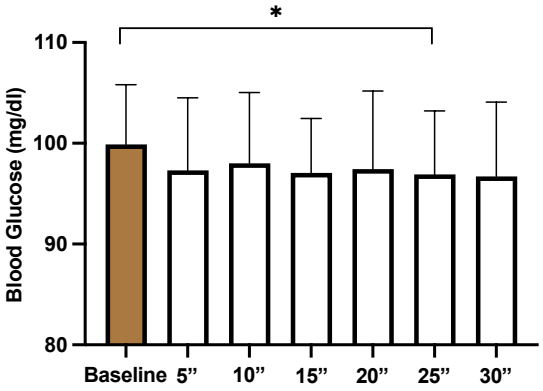
Figure 2. A: Energy expenditure at baseline and during ES. B: Energy expenditure at baseline compared to mean of energy expenditure during ES (B).

Acute Effect of ES on Blood Glucose

Figure 3A is a time course of the changes in blood glucose while resting and during 30 min of ES. There was no significant change in blood glucose level at any time-points during ES except at 25min ($p=0.03$) compared to baseline (Figure 3A; $p = 0.27$). Mean blood glucose during ES was significantly lower compared to pre-stimulation period (Figure 3B; $p = 0.04$).

Figure 3

A)



B)

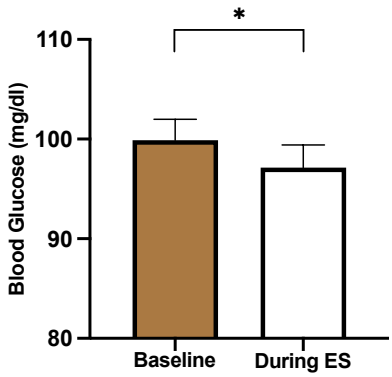


Figure 3. A: Bar graph depicting blood glucose at baseline and during ES. B: Blood glucose at baseline compared to mean of energy expenditure during ES (B). *p <0.05

Acute Effect of ES on RQ and Blood Lactate

There was no significant difference between baseline and any time-points during ES in RQ (Figure 4A; p = 0.17) and blood lactate (Figure 5A; p = 0.44). Mean RQ and blood lactate during ES were also not different compared to pre-stimulation period (Figure 4B; p = 0.12, Figure 5B p = 0.73 respectively).

Figure 4

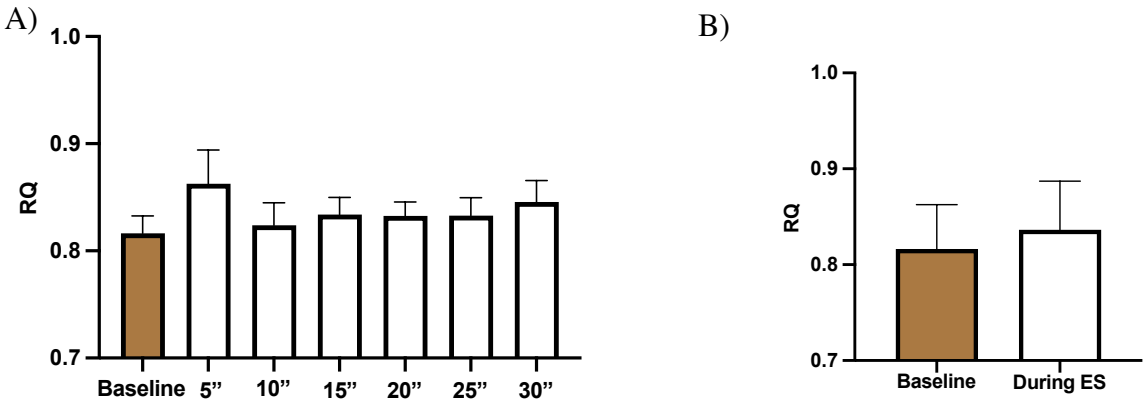


Figure 4. A: Bar graph depicting RQ at baseline and during ES. B: RQ at baseline compared to mean of energy expenditure during ES (B).

Figure 5

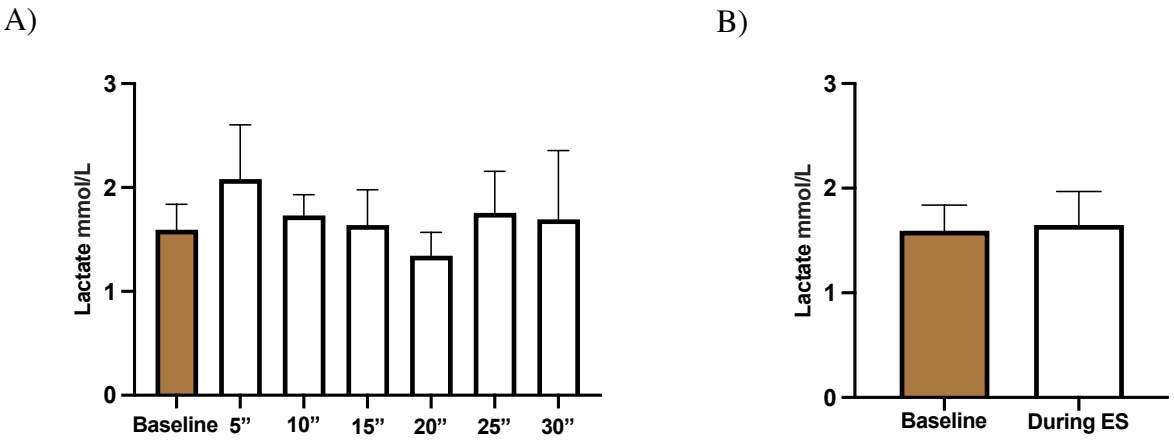


Figure 5. A: Bar graph depicting blood lactate at baseline and during ES. B: Blood lactate at baseline compared to mean of energy expenditure during ES (B).

Discussion

An elevated energy expenditure and ability to utilize glucose during exercise performance has long been associated with improved insulin sensitivity and glucose metabolism [144]. However, whether ES induced muscle contraction effectively increase whole body energy expenditure and glucose utilization is not clear. The purpose of this study was to determine the acute effects of ES on whole body energy expenditure and glucose metabolism in a sedentary overweight or obese Hispanic population. The principal finding of this investigation is that while one session of ES can improve glucose metabolism it may not effect substrate utilization and energy expenditure in healthy overweight/obese population. To our knowledge, this is the first study that looked into the acute effect of ES on fasting blood glucose during ES in an overweight or obese Hispanic population. This study in the Hispanic population is important as those who are identified as Hispanic have a much greater risk of developing T2DM [145] and thus, intervention in this population is required.

The findings of this study show no changes in energy expenditure and substrate utilization during ES in an overweight/obese population. To date, only three other studies have investigated the changes in energy expenditure during ES [96, 120, 121]. The results are in agreement with a previous study in populations with T2DM by Jabbour et al. [96]. On the other hand, two other studies by Chen et al. [121] and Hsu et al. [120] on healthy active population reported an increase in energy expenditure and RQ during ES. Higher RQ was found during ES compared to baseline RQ when participants rested [120, 121]. In contrast to Chen et al.[121] and Hsu et al. [120] investigations, which recruited active participants with normal BMI, the current study comprised 8 sedentary individuals with the BMI of 37.57 ± 2.43 kg/m2 and fat free mass (%) of 52.18 ± 3.58. Higher muscle mass increases energy expenditure because muscle is a highly active tissue that constantly needs energy to perform all of its cellular functions.[146]. Lower muscle mass in our study participants may explain a lack of change in energy expenditure in this current study.

Blood glucose levels, in this current study, decreased significantly during ES compared to the baseline. To our knowledge, seven studies have investigated the acute impact of ES on glucose metabolism during stimulation [96-98, 106, 107, 110, 121]. In agreement with this study, six studies out of these seven studies have reported improvement in glucose metabolism during ES [96-98, 106, 107, 110] and one study did not find any changes in blood glucose during stimulation [121]. Two studies by Hamada et al. examined the effect of ES on glucose uptake during a hyperinsulinemic-euglycemic clamp [106, 107]. Hamada et al. reported that a single bout of ES can significantly increase the whole-body glucose uptake. Three studies; two by Miyamoto et al in T2D [97, 98] and one by Kameda et al. [110] in an obese population, showed a single bout of ES after a meal can effectively attenuate postprandial hyperglycemia in T2DM and obese population compared to the baseline when participants were at rest. In spite of the fact that Jabbour et al [96] found a significant decrease in blood glucose level during OGTT, Chen et al. [121] did not find any changes in blood glucose level compared with the baseline when participants were at rest with no ES. Therefore, the results of present study which is the first study that investigated the acute effect of ES on fasting blood glucose, show that acute EE improve glucose metabolism in healthy overweight or obese population.

ES of the quadriceps muscles for 45 minutes has been demonstrated to result in a 40% decrease in muscle glycogen content in an insulin-independent pathway [79]. Kim et al [147] also reported that 60 min of ES reduced muscle glycogen concentration [147]. Muscle contraction induced by ES can increase glucose disposal rate, mainly from insulin independent pathway, by utilization of intramuscular glycogen in contracting muscle [106, 107]. The motor units for type II fibers are more active due to larger axonal diameter and lower electrical resistance against external ES, in contrast to the orderly recruitment of motor units during voluntary contraction [148]. The preferential activation of type II fibers, which have a greater capability for using glycogen in humans, can thus be caused by ES [55]. Furthermore, glycogenolysis rates during ES are two times higher in type II fibers than in type I fibers [149]. Although no studies in people have been done to evaluate a potential association between fiber type and glucose transport during ES, research in

rats have revealed that type II fibers can have higher glucose transport activity than type I fibers when ES is used [150, 151].

The RQ and blood lactate concentration were not different between baseline and during ES in this present study. Elevation in RQ and blood lactate concentration indicate an increase in carbohydrate utilization and promotion of anaerobic glycolysis that confirms glucose uptake in the whole body [103]. However, it has been reported that since free fatty acid (FFA) uptake may increase proportionally with muscle glucose uptake during muscle contraction [152], total body RQ and the RQ of both leg [153] and forearm [154] muscles in humans stay roughly the same as at rest, between 0.68 to 0.79 [153]. Despite increased muscle uptake, plasma FFA levels rise during exercise [153], perhaps due to decreased plasma insulin with loss of its antilipolytic effect and to increased circulating lipolytic agents [155]. Moreover, individuals with metabolically healthy overweight/obesity have higher fasting fat utilization which means lower fasting RQ than metabolically unhealthy individuals [156]. Together, these findings may be the primary reason as to why the RQ was unchanged in this current study despite decreases in blood glucose.

Increase in lactate concentration in the working muscle is associated with an increase in exercise intensity and muscle contraction [157]. The rate of lactate removal is In the resting state and low intensity exercise is proportional to moderate increases in blood lactate concentration that leads to unchanged lactate level during exercise [158]. Jorfeldt [159] found that a significant portion (52%) of the lactate taken up was oxidized simultaneously with the production and release of lactate from contracted muscles. It was found that during low-intensity exercise, active muscle generates and releases lactate into the circulation while simultaneously absorbing and oxidizing lactate from blood [159-161]. Lactate starts to accumulate in muscle at a relative work load of about 50-55% Vo2max in untrained subjects [162] and below this intensity any transient net lactate production at the onset of exercise leads to oxidative lactate removal in the muscle [162]. This theory is supported by the discovery that exercise at a low intensity does not significantly result in the release of lactate from muscle [163] and accumulation in blood [162].

It has been reported that obesity and fat thickness are principal factors that significantly influence the effect of ES on muscle contraction due to high resistivity of fat tissue [69, 164]. It has also been reported that there is a significantly high correlation between BMI and subcutaneous fat that makes BMI a reliable predictor of subcutaneous fat thickness [165, 166]. In the study by Doheny et al., it was reported that the effect of ES was relatively lower for people with greater fat thicknesses [164]. Another study by Maffuletti et al. reported that ES tolerance at motor thresholds was significantly reduced in obese individuals compared to non-obese counterparts [69]. In addition, it was reported that female and obese subjects have been shown to have lower pain thresholds, and diminished pain tolerance to ES than their non-obese and male peers [69]. In this current study, the range of BMI of participants was from 32.50 kg/m^2 to 50.65 kg/m^2 with 51.82% ± 1.01 of body fat, which is classified as having obesity. It is also important to take into account that the majority of the participants in this study were females (75%). Therefore, it can be conjectured that obesity, fat thickness, and gender related differences in pain tolerance may simply be the consequence of the effect of ES on muscle contraction and eventually in caused low contraction in muscles.

The small sample size is a limitation of this study. However, this is the first study conducted in a healthy overweight or obese Hispanic population, who are at high risk for developing T2DM. The findings of this study show acute ES can decrease fasting blood glucose and without changing energy expenditure during ES. The intensity of ES is another limitation of our study. Participants were instructed to set the intensity to the maximum level that they can tolerate with no discomfort. Future research is needed to determine whether gender has an impact on how intensity of ES affects muscle contraction due to previous studies that reported men can tolerate a significantly higher intensity of ES than women [167].

In summary, the present study provides evidence that, acute ES results in enhancement of blood glucose in sedentary overweight/obese population. This study has also demonstrated that EE may not increase during ES in this population. Further studies are necessary to determine whether the longitudinal ES intervention and lean body mass can impact energy expenditure.

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Vita

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