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Effects of Neuromuscular Electrical Stimulation on Insulin Sensitivity and Glycemic Control: A systematic Review and Meta-Analysis

Michael James Sanchez
University of Texas at El Paso

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EFFECTS OF NEUROMUSCULAR ELECTRICAL STIMULATION ON INSULIN
SENSITIVITY AND GLYCEMIC CONTROL: A SYSTEMATIC REVIEW
AND META ANALYSIS

MICHAEL JAMES SANCHEZ

Master's Program in Kinesiology

APPROVED:

Sudip Bajpeyi, Ph.D., Chair

Kisuk Min, Ph.D.

Francisco Agullo, M.D., FACS

Stephen L. Crites, Jr., Ph.D.
Dean of the Graduate School

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by

Michael James Sanchez

2020

Dedication

I dedicate my thesis work to my wife and daughters that unselfishly supported and believed in me. Thank you for always understanding when I was not always able to be present for everything that was happening. Your persistent love has allowed me to complete this goal. Valerie, you are such a loving and understanding woman. Thank you for watching over the girls during all those times I couldn't be there. Kloey and Klaire, daddy loves you and hope you are remembering all the good habits and hard work it takes to get what you want in life. I love you three so very much.

To my parents and grandparents that are watching over me, I hope you are all proud of the hard work I put into this accomplishment. I carry the lessons you all instilled in me. I will never forget them and often relied on them during difficult times.

To Dr. Bajpeyi, for not only being a great mentor but for also being a friend. Your endless dedication to helping me succeed will not be forgotten. You are a great example of a caring and invested educator. I hope to become a dedicated researcher and educator like you one day.

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SENSITIVITY AND GLYCEMIC CONTROL: A SYSTEMATIC REVIEW
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by

MICHAEL JAMES SANCHEZ, B.S.

THESIS

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for the Degree of

MASTER OF SCIENCE

Department of Kinesiology

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Abstract

Background: Neuromuscular electrical stimulation (NMES) is an effective method to induce involuntary muscle contraction, particularly for populations that are more prone to physical incapacities and metabolic disease.

Purpose: To evaluate existing evidence to determine the effectiveness of NMES on glycemic control and insulin sensitivity.

Methods: Electronic search consisted of MEDLINE (PubMed), EMBASE, Cochrane Library, Google Scholar, and Web of science to identify existing original research studies that investigated the effects of NMES on glycemic control and insulin sensitivity in humans. Studies that met inclusion criteria for the systematic review were then considered for meta-analysis if the studies were designed as randomized controlled trials. Risk of bias and quality assessment were performed for all studies. Effect sizes were calculated as the standardized mean difference and meta-analyses were completed using a random-effects model.

Results: 31 studies met the inclusion criteria for systematic review and of those, 10 studies qualified for the meta-analysis. The meta-analysis comprised of 189 subjects which reported NMES resulted in an improvement in insulin sensitivity (MD: 0.41; 95% CI, 0.09 to 0.72; $p=0.01$; $I^2=11\%$).

Conclusions: Existing evidence suggest that NMES can effectively improve glycemic control (acute) and insulin sensitivity (chronic) predominantly in middle-aged and elderly men and women with type 2 diabetes, obesity, and spinal cord injury. NMES could be considered as an alternate therapeutic strategy to improve insulin sensitivity in populations that are faced with physical incapacities and metabolic disease.

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Background

Physical inactivity increases risk for metabolic diseases such as insulin resistance, obesity, type 2 diabetes and is the fourth leading risk factor for death worldwide. [1-4] Adhering to CDC recommended physical activity (150 min/week) could prevent 1 in 12 cases of diabetes, which may decrease the financial burden on the health care system. [5] It is well established that muscle contraction through endurance and resistance exercise is effective in improving insulin sensitivity in all populations. [6-8] Muscle contraction induced by electrical pulse stimulation in human myotubes (*in-vitro*) as well as in isolated rat skeletal muscle have also been shown to upregulate glucose uptake. [9, 10] Therefore, the possibility of improving insulin sensitivity by inducing muscle contraction as an alternative therapeutic approach has been of particular interest for populations that are unable to perform regular physical activity and/or are insulin resistant.

Neuromuscular electrical stimulation (NMES) is an alternate strategy to induce involuntary contraction of skeletal muscle via depolarization of the motor axons and nerves being stimulated through an electrical current. [11-13] NMES has been widely used across the field of rehabilitation to prevent muscle loss and to regain muscle mass and function in individuals who experience spinal cord or sports injuries, as well as metabolic disease. [14-17] Electrically induced muscle contraction has also shown to be effective in acutely preventing hyperglycemic response when used preoperatively for those undergoing general anesthesia. [18] Skeletal muscle being the major site for insulin stimulated glucose uptake [21, 22], plays an important role in glycemic control and regulation of whole-body glucose metabolism. Muscle contraction, on the other hand, can effectively lead to glucose uptake in the absence of insulin. [19-21] Use of electrical stimulation of the quadriceps femoris muscle following spinal cord injury resulted in increased muscle cross sectional area. [72] Translocation of glucose transporter (GLUT-4) to muscle membrane has been reported after insulin stimulation (insulin dependent) as well as with muscle contraction that uses an insulin independent glucose uptake pathway. [22, 26-28] It has been suggested that an increase in glucose metabolism with electrical stimulation is due in part to the preferential activation of

glycolytic Type IIA muscle fibers due to its larger axonal diameter. [22-24] This is also supported by rodent studies reporting preferential recruitment of axons with larger diameter through NMES. [25-28] Electrical stimulation leads to activation of anaerobic pathways [74] as a source of ATP. An accelerated amount of hydrogen ions follows the increased accumulation of skeletal muscle lactate during electrical stimulation. [62] It has also been reported that a single bout of NMES significantly increased carbohydrate oxidation and whole-body glucose uptake. [35, 46] Therefore, it is important to evaluate if acute and chronic use of NMES as an effective therapeutic strategy to improve glycemic control and insulin sensitivity, respectively in both healthy and metabolically diseased populations. [8, 9, 14, 29]

NMES is frequently used in clinical settings for improving neuromuscular function and strength in disused/immobilized limbs [16, 29-32], and have primarily focused on populations with spinal cord injury (SCI), obesity, and type 2 diabetes (T2DM). [13, 14, 22, 33-36] Existing literature that assessed the effectiveness of NMES in improving glycemic control, insulin sensitivity and metabolic health is not clear. This gap in knowledge is due to highly variable NMES protocols used (frequency, duration, and length of intervention), population studied, variable testing methods used to access insulin sensitivity, and lack of control group in several studies. Therefore, the primary purpose of this comprehensive systematic review and meta-analysis was to evaluate the existing evidence to determine the effectiveness of NMES as an alternative therapeutic approach to improve glycemic control (acute use) and insulin sensitivity (chronic use). As improvements in insulin sensitivity has often been connected to whole body substrate utilization and lean mass, we have also explored the existing literature to determine the effects of NMES on substrate utilization and body composition

Table 1: Characteristics of included studies

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μ s)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Arisianti et al. 2016	N=20 NMES=10 Passive Stretching=10	Men and women with T2DM (≥ 55 years old)	3x/week for 4 weeks	30 min	20 Hz	200 μ s	60 mA	Fasting Blood Glucose	BG: Decreased	NA	NA	BG was measured before and after intervention.
Arisianti et al. 2017	N=20 NMES=10 Control=10	Men and women with T2DM (≥ 35 years old)	3x/week for 4 weeks	30 min	20 Hz	200 μ s	NA	Fasting Blood Glucose	BG: Decreased	NA	NA	Breakfast of 2 pieces of bread and a cup of tea (26g carb) before intervention. Measured BG 30 min pre/post.
Belliveau et al. 2006	N=8 NMES=8 Control=8	Men with T2DM (41-65 years old)	One session (acute)	60 min	8 Hz	200 μ s	30-60 mA	OGTT	BG: Decreased	NA	NA	Following 12 hour fast, BG measured during OGTT (75g) at rest (0 min), 60 min, and 120 min.
Catalogna et al. 2016	N=12 NMES=5 Control=6 Drop out=1	Men and women with T2DM (45-75 years old)	7x/week for 2 weeks	5 min	1.33 Hz / burst mode of 16 Hz	150 μ s	5-10 mA	MGTT	BG: Decreased Postprandial Glucose: Decreased	NA	NA	Following 8 hour fast, BG was monitored prior to breakfast (50g carbohydrate) and then every 30 min for 2 hours.
Chilibeck et al. 1999	NMES=5 Control=NA	Middle-aged men and women with SCI (31-50 years old)	3x/week for 8 weeks	30 min	30 Hz	NA	10-140 mA	OGTT	IS index: Increased	NA	NA	Following 12 hour fast, BG measured during OGTT (75g) at rest (0 min) and at 30 min, 60 min, 90 min, and 120 min.
Erickson et al. 2017	NMES=14 Control=NA	Men and women with SCI (30-63 years old)	3-5x/week for 16 weeks	10-75min	2-7 Hz	200 μ s	Visual vigorous muscle contraction	OGTT	BG: No change HOMA-IR: No change HbA1c: Decreased	Bilateral quadriceps muscle: No change (MRI)	NA	Following overnight fast, blood measured during OGTT (75g) at rest (0 min), 30 min, 60 min, 90 min, and 120 minutes.

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μs)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Galvan et al. 2019	N=10 NMES=5 Control=5	Overweight/. obese men and women (18-54 years old)	3x/week for 4 weeks	30 min	50 Hz	300 μs	Max tolerable	OGTT	BG: Decreased Postprandial Glucose: Decreased Glucose AUC: Decreased	BW: No change BMI: No change FM: No change LM: No change (DXA)	RQ: No change Lactate: Increase (Indirect Calorimetry)	All participants provided diet 55% carb, 15% protein, 30% fat. Tests were performed after overnight fast. Blood measured during OGTT (75g) at rest (0 min), and 30 min, 60 min, 90 min, 120 min, 150 min, and 180 minutes.
Giggins et al. 2017	NMES=13 Control=NA	Men with T2DM (45.1-58.9 years old)	6x/week for 8 weeks	60 min	4-19 Hz	760 μs	Max tolerable	Fasting Blood Glucose	BG: Decreased HbA1c: No change	BW: Decreased Body fat: Decreased LM: No change (DXA)	NA	Following overnight fast. Blood sample was collected to determine BG and HbA1c.
Gorgey et al. 2011	N=9 NMES+Diet=5 Diet group=4	Men with SCI (26-44 years old)	2x/week for 12 weeks	NA	30 Hz	450 μs	Raised until visible contraction	OGTT	Glucose AUC: Decreased Insulin AUC: No change HOMA-IR: No change	BW: No change BMI: No change FM: No change LM: No change CSA: Increased (DXA)	NA	Two groups; NMES+diet vs Diet. Tests were performed following 12 hour fast to measure fasting and post challenge glucose, insulin and lipid profile. NMES session was determined by the completion of 40 leg extensions.
Griffin et al. 2007	NMES=18 Control=NA	Men and women with SCI (25-57 years old)	2-3x/week for 10 weeks	30 min	50 Hz	NA	Increased to promote a cadence of 49 revolutions	OGTT	BG: Decreased Insulin level: Decreased	BW: Increased FM: No change LM: Increased (DXA)	NA	Following 12 hour fast, Blood samples were drawn during OGTT (75g) at rest (0 min), 30 min, 60 min, 120 min, and 180 min
Guzman et al. 2019	NMES=16 Control=NA	Men and women with T2DM (18-30 years old)	1x/week for 4 weeks	20 min	5,10, and 50 Hz	400 μs	Max tolerable	Fasting BG	BG: Decreased	NA	NA	First session (control condition) evaluated glycemic response to meal. NMES applied other three sessions. 20 min, 30 min, 60 min, 90 min after NMES measurements performed.

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μ s)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Hamada et al. 2003	NMES=8 Control=NA	Young healthy males (24.2-25.4 years old)	One session (Acute)	20 min	20 Hz	0.2 μ s	Limit of 80 mA	Clamp	GDR: Increased	NA	RER: Increased Lactate: Increased VO2: Increased (Indirect Calorimetry)	Blood samples for insulin measurements were obtained at the beginning and the end of ES and every 30 min during the poststimulation period of 90 min
Hamada et al. 2003(Jan)	NMES=8 Control=NA	Young healthy males (22.8-24 years old)	One session (Acute)	20 min	20 Hz	0.2 μ s	Limit of 80 mA	Clamp	GDR: Increased Blood Glucose: No change Insulin Level: No change	NA	RER: Increased Lactate: Increased VO2: Increased (Indirect Calorimetry)	Blood samples for insulin were obtained at pre/post of ES and every 30 min during the poststimulation
Jabbour et al. 2015	NMES=8 Control=NA	Middle-aged men and women with T2DM (39-65 years old)	One session (Acute)	60 min	8 Hz	200 μ s	Max tolerable	OGTT	BG: Decreased	NA	NA	First session: Familiarization of NMES protocol. Tests were performed following 12 hour fast. Blood measured during OGTT (75g) at rest (0 min), and at 60 min, and 120 min.
Jeon et al. 2002	NMES=7 Control=NA	Middle-aged men and women with SCI (30-53 years old)	3x/week for 8 weeks	30 min	30 Hz	NA	10-140 mA	OGTT / Clamp	BG: Decreased	NA	NA	Following 12 hour fast. BG was measured during OGTT (76g) at rest (0 min), 30 min, 60 min, 90 min, and 120 min.
Jeon et al. 2010	N=8 NMES=6 Drop out=2	Middle-aged men with SCI (24-56 years old)	3-4x/week for 12 weeks	2 min	NA	NA	Max tolerable	Fasting BG	BG: Decreased HbA1c: No change	BW: Decreased FM: Decreased LM: No change (DXA)	NA	Following overnight fast, two blood samples were obtained pre/post 12 weeks of NMES-rowing training. NMES session was determined by the completion of 25-30 strokes per min with maximum power output for 2 minutes

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μ s)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Joubert et al. 2014	NMES=18 Control=NA	Men and women with T2DM (49-68 years old)	One session (Acute) followed by 6x/week	25 min	35 Hz	350 μ s	Max tolerable	Clamp	Insulin sensitivity index: Increased	NA	Energy Expenditure: No change	IS was assessed with EHC at baseline, 1 hour after a single NMES session, and 12–15 hours after the last session of a training week with daily NMES sessions
Kameda et al. 2010	NMES=14 Control=NA	Middle-aged obese and pre-obese men (42.1-47.7 years old)	One session (Acute)	20 min	4 Hz	0.2 μ s	Max tolerable	Fasting BG	BG: Decreased Glucose AUC: Decreased Insulin AUC: Decreased	NA	RQ: No change Lactate: Increased (Indirect Calorimetry)	Following 12 hour fast. Experimental trial: 12 hour fasted blood draw followed by breakfast (48% carbs, 50% fat, and 2% protein). 10 min after eating, NMES 20 min session. Blood samples collected at 30 min, 60 min, 90 min, and 120 min.
Li et al. 2018	N=11 NMES=6 High protein diet=5	Middle-aged men and women with SCI (37-58 years old)	3x/week for 8 weeks	30 min	50 Hz	450 μ s	NA	OGTT	BG: Decreased Insulin AUC: Decreased Fasting insulin: No change Matsuda Index: No change. HOMA-IR: No change Glucose AUC: No change	Body Mass: Decreased FM: Decreased LM: No change Android Fat Mass: Decreased (DXA)	NA	Following 1-12 hour fast. BG measured during OGTT (75g) at rest (0 min), 60 min, 90 min, and 120 min.
Mahoney et al. 2005	NMES=5 Control=NA	Men with SCI (30.7-40.5 years old)	2x/week for 12 weeks	NA	30 Hz	450 μ s	NA	OGTT	BG: Trend decreased Insulin: No change	Quadriceps femoris muscle CSA: Increased (MRI)	NA	Following overnight fast. BG was measured during OGTT (75g) at rest (0 min), 60 min, 90 min, and 120 min. BG and insulin measured pre/post resistance exercise training. NMES session was determined by the completion of 4 sets of 10 unilateral, dynamic knee extensions.

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μ s)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Man et al. 2011	N=52 TENS=26 Control=26	Middle-aged women (35-75 years old)	One session (Acute)	30 min	15 Hz	10 mA	NA	Fasting BG and Insulin	BG: Decreased HOMA-IR: Increased	NA	NA	Plasma glucose and insulin measured before, 30 min, 60 min, 90 min, and 120 min after TENS.
Miyamoto et al. 2011	NMES=11 Control=NA	Middle-aged men with T2DM (54.3-59.7 years old)	One session (Acute)	30 min	4 Hz	0.2 μ s	Max tolerable	Fasting BG	BG: Decreased Insulin Level: No change	NA	RQ: Increased Lactate: Increased VO2: Increased (Indirect Calorimetry)	Analyzed at rest (0 min), and 30 min, 60 min, 90 min, and 120 min following breakfast (61% carbs, 21% fat, and 18% protein). Two sessions; one 30 min EMS , and one 30 min complete rest.
Miyamoto et al. 2014	N=18 Men=10 Women=8	Men and women with T2DM (47.1-75.8 years old)	One session (Acute)	30 min	4 Hz	0.2 μ s	6.0 ml/kg/min oxygen consumption	Fasting BG	BG: Decreased HbA1c: No change HOMA-IR: No change	NA	RQ: Increased Lactate: Increased VO2: Increased (Indirect Calorimetry)	30-min NMES vs complete rest. Blood samples taken 30 min before NMES and 30 min, 60 min, 90 min, and 120 min after NMES.
Miyamoto et al. 2018	N=14 NMES=14 Control=14	Elderly men with T2DM (60.2-66.2 years old)	5x/week for 8 weeks	40 min	4 Hz	0.2 μ s	Max tolerable	Fasting BG	BG: Decreased HbA1c: No change	BW: No change BMI: No change FM: Increase LM: No change (BIA)	NA	Baseline evaluation and after 8 weeks assessed all parameters
Mohr et al. 2001	NMES=10 Control=NA	Middle-aged men and women with SCI (27-45 years old)	3x/week for 12 months followed by 1x/week for 6 months	30 min	30 Hz	350 μ s	120 mA	OGTT / Clamp	BG: No change	NA	NA	OGTTs performed pre and post 12 and 18 months of training. The first blood sample (time 0) drawn after 20 min of rest, and the subject ingested 75g of glucose solution. Blood samples drawn every 5 min for both OGTT and Clamp.

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μ s)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Poole et al. 2005	NMES=5 Control=NA	Middle-aged men and women with T2DM (21-55 years old)	1x/day for 12 weeks	240 min	50 Hz	NA	40 mA	OGTT / Clamp	BG: No change Insulin level: No change HbA1c: No change	BW: No change BMI: No change FM: No change LM: No change (BIA)	Energy expenditure: Increased	Acute changes in glucose uptake measured in 5 subjects. Body composition and insulin sensitivity measured before and after 12 weeks daily use of NMES
Sharma et al. 2010	N=20 NMES=10 Control=10	Men and women with T2DM (>55 years old)	3x/week for 2 weeks	40 min	50 Hz	NA	Max tolerable	Fasting BG	BG: Decreased	NA	NA	Two pieces of bread and a cup of tea consumed 3 to 4h before the start of experiment to reduce risk of hypoglycemia 40 min NMES . Blood samples taken at the baseline and end of first and sixth session.
Van Buuren et al. 2015	NMES=15 Control=NA	Elderly men and women with T2DM (57.91-65.5 years old)	2x/week for 10 weeks	20 min	80 Hz	NA	Max tolerable	Fasting BG	BG: Decreased HbA1c: Decreased	BW: No change FM: No change LM: No change (BIA)	NA	Measurements occurred before and within 1 week of finishing NMES intervention.
Vivodtzev et al. 2013	N=14 NMES=7 Control=7	Men and women with Cystic fibrosis (21-43 years old)	4x/week for 6 weeks	30 min	35 Hz for 2 weeks followed by 50 Hz for 4 weeks	400 μ s	Max tolerable	Fasting BG	BG: Decreased HOMA-IR: Decreased	Mid-Thigh circumference and quadricep strength: Increased	NA	Two groups; NMES+ERGO training and control+ERGO training. Parameters evaluated at baseline and at the end of NMES and Ergo program.
Wall et al. 2012	NMES=6 Control=NA	Elderly men with T2DM (68-72 years old)	One session (Acute)	60 min	60 Hz	500 μ s	Max tolerable	OGTT	BG: Decreased Insulin level: No change	NA	NA	Participants provided standardized meal day pre-testing (62%carb, 12%fat, 16% protein). Plasma glucose and insulin concentrations were measured before, during and after 60 min of NMES.

Study	Number of participants	Study population	NMES Intervention	NMES duration (min)	NMES frequency (Hz)	NMES pulse width(μ s)	NMES Intensity	Method to measure IS	IS outcome	Body composition (Methods)	Substrate utilization (Methods)	Study Design (Notes)
Wittmann et al. 2016	N=75 NMES=24 NMES+Diet=21 Control=22 Drop out=8	Elderly women with Sarcopenic obesity (≥ 70 years old)	1x/week for 26 weeks	11 to 20 min	85 Hz	350 μ s	Borg rates of perceived exertion of 5-6 on a 10 point scale	Fasting BG	BG: No change	Waist Circumference: Decreased (DXA)	NA	Following overnight fast both before and 6 months after NMES intervention. NMES+Diet group was provided with a high protein supplement (caloric value of 638KJ and contained 21g whey protein 10g carb 3g fat).

List of Abbreviations

NMES: Neuromuscular electrical stimulation

IS: Insulin sensitivity

T2DM: Type 2 diabetes mellitus

SCI: Spinal cord injury

OGTT: Oral Glucose Tolerance Test

MGTT: Meal Glucose Tolerance Test

Hyperinsulinemic Euglycemic Clamp

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

HbA1c: Glycated Hemoglobin

BG: Blood glucose

GDR: Glucose Disposal Rate

BW: Body weight

FM: Fat mass

LM: Lean mass

CSA: Cross sectional area

MRI: Magnetic Resonance Imaging

DXA: Dual energy X-ray Absorptiometry

BIA: Body Impedance Analysis

RER: Respiratory Exchange Ratio

RQ: Respiratory Quotient

VO2: Oxygen Consumption

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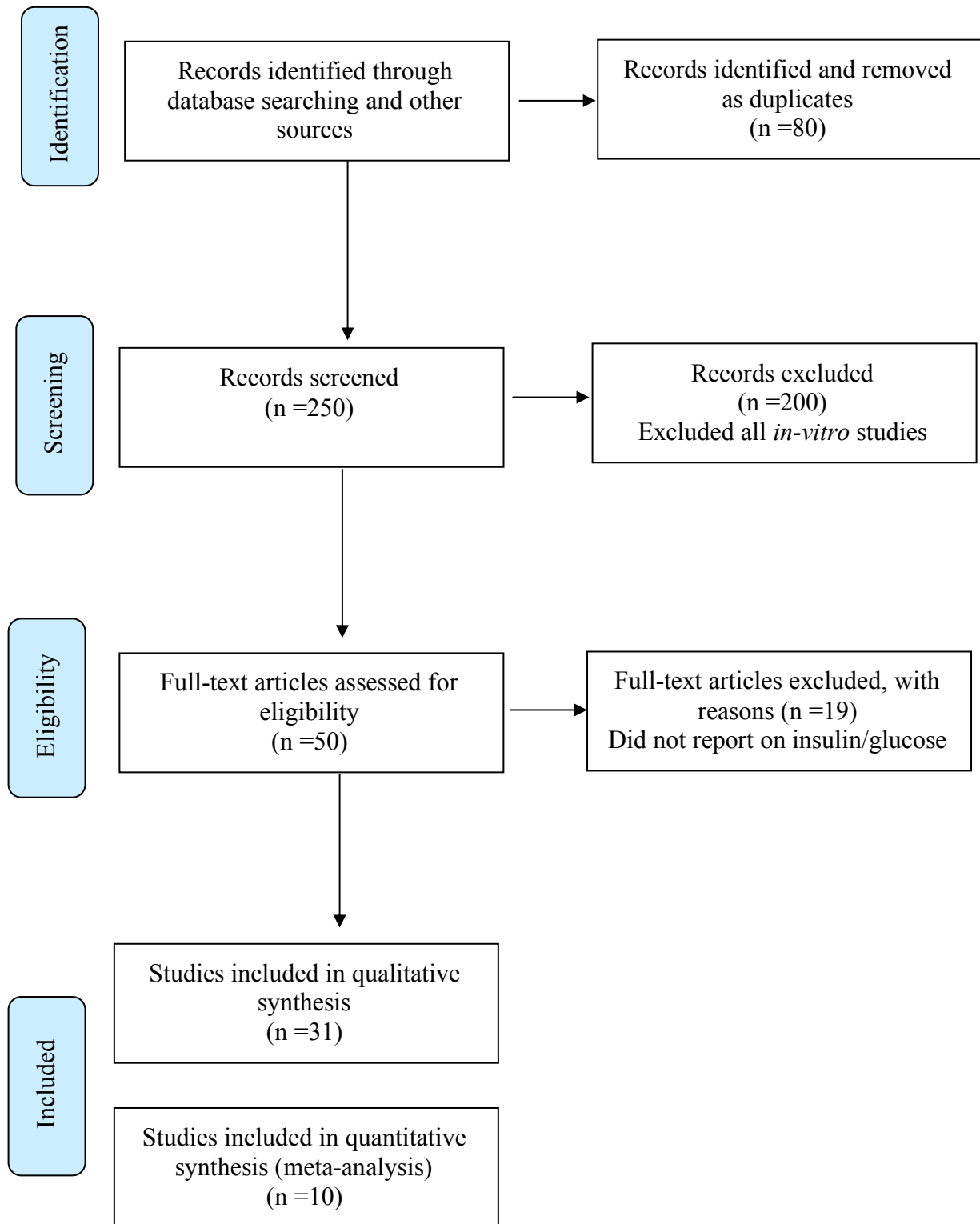


Figure 1: Flow diagram of search strategy.

Methods

Electronic Search Strategy and Eligibility Criteria

This systematic review and meta-analysis were performed in accordance with the Cochrane Collaboration [37] and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [38] (**Figure 1**). The protocol of the study was registered on International Prospective Register of Systematic Review (PROSPERO) (CRD42020192491). Randomized controlled trials that evaluated the effects of NMES on glycemic control and/or insulin sensitivity were included. A computerized search was performed on MEDLINE (PubMed), EMBASE, Cochrane Library, Google Scholar, and Web of science to identify all potential literature. Various combinations of keywords and mesh words relating to neuromuscular electrical stimulation were used in the search (**Appendix A**). References of selected studies were further reviewed to include any additional studies that may not have been found through search terms. The search was not restricted to any geographical region, gender or population, but was restricted to studies published in English language and conducted on human subjects.

Study Selection

In the initial search, four researchers (MS, MG, AM, SS) independently located and reviewed all articles by title and abstract text to ensure that the following inclusion criteria were met for the systematic review: 1) studies administered neuromuscular electrical stimulation on skeletal muscle, 2) articles reported data from original research and 3) articles reported glycemic control and/or insulin sensitivity data. Studies that met inclusion criteria for the systematic review were then considered for meta-analysis if the following additional criteria were met: 1) studies were conducted with a placebo or equivalent control group and 2) articles presented both pre and

post NMES intervention data for primary outcome measures with mean and standard deviation or standard error of mean values. All reviewers reviewed the selected articles and collectively resolved any discrepancies for initial inclusion. After the potential articles were identified based on the initial criteria, a full text review of all articles was performed before proceeding to data extraction.

Data Collection/Extraction

Authors independently extracted all relevant data needed for both systematic review and meta-analysis. Extracted data included characteristics of participants (age, gender, body mass index (BMI), and health status), sample size, intervention type (acute or chronic), anatomical location of NMES application, NMES application protocols (frequency, intensity, duration/session and length of intervention), testing methods used to assess insulin sensitivity, and effects of NMES on glycemic control, insulin sensitivity, substrate utilization and body composition. Meta-analysis was limited to analyzing the effects of NMES on glycemic control and insulin sensitivity. Due to the limited number of studies that met the inclusion criteria, it was not achievable to conduct a meta-analysis to determine the effects of NMES on substrate utilization (n=1) and body composition (n=4). Following the data extraction phase, all reviewers verified entered data to confirm the accuracy.

Risk of Bias and quality assessment

Reviewers independently assessed the risk of bias for the studies included in meta-analysis using the Cochrane Collaboration's Risk of Bias tool (RoB₂). [39] Studies were assessed for the following criteria: random sequence generation, allocation concealment, blinding participants, blinding of outcome assessment, incomplete data reporting, and selective reporting.

Data Analysis

The meta-analysis was carried out to determine the effects of NMES on insulin sensitivity, the primary outcome measure of the study. Continuous outcomes were reported as the mean difference (MD) and standardize mean difference (SMD) from pre to post treatment in each group with 95% confidence interval (95% CI). Random effect models were used to combine data in Review Manager (version 5.3). The statistical heterogeneity among studies was tested using I^2 statistics. I^2 values 25-50% were considered indicative of low heterogeneity, 50-75% were considered moderate heterogeneity and values above 75% were considered to have a high degree of heterogeneity. A p value ≤ 0.05 was considered statistically significant.

Results

Study Selection

The PRISMA flow diagram details the database search results along with all exclusion rationale (**Figure 1**). Of the 330 original identified studies through the database search, 280 studies were excluded for having been identified as a duplicate or *ex-vivo* or animal studies. Of the remaining 50 studies, 19 studies were removed after a thorough full-text assessment revealed that studies did not report on primary outcome measures. The remaining 31 studies met the inclusion criteria for the systematic review, while 10 randomized controlled longitudinal studies met inclusion criteria for the meta-analysis.

Population Characteristics

Table 1 describes the population characteristics of the reviewed studies. The 31 studies in this systematic review were conducted on healthy individuals (n=3) and populations with obesity (n=3), T2DM (n=15), spinal cord injuries (n=9), and cystic fibrosis (n=1). Data from these 31 studies consisted of a total of 472 young, middle age, and elderly (18 to 76 years old) healthy weight, obese, population with T2DM or spinal cord injury where sample size in each intervention study ranged from 5-75. Among all included studies, 18 studies included male and female genders whereas 11 studies were conducted on only male subjects and two studies were conducted on only female subjects. 10 longitudinal studies included in the meta-analysis consisted of a total of 189 young healthy weight, obese, population with T2D or spinal cord injury where sample size in each intervention ranged from 9-46. In the meta-analysis a total of 96 participants were allocated to NMES group while 93 participants were allocated to control/placebo group.

Study design and methods used to measure primary outcome

Table 1 reports the study design and testing methods used to measure glycemic control, insulin sensitivity, substrate utilization and body composition in all studies included in this

systematic review. 10 studies reported on acute effects and 22 studies reported on chronic effects of NMES, with one of those studies reporting on both acute and chronic effects of NMES. Studies reported one or multiple measures of insulin sensitivity including the fasting blood glucose (n=14) [18, 35, 40-51], fasting insulin (n=11) [13, 18, 31, 35, 44-46, 52-55], homeostatic model assessment index (HOMA-IR) (n=4) [18, 35, 44, 52], Matsuda index (n=1) [56], oral glucose tolerance test (OGTT) (n=13) [13, 22, 31, 32, 52-60], meal glucose tolerance test (MGTT) [57], HbA1c (n=5) [13, 14, 35, 42, 49], and hyperinsulinemic euglycemic clamp (n=6) [13, 14, 33, 34, 55, 60]. Among all longitudinal studies that met the inclusion criteria for meta-analysis (N=10), all reported fasting blood glucose before and after NMES intervention. Additionally, other relevant insulin sensitivity measures were also reported. This includes fasting insulin (n=4) [50, 56, 57, 61], HOMA-IR (n=3) [50, 56, 61], Matsuda index (n=1) [56], MGTT (n=1) [57], OGTT (n=2) [56, 58], Glucose area under the curve (AUC) (n=3) [56, 58, 61], Insulin area under the curve (AUC) (n=2) [56, 61], and Glycated Hemoglobin (HbA1c) (n=2) [47, 50].

Overview of Neuromuscular Electrical Stimulation Parameters

The NMES protocols used in included studies are outlined in **Table 1**. This includes information reported on frequency, intensity, number of sessions, duration of sessions, and length of NMES interventions. NMES frequency below 50 Hz has generally been accepted as a low frequency [22, 33, 62], and a frequency of 50 Hz or above is considered as high frequency. [52, 58, 62-64] Therefore, alongside presenting the specific frequency reported in articles, we have also reported frequency as “low” or “high” for a better understanding of the role of NMES frequency on outcome measures. Twenty studies reported to use low frequency, eight reported to use high frequency, two studies reported to use both low and high frequency, while one study did not specify the selected frequency for NMES application. Although most studies reported on frequency and duration, NMES intensity was inconsistently reported across studies. Most of the studies reported intensity as up to maximum tolerable levels (n=13), whereas some studies reported a range from

5-140 mA (n=9). One study reported intensity by oxygen consumption, and eight studies did not report on NMES intensity. Duration of NMES session varied among studies whereas majority of the studies reported 20-30 minutes of NMES per session. Most studies ranged from 2-8 weeks in duration of NMES intervention. Among the 10 studies included in meta-analysis, five studies reported to use low frequency, four reported to use high frequency, while one study reported to use both low and high frequency for NMES application. Four studies reported intensity as up to maximum tolerable level, one reported intensity at 60 mA, one study reported intensity at 5-10 mA, and four studies did not report NMES intensity. Duration of NMES session and length of NMES intervention also varied among studies included in meta-analysis. Majority of the studies reported session times ranging from 5-40 minutes with the most common intervention duration lengths of 2-8 weeks.

Risk of bias

Figures 2 and 3. summarizes the assessment of quality and risk of bias of the studies. All reviewers used the Cochrane Collaboration's risk of bias (ROB) tool when evaluating the included studies (**Figures 3**). Risk of bias assessment reported an overall outcome of low to moderate, as illustrated in **Figures 2**, which shows quality assessment results for each risk of bias item.

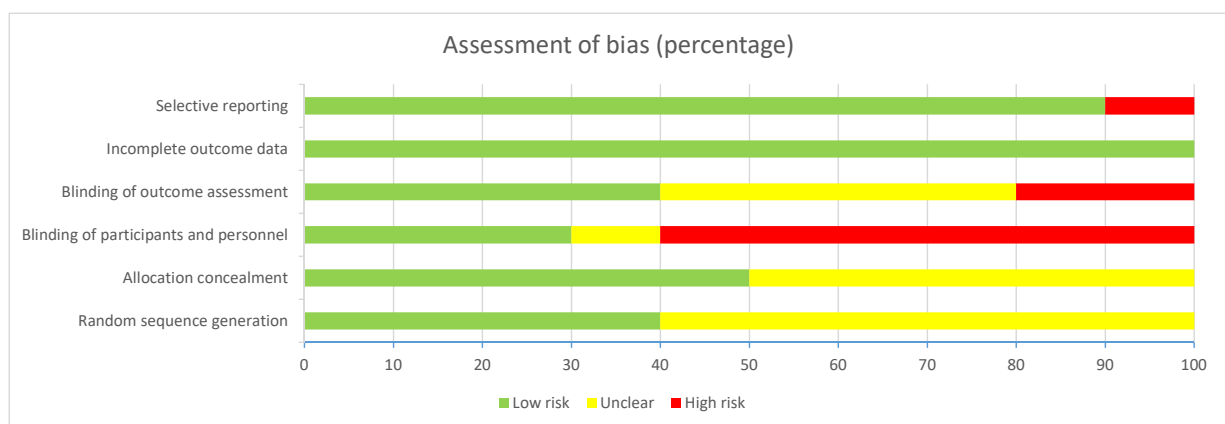


Figure 2: Assessment of bias (percentage) for studies included in meta-analysis.

Outcome of Included Studies

Acute effects of NMES on glycemic control

Among 31 studies included in this systematic review, 10 studies investigated acute effects of NMES on glycemic control in populations with hyperglycemia and T2DM (n=6), obesity (n=1), as well as in a healthy population (n=3). All studies reported NMES being effective at acutely improving glycemic control. Seven studies [18, 22, 35, 46, 47, 55, 60] reported a significant decrease in blood glucose and remaining three studies reported an increase in glucose disposal measured during hyperinsulinemic euglycemic clamp [33, 34] with acute application of NMES. Overall, present evidence strongly indicates increased glycemic control during NMES.

Chronic effects of NMES on Insulin Sensitivity

There were 22 longitudinal studies that investigated the chronic effects of NMES on insulin sensitivity were included in this systematic review. Except for four studies that investigated young adult population [13, 43, 50, 58], all studies were conducted in middle-aged and elderly men and women. Majority of the studies (n=16) reported improvement in insulin sensitivity measured by various methods including fasting blood glucose [40-42, 44, 47, 48], OGTT [31, 32, 53, 56, 61], MGT [57], HbA1c [49, 52], and hyperinsulinemic euglycemic clamp [14, 60], while two studies reported no changes in blood glucose as measured by fasted blood glucose [51], and hyperinsulinemic euglycemic clamp. [55]

Meta-Analysis

10 longitudinal studies met the inclusion criteria for a meta-analysis to examine the effectiveness of NMES on insulin sensitivity. There was a significant effect of NMES on improving insulin sensitivity (MD: 0.41; 95% CI: 0.09 to 0.72; p=0.01; I²= 11%) (**Figure 3**). The methods used to assess insulin sensitivity varied among studies, and different marker of insulin sensitivity was reported. Therefore, additional analysis was performed to determine the effects of

NMES on fasting glucose, which was reported in all the included studies except one (n=9) (**Figure 4**). Similarly, there was a significant effect of NMES on lowering fasting blood glucose (MD: 0.48; 95% CI: 0.17 to 0.78; $p=0.002$; $I^2=0\%$). In order to understand the impact of methods used to assess insulin sensitivity, we stratified the analysis by methods used to assess insulin sensitivity in all the included studies. Although meaningful effects of NMES cannot be concluded due to limited number of studies reporting specific methods, a forest plot has been presented to describe the outcome for each study (**Figure 5**).

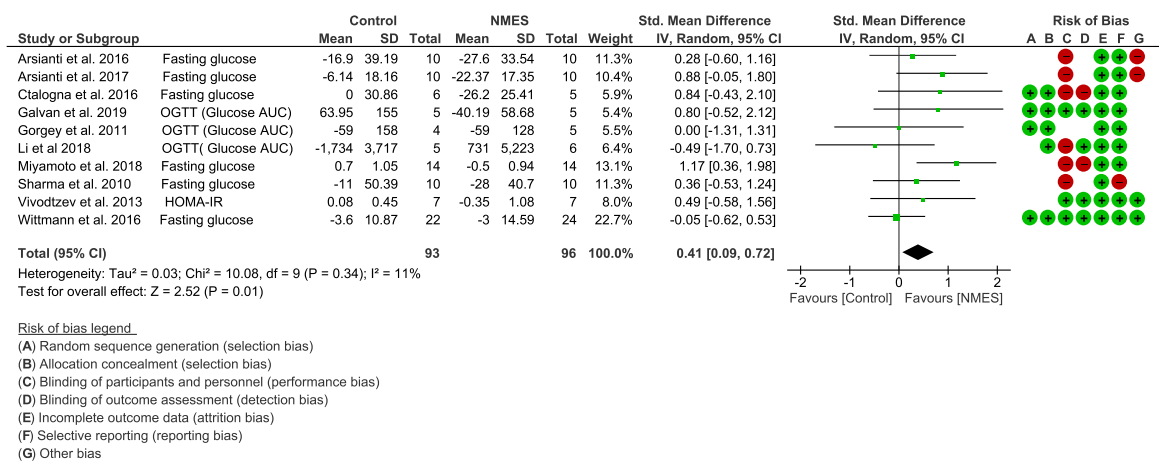


Figure 3: Forest plot indicating effects of NMES on insulin sensitivity. Risk of bias assessment, blank areas indicate unclear risk of bias.

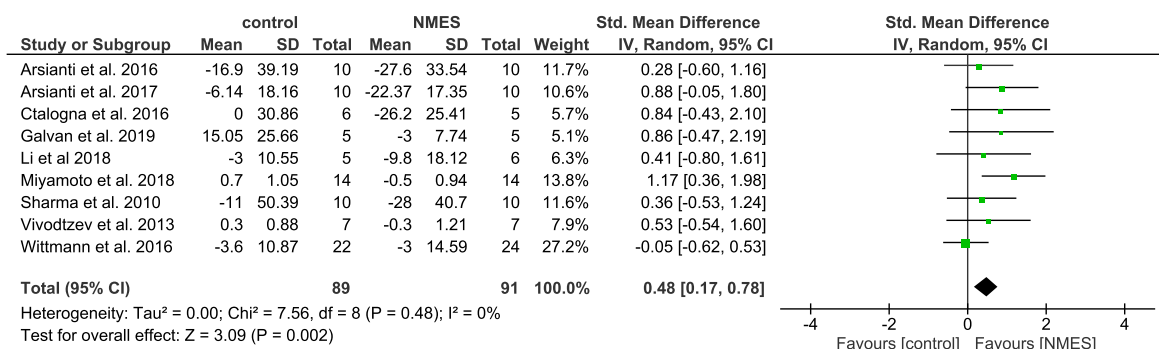


Figure 4: Forest plot indicating effects of NMES on fasting blood glucose.

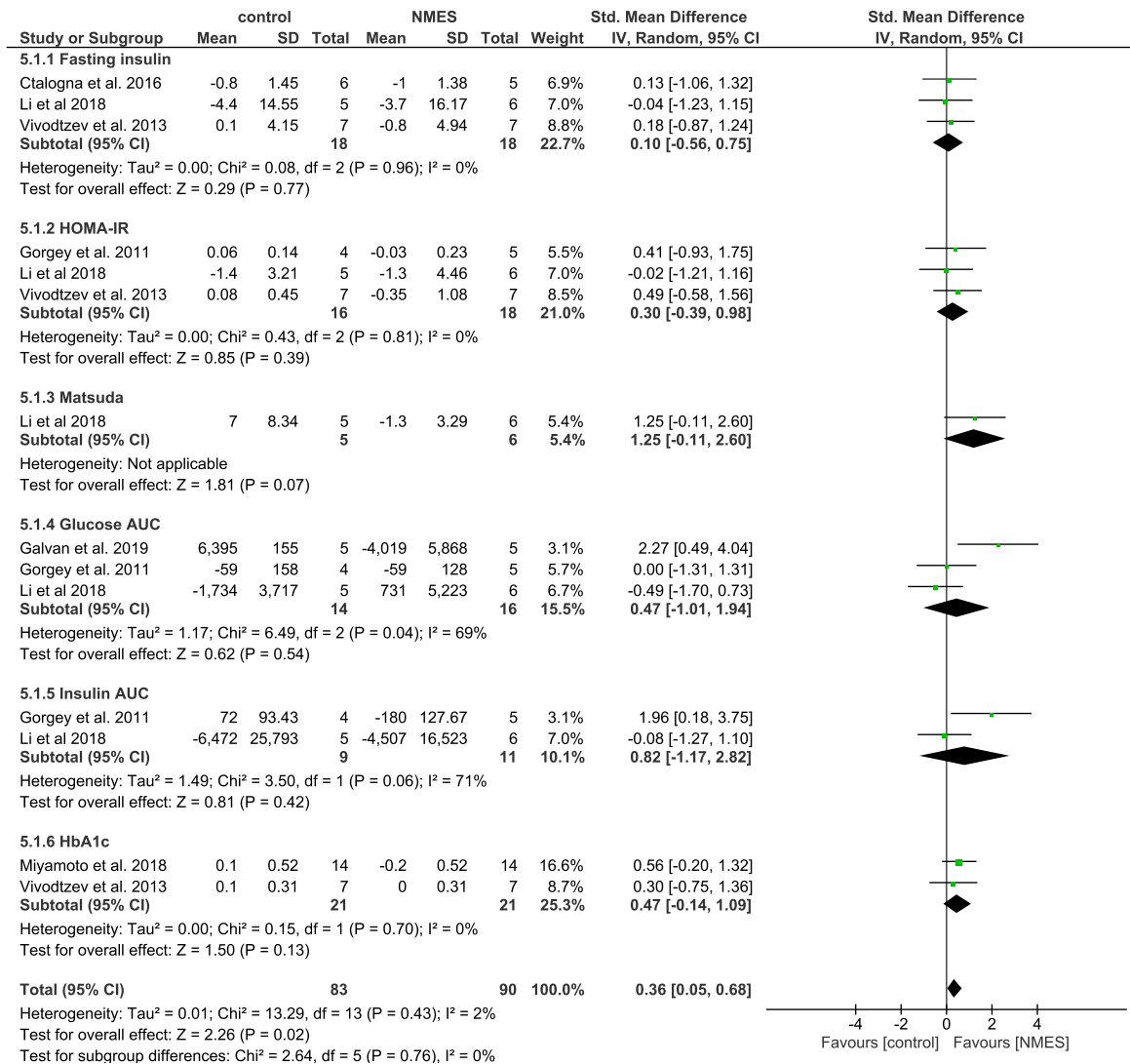


Figure 5: Forest plot indicating effects of other methods used to assess insulin sensitivity.

Substrate Utilization

To our knowledge five studies have reported the acute effects of NMES on substrate utilization measured by Respiratory Quotient (RQ) or Respiratory Exchange Ratio (RER), oxygen consumption (VO_2), and lactate production. All of these studies indicate increased glucose utilization during NMES application as measured by increased RQ [33-35, 46], increased lactate level [33-35, 45, 46] and elevated oxygen utilization [33-35, 46] (**Table 1**). Additionally, two studies reported energy expenditure during NMES. One of these studies reported an increase [13],

and another study [14] reported no change in energy expenditure. Only one study, to our knowledge, investigated the chronic effects of NMES on substrate utilization [59] and reported no change in resting substrate utilization and energy expenditure after four weeks of NMES.

Body Composition

Table 1 summarizes the outcomes of body composition in nine studies among the articles selected for systematic review that reported the body composition parameters at baseline and at the end of the NMES intervention. Six studies [31, 42, 56, 58, 60, 61] used dual-energy X-ray absorptiometry (DXA), and three studies [13, 47, 49] used bio-electrical impedance assessment (BIA) to assessed body composition. No significant changes in body composition were reported in majority of the studies [13, 49, 58, 61], two studies [42, 44] reported a significant reduction in total body weight and body fat without any changes in lean body mass. One study reported significant increase in body mass and lean muscle mass [31] and one study [47] reported a significant increase in body fat after NMES treatment without any change in body weight and lean mass. One study [56] was a combination of exercise and NMES and reported a significant decrease in body mass and fat mass, as well as a trend for decrease in android fat mass.

Discussion

The aim of this systematic review and meta-analysis was to investigate the effects of NMES on glycemic control and insulin sensitivity. Based on the existing evidence we conclude that acute application of NMES is effective in increasing glucose utilization and improving glycemic control, while chronic use of NMES is effective in improving insulin sensitivity especially in populations with type 2 diabetes and spinal cord injury.

NMES is an alternate strategy to induce muscle contraction and has been widely used in rehabilitation settings to prevent loss of muscle mass and strength. [16, 29-32] The electrical current that is produced with application of NMES results in changes to the membrane potential of the stimulated axon terminals, which in turn releases calcium. This initiates the signaling cascade that leads to skeletal muscle contraction. Although muscle contraction is generally an energy requiring mechanism, there is lack of data in literature that assessed energy expenditure during NMES. Two studies [13, 58] reported an elevated level of energy expenditure during NMES while one reported no change. [14] Elevated ATP utilization has been shown in skeletal muscle after intermittent NMES application. [65] Several studies indicated use of glycolytic source as substrate during NMES application. [40-42, 57-59, 62] Electrical stimulation has been shown to increase glucose uptake in cell culture model [66] as well as in isolated muscle using animal model. [67] Increase in GLUT4 content and GLUT4 translocation to cell membrane has been well documented during exercise performance in both healthy and population with type 2 diabetes. [68, 69] Muscle contraction induced by electrical stimulation, on the other hand, has also shown to effectively increase CAMKII and Akt phosphorylation [70], upregulate GLUT4 content and translocation [53], deplete muscle glycogen content [63], increase glucose uptake from peripheral circulation [18, 22, 33-35, 45, 46, 54, 59] and increase whole body glucose utilization. [33-35, 46, 49, 58] Downregulation of insulin dependent glucose uptake pathway has often been reported in upstream signaling molecules such as IRS1, PI3K, and Akt phosphorylation [70] with little to no

impact on GLUT4 content and GLUT4 translocation in insulin resistant and population with T2DM. [68] Therefore, NMES induced muscle contraction may serve as an alternative therapeutic strategy to improve glycemic control and insulin sensitivity especially in sedentary and insulin resistant population via calcium signaling. [19] This hypothesis is further supported by studies reporting increase AMPK- α and CaMKII, that stimulates muscle glucose uptake in patients with SCI. Moreover, a study by Joubert et al. also reported a greater degree of improvement in insulin sensitivity measured by hyperinsulinemic euglycemic clamp after one week of NMES in population with T2DM who were relatively more insulin resistant and a higher BMI. [14]

Acute effects of NMES on glycemic control

Existing evidence strongly suggests the effectiveness of NMES to improve glycemic control. Several studies reported decrease in blood glucose level [14, 18, 22, 33-35, 45, 46, 54, 59], increased whole body glucose utilization measured by RQ [33-35, 46], increased lactate production [33-35, 46], and elevated glucose uptake measured by hyperinsulinemic euglycemic clamp [14, 33, 34], during or immediately after NMES application. Additionally, increased glycolytic enzyme activity [70] and recruitment of type II fibers [24] have also been reported during the NMES session. Hamada et al. reported an increased glucose uptake during NMES that lasted for at least 90 minutes following the NMES, suggesting elevated level of glucose utilization after cessation of NMES. Among all studies that reported glucose utilization during NMES, reported increased glucose utilization during NMES regardless of stimulation frequency (low or high) and NMES intensity. Effectiveness of NMES in glucose utilization was evident in healthy as well as population with T2DM and SCI. Therefore, use of NMES holds promising potential as an alternative strategy to improve glycemic control in all populations. Future investigation to determine optimum frequency, intensity, and duration for NMES use could be beneficial for population with hyperglycemia and insulin resistance. It should be noted that although longitudinal

studies evaluated effects of NMES on insulin sensitivity, were mainly limited to populations with type 2 diabetes and spinal cord injury

Chronic effects of NMES on insulin sensitivity

This is the first systematic review, to our knowledge, to investigate the effectiveness of NMES on insulin sensitivity. The majority of the studies indicated an improvement in insulin sensitivity after NMES intervention. To further confirm this conclusion, a meta-analysis was performed including only randomized controlled trials conducted in humans. Meta-analysis results strongly suggest that NMES can be used as an alternative strategy to improve insulin sensitivity. Methods used to assess insulin sensitivity varied across studies. However, all but one study [61] included in meta-analysis, reported on fasting blood glucose before and after the intervention. A significant decrease in fasting blood glucose was reported by all studies, with the exception of Wittman et al. [51] This lack of improvement may be due to use of NMES only once a week and/or due to very low intensity of NMES used in this study. Due to small number of studies that met the inclusion criteria for meta-analysis, it is unknown how the methods used to assess meta-analysis may impact the effectiveness of NMES. However, as our analysis strongly suggest an impact of NMES on fasting glucose, it can be expected that the effectiveness can be confirmed using more sensitive methods to measure insulin sensitivity, such as hyperinsulinemic euglycemic clamp. However, future studies should confirm this. With the exception of Wittman et al, all studies in the meta-analysis reported favoring NMES as an effective intervention in improving insulin sensitivity, regardless of frequency (low or high), varied session times, duration and intensity. NMES intervention was shown to be effective in improving Insulin sensitivity.

NMES Protocol

Although our findings strongly suggest the effectiveness of NMES to improve glycemic control and insulin sensitivity, a specific recommendation of NMES protocol has not been

established. Lack of randomized control trials along with varied study population makes this challenging to determine effective recommendation. Present literature indicates both low and high intensity NMES with varied frequency has been effective in acute increase in glucose utilization as well as improving insulin sensitivity. It is important to note that many patients complain of discomfort, pain and limitations on subjective tolerance [14, 22], particularly under high frequency and high intensity stimulation. While considering NMES protocol, it is important to consider safety and comfort of the individuals, and the target population (e.g. insulin resistant or having physical limitations to perform physical activities etc.). Jabbour et al., reported a significant decrease in glucose concentrations after an acute (1 hour) session of low frequency NMES (8 Hz) in a middle-aged population with T2DM and reported to be tolerable by all participants [22]. Several studies with use of low frequency NMES reported increase in glucose utilization with variable NMES intensity. [14, 18, 22, 32-35, 40-43, 45-47, 52, 53, 57, 59-61] It has been suggested that use of low frequency is effective in largely activating glycolytic type II muscle fibers [22, 24] and improve insulin sensitivity. These findings are also supported by Joubert et al., 2015 [14], demonstrating that after a single session of 25-minutes of low frequency (35 Hz) NMES, a significant increase in glucose uptake measured by the hyperinsulinemic euglycemic clamp in a population with T2DM. On the other hand, when a chronic high frequency protocol was applied to individuals with T2DM, no significant changes to glucose uptake was reported and it was noted that participants were unable to tolerate NMES intensities above 40 mA (approximately 10% of maximum voluntary contraction). [13] Poor tolerability is often explained as a limiting factor in many studies. Many studies used a maximum tolerable intensity which indicates a varied intensity among study participants. Present literature supports the improvement in insulin sensitivity when high frequency NMES was used. High frequency NMES has been shown to be effective in majority of the studies [31, 43, 48, 49, 54, 56, 58], except for two studies [13, 51] that have not only used very low NMES frequency, but also used NMES only once a week, which might explain no significant improvement in insulin sensitivity. Limited studies have specifically investigated the role of NMES frequency and intensity on glycemic control. Jabbour et al. showed that a greater glucose

uptake was achieved when higher intensity of NMES was applied compared to a lower intensity [22], and showed a significant correlation between stimulation intensity and blood glucose levels noting that the contraction intensity substantially contributes to acute glucose metabolism. Most of the studies that reported improvement in insulin sensitivity have used between 2-3 sessions per week of NMES and 4-8 weeks NMES intervention.

Taken together, the present evidence suggests that regardless of frequency and intensity used, NMES is effective in improving insulin sensitivity while higher intensity indicating greater glycemic control. NMES use between 2-3/week with a minimum duration of 2 weeks seems to effectively improve insulin sensitivity in population with insulin resistance or those with inability to exercise on a regular basis.

Effects of NMES on substrate utilization and body composition

Although the primary purpose of this review was to determine effects of NMES on glycemic control and insulin sensitivity, we also explored the effects of NMES on whole body substrate utilization and body composition. A greater reliance on whole body fat oxidation and metabolic flexibility has been well established with insulin sensitivity. [73] Given skeletal muscle is the largest site for insulin stimulated glucose uptake and has been associated with insulin sensitivity [31, 32, 61], we aimed to determine if NMES is also effective in improving whole body substrate utilization and body composition. There were only five studies that reported on whole body substrate oxidation during acute use of NMES, measured by indirect calorimetry. These studies indicated increased in whole body carbohydrate utilization during NMES. There is lack of longitudinal studies that assessed effects of chronic use of NMES on whole body substrate utilization. To the best of our knowledge, there is only a pilot study that investigated the chronic effects of NMES on whole body substrate utilization and reported no effects of NMES. Effects of chronic use of NMES on body composition is also limited. Most studies indicated there was no change in body composition [47, 56, 58] or gain in muscle mass. However, it should be noted that

one study reported that NMES has the capability to increase lean body mass [31], as well as muscle force and strength when stimulated at a frequency of at least 50 Hz. Overall, the limited data indicates no change in body composition after NMES use. Future studies should investigate long term effects of NMES on substrate utilization and body composition to be understand if the NMES induced improvement in insulin sensitivity can be achieved independent of concurrent improvement in substrate utilization and muscle mass.

Limitations

Our study has some limitations. First, our meta-analysis is limited by small number of randomized controlled trial that has been conducted to determine the effects of NMES on insulin sensitivity. However, this is the first comprehensive review that has reviewed all existing literature to address the effectiveness of NMES on improving insulin sensitivity. The systematic review with meta-analysis strongly indicates the effectiveness of NMES in improving glycemic control and insulin sensitivity. Second, two studies included in this meta-analysis incorporated exercise in addition to NMES treatment. However, the outcome does not change when those two studies were excluded from the analysis. Third, most of the studies that utilized NMES were predominantly conducted in population with T2DM and SCI. Therefore, present evidence may not be translatable to all population. Future studies should investigate the effectiveness of NMES in healthy population.

Summary

In summary, this is the first comprehensive systematic review with meta-analysis to determine the effects of NMES on insulin sensitivity. Our analysis strongly suggests that NMES can effectively improve glycemic control (acute) and increase insulin sensitivity (chronic), mainly in population with T2DM and those incapable of doing regular exercise (SCI). Present literature is not adequate to conclude the effects of NMES on substrate utilization or body composition. Our

results strongly suggest the promising potential of NMES use as an alternative therapeutic to improve insulin sensitivity.

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Appendix

APPENDIX A: Literature Search Strategies

Electronic databases: MEDLINE (PubMed), EMBASE, Cochrane Library, Google Scholar, and Web of science.

Neuromuscular electrical stimulation OR

NMES OR

electromyostimulation OR

EMS OR

electrical stimulation OR

electrical muscle stimulation OR

electrical pulse stimulation OR

EPS

AND

blood glucose OR

insulin sensitivity OR

glucose OR

insulin OR

metabolic health OR

metabolic improvement OR

metabolic

AND

muscle

Vita

Michael earned a Bachelor of Science in Kinesiology from The University of Texas at El Paso (UTEP) and is earning his Master of Science in Kinesiology. During his time as a graduate student, Michael worked as a Teaching Assistant for the Department of Kinesiology.

During his academic career Michael received the Terry Transfer Scholarship. As a research assistant under the supervision of Dr. Sudip Bajpeyi, in the Metabolic, Nutrition & Exercise Research (MiNER) Laboratory, Michael earned several awards including the 2020 Dodson Research Grant, the Texas American College of Sports Medicine (TACSM) Student Research Development Award (SRDA), and the American College of Sports Medicine (ACSM) Steven M. Horvath Travel Award.

Michael plans to pursue a career in research, focusing on metabolic health and disease; to help better understand its implications on the El Paso and surrounding regions. He will be starting his Ph.D. in Interdisciplinary Health Sciences this coming Fall under the direction of Dr. Sudip Bajpeyi.

Contact Information: mjsanchez6@miners.utep.edu