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Case Report

Effects of five months of combined semaglutide and hybrid functional electrical stimulation cycling on an individual with spinal cord injury, obesity and type-2 diabetes: case report

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Abstract

Background: Functional Electrical Stimulation (FES) cycling programs, especially hybrid FES cycling programs that combine voluntary arm cycling with electrically evoked leg cycling can help improve the activity levels of individuals with SCI. In addition, the development of glucagon-like peptide-1 receptor agonist (semaglutide) medications have been shown to be helpful to able-bodied individuals as well as those with SCI for treating type-2 diabetes and obesity. However, to date, there has been no evidence provided regarding the combination of FES cycling and semaglutide for weight loss and treatment for type-2 diabetes.

Case Presentation: A 48-year-old female with chronic T12 American Spinal Cord Injury Association Impairment Scale (AIS) C, neurogenic obesity, and type-2 diabetes underwent five months of treatment with semaglutide and total body exercise. Because of the subject's deconditioned state, the exercise began with five weeks of preliminary strengthening exercises [seated rows and single arm punches for the upper body and Neuromuscular Electrical Stimulation (NMES) resistance training with the legs] before transitioning to a hybrid FES cycling program.

Discussion: After five months of exercise combined with semaglutide, the patient had major improvements in total weight which decreased by 9.7%, total body fat mass decreased 10.5%, Glycated Hemoglobin (HbA1c) decreased from 6.6% to 5.0%, High-Density Lipoprotein (HDL) cholesterol increased by 18.7%, c-reactive protein level decreased by 34% and the participant's VO_{2peak} (aerobic fitness) improved by 15.6%.

Conclusion: After five months of exercise using electrically evoked leg exercise combined with voluntary arm exercise, and the use of semaglutide, the participant demonstrated improvements in body composition, glycemic measures, lipid profile, inflammatory markers, aerobic fitness, and functional outcomes. Because of the simultaneous use of semaglutide and exercise training it is difficult to determine the singular impact of each intervention.

Keywords: Spinal cord injury, Semaglutide, Hybrid functional electrical stimulation cycling, Obesity, Diabetes

Introduction

The prevalence of neurogenic obesity has been reported to be as high as 80–97% in individuals with Spinal Cord Injury (SCI) [1]. Neurogenic obesity is the neurologically driven form of obesity that combines fat gain with muscle loss (sarcopenia) and bone loss leading to osteoporosis, sympathetic blunting, anabolic deficiency, and blunted satiety [1]. The combination of chronic physical inactivity and obesity, especially with visceral adiposity, within the SCI population has

also been linked to systemic inflammation and metabolic syndrome [2-4]. Metabolic syndrome, which includes the combination of decreased lean mass (skeletal muscle and bone), increased fat mass (visceral, subcutaneous, and intramuscular adiposity), dyslipidemia (increased low-density lipoprotein, increased triglycerides, and decreased high-density lipoprotein), and hyperglycemia is highly associated with cardiometabolic diseases such as type-2 diabetes and neurogenic obesity [5-7]. While Glucagon-Like Peptide-1 receptor agonist (GLP-1) medications such as semaglutide have been shown to decrease body mass and diabetes blood markers in the able-bodied population [8] there is very little information regarding the use of GLP-1 medications on those with SCI. Juszezak et al. [9] completed a case report on a male in his late 40's with C6 American Spinal Injury Association Impairment scale (AIS) B SCI and demonstrated a weight loss of 11.5 kg over three months with the use of tirzepatide without exercise. Cirnigliaro et al. [10] completed a case control series showing that GLP-1 medications helped reduce body weight by 6 kg and fat mass by 4.4 kg without exercise for those with SCI. Physical activity has also been shown to be helpful in increasing lean mass, decreasing fat mass, and reducing the risk of cardiometabolic diseases in both the abled-bodied population and those with SCI [11–13].

While both semaglutide and physical exercise have been shown to help treat cardiometabolic conditions separately, to date there has been no published evidence of the effects of combining semaglutide and exercise for individuals with SCI. The purpose of this case report is to highlight the effects of combining semaglutide and hybrid Functional Electrical Stimulation (FES) cycling in an individual with chronic paraplegia, neurogenic obesity, type-2 diabetes, and metabolic syndrome. Because of the long distance to the exercise laboratory for the participant (1.5 hours by automobile), high intensity interval FES cycling was chosen as the protocol so that the participant would need to travel only twice per week. High intensity interval training has been noted to deliver similar benefits to continuous moderate intensity exercise with less exercise volume [13]. However, because of the patient's deconditioned state, there was a five week preliminary exercise program of strengthening and conditioning to prepare the patient for the more intense exercise involved with high intensity interval hybrid FES cycling. We hypothesized that combining semaglutide with hybrid FES cycling would improve body composition, glycemic control, cardiovascular fitness, and functional performance beyond what would be expected from either intervention alone.

Case Description

Patient history

The participant was a 48-year-old Caucasian female who sustained a T12 International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)/American Spinal Injury Association impairment scale C SCI 24 years earlier due to an automobile accident. She underwent recovery and rehabilitation efforts after injury and has been independent in manual wheelchair travel and transfers over the past 24 years. She is married and employed as a part-time worker in her home. However, she has maintained a generally inactive lifestyle because of SCI and the reduced physical activity options for wheelchair users. Over the 24 years since her injury she has developed neurogenic obesity, hyperglycemia resulting in type-2 diabetes which was diagnosed at age 48 and just prior to starting the semaglutide medication and the hybrid FES cycling program. The patient was also being treated for hypertension and recent blood tests indicated dyslipidemia. The patient was 175 cm tall and 87.1 kg in weight. Her calculated Body Mass Index (BMI) was 28.4 which is categorized as being overweight in the non-SCI population. However, the accepted BMI reference for obesity in individuals with a chronic SCI is 22 kg/m² [14]. Her body fat percentage was 51.7% as determined by Dual energy X-ray Absorptiometry (DXA) which also demonstrated neurogenic obesity. Combining the diagnoses of obesity, diabetes, hypertension, and dyslipidemia results in an overall condition of metabolic syndrome according to the International Diabetes Federation [15].

Other medications taken were Gabapentin 800 mg three times per day for pain, Nebivolol 20 mg per day for hypertension, oxybutynin 10 mg per day for bladder control, and a cranberry capsule 500 mg per day to help with urinary tract infections.

Exam/testing

Before enrolling in the exercise program, the patient reviewed and completed an informed consent. Pre and post program testing consisted of a DXA using a GE Healthcare Lunar Prodigy Advance scanner (Diegem, Belgium). Both DXA scans were performed by the same trained technician with the participant in a supine position. The legs were slightly internally rotated as recommended by the International Society for Clinical Densitometry with Velcro straps to secure the legs to prevent an untimely spasm from causing an extremity to involuntarily flex and bump the scanner. All metal such as belt buckles, rings, and earrings were removed prior to scanning. The scanning was to determine total body fat and lean mass, body fat percentage, and bone mineral density. A fasting finger prick capillary blood droplet test (ChooseHealth, Austin, Tx) was performed to retrieve blood lipid, glucose, and glycated hemoglobin level testing, as well as c-reactive protein for systemic inflammation. Four blood droplets were placed on each of two panels which were sent to the laboratory via mail (CoreMedica, Lee's Summit, MO) for analysis. The patient also completed an arm crank peak oxygen utilization (VO_{2peak}) exercise test using an 881 Monark Arm Crank Ergometer (Vansbro, Sweden), with the VO_{2peak} measurements analyzed with the Parvo Medics TrueOne 2400 Metabolic Measurement System (Murray, Utah). The term VO_{2peak} is used instead of $VO_{2maximum}$ to indicate that it is the highest VO_2 measured under pathological conditions (SCI) [16]. The patient performed arm cycling at 50 revolutions per minute. After a minute warm up without resistance the cycling intensity was increased by 10 watts every two minutes until the participant could no longer maintain the cycling cadence for 30 seconds. The patient also performed a 10-Meter Wheelchair Propulsion Test with the participant starting in a still position in their wheelchair. Once the participant started to propel the wheelchair the time and number of pushes were counted until the participant had traveled 10 meters. A modified Functional Independent Measurement Transfer was completed using time in place of assistance since the patient transfers independently. The timed transfers were from sitting in a wheelchair to laying supine on a mat. The patient's goals for taking the semaglutide injections and starting the exercise program (hybrid FES cycling) were to treat the tytpe-2 diabetic condition and lose weight. She also hoped to improve her physical fitness level and improve her overall functional abilities in performing activities of daily living as she reported feeling chronically fatigued.

Program

The patient was prescribed 0.25 mg injections of semaglutide once weekly for the introductory dose and then increased to 0.5 mg and then 1.0 mg. The increases were ~ 5 weeks apart and were intended to provide greater therapeutic doses. The incremental dose increases were provided by her primary care physician. The following exercise program was designed as an adjunct treatment to help with the management of weight loss, type-2 diabetes, metabolic syndrome, and general physical fitness. The initial strengthening and conditioning program consisted of voluntary wall pulley exercises (seated rows and single arm punches) for the arms and the upper body with weight increments as tolerated and neuromuscular electrical stimulation (NMES) resistance training (knee extension exercises with the legs starting without weight, then adding 1 kg strap weights to the ankles as able to a maximum of 3 kgs). Electrical stimulation was provided through surface electrodes placed on the proximal and distal quadriceps muscle groups. All exercises consisted of four sets of ten repetitions and scheduled for twice weekly. The hybrid FES cycling using the high intensity interval training protocol was performed on a BerkelBike Tricycle (Sint-Michielsgestel, The Netherlands) which was mounted on a Wahoo KickR Snap Wheel-on Bike Trainer so that the cycling was stationary to allow vital sign measurements. With the T12 AIS C injury the patient had full use of the upper extremities and some motor and sensation in the lower extremities. Because of the sensation in the lower extremities the electrical stimulation was limited to an amplitude/intensity of 70–90 mA for comfort of the participant and a constant frequency of 35 Hz and pulse width of 300 µs for the quadriceps, hamstrings, and gluteal muscle groups. Electrodes were placed as previously described in Dolbow et al. [17]. After the initial five weeks of muscle strengthening and conditioning, the participant began the hybrid FES cycling program (**Table 1**). The interval program began with 2 minutes of high intensity cycling interspersed with two minutes of low intensity cycling. As the participant tolerated the intervals were advanced to 4 minutes of both high and low intensity intervals. Training sessions were 30 minutes in duration with a two minute warm up and two minute cool down before and after the 30 minute sessions. The cadence was self-paced with a recommendation of 30 revolutions per minute (rpm). Using the Borg 10-point rating of perceived exertion scale the high intensity intervals were level 8 (hard to very hard) and the low intensity recovery intervals were level 2 (easy). The electrical stimulation intensity started at 70 mA and increased to 90 mA with a frequency of 35 Hz and pulse width of 300 µs maintained throughout the sessions. The electrical stimulation intensity levels were gaged by production of visible muscle contractions and the comfort level of the patient. The participant was scheduled to attend twice weekly but was able to attend on average 1.7 times per week due to scheduling issues and one period of illness unrelated to the program.

The left leg had more voluntary motor activity than the right which allowed a better performance with the NMES resistance training reaching the 3 kg maximum resistance while the right leg required active assistance in addition to the electrical stimulation for knee extension. Minimal improvement was observed in the right leg with the regular protocol which was far below the improvement of the left leg. For the upper body strengthening program the resistance for seated rows advanced from 18 to 30 kgs and the single arm punches from 9 to 15 kgs in both upper extremities. While the program recommended twice weekly sessions, the participant completed 9 resistance training sessions over five weeks.

After five months, the combined initial muscle strengthening program followed by the hybrid FES cycling program with a high intensity interval training protocol in conjunction with a weekly injection of semaglutide, the participant demonstrated several benefits related to body composition (**Table 2**) and healthy lipid, glucose, and inflammation blood measures (**Table 3**).

Table 1. Hybrid FES cycling parameters.

	High Intensity	Low Intensity
Interval Times	2 minutes 4 minutes 30 minute sessions	2 minutes 4 minutes 30 minute sessions
Electrical stimulation Quadriceps, Hamstrings, Gluteal muscles	Frequency 35 Hz Pulse Width 300 µs Amplitude 70–90 mA	Frequency 35 Hz Pulse Width 300 µs Amplitude 70–90 mA
Cycling Cadence	30 rpm Self-paced	30 rpm self-paced
Intensity Levels	8 (Hard-Very hard) 10 pt Borg RPE Scale	2 (Easy) 10 pt Borg RPE Scale

Table 2. Body composition changes.

Measurements	Pre-Program	Post-Program	Changes after 5 Months
Weight kg	87.1	78.7	-9.6%
Total Fat Mass kg	43.7	39.1	-10.5%
Subcutaneous Fat volume m^3	0.00363	00315	-13.2%
Visceral Fat volume m^3	0.0028	0.0022	-21.4%
Total Lean Mass kg	38.2	34.6	-9.4%
Bone Mass g/cm^2	1.223 t score ~0.19	1.274 t score ~0.62	+4.2%

Table 3. Blood glucose, lipid, and inflammation profiles.

Measurements	Pre-Program	Post-program	Percent Change
Glucose mg/dL	102	95.7	-6%
HbA1c %	6.6 High	5.0 Normal	-24%
Cholesterol mg/dL	156	182	+16%
LDL mg/dL	88	119	+35%
HDL mg/dL	32 Low	38 Low	+18.7%
Triglycerides mg/dL	177 High	127 Normal	-28,2%
C-Reactive Protein mg/L	4.1 High	2.7 Normal	-34%

The participant's weight decreased by 9.7% from 87.1 to 78.6 kg. Total body fat mass decreased 10.5% from 43.7 to 39.1 kg which included a 21.4% decrease in visceral fat and a 13.2% decrease in subcutaneous fat volume. Unfortunately, total body lean mass also decreased from 38.2–34.6 kg (9.4%). Total body bone mineral density increased by 4.2% from 1.223 to 1.274 g/cm^2.

Regarding blood glucose and lipid measures, the fasting glucose level reduced by 6% from 102 to 95.7 mg/dL and the glycated hemoglobin (HbA1c) decreased from a high 6.6% to a normal level of 5.0%, a reduction of 24% (normal<5.7%). The triglyceride level decreased from a high of 177 to a normal 127 mg/dL level which is a 28% reduction (normal<150mg/dL) and the heart protective High-Density Lipoprotein (HDL) cholesterol level increased by 18.7 % from 32 to 38 mg/dL (normal>50 for women). Total cholesterol and Low-Density Lipoprotein (LDL) cholesterol increased but remained at normal levels. Lastly, c-reactive protein level decreased by 34% from a high level of 4.1 to a normal level of 2.7 mg/L (normal<3.0 mg/L) which may reflect a decrease in systemic inflammation in the body. The participant had a diagnosis of hypertension, and her blood pressure fluctuated throughout the five-month program with most measures within normal limits (<120/80 mg/Hg). While the exercise protocol may have been helpful for maintaining normal blood pressure, the participant was also taking 20 mg of Nebivolol daily to control for hypertension.

The participant also improved in aerobic fitness and physical functioning (**Table 4**).

The gold standard test for aerobic fitness is the VO_{2peak} graded exercise test. The participant's VO_{2peak} score increased by 15.6% using an arm crank graded exercise test. Additionally, the participant improved in the 10-meter wheelchair propulsion test [18,19], reducing the time from 10.48 seconds to 6.17 seconds and reduced the number of arm pushes required from 8.5 to 7. Likewise, the timed transfer from sitting in the wheelchair to laying supine on a mat decreased from 12.84 seconds to 7.5 seconds.

Discussion

The participant in this report has a chronic T12 AIS C SCI. The participant also carried a diagnosis of obesity, type-2 diabetes, and hypertension. The subject's baseline measures are consistent with conditions including hyperglycemia, dyslipidemia, obesity, and systemic inflammation. In addition, HTN, dyslipidemia, hyperglycemia, obesity, and systemic inflammation are the hallmarks of metabolic syndrome. However, when viewing the post-program values, we see that many of those measures associated with the diagnosed conditions had been converted to normal measurement values. Hyperglycemia values related to type-2 diabetes resolved as the HbA1c levels went from high to normal and the blood glucose levels transitioned to normal. The dyslipidemia levels demonstrate nearly complete resolution with triglyceride levels transitioning from high to normal, total cholesterol and LDL levels remaining normal and HDL levels improving toward normal. The participant significantly decreased overall body weight, fat mass (including visceral and subcutaneous volumes) and increased bone mineral density. The one negative result was the loss of lean mass which is implicitly muscle mass since bone increased. During large amounts of weight loss, it is typical to decrease lean mass as well as fat mass. The importance of exercise during this time is to help preserve lean mass. With a low exercise adherence rate of just 1.7 times per week, and the limited strength of muscle contractions because of low electrical stimulation parameters due to intact sensation, it is not surprising that the lean mass was not preserved at a higher rate.

Lastly, the right leg appeared to be especially lacking in the ability to respond to resistance training as shown by the lack of response during the NMES resistance training phase. The poorer performance of the right leg even with electrical stimulation caused concern for possible partial lower motor neuron injury. The contractions of the quadriceps muscle group in the right leg, while visible, were less vigorous and less responsive functionally than the quadriceps muscle group of the left leg. While fat mass and lean mass declined in all

Table 4. Aerobic fitness and function.

Measurements	Pre-Program	Post-Program	Percent Change
Aerobic Fitness VO^{2}Peak ml/kg/m	12.2	14.1	+15.6%
10 Meter W/C Propulsion Test	10.48 seconds 8.5 pushes	6.17 seconds 7 pushes	+41%
Timed Transfer Test W/C to Mat Supine	12.84 seconds	7.5 seconds	+41.5%

regions of the body (arms, trunk and legs) the size of the left leg was much larger than the right with 56% greater lean mass and 43% more fat mass. The thought that the right leg may have lower motor neuron involvement is speculative as no H reflex or other testing was performed to verify partial lower motor neuron injury, although the poor response to electrical stimulation and the fact SCIs below T10 are more likely to have lower motor neuron involvement make this a possibility [20].

Depending on the level of involvement and possible degree of denervation in the quadriceps muscle group of this individual with T12 AIS C SCI injury, regular electrical stimulation parameters may be less effective or ineffective requiring a long pulse width stimulation protocol to elicit denervated muscular responses [21].

The participant's BMI decreased from 28.4 to 25.7 kg/m^2. Both measures are in the overweight range for the non-SCI population and obese using the BMI modified for individuals with SCI (22 kg/m^2). However, because of the effects of paralysis, BMI generally underestimates the body fat percentage of individuals with SCI [2]. The body fat percentage as determined by DXA scans decreased slightly from 51.7 to 51.2 which demonstrates the combined loss of fat and muscle with more fat than muscle being lost. The observed changes in body composition, blood glucose and lipid measures, an inflammation marker, aerobic fitness and functional testing measures occurred during concurrent administration of semaglutide and exercise, although the relative contribution of each intervention cannot be determined. There were no negative reactions or side effects reported or observed from the semaglutide or hybrid FES cycling. The authors recommend engaging in high intensity interval training at least twice per week for 30–60 minutes or the recommended 150 minutes or more of moderate intensity continuous exercise to optimize the benefits. The authors also want to note that nutritional counseling was not part of the program but may also provide increased benefits. To the knowledge of the authors, this is the first report of the combined use of GLP-1 medication and a hybrid high intensity interval training FES-cycling program for an individual with SCI. However, the results are supported by the singular use of Tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 medication in a case report of an individual with chronic C6 SCI with diabetes mellitus, obesity, and metabolic syndrome losing 14.9 kgs and maintaining normal blood lipid, glucose and hemoglobin A1c blood levels over a one-year period [9]. Likewise, a case series involving three individuals with chronic SCI found benefits regarding weight loss and glycemic control with the use of a GLP-1 medication over a 26-week period. [10] Similar to those without SCI, high intensity interval training has been fairly well established as being able to provide an array of benefits to body composition and physical fitness, including increasing lean mass, decreasing fat mass, and improving aerobic fitness [11–13]. However, the results of this current case of combined semaglutide and hybrid high intensity interval training FES cycling cannot be generalized to the overall SCI population but can provide insight into what is possible. A large cohort randomized control trial would help verify the magnitude of the benefits that can be provided by the combination of semaglutide and hybrid high intensity interval training FES cycling.

Limitations

There were several limitations regarding this case report. First, this case report was on one individual which did not allow comparison to other individuals with SCI and does not allow an inference of the results to the overall SCI population. Because there was simultaneous treatment of hybrid FES cycling and semaglutide medication, it is impossible to determine what percentage of the results were due to either treatment singularly. In addition, the participant performed hybrid FES cycling at a low frequency of 1.7 times per week and used low electrical stimulation amplitude due to the patient's intact sensation. These factors may have reduced the potential benefits from exercise. Lastly, the patient was not provided nutritional counseling regarding portion sizes, appropriate food choices, and the need to include adequate amounts of protein to help with the maintenance of muscle mass.

Conclusion

Five months of exercise using electrically evoked leg exercise combined with voluntary arm exercise, and the use of semaglutide, provided significant benefits in weight reduction, decreased fat mass and decreased body fat percentage, improved aerobic fitness, improved blood glucose, lipid and inflammation markers, improved wheelchair propulsion and transfers. The observed improvements in wheelchair propulsion, transfer performance, and aerobic capacity are consistent with broader neurorehabilitation literature demonstrating that structured rehabilitation interventions can enhance functional independence and physical performance in individuals with neurological impairments [21]. However, because the case study reflects the results of a single patient it demonstrates what is possible as opposed to providing generalization to the overall SCI population. A large cohort randomized control trial would help verify the magnitude of the benefits that can be provided by the combination of semaglutide and hybrid high intensity interval training FES cycling.

Conflict of Interest

The authors have no conflicts of interest to declare.

Patient Consent

Patient provided informed consent.

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