Research Article

Preliminary observations on the administration of a glucagon-like peptide-1 receptor agonist on body weight and select carbohydrate endpoints in persons with spinal cord injury: A controlled case series

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Context/Objective: To describe the effect of semaglutide, a glucagon-like peptide-1 (GLP-1) agonist, to reduce body weight and improve glycemic control in overweight or obese individuals with spinal cord injury (SCI).
Design: Open-label, randomized drug intervention case series.
Setting: This study was performed at James J. Peters VA Medical Center (JJP VAMC) and Kessler Institute for Rehabilitation (KIR).
Participants: Five individuals with chronic SCI meeting criteria for obesity and abnormal carbohydrate metabolism.
Intervention: Administration of semaglutide (subcutaneously once per week) versus no treatment (control) for 26 weeks.
Outcome Measures: Change in total body weight (TBW), fat tissue mass (FTM), total body fat percent (TBF%), and visceral adipose tissue volume (VAT_{vol}) was determined at baseline and after 26 weeks using Dual energy X-ray absorptiometry; fasting plasma glucose (FPG) concentration and serum glycated hemoglobin (HbA1C) values were obtained at the same two time points.
Results: In 3 participants, after 26 weeks of semaglutide administration, TBW, FTM, TBF%, and VAT_{vol} decreased, on average, by 6, 4.4 kg, 1.7%, and 674 cm^3, respectively. In addition, values for FPG and HbA1c decreased by 17 mg/dl and 0.2%, respectively. After 26 weeks of observation in the 2 control participants, TBW, FTM, TBF% and VAT_{vol} increased on average by 3.3 , 4.5 kg, 2.5%, and 991 cm^3, respectively. The average values for FPG and HbA1c also increased by 11 mg/dl and 0.3%, respectively.
Conclusions: Administration of semaglutide for 26 weeks resulted in favorable changes in body composition and glycemic control, suggesting a reduced risk for the development of cardiometabolic disease in obese individuals with SCI.
Trial registration: ClinicalTrials.gov identifier: NCT03292315.

Keywords: Spinal cord injury, Glucagon like peptide-1 (GLP-1), Semaglutide, Fasting plasma glucose, Hemoglobin a1c

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Introduction

Spinal cord injury (SCI) results in marked unfavorable changes in soft tissue body composition and carbohydrate and lipid metabolism (1). After an initial rapid loss of lean tissue below the neurological level of injury (2), a more insidious and progressive loss of sublesional lean tissue is observed (3, 4). This decrease in lean tissue is accompanied by an increased total body adiposity (4) and, notably with respect to metabolic considerations, the accumulation of fat in the abdominal (e.g. visceral) compartment (5). These adverse changes to body composition contribute to, and are associated with, a higher prevalence of insulin resistance and disorders of carbohydrate metabolism [e.g. impaired glucose tolerance and type 2 diabetes mellitus (T2DM)] than that reported in the general population (6). The primary approach to treat T2DM in the general population should be lifestyle modification such as diet and exercise. People with SCI experience extreme levels of inactivity and can only achieve 10-20% of the exercise of able-bodied people which explains in part barriers that have been reported when intervening with lifestyle modification alone (7–11).

Adjunctive pharmacological approaches to treat carbohydrate disorders in the general population may include one or more of the following agents: insulin, sulphonylureas, biguanides, thiazolidinediones (glitasones), and/or sodium-glucose cotansporter-2 (SGLT-2) inhibitors (12–19). In addition, a class of gastrointestinal hormones known as incretins, glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released into the circulation from enteroendocrine cells in response to food ingestion and nutrients in the small intestines (12–14). Together, incretin hormone release accounts for 50-70% of the total post-prandial insulin secretion (15). Specifically, GLP-1 is produced by L-cells in the ileum, colon, and rectum with its mechanism of action to increase post-prandial insulin secretion from pancreatic beta cells in a glucose dependent manner, to slow gastric emptying, and to suppress glucagon secretion (14). To elevate and sustain GLP-1 effects, endogenous GLP-1 receptor agonists have been developed that bind specifically to the GLP-1 receptor. This class of medication is resistant to degradation from the enzyme dipeptidyl peptidase-4 (DPP-4), leading to sustained stimulation of the GLP-1 receptor. In contrast to the short-acting GLP-1 receptor agonists that have a half-life of 2-4 h. longer acting GLP-1 receptor agonists exhibit a half-life $>$ 12 h, and more recently developed agents demonstrate a half-life as long as 14 days (16, 17).

In 2005, the GLP-1 receptor agonist exenatide was approved by the Food and Drug Administration (FDA) for the treatment of T2DM. In 2017, semaglutide (18), received approval from the FDA for the same indication. Treatment with GLP-1 receptor agonists has increased over the past several years because of their mechanism of action to increase insulin secretion and inhibit glucagon release in a glucose-dependent manner, as well as lower less risk of hypoglycemia than that of sulfonlyureas (19). Numerous multi-ethnic and multi-national trials have been performed with semaglutide in the non-SCI population that demonstrated reductions in mean HbA1c levels, body weight, and fat mass (20–22), but there have been no reports in persons with SCI. Our report describes the results from a small cohort of SCI participants that tested the once weekly subcutaneous administration of semaglutide for 26 weeks on body composition measurements such as lean tissue mass (LTM), fat tissue mass (FTM), and bone mineral content (BMC), and also carbohydrate metabolism in obese persons with chronic SCI who are wheelchair-dependent.

Methods

Five wheelchair-dependent participants with SCI (three treatment, two control) between 18 and 65 years of age were included in data analysis. These subjects completed a larger clinical trial that ended prematurely due to the COVID-19 pandemic and the ensuing expiration of the funding period. Men and women with SCI were considered for participation if they had chronic (e.g. duration of injury greater than three years) stable SCI regardless of level or completeness of neurological injury as long as they were non-ambulatory which was defined as not able to weight bear for more than 20% of the day. Participants were required to meet or exceed the threshold values for obesity determined by percent body fat [$>$25% for men and $>$35% for women using a dual-energy x-ray absorptiometry scan (DXA)] (23, 24). In addition, the participants were determined to be pre-diabetic by the hemoglobin A1c (HbA1c; 5.7-6.4%), or impaired glucose tolerance [fasting serum glucose value between 100–125 mg/dl and/or the 2-hour serum glucose concentration between 140–200 mg/dl after the administration of a 75-gram glucose load administered during the oral glucose tolerance test (OGTT)] (25). Participants were excluded from participation in the study if they had a personal and/or family history of medullary thyroid carcinoma; personal and/or family history of multiple endocrine neoplasia syndrome type 2; personal and/or family history of pancreatitis; existing diagnosis of

diabetes mellitus, or identified as having diabetes mellitus from of a standard 75-gram OGTT using the American Diabetes Association Diagnosis and Classification of Diabetes Mellitus criteria (26); currently receiving pharmacological treatment for impaired glucose metabolism; reduced kidney function [by glomerular filtration rate (GFR <60 ml/min) or abnormal liver function tests (LFT) such as aspartate aminotransferase (AST) and alanine transaminase (ALT) (any single value of ≥ 2.5 times above the upper limit of normal)]; elevated calcitonin level > 50 pg/mL (to exclude thyroid cancer); pregnancy or women who may become pregnant during the course of the study, or those who are nursing, medically unstable due to an acute illness or infection, and diminished mental capacity to provide informed consent (determined by the study physician and/or primary care physician). The study was approved by the institutional review boards of the Kessler Institute for Rehabilitation (KIR) and the James J. Peters Veterans Affairs Medical Center (JJP VAMC). Written informed consent was obtained from each subject prior to study participation. The clinical trial was registered with http://www.clinicaltrials.gov **(**NCT03292315**).**

Procedures

Participants had baseline (BL) assessments performed and were randomized by the research pharmacist in a 1:1 manner to receive once-weekly semaglutide (Ozempic) by subcutaneous injection in the lateral abdomen region for 26 weeks. Due to the open label nature of this study, only the investigators were blinded to group assignment. In the active drug treatment group, semaglutide was initially administered at a dose of 0.25 mg once a week for 4 weeks. If required glycemic control was not achieved [e.g. fasting plasma glucose (FPG) < 100 mg/dL; HbA1c $< 5.6\%$] at 4 and 8 weeks, the dosage was increased to 0.50 and 1.0 mg, respectively, for the remaining weeks of the study. All of the participants in the active drug treatment group required the 1.0 mg dose to achieve glycemic control below the cutoff values required for inclusion in the study. Participants in the control group were followed without receiving treatment other than the laboratory determinations to monitor for changes in glucose metabolism over the course of the study. For safety considerations and evaluation of efficacy, a dose titration regimen was initiated that conformed to the guidelines for the use of semaglutide (18). Body composition and fasting laboratory determinations were performed at parallel time points in the treatment and control groups. Medical history, cigarette smoking, and sedentary lifestyle were obtained by self-report from each participant at baseline and at the 26-week follow-up visit. For the purpose of this report, sedentary lifestyle was defined as < 20 min of moderate to vigorous intensity aerobic activity twice per week (27).

Laboratory and safety assessments

Laboratory and safety assessments were completed at baseline and repeated at the 4-, 8-, and 26-week time points. Participants were instructed to arrive in the morning between 8:00 and 10:00 am after a 12-hour fast, and abstain from alcohol, caffeine, and strenuous exercise for 24 h prior to obtaining laboratory determinations. FPG concentrations were obtained and analyzed on an automated glucose analyzer (YSI 2300 STAT Plus, YSI Life Sciences, Yellow Springs, OH) and specimens for HbA1c determination were sent to a commercial laboratory (LabCorp, Raritan, NJ, USA). Serum samples were obtained for the determination of the GFR and LFT as determined by AST and ALT (LabCorp, Raritan, NJ, USA). If GFR values decreased to <60 ml/min, or if either LFT increased ≥ 2.5 standard deviations above the upper limit of normal, the participant was discontinued from drug and terminated from the study protocol. Furthermore, to additionally monitor for adverse events during the study, each participant had their health monitored weekly by phone to identify any deviation from baseline status. To evaluate the possible effect of administration of semaglutide on the participant's bowel regimen, the 10 Question Bowel Function Survey (BFS) and the Bowel Management item bank short form used in previous clinical trials in persons with SCI (28, 29), was obtained at baseline and repeated at the 4-, 8-, and 26-week time points.

Body composition measurements

A total body scan was performed in accordance with the manufacturer guidelines (light clothing and free from all metal and plastic objects) using a fan-beam DXA (GE Lunar iDXA, platform version 16.0, Madison, Wisconsin, USA). Prior to completing the DXA scan, participants were asked to wear minimal clothing (shorts and t-shirt), empty their bladder, and to be well hydrated (30). The knees and ankles were strapped using velcro straps to mitigate the impact of any contractures and spasms while optimizing the quality of the image obtained. To analyze the results from each total body scan, proprietary software algorithms from the manufacturer were used to segment the body and trunk into the upper and lower extremities using the standard regions of interest by a single

Table 1 Characteristics of the Study Participants.

ID #	Age (y)	Height (cm)	Weight (kg)	BMI (kg/m^2)	DOI (y)	LOI	ISNCSCI (A/B/C/D)	Smokers (Y/N)	Sedentary Lifestyle (Y/N)
Semaglutide (n = 3)									
S1	58	188.0	105.5	29.8	39	T6	A	N	Y
S2	36	198.1	119.6	30.5	17	L2	C	N	Y
S3	47	172.7	84.5	28.2	28	C5-6	A	N	Y
Mean	47	186.3	103.2	29.5	28	—	—	—	—
(SD)	(11)	(12.8)	(17.7)	(1.2)	(11)				
Control (n = 2)									
C1	56	182.9	117.1	35.5	25	T7	B	N	Y
C2	50	180.3	96.3	29.7	33	C5-6	A	N	Y
Mean	53	181.6	106.7	32.6	29	—	—	—	—
(SD)	(4)	(1.8)	(14.7)	(4.1)	(6)				

Abbreviations: BMI = body mass index; cm = centimeters; DOI = duration of injury; ISNCSCI = International Standards for Neurological Classification on Spinal Cord Injury; kg = kilogram; LOI = level of injury; m = meters; SD = standard deviation; y = years; Y/N = yes/no.

investigator who was located at each institution. As part of the daily quality assurance (QA) during the study, a required primary calibration phantom, as well as a secondary QA phantom lumbar spine phantom (reference value 30% fat) was scanned > 200 times with the CV % determined to be 0.9%. Recent work from our group demonstrated the short-term ("on and off" the table) precision error is less than 5.6%, 2.7%, 3.8%, 3.5%, 5.8%, and 2.3% for arms, legs, trunk, android, gynoid, and total body fat tissue mass, respectively (31). Height was calculated from the DXA total body scan skeletal length using the linear pixel count method (32), by employing electronic calipers to measure from the top of the skull to the bottom of the calcaneus. A Total body weight (TBW) was calculated from the DXA total mass with the agreement between DXA total mass and scale weight typically within 1% (33). The FTM, total body fat percent (TBF%), lean tissue mass, and bone mineral content values were obtained from the DXA soft tissue attenuation according to the manufacturer's standard analysis. Visceral adipose tissue volume (VAT_{vol}) was obtained from the abdominal android fat tissue mass region by applying the iDXA enCore^{TM} CoreScan software, as previously described (34, 35) and validated in the SCI population (36).

Statistical analysis

Continuous variables were reported for individual participants and as and mean ± SD, where applicable. Due to the small sample size both groups, inferential statistics could not be determined. As a result, the change in body composition and laboratory values over the 26-week period was reported as the absolute change (delta). Mean and SD values were computed using IBM SPSS (Version 22, Armonk, NY).

Results

Table 1 presents individual and group demographic characteristics. Study participants were male between the ages of 47 and 58 years old who had a duration of SCI between 17 and 39 years. Body mass index (BMI) values ranged between 28.2 and 35.5 kg/m^2 (Table 1). During the entire study AST, ALT, and GFR values remained within normal limits for all participants in both groups (Table 2). The 10 Question BFS and the Bowel Management item bank demonstrated no change bowel function over the course of the study. In 3 participants, after 26 weeks of semaglutide administration, TBW, FTM, TBF%, and VAT_{vol} decreased, on average, by 6, 4.4 kg, 1.7%, and 674 cm^3, respectively (Table 3). In addition, values for FPG and HbA1c decreased by 17 mg/dl and 0.2%, respectively (Table 2). After 26 weeks of observation in the 2 control participants, TBW, FTM, TBF% and VAT_{vol} increased on average by 3.3, 4.5 kg, 2.5%, and 991 cm^3, respectively (Table 3). The average values for FPG and a HbA1c values also increased by 11 mg/dl and 0.3%, respectively (Table 2). The change in LTM and BMC revealed an average decreased of 1.4 kg and 27 g in the 3 participants in the semaglutide group and 1.2 kg and 59 g in the 2 participants in the control group, respectively (Table 3).

Discussion

In several clinical trials in the general population with T2DM, investigators reported the effect of semaglutide administration to induce weight loss and improve

Table 2 Safety and Glycemic Laboratory Values from a Trial Investigating 26 weeks of Semaglutide Administration and No Treatment Controls in a Cohort of men with Chronic Spinal Cord Injury.

	AST (IU/L, NR: 0-40)				ALT (IU/L, NR: 0-44)				GFR (ml/min, NR: > 59)				FPG (mg/dl)				HbA1C (%)			
	BL	4W	8W	26W	BL	4W	8W	26W	BL	4W	8W	26W	BL	4W	8W	26W	Δ	BL	4W	8W	26W	Δ
Semaglutide																						
S1	18	16	17	14	23	19	18	17	100	100	97	94	101	79	76	82	−19	6.2	6.1	6	5.9	−0.3
S2	17	17	17	14	19	21	19	13	154	145	143	151	100	71	73	87	−13	5.6	5.5	5.3	5.6	0
S3	19	25	16	16	17	21	20	18	118	105	108	110	97	87	78	77	−20	5.7	5.8	5.5	5.4	−0.3
Mean	18	19	17	15	20	20	19	16	124	117	116	118	102	79	76	82	−17	5.8	5.8	5.6	5.6	−0.2
(SD)	(1)	(5)	(1)	(1)	(3)	(1)	(1)	(3)	(27)	(25)	(24)	(29)	(3)	(8)	(3)	(5)	(4)	(0.3)	(0.3)	(0.4)	(0.3)	(0.1)
Control																						
C1	—	—	—	—	—	—	—	—	—	—	—	—	172	165	170	185	+13	5.4	5.3	5.8	5.7	+0.3
C2	—	—	—	—	—	—	—	—	—	—	—	—	77	86	78	86	+9	4.8	5.1	5.0	5.2	+0.4
Mean	—	—	—	—	—	—	—	—	—	—	—	—	125	126	124	136	+11	5.1	5.2	5.4	5.5	+0.3
(SD)													(67)	(56)	(65)	(70)	(3)	(0.4)	(0.1)	(0.6)	(0.4)	(0.1)

Abbreviations: AST = *aspartate aminotransferase*; ALT = alanine transaminase; BL = baseline; FPG = fasting plasma glucose; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; IU/L = international units per liter; mg/dL = mg per deciliter; ml/min = milliliters per minute; NR = normal range; SD = standard deviation; W4 = week 4; 8W = week 8; 26W = week 26; Δ = change in values from BL to week 26.

carbohydrate metabolism (37–39). In the study presented, an improvement in carbohydrate metabolism was observed as evidenced by a decrease in weight loss, fat tissue mass, FBG, and HbA1c in 3 obese men with chronic SCI who received once-weekly semaglutide. The mechanism responsible for this weight loss has been attributed to a decrease in energy intake due to enhanced satiety (16). These changes are believed to be centrally mediated in areas of the brain responsible for appetite control and reward (40, 41). Thus, the findings presented suggest that the favorable changes were a direct effect from the semaglutide treatment. To the best of our knowledge, this is the first randomized open-label drug intervention case series evaluating the effects of 26 weeks of once-weekly semaglutide administration on measures of body composition and biomarkers of glucose metabolism in persons with chronic SCI.

In a study by Davies *et al.* (42), a phase 2, randomized, placebo-control, parallel-group, dosage-finding, 26-week trial was completed in 632 participants with T2DM without modification of diet or physical activity resulted in significant reduction in mean total body weight that were greater with oral semaglutide [dosage-dependent range, −2.1 kg (95% CI: −3.1 to −1.0, $P < 0.01$) to −6.9 kg (95% CI: −8.0 to −5.8, $P < 0.001$)] and subcutaneous semaglutide [−6.4 kg (95% CI: −7.5 to −5.3, $P < 0.001$)] vs placebo [−1.2 kg (95% CI: −2.3 to −0.1)]. In a randomized, double-blind, placebo controlled, phase 2 clinical trial in 957 non-diabetic participants, subcutaneous semaglutide and liraglutide were tested as candidate anti-obesity medications in persons from populations with obesity (the cohort was collected in 8 countries at 71 clinical sites); semaglutide resulted in greater weight loss when compared with placebo or once daily 3.0 mg liraglutide (39).

The magnitude of subcutaneous semaglutide-induced weight loss exceeded the FDA's criteria for the prescription of an anti-obesity medication, and no major safety concerns were observed. In a large-scale randomized control trial (RCT) in adults who were overweight or obese, subcutaneous semaglutide administration for up to 68 weeks (n = 535) resulted in progressive weight loss over the entire study period. This weight loss was associated with improvements in glucose and lipid metabolism when compared to a cohort that was switched to placebo at 20 weeks, with body weight being regained in this group (n = 268) (43). These findings are a strong impetus to conduct clinical trials in the future designed to administer semaglutide for longer periods of time in persons with SCI,

Table 3 Total Body DXA Variables from a Trial Investigating 26 weeks of Semaglutide Administration and No Treatment Controls in a Cohort of men with Chronic Spinal Cord Injury.

	TBW (kg)			FTM (kg)			TBF%			VAT_{vol} (cm^3)			LTM (kg)			BMC (g)		
	BL	26W	Δ	BL	26W	Δ	BL	26W	Δ	BL	26W	Δ	BL	26W	Δ	BL	26W	Δ
Semaglutide																		
S1	105.5	102.0	−3.5	39.0	36.6	−2.4	38	35.8	−2.2	3624	2731	−893	63.6	62.7	−0.9	2844	2766	−78
S2	119.6	112.3	−7.3	58.4	51.2	−7.2	48.8	47	−1.8	2443	1815	−638	57.9	57.8	−0.1	3264	3261	−3
S3	84.5	77.5	−7.0	35.4	31.7	−3.7	41.9	40.9	−1	2502	2002	−500	46.9	43.6	−3.3	2210	2210	0
Mean	103.2	97.3	−6.0	44.3	39.8	−4.4	42.9	41.2	1.7	2856	2183	−674	56.1	54.7	−1.4	2773	2746	−27
(SD)	(17.7)	(17.9)	(2.1)	(12.4)	(10.1)	(2.5)	(5.5)	(5.6)	(0.6)	(665)	(484)	(200)	(8.5)	(9.9)	(1.7)	(531)	(526)	(44)
Control																		
C1	117.1	123.6	+6.5	49.2	59.2	+10.1	43.1	49.2	+6.1	3253	5209	+1956	64.8	61.4	−3.3	3098	2997	−101
C2	96.3	96.8	+0.5	46.0	44.9	−1.1	47.7	46.6	−1.1	2156	2181	+25	47.4	49.0	+1.0	2899	2883	−16
Mean	106.7	110.0	+3.3	47.5	52.1	+4.5	45.4	47.9	+2.5	2705	3695	+991	56.1	55.2	−1.2	2999	2940	−59
(SD)	(14.7)	(19.3)	(4.6)	(2.3)	(10.2)	(2.5)	(3.3)	(1.8)	(5.1)	(776)	(2141)	(1365)	(12.3)	(8.8)	(3.0)	(141)	(81)	(60.1)

Abbreviations: DXA = dual energy X-ray absorptiometry; BL = baseline; FTM = fat tissue mass; kg = kilogram; g = grams; TBF% = total body fat percent; TBW = total body weight; LTM = lean tissue mass; BMC = bone mineral content; VAT_{vol} = visceral adipose tissue volume; 26W = 26 week; Δ = change in values from BL to week 26.

as well as in other cohorts of individuals who are chronically immobilized. Thus, the weight loss achieved after 6 months of semaglutide treatment had substantial life changing effects on both physical function and psychological benefit for the study participants. Similar benefits would be anticipated to be observed in persons with SCI in whom a sedentary lifestyle and decreased total energy expenditure results in an exceptionally high prevalence of sarcopenia and neurogenic obesity that ranges between 67 and 97% (44–46), and physical deconditioning that falls substantially below that of the non-SCI population (47).

Limitations and future directions

There are several limitations associated with this case series. The small sample size necessitates the use of descriptive statistics from our observations, making the generalizability of these findings limited without formal hypothesis testing on the effects of 26 weeks of once-weekly subcutaneous semaglutide on body composition and carbohydrate metabolism, as well as on other cardiometabolic measures that were not performed in this work. The small number of participants in this study limited our ability stratify by age, sex, level of lesion, and International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) grade and to control for additional inter-individual general and SCI-specific characteristics that may confound the findings. In addition, the authors did not quantify periodic changes in resting and total energy expenditure and caloric consumption over the course of the study and did not perform a 6 month follow-up visit to monitor "weight regain" following cessation of semaglutide. As such, the effect of diet and physical activity on the changes in body compostion and carbohydrate metabolism observed in this study cohort cannot be fully understood. Future double-blinded RCTs should be performed in a larger number of homogeneous SCI participants which would enable a formal statistical analysis to adequately control for potential confounders.

Conclusion

Once-weekly semaglutide administration for 26 weeks resulted in favorable changes in body composition and glycemic control. This case series presents the effect of semaglutide administration alone on carbohydrate metabolism and weight loss in persons with chronic SCI. Future RCT's are necessary to examine if weight loss from semaglutide administration can improve quality of life in obese persons with chronic SCI who are wheelchair-dependent.

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Disclaimer statements

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Conflicts of interest Authors have no conflict of interests to declare.

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