Original Article

Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury

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Design: Longitudinal training.

Objectives: The purpose was to determine the effect of electrical stimulation (ES)-assisted cycling (30 min/day, 3 days/week for 8 weeks) on glucose tolerance and insulin sensitivity in people with spinal cord injury (SCI).

Setting: The Steadward Centre, Alberta, Canada.

Methods: Seven participants with motor complete SCI (five males and two females aged 30 to 53 years, injured 3–40 years, C5–T10) underwent 2-h oral glucose tolerance tests (OGTT, $n=7$) and hyperglycaemic clamp tests ($n=3$) before and after 8 weeks of training with ES-assisted cycling.

Results: Results indicated that subjects' glucose level were significantly lower at 2 h OGTT following 8 weeks of training (122.4 ± 10 vs 139.9 ± 16 , $P=0.014$). Two-hour hyperglycaemic clamps tests showed improvement in all three people for glucose utilisation and in two of three people for insulin sensitivity.

Conclusions: These results suggested that exercise with ES-assisted cycling is beneficial for the prevention and treatment of Type 2 diabetes mellitus in people with SCI.

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Introduction

Risk of diabetes mellitus (DM) and cardiovascular disease is increasing in people with spinal cord injury (SCI) with longer life expectancy.^{1–4} Findings show that people with SCI have a three to five times higher risk of developing DM than the able-bodied population.^{5–9} Bauman and Spungen⁵ demonstrated that 22% of subjects with SCI had DM as compared to only 6% in an able-bodied control group. Sixty-two per cent of subjects with quadriplegia and 50% of those with paraplegia had abnormal glucose tolerance compared to 18% of controls. This high prevalence of DM and impaired glucose tolerance (IGT) has been attributed to changes in body composition^{10–13} and muscle characteristics^{14–17} after the injury. These changes occur due to inactivity^{18,19} and motor neuron

paralysis¹⁴ in people with SCI. Therefore, the prevention and treatment of DM in people with SCI need to be investigated.

Exercise is considered a cornerstone in the prevention and treatment of DM.^{20–23} Aerobic endurance exercise has traditionally been advocated as the most suitable exercise mode to prevent and treat DM.^{24–28} Exercise has been proven to be effective in improving muscular,^{21,26,27} adipose tissue^{20,23,28} and whole body insulin sensitivity.^{21,22,25} In one study, 10 subjects with Type 2 DM who had significant insulin resistance and eight controls without insulin resistance were trained with 1 h of stair climbing for 6 weeks.²¹ Insulin sensitivity was measured before and after one bout of exercise and 6 weeks of physical activity with euglycaemic and hyperglycaemic clamp tests. Results demonstrated that physical training significantly improved insulin sensitivity in both the insulin resistance group and the control group by 43% compared to two

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drugs; metformin (16–25%) or troglitazone (about 20%). The underlying mechanisms responsible for the improvements in muscle glucose metabolism are not fully understood but they seem to involve increases in the glucose transporter protein (GLUT-4),²⁸ increased blood flow,²⁹ body composition^{20,23} and enzyme activities.^{26,27}

Although, there is enough evidence to conclude that exercise improves insulin sensitivity in the general population, there is a lack of information with respect to the effects of exercise on insulin sensitivity in people with SCI. Also, it is very difficult for people with SCI to exercise at an appropriate intensity for improvement in insulin sensitivity due to many limitations.^{30,31} In the 1980s, exercise modalities such as functional electrical stimulation (FES) or electrical stimulation (ES)-leg cycle ergometry became popular among people with SCI. Since then, research has clearly shown physiological benefits with ES-assisted cycling with respect to cardiovascular,^{32–35} muscular,^{36–38} pulmonary^{39–41} and hormonal adaptations.^{42,43} However, there are very limited studies examining the effects of ES-assisted exercise on insulin sensitivity in people with SCI. Therefore, the purpose of the study was to investigate the effect of ES-assisted cycling on glucose tolerance and insulin sensitivity in people with SCI. It was hypothesised that 8 weeks of exercise performed three times/week, 30 min/day at approximately 50%–60% of $\text{VO}_{2\text{max}}$ would improve both insulin sensitivity and glucose tolerance.

Methods

Subjects

Seven individuals (five males, two female; aged 30–53 years) with motor-complete spinal cord injury (3–40 years post injury involving levels C5–T10) gave their written informed consent to participate in the study after the protocol was approved by the Ethics Committee at the University of Alberta and University Hospital. Subjects underwent full medical examinations by a physician before participating in the study. Individuals with pacemaker implants, uncontrolled arrhythmias, uncontrolled angina, congestive heart failure, current deep venous thrombosis, severe skin

reaction to surface electrodes or ES, less than 90° of flexion at hips and knees, severe lower extremity spasticity, severe DM, and a regular regime were excluded from the study. Characteristics of subjects are presented in Table 1.

Exercise training

Subjects trained using a computer controlled FES-leg Cycle Ergometer (ERGYS II; Therapeutic Alliance, Fairborn, OH, USA) for an accumulated duration of 30 min cycling, 3 days per week, for 8 weeks. With the ERGYS II system, electrical stimulation (monophasic rectangular phase, 30 Hz, 10 to 140 mA) was applied through surface electrode (one reference, one active electrode; 4.5×10 cm) to the gluteal, hamstring, and quadriceps muscles in a computer controlled sequence to allow pedalling of the cycle ergometer at 50 rpm. Training sessions began with a 1-min warm-up of technician-assisted pedalling at 45 rpm. The intensity was initially set at the inherent resistance in the ergometer alone (approximately 6 w), and an attempt was made to progressively increase the resistance over an 8-week period. Following the warm-up, electrical stimulation intensity was progressively increased until the subjects were pedalling unassisted at 50 rpm. If the subjects could not maintain a pedal cadence of 45 rpm with maximal stimulation, the resistance was decreased for the subjects to pedal at 50 rpm. If the pedalling rate decreased to less than 40 rpm, assistance was provided to complete the next time interval divisible by 10 min. For example, if the subject was unable to maintain a cadence of 40 rpm after 17 min of exercise, assistance was provided until 20 min. After each exercise interval, a 2-min cool-down (technician-assisted pedalling at 45 rpm) and 3-min rest period was provided. The training sessions had a maximum of three exercise intervals to complete 30 min of exercise.

Two-hour oral glucose tolerance

Three days (72 h) prior to the test, each subject was asked to consume a weight-maintaining diet containing at least 200 g of carbohydrates per day and to refrain from strenuous physical activity. Testing was per-

Table 1 Characteristics of subjects

Subject	Gender	Age (years)	Injury duration (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Injury level	Smoking	FPG (mg/dl)
S1	M	30	8	165	56	20.6	C5	N	81
S2	M	40	3	185	113.7	33.2	C5	N	99
S3	M	53	40	158	74.2	29.7	T6	N	77
S4	M	50	30	157	77.9	31.6	T4	N	87
S5	M	42	10	186	115	33.2	C6	N	88
S6	F	49	34	165.1	74.5	27.3	T10	N	81
S7	F	50	18	166	76.1	27.6	T8	N	79

LOI = location of injury, DOI = duration of injury, BMI = body mass index, FPG = fasting plasma glucose

formed after a 12-h overnight fast at the Department of Clinical Investigations, University of Alberta Hospital. One intravenous polyethylene catheter was inserted into the antecubital vein to collect blood samples. Normal saline was used to keep veins from clotting. One baseline blood sample was drawn from the subjects. After collection of the baseline sample, subjects were asked to drink 76 g of glucose in an orange flavoured drink over a 5-min period. After drinking 75 g of glucose, blood samples were drawn at 30, 60, 90 and 120 min. All samples were collected in red top testing tubes and centrifuged within 30 min after the collection of the sample. Serums were transferred to polyethylene containers and kept at -70°C until analyzed.

Hyperglycaemic clamp test^{44,45}

The hyperglycaemic clamp test was used in this study for the following reason. The hyperglycaemic clamp technique can measure beta-cell sensitivity to glucose as well as the amount of glucose metabolised by the body following a controlled hyperglycaemic stimulus. People with SCI have higher risk of developing Type 2 DM but we did not know whether they have lower insulin secretion capacity or peripheral tissue insulin resistance. Therefore, we utilised the hyperglycaemic clamp test, which can measure both insulin secretion and insulin sensitivity. Three days (72 h) prior to the test, each subject was asked to consume a weight-maintaining diet containing at least 200 g of carbohydrate per day and to refrain from strenuous physical activity. All tests were performed in the morning after a 12-h overnight fast at the Department of Clinical Investigations, University of Alberta Hospital. The test required the insertion of two intravenous lines. One intravenous polyethylene catheter was inserted in the antecubital vein of the left arm for the infusion of 20% dextrose in water. A second polyethylene catheter was inserted into the right hand, wrist vein or antecubital vein for obtaining blood samples. Both arms were kept warm with an electrical heating pad to allow sufficient arterial-venous shunting to 'arterialise' the venous blood.

Three blood samples were collected at 30, 20 and 10 min prior to glucose infusion to measure basal glucose and insulin levels. When a fasting basal level was established, the clock was set to zero and the glucose infusion commenced to obtain target glucose level. Target glucose level was calculated by adding 98 mg/dl to basal glucose level. The goal of the hyperglycaemic clamp was to raise the blood glucose concentration to a fixed hyperglycaemic plateau and maintain it for 120 min. This goal was accomplished by intravenous glucose infusion consisting of two phases: (1) a 10-min 'priming dose' for raising glucose concentrations in plasma and extravascular glucose compartments to the desired plateau, and (2) a 'maintenance dose' that was computed at 5-min intervals throughout the test. The priming dose was

calculated based on body surface area. After the priming dose, the computation for the periodic adjustments in the glucose infusion was made every 5 min and was based on a negative feedback principle. Blood samples were collected at 2, 4, 6, 8 and 10 min to measure glucose and insulin levels. After 10 min, blood samples were taken every 5 min for glucose measurements and every 10 min for insulin measurements for the duration of the protocol (120 min).

Analytic procedure

Tubes containing blood were centrifuged (2000 rpm, 15 min) to separate serum and plasma. Plasma glucose was measured on site using a glucose analyzer (Glucose Analyzer II, Beckman Instruments, Irvine, CA, USA). Serum was stored at -70°C for insulin analysis. Insulin was analyzed using radioimmunoassay with Coat-A-Count kits (Diagnostic Products, Los Angeles, CA, USA).

Study design

Two-hour OGTTs were performed on five male and two female subjects and hyperglycaemic clamps were performed on three male subjects. Pre-training OGTT and hyperglycaemic clamp tests were performed before any exercise training. Post-training OGTT and hyperglycaemic clamp tests were performed 48 and 72 h, respectively, after the last bout of exercise training.

Statistical analysis

The nonparametric Friedman Test for paired data was used to determine statistical significance at $P < 0.05$ (two-tailed testing). The data are presented as mean $\pm$ standard error of the mean (SEM).

Figure 1 Glucose response to 2-h OGTT

Results

Training

At the beginning of the programme, no subject was able to complete 30 min of continuous exercise at the inherent resistance in the ergometer alone. After 8 weeks of training with ES-assisted cycling, four out of

seven subjects were exercising at 9.15 ± 3.52 Watts. Three subjects did not complete 10 min of continuous cycling until the end of the 8 weeks of training. Mean PO after 8 weeks of training was 5.2 ± 2.0 Watts. The mean total work output during the last week of the study was 28.08 kJ (kJ = watts $\times$ time (s)/1000).

Two-hour oral glucose tolerance test

The 2-h glucose levels significantly decreased after 8 weeks of training (pre-training: 140 ± 16 vs post-training 122.4 ± 10 mg/dl, $P=0.014$) in all seven subjects. The 2-h insulin levels also decreased after 8 weeks of training but it did not reach statistical significance (pre-training: 118.4 ± 42.6 ; post training: 87.5 ± 10 μ U/ml). The result of 2-h OGTT is presented in Figures 1 and 2.

Hyperglycaemic clamp test

The hyperglycaemic clamp tests were attempted on seven subjects for pre-training insulin sensitivity measurement. However, hyperglycaemic clamp tests were successfully performed only on three subjects for

Figure 2 Pre-training diagnosis of DM and IGT. DM=2h glucose value higher than 200 mg/dl, IGT=2 h glucose value higher than 140 and lower than 200 mg/dl, Normal=2 h glucose value lower than 140 mg/dl

Figure 3 Pre- and post-training insulin sensitivity measure by hyperglycaemic clamp tests on subject #2, #3 and #4 ($\square$ = pre-training; $\blacksquare$ = post-training)

Figure 4 Pre- and post-training 90–120 min glucose utilisation during hyperglycaemic clamp test on subject #2, #3 and #4 ($\square$ = pre-training; $\blacksquare$ = post-training)

both pre-training and post-training due to technical problems (blood collections and computer software problem). Therefore, the results of the hyperglycaemic clamps are presented for each individual case. Plasma glucose levels were not different between pre and post training hyperglycaemic clamps. Coefficients variation for plasma glucose levels during hyperglycaemic clamps were $4.54 \pm 1.99\%$ for pre-training and $4.76 \pm 2.03\%$ for post-training. The result of the hyperglycaemic clamp test is presented in Table 2 and Figures 3 and 4.

Subject 2 The glucose utilisation during the last 30 min (90–120 min) of the hyperglycaemic clamp test increased from pre-training (4.78 ± 0.75 mg glucose/kg/min) to post-training (6.28 ± 1.04 mg glucose/kg/min) after 8 weeks of ES-assisted cycling. However, there was no change in insulin sensitivity between pre-training (4.69 mg glucose/kg/min per $\mu\text{U/ml}$ of insulin) and post-training (4.61 mg glucose/kg/min per $\mu\text{U/ml}$ of insulin). The early phase (0–19 min) and late phase (20–120 min) incremental area under the insulin curve increased from 368.7 to 495 $\mu\text{U/ml}$ and 2114.5 to 3500.4 $\mu\text{U/ml}$ after training, respectively.

Subject 3 The glucose utilisation during the last 30 min (90–120 min) of the hyperglycaemic clamp test increased from pre-training (7.2 ± 2 mg glucose/kg/min) to post-training (12.52 ± 2.47 mg glucose/kg/min) after completing 8 weeks of ES-assisted cycling (Figure 4). Insulin sensitivity also improved after the training from pre-training (11.45 mg glucose/kg/min per $\mu\text{U/ml}$ of insulin) to post-training (16.58 mg glucose/kg/min per $\mu\text{U/ml}$ of insulin). The early and late phase incremental area under the insulin curve increased from -2.23 to 58.73 $\mu\text{U/ml}$ and 1119 to 1322 $\mu\text{U/ml}$ respectively.

Subject 4 The glucose utilisation during the last 30 min of the hyperglycaemic clamp test increased from pre-training (5.14 ± 7.3 mg glucose/kg/min) to post-training (5.4 ± 1.04 mg glucose/kg/min) after completing 8 weeks of training with ES-assisted cycling. The insulin sensitivity also improved after training from pre-training (6.77 mg glucose/kg/min per $\mu\text{U/ml}$ of insulin) to post-training (10.43 mg glucose/kg/min per $\mu\text{U/ml}$ of insulin). The early phase incremental area under the insulin curve increased from 130.23 to 75.5 $\mu\text{U/ml}$ and the late phase serum incremental area

under the curve decreased from 1405 to 897 $\mu\text{U/ml}$ after the training.

Discussion

In the present study, the effect of 8 weeks of ES-assisted cycling on glucose tolerance and insulin sensitivity in people with SCI was investigated. Results indicated that training with ES-assisted cycling significantly improved glucose tolerance in all seven individuals. Insulin sensitivity improved in two of three subjects tested during a hyperglycaemic clamp test. The OGTT results indicated that glucose level 2 h after intake of 75 g of glucose decreased by 15.3% after 8 weeks of training compared to pre-training level (pre-training: 140 ± 16 vs post-training: 122.4 ± 10 mg/dl, $P=0.014$). Among seven participants, four had IGT and one had DM before the exercise training. After 8 weeks of training with ES-assisted cycling, three participants who had IGT became normal and one with DM before normal based on the results from 2-h OGTT. Diagnosis of DM and IGT was made based on the recommendation of 'The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus'.⁴⁶ According to the insulin secretion during hyperglycaemic clamps, subjects in our study did not show normal beta cell sensitivity. Results from hyperglycaemic clamp tests indicated that glucose utilisation improved in all subjects ($n=3$) and insulin sensitivity improved in two of three subjects after 8 weeks of training. These findings support the hypothesis that training with ES-assisted cycling would improve glucose tolerance. In our knowledge, this study was the first study to measure insulin sensitivity by the hyperglycaemic clamp test in people with SCI.

When combined, the results from the 2-h OGTT and the hyperglycaemic clamp test suggest that exercise with ES-assisted cycling is an effective method to prevent and treat DM in population with SCI. Similar to our results, Hjeltne *et al*⁴³ recently found that ES-assisted cycling increased insulin-mediated glucose disposal by $33 \pm 13\%$.⁴³ They also reported that after 8 weeks of training, basal and insulin stimulated glucose transport activity were increased by 1.6- and 2.1-fold, respectively, compared to pre-training level. The subjects in their study completed seven exercise sessions (30 min/session) per week, more than double the frequency of training compared to the protocol we used in the present study. The training

Table 2 Results of hyperglycaemic clamp test

Subject	Hyperglycaemic clamp test result					
	Insulin sensitivity		Glucose utilisation (90–120 min)		Insulin level (90–120 min)	
	(mg glucose/kg/min/ $\mu\text{U/ml}$ of insulin)		(mg glucose/kg/min)		($\mu\text{U/ml}$)	
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training
S2	4.69	4.61	4.78 ± 0.75	6.28 ± 1.04	102	136.13
S3	11.45	16.58	7.2 ± 2	12.52 ± 2.47	62.88	75.5
S4	6.7	10.43	5.14 ± 7.3	5.4 ± 1.04	75.88	51.8

frequency from the study of Hjeltne *et al*⁴³ was rather unrealistic since many people with SCI are unable to exercise seven times per week. However, our data suggested that exercising with ES-assisted cycling only three times per week could also have beneficial effects on glucose metabolism in people with SCI.

The mechanism for the improved insulin sensitivity and glucose utilisation in the present study was not clear. However, we may speculate on possible mechanisms for improvement in glucose tolerance and insulin sensitivity from an understanding of muscular changes after the SCI and training. Following SCI, skeletal muscles below the level of an upper motor neuron lesion undergo marked changes in morphological,^{14,15} metabolic⁴³ and contractile properties.³⁸ Significant changes in skeletal muscle of people with SCI include a pronounced reduction in the proportion of Type I and Type IIa fibres,^{36,37} reduced capillary density,⁴⁷ GLUT-4^{47,48} contents and an increment in the proportion of Type IIb fibres.^{35,36} Interestingly, muscle fibre Type proportion, capillarisation, and GLUT-4 content appear to be correlated with insulin sensitivity.⁴⁹ This was demonstrated by Lillioja who compared the capillary density and muscle fibre type in the vastus lateralis with in-vivo insulin sensitivity determined by the euglycaemic clamp.⁴⁹ They found that insulin sensitivity was positively correlated with per cent Type I fibres ($r=0.29$) as well as capillary density ($r=0.63$) and negatively correlated with per cent Type IIb fibres ($r=-0.38$). Therefore, it is suggested that muscular changes after paralysis could be one cause of insulin resistance in this population.

ES-assisted cycling reverses these changes in muscle characteristics.^{36–38,43,47} Twelve months of training showed that fibres containing myosin heavy chain (MHC) 2b were reduced to 2.3% (37.2% before training), fibres containing both MHC 2a and 2b decreased to 4.6% (40.7% before training), while fibres containing only MHC 2a increased to 91.2% (21.2% before training).³⁶ In another study, 8 weeks of training (seven sessions/week, 30 min/session) increase Type I fibres ($5 \pm 2\%$ vs $2 \pm 1\%$) and Type 2a ($55 \pm 8\%$ vs $35 \pm 7\%$) and decreased Type 2b fibres ($39 \pm 5\%$ vs $64 \pm 8\%$) in quadriplegic subjects.⁴³ Research in our facility with people with SCI and 8 weeks of training (three times/week, 30 min/time) showed 72% increases in GLUT-4 content, and 52% increases in GLUT-1 content.⁴⁷ These results are lower than those found in Hjeltne *et al*⁴³ who showed 378% increases in GLUT-4 content in people with SCI. The difference between studies has been associated with training frequency (3 days/week vs 7 days/week, respectively). Research in our facility has also shown that 8 weeks of training (three times/week, 30 min/time) increased fibre area and capillary number by 23 and 39%, respectively.³⁸ Increased capillarisation may result in increased delivery of insulin to muscle, which would increase glucose tolerance. One can therefore speculate that changes in muscle characteristics after the ES-assisted

training may have improved insulin sensitivity in the present study.

Exercise training

The maximum resistance attained by the subjects with ES-assisted cycling was 2/8 kp (12.2 W) and the average exercise resistance attained was 0.86/8 kp in the present study. Throughout the training, a large variability in exercise capacity among subjects was observed. Three subjects could not pedal for more than 5 min and were provided assistance during their three 10-min intervals. In contrast, four subjects were able to complete 30 min of continuous exercise within the first 3 weeks of training with ES-assisted cycling and began to add resistance. The average resistance attained by these four subjects was $1.54/8 \pm 0.59$ kp. This result is consistent with Mohr *et al* who reported that eight out of 10 subjects pedalled the ERGYS continuously for 30 min with the first 3 weeks of training.³⁶ Although our findings are in concert with Mohr *et al*³⁶ there exists a great deal of variability among subjects with respect to pedalling ability.

In the present study, exercise PO with ES-assisted cycling was significantly lower than reported cycling PO in the able bodied subjects. Kjaer *et al* compared metabolic response in people with SCI exercising with ES-assisted cycling and able-bodied controls exercising on a cycle ergometer at the same power output and same oxygen consumption.⁴² Results showed that when groups were compared at equal oxygen consumption, the resistance of the cycle ergometer in the control group was four times higher than the resistance attained on the ES-assisted cycle ergometer in the SCI group. Moreover, when groups were compared at the same PO, the metabolic rate in controls was significantly lower than SCI group. In another study, steady-state physiologic responses of 12 subjects with SCI during exercise with ES-assisted cycling were compared to six able-bodied individuals performing voluntary leg cycle ergometry at equal PO.⁵⁰ Results showed that ES-assisted cycling elicited significantly higher oxygen consumption, ventilation and heart rate responses from the SCI group compared to controls. Authors attributed these differences to the inefficiency of exercise with ES-assisted cycling due to the lack of voluntary physiological activation of the paralysed muscles, the deteriorated condition of these muscles, and the inappropriate biomechanics for the movements.⁵⁰ Although low efficiency is not recommended to improve performance in skilled activities, it can be beneficial to increase metabolic rate and improve fitness in people with SCI.

In the present study, PO achieved by ES-assisted cycling appears low, but it represented an exercise intensity of approximately 55% of the $\text{VO}_{2\text{max}}$ achieved by arm crank ergometry. The subject's absolute $\text{VO}_{2\text{max}}$ determined during arm crank exercise was 1.46 ± 1.19 L/min and the peak oxygen consump-

tion determined during ES-assisted cycling exercise was 0.8 ± 0.34 L/min.⁵¹ Interestingly, Braun *et al* demonstrated that low intensity exercise (50% of $\text{VO}_{2\text{max}}$) over a longer duration improved insulin sensitivity to a level similar to high intensity exercise (75% of $\text{VO}_{2\text{max}}$) over a shorter duration in able bodied subjects.²⁹ One recent study also reported that habitual, nonvigorous physical activity improved insulin sensitivity as well as vigorous physical activity.²⁵ Therefore, the intensity of the exercise in the present study was sufficient to improve glucose tolerance and insulin sensitivity in the subjects.

In summary, we demonstrated that 8 weeks of ES-assisted cycling training improved glucose tolerance and might have improved insulin sensitivity. The mechanism for improved glucose tolerance and insulin sensitivity was not established in this study. However, improvements are most likely attributed to changes in muscle characteristics as a result of increased muscular activity of the paralysed muscle. We conclude that regular exercise with ES-assisted cycling may be a useful tool for the prevention and treatment of IGT or DM in people with SCI.

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