Diabetes & Metabolism 45 (2019) 268–275

Available online at ScienceDirect www.sciencedirect.com

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Original article

Effect of liraglutide on physical performance in type 2 diabetes: Results of a randomized, double-blind, controlled trial (LIPER2)

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ARTICLE INFO

Article history:
Received 13 February 2018
Received in revised form 31 July 2018
Accepted 23 August 2018
Available online 14 September 2018

Keywords:
Diabetes
Ergometry
GLP-1 agonist
Maximum oxygen consumption
Randomized controlled trial
Ventricular function

ABSTRACT

Aims. – To assess the effect of the GLP-1 analogue liraglutide on measures of cardiac function and physical performance in patients with type 2 diabetes (T2D).
Methods. – In this phase-IV randomized double-blind placebo-controlled parallel-group clinical trial at a tertiary hospital, T2D patients with HbA_{1c} levels of 7–10% with oral agents and/or intermediate-/long-acting insulin were allocated (computer-generated randomization, ratio 1:1) to either liraglutide 1.8 mg/day or a placebo for 6 months. The primary endpoint was maximum oxygen consumption (VO_{2max}) during cycle ergometry, while other procedures included a 6-min walk test, echocardiography, anthropometry and blood tests. Safety endpoints were also monitored, and an intention-to-treat analysis was performed.
Results. – A total of 24 patients (15 women) aged 52 (11.7) years, with diabetes duration of 8.7 (5.8) years, BMI 34.98 (6.2) kg/m^2 and HbA_{1c} 8.2% (0.68%), were randomized to liraglutide 1.8 mg daily or placebo. There were no differences in VO_{2max} [17.98 (4.8) vs. 15.90 (4.96) mL/kg/min; $P > 0.10$], VE/VCO_2 slope [30.18 (4.8) vs. 32 (4.49)], left ventricular ejection fraction or 6-min walk test [530.7 (86) vs. 503.9 (84) m] at 6 months. HbA_{1c} was lower (6.7% vs. 7.7%; $P = 0.005$), with a trend towards lower maximum systolic blood pressure during ergometry [171.7 (24.4) vs. 192.5 (25.6); $P = 0.052$] in the liraglutide group at the end of the study. There were no severe adverse events.
Conclusion. – In this trial, liraglutide improved glycaemic control in T2D, but had no significant effects on either physical performance or myocardial function.

Introduction

Glucagon-like peptide (GLP)-1 analogues are approved for the treatment of type 2 diabetes (T2D) and obesity based on their glucose- and weight-lowering effects. Known cardiovascular effects include reduced blood pressure [1–3] and increased pulse rates [2–4], while large clinical trials have been performed to assess their effect on cardiovascular events in patients with T2D [5–8]; a recent meta-analysis concluded that they decrease cardiovascular mortality by 13% [9].

Abbreviations: GLP-1, glucagon-like peptide-1; LIPER2, (effect of) liraglutide on physical performance in type 2 diabetes; ITT, intention to treat; PP, per-protocol; VO_{2max}, maximum oxygen consumption; SBP, systolic blood pressure; DBP, diastolic blood pressure; RER, respiratory exchange ratio; VE/VO_{2max}, ventilatory equivalent for oxygen at maximum oxygen consumption; VE/VCO2AT, ventilatory equivalent for carbon dioxide at the anaerobic threshold.

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https://doi.org/10.1016/j.diabet.2018.08.010
1262-3636/

However, few studies specifically assessing GLP-1 effects on physical performance and measures of myocardial function are available. At the time the present study was designed, clinical trials were scarce and their results controversial. An early non-randomized pilot study showed improved left ventricular function when GLP-1 was infused in patients with acute myocardial infarction and heart failure [10]. A small open-label randomized study showed that perioperative GLP-1 infusion during coronary bypass surgery led to a non-significant reduced need for inotropic drugs [11]. Two small randomized controlled trials showed the positive effects of acute GLP-1 infusions in patients with ischaemic heart disease [12,13] whereas, in a larger trial, administration of exenatide had no impact on left ventricular ejection fraction (LVEF) or infarct size [14].

To our knowledge, no trial has previously assessed the effect of GLP-1 analogues on physical performance. However, it would be reasonable to expect such an impact, given their effect on weight loss and potential consequences on ventricular function. Thus, the aim of our trial was to assess the effect of liraglutide, a GLP-1 receptor agonist, on clinically relevant measures of physical performance and myocardial function in patients with T2D.

Subjects and methods

Trial design and oversight

This study of the Effect of Liraglutide on Physical Performance in Type 2 Diabetes (LIPER2) was a single-centre randomized double-blind, placebo-controlled, parallel-group, phase-IV trial to assess the effect of liraglutide on physical performance and myocardial function. The LIPER2 design has been described elsewhere [15] and registered (www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005197-63). Participants with T2D were randomized in a 1:1 ratio to receive either 1.8 mg liraglutide (Victoza®, Novo Nordisk) or placebo daily for 6 months.

The study was approved by the Ethics Committee of the Complejo Hospitalario Universitario Insular Materno-Infantil in Las Palmas, Spain, and by the Spanish Agency of Medicine and Sanitary Products (AEMPS). Before inclusion, patients received oral and written information and signed an informed consent document. Data accuracy and compliance with the study protocol, Good Clinical Practice International Guidelines and national regulations were assessed by qualified external staff employed by CRAnarias SL, Las Palmas de Gran Canaria, Spain.

The LIPER2 trial was approved and funded by Novo Nordisk (Bagsvaerd, Denmark). The investigators designed and conducted the study, performed all study analyses, wrote the report and are responsible for its contents; Novo Nordisk had no role in the collection, analysis, interpretation, writing or publication of these data. The principal investigator had full access to all data, and bears the final responsibility for the decision to submit this paper for publication.

Patients

Patients with T2D were identified at outpatient clinics of the Endocrinology Department and at primary-care centres in the area, and invited to participate. Inclusion and exclusion criteria have been described elsewhere [15]. Briefly, the study recruited T2D patients treated with oral agents (including metformin if tolerated and not contraindicated) or a maximum of two intermediate- or long-acting insulin injections per day, or a combination of both, and with HbA_{1c} levels between 7% and 10%. The main exclusion criteria were severe renal, cardiac or hepatic failure, existing or planned pregnancy, breastfeeding, inadequate contraception, and intolerance, allergy or contraindications to liraglutide treatment (for example, a history of pancreatitis). Patients were also excluded if they had been treated with GLP-1 agonists or dipeptidyl peptidase (DPP)-4 inhibitors in the 3 months before screening (to avoid potential overlap of mechanisms of action), or if they had exercise-induced myocardial ischaemia, planned revascularizations or were not able to perform cycle ergometry.

Procedures

Patients were assessed at a screening visit after giving their informed consent. If they fulfilled all of the inclusion criteria and none of the exclusion criteria, a baseline visit was scheduled within a month and participants were randomized into treatment groups. Participants were again assessed at 3 months (for safety) and at 6 months after treatment initiation. Additional telephone contact was used to evaluate treatment tolerability and the need for concomitant treatment adjustments within 2 weeks of starting the study treatment. In patients with $HbA_{1c} > 8\%$ at the 3-month visit, insulin could be started or adjusted as deemed appropriate. Concomitant oral agents could be reduced in cases of hypoglycaemia.

Outcomes

The primary endpoint was physical fitness or performance as defined by maximum oxygen consumption (VO_{2max}), using BreezeSuite 6.4 software (MGC Diagnostics Corporation, St Paul, MN, USA), during a cycle ergometer test (ergoselect, ergoline GmbH, Bitz, Germany) performed at the end of the study. An incremental protocol was used: the first 3 min were without resistance, but thereafter increased by 10–20 W/min. Total duration of the test rarely exceeded 10–12 min. Ergometry and VO_{2max} measurements were performed according to international guidelines at our Rehabilitation and Physical Medicine Department at baseline and at the end of the study, as previously described [15]. Maximum exertion ergometry [heart rate > 85% of theoretical maximum, respiratory exchange ratio (RER) > 1.10] was the goal, and participants were encouraged to perform their very best.

Secondary endpoints involved other fitness-related variables recorded during ergometry, a 6-min walk test and transthoracic echocardiograpy [15]. The ventilatory equivalent for oxygen at maximum oxygen consumption (VE/VCO_2) slope, a marker of ventilatory efficiency, was added to the initial list of secondary endpoints to conform with recent guidelines [16], and was possible for 23 participants at baseline and 20 subjects during follow-up. Glycaemic control was assessed using HbA_{1c} levels as measured by high-performance liquid chromatography (HPLC), using an National Glycohemoglobin Standardization Program (NGSP)/Diabetes Control and Complications Trial (DCCT)-based standard, and by examining patients' glucose registries. Hypoglycaemic episodes, daily insulin doses and other concomitant medications were also registered. All laboratory measurements were performed at our hospital biochemistry department. Quality of life was assessed by a standardized questionnaire of health status [EQ-5D-5L, Spain (Spanish) v.2© 2009, EuroQoL Foundation, Rotterdam, The Netherlands], while spontaneous physical activity was recorded using a wearable Holter device (SenseWear® Pro, BodyMedia, Pittsburgh, PA, USA) for 3 days. The most complete record (usually on the second day) was employed for assessment.

Both primary and secondary endpoints were assessed at baseline and at the end of the study (at 6 months) except for those related to glucose control, which were also evaluated at an additional 3-month visit.

Safety endpoints included standardized reports of adverse events (AEs), blood counts, liver and kidney function, electrolytes, lipase, amylase, cancer antigen (CA) 19-9 blood tests and calcitonin. A general physical examination was performed at baseline and at the end of the study. A pregnancy test was performed in all women of childbearing potential before randomization and during follow-up. In addition, at the end of the study, endoscopic ultrasound was offered to patients to assess pancreatic architecture, with a separate standard consent form provided and signed before this examination.

Statistical analysis

At the final external monitoring on completing the study, the treatment assignment list was opened by an individual external to the study, thereby allowing the two treatment groups to be separated for blinded analyses by study investigators. These were performed on an intention-to-treat (ITT) and per-protocol (PP) basis, as described in the statistical plan [15]. For the ITT analysis, all randomized subjects were included, regardless of whether or not they had completed the study or taken the medication throughout the study; if a variable was missing at follow-up, the last available observation was carried forward. For the PP analysis, only the results of patients who had taken all of the treatment medication and completed the study were analyzed, with no adjustments made for missing variables.

Comparisons between the intervention and placebo groups were performed using chi-squared (qualitative data), Student's *t* (quantitative data, Gaussian distribution) and Mann–Whitney U (quantitative, non-Gaussian) tests. Paired analyses were also performed to compare the beginning and end of treatment in each group (Student's *t* and Wilcoxon's test). A bilateral $P < 0.05$ was considered significant.

Sample size calculation in the statistical protocol has been described elsewhere [15]. Briefly, it was estimated that including 15 patients per group would enable detection of a between-group difference of 5 mL/kg * min in VO_{2max} with 98% power and a bilateral alpha of 5%, which was within the lower range of effect reported in older men participating in training programmes [17]. This meant that even in the event of an unexpectedly high dropout rate of 25%, the power to detect this difference between groups would still be 90%.

Results

The present trial was carried out between June 2013 and August 2016. Patient recruitment took longer than expected especially because of the frequent use of DPP-4 inhibitors. In addition, the study was extended for as long as the expiry date of the second lot of study treatment allowed. A total of 35 participants were screened, but 24 were randomized and 23 completed the study (Fig. 1). After screening, three participants withdrew their consent, four were excluded because of $HbA_{1c} > 10\%$ at the baseline visit, two due to $HbA_{1c} < 7\%$, one because of a history of pancreatitis and another because of knee osteoarthritis precluding cycle ergometry. Of the 24 randomized patients, one stopped taking the study drug (placebo) a few weeks into the study because of fears of pancreatic cancer, one interrupted the treatment (liraglutide) 12 weeks into the study due to persistent side-effects despite dose reduction and one was lost to follow-up after the baseline visit (placebo group)

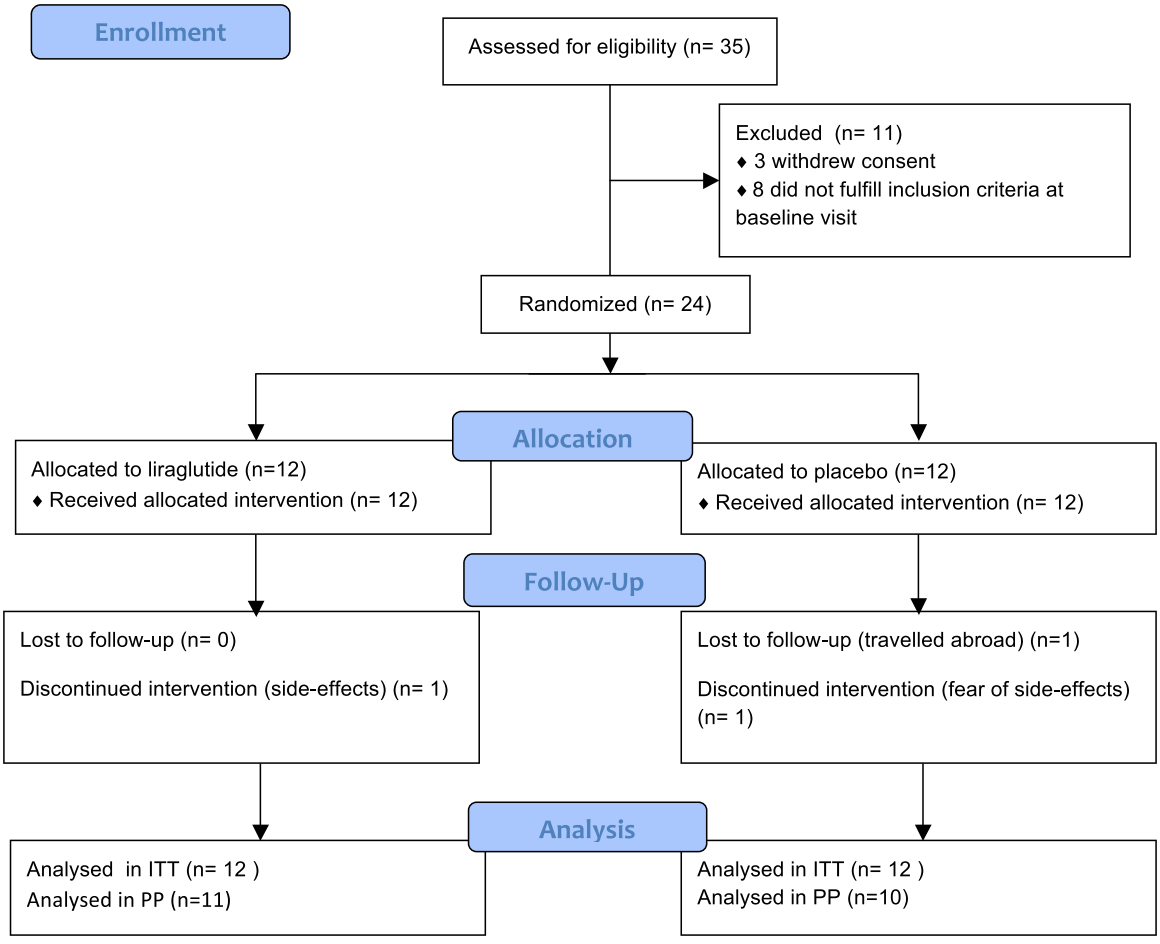

Fig. 1. Flow diagram of trial participant selection.

because of travel. Of the 21 patients taking the study drug at the end of the study, all but one were taking the full dose (1.8 mg/day) of liraglutide (or placebo).

One patient, who was taking statin treatment at the baseline visit, had her lipid profile and apolipoprotein B concentrations at the 6-month visit discarded and replaced by her baseline values. Another patient had C-reactive protein (CRP) values > 5, which were attributed to acute infection/inflammation and therefore not included in our analysis. A further patient (with a known diagnosis of proliferative retinopathy), who could not perform the final ergometry test due to active vitreous haemorrhage, had the missing result replaced by baseline values for the ITT analysis.

Baseline features

Of the 24 randomized participants, 15 (62.5%) were women with a mean [standard deviation (SD)] age of 52.8 (11.7) years, duration of diagnosed diabetes of 8.7 (5.8; range: 0–20) years, body mass index (BMI) of 34.98 (6.2) kg/m^2, waist circumference of 112.1 (11.6) cm and HbA_{1c} of 8.2% (0.68; range: 7.2–9.6%). All were treated with metformin: six with sulphonylurea (SU); five with insulin; three with both insulin and SU; and two with insulin and repaglinide. No differences were found between treatment groups in gender distribution, age or diabetes duration (Table 1).

Primary endpoint

No significant differences were found in values of maximum oxygen consumption (Table 2).

Secondary endpoints

There were no statistically significant differences at baseline or at the end of the study for other ergometry-related variables, although maximum systolic blood pressure tended to be lower after treatment with liraglutide (Table 2). The increment in VO_{2max} was calculated by subtracting the initial value from that obtained at the end of the study and then comparing values between treatment groups. Increments of 0.167 (1.80) mL/kg/min and 1.008 (1.92) mL/kg/min were seen in the placebo and liraglutide groups, respectively (P = 0.20).

In addition, there were no significant differences between groups at baseline or during follow-up in O_2 saturation measurements (resting, final, minimum; data not shown), heart rate (resting, 6-min, average), metres (m) walked (Table 2), blood pressure or perceived exertion (Borg scale; data not shown). Increments of distance walked were calculated and compared in the placebo and liraglutide groups, but no significant differences were found [22.2 (37.0) m and 25.9 (34.1) m, respectively; P = 0.80]. Neither were significant differences found at either baseline or at the end of the study in estimated total calorie expenditures, numbers of steps, physical activity times, sleep duration or metabolic equivalents (METs)/24 h (data not shown).

Table 1
Baseline features of the 24 randomized study participants.

	Placebo	Liraglutide
Age [years (SD)]	52.6 (13.8)	53.2 (9.7)
Gender (women, *n*)	8	7
Diabetes duration [years (SD)]	7.42 (4.1)	10.0 (7.2)
Retinopathy (*n*)	1	2
Coronary artery disease (*n*)	0	2
Transient ischaemic attack (*n*)	0	1
Diabetes treatment (*n*)		
Metformin	12	12
Sulphonylurea	5	5
Repaglinide	2	0
Insulin	7	3
Hypertension (*n*)	7	8
Dyslipidaemia (*n*)	5	6
Current smoking (*n*)	2	3
Other treatments		
Aspirin	7	7
Renin–angiotensin axis inhibitor	8	10
Statin	6	7

Overall, participants had normal LVEF values at entry [0.63 (0.06)], whereas 33%, 17% and 21% of participants had mild, moderate and severe ventricular hypertrophy, respectively. Regarding diastolic function, 62.5% showed grade 1 and 16.6% grade 2 dysfunction, whereas 20.8% displayed normal function [18]. No significant differences were noted between treatment groups in LVEF, ventricular mass or measures of diastolic function at baseline or at the end of the treatment period (Table 3). Paired analyses showed no differences between baseline and 6-month values (Table 3), nor were there any differences when comparing between-group differences (Table S1; see supplementary data associated with this article online).

Both fasting glucose and HbA_{1c} were significantly lower in the liraglutide group at both 3 and 6 months, although paired analyses revealed that HbA_{1c} improved significantly in both treatment groups (Table 4). Three patients initiated new insulin treatments due to persistent hyperglycaemia (two in the placebo group, one in the liraglutide group); in one further patient (in the placebo group), insulin dose was increased whereas, in six patients (one taking placebo, five taking liraglutide), their insulin or SU doses were decreased. However, no significant differences were observed between groups in average insulin doses at baseline or at the end of the study.

Regarding anthropometric and other laboratory results (Table 5), there were already differences between treatment groups in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides and CRP at baseline. However, paired analyses showed no significant differences in any of these variables between baseline and end of the study. In addition, no significant differences were found at either baseline [76.3 (17.9) vs. 74.3 (14.7) points] or end of the study [85.3 (13.5) vs. 76.7 (16.8) points] between placebo and liraglutide groups in global visual analogue scale scores of the EQ-5D-5L health questionnaire or any of the subscales (data not shown). Paired analyses also showed no significant changes in any study group either.

Per-protocol analysis

When only patients who completed the study treatment throughout the study were analyzed with no imputations performed for missing data, the study sample size was reduced to 21 (20 for ergometry). Repeat analyses arrived at similar conclusions, except that the VO_{2max} tended to be higher (P = 0.084) while the ventilatory equivalent for carbon dioxide at the anaerobic threshold (VE/VCO_{2AT}) was significantly lower in the liraglutide group at the end of the study (P = 0.048).

Safety analysis

No serious AEs or side-effects were reported or identified during the study (Table S2; see supplementary data associated with this article online). However, all patients in the liraglutide group reported some form of gastrointestinal symptom, although most were self-limiting and described as mild in 50% (six patients). In the titration phase during the first month, two patients increased their doses more slowly than initially planned (weekly). At 3 months, all but one of our participants—a patient who had side-effects (gastrointestinal symptoms, abnormal liver tests) with

Table 2
Ergometry and 6-min walk test results at baseline and at 6 months (end of study) for participants treated with placebo and with liraglutide.

	Baseline	*P* (vs. placebo)	End of study	P (vs. placebo)	*P* (vs. baseline)
Ergometry					
VO_{2max} (mL/kg/min)					
Placebo	15.88 (4.91)		15.90 (4.96)		0.93
Liraglutide	16.96 (4.32)	0.41	17.98 (4.8)	0.31	0.095
Theoretical VO_{2max} (%)					
Placebo	76.7 (11.7)		78.2 (11.3)		0.66
Liraglutide	80.9 (12.9)	0.42	83.3 (17.7)	0.43	0.51
Duration of cycle ergometry (s)					
Placebo	691 (180)		702 (178)		0.63
Liraglutide	728 (206)	0.64	739 (214)	0.71	0.44
VCO_{2AT} (mL/kg/min)					
Placebo	9.8 (3.1)		9.6 (3.2)		0.29
Liraglutide	10.0 (2.2)	0.41	10.0 (2.1)	0.61	0.97
Maximum heart rate (bpm)					
Placebo	140.6 (20.5)		145.2 (17.5)		0.25
Liraglutide	139.3 (23.5)	0.89	141.9 (22.2)	1.00	0.59
Maximum heart rate (%)					
Placebo	83.8 (8.3)		86.8 (7.4)		0.22
Liraglutide	83.3 (11.5)	0.92	85.4 (14.5)	0.77	0.47
Resting systolic blood pressure (mmHg)					
Placebo	135.8 (20.8)		127.1 (12.6)		0.12
Liraglutide	130.7 (10.1)	0.54	125.5 (17.4)	0.80	0.34
Resting diastolic blood pressure (mmHg)					
Placebo	80.0 (12.0)		77.5 (12.2)		0.53
Liraglutide	78.2 (8.7)	0.69	74.1 (8.3)	0.69	0.20
Maximum systolic blood pressure (mmHg)					
Placebo	187.5 (32.2)		192.5 (25.6)		0.87
Liraglutide	179.6 (27.3)	0.52	171.7 (24.4)	0.045	0.18
Maximum diastolic blood pressure (mmHg)					
Placebo	86.7 (12.5)		87.9 (12.0)		0.86
Liraglutide	89.6 (13.7)	0.59	82.1 (10.5)	0.22	0.046
Maximum load (W)					
Placebo	101.3 (50.5)		105.0 (52.7)		0.17
Liraglutide	109.2 (47.3)	0.84	108.2 (51.1)	0.74	0.30
RER_{max}					
Placebo	1.22 (0.13)		1.23 (0.13)		0.77
Liraglutide	1.21 (0.13)	0.88	1.30 (0.12)	0.17	0.054
VE/VO_{2max}					
Placebo	36.9 (5.3)		39.8 (8.2)		0.14
Liraglutide	37.0 (5.4)	0.97	40.0 (7.9)	0.96	0.27
VE/VCO_2 slope					
Placebo	29.9 (8.2)		32.0 (4.5)		0.31
Liraglutide	29.8 (3.3)	0.35	30.2 (4.8)	0.36	0.81
VE/VCO_{2AT}					
Placebo	30.9 (4.7)		32.1 (4.3)		0.09
Liraglutide	31.3 (3.5)	0.53	29.7 (2.4)	0.13	0.14
Heart rate recovery 1st minute (bpm)					
Placebo	20.8 (10.2)		22.8 (8.5)		0.31
Liraglutide	21.0 (9.5)	0.95	24.4 (10.2)	0.69	0.21
6-min walk test					
Distance walked (m)					
Placebo	481.8 (92)		503.9 (84)		0.06
Liraglutide	504.8 (88)	0.54	530.7 (86)	0.45	0.023
Resting heart rate (bpm)					
Placebo	87.4 (16.5)		86.6 (16.2)		0.82
Liraglutide	78.6 (13.8)	0.17	81.6 (13.4)	0.42	0.20
6-min heart rate (bpm)					
Placebo	117.1 (18.8)		122.8 (19.7)		0.23
Liraglutide	116.9 (19.5)	0.18	121.1 (29.4)	0.87	0.39

Data are expressed as means (standard deviations).
VO_{2max}: maximum oxygen consumption; VCO_{2AT}: carbon dioxide at anaerobic threshold; RER_{max}: maximum respiratory exchange ratio; VE/VO_{2max}: ventilatory equivalent for oxygen at maximum oxygen consumption; VE/VCO_{2AT}: ventilatory equivalent for carbon dioxide at anaerobic threshold.

a dose of 0.6 mg/day, leading to treatment interruption—were taking the full dose of 1.8 mg/day. At 6 months, one patient had his dose reduced to 1.2 mg/day due to unacceptable diarrhoea with the full dose but, otherwise, the rest of the participants completed the trial with 1.8 mg/day. Nausea was the most common symptom, followed by abdominal pain, diarrhoea and vomiting. Three patients (25%) in the liraglutide group reported upper respiratory tract infections (URTIs) or flu, and one complained of headaches.

In the placebo group, three (25%) patients reported gastrointestinal symptoms, although no patient interrupted or reduced the treatment dose due to side-effects. Two patients reported URTIs or flu, and two reported headaches. A total of seven patients taking the placebo reported some form of AE during the study.

Lipase and amylase were higher with liraglutide (Table 4), but no episodes of acute pancreatitis were diagnosed. Also, no differences were seen in CA 19-9 or liver enzymes, nor were there any significant increases in calcitonin in either of our treatment groups.

Table 3
Echocardiographic findings at baseline and at 6 months of treatment (end of study).

	Baseline	*P* (vs. placebo)	End of study	*P* (vs. placebo)	*P* (vs. baseline)
Left ventricular ejection fraction					
Placebo	0.64 (0.05)		0.66 (0.04)		0.32
Liraglutide	0.62 (0.07)	0.30	0.63 (0.06)	0.26	0.46
Left ventricular mass (g)					
Placebo	202 (63)		195 (56)		0.40
Liraglutide	225 (68)	0.27	221 (80)	0.35	0.33
Telediastolic ventricular diameter (mm)					
Placebo	46.7 (7.8)		49.1 (6.9)		0.14
Liraglutide	46.9 (6.4)	0.94	46.0 (6.0)	0.26	0.58
E-wave deceleration time (ms)					
Placebo	227 (39)		207 (55)		0.26
Liraglutide	205 (34)	0.15	194 (37)	0.51	0.27
E/A ratio					
Placebo	0.87 (0.28)		0.94 (0.28)		0.18
Liraglutide	0.94 (0.21)	0.27	0.90 (0.25)	0.66	0.48
Average E/E′ ratio					
Placebo	9.7 (2.6)		10.6 (3.9)		0.58
Liraglutide	8.8 (2.3)	0.49	10.0 (4.1)	0.75	0.19
Left atrial diameter (mm)					
Placebo	39.4 (3.8)		40.7 (5.8)		0.33
Liraglutide	41.8 (5.8)	0.26	40.4 (4.6)	0.93	0.24

Data are expressed as means (standard deviations).
E/A: ratio of early to late ventricular filling velocity; E/E′: ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity.

Endoscopic ultrasound was performed in only five patients (four in the placebo group, one in the liraglutide group). Two had normal findings (one in each group), whereas the other three showed indeterminate (previously unknown) chronic pancreatitis.

Discussion

Our randomized double-blind placebo-controlled clinical trial (LIPER2) assessed the effect of 6-month treatment with liraglutide on measures of physical performance and ventricular function in T2D patients with baseline HbA_{1c} levels of 7–10%. Neither the main outcome—the VO_{2max} at 6 months—nor the increment in VO_{2max} during the study differed significantly between treatment groups.

Several trials assessing ventricular function have been published since the LIPER2 trial began, most using echocardiography (for a review, see Scheen [19]). However, to our knowledge, this is the first-ever study to assess the effect of a GLP-1 analogue on VO_{2max}, the gold standard for assessing cardiovascular fitness. Other strengths of our study include its placebo-controlled randomized design, good patient retention, no concomitant use of DPP-4 inhibitors and wide extent of study procedures, comprising ergometry, echocardiography, 6-min walk test, Holter monitoring for physical activity, health-related quality of life assessment, and large array of clinical and laboratory tests. In the end, other than the expected improvement in glycaemic control, a non-significant 1-mL/kg.min increase in VO_{2max} was noted with liraglutide. In addition, although the number of steps taken during the 6-min walk test increased significantly with liraglutide, the increase did not differ between groups.

Table 4
Glycaemic control and other safety variables at baseline, and at 3 (12 weeks) and 6 months (end of study).

	Baseline	*P* (vs. placebo)	12 weeks	*P* (vs. placebo)	End of study	*P* (vs. placebo)	*P* (vs. baseline)
Fasting glucose (mg/dL)							
Placebo	189.9 (57.5)		181.2 (35.1)		158.2 (27.0)		0.083
Liraglutide	162.8 (26.4)	0.15	131.2 (36.9)	0.001	124.7 (22.0)	0.003	0.008
HbA_{1c} (%)							
Placebo	8.4 (0.79)		8.2 (0.89)		7.7 (0.75)		0.012
Liraglutide	8.0 (0.46)	0.09	6.5 (0.73)	< 0.005	6.7 (0.69)	0.002	< 0.005
Insulin dose (IU/day)							
Placebo	16.4 (25.7)				19.4 (25.5)		0.11
Liraglutide	36.8 (86.0)	0.98			33.8 (84.9)	0.76	0.47
Insulin dose (IU/kg.day)							
Placebo	0.18 (0.28)				0.21 (0.28)		0.063
Liraglutide	0.33 (0.70)	0.93			0.31 (0.68)	0.67	0.5
Patients with hypoglycaemia (*n*)							
Placebo			4		3		
Liraglutide			3	0.67	3	1.0	
C-peptide (ng/mL)							
Placebo	2.71 (0.91)				2.68 (1.02)		0.79
Liraglutide	2.90 (1.00)	0.65			2.90 (2.25)	0.77	0.99
Amylase (U/L)							
Placebo	57.4 (30.6)		58.5 (22.6)		55.5 (20.1)		0.21
Liraglutide	72.1 (33.0)	0.03	82.8 (34.3)	0.03	86.7 (34.0)	0.001	0.005
Lipase (U/L)							
Placebo	36.7 (36.3)		36.7 (22.6)		24.0 (9.4)		0.086
Liraglutide	42.6 (20.0)	0.14	63.1 (32.6)	0.01	58.9 (25.6)	0.001	0.03

Data are expressed as means (standard deviations); to convert glucose to SI units (mmol/L), divide by 18; to convert C-peptide to nmol/L, multiply by 0.333.

Table 5
Anthropometry and other laboratory results.

	Baseline	*P* (vs. placebo)	End of study	*P* (vs. placebo)	*P* (vs. baseline)
Weight (kg)					
Placebo	97.3 (14.8)		95.8 (14.8)		0.029
Liraglutide	93.2 (21.0)	0.59	88.3 (20.1)	0.31	0.001
Body mass index (kg/m^2)					
Placebo	35.89 (5.96)		35.31 (5.68)		0.033
Liraglutide	34.07 (6.56)	0.49	32.25 (6.10)	0.078	0.001
Waist circumference (cm)					
Placebo	114.2 (10.4)		112.5 (10.1)		0.19
Liraglutide	110.1 (12.7)	0.40	107.4 (14.1)	0.32	0.006
Total cholesterol (mg/dL)					
Placebo	196.6 (41.8)		187.8 (35.9)		0.16
Liraglutide	167.7 (27.4)	0.068	173.8 (50.9)	0.44	0.93
LDL cholesterol (mg/dL)					
Placebo	114.8 (28.7)		114.1 (29.0)		0.95
Liraglutide	91.7 (29.3)	0.059	101.6 (47.5)	0.45	0.60
HDL cholesterol (mg/dL)					
Placebo	50.8 (5.9)		49.5 (7.1)		0.25
Liraglutide	38.2 (7.5)	< 0.005	40.9 (8.6)	0.014	0.10
Triglycerides (mg/dL)					
Placebo	156.3 (130.6)		121.2 (75.6)		0.083
Liraglutide	188.3 (55.0)	0.052	184.3 (100.9)	0.028	0.70
Apolipoprotein B (mg/dL)					
Placebo	105.0 (25.1)		96.5 (23.3)		0.12
Liraglutide	95.3 (15.2)	0.27	91.8 (26.5)	0.49	0.54
C-reactive protein (mg/dL)					
Placebo	0.66 (0.30)		0.64 (0.30)		0.57
Liraglutide	0.37 (0.24)	0.036	0.31 (0.29)*	0.017	0.99
NT-proBNP (pg/mL)					
Placebo	38.3 (31.8)		41.3 (37.9)		0.68
Liraglutide	53.7 (43.8)	0.34	43.3 (52.7)	0.77	0.48

Data are expressed as means (standard deviations); to convert cholesterol to mmol/L, multiply by 0.0256; to convert triglyceride to mmol/L, multiply by 0.0113; to convert apolipoprotein B to g/L, multiply by 0.01; to convert C-reactive protein to nmol/L, multiply by 95.24; to convert NT-proBNP (N-terminal pro-brain natriuretic peptide) to pmol/L, multiply by 0.1182.

Several explanations may have led to the non-significant difference in our primary outcome [20]. First, while a truly neutral effect of liraglutide on physical performance is possible, our sample size was certainly an issue, as it was calculated to detect a larger (5 mL/kg.min), perhaps somewhat optimistic, change in VO_{2max}. Indeed, in order to detect a 1-mL/kg.min difference (4.8 SD) with a power of 80% and bilateral alpha of 0.05, a multicentre trial with a sample size of 726 patients would have been necessary. It is also reasonable to assume the possible presence of minor undetected effects (type 2 error), as pointed out by other outcomes. Furthermore, the fact that our participants already had normal LVEFs makes it difficult to achieve improvements in systolic function; however, strain analysis (not performed in this trial) might have detected more subtle changes in systolic function [21]. Moreover, while our treatment regimen and dosing were probably adequate, as reductions in cardiovascular events and mortality were previously confirmed in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study [5], our 6-month trial duration may not have been enough to see any effect on physical performance. However, an ongoing randomized trial assessing diastolic ventricular function and VO_{2max} in young people with T2D treated with liraglutide or sitagliptin should soon report its outcomes and add to the current knowledge [22].

In patients with preexisting chronic heart failure, liraglutide has shown no positive effects on ventricular function [23,24]. The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial assessed the effect of liraglutide (vs. placebo) on clinical stability in 300 patients with preexisting chronic heart failure and recent hospitalization [24]. However, no significant benefits were observed in death rates, new admissions due to heart failure, 6-min walk test, LVEF or markers of myocardial function. In fact, in the 178 T2D patients included in FIGHT, there was an almost significant trend suggesting harm [hazard ratio (HR): 1.51 (1.00–2.29); $P = 0.05$] for the endpoint combining mortality, hospitalization for heart failure and emergency department visits. Another trial of left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) assessed the effects of liraglutide (vs. placebo) in 241 patients (30% with diabetes) with LVEFs $\leq$ 45% and stable chronic heart failure. LV systolic function was not affected by treatment, but serious cardiac events were more frequent with the intervention [23].

As an adjunct to exercise in T2D patients, liraglutide apparently blunted some of the positive effects of exercise on LV diastolic function [25], which is consistent with some of the findings in the LIVE study [23]. On the other hand, a smaller open-label randomized trial assigning patients with heart failure and ischaemic heart disease to either liraglutide, sitagliptin or glargine showed improvements in LVEF, 6-min walk test and other markers of ventricular function only with liraglutide [26]. However, no direct comparisons were made with the other treatments.

Our present trial has several limitations, the main one being its small sample size: given the regular use of DPP-4 inhibitors in the treatment of T2D, which was one of our exclusion criteria, recruiting patients took longer than originally planned. In addition, VO_{2max}, our primary endpoint, is highly dependent on age, gender and body weight. Yet, our calculated VO_{2max} per kg body weight, and age and gender distributions, were similar between our treatment groups, while the percentage of theoretical VO_{2max} achieved was also calculated and, again, did not differ between groups. Furthermore, the 6-min walk test used to assess physical performance is useful for patients with New York Heart Association (NYHA) functional class II/III, but has lower predictive value in class I patients. Yet, despite this, a significant increase in this walking measure was found with liraglutide, although the difference was similar with placebo as well. Spontaneous physical

activity was assessed at baseline and at the end of the study, but did not differ between treatment groups, although differences arising during the study period that may have influenced these results cannot be ruled out.

Conclusion

This small-scale randomized placebo-controlled trial failed to show any significant effect of liraglutide on VO_{2max} or any other measure of physical performance or myocardial function.

Authors' contributions

AMW designed the study, analyzed the data and wrote the manuscript. AMW, MPA, MJL and FJN recruited and followed the patients. GM, MAL, CA and NA guided the patients in their performance and interpreted the ergometries, the 6-minute walk test and Holter physical activity monitoring. HM and LS performed the echocardiography, and recorded, analyzed and interpreted the results. AD managed the study drug and assured the double-blind nature of the trial. AC performed the echoendoscopy studies. All authors had access to the data, read the manuscript critically and accepted the final version.

UTN: U1111-1128-8762.

Registered at: www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005197-63.

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Disclosure of interest

Speaker's fees were received by FNM from Novo Nordisk, by MJLM from Boehringer Ingelheim and Merck Sharpe & Dome (MSD), and by MPAR from Novo Nordisk, Boehringer Ingelheim and MSD.

The LIPER2 trial was approved and funded by Novo Nordisk. However, the investigators designed and conducted the study, performed all study analyses, wrote the manuscript and are responsible for its contents, while Novo Nordisk had no role in the collection, analysis, interpretation, writing or publication of the data. The investigators had full access to all data and have the final responsibility for the decision to submit this paper for publication.

Acknowledgments

We are grateful to Novo Nordisk (Bagsvaerd, Denmark) for providing the funding, as well as the study drug and placebo, for this trial.

Appendix A. Supplementary data

Supplementary data related to this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2018.08.010.

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