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Published in:
Diabetes, Obesity and Metabolism

DOI:
10.1111/dom.12797

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes

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Funding information
The study was an investigator-initiated study sponsored by Novo Nordisk, who also sponsored the liraglutide and the placebo pens. Novo Nordisk had no role in the study design, data analysis or reporting of results.

Aims: To investigate the effects of exercise in combination with a glucagon-like peptide-1 receptor agonist (GLP-1RA), liraglutide, or placebo for the treatment of type 2 diabetes.

Methods: Thirty-three overweight, dysregulated and sedentary patients with type 2 diabetes were randomly allocated to 16 weeks of either exercise and liraglutide or exercise and placebo. Both groups had three supervised 60-minute training sessions per week including spinning and resistance training.

Results: Glycated haemoglobin (HbA1c) levels dropped by a mean standard deviation of 2.0% ± 1.2% (from 8.2% ± 1.4%) in the exercise plus liraglutide group vs 0.3% ± 0.9% (from 8.0% ± 1.2%) in the exercise plus placebo group (P < .001), and body weight was reduced more with liraglutide (−3.4 ± 2.9 kg vs −1.6 ± 2.3 kg; P < .001). Compared with baseline, similar reductions were seen in body fat (exercise plus liraglutide: −2.5% ± 1.4% [P < .001]; exercise plus placebo: −2.2% ± 1.9% [P < .001]) and similar increases were observed in maximum oxygen uptake (exercise plus liraglutide: 0.5 ± 0.5 L O2/min [P < .001]; exercise plus placebo: 0.4 ± 0.4 L O2/min [P = .002]). Greater reductions in fasting plasma glucose (−3.4 ± 2.3 mM vs −0.3 ± 2.6 mM, P < .001) and systolic blood pressure (−5.4 ± 7.4 mm Hg vs −0.6 ± 11.1 mm Hg, P < .01) were seen with exercise plus liraglutide vs exercise plus placebo. The two groups experienced similar increases in quality of life during the intervention.

Conclusions: In obese patients with type 2 diabetes, exercise combined with GLP-1RA treatment near-normalized HbA1c levels and caused a robust weight loss when compared with placebo. These results suggest that a combination of exercise and GLP-1RA treatment is effective in type 2 diabetes.

KEYWORDS
exercise, GLP-1, GLP-1 receptor agonist, glucagon-like peptide-1, liraglutide, randomized study, type 2 diabetes

1 | INTRODUCTION

Physical activity is one of the three cornerstone recommendations (along with diet and medication) in the treatment of type 2 diabetes.1–5

Exercise training improves aerobic capacity and muscular strength and is often associated with fat loss and increased muscle mass. Furthermore, exercise training has a beneficial effect on insulin-mediated glucose uptake and is associated with increased glucose transporter
4 (GLUT4) expression and improved insulin signalling in skeletal muscle.\textsuperscript{6,7} Despite several studies reporting significant reductions in glycated haemoglobin (HbA1c) of 0.4% to 0.6% after increasing the level of physical activity, it is often not sufficient to normalize glycemic control in patients with type 2 diabetes.\textsuperscript{2,8,9} Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from enteroendocrine L cells located in the distal jejunum and ileum in response to meal ingestion. GLP-1 is known mainly for its glucose-lowering and satiety-promoting effects.\textsuperscript{10} Since 2006, GLP-1 receptor agonists (GLP-1RAs) have been used for the treatment of patients with type 2 diabetes.\textsuperscript{11} Liraglutide is a once-daily administered GLP-1RA with beneficial effects on HbA1c levels, body weight and body composition in obese dysregulated patients with type 2 diabetes.\textsuperscript{11} Nevertheless, a substantial proportion of GLP-1RA-treated patients do not reach glycaemic targets.

Exercise and GLP-1RAs have each been used for the treatment of patients with type 2 diabetes for several years; however, the combination of the two has, to our knowledge, never been evaluated in prospective trials before. We hypothesized that exercise training combined with GLP-1RA treatment would result in clinically relevant improvements in HbA1c and a range of other health-related variables, in obese, sedentary and dysregulated patients with established type 2 diabetes.

2 | METHODS

2.1 | Study design and endpoints

The study was a 16-week, randomized, double-blind, placebo-controlled study conducted at the Center for Diabetes Research, Gentofte Hospital, University of Copenhagen, Denmark. The study was conducted in accordance with the international Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The study was designed and conducted by the authors, and the authors vouch for the data and analyses, as well as the fidelity of this report to the study protocol. The study was an investigator-initiated study, sponsored by Novo Nordisk, but Novo Nordisk had no role in the study design, data analysis or reporting of results. The primary endpoint was change in HbA1c (from baseline until end of study (16 weeks)). Secondary outcomes included changes in body weight, body composition, maximum oxygen uptake (VO\textsubscript{2max}), fasting plasma glucose (FPG), serum insulin, serum C-peptide, plasma glucagon, plasma concentrations of incretin hormones, liver enzymes, lipids, blood pressure, heart rate and quality of life (QoL). Further secondary outcomes, insulin resistance and \(\beta\)-cell function, were evaluated by homeostatic model assessment (HOMA-IR and HOMA-\(\beta\), respectively).

Patients were recruited from the Diabetes Outpatient Clinic at Gentofte Hospital, Denmark, and through advertisement. Oral and written informed consent were obtained before inclusion. Inclusion criteria were: age >18 years; type 2 diabetes treated with diet and/or metformin; HbA1c between 7% and 11% (53-97 mmol/mol), body mass index (BMI) > 25 kg/m\(^2\); and sedentary lifestyle (self-reported physical activity <150 min/wk). Exclusion criteria were clinically relevant cardiovascular disease, impaired liver function, anaemia and/or impaired renal function. Eligible patients were randomly assigned to either exercise training plus liraglutide (exercise plus liraglutide) or to exercise training plus placebo (exercise plus placebo) for 16 weeks (Figure 1). An employee otherwise not involved in the study carried out the randomization at a 1:1 ratio from a prespecified randomization list. The exercise training consisted of three 60-minute supervised training sessions per week (in groups). Twice per week the patients participated in swimming sessions (Indoor Body Bike Supreme; Pedan, Køge, Denmark) with an average intensity of 65% to 85% of maximum heart rate (monitored by RS300X; Polar, Kempele, Finland). The programme for swimming sessions was modelled on traditional swimming programs with music and focusing on cardio-training with incorporated high-intensity intervals of 30-second sprints (4-10 repetitions) followed by 1 minute of active recovery. The third session consisted of 8 different resistance exercises (squat, lunges, biceps, triceps, whole-body [modulated Olympic lift], bench press, shrugs and plank), and 3 sets of 12 repetitions with 30-second to 45-second rests between each set in order to recruit the major muscle groups. Resistance exercise training was performed with barbells (Reebok, Canton, Massachusetts) with individually adjustable weight loads. Exercise training compliance was defined as no less than 85% participation. All exercise sessions were conducted under the supervision of trained exercise physiologists (P.M. and S.N.). The patients were repeatedly instructed not to change their diet or physical activity during the study period except for the study intervention. A questionnaire describing the frequency and composition of the daily food intake before, midway and at the end of the study was used. The study drugs used were the GLP-1 analogue, liraglutide (Victoza), and placebo, which were supplied by Novo Nordisk in blinded pens for subcutaneous (s.c.) injections. After baseline evaluation, the patients received once-daily s.c. injections of 0.1 mL of study medication (0.6 mg liraglutide or placebo) in the evening for 1 week, 0.2 mL (1.2 mg liraglutide or placebo) the following week and thereafter 0.3 mL (1.8 mg liraglutide or placebo) for the remaining study period. Patients were examined in the fasting state at baseline and at the end of the study with blood samples, blood pressure, resting heart rate, dual-energy X-ray absorptiometry scan and physical fitness test. End of study examinations were performed after the last liraglutide or placebo dose was given, the evening before and 42 to 75 hours after the last bout of exercise.

2.2 | Experimental procedures

A dual-energy X-ray absorptiometry scan (DPX-iQ Lunar, General Electric Lunar Corporation, Madison, Wisconsin) was performed to assess body composition. Fat distribution was evaluated as the relative proportion of fat tissue in the android (abdominal) and the gynoid (hip and thigh) regions. The physical fitness level of the patients (VO\textsubscript{2max}) was estimated from a two-step sub-maximum bicycle test at baseline and at the end of the intervention. Each patient worked at two different workloads on a stationary bicycle ergometer (Monark ergomedic 839 E, Monark, Vansbro, Sweden). The workload was increased until a heart rate of 110 to 120 beats/min was achieved. At steady-state heart rate, oxygen uptake was measured (MasterScreen CPX system; Intramedic, Gentofte, Denmark). The workload was then increased to achieve a heart rate of 140 to 160 beats/min and oxygen uptake at steady state was measured again. The duration of the test was 10 to 12 minutes. VO\textsubscript{2max} was estimated from the measurements of VO\textsubscript{2} during the two-
2.3 | Analytical assessment

A colorimetric assay was used to measure HbA1c (Vitros 5.1 FS; Ortho-Clinical Diagnostics, Linden, New Jersey). Concentrations of glucose were measured by the glucose oxidase method, using a glucose analyser (Yellow Springs Instrument model 2300 STAT plus analyser; YSI Inc., Yellow Springs, Ohio). Insulin and C-peptide concentrations were measured using a two-sided electrochemiluminescence immunoassay (Siemens Healthcare, Ballerup, Denmark). Concentrations of total GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon were measured by radioimmunoassays, as previously described. Assessment of triglycerides and lipids was measured using reflectance spectrophotometry (Vitros 5.1, Johnson & Johnson, Ortho-Clinical Diagnostics, New Brunswick, New Jersey).

2.4 | Calculations and statistical methods

Steady-state insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were estimated using the HOMA2 calculator. The statistical analyses were performed using STATA 12.1 (STATA Corp, LP, College Station, Texas). Data are reported as mean ± standard deviation; in case of non-normal distribution, data were log-transformed and back-transformed. Estimates are reported as geometric means with 95% confidence interval (CI). Differences between mean values in the two groups were analysed using Student’s t-test. Analyses of between-group differences were performed by analysis of covariance (ANCOVA) with the end-of-study value as the dependent variable.
and the baseline value as the independent variable. P values of <.05 were considered to indicate statistical significance. The statistical analyses were performed by P.M. and M.T.J.

2.5 Study registration

The study was approved by the Danish Medicines Agency (EudraCT number: 2011-002739-24) and the Scientific-Ethical Committee of the Capital Region of Denmark (registration number: H-4-2011-073), notified to the Danish Data Protection Agency (reference number 2007-58-0015) and registered at ClinicalTrials.gov (ID: NCT01455441). The study conformed to the latest revision of the Declaration of Helsinki. The study was monitored by the Good Clinical Practice unit of University of Copenhagen and was conducted in compliance with the protocol and national guidelines including Clinical Trials Directive 2001/20/EC.

3 RESULTS

From December 2011 to March 2013, a total of 34 patients were enrolled in the study, of whom 33 completed the full study. One patient was excluded because of lack of exercise compliance. Patient characteristics were similar in the two groups (Table 1). Medical treatment was similar in the groups and remained unchanged during the study. Besides metformin, patients received no medication known to interfere with glucose metabolism.

3.1 Glycated haemoglobin

Patients receiving exercise plus liraglutide experienced pronounced reductions in HbA1c, whereas no significant change was observed in the exercise plus placebo group (Table 2, Figure 2A). In the exercise plus liraglutide group, 77% of patients obtained an HbA1c <7% (53 mmol/mol) and 53% normalized their HbA1c concentration (<6.0% [42 mmol/mol]). In the exercise plus placebo group, the corresponding values were 25% and 6%, respectively (Figure 2F).

3.2 Body weight and body composition

The mean (range) body weight was reduced by 3.4 (~8.5 kg to +2.3) kg in patients treated with exercise plus liraglutide, whereas it remained unchanged with exercise alone (~1.6 [-9.3 to +2.8] kg; Figure 2C). A significant reduction in body fat (%) was observed in both groups (Table 2, Figure 2D). Furthermore, gynoid and android fat (%) decreased significantly in both groups, with no difference between the groups. Lean body mass was unchanged from baseline in both groups (Table 2). Data from the simple questionnaire inquiring about the frequency and composition of the daily food intake before, midway and at the end of the study showed little or no change in food intake between the groups over 16 weeks.

3.3 Exercise compliance and physical fitness

Overall exercise compliance was 89% ± 4%, equal to ~2 hours and 41 min/wk during the 16-week intervention period. During spinning sessions, the mean intensity was 77% ± 2% of estimated maximum heart rate, with no difference between the groups. VO2max increased significantly, by ~17% in both groups, after 16 weeks (Figure 2E).

3.4 FPG, insulin, C-peptide and HOMA-IR/β

A significant effect on FPG was seen with exercise plus liraglutide, whereas exercise plus placebo had no effect on FPG level (Figure 2B). No changes were observed in fasting levels of insulin and C-peptide, respectively, in any of the groups. The estimated HOMA-IR and estimated steady-state β-cell function, HOMA-β, were both significantly improved with exercise plus liraglutide, whereas no changes were observed with exercise plus placebo (Table 3).

3.5 Lipids, liver enzyme, glucagon, GLP-1 and GIP concentrations

Lipids were unchanged after the interventions in both groups (Tables 2 and 3). Alanine transaminase decreased in both groups, whereas aspartate transaminase remained unchanged. No changes in fasting glucagon, GLP-1 or GIP were observed (Table 3).

3.6 Blood pressure and heart rate

A significant reduction in systolic blood pressure was found in the exercise plus liraglutide group. No changes were seen in diastolic blood pressure or heart rate (Table 2).

3.7 Health-related QoL

The health-related QoL summary score was significantly improved in the general health component and the physical function component in both groups without differences between the groups in any of the components (data not shown).
3.8 | Adverse events

Gastrointestinal side effects (mild/moderate and transient nausea, vomiting and diarrhoea) were observed in 24% of the patients in the exercise plus liraglutide group vs 6% in the exercise plus placebo group. No episodes of hypoglycaemia were reported. No serious adverse events (including pancreatitis) were seen in the study.

4 | DISCUSSION

We show, for the first time, that overweight dysregulated and sedentary patients with type 2 diabetes receiving supervised exercise training in combination with the GLP-1RA liraglutide for 16 weeks achieved: (1) improved glycaemic control; (2) reduction in body weight; and (3) decreased systolic blood pressure compared with patients receiving supervised exercise training combined with placebo. In both groups, improvements in physical fitness, body fat and QoL were observed. Lean body mass was unchanged in both groups, despite weight loss. The overall safety profile of liraglutide was consistent with findings in previous reports.19,20 Interestingly, no changes in resting heart rate were detected in any of the groups, which is in contrast to previous studies with continuously acting GLP-1RAs, which reported a sustained increase in heart rate of approximately 2 to 4 beats/min.19-21 Thus, further studies are warranted to elucidate whether exercise training is able to neutralize the well-known increase in heart rate seen with this class of glucose-lowering drugs.

A significant limitation of the present study is the relatively small sample size of patients, reducing the power to detect subtle changes and increasing the risk of type II statistical errors. Despite this, we were able to demonstrate clinically relevant differences between the two groups. Another limitation of the study is the absence of diet records, which could have shown possible changes in diet after GLP-1RA treatment. Strengths of the study include the validated methods used; the study was performed as a single-centre, randomized, double-blind, placebo-controlled study, with only few physicians and experienced exercise physiologists involved (all the
FIGURE 2  Glycated haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), body composition and maximum oxygen uptake (VO2max). A. HbA1c in exercise plus liraglutide (green at baseline and green pattern at end of study), exercise plus placebo (blue at baseline and blue pattern at end of study). B. FPG in exercise plus liraglutide (green at baseline and green pattern), exercise plus placebo (blue at baseline and blue pattern at end of study). C. Differences in body weight in exercise plus liraglutide (green blue at baseline and green pattern at end of study), exercise plus placebo (blue at baseline and blue pattern at end of study). D. Differences in fat mass in exercise plus liraglutide (green at baseline and blue pattern at end of study), exercise plus placebo (blue at baseline and blue pattern at end of study). E. Estimated VO2max in exercise plus liraglutide (green at baseline and green pattern at end of study), exercise plus placebo (blue at baseline and blue pattern at end of study). F. Proportions of patients achieving HbA1c targets after the intervention. Exercise plus liraglutide (green) exercise plus placebo (blue). Data are mean ± standard error of the mean. Significant differences (P < .05) between the groups are indicated by asterisks (*) and significant differences (P < .05) within the groups are indicated by hatch signs (#).
In conclusion, the combination of supervised exercise training and liraglutide induced major improvements in glycaemic control and may be an attractive treatment option for obese, dysregulated patients with type 2 diabetes on diet and/or metformin who are able to perform moderate- to high-intensity exercise training.

**ACKNOWLEDGMENTS**

The authors thank all participants for spending time on this project, and they are grateful for expert technical assistance from Jytte Hovgaard, The Good Clinical Practice Unit of Copenhagen University, Denmark. Finally, the authors are grateful for the cooperation with monitor Stine Hovgaard, The Good Clinical Practice Unit of Copenhagen University, Denmark.

**Conflict of interest**

P. M. S. N. P. G. J. H. S. M. T. J. and J. S have no conflicts of interest. J. J. H has served on scientific advisory panels for Glaxo, Smith, Kline, Novo Nordisk, Zealand Pharmaceuticals, AstraZeneca, Sanofi, MSD, Intarcia, Hamni, has served as a consultant to Novo Nordisk, and has received research support from AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, Zealand Pharma. A. A. R. is a shareholder in Novo Nordisk. F. K. K. has no conflicts of interest.
on scientific advisory panels for Amgen, AstraZeneca, Boehringer, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda, has served as a consultant to AstraZeneca, Boehringer, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda, has received research support from Novo Nordisk and served on the Speakers Bureau for AstraZeneca, Boehringer, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Novartis, Sanofi and Takeda.

Author contributions
P. M. contributed to the study design and recruitment of participants, including instruction in study medication, performed screening visits, testing, exercise training and statistical analyses, researched the data and wrote the manuscript. S. N. contributed to the study design and recruitment of participants, performed screening, tests and exercise training and reviewed the manuscript. P. G. J. reviewed/editied the manuscript. H. S. contributed to recruitment of participants and reviewed/editied the manuscript. M. T. J performed the statistical analyses and reviewed/editied the manuscript. J. S. performed the screening visits, and reviewed and edited the manuscript. J. J. H. analysed plasma for incretin hormones and glucagon and reviewed/editied the manuscript. B. K. reviewed/editied the manuscript. E. A. R. contributed to the study design and reviewed/editied the manuscript. F. K. K. contributed to the study design and reviewed/editied the manuscript. T. V. contributed to the study design, contributed to the interpretation of the results, data management and reviewed/editied the manuscript. P. M. and T. V. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior presentation: Parts of the study were presented at the 74th Scientific Meeting of the American Diabetes Association, San Francisco, California, June 13-17, 2014 and at the 50th European Association for the Study of Diabetes Annual Meeting, Vienna, Austria, September 15-19, 2014.

REFERENCES