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One-Year Follow-up on Liraglutide Treatment for Prediabetes and Overweight/Obesity in Clozapine- or Olanzapine-Treated Patients

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Abstract

Objective: Treatment with most antipsychotics is associated with an increased risk of weight gain and metabolic disturbances. In a randomized trial, we previously demonstrated that 16 weeks of glucagon-like peptide-1 receptor agonist liraglutide treatment vs. placebo significantly reduced glucometabolic disturbances and body weight in prediabetic, overweight/obese schizophrenia-spectrum disorder patients treated with clozapine or olanzapine. The aim of this study was to investigate whether the beneficial effects of the 16-week intervention were sustained beyond the intervention period.

Method: One year after completion of the intervention, we investigated changes in body weight, fasting glucose, glycated hemoglobin, C-peptide and lipids comparing one-year follow-up levels to end of treatment (week 16) and baseline (week 0) levels.

Results: From end of treatment to the one-year follow-up, body weight had increased in the liraglutide-treated group. However, compared to baseline levels, the placebo-subtracted body weight loss remained significantly reduced (-3.8 kg, 95% CI: -7.3 to -0.2, $P = 0.04$). Fasting glucose, glycated hemoglobin, C-peptide and lipids had each returned to baseline levels one year after stopping liraglutide.

Conclusion: The body weight reduction during 16 weeks of liraglutide treatment was partially sustained one year after the intervention was completed. However, the improvements in other metabolic parameters returned to baseline levels.

Keywords

Clozapine, olanzapine, liraglutide, GLP-1, overweight, prediabetes, schizophrenia

Significant Outcomes

- One year after the end of intervention, body weight reduction was still partially and significantly sustained in the liraglutide-treated group.
- Twelve patients in the liraglutide group and six patients in the placebo group developed overt type 2 diabetes (29.3% vs. 13.0%, $P = 0.07$).
- All other metabolic parameters, i.e. fasting plasma glucose, glycated hemoglobin, C-peptide and lipid profile, had returned to baseline levels one year after cessation of the liraglutide treatment.

Limitations

- The dropout rate at the one-year follow-up was 8.3%, thus reducing the statistical power.
- No restrictions of changes in medication, e.g., antidiabetic and antipsychotic medications, were enforced during the one-year naturalistic follow-up period.
- When determining the development of type 2 diabetes, elevated fasting plasma glucose levels or HbA1c levels were not confirmed by a second measurement as recommended by the American Diabetes Association.

Introduction

Patients with schizophrenia have a reduced life expectancy of 20 years compared to the background population (1). The reduced life expectancy is mainly due to an increased prevalence of cardiovascular morbidity most likely caused by an interaction between genetic, life style and treatment factors, including antipsychotic side effects (2–7). The second-generation antipsychotics clozapine and olanzapine are two of the most effective compounds in the treatment of schizophrenia (8–13), but compared to other antipsychotics, these compounds also induce the greatest body weight gain and confer the highest risk of metabolic disturbances (2–7). Therefore, patients with schizophrenia treated with antipsychotics, particularly clozapine or olanzapine, are at increased risk of developing overweight/obesity, metabolic abnormalities, type 2 diabetes (T2D) and consequently cardiovascular disease (2–7,14–17).

In antipsychotic-treated patients, only modest or no reductions in cardiovascular risk factors have been reported with lifestyle interventions, e.g. diet, exercise and reduction of alcohol and tobacco consumption (18–20). Similarly, only modest effects on impaired glucose tolerance and overweight have been reported with several different pharmacological interventions (21–25). The most consistent results have been reported for metformin, which is the first-line treatment option for T2D (26). Metformin has been shown to induce a small body weight reduction of approximately 3 kg in antipsychotic-treated patients (21–25). Thus, an urgent need for novel treatment strategies still exists.

Recently, pharmacological intervention with incretin-based therapies used for treatment of T2D and obesity has been suggested for treatment of antipsychotic-treated patients (27,28). Glucagon-like peptide-1 (GLP-1) is an incretin hormone, which is secreted from the small

intestine in response to nutrients. GLP-1 increases insulin secretion from the beta cells and decreases glucagon secretion from the alpha cells of the pancreas (29,30), resulting in increased glycemic control. In addition, GLP-1 has an inhibitory effect on gastric emptying, appetite and food intake and can induce body weight reduction (31). Liraglutide is a GLP-1 receptor agonist (GLP-1RA) with 97% homology to naturally occurring GLP-1 (29), administered once-daily as a subcutaneous injection.

Several studies have shown beneficial effects of liraglutide treatment on glucose metabolism and excess body weight in non-psychiatric patients with or without prediabetes or T2D (32–38). Previously, we reported that 16 weeks of treatment with liraglutide vs. placebo in overweight or obese patients with prediabetes and a schizophrenia-spectrum disorder on stable treatment with olanzapine or clozapine improved glucose tolerance and metabolic disturbances and induced a placebo-subtracted mean body weight reduction of 5.3 kg (weight reduction of 5.2 in the treatment group vs. a weight gain of 0.5 in the placebo group) (39). Two other randomized clinical trials also evaluated a GLP-1RA, exenatide 2 mg s.c. once-weekly, in patients with schizophrenia or schizo-affective disorder treated either with clozapine (40,41) or a mixture of antipsychotics (41–43). One study showed a significant weight reduction of 5.3 kg in the treatment group vs. 1.1 kg in the placebo group ($P = 0.02$) (40), while the other one did not show any difference (2.2 kg in the treatment group vs. 2.2 kg in the placebo group, $P = 0.98$) (42,43). However, to what degree the statistically significant and clinically meaningful improvements observed during active liraglutide treatment are sustained after liraglutide is stopped is unknown.

Aims of the study

To investigate whether 16 weeks of treatment with liraglutide has sustained effects on body weight and glucometabolic disturbances in prediabetes patients with schizophrenia-spectrum disorder on stable treatment with clozapine or olanzapine.

Materials and Methods

Overview

A 16-week, randomized, double-blinded, placebo-controlled trial with liraglutide was conducted from May 1, 2013, to February 25, 2016, at two psychiatric centers in Denmark. The study enrolled overweight/obese patients with prediabetes, diagnosed with a schizophrenia-spectrum disorder and treated with clozapine or olanzapine (39). One year after the patients had completed the intervention, they were invited back for a one-year follow-up visit. The follow-up visit was completed with the last patient's last visit on March 14, 2017. The study was approved by the local ethics committees and the Danish Health Authority. All patients provided oral and written consent before entering the study. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. On the informed consent form, patients were informed that the blinding would be maintained until last patients last visit (LPLV) and until the statistical analyses had been performed for the intervention period (week 0 to week 16). As the recruitment period was quite extensive, lasting from May 2013 to November 2016, LPLV was not accomplished before February 2016. Consequently, the majority of the patients had already attended their one-year follow-up (week 68) before LPLV was completed, and therefore, we decided to extend the blinding of the few remaining patients to increase the trial validity. Importantly, no patients asked to be unblinded before the end of the one-year follow-up, and all patients did receive promptly notification, as soon as their one-year follow-up (week 68) was completed.

Previous details of the study protocol have been published (ClinicalTrials: NCT01845259) (44).

Study Population

Patients enrolled in the clinical trial were between 18 and 65 years old, diagnosed with a schizophrenia-spectrum disorder (schizoaffective disorder excluded) according to the International Classification of Diseases 10th edition (ICD-10) (45) or the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (46), and were treated with either clozapine or olanzapine for at least 6 months without any change of dose at least 30 days prior to inclusion. Additionally, the enrolled patients had prediabetes (44) and were overweight or obese with a body mass index (BMI) $\geq$27 kg/m^2 at baseline (week 0). Prediabetes was defined as either impaired fasting plasma glucose (IFG) (fasting plasma glucose level between 6.1 mmol/l and 6.9 mmol/l), elevated glycated hemoglobin (HbA1c, between 43 mmol/mol and 47 mmol/mol) or impaired glucose tolerance (IGT) (two-hour plasma glucose above 7.8 mmol/l during a 75-g oral glucose tolerance test (OGTT). Key exclusion criteria were type 1 diabetes and T2D, other serious somatic illnesses and treatment with glucose-lowering drugs.

Procedure

Included patients in the efficacy study were randomly assigned to receive either liraglutide (starting dose of 0.6 mg which was up-titrated to 1.8 mg during the initial two weeks) or placebo administrated subcutaneously once-daily for 16 weeks. At baseline (week 0) and every four weeks until the end of treatment (week 16), and at the one-year follow-up (week 68), fasting blood samples for plasma glucose, HbA1c, C-peptide, lipid profile and liver function were collected, and body weight, waist circumference and blood pressure were

measured. At these timepoints, rating scales, i.e., quality of life, severity of psychiatric illness, daily functioning and alcohol consumption, were also performed using the Schizophrenia Quality of Life Scale (SQLS) (47), the Clinical Global Impression Scale – severity (CGI-S) (48), Global Assessment of Function (GAF) (49), and the Alcohol Use Disorders Identification Test (AUDIT) (50), respectively.

Changes in medication, psychiatric and somatic diagnoses, and diet and exercise habits were recorded throughout the 16-week trial and at the one-year follow-up. Treatment between 16 and 68 weeks was by clinician's choice and naturalistic. Tobacco and alcohol use were recorded at baseline and the one-year follow-up visit.

Endpoints

Endpoints were the proportion of patients who developed overt T2D (defined as fasting plasma glucose ≥7 mmol/l or HbA1c ≥48 mmol/mol or a random glucose measurement ≥11.0 mmol/l in a patient with classic symptoms of hyperglycemia (51)) or treatment with antidiabetic medication (because of development of T2D diagnosed by a general practitioner) and changes in fasting plasma glucose, HbA1c, C-peptide, insulin resistance, beta cell function and insulin sensitivity estimated by the homeostasis model assessment 2 (HOMA-2), lipid profile, liver function, body weight, waist circumference and blood pressure. Also, quality of life, severity of psychiatric illness, daily functioning and alcohol consumption were evaluated. The endpoints were evaluated from end of treatment (week 16) to the one-year follow-up (week 68) and from baseline (week 0) to the one-year follow-up (week 68).

Statistical Analysis

Analyses were performed using SAS 9.4 with alpha set at 0.05 and two-sided testing. A modified intention-to-treat principle was used, supplemented with a per-protocol sensitivity analysis. Patients who received at least one dose of liraglutide or placebo and who had at least one assessment after baseline were included in the analyses (n=96). Baseline observations were analyzed using one-way analysis of variance and χ^2 test for continuous and categorical variables, respectively. The categorical variables, i.e., proportion of patients developing T2D, were analyzed using χ^2 test. Continuous outcomes were analysed using a mixed model of repeated measurements, including age, sex, baseline BMI, baseline illness severity and duration and treatment with clozapine, olanzapine, both or none of them as fixed effects as well as the baseline value of the relevant variable as a covariate.

Results

One-hundred-and-three patients were included in the study and randomised at baseline to receive either liraglutide or placebo. The randomization resulted in comparable groups at baseline (supplementary Tables S1 and S2) (39). In total, 96 patients completed the 16 weeks of treatment (liraglutide group 88.5% vs. placebo group 98.0%) (Figure 1).

One year after end of treatment (68 weeks from baseline), 88 of the 96 patients completed the follow-up visit (liraglutide group 89.1% vs. placebo group 94.0%); 7 of the 96 patients declined to attend the one-year visit and one patient had died (cause unknown) (Figure 1). Additionally, one patient had received an intensive lifestyle intervention during hospitalisation in a foreign country after completion of the trial, which resulted in a body weight reduction of 112 kg (from 215 to 102 kg). The patient was excluded as an outlier from further analyses (Figure 1). Thirteen patients who, at the one-year follow-up, had been treated

with antidiabetic medication (n=9) or who had discontinued treatment with antipsychotic medication (n=4) were excluded from the per-protocol analysis (Table S5).

Baseline (week 0) to End of Treatment (week 16)

As previously reported, compared to placebo, 16 weeks of treatment with liraglutide resulted in significant improvements in glucose tolerance and glycemic control (measured by OGTT, fasting plasma glucose and HbA1c), increased beta cell function (calculated by HOMA-2), and reduction in total cholesterol and low-density lipoprotein (LDL). Additionally, a body weight reduction of 5.3 kg and reductions in waist circumference and visceral fat (evaluated by DXA (Dual energy X-ray absorptiometry) scan) were reported (Table S1) (39). One patient in the placebo group developed T2D between weeks 12 and 16 (Table S3).

No difference between the liraglutide group and the placebo group was observed in the scores in the psychiatric rating scales (Table S1).

End of Treatment (week 16) to One-year Follow-up (week 68)

During the period from end of treatment (week 16) to the one-year follow-up (week 68), 12 patients from the liraglutide group and five from the placebo group (29.3% vs. 10.9%) had developed T2D (Table 2). Of these, four and three patients respectively had been diagnosed before follow-up and had already initiated treatment with metformin (Table S3). Additionally, one patient from each group had started liraglutide treatment for obesity.

Two patients from the liraglutide group and one from the placebo group had changed treatment with clozapine or olanzapine to other antipsychotics, whereas one patient from the liraglutide group had stopped all antipsychotic treatment (Tables S4 and S5).

After cessation of treatment, the liraglutide group (within-group analyses) had a significant increase in body weight, BMI, waist circumference, LDL and high-density lipoprotein (HDL) (Table 1). No changes were observed in the placebo group except for a small increase in HDL and a decrease in GAF (Table 1). Compared to placebo (between-group analyses), the liraglutide group developed poorer glucometabolic control, i.e., increased HbA1c (3.6 mmol/mol (95% CI 1.6 to 5.6 mmol/mol), P = 0.0005), fasting plasma glucose (relative change 1.13 (95% CI 1.06 to 1.21), P = 0.0005) and total cholesterol (relative change 1.08 (95% CI 1.01 to 1.16), P = 0.02), as well as a decrease in beta cell function (relative change 0.78 (95% CI 0.68 to 0.89), P = 0.0004) (Table 2).

Baseline (week 0) to One-year Follow-up (week 68)

Compared to the placebo group (between-group analyses), the liraglutide group maintained a significant body weight loss of 3.8 kg (P = 0.04) and a reduction in BMI of 1.6 kg/m^2 (P = 0.02) from baseline to one-year follow-up (Table 2). Data from the per-protocol analysis was consistent with these results (Tables S6 and S7).

No difference in the number of patients developing T2D was found between the two groups, as 12 patients in the liraglutide group (29.3%) compared to six patients in the placebo group (13.0%) developed T2D (odds ratio 2.76 (95% CI 0.93 to 8.21), P = 0.07) from baseline to the one-year follow-up. No difference was found between the liraglutide group and the placebo group from baseline to one-year follow-up in fasting plasma glucose, HbA1c, C-peptide, HOMA-2 measurements, lipids, liver parameters, waist circumference or blood pressure (Table 2). Changes in the dose of clozapine and olanzapine were not statistically different between the two groups, nor was the switch from one type of antipsychotic medication to another (Table S4).

Discussion

At the one-year follow-up (week 68), the originally liraglutide-treated group experienced an increase in body weight from end of liraglutide treatment (week 16). Nonetheless, the placebo-subtracted body weight reduction obtained during the 16-week intervention period was partially sustained during the follow-up period and, hence, the net body weight reduction was still statistically significant compared to baseline.

From baseline (week 0) to one-year follow-up (week 68), 12 patients in the liraglutide group (29.3%) and six patients in the placebo group (13.0%) developed overt T2D. Even though the incidence was numerically more than double in the liraglutide group compared to the placebo group, the patient population was small and no statistically significant difference was found. Moreover, T2D diagnosed solely based on one elevated blood test (fasting plasma glucose or HbA1c), was not confirmed by a second measurement as suggested by the American Diabetes Association (51), further limiting the conclusions that can be drawn from a finding that is counterintuitive also when considering the overall sustained body weight advantages in the liraglutide group.

The results of the one-year-follow-up indicate that a liraglutide-intervention period of 16 weeks is insufficient to inhibit development of T2D from prediabetes. At the one-year follow-up (week 68), levels of fasting plasma glucose, HbA1c, cholesterol and amylase had returned to the pre-intervention baseline levels without any statistical differences between the liraglutide and the placebo group.

Strengths of the present study include the long follow-up period of one year, and the extension of the blinding of treatment from week 16 to week 68 for all patients included in this analysis. Moreover, the dropout rate was low in both the intervention period and the follow-up period, with 89.6% completing the one-year follow-up visit. Despite the fact that metabolic disturbances and body weight gain are observed in patients treated with several types of antipsychotics (2–7,14,15), only patients on stable treatment with clozapine or olanzapine were enrolled in this randomized clinical trial. On the one hand, including only this selected group of patients limits the trial's generalizability. On the other hand, these antipsychotics were chosen because they are known to cause the greatest body weight gain and metabolic abnormalities, thus conferring an even greater risk of cardiovascular morbidity and mortality (4–7,16,17).

Limitations of this study include that antipsychotic medications were not stable in all patients. However, changes in dose of clozapine and olanzapine were not different between groups. Only three patients discontinued treatment with clozapine or olanzapine (but continued treatment with other antipsychotic medication), and only one patient stopped all antipsychotic treatment. Moreover, the per-protocol analysis was consistent with the intent-to-treat results. Further, T2D was defined according to the American Diabetes Association's criteria: fasting plasma glucose ≥7 mmol/l, HbA1c ≥48 mmol/mol or a random glucose measurement ≥11.0 mmol/l in a patient with classic symptoms of hyperglycemia (51) or if the patient's general practitioner had diagnosed the patient with T2D and initiated antidiabetic medication. However, if T2D was diagnosed solely based on one elevated blood test, it was not confirmed by a second measurement, which is recommended by the guidelines. Although at the one-year follow-up, the body weight and BMI remained partially reduced, waist circumference was back to baseline and we lacked sophisticated assessments of body fat distribution.

Nevertheless, the partial body weight loss found at the one-year follow-up is still clinically relevant because even a modest persistent reduction in body weight can help delay the progression from prediabetes to T2D (52,53).

Hence, the findings of this study are consistent with other studies investigating the effects of liraglutide after cessation of treatment in non-psychiatric overweight/obese, prediabetes or T2D patients (32,36,54). These studies have collectively demonstrated no sustained effect on glucose homeostasis after cessation of treatment but a partially sustained reduction in body weight up to 12 weeks after end of treatment (32,36,54). In the present study, the follow-up period was much longer (52 weeks) and even then, a partial body weight loss was sustained, which could indicate a more durable effect in antipsychotic-treated patients. However, since the body weight reduction was only partial, the results suggest that patients treated with antipsychotic medications will need persistent, long-term GLP-1RA treatment to maintain improvements in metabolic parameters.

Liraglutide has not been detected to cause drug interactions with antipsychotic medication used for schizophrenia (55), and in this study no change in CGI-S or SQLS was found during the intervention period (39) nor at the follow-up.

It would be of interest to evaluate the cost-effectiveness of liraglutide in patients with prediabetes. Several studies have evaluated the cost-effectiveness of liraglutide to other types of GLP-1RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and/or sulphonylureas in patients with T2D (56–58), but no studies evaluating the cost-effectiveness of liraglutide in prediabetic patients have been published to the best of our knowledge.

Patients treated with antipsychotic medications are known to have a reduced life-expectancy mainly due to cardiovascular disease (16), and therefore GLP-1RAs could offer an attractive new treatment option. While liraglutide is administered as a once-daily injection, which may limit the compliance and widespread use in clinical practise, several once-weekly GLP-1RAs are already on the market, which might be more suitable for psychiatric patients instead of daily injections (40,59).

However, the effects of other available GLP-1RAs, e.g. the once-weekly exenatide, need further investigation, as one study treating overweight/obese antipsychotic-treated patients with exenatide only found a significant difference in plasma glucagon when compared to placebo (42,43).

Additionally, the long-term use of other pharmacological interventions needs to be further elucidated. Metformin in antipsychotic-treated patients has demonstrated varying effects on dysglycemia and excess body weight (21–25), with a non-significant reduction in fasting plasma glucose and an average body weight loss of approximately 3 kg (21–25). However, potential long-term effects on excess body weight and prediabetes status after cessation of metformin in antipsychotic-treated patients remain largely unknown.

In conclusion, although the body weight reduction was diminished during the follow-up period, the liraglutide-treated group still retained a significant body weight reduction at the one-year follow-up visit compared to the placebo group. In contrast, the improvements in other glucometabolic parameters, e.g. fasting plasma glucose, HbA1c and lipid levels, had returned to pre-intervention baseline levels, and no significant difference in the proportion of patients developing T2D was found. Taken together, these findings suggest that

overweight/obese patients with schizophrenia and prediabetes who are treated with olanzapine or clozapine should receive long-term treatment with liraglutide in order to uphold the achieved cardiometabolic benefits.

Conflict of Interest

This study was supported by an unrestricted grant (Dr. Fink-Jensen) and receipt of liraglutide and the liraglutide placebo pens from Novo Nordisk A/S, Capital Region Psychiatry Research Group, The foundation of King Christian X, and one-year pregraduate research grants from the Lundbeck Foundation (Dr. Jespersen and Dr. Svensson).

Dr. Larsen reports being an employee at Novo Nordisk A/S.

Dr. Schjerning reports receiving speaker honoraria from Lundbeck Pharma.

Dr. Nielsen reports receiving speaker honoraria from Hemocue, Lundbeck, and Bristol-Myers Squibb and research grants from H. Lundbeck and Pfizer.

Dr. Holst reports consulting for Merck Sharp & Dohme, Novo Nordisk A/C, and Roche.

Dr. Correll reports consulting and/or advising or receiving honoraria from AbbVie, Acadia, Actavis, Actelion, Alexza, Alkermes, Bristol-Myers Squibb, Cephalon, Eli Lilly and Company, Forum, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, Medavante, Medscape, Merck Sharp & Dohme, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, Takeda, Teva, and Vanda; providing expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; serving on a data safety monitoring board for Eli

Lilly and Company, Janssen, Lundbeck, Pfizer, Takeda, and Otsuka; and receiving grant support from Bristol-Myers Squibb, Otsuka, Lundbeck, and Takeda. Dr Vilsbøll reports receiving lecture fees from Amgen, AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk A/C, Sanofi, and Zealand Pharma and serving on the advisory boards of AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk A/C, and Sanofi.

Dr. Fink-Jensen reports sponsoring the study and receiving an unrestricted grant from Novo Nordisk A/S. No other disclosures were reported.

Figure 1: Flowchart

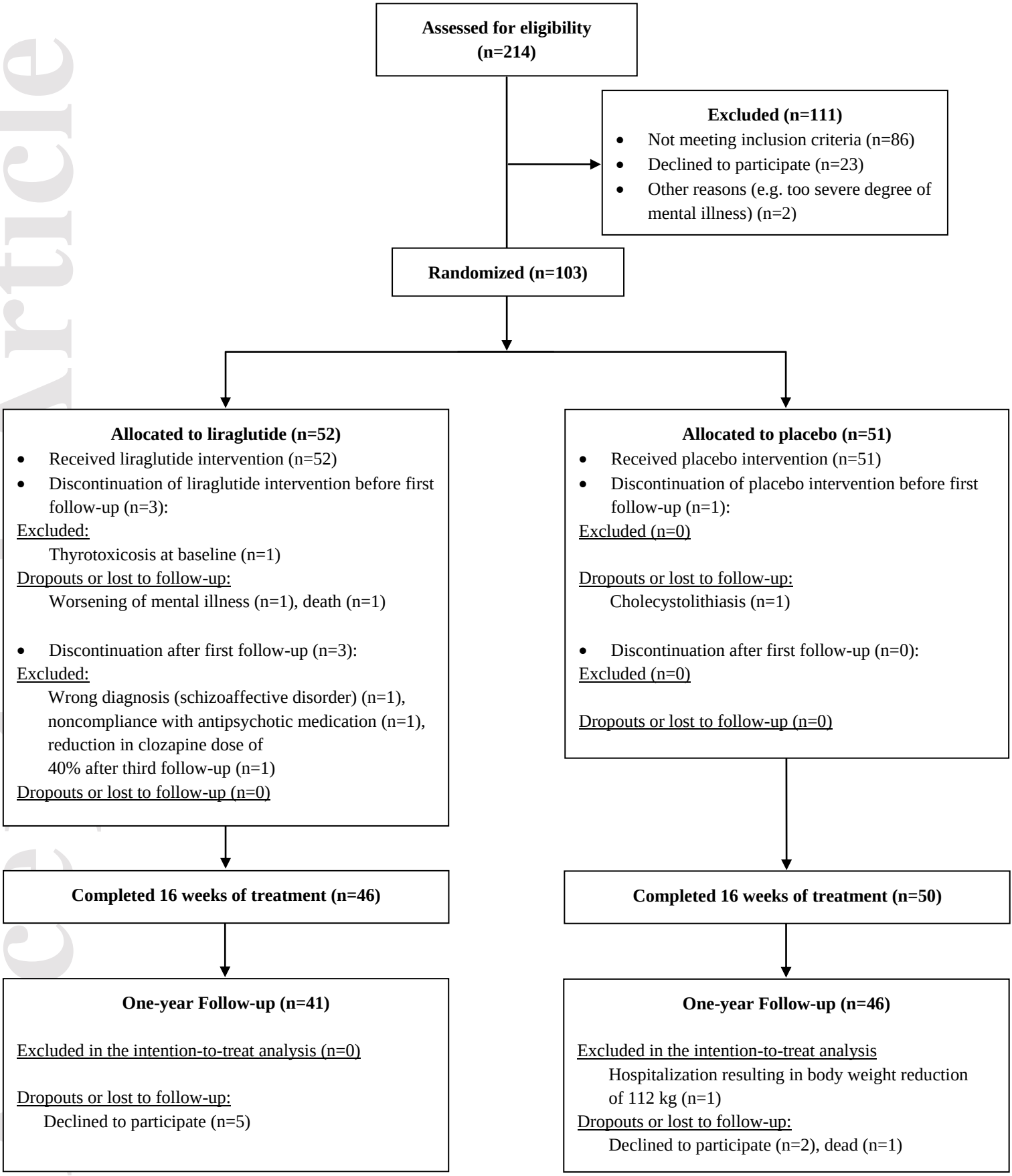

Table 1: Changes in the two treatment groups throughout the study period

	End of Treatment to One-year Follow-up (week 16 to 68)				**Baseline to One-year Follow-up (week 0 to 68)**			
Outcome	Liraglutide (n=41)	*P value*	Placebo (n=46)	*P value*	Liraglutide (n=41)	*P value*	Placebo (n=46)	*P value*
Anthropometric and blood pressure parameters								
Weight, kg	2.4 ± 1.0	0.02	-0.3 ± 1.2	0.83	-2.4 ± 1.1	0.03	0.1 ± 1.3	0.94
BMI, kg/m^2	0.9 ± 0.3	0.006	0.1 ± 0.5	0.84	-0.7 ± 0.4	0.05	0.2 ± 0.5	0.71
Waist circumference, cm	3.3 ± 1.0	0.002	-0.03 ± 1.2	0.98	-0.8 ± 1.1	0.51	0.4 ± 1.02	0.66
Systolic BP, mmHg	-0.6 ± 2.3	0.81	0.6 ± 1.7	0.74	-2.04 ± 1.8	0.27	1.7 ± 1.9	0.38
Diastolic BP, mmHg	1.6 ± 1.5	0.30	1.9 ± 1.3	0.14	2.1 ± 1.6	0.21	4.3 ± 1.3	0.002
Glucose metabolism								
Development of T2D, n (%)	12 (29.3)		5 (10.9)		12 (29.3)		6 (13.0)	
Hemoglobin A1c, mmol/mol	3.5 ± 0.8	<0.0001	-0.4 ± 0.4	0.43	1.2 ± 0.7	0.09	0.4 ± 0.5	0.43
Fasting glucose	1.13 ± 1.02	<0.0001	0.99 ± 1.02	0.57	1.01 ± 1.02	0.59	0.98 ± 1.02	0.31
C-peptide	0.94 ± 1.05	0.18	0.97 ± 1.04	0.39	0.99 ± 1.04	0.73	0.93 ± 1.04	0.11
Insulin resistance [a]	0.99 ± 1.05	0.63	0.97 ± 1.04	0.64	1.01 ± 1.04	0.93	0.93 ± 1.05	0.21
Beta cell function [a]	0.77 ± 1.04	<0.0001	0.98 ± 1.04	0.22	0.99 ± 1.04	0.56	0.97 ± 1.04	0.10
Insulin sensitivity [a]	1.02 ± 1.05	0.70	1.02 ± 1.04	0.64	1.01 ± 1.04	0.88	1.07 ± 1.05	0.21
Lipid parameters								
Total cholesterol	1.07 ± 1.02	0.003	1.01 ± 1.02	0.67	0.97 ± 1.02	0.11	0.99 ± 1.02	0.50
LDL, mmol/l	0.2 ± 0.1	0.008	0.003 ± 0.08	0.97	-0.1 ± 0.1	0.15	-0.05 ± 0.1	0.54
HDL	1.06 ± 1.03	0.05	1.07 ± 1.03	0.01	0.97 ± 1.03	0.87	1.06 ± 1.03	0.04
VLDL	1.04 ± 1.10	0.61	0.82 ± 1.05	0.26	0.98 ± 1.08	0.68	0.80 ± 1.09	0.04
Triglycerides	1.02 ± 1.06	0.74	0.93 ± 1.05	0.24	0.89 ± 1.08	0.05	0.90 ± 1.09	0.13
Liver parameters								

	End of Treatment to One-year Follow-up (week 16 to 68)				Baseline to One-year Follow-up (week 0 to 68)			
Outcome	Liraglutide (n=41)	*P value*	Placebo (n=46)	*P value*	Liraglutide (n=41)	*P value*	Placebo (n=46)	*P value*
ALT	1.00 ± 1.08	0.94	1.06 ± 1.06	0.29	0.88 ± 1.09	0.07	0.96 ± 1.06	0.55
AST	0.98 ± 1.07	0.65	0.99 ± 1.03	0.74	0.94 ± 1.05	0.18	0.93 ± 1.04	0.07
Alkaline phosphatase	1.03 ± 1.03	0.20	1.04 ± 1.02	0.12	0.97 ± 1.03	0.27	1.01 ± 1.02	0.83
Amylase	0.88 ± 1.04	0.001	1.10 ± 1.05	0.06	1.11 ± 1.03	0.001	1.08 ± 1.04	0.06
Psychiatric Rating Scales								
SQLS - Psychosocial [b]	5.3 ± 3.5	0.14	5.2 ± 2.6	0.05	3.5 ± 2.8	0.22	2.7 ± 2.8	0.35
SQLS - Motivation and energy [b]	1.4 ± 3.0	0.65	-5.03 ± 2.9	0.09	-0.09 ± 3.1	0.98	-5.9 ± 3.4	0.09
SQLS - Side effects [b]	4.7 ± 4.0	0.25	1.5 ± 2.8	0.58	-0.8 ± 3.3	0.81	-1.0 ± 2.8	0.73
CGI - Severity [c]	-0.09 ± 0.1	0.51	0.2 ± 0.1	0.05	-0.09 ± 0.1	0.53	0.3 ± 0.1	0.02
GAF [d]	-1.2 ± 0.9	0.21	-3.2 ± 1.3	0.02	-1.5 ± 1.0	0.15	-2.4 ± 1.0	0.02
AUDIT [e]	1.17 ± 1.14	0.25	1.15 ± 1.12	0.22	1.11 ± 1.19	0.55	0.90 ± 1.12	0.37

Abbreviations: ALT, alanine aminotransferase; AST aspartate aminotransferase; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; BP, blood pressure; CGI-Severity, Clinical Global Impressions Scale severity score; GAF, Global Assessment of Functioning scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SQLS, Schizophrenia Quality of Life Scale; T2D, type 2 diabetes; VLDL, very low-density lipoprotein.

For fasting glucose, C-peptide, insulin resistance, beta cell function, insulin sensitivity, total cholesterol, HDL, VLDL, triglycerides, liver parameters and AUDIT, the changes are based on logarithmically transformed data because of skewed distributions and therefore presented as relative changes.

[a] Estimated using HOMA2 measures.
[b] Scores range from 0 to 100, with higher scores indicating poorer quality of life.
[c] Scores range from 0 to 7, with higher scores indicating higher illness severity.
[d] Scores range from 0 to 100, with higher scores indicating a higher function of daily living.
[e] Scores range from 0 to 40, with higher scores indicating a higher alcohol use.

Table 2: Estimated difference between treatment groups

Outcome	End of Treatment to One-year Follow-up (week 16 to 68)		Baseline to One-year Follow-up (week 0 to 68)	
	Liraglutide vs. Placebo (95% CI)	*P value*	Liraglutide vs. Placebo (95% CI)	*P value*
Anthropometric and blood pressure parameters				
Weight, kg	1.5 (-1.8 to 4.7)	0.38	-3.8 (-7.3 to -0.2)	0.04
Body mass index, kg/m^2	0.2 (-1.0 to 1.4)	0.73	-1.6 (-2.8 to -0.3)	0.02
Waist circumference, cm	1.2 (-1.8 to 4.2)	0.43	-2.7 (-6.0 to 0.6)	0.11
Systolic BP, mmHg	1.5 (-5.2 to 8.2)	0.65	-3.3 (-8.3 to 1.6)	0.18
Diastolic BP, mmHg	0.18 (-4.5 to 4.8)	0.94	-2.9 (-7.1 to 1.4)	0.18
Glucose metabolism				
Development of T2D, odds ratio	3.31 (1.05 to 10.43)	0.06	2.76 (0.93 to 8.21)	0.07
Hemoglobin A1c, mmol/mol	3.6 (1.6 to 5.6)	0.0005	1.3 (-0.5 to 3.2)	0.16
Fasting glucose	1.13 (1.06 to 1.21)	0.0005	1.03 (0.97 to 1.10)	0.28
C-peptide	0.96 (0.85 to 1.10)	0.57	1.09 (0.96 to 1.23)	0.17
Insulin resistance [a]	1.00 (0.88 to 1.15)	0.95	1.11 (0.98 to 1.27)	0.11
Beta cell function [a]	0.78 (0.68 to 0.89)	0.0004	1.01 (0.91 to 1.13)	0.82
Insulin sensitivity [a]	1.00 (0.97 to 1.14)	0.96	0.91 (0.79 to 1.03)	0.14
Lipid parameters				
Total cholesterol	1.08 (1.01 to 1.16)	0.02	1.00 (0.94 to 1.06)	0.94
LDL, mmol/l	-0.3 (-0.5 to 0.01)	0.06	-0.1 (-0.4 to 0.2)	0.51
HDL	0.98 (0.90 to 1.07)	0.64	0.94 (0.87 to 1.03)	0.17
VLDL	1.16 (0.91 to 1.48)	0.23	1.09 (0.88 to 1.37)	0.42
Triglycerides	1.12 (0.91 to 1.38)	0.27	1.03 (0.85 to 1.25)	0.74
Liver parameters				
ALT	0.93 (0.77 to 1.11)	0.40	0.87 (0.72 to 1.06)	0.16
AST	0.98 (0.85 to 1.13)	0.81	0.97 (0.86 to 1.10)	0.64
Alkaline phosphatase	0.98 (0.90 to 1.07)	0.63	0.95 (0.87 to 1.04)	0.26
Amylase	0.82 (0.70 to 0.96)	0.02	1.03 (0.91 to 1.17)	0.65
Psychiatric Rating scales				
SQLS - Psychosocial [b]	-3.1 (-13.3 to 7.1)	0.54	-1.7 (-9.8 to 6.3)	0.67
SQLS - Motivation and energy [b]	-1.9 (-7.3 to 11.04)	0.68	-1.2 (-10.8 to 8.4)	0.80
SQLS - Side effects [b]	3.8 (-7.8 to 15.4)	0.52	6.6 (-3.3 to 16.5)	0.19
CGI - Severity [c]	-0.4 (-0.8 to 0.05)	0.08	-0.5 (-0.9 to 0.01)	0.05
GAF [e]	2.3 (-1.6 to 6.2)	0.24	0.5 (-2.9 to 3.9)	0.78
AUDIT [e]	0.90 (0.59 to 1.37)	0.60	1.18 (0.76 to 1.84)	0.45

Abbreviations: ALT, alanine aminotransferase; AST aspartate aminotransferase; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; BP, blood pressure; CGI-Severity, Clinical Global Impressions Scale severity score; GAF, Global Assessment of Functioning scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SQLS, Schizophrenia Quality of Life Scale; T2D, type 2 diabetes; VLDL, very low-density lipoprotein.

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