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Effect of 52-week liraglutide treatment on diabetes risk and glycaemic control in women with obesity and prior gestational diabetes. A randomized, double-blind, placebo-controlled study

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ABSTRACT

Aims: We investigated the effect of 52-week liraglutide treatment on the incidence of type 2 diabetes (T2D) compared with placebo treatment in women with obesity and previous gestational diabetes (pGDM) requiring medical treatment. As secondary outcomes, the prevalence of pre-diabetes and glycaemic control were investigated.

Methods: Women were randomized to once daily subcutaneous liraglutide 1.8 mg or placebo for 52 weeks. Oral glucose tolerance test, C-peptide, insulin, HbA1c and lipids were determined at baseline, 26 weeks, and 52 weeks.

Results: In total, 75 women [mean age of 34.5 years, median BMI of 38.0 kg/m^2] were assigned to liraglutide (n = 37) or placebo (n = 38). At 52 weeks, T2D was diagnosed in 3% (n = 1) of the liraglutide group and 8% (n = 2) of the placebo group (p = 0.58), and prediabetes in 27% (n = 9) and 58% (n = 15), respectively (p = 0.032). In intention-to-treat analysis, 52-week liraglutide treatment reduced fasting glucose [group × time interaction p = 0.0047; estimated treatment difference (ETD) at 52 weeks −0.5 mmol/L, p = 0.0020], HbA1c [p = 0.020; ETD -0.2% (−2.1 mmol/mol), p = 0.056], weight (p = 0.0087; ETD -6.2 kg, p = 0.20) and waist circumference (p = 0.022; ETD -3.9 cm, p = 0.25), and improved Matsuda index (p = 0.049; ETD 0.7, p = 0.011) compared with placebo.

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Conclusions: Liraglutide reduces the prevalence of prediabetes and improves glycaemic control in women with obesity and pGDM. Due to few T2D cases, the effect of liraglutide on diabetes risk could not be reliably assessed.

1. Introduction

Gestational diabetes (GDM), a hyperglycemic state detected during pregnancy, is an established risk factor for later diabetes. Gestational diabetes is estimated to affect about 14% of pregnancies worldwide when using the diagnostic criteria of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (Wang et al., 2022).

The proportion of women who develop type 2 diabetes (T2D) after GDM varies between 3 and 70 percent, depending on the study population and follow-up time (Kim et al., 2002). The relative risk for T2D is 9.5 times higher in women with previous GDM (pGDM) than in women with a normoglycemic pregnancy. This risk is 17 times higher in the first five years after delivery (Vounzoulaki et al., 2020). One study showed a higher cumulative incidence of T2D in the first five postpartum years after GDM, which then seemed to reach the plateau after ten years (Kim et al., 2002). However, in recent studies the cumulative incidence of T2D has steadily increased over time after GDM (Vounzoulaki et al., 2020; Li et al., 2020; Perämäki et al., 2023).

Two major metabolic disorders, namely insulin resistance (IR) and β-cell dysfunction, play a major role in the pathogenesis of GDM (Homko et al., 2001). Insulin resistance related to latter part of pregnancy ("physiological insulin resistance of pregnancy") is exacerbated in women with obesity (Catalano, 2014). Insulin-requiring gestational diabetes and high body mass index (BMI) are known to be risk factors for T2D after GDM (Choi et al., 2022; Dennison et al., 2021; Rayanagoudar et al., 2016).

Early-onset type 2 diabetes (<40 years) appears to lead to more complications such as retinopathy, chronic kidney disease, neuropathy, and carotid artery plaque, than later-onset T2D (Soheilipour et al., 2023). Approximately one in three T2D patients develop cardiovascular disease which is a major cause of mortality among people with T2D (Einarson et al., 2018). A recently published study found that all-cause mortality and especially cardiovascular mortality is higher the earlier T2D is diagnosed (Kaptoge et al., 2023). The relative risk for a nonfatal myocardial infarct or a death caused by a coronary heart disease is greater in women with T2D than in men with T2D (Cosentino et al., 2020; Juutilainen et al., 2004).

Therefore, it is important to start prevention of T2D early after GDM. Pioglitazone, metformin, and intensive lifestyle modification have previously been shown to reduce the incidence of diabetes or delay its onset in women at high risk for T2D (Diabetes Prevention Program Research Group, 2019; Xiang et al., 2006). Improvement of glucose metabolism in women with pGDM has also been observed when a dipeptidyl peptidase 4 inhibitor or sodium-glucose cotransporter 2 inhibitor has been combined with metformin (Elkind-Hirsch et al., 2018, 2020a; Daniele et al., 2020). Although lifestyle interventions have shown good results in preventing diabetes after GDM, the effectiveness of lifestyle interventions may remain low due to very low engagement especially during the first postnatal year (O'Reilly et al., 2016).

Liraglutide is a glucagon-like peptide-1 receptor-agonist (GLP1-agonist) used for the treatment of T2D and obesity. Liraglutide reduces appetite and energy intake causing weight loss (van Can et al., 2014). As it stimulates pancreatic insulin secretion depending on glucose levels, it causes hypoglycemia only when used in conjunction with other antiglycemic therapy such as insulin and sulfonylureas (Drucker and Nauck, 2006; Whitten, 2016). Liraglutide has been shown to reduce the risk of major cardiovascular events in patients with T2D and high cardiovascular risk (Marso et al., 2016). It has also been shown to reduce lipotoxicity-induced inflammation in rats, and inflammation in patients with type 2 diabetes (Ao et al., 2020; Hogan et al., 2014).

We investigated the effect of 52-week liraglutide treatment, started within 25 months postpartum, on the incidence of T2D compared with placebo treatment in women with obesity and pGDM requiring medical treatment. As secondary outcomes, the prevalence of prediabetes and glycemic control were investigated.

2. Materials and methods

2.1. Study design

The study was an investigator-initiated, multi-center, placebo-controlled, double-blinded, randomized intervention trial. The subjects and researchers were blinded.

Four university hospitals in Finland participated in the study: Turku University Hospital (coordinating center), Oulu University Hospital, Tampere University Hospital and Kuopio University Hospital.

The study protocol was approved by the Finnish Medicines Agency (Fimea) (Clinical Trial number74-2019, protocol T160/2018) and permission for clinical trial was obtained from Turku Clinical Research Centre (T160/2018). The study was registered at EudraCT: 2018-002425-34 and at ClinicalTrials.gov as NCT04324229.

The study protocol, written information for subjects and consent form were approved by the Institutional Ethical Board of Turku University Central Hospital (Diary number 90/1800/2018). The study was conducted according to Good Clinical Practice standards. The participants were not paid for participating in the study.

2.2. Subject enrollment

The inclusion criteria applied for subject selection were as follows: (I) BMI ≥30 kg/m^2, (II) pGDM [P-glucose at 75 g 2-h OGTT ≥5.3 (fasting), 10.0 (1h), 8.6 (2h) or fasting P-glucose >5.5 mmol/l in more than 50 % of weekly home measurements] treated with metformin and/or insulin in the last pregnancy, (III) delivery ≤25 months ago. Prospective study subjects were excluded if they (I) had Type 1 or Type 2 diabetes mellitus, (II) end stage renal disease, (III) severe hepatic insufficiency, (IV) acute pancreatitis, (V) inflammatory bowel disease, (VI) were using metformin, betablockers or oral corticosteroids regularly or (VII) were breastfeeding. If the study subject became pregnant during the 52-week study product period, she was withdrawn from the study.

Women who met the criteria and were willing to participate in the study signed the consent form and were enrolled into the study. For ethical and safety reasons, enrollment could be done after the end of breastfeeding. After randomization and before starting the study product, subjects underwent oral glucose tolerance test (OGTT, 75 g glucose) to rule out diabetes (Fig. 1).

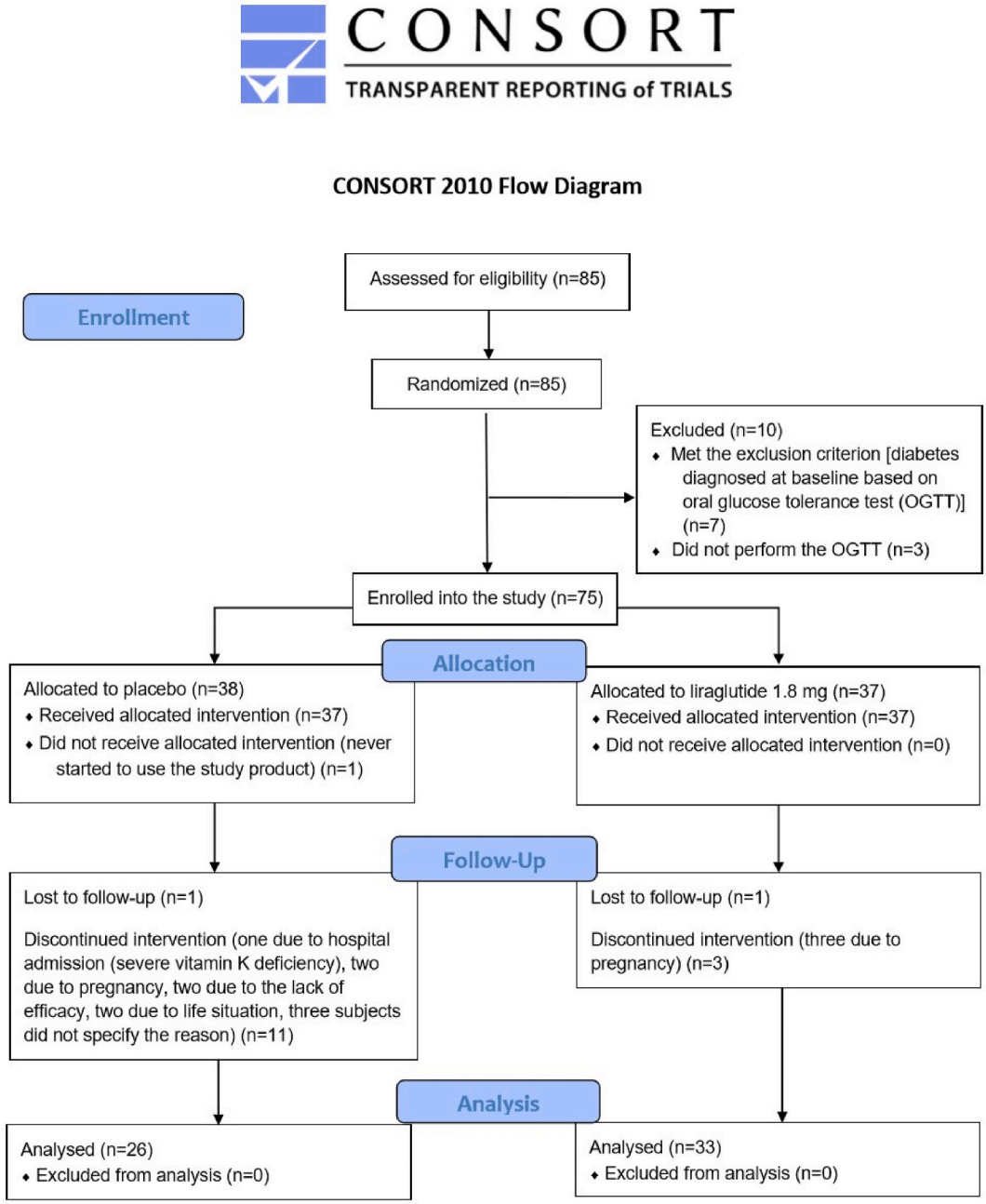

Fig. 1. CONSORT 2010 Flow Diagram.

2.3. Treatment and assessments

The women were randomized either to liraglutide (Victoza® 1.8 mg, strength 6 mg/ml) or placebo group. The study product was administered subcutaneously once a day. The dose was 0.6 mg for the first week, 1.2 mg for the second week and 1.8 mg after that. The study product was provided in a prefilled pen. The subjects collected the study products from the centers every three months.

Before starting the study product, retinographies were taken and a urine pregnancy test was performed to rule out pregnancy. Subjects were required to use an effective contraceptive method for the 52-week study period. Contraception was allowed to be a condom, intrauterine contraception device, a contraceptive capsule or oral hormonal contraception. All participants received similar verbal and written lifestyle guidance before starting the study product.

The clinical measurements, including weight, BMI, waist circumference, blood pressure and heart rate, and laboratory tests, including 75 g OGTT, insulin, C-peptide, HbA1c and lipids, were performed at baseline, 26 weeks and 52 weeks. The follow-up call was scheduled one month after the start of the study and drug dispensing visits were scheduled at research nurse at 3 months and 9 months. Treatment adherence was monitored by returning the used pens to the study nurse. Subjects with incident diabetes during trial were withdrawn from further study-specific procedures.

2.4. Determination of sample size

The sample size was initially calculated for five years, a one-year intervention period and a four-year follow-up period. The average cumulative incidence of T2D in the first five years after gestational diabetes is 36% (Kim et al., 2002).

In prediabetic subjects, lifestyle intervention with the average weight loss of 5.6 kg during 2.8 years reduced the incidence of diabetes by 58% (Knowler et al., 2002). It has also been shown that during 56 weeks of treatment of patients with T2D living with obesity, liraglutide 1.8 mg treatment resulted in 4.7% (5.0 kg) weight reduction (Davies et al., 2015).

Based on these findings we expected that the treatment with liraglutide would decrease the incidence of T2D by at least 58%. With calculation 0,42 × 36%, the incidence of T2D in liraglutide group in five years would be 15%. We expected that the incidence of T2D in the liraglutide group would be even lower, as liraglutide not only causes weight loss, but also decreases inflammation and improves the beta cell function (Ao et al., 2020; Hogan et al., 2014; Kim et al., 2014). Because the effect of liraglutide is additional to lifestyle changes, we estimated that the incidence of diabetes is 10% in liraglutide group.

We calculated the sample size at clincalc.com using Sample Size Calculator (Kane). We selected two independent study groups and dichotomous primary outcome (development of T2D - yes/no). We chose 36% for the anticipated incidence of T2D in placebo group and 10% for liraglutide group with an enrollment ratio of 1. We chose 0.05 for two-sided type I error and 80% for power. With these numbers we got a sample size of 40 people in each group, 80 in total.

2.5. Randomization and treatment allocation

The women who met the eligibility criteria were allocated randomly in the liraglutide and placebo groups. Randomization was performed by Novo Nordisk using center-stratified block randomization with a block size of two. Each box containing the study product was encoded by Novo Nordisk. An independent nurse who did not otherwise participate in the study had a list of codes and related products. The nurse informed the research centers which subject was assigned to the research product containing a particular code and which safety envelope belonged to every study subject. Each study center had sealed envelopes containing information about the treatment the subject received.

2.6. Measurements

Type 2 diabetes was defined according to World Health Organization (WHO) criteria as fasting plasma glucose $\geq$7.0 mmol/L or 2-h plasma glucose $\geq$11.1 mmol/L (World Health Organization & International Diabetes Federation). Plasma glucose was determined during a 75 g OGTT at 0 (fasting sample), 30 min, 60 min and 120 min.

Plasma insulin and serum C-peptide were determined during the OGTT at time points 0, 30min, 60min and 120min. Area under the curve (AUC) values for glucose, insulin and C-peptide were calculated from OGTT time points (0, 30min, 60min, 120min). Insulin resistance (IR) and beta cell function (%B) were assessed using The Homeostasis Model Assessment (HOMA2) Calculator (Radcliffe Department of Medicine). Insulin sensitivity during OGTT was determined using Matsuda index which is calculated using formula 10000/square root of ([fasting glucose x fasting insulin] x [mean glucose x mean insulin during OGTT]) (Matsuda and DeFronzo, 1999). Prediabetes was defined according to WHO criteria as impaired fasting plasma glucose (IFG, 6.1–6.9 mmol/L) and/or impaired glucose tolerance (IGT, 2 h plasma glucose of 7.8–11.0 mmol/L in 75 g OGTT) (World Health Organization & International Diabetes Federation). Laboratory tests were determined in the laboratories of each of the four university hospitals.

2.7. Data management and statistical analyses

In each center, the data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at University of Turku. The REDCap data was stored in a secure centralized database, which was accessible to researchers and research nurses involved in the study (Harris et al., 2009, 2019). Data were transferred from Redcap to JMP Pro (version 17.0.0) for statistical analyses. In the repeated measures analysis, time, group and time × group interaction were fixed effects, but only the

time × group interaction result was examined. If the time × group interaction of any continuous variable was statistically significant in the repeated measures analysis, an additional repeated measures analysis where detailed contrasts (baseline vs 26 weeks, baseline vs 52 weeks, 26 weeks vs 52 weeks) were programmed was performed for that variable using SAS [Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA)].

Both the intention-to-treat (ITT) analysis and per protocol (PP) analysis were conducted. For categorical variables, odds ratios were calculated and Fisher's test was used to calculate p-values. Continuous outcomes were evaluated using a linear mixed model suitable for repeated measurements using an unstructured covariance pattern. The mixed model permits missing data assuming that the missing data is random, which was true in this case. Data that did not follow a normal distribution were log- or square root transformed before being analyzed by repeated measurements. The results of the logarithmic and square root transformed data were reverted to the original scale for the tables, and estimated treatment differences (ETDs) were reported. A 95% confidence interval was used, and $p < 0.05$ (two-tailed) was considered statistically significant.

3. Results

3.1. Subject disposition and timeline

In total, 85 women were enrolled in the study. Of these, 82 women with pGDM underwent the OGTT at baseline (41 in Turku University Hospital, 9 in Tampere, 11 in Oulu and 21 in Kuopio). Type 2 diabetes was diagnosed in seven women at baseline based on OGTT, so 75 subjects were included in the final study population; 37 in the liraglutide group and 38 in the placebo group (Fig. 1). The first subject started the 52-week treatment on 9/2020 and the last subject on 10/2022.

Fifty-nine subjects completed the study. The completion rate of the study was lower in the placebo group (26 subjects, 68%) than in the liraglutide group (33 subjects, 89%). The reasons for discontinuing the study are summarized in Supplementary Table 1.

The following paragraphs describe the results of the ITT analysis.

3.2. Demographic and baseline characteristics

The study population consisted of women with a mean age of 34.5 years (SD 5.4), a median BMI of 38.0 kg/m^2 (Q1-Q3 34.3–43.8) and a mean time since latest pregnancy of 12.8 months (SD 4.1). All subjects were Caucasian. Baseline parameters for each group and both analyses are listed in Table 1. In total, 77% of the subjects met the criteria for metabolic syndrome and 41% of the subjects met the criteria for prediabetes. Sixty-five percent of women had a family history of T2D.

3.3. Primary outcome

During the study period of 52 weeks, T2D was diagnosed in 3% (n = 1) of the liraglutide group and in 7.7% (n = 2) of the placebo group (p = 0.58) (Table 2). The first T2D diagnosis occurred at 26 weeks in the placebo group and at 52 weeks in the liraglutide group (Table 2).

Table 1
Demographic characteristics at baseline.

	Intention-to-treat analysis		Per protocol analysis	
	Liraglutide	Placebo	Liraglutide	Placebo
Number of subjects	37	38	33	26
Age (years)	34.7 (5.4)	34.3 (5.6)	35.0 (5.32)	35.4 (5.6)
Time since delivery (months)	12.8 (4.1)	12.8 (4.2)	13.0 (4.0)	11.7 (3.8)
Family history of T2D	25 (68)	24 (63)	24 (73)	17 (65)
GDM treatment in the latest pregnancy				
Insulin treatment	15 (42)	13 (34)	12 (38)	8 (31)
Metformin treatment	7 (19)	5 (13)	7 (22)	4 (15)
Insulin + metformin	14 (39)	20 (53)	13 (41)	14 (54)
Weight (kg)	105.5 (26.1)	105.6 (17.9)	105.8 (26.7)	105.4 (18.5)
BMI (kg/m^2)	38.6 (7.5)	39.4 (5.8)	38.8 (7.4)	38.8 (5.4)
Waist circumference (cm)	114.6 (15.7)	114.3 (13.1)	114.8 (15.9)	112.5 (11.9)
Systolic Blood Pressure (mmHg)	131.2 (15.1)	134.1 (18.2)	130.8 (15.7)	133.2 (19.8)
Diastolic Blood Pressure (mmHg)	83.0 (11.9)	87.4 (11.9)	83.9 (12.3)	86.3 (12.3)
Heart rate (/min)	75.4 (11.5)	79.0 (10.6)	74.6 (11.3)	77.8 (10.9)
Prediabetes	15 (41)	16 (42)	14 (42)	13 (50)
• IFG	• 13 (35)	• 15 (39)	• 12 (36)	• 12 (46)
• IGT	• 6 (16)	• 6 (16)	• 5 (15)	• 6 (23)
Metabolic Syndrome	25 (71)	31 (82)	21 (68)	20 (77)

Data are mean (SD) for continuous variables, and n (%) for categorical variables. Abbreviations: BMI, body mass index; IFG, impaired fasting glucose; IGT; impaired glucose tolerance.

Table 2
Outcomes of the glucose metabolism and related indexes in liraglutide 1.8 mg and placebo groups by time.

	Baseline		Week 26			Week 52			
	Liraglutide	Placebo	Liraglutide	Placebo	ETD, p-value[a]	Liraglutide	Placebo	ETD, p-value[a]	p-value[b]
Primary outcome									
Type 2 diabetes	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	–	1 (3.0)	2 (7.7)	0.38 (0.03; 4.4, p = 0.58)	–
Secondary outcomes									
Prediabetes	15 (40.5)	16 (42.1)	6 (17.1)	16 (53.3)	0.2 (0.06; 0.6, p = 0.0035)	9 (27.3)	15 (57.7)	0.3 (0.09; 0.8, p = 0.032)	–
Impaired fasting glucose	13 (35.1)	15 (39.5)	4 (11.1)	14 (46.7)	0.1 (0.04; 0.5, p = 0.0019)	7 (21.2)	12 (46.2)	0.3 (0.1; 1.0, p = 0.053)	–
Impaired glucose tolerance	6 (16.2)	6 (15.8)	3 (8.6)	10 (33.3)	0.2 (0.05; 0.8, p = 0.027)	8 (24.2)	6 (23.1)	1.07 (0.3; 3.6, p = 1.00)	–
Fasting Glucose (mmol/L)	5.8 (5.7; 6.0)	5.9 (5.8; 6.1)	5.6 (5.4; 5.7)	6.0 (5.8; 6.2)	−0.5 (−0.7;-0.2, p = 0.0009)	5.6 (5.4; 5.8)	6.1 (5.9; 6.3)	−0.5 (−0.8;-0.2, p = 0.0020)	0.0047
Glucose at 30 min of OGTT (mmol/L)	9.3 (8.7; 9.8)	9.3 (8.8; 9.9)	8.5 (8.0; 9.1)	9.2 (8.6; 9.8)	−0.7	8.4 (7.8; 8.9)	9.3 (8.7; 9.9)	−0.9	0.097
Glucose at 60 min of OGTT (mmol/L)	9.1 (8.4; 9.8)	9.0 (8.3; 9.8)	8.3 (7.4; 9.1)	9.1 (8.2; 10.0)	−0.8	8.2 (7.3; 9.0)	9.4 (8.5; 10.4)	−1.2	0.067
Glucose at 120 min of OGTT[c] (mmol/L)	6.6 (6.2; 7.0)	7.0 (6.7; 7.4)	5.6 (5.1; 6.2)	6.7 (6.1; 7.3)	−1.1	6.2 (5.6; 6.8)	7.0 (6.3; 7.7)	−0.8	0.31
Glucose AUC (mmol/L x min)	975.5 (923.3; 1027.8)	994.1 (942.1; 1046.1)	878.6 (812.1; 945.2)	977.8 (908.2; 1047.4)	−99.2	894.6 (823.4; 965.8)	1008.1 (931.4; 1084.8)	−113.5	0.066
Fasting insulin[c] (mU/L)	20.7 (16.5; 25.3)	23.6 (19.2; 28.5)	18.4 (15.4; 21.7)	21.8 (18.3; 25.6)	−3.4	17.6 (14.8; 20.6)	22.5 (19.1; 26.2)	−4.9	0.53
Insulin at 30 min of OGTT[c]	95.5 (79.5; 113.1)	106.6 (89.9; 124.7)	99.3 (83.7; 116.2)	108.4 (91.4; 126.8)	−9.1	89.1 (72.2; 107.7)	112.7 (91.8; 135.7)	−23.6	0.46
Insulin at 60 min of OGTT[c]	123.5 (101.1; 144.3)	135.1 (111.8; 160.7)	162.3 (134.4; 192.8)	139.4 (112.4; 169.4)	22.9 (p = 0.27)	121.6 (96.5; 149.6)	135.7 (107.5; 167.1)	−14.1 (p = 0.48)	0.039
Insulin at 120 min of OGTT[c]	85.3 (68.1; 104.5)	100.3 (81.8; 120.7)	85.9 (64.9; 109.7)	109.0 (84.6; 136.6)	−23.1	83.8 (61.4; 109.6)	112.7 (85.5; 143.8)	−28.9	0.55
Insulin AUC[c] (U/L x min)	11.6 (9.7; 13.6)	12.9 (10.9; 15.0)	13.5 (11.4; 15.7)	13.4 (11.3; 15.8)	0.03	11.1 (9.0; 13.4)	13.5 (11.1; 16.2)	−2.4	0.064
Fasting C-peptide[c] (nmol/L)	1.1 (1.0; 1.2)	1.1 (1.0; 1.3)	1.1 (1.0; 1.2)	1.2 (1.0; 1.3)	−0.1 (p = 0.70)	1.0 (0.9; 1.1)	1.2 (1.1; 1.3)	−0.2 (p = 0.036)	0.032
C-peptide at 30 min of OGTT[c]	2.6 (2.3; 2.9)	2.8 (2.5; 3.1)	2.7 (2.4; 3.0)	2.7 (2.4; 3.0)	0.0	2.5 (2.2; 2.8)	2.9 (2.5; 3.2)	−0.4	0.12
C-peptide at 60 min of OGTT[c]	3.6 (3.2; 4.0)	3.7 (3.3; 4.1)	4.3 (3.9; 4.8)	3.7 (3.3; 4.1)	0.6 (p = 0.019)	3.6 (3.2; 4.1)	3.6 (3.1; 4.1)	0.0 (p = 0.88)	0.0017
C-peptide at 120 min of OGTT[c]	3.2 (2.9; 3.6)	3.4 (3.0; 3.8)	3.3 (2.9; 3.7)	3.5 (3.0; 3.9)	−0.2	3.2 (2.8; 3.6)	3.4 (3.0; 3.9)	−0.2	0.85
C-peptide AUC (nmol/L x min)	363.0 (326.3; 399.7)	381.4 (345.5; 417.8)	401.3 (368.8; 433.8)	378.5 (345.5; 411.5)	22.8 (−23.5:69.1, p = 0.33)	359.1 (321.1; 397.1)	380.7 (341.1; 420.3)	−21.6 (−76.5; 33.2, p = 0.43)	0.015
HbA1c (%)	5.6	5.6	5.4	5.7	−0.3	5.5	5.7	−0.2	0.020
HbA1c (mmol/mol)	38.1 (36.6; 39.5)	37.7 (36.3; 39.1)	35.5 (34.0; 37.0)	38.3 (36.6; 40.0)	−2.8 (−5.0;-0.5, p = 0.017)	36.4 (35.0; 37.7)	38.5 (36.8; 40.2)	−2.1 (−4.3; 0.06, p = 0.056)	
HOMA2-IR[d]	2.4 (2.2; 2.7)	2.6 (2.3; 2.9)	2.5 (2.2; 2.7)	2.6 (2.3; 2.9)	−0.1 (p = 0.38)	2.3 (2.0; 2.5)	2.7 (2.5; 3.1)	−0.4 (p = 0.016)	0.046

(*continued on next page*)

Table 2 (*continued*)

	Baseline		Week 26			Week 52			
	Liraglutide	Placebo	Liraglutide	Placebo	ETD, p-value[a]	Liraglutide	Placebo	ETD, p-value[a]	p-value[b]
HOMA2 -%B[d]	126.7 (116.1; 138.2)	130.8 (120.0; 142.5)	143.8 (132.0; 156.8)	127.7 (116.8; 139.6)	−16.1 (p = 0.060)	133.4 (122.8; 145.0)	129.0 (118.2; 140.8)	−4.4 (p = 0.58)	0.0037
Matsuda Index[d]	2.1 (1.8; 2.5)	1.9 (1.6; 2.2)	2.3 (1.9; 2.7)	1.9 (1.6; 2.2)	0.4 (p = 0.12)	2.5 (2.1; 3.0)	1.8 (1.5; 2.2)	0.7 (p = 0.011)	0.049

The outcomes are obtained from the intention-to-treat population (n = 75) excluding HbA1c which was obtained from 28 subjects. Data are mean (95% CI) for absolute measures, mean (95% CI; p value) for ETDs and n (%) for categorical variables with ETD as odds ratio (95% CI). The log- and square root -transformed results have been converted back to the original scale for easier visualization. Abbreviations: ETD, estimated treatment difference; OGTT, oral glucose tolerance test; AUC, area under the curve.

[a] We report p-values for ETD's only for those variables for which the group × time interaction was statistically significant. 95% CI is reported only for those variables where log or square root -transformed data were not used.

[b] group × time interaction.

[c] Analysis performed with square root -transformed values.

[d] Analysis performed with log-transformed values.

3.4. Secondary outcomes

3.4.1. Glycaemic control

At 52 weeks, the prevalence of prediabetes was significantly lower in liraglutide group compared to placebo (OR = 0.28 [0.09; 0.82], p = 0.032). In the liraglutide group, the proportion of women with prediabetes decreased from 41% (n = 15) to 27% (n = 9) during the 52 weeks, while in the placebo group, the proportion of women with prediabetes increased from 42% (n = 16) at baseline to 58% (n = 15) at 52 weeks. In the liraglutide group, the percentage of women with IFG decreased from 35% (n = 13) to 21% (n = 7) while in the placebo group, the percentage of women with IFG increased from 39% (n = 15) at baseline to 46% (n = 12) at 52 weeks. At 52 weeks, the OR for IFG was 0.31 (0.10; 0.98, p = 0.053) (Table 2). There were no significant differences in the prevalence of IGT between the groups (Table 2).

Liraglutide treatment significantly lowered fasting plasma glucose (FPG) and HbA1c levels when compared with placebo during the 52-week trial (p = 0.0047 and p = 0.020 respectively). At 52 weeks, the ETD for FPG was −0.5 mmol/L (95% CI from −0.8 to −0.2, p = 0.0020) (Table 2, Fig. 2). In the liraglutide group, FPG decreased by 0.2 mmol/L and HbA1c by 0.1% (1.7 mmol/mol) during the 52-week treatment, when compared to baseline values (95% CI for FPG from −0.41 to −0.030, p = 0.024 and 95% CI for HbA1c from −2.4% to −2.2% (−3.2 to −0.2 mmol/mol), p = 0.031). The reduction in FPG and HbA1c was already observed at 26 weeks (Table 2). No significant changes in FPG or HbA1c were observed in the placebo group, when compared to baseline values.

During the 52-week trial, plasma glucose responses during OGTTs (AUC) did not differ significantly between the groups (p = 0.066).

3.4.2. Weight, BMI, waist circumference, metabolic syndrome, blood pressure, heart rate and lipids

Weight, BMI, and waist circumference significantly decreased with liraglutide treatment during the 52-week trial compared with placebo treatment (p = 0.0087, p = 0.0068 and p = 0.022 respectively). In the liraglutide group, weight decreased by 4.9 kg (p < 0.0001), BMI by 1.7 kg/m^2 (p < 0.0001) and waist circumference by 4.6 cm (p = 0.0005) between 0 and 52 weeks. These improvements were already seen at 26 weeks (Table 3). No significant changes in weight, BMI or waist circumference were observed in the placebo group during the 52 weeks (Table 3).

Heart rate increased slightly in the liraglutide group, but this change was not statistically significant (Table 3). No changes in systolic or diastolic blood pressure were observed between the groups (Table 3). Liraglutide did not affect total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides (Table 4). The percentage of women with metabolic syndrome decreased in both groups but slightly more in the liraglutide group (Table 3).

3.4.3. Insulin, C-peptide, beta cell function, insulin resistance and insulin sensitivity

Insulin sensitivity, as assessed by the Matsuda index, increased significantly with liraglutide treatment during the 52-week trial compared with placebo (p = 0.049). At 52 weeks, the ETD for Matsuda index was 0.7 (p = 0.011) (Table 2, Fig. 2). In the liraglutide-group, Matsuda index was significantly higher at 52 weeks when compared with baseline value (p = 0.0054), while in the placebo group, Matsuda index at week 52 was comparable with baseline value (p = 0.52).

There was also a statistically significant difference in fasting insulin resistance, as assessed by the HOMA2-IR, between the groups during the 52-week trial (p = 0.046). Indeed, at 52 weeks, HOMA2-IR was significantly smaller in liraglutide group, when compared with placebo group (ETD -0.4 [p = 0.016]) (Table 2), although no significant changes in the HOMA2-IR values between 52 weeks and baseline were observed either in liraglutide nor placebo group.

There was a statistically significant difference in fasting beta cell function as assessed by the HOMA2-%B between the groups during the 52-week trial (p = 0.0037). HOMA2-%B increased by 14 % between 0 and 26 weeks in the liraglutide group (p < 0.0001). However, the HOMA2-%B decreased between 26 and 52 weeks, remaining slightly above the baseline level, so there was no

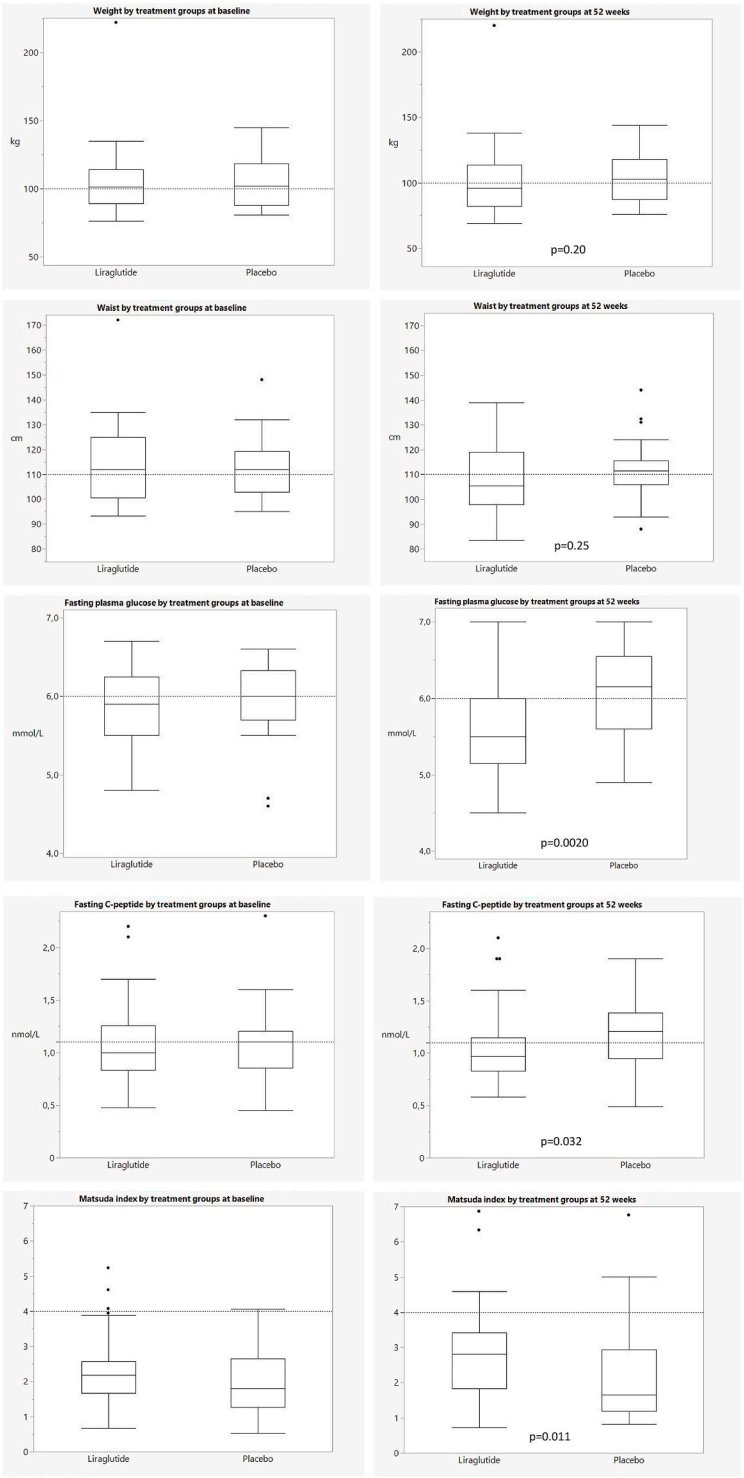

Fig. 2. Box plots of weight, waist circumference, fasting plasma glucose, fasting C-peptide and Matsuda index by treatment groups at baseline and the end of the 52-week treatment period. The graphs are generated from the original data (n = 59), but the p-values are based on a repeated measures analysis that also used log- or square-root transformed data to achieve a normal distribution. Details of the data used in the repeated measures analysis can be found in Tables 2 and 3.

statistically significant change in HOMA2-%B between 0 and 52 weeks (Table 2). No significant changes in HOMA2-%B were observed in the placebo group (Table 2).

Insulin and C-peptide levels at different time points of the OGTT are shown in Table 2. During the 52-week trial, serum insulin responses during OGTTs (AUC) did not differ between the groups (p = 0.064) (Table 2). During the 52-week trial, a statistically significant difference was observed between the groups for C-peptide responses during OGTTs (AUC) (p = 0.015). However, there was no statistically significant difference between the groups at 52 weeks (Table 2).

Table 3
Outcomes of the physiological measurements and metabolic syndrome in liraglutide 1.8 mg and placebo groups by time.

	Baseline		Week 26			Week 52			
	Liraglutide	Placebo	Liraglutide	Placebo	ETD, p-value[a]	Liraglutide	Placebo	ETD, p-value[a]	p-value[b]
Weight[c] (kg)	103.1 (96.9; 109.7)	104.1 (97.9; 110.7)	98.2 (91.9; 104.8)	103.8 (97.2; 110.8)	−5.6 (p = 0.24)	98.2 (91.8; 105.0)	104.4 (97.6; 111.6)	−6.2 (p = 0.20)	0.0087
BMI[d] (kg/m^2)	38.3 (36.2; 40.4)	39.2 (37.1; 41.3)	36.5 (34.4; 38.7)	39.0 (36.8; 41.3)	−2.5 (p = 0.11)	36.5 (34.3; 38.7)	39.3 (37.0; 41.6)	−2.8 (p = 0.082)	0.0068
Waist circumference[d] (cm)	114.1 (109.5; 118.8)	113.9 (109.4; 118.5)	109.0 (104.5; 113.7)	113.7 (109.0; 118.5)	−4.6 (p = 0.17)	109.5 (104.9; 114.2)	113.4 (108.7; 118.2)	−3.9 (p = 0.25)	0.022
Systolic blood pressure (mmHg)	131.1 (125.6; 136.6)	134.1 (128.6; 139.5)	127.6 (123.2; 132.0)	132.3 (127.5; 137.1)	−4.7	128.0 (122.4; 133.5)	133.2 (127.1; 139.2)	−5.2	0.83
Diastolic blood pressure (mmHg)	82.9 (79.0; 86.8)	87.4 (83.5; 91.3)	80.3 (77.3; 83.3)	84.8 (81.5; 88.1)	−4.5	81.0 (77.5; 84.6)	84.4 (80.5; 88.2)	−3.4	0.83
Heart rate (/min)	75.4 (71.7; 79.0)	78.7 (75.0; 82.4)	79.9 (76.4; 83.4)	77.2 (73.4; 81.0)	2.7	80.4 (76.9; 83.9)	79.3 (75.5; 83.1)	1.1	0.060
Metabolic syndrome [n (%)]	25 (71.4)	31 (81.6)	19 (52.8)	23 (79.3)	0.29 (0.096; 0.89, p = 0.037)	19 (59.4)	18 (75.0)	0.49 (0.15; 1.56, p = 0.26)	

The outcomes are obtained from the intention-to-treat population. Data are mean (95% CI) for absolute measures, mean (95% CI; p value) for ETDs and n (%) for categorical variables with ETD as odds ratio (95% CI). The log- and square root -transformed results have been converted back to the original scale for easier visualization. Therefore, the values are not absolute and may differ from Table 2. Abbreviations: ETD, estimated treatment difference; BMI, body mass index.

[a] We report p-values for ETD's only for those variables for which the group × time interaction was statistically significant. 95% CI is reported only for those variables where log or square root -transformed data were not used.

[b] group × time interaction.

[c] Analysis performed with square root -transformed values.

[d] Analysis performed with log-transformed vales.

Table 4
Outcomes of the lipids in liraglutide 1.8 mg and placebo groups by time.

	Baseline		Week 26			Week 52			
	Liraglutide	Placebo	Liraglutide	Placebo	ETD, p-value[a]	Liraglutide	Placebo	ETD, p-value[a]	p-value[b]
Total cholesterol[c] (mmol/l)	4.5 (4.2; 4.8)	4.5 (4.2; 4.8)	4.4 (4.1; 4.6)	4.4 (4.1; 4.7)	0.0	4.4 (4.2; 4.7)	4.5 (4.2; 4.7)	−0.1	0.86
HDL cholesterol[c] (mmol/l)	1.3 (1.1; 1.4)	1.2 (1.1; 1.3)	1.3 (1.2; 1.4)	1.2 (1.1; 1.3)	0.1	1.2 (1.1; 1.3)	1.2 (1.1; 1.3)	0.0	0.79
LDL cholesterol (mmol/l)	2.8 (2.6; 3.1)	2.8 (2.6; 3.1)	2.7 (2.4; 2.9)	2.8 (2.6; 3.1)	−0.1	2.8 (2.6; 3.1)	2.9 (2.6; 3.1)	−0.1	0.28
Triglyceride[d] (mmol/l)	1.4 (1.2; 1.6)	1.5 (1.3; 1.7)	1.2 (1.0; 1.3)	1.4 (1.2; 1.5)	−0.2	1.1 (1.0; 1.2)	1.3 (1.1; 1.5)	−0.2	0.38

The outcomes are obtained from the intention-to-treat population. Data are mean (95% CI) for absolute measures and mean (95% CI; p value) for ETDs. The log- and square root -transformed results have been converted back to the original scale for easier visualization. Abbreviations: ETD, estimated treatment difference.

[a] We report p-values for ETD's only for those variables for which the group × time interaction was statistically significant. 95% CI is reported only for those variables where log or square root -transformed data were not used.

[b] group × time interaction.

[c] Analysis performed with log-transformed values.

[d] Analysis performed with square root -transformed values.

3.5. ITT vs PP analysis

The results of the PP analysis can be seen in Appendix1. In contrast to the ITT analysis, the PP analysis showed a significant increase in heart rate in the liraglutide group and no statistically significant changes in fasting C-peptide levels, HbA1c or HOMA2-%B between the groups (note the small number of subjects (n = 21) for HbA1c).

3.6. Safety and tolerability

One case of cholecystitis requiring surgery occurred in the liraglutide group. The safety envelope was not opened, and the participant was able to continue using the study product two weeks after the surgery. Three subjects became pregnant in the liraglutide group and discontinued the study. One had stopped taking the study product before becoming pregnant. One subject used the study product for six weeks and the other for ten weeks while pregnant. Several subjects in the liraglutide group reported nausea at the beginning of the study product period, but nausea eased or resolved completely within weeks. One subject in the liraglutide group reported a significant increase in resting heart rate and two subjects reported injection site reactions which stopped occurring over time. None of the subjects reported occurrence of depression as a side effect. However, it should be noted that the study subjects reported adverse effects in general and were not specifically asked about the occurrence of depression.

One subject in the liraglutide group used the study product for 6 months at a dose of 1.8 mg/day, but then reduced the dose to 1.2 mg due to persistent diarrhea.

4. Discussion

In this randomized placebo-controlled study, liraglutide treatment did not decrease the incidence of T2D. However, we demonstrated the efficacy of 52-week liraglutide versus placebo treatment in reducing weight, BMI, waist circumference, fasting plasma glucose, and insulin resistance, and in improving insulin sensitivity in women with obesity and pGDM.

The study population was at high risk of developing T2D because they had a median BMI of 38.0 kg/m^2 emphasizing the significant obesity and had GDM requiring medication in their most recent pregnancy. As mentioned earlier, the original intention was to have a 4-year follow-up after the 52-week treatment period and assess the effect of liraglutide on T2D risk during this time. However, for ethical reasons, we shortened the study to two years consisting of a 52-week study product period and one year of open-label follow-up. Ethical reasons included the subjects' hopes for a new pregnancy and their wish to continue or start using the same or a different GLP-1 analogue after the 52-week study period. During the 52-week study period, the number of people who developed the major endpoint, T2D, was small, so the effectiveness of liraglutide in preventing T2D cannot be reliably assessed based on this study. Despite the small number of subjects, statistically significant differences were still obtained highlighting the effectiveness of liraglutide in reducing weight and waist circumference and enhancing glucose metabolism. Further studies with longer follow-up periods and larger numbers of subjects are needed.

In this study, we chose to apply a dose of 1.8 mg of liraglutide because of a new treatment indication and to minimize side effects. Although 3.0 mg has been found to be more effective in reducing weight and improving glycaemic control, it causes more gastrointestinal adverse effects (Davies et al., 2015). FDA has approved liraglutide for the treatment of T2D at a dose of 1.2–1.8 mg/day and for weight loss at a dose of 3.0 mg/day (Tucker, 2014). No treatment dose has been defined for the prevention of diabetes, as liraglutide does not yet have such an indication, so the use of liraglutide in this study was off-label. There are currently more effective GLP-1 agonists available than liraglutide, which in the context of this study would be worth investigating in women with obesity and pGDM (Rubino et al., 2022).

Recently, Foghsgaard et al. studied the effect of 52-week liraglutide treatment with 1.8 mg in women with overweight or obesity and pGDM. In addition to improved glucose tolerance in OGTT (AUC) [ETD -173 (95% CI -250;-97) mmol/L x min], they found that liraglutide improved fasting plasma glucose [ETD -0.2 (95% CI -0.4;-0.1) mmol/L], HbA1c [ETD -0.2% (−2.2 (95% CI -3.5;-0.8) mmol/mol)] and bodyweight [ETD -3.9 (95% CI -6.2;-1.6) kg] (Foghsgaard et al., 2024). In terms of weight loss, our results are in line with other studies. The average weight loss of 4.8% is comparable to the study (Davies et al., 2015) in which patients with T2D used liraglutide 1.8 mg for 56 weeks (weight loss of 4.7 %, 5.0 kg), but slightly lower in percentage terms than in the study of Foghsgaard et al. (2024). In the liraglutide group, the subjects' weight decreased for the first six months and remained stable thereafter, which is nearly in line with the results of other studies in which liraglutide 1.8 mg has been administered (Davies et al., 2015; Foghsgaard et al., 2024). ETD of −0.5 mmol/L for fasting glucose in our study is slightly higher than in the study of Foghsgaard et al. (2024). Unlike the study of Foghsgaard et al. (2024), our study found no significant difference between the groups in glucose tolerance during OGTT as assessed by AUC. This may be partly explained by the small sample size of this study and a relatively large standard error, reflecting the dispersion in the results.

In contrast to the Foghsgaard et al. study (2024), Matsuda index showed an improvement in insulin sensitivity in the liraglutide group in the current study. The difference may be due to the slightly different study population, as the subjects in our study had BMI of at least 30 kg/m^2, while the subjects in the study of Foghsgaard et al. had BMI of 25–45 kg/m^2 (Foghsgaard et al., 2024). As weight and waist circumference decreased, the amount of visceral fat likely decreased, leading to a reduction in hepatic insulin resistance and improved insulin sensitivity. However, a recent study suggests that liraglutide has a weight-loss independent effect on insulin sensitivity in individuals with obesity and prediabetes. The study found an improvement in the Matsuda Index even before weight loss (Mashayekhi et al., 2024). However, in our study, weight loss is a confounding factor and the independent effect of liraglutide on the improvement in insulin sensitivity cannot be reliably assessed. It is possible that the improvement in insulin sensitivity is also due to a

reduction in inflammation, but further research on this is still needed. Like Foghsgaard et al., we did not detect any changes in lipids in our study.

Previously, the effect of 80–84 weeks of a combination of liraglutide and metformin on HOMA-IR compared with a combination of metformin and placebo in women with overweight/obesity and pGDM was studied, but no statistically significant difference was observed (Elkind-Hirsch et al., 2020b). In this study we demonstrated that liraglutide significantly reduced insulin resistance compared with placebo treatment. In terms of the HOMA2-%B, a significant improvement of 14% was seen in the liraglutide group between 0 and 26 weeks in the ITT analysis. Compared to the study by Elkind-Hirsch et al. (2020), our subjects had on average 5 kg more weight at baseline and fasting glucose was on average 0.6–0.7 mmol/L higher, so the difference in the reduction of insulin resistance may be explained by the slightly worse metabolic status of our subjects (Elkind-Hirsch et al., 2020b). Few studies can be found reporting an effect of liraglutide on HOMA2-%B in subjects without T2D. In one study, 26 weeks of liraglutide treatment improved HOMA2-%B from 51% to 92%, but the subjects already had T2D and a much lower HOMA2-%B at baseline than the subjects in our study (Schiavon et al., 2021). Another study of subjects with T2D reported that liraglutide improved HOMA2-%B by 41% (from 85.86 to 120.81) during one year, but at five years HOMA2-%B was only 21% better than baseline (Rasouli et al., 2024).

The limitations of the study, in addition to the small sample size, few T2D cases and a short follow-up period, include the lack of data regarding the impact of lifestyle on the results and the lack of drug wash-out period. In this study, the liraglutide group and the placebo group were given similar verbal and written lifestyle guidance. Assessing the impact of lifestyle guidance could have been improved by using the intensive lifestyle group as a control group and recording calorie intake and physical activity levels at the beginning and end of the study. The study did not include a drug wash-out period, so based on this study it is not possible to examine whether the results are maintained after stopping liraglutide treatment. However, this research population still has an examination visit and laboratory tests, including an OGTT, at two years, so additional information on the permanence of the changes will be obtained then. According to the study of Fogshgaard et al., the positive effects on OGTT and fasting glucose were lost after a one-week wash-out (Foghsgaard et al., 2024).

With increasing prevalence of maternal obesity and GDM, the postnatal period after the end of breastfeeding offers an opportunity to improve maternal health and reduce the weight of women living with obesity (Wang et al., 2022; Poston et al., 2016). While it may be difficult to realize and engage in lifestyle interventions, other options to get weight loss started are also needed. This study showed that one year of liraglutide treatment started no later than 25 months after delivery has beneficial effects on maternal weight and glycaemic control compared with placebo treatment.

In conclusion, due to few T2D cases and a short follow-up, the effect of liraglutide on diabetes risk could not be reliably assessed. This study supports the findings of previous studies on the effectiveness of liraglutide on weight loss and glycaemic control. The study showed that liraglutide also reduced insulin resistance and increased insulin sensitivity in women with obesity and pGDM. Since a significant difference in the prevalence of prediabetes at the end of the study period was found between the liraglutide and placebo groups, liraglutide, at least when used continuously, could be a potential drug option in this population with a high risk of diabetes. Further research is needed to determine whether liraglutide reduces the incidence of T2D in the longer term and whether the beneficial effects of liraglutide on weight, glycaemic control, insulin resistance and insulin sensitivity are maintained after stopping liraglutide treatment.

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CRediT authorship contribution statement

Roosa Perämäki: Writing – original draft, Investigation, Formal analysis, Data curation. **Meri-Maija Ollila:** Writing – review & editing, Methodology, Investigation. **Janne Hukkanen:** Writing – review & editing, Methodology. **Marja Vääräsmäki:** Writing – review & editing. **Jukka Uotila:** Writing – review & editing. **Saara Metso:** Writing – review & editing, Investigation. **Heidi Hakkarainen:** Writing – review & editing, Investigation. **Reeta Rintamäki:** Writing – review & editing. **Eliisa Löyttyniemi:** Writing – review & editing, Methodology, Formal analysis. **Heidi Immonen:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Risto Kaaja:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2025.100596.

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