Glucose-Lowering Effects and Low Risk of Hypoglycemia in Patients With Maturity-Onset Diabetes of the Young When Treated With a GLP-1 Receptor Agonist: A Double-Blind, Randomized, Crossover Trial

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OBJECTIVE

The most common form of maturity-onset diabetes of the young (MODY), hepatocyte nuclear factor 1α (HNF1A diabetes: MODY3) is often treated with sulfonylureas that confer a high risk of hypoglycemia. We evaluated treatment with GLP-1 receptor agonists (GLP-1RAs) in patients with HNF1A diabetes.

RESEARCH DESIGN AND METHODS

Sixteen patients with HNF1A diabetes (8 women; mean age 39 years [range 23–67 years]; BMI 24.9 ± 0.5 kg/m^2 [mean ± SEM]; fasting plasma glucose [FPG] 9.9 ± 0.9 mmol/L; HbA$_{1c}$ 6.4 ± 0.2% [47 ± 3 mmol/mol]) received 6 weeks of treatment with a GLP-1RA (liraglutide) and placebo (tablets), as well as a sulfonylurea (glimepiride) and placebo (injections), in randomized order, in a double-blind, crossover trial. Glimepiride was up-titrated once weekly in a treat-to-target manner; liraglutide was up-titrated once weekly to 1.8 mg once daily. At baseline and at the end of each treatment period a standardized liquid meal test was performed, including a 30-min light bicycle test.

RESULTS

FPG decreased during the treatment periods (−1.6 ± 0.5 mmol/L liraglutide [*P* = 0.012] and −2.8 ± 0.7 mmol/L glimepiride [*P* = 0.003]), with no difference between treatments (*P* = 0.624). Postprandial plasma glucose (PG) responses (total area under the curve) were lower with both glimepiride (2,136 ± 292 min × mmol/L) and liraglutide (2,624 ± 340 min × mmol/L) compared with baseline (3,127 ± 291 min × mmol/L; *P* < 0.001, glimepiride; *P* = 0.017, liraglutide), with no difference between treatments (*P* = 0.121). Eighteen episodes of hypoglycemia (PG ≤3.9 mmol/L) occurred during glimepiride treatment and one during liraglutide treatment.

CONCLUSIONS

Six weeks of treatment with glimepiride or liraglutide lowered FPG and postprandial glucose excursions in patients with HNF1A diabetes. The glucose-lowering effect was greater with glimepiride at the expense of a higher risk of exclusively mild hypoglycemia.

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A slide set summarizing this article is available online.

Maturity-onset diabetes of the young (MODY) is responsible for 1–2% of all cases of diabetes. MODY is a heritable, monogenic form of diabetes, is not insulin dependent at onset, and often is diagnosed at a young age (1). It is genetically heterogeneous; mutations in more than eight different genes give rise to specific forms of MODY. The majority of patients who are diagnosed with MODY have mutations in the hepatocyte nuclear factor 1α (*HNF1A*) gene (HNF1A diabetes, or MODY3) (2–5). HNF1A diabetes is characterized by rapid progression from impaired glucose tolerance to a progressive diabetes due to a continuous loss of β-cell function (4,6). HNF1A diabetes often develops abruptly with classic hyperglycemic symptoms such as polyuria and polydipsia, which is why misclassification as type 1 diabetes (7) frequently occurs. Patients with HNF1A diabetes have the same risk of developing diabetic micro- and macrovascular complications as patients with type 2 diabetes, and strict glycemic control combined with proper treatment of complications is crucial for a good prognosis. The *HNF1A* defect results in reduced concentrations of ATP in β-cells, which in turn lowers insulin secretion. Sulfonylureas (SUs) bind to a membrane protein closely related to the ATP-dependent potassium (K^+) channel (K_{ATP} channel) in the β-cell, thereby closing the channel (8). Closing the K_{ATP} channel causes membrane depolarization, leading to the opening of the voltage-gated calcium (Ca^{2+}) channel and increasing intracellular Ca^{2+} concentration, eliciting insulin secretion. Hence, the use of SUs in patients with HNF1A diabetes can bypass their reduced concentrations of ATP and stimulate insulin secretion. Because of a high sensitivity to SUs (4,9,10) combined with normal or even increased insulin sensitivity, this treatment is effective in lowering of plasma glucose (PG). However, because of the glucose-independent mechanism of SUs, treatment often is associated with hypoglycemia even when using relatively low doses (4,11). In 2006, Tuomi et al. (11) demonstrated that during physical exercise in patients with HNF1A diabetes (light cycling for 30 min approximately 2 h after ingesting a meal), hypoglycemia was observed in 40% of subjects treated with an SU (glibenclamide); one patient experienced hypoglycemia for 12 h. In contrast to the glucose-independent insulinotropic effect of SUs, GLP-1 receptor agonists (GLP-1RAs) exert an insulinotropic effect in a strictly glucose-dependent manner, with no effect at PG concentrations <4–5 mmol/L (12,13), translating into a low risk of hypoglycemia. Therefore, GLP-1RA treatment might be safe and efficacious for patients with HNF1A diabetes, but so far only a few cases have been reported (14–16).

The objectives of this trial were to compare the effects of 6 weeks of treatment with the GLP-1RA liraglutide and glimepiride on fasting PG (FPG) and the risk of hypoglycemia in patients with HNF1A diabetes.

RESEARCH DESIGN AND METHODS

Trial Design and End Points

This double-blind, randomized, crossover trial was conducted from September 2012 to August 2013 in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All clinical visits and experiments were conducted at Diabetes Research Center, Department of Medicine, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark.

The primary end point was FPG after 6 weeks of treatment. Secondary end points encompassed the number and severity of hypoglycemic episodes, serum fructosamine, and responses of pancreatic hormones (insulin, C-peptide, and glucagon) and counterregulatory hormones (growth hormone, cortisol, epinephrine, and norepinephrine) following a test meal combined with a 30-min bicycle test.

After receiving thorough information about the trial and signing informed consent, each patient was screened and evaluated according to inclusion and exclusion criteria. Inclusion criteria included Caucasian race, presence of HNF1A diabetes, older than 18 years of age; BMI >19 kg/m^2; normal hemoglobin of >8.2 mmol/L (males) and >7.2 mmol/L (females); normal blood pressure (<160/100 mmHg); informed consent; capability of performing a light cycling test (heart rate 100–120 bpm during 30 min); use of intrauterine or hormonal contraception (women). Exclusion criteria included heart failure (New York Heart Association class III or IV); plasma creatinine concentrations >130 μmol/L and/or albuminuria; liver disease (alanine aminotransferase and/or aspartate aminotransferase more than twice the upper limit of normal serum concentrations); anemia; acute or chronic pancreatitis; goiter or thyroid cancer; pregnancy or breast feeding; inability to complete the trial; treatment-naïve patients with HbA_{1c} <7.0% (53 mmol/mol); treatment with medicine that could not be paused for 12 h; and known allergy to trial medication.

Trial Medication

After a 1-week washout of blood glucose–lowering drugs, patients were randomized to receiving either *1*) once-daily injections of liraglutide plus placebo tablets or *2*) once-daily injections of placebo plus glimepiride tablets for 6 weeks. After ending the first treatment period and following a 1-week washout, patients received the treatment that they were not randomized to in period 1. Randomization codes were provided by the central hospital pharmacy, and the patients were allocated to treatment groups by a nonblinded colleague who was otherwise not involved in the trial. Adequate randomization was ensured by stratification based on a computer-generated random number sequence. The principal investigator (S.H.Ø.) enrolled the patients but remained blinded throughout the trial period and data analyses. Eight patients started taking liraglutide plus placebo and 8 patients started taking glimepiride plus placebo. Liraglutide (Victoza) and placebo injection pens were indistinguishable (provided in sequentially numbered containers) and provided by Novo Nordisk A/S; identical appearing glimepiride and placebo tablets (encapsulation) were provided by the central hospital pharmacy. Capsules with glimepiride and placebo were each provided in 0.5 and 1.0 mg doses. Patients were initiated on a dose of glimepiride, which was 0.5 mg lower than their regular daily dose of glimepiride (or the analogous dose of another SU), and up-titrated with 0.5 mg glimepiride/placebo daily every week in a treat-to-target manner (weekly mean FPG goal in the range of 5.0–5.9 mmol/L). Liraglutide/placebo was initiated at 0.6 mg once daily and escalated by 0.6 mg every week to the target dose of 1.8 mg once daily. During the full trial period of 14 weeks (2 periods

of 6 weeks of treatment and 2 1-week washouts) the patients self-monitored blood glucose (SMBG) and registered episodes of hypoglycemia and trial medication dosages in a diary. Hypoglycemia was classified as *1*) mild hypoglycemia (documented symptomatic hypoglycemia confirmed by PG reading <4.0 mmol/L *or* asymptomatic hypoglycemia with PG <4.0 mmol/L) or *2*) severe hypoglycemia (symptoms of hypoglycemia with need for assistance from another person). If no PG value was available, neurological recovery following normalization of PG was considered sufficient evidence of hypoglycemia.

Clinical Visits

Experiments took place on three occasions: at baseline (after washout of blood glucose–lowering drugs) and at the end of both treatment periods. Each patient was served a standardized liquid test meal consisting of 250 mL Nutridrink Compact (Nutricia, Allerød, Denmark) containing 375 kcal (46 g carbohydrate, 14.5 g fat, 15 g protein). Acetaminophen (Panodil) 1.5 g dissolved in 50 mL water was added to evaluate gastric emptying. The patients were examined after a 10-h overnight fast. The trial medication was taken 30 min before the test meal (ingested from time 0–10 min). No medication was taken at the baseline visit. A 30-min bicycling test (target heart rate 100–120 bpm) was performed at time 150–180 min. Symptoms of hypoglycemia were monitored, and PG concentrations were measured at prespecified time points and in the event of symptoms of hypoglycemia. Blood samples also were drawn at prespecified time points, as indicated in Fig. 1.

Blood Samples

Blood was collected into dry tubes for coagulation (20 min at room temperature) for analyses of insulin, C-peptide, fructosamine, cortisol, and growth hormone (somatotropine). To analyze glucagon, blood was collected into chilled tubes containing EDTA and aprotinin (500 kIU/mL blood; Trasylol; Bayer, Leverkusen, Germany). To analyze catecholamines (epinephrine and norepinephrine), blood was collected into chilled tubes containing a mixture of ethyleneglycol tetraacetic acid, reduced glutathione, sodium hydroxide, and water. To analyze acetaminophen (Panodil; GlaxoSmithKline A/S, Copenhagen, Denmark), blood was collected into chilled tubes containing heparin. EDTA, heparin, and tubes for analysis of catecholamines were immediately cooled and kept on ice until centrifugation.

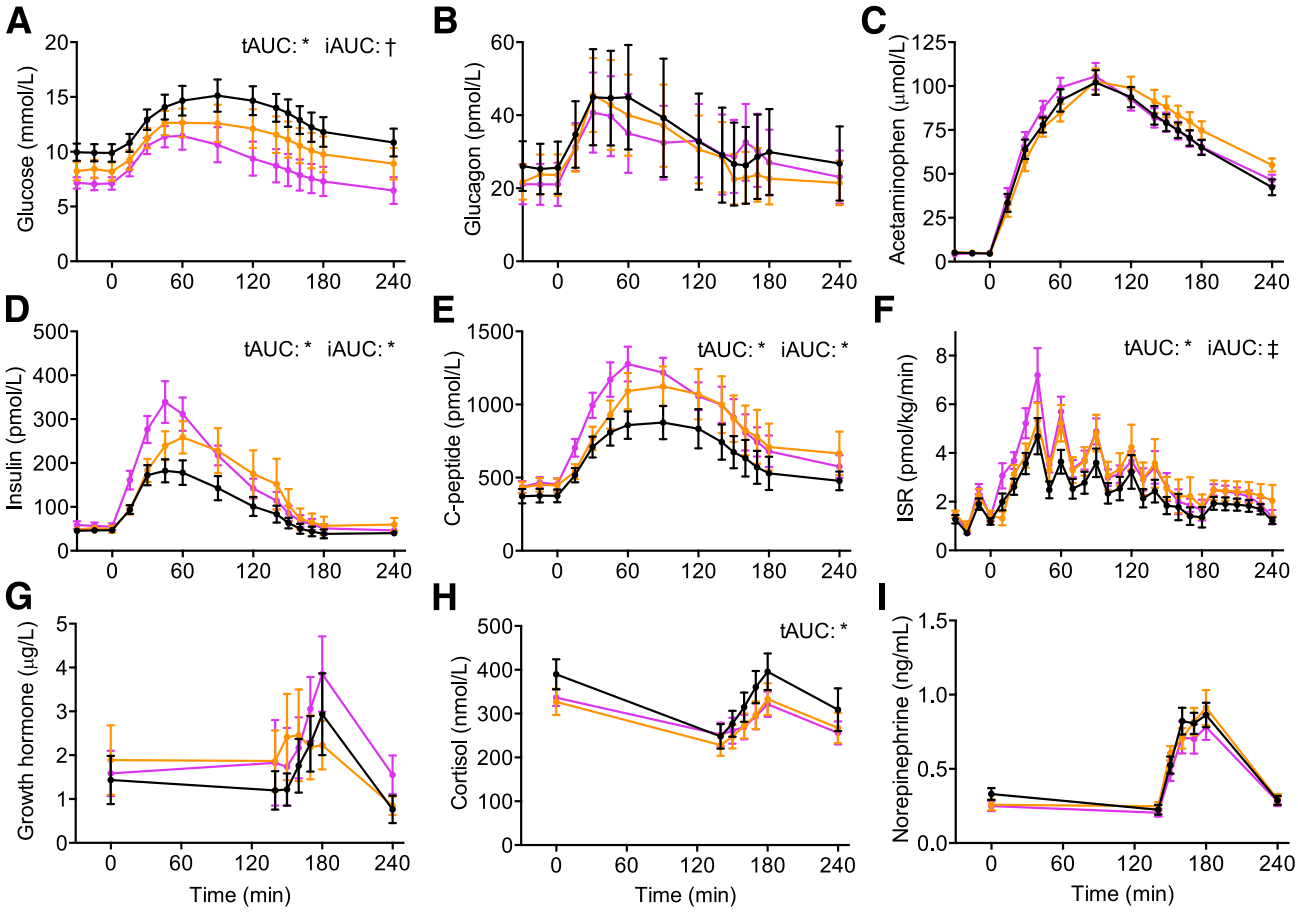

Figure 1—Glucose and hormone responses: PG (*A*), plasma glucagon (*B*), plasma acetaminophen (*C*), serum insulin (*D*), serum C-peptide (*E*), ISR (*F*), serum somatotropine (growth hormone) (*G*), serum cortisol (*H*), serum norepinephrine (*I*). Data are mean values ± SEMs derived from a standardized liquid meal test at baseline (black line; after a 1-week washout of blood glucose–lowering drugs) and at the end of each period of treatment with liraglutide (orange line) and glimepiride (purple line). *Significant difference ($P < 0.05$) from baseline with both treatments, but no difference between treatments. †Significant difference ($P < 0.05$) between baseline and glimepiride. ‡Significant difference ($P < 0.05$) from glimepiride of both baseline and liraglutide but no difference between baseline and liraglutide. Further details are provided in Tables 2 and 3. iAUC, incremental area under the curve.

All samples were centrifuged for 20 min at 1,200*g* and 4°C. Serum samples for insulin, C-peptide, fructosamine, cortisol, and growth hormone analyses and plasma samples for catecholamine analyses were stored at −80°C until analysis; plasma samples for acetaminophen and glucagon analyses were stored at −20°C until analysis. For bedside glucose measurements, blood was collected into fluoride tubes followed by immediate centrifugation at 7,400*g* for 2 min at room temperature.

Analytical Procedures

During the meal tests, PG concentrations were measured by the glucose oxidase method, using a glucose analyzer (Yellow Springs Instrument Model 2300 STAT Plus analyzer; YSI Inc., Yellow Springs, OH). SMBGs were measured using standard glucose meters (Contour next USB glucose meter; Bayer, Germany). Serum insulin and C-peptide concentrations were measured using a two-sided electrochemiluminescence immunoassay (Siemens Healthcare, Ballerup, Denmark) (17,18). Serum fructosamine concentrations were measured using a colorimetric assay (Roche, Germany). Serum somatotropine (growth hormone) was measured using chemiluminescence immunoassay (IDS Nordic, Denmark), and serum cortisol was measured using a competitive immunoassay (ADVIA Centaur CP; Siemens Healthcare). The glucagon assay is directed against the COOH-terminal of the glucagon molecule (antibody code no. 4305) (19). Plasma acetaminophen was measured by the Vitros ACET slide method (Ortho-Clinical Diagnostics, Johnson & Johnson, Denmark). Plasma catecholamines were measured using noradrenaline and adrenaline research ELISAs (Labor Diagnostika Nord, Germany). Heart rate was monitored with a Garmin Forerunner310XT watch and heart rate sensor.

Statistical Methods

Linear mixed-effect modeling was used for analysis of repeated measures using R statistical software (R Foundation for Statistical Computing, Wirtschaftsuniversität, Vienna, Austria). Data were transformed according to distribution pattern. A "top-down" modeling strategy, with family identity as random variable, was used (20). A homogeneous or heterogeneous residual variance structure was chosen according to likelihood ratios. Bonferroni adjustments were used as post hoc analysis. Baseline, peak, and area under the curve (AUC) values are expressed as mean ± SEM. Differences resulting in P values <0.05 were considered significant. AUC values were calculated using the trapezoidal rule and are presented as total AUCs (tAUCs) if not otherwise stated. Insulin secretion rate (ISR) values were calculated by deconvoluting measured C-peptide concentrations and applying population-based parameters for C-peptide kinetics, as described previously (21–23). ISR is expressed as picomoles of insulin secreted per minute per kilogram body weight. Insulin resistance was calculated according to HOMA (HOMA-IR) from fasting plasma insulin and FPG (24). The number and severity of hypoglycemic episodes was registered on experimental days and from SMBG and diaries.

The primary outcome (FPG) was used to calculate the sample size. With an expected end-of-treatment value of 8.4 mmol/L (SD 2.5) (25), and with α set to 5% and statistical power to 80%, the estimated sample size was 12 in each arm to detect a difference in FPG of 2 mmol/L. We included 16 patients in each arm to increase the statistical power of the primary end point.

RESULTS

Participants

Anthropometric data (from screening visit) are given in Table 1. Sixteen patients were included (8 women, 8 men) with the following characteristics at the screening visit: age 39 years (range 23–67 years); mean BMI ± SEM 24.9 ± 0.5 kg/m^2; HbA_{1c} 6.4 ± 0.2% (47 ± 3 mmol/mol). All patients had a disease-causing heterozygous loss-of-function mutation in *HNF1A* confirmed by Sanger sequencing of the gene. Fifteen patients were treated with oral blood glucose–lowering drugs at inclusion (glimepiride [n = 11]; repaglinide [n = 2]; tolbutamide [n = 1]; gliclazide [n = 1]), and one patient was treated with diet only. Apart from their regular blood glucose–lowering drugs, none of the patients used any drugs suspected of influencing glucose tolerance or insulin, C-peptide, or incretin hormone responses. One patient (woman, age 24 years, BMI 20.5 kg/m^2, HbA_{1c} 5.6% [38 mmol/mol], treated with glimepiride before inclusion) withdrew from the trial 4 days after randomization because of diarrhea, nausea, and vomiting during initiation of the first treatment period (liraglutide), but the rest (15 patients) adhered to the protocol. Data from the withdrawn patient are excluded from the analyses. Patients 1 and 14, as well as patients 6 and 11 (Table 1), were first-degree relatives (mother/daughter).

Glycemic Regulation

Time courses for PG from the meal tests are illustrated in Fig. 1*A*. FPG, minimum, peak, AUC, fructosamine, HbA_{1c}, and HOMA-IR values are given in Table 2. Both treatments resulted in significantly lower FPG compared with baseline. FPG tended to be lower during glimepiride treatment than during treatment with liraglutide. Both treatments exhibited lower minimum values compared with baseline; glimepiride lowered peak PG. For minimum values, glimepiride treatment showed lower values than liraglutide treatment, but no difference in the peak values of the treatments was found. Glucose responses (tAUC) were different from baseline, but only glimepiride lowered incremental AUC, and no difference between the treatments was found. Fructosamine, HbA_{1c}, and HOMA-IR levels were unaltered from baseline to the end of each treatment period, and no difference was found between the treatments.

Hypoglycemia

A total of 19 hypoglycemic events were reported; 10 events were reported by SMBG and 9 events were reported on experimental days. One event was reported during treatment with liraglutide (minimum value 3.5 mmol/L) and 18 events during treatment with glimepiride (mean minimum value ± SEM 3.3 ± 0.1 mmol/L). All episodes of hypoglycemia were mild. In 17 of the events, blood glucose was in the range of 3.1–3.9 mmol/L, and in 2 events it was in the range of 2.0–3.0 mmol/L. Symptoms of hypoglycemia were present during 14 events, including the 2 events in the lower range and the single event during liraglutide treatment. No symptoms were present during the five events measured during experimental days. During glimepiride treatment, 10 patients (67%) experienced a hypoglycemic event: 6 patients had 1 event, 1 patient had 2 events, 2 patients had 3

events, and 1 patient had 4 events. In contrast, only one patient (7%) experienced hypoglycemia during liraglutide treatment (this patient experienced three events during glimepiride treatment). No hypoglycemic episodes occurred during washout weeks and at the experimental day at baseline. The two events in the low range occurred during glimepiride treatment but were not related to physical activity. In total, six episodes occurred during the cycling test (mean minimum value ± SEM 3.4 ± 0.1 mmol/L), including the single event during liraglutide treatment.

Insulin, C-peptide, and ISR

Figure 1 illustrates time courses for insulin (panel *D*), C-peptide (panel *E*), and ISR (panel *F*), and fasting, peak, and AUC serum values are given in Table 2. No differences in fasting values of insulin were found from baseline or between treatments, but similarly higher fasting C-peptide and ISR values were found during both treatments compared with baseline. Both treatments exhibited higher peak values and responses of insulin and C-peptide compared with baseline but no differences between treatments. Both treatments resulted in superior peak ISR values and responses (tAUC) compared with baseline; there was no difference in peak values between the treatments, but glimepiride treatment showed a higher ISR response (incremental AUC) than with liraglutide treatment. Glimepiride generally exhibited a greater insulin secretory response than liraglutide, although the differences in tAUC were not statistically significant.

Glucagon

Time courses for glucagon are illustrated in Fig. 1*B*, and fasting, peak, and AUC plasma values are given in Table 2. Similar fasting and peak glucagon values and responses were found at baseline and during both treatments. During the bicycle test (150–180 min) (Fig. 1*B*), there was a tendency toward a higher glucagon response during glimepiride treatment.

Acetaminophen

Time courses for acetaminophen are illustrated in Fig. 1*C*, and fasting, peak, and AUC plasma values are given in Table 3. No differences in gastric emptying were found from baseline or

Table 1—Anthropometric data of patients (*n* = 8 women, *n* = 8 men)

Patient	Sex	Age (years)	BMI (kg/m^2)	HbA_{1c}, % (mmol/mol)	Glucose-lowering drugs at inclusion	End dose (mg)		Hypoglycemic events, liraglutide (*n*)	
						Liraglutide	Glimepiride	Liraglutide	Glimepiride
01*	F	27	24.0	8.1 (65)	Glimepiride 1.5 mg × 1	1.8	4.0	—	—
02	F	54	26.5	6.5 (48)	Tolbutamide 500 + 250 + 250 mg	1.8	2.5	—	—
03	M	27	24.3	5.4 (36)	Glimepiride 1.5 mg × 1	1.8	4.0	—	1
04	M	38	24.4	6.5 (48)	Repaglinide 0.5 mg × 2	1.8	3.0	—	1
05	M	24	25.1	7.0 (53)	No treatment	1.8	1.0	—	1
06†	F	23	25.4	4.7 (28)	Glimepiride 0.5 mg × 1	1.8	1.0	—	1
07‡	F	24	20.5	5.6 (38)	Glimepiride 1.0 mg × 1	NA	NA	—	—
08	M	71	26.7	6.8 (51)	Gliclazide 30 mg × 1	1.8	3.0	—	1
09	F	25	21.3	5.4 (36)	Repaglinide 1 mg × 1	1.8	1.0	—	1
10	F	67	22.9	6.6 (49)	Glimepiride 4.0 mg × 1	1.8	4.0	—	—
11†	F	53	26.4	6.4 (46)	Glimepiride 1.5 mg × 1	1.8	3.5	—	4
12	M	34	27.5	7.0 (53)	Glimepiride 1.0 mg × 1	1.8	3.5	—	3
13	M	29	26.0	5.5 (37)	Glimepiride 1.5 mg × 1	1.8	1.5	—	—
14*	F	56	24.5	7.9 (63)	Glimepiride 4.0 mg × 1	1.8	4.0	—	—
15	M	42	27.9	6.3 (45)	Glimepiride 3.0 mg × 1	1.8	2.0	1	3
16	M	28	24.4	7.3 (56)	Glimepiride 1.0 mg × 1	1.8	1.0	—	2
Mean ± SEM		39 (range 23–67)	24.9 ± 0.5	6.4 ± 0.2 (47 ± 3)		1.8 ± 0	2.5 ± 0.3	1	18

Data are derived from the screening visit (*n* = 16). F, female; M, male; NA, not applicable. *†Patients are related (mother and daughter). ‡Patient withdrew from the trial because of intolerable vomiting and diarrhea during the initiation of the first treatment period (liraglutide 0.6 mg, once daily).

Table 2—Glucose, insulin, C-peptide, ISR, and glucagon values by treatment group

	Baseline (0) (n = 15)	Liraglutide (1) (n = 15)	Glimepiride (2) (n = 15)	P*
Glucose				
FPG (mmol/L)	9.9 ± 0.8†(1,2)	8.2 ± 0.8†(0)	7.2 ± 0.6†(0)	0.002
Minimum PG (mmol/L)	9.3 ± 0.9†(1,2)	7.5 ± 0.9†(0,2)	5.2 ± 0.7†(0,1)	<0.001
Peak PG (mmol/L)	15.8 ± 1.3†(2)	14.2 ± 1.5	12.7 ± 1.2†(0)	0.029
tAUC (min × mmol/L)	3,127 ± 291†(1,2)	2,624 ± 340†(0)	2,136 ± 292†(0)	<0.001
iAUC (min × mmol/L)	746 ± 131†(2)	637 ± 164	430 ± 171†(0)	0.018
Fructosamine (μmol/L)	294 ± 16	296 ± 20	273 ± 14	0.170
HbA_{1c} (%)	6.6 ± 0.3	6.7 ± 0.4	6.2 ± 0.3	0.260
HbA_{1c} (mmol/mol)	48 ± 3	49 ± 5	44 ± 3	0.223
HOMA-IR	3.0 ± 0.5	2.6 ± 0.5	2.5 ± 0.3	0.501
Insulin				
Fasting (pmol/L)	46 ± 6	50 ± 7	57 ± 7	0.372
Peak values (pmol/L)	216 ± 29†(1,2)	314 ± 54†(0)	354 ± 46†(0)	<0.001
tAUC (min × nmol/L)	23 ± 3†(1,2)	34 ± 7†(0)	36 ± 3†(0)	<0.001
iAUC (min × nmol/L)	12 ± 2†(1,2)	22 ± 5†(0)	23 ± 3†(0)	<0.001
C-peptide				
Fasting (pmol/L)	376 ± 46	443 ± 44†(0)	452 ± 39†(0)	0.012
Peak values (pmol/L)	1,000 ± 130†(1,2)	1,345 ± 177†(0)	1,408 ± 132†(0)	<0.001
tAUC (min × nmol/L)	163 ± 22†(1,2)	207 ± 30†(0)	219 ± 19†(0)	<0.001
iAUC (min × nmol/L)	73 ± 12†(1,2)	100 ± 21†(0)	110 ± 14†(0)	<0.001
ISR				
Fasting (pmol/kg/min)	1.3 ± 0.2†(1,2)	1.5 ± 0.2†(0)	1.5 ± 0.1†(0)	0.035
Peak values (pmol/kg/min)	5.4 ± 0.8†(1,2)	7.1 ± 0.9†(0)	8.1 ± 1.1†(0)	0.002
tAUC (pmol/kg)	613 ± 89†(1,2)	783 ± 127†(0)	821 ± 80†(0)	<0.001
iAUC (pmol/kg)	268 ± 44†(2)	382 ± 93†(2)	421 ± 61†(0,1)	0.011
Glucagon				
Fasting (pmol/L)	26 ± 7	23 ± 5	21 ± 6	0.434
Peak values (pmol/L)	58 ± 15	51 ± 12	47 ± 11	0.104
tAUC (min × nmol/L)	8 ± 3	7 ± 2	7 ± 2	0.473
iAUC (min × nmol/L)	2 ± 1	2 ± 1	2 ± 1	0.565

Data are mean values ± SEM derived from a standardized liquid meal test at baseline (0) (after a 1-week washout of blood glucose–lowering drugs) and at the end of each period of treatment with liraglutide (1) and glimepiride (2). iAUC, incremental area under the curve. *P values are derived from repeated-measures ANOVA for variations between treatments and baseline. †Significant difference ($P < 0.05$) from the period given in parentheses (post hoc analysis).

between the treatments according to peak acetaminophen, AUC, or to time to peak values.

Counterregulatory Hormones

Time courses for the counterregulatory hormones are illustrated in Fig. 1 (growth hormone [panel *G*]; cortisol [panel *H*]; norepinephrine [panel *I*]), and fasting, peak, and AUC values are given in Table 3. Similar fasting serum growth hormone concentrations, peak values, and responses were found at baseline and during both treatments. A tendency toward an increased counterregulatory growth hormone response was seen during the bicycle test (150–180 min) (Fig. 1*G*) during glimepiride treatment. The interventions did not affect fasting serum cortisol concentrations, but comparably lower peak values were observed during both treatments compared with baseline. During liraglutide treatment, a lower cortisol response was found compared with baseline, and this response was similar to that found after glimepiride treatment. Both treatments tended to suppress cortisol responses (Fig. 1*H* and Table 3). No differences in fasting or peak plasma concentrations of norepinephrine (Fig. 1*I* and Table 3) or epinephrine (Table 3) were found. An increased counterregulatory response of epinephrine, but not norepinephrine, was seen during glimepiride treatment (Table 3).

Adverse Events

Adverse events reported during the trial period primarily concerned hypoglycemia; other events included tiredness (one report), reduced appetite (two reports), heartburn (one report), nausea (one report), and vomiting and diarrhea (one report). All events were evaluated as being related to trial medication and were mild (except for the case of vomiting and diarrhea, which was moderate and made the patient withdraw from the trial) and transient. Except for the report of tiredness and one report of reduced appetite, all nonhypoglycemic events occurred during liraglutide treatment.

CONCLUSIONS

The primary findings of this randomized, double-blind, crossover trial were *1*) FPG was reduced after 6 weeks of treatment with liraglutide and glimepiride, *2*) glimepiride treatment had a more pronounced effect on glucose excursions compared with liraglutide treatment, and *3*) there was an almost 10-fold higher risk of exclusively mild hypoglycemia during glimepiride treatment compared with liraglutide treatment.

A crossover design was chosen because of the low prevalence of HNF1A diabetes. Patients were included only

Table 3—Acetaminophen, growth hormone, cortisol, norepinephrine, and epinephrine values by treatment group

	Baseline (0) (n = 15)	Liraglutide (1) (n = 15)	Glimepiride (2) (n = 15)	P*
Acetaminophen				
Fasting (μmol/L)	0 ± 0	0 ± 0	0 ± 0	0.524
Peak values (μmol/L)	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.535
tAUC (min × mmol/L)	17 ± 1	18 ± 1	18 ± 1	0.345
iAUC (min × mmol/L)	16 ± 1	17 ± 1	17 ± 1	0.320
Time to peak (min)	82 ± 6	96 ± 8	85 ± 5	0.138
Growth hormone				
Fasting (μg/L)	1.4 ± 0.6	1.9 ± 0.8	1.6 ± 0.5	0.591
Peak values (μg/L)	4.1 ± 1.0	4.2 ± 1.1	5.2 ± 1.0	0.288
tAUC (min × μg/L)	368 ± 81	446 ± 125	499 ± 112	0.098
iAUC (min × μg/L)	24 ± 96	−7 ± 127	119 ± 153	0.717
Cortisol				
Fasting (nmol/L)	390 ± 34	327 ± 30	336 ± 19	0.074
Peak values (nmol/L)	505 ± 32†$^{(1,2)}$	398 ± 34†$^{(0)}$	415 ± 22†$^{(0)}$	0.011
tAUC (min × μmol/L)	78 ± 5†$^{(1,2)}$	67 ± 5†$^{(0)}$	69 ± 5†$^{(0)}$	0.039
iAUC (min × μmol/L)	−15 ± 7	−11 ± 5	−11 ± 4	0.780
Norepinephrine				
Fasting (ng/mL)	0.33 ± 0.04	0.26 ± 0.04	0.25 ± 0.03	0.125
Peak values (ng/mL)	0.95 ± 0.09	0.99 ± 0.12	0.86 ± 0.10	0.238
tAUC (min × ng/mL)	100 ± 9	99 ± 10	87 ± 9	0.151
iAUC (min × ng/mL)	21 ± 6	37 ± 6	28 ± 5	0.095
Epinephrine				
Fasting (ng/mL)	0.03 ± 0.00	0.03 ± 0.01	0.02 ± 0.01	0.509
Peak values (ng/mL)	0.11 ± 0.04	0.10 ± 0.04	0.17 ± 0.05	0.099
tAUC (min × ng/mL)	8 ± 2	9 ± 2	13 ± 3	0.677
iAUC (min × ng/mL)	2 ± 1†$^{(2)}$	2 ± 1†$^{(2)}$	7 ± 2†$^{(0,1)}$	0.028

Data are mean values ± SEM derived from a standardized liquid meal test at baseline (0) (after a 1-week washout of blood glucose–lowering drugs) and at the end of each period of treatment with liraglutide (1) and glimepiride (2). iAUC: incremental area under the curve. *P values are derived from repeated-measurement ANOVA for variations between treatments and baseline. †Significant difference ($P < 0.05$) from the period given in parentheses (post hoc analysis).

when in a stable condition, and no adjustments to medicine were made 2 months before inclusion. To reduce a potential carryover effect, treatment periods were preceded by a 1-week washout period. In addition, a rather short treatment duration (6 weeks) was chosen to minimize inadequate compliance and patient withdrawal due to potential side effects.

SU acts by closing the K_{ATP} channels in β-cells, which causes depolarization with subsequent influx of calcium and insulin secretion. Because of the specific HNF1A β-cell defect reducing glucose metabolism and ATP production, combined with a high sensitivity to SU (4,9,10), patients with HNF1A diabetes treated with these drugs often are prone to hypoglycemia (4,11). In addition, preclinical studies indicated that SU therapy may lead to an accelerated loss of β-cell function and/or β-cell mass, which may lead to treatment failure (26,27). The risk of hypoglycemia during acute treatment with glibenclamide and nateglinide in patients with HNF1A diabetes has previously been investigated (11); after receiving a single dose of test medicine immediately before a test meal, in combination with a mild cycling test (30 min), 6 of 15 patients experienced hypoglycemia during glibenclamide treatment, whereas no events of hypoglycemia occurred during nateglinide treatment. In our trial, we chose glimepiride because it is the most commonly prescribed glucose-lowering drug for patients with HNF1A diabetes. The glimepiride treatment algorithm may have been too aggressive during the study, since many patients ended at a higher dose than they started with at inclusion (Table 1). Since the included patients were young and had no complications, target HbA_{1c} was 6.5% (48 mmol/mol) or less. This may explain the majority of the hypoglycemic events, but, clearly, some patients are more prone to hypoglycemia than others and may benefit from alternative treatment (i.e., liraglutide).

GLP-1 receptor activation on β-cells results in activation of adenylate cyclase and subsequent elevation of cAMP. Both cAMP and activated protein kinase A may influence secretory events distal to the generation of ATP by glucose metabolism (28–30). Our hypothesis was that, like SUs, a GLP-1RA might be capable of bypassing the decreased concentrations of ATP and thereby stimulate secretion of insulin and consequently reduce PG. In addition, GLP-1 may have direct effect on the K_{ATP} channel (31,32).

In this trial, treatment with both an SU and a GLP-1RA reduced FPG and postprandial glucose excursions; this occurred to the greatest extent during glimepiride treatment. These results correlate well with the theory that glimepiride bypasses the glucose-dependence of insulin secretion, whereas the GLP-1 effects are strictly glucose dependent. However, since GLP-1 may enhance the sensitivity of the K_{ATP} channels to ATP, it may still amplify the weaker signals generated in HNF1A diabetes (33). In addition, as mentioned earlier, GLP-1 may effect β-cell secretion downstream of the K_{ATP} channels. These differential effects of glimepiride and liraglutide also are reflected in the postprandial ISR response, which was more pronounced during glimepiride treatment.

GLP-1 has been shown to have dose-dependent inhibitory effects on glucagon secretion in patients with type 2 diabetes and in healthy individuals (18). Therefore, we expected reduced glucagon responses during treatment with liraglutide. However, neither of the treatments had any significant effect on glucagon concentrations. Whether patients with *HNF1A* defects have an altered α-cell function remains unknown. We previously showed that patients with HNF1A diabetes suppress glucagon normally following intravenous glucose but have an inappropriate hyperglucagonemic response to oral glucose (34), similar to patients with type 2 diabetes (35,36).

No difference in gastric emptying was seen with any of the treatments. This can be due to the rather crude measurement of gastric emptying using acetaminophen (in contrast to more exact methods such as scintigraphy), to the

limited number of patients, or simply because of a declining effect of GLP-1RAs on gastric emptying with time because of receptor desensitization or tachyphylaxis (37–39). Furthermore, no previous reports have indicated differences in gastric emptying in patients with HNF1A diabetes compared with healthy control subjects (25,34).

No previous controlled studies prospectively examined the effect of GLP-1RAs in patients with HNF1A diabetes. The findings in our trial are, however, consistent with recent case studies reporting beneficial effects of dipeptidyl peptidase-4 inhibitors in patients with HNF1A diabetes when combined with other oral glucose-lowering drugs (14,15) or with liraglutide as adjunct therapy to SU and basal insulin (16). Whether monotherapy with GLP-1RA is sufficiently effective to maintain an acceptable long-term glycemic regulation in patients with HNF1A diabetes is not clear from our trial. Because of the different modes of action, a combination therapy using low or submaximal doses of SU (e.g., 0.5 mg of glimepiride once daily) *and* low or submaximal doses of GLP-1RA (e.g., 0.6 mg liraglutide once daily) in patients with HNF1A diabetes might be an interesting option to explore further. This combination is based on the hypothesis that SUs will effectively close K_{ATP} channels, thereby synergizing with the effects of GLP-1RA, resulting in enhanced β-cell function in a glucose-dependent fashion and lowering PG, with a reduced risk of hypoglycemia. Many patients with HNF1A diabetes are well treated with SU monotherapy, but GLP-1RA monotherapy could be considered in patients who are particularly prone to hypoglycemia or are gaining weight. Patients with HNF1A diabetes are known to have a continuous loss of β-cells and β-cell function (6), and GLP-1RAs are known to reduce β-cell apoptosis in preclinical settings (40); therefore treatment with GLP-1RAs might slow the rate of β-cell loss in HNF1A diabetes.

When considering GLP-1RAs as a potential treatment in patients with HNF1A diabetes, the glucose-lowering effects, side effects, and the method of administration (oral vs. injection) as well as the cost of the drug must always be considered for each individual patient. Individualized therapy is crucial for patients with HNF1A diabetes to obtain acceptable glycemic regulation with a low risk of hypoglycemia and any other side effects (9,10,16). In conclusion, GLP-1RAs may have a place in the treatment of patients with HNF1A diabetes, especially when hypoglycemia is a problem.

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Author Contributions. S.H.Ø. designed the trial, performed all experiments, researched the data, and wrote the manuscript. J.I.B. performed the statistical analyses and reviewed and edited the manuscript. T.H. designed the trial, recruited MODY patients, and reviewed and edited the manuscript. O.P. recruited MODY patients and reviewed and edited the manuscript. J.F. analyzed plasma for catecholamines and reviewed the manuscript. J.J.H. analyzed plasma for incretin hormones and glucagon and reviewed and edited the manuscript. F.K.K. and T.V. designed the trial and reviewed and edited the manuscript. S.H.Ø. is the guarantor of this work and, as such, had full access to all the data in the trial and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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