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Research paper

A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome

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ABSTRACT

OBJECTIVE The long-acting glucagon-like peptide 1 receptor agonist liraglutide is linked to progressive and sustained weight loss in obese people with diabetes. However, its efficacy and safety in women with polycystic ovary syndrome (PCOS) has not yet been addressed. DESIGN Thirty-two obese women (aged 27.6±7.2 years, BMI 39.5±6.2 kg/m^2) with newly diagnosed PCOS were randomized to receive either liraglutide 1.2 mg QD sc (n=17) or metformin 1000 mg BID po (n=15) for 12 weeks; 28 patients completed the study (14 on liraglutide and 14 on metformin). The main outcome was change in body weight. RESULTS Intention-to-treat analysis showed significant BMI (-0.98 kg/m^2; p<0.001), body weight (-2.52 kg; p<0.001), waist circumference (-3.38 cm; p<0.001) and whole-body fat mass (-1.26%; p<0.001) reduction in both treatment arms without significant differences between therapeutic groups. However, in a subgroup of patients (n=9) with insulin resistance ($HOMA_{IR}$ >2), severe obesity and higher odds ratio for the metabolic syndrome (OR=3.9), the patients fared much better with liraglutide than with metformin (mean BMI decreased 2.13 kg/m^2 vs. 0.62 kg/m^2, respectively). CONCLUSIONS Short-term liraglutide treatment was associated with significant weight loss in a subset of obese patients with newly diagnosed PCOS and a higher metabolic risk profile.

Key words: GLP-1 receptor agonist, Liraglutide, Metformin, Obesity, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is closely associated with obesity, with a prevalence of between 50% and 80%.[1-4] Most obese women demonstrate serious reproductive and metabolic abnormalities with alterations in satiety and appetite.[5] Since it is recognized that modest weight loss of even less than 10% substantially improves the reproductive and metabolic profile of these patients,[6,7] weight reduction is of major importance. Lifestyle modification is regarded as the

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first line of treatment but its limitation is poor long-term compliance.[8] Thus, in the majority of patients pharmaceutical intervention is an additional essential therapeutic aid to lifestyle changes. However, weight management by classic therapeutic modalities usually remains unsatisfactory and identification of new effective and safe treatments for weight reduction in PCOS should be addressed.

Glucagon-like peptide-1 (GLP-1) based therapy was recently introduced as a new treatment for patients with type 2 diabetes mellitus. Treatment with GLP-1 receptor agonist enhances the endogenous secretion of insulin induced by meal ingestion and inhibits glucagon secretion, thereby improving glucose homeostasis. In addition, it also delays gastric emptying and inhibits appetite, which often results in weight loss.[9] This therapy has produced progressive and sustained weight loss in obese people with and without diabetes.[10]

Until now, only one study has addressed GLP-1 agonist treatment in PCOS, providing evidence that combined treatment with short-acting GLP-1 receptor agonist exenatide and metformin was superior to exenatide and metformin monotherapies in improving menstrual cyclicity and hormonal and metabolic parameters in overweight women with PCOS.[11]

The potential efficacy and safety of long-acting GLP-1 receptor agonist liraglutide has not yet been evaluated in a PCOS population. Here we report the results of a 12-week open-label, randomized, prospective study designed to directly compare the therapeutic effects of liraglutide (LIRA) and metformin (MET) in obese women with newly diagnosed PCOS.

SUBJECTS AND METHODOLOGY

We recruited 32 women with PCOS diagnosed by the National Institute of Child Health and Human Development (NICHD) criteria.[12] Clinical hyperandrogenism was defined by the presence of hirsutism, represented by a modified Ferriman-Gallwey (FG) score of eight or more, persistence of acne during the third decade of life or later or the presence of androgenic alopecia. No attempts were made to grade the severity of acne or alopecia. Hyperandrogenemia was defined as a total or free testosterone, androstenedione and/or dehydroepiandrosterone sulphate (DHEAS) level above the 95th percentile of normal population values. Menstrual dysfunction was defined by more than six cycles with a length of more than 35 days (oligomenorrhea) and/or when the patient had not had any menstrual bleeding for 3 consecutive months (amenorrhea) during the previous year. All patients had normal serum prolactin concentrations and thyroid function tests. Possible Cushing's syndrome or congenital (non-classic) adrenal hyperplasia were excluded.[12] Women with diagnosed PCOS were eligible for enrollment if they were aged 18 years to menopause and were obese (body mass index: BMI ≥30). Exclusion criteria were known type 1 or type 2 diabetes mellitus, history of carcinoma, personal or family history of MEN 2, significant cardiovascular, kidney or hepatic disease and the use of medications known or suspected to affect reproductive or metabolic functions, or statins within 90 days prior to study entry. None of the patients had ever taken insulin-sensitizing drugs prior to the study. All subjects were informed of the study aims and provided written consent before entering the study, which was conducted in accordance with the Declaration of Helsinki and approved by the National Ethical Committee. The study is registered on http://www.clinical trials.gov/:No. NCT01899430.

Experimental protocol

The patients were randomly allocated to a 12-week treatment with either metformin (MET) 1000 BID p.o. or liraglutide (LIRA) 1.2 mg QD subcutaneously. As a method of randomization the RAND programme in Excel was used. In the LIRA group, liraglutide was initiated at a dose of 0.6 mg injected sc once per day and increased to 1.2 mg/day after 1 week. In the MET group, metformin was initiated at a dose of 500 mg once per day and increased by 500 mg every 3 days up to 1000 mg BID.

At baseline and at study endpoint all patients underwent standard anthropometric measurements: height, weight, waist circumference and blood pressure. Waist circumference was measured in a standing position midway between the lower costal margin and the iliac crest. BMI was calculated as the weight in kilograms divided by square of height in meters. Moreover, measurement of whole-body composition on a Hologic Dual Energy X-ray Absorptiometer

(DXA) was performed in all subjects at baseline and at study endpoint as described previously.[13] A fasting blood sample was drawn for determination of glucose, insulin and other parameters, followed by a standard 75 g oral glucose tolerance test (OGTT). Safety parameters (complete blood count, liver and renal function and serum electrolytes) were assessed before and after 12 weeks of study treatment. All the blood samples were centrifuged and the separated serum was kept frozen at -80° C until the time of the assay.

Impaired glucose tolerance (IGT) was identified by 2h glucose levels between 7.8 and 11 mmol/l, as defined by the American Diabetes Association criteria.[14]

Since the majority of patients were oligoamenorrhoic during the previous year, the assessment of the subjects was not based on any specific stage of the menstrual cycle.

The women were advised to strictly use barrier contraception. All patients were provided with glucose-monitoring devices and supplies and educated on their use. They were instructed to measure blood glucose levels for any signs and symptoms suggesting low blood glucose. Hypoglycemia was defined according to the American Diabetes Association criteria as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement below 3.9 mmol/l.[15] They were also instructed to report any side effects during the treatment. Lifestyle intervention was not actively promoted.

ASSAYS

Glucose levels were determined using a standard glucose oxidase method (Beckman Coulter Glucose Analyzer, Beckman Coulter Inc CA, USA). LH and FSH were determined using an immunometric assay (Diagnostic Products Corporation, LA). Androstenedione and DHEAS were measured by specific double antibody RIA using 125 I-labeled hormones (Diagnostic Systems Laboratories, Webster, Tx). Total and free testosterone levels were measured by coated tube RIA (DiaSorin, S.p.A, Salluggia, Italy, and Diagnostic Products Corporation, LA, respectively). Insulin was determined by immunoradiometric assay (Biosource Europe S.A., Nivelles, Belgium). Intraassay variations ranged from 1.6 to 6.3% and interassay variations ranged from 5.8 to 9.6 % for the applied methods. Pre- and posttreatment samples from each patient were assayed in the same assay run.

Determination of metabolic syndrome

According to the new International Diabetes Federation definition, the metabolic syndrome is defined as central obesity (defined as waist circumference >80 cm) plus any two of the following four factors: raised triglycerides ≥1.7 mmol/L, reduced HDL cholesterol <1.29 mmol/L in females, raised blood pressure (systolic BP ≥130 or diastolic BP ≥85 mm Hg), raised fasting plasma glucose (FPG) ≥5.6 mmol/L.

Determination of insulin resistance (IR)

Homeostasis model assessment ($HOMA_{IR}$) score calculation was applied as a measure for IR. The estimate of IR by $HOMA_{IR}$ score was calculated with the following formula: fasting serum insulin (mU/l) x fasting plasma glucose (mmol/l)/22.5.[16] $HOMA_{IR}$ score values 2.0 were considered as a cut-off point for IR as published previously.[17]

Assessment of human body composition by Dual Energy X-ray Absorptiometry

Whole-body composition was assessed by a Dual Energy X-ray Absorptiometer (DXA) (Discovery A; Hologic, Waltham, MA, USA) with the software provided by the manufacturer (QDR for Windows Version 12.5). The instrument generates values for whole-body fat mass, lean body mass and bone mineral content.

Statistical analysis

Results are presented as mean ± standard deviation (SD). The differences between treatment groups were checked and confirmed using the Mann-Whitney test with Bonferroni correction. Treatment impact on the primary and secondary outcome measures was analyzed with evaluable patients' data and using a repeated-measures linear mixed-effects model with time points (baseline, 3 months) and therapeutic groups (liraglutide arm, metformin arm). Additionally, exploratory data analysis using hierarchical agglomerative clustering of scaled (z-score normalized) relevant baseline parameter values (Euclidean distance, Ward method) strongly suggested the existence of two patient subsets, subsequently designated

Subset 1 and Subset 2. The possibility was further explored by *post hoc* analyses of subsets by baseline parameter values (using the Mann-Whitney test with Bonferroni correction) and by comparison of outcomes using a repeated-measures linear mixed-effects model analogous with inclusion of subsets and their interactions. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the "R" statistical software package (version 2.15.1).[18]

Table 1. Baseline characteristics of the study participants

Parameter	Liraglutide (n = 17)	Metformin (n = 15)	P values
Age (yr)	29.5 ± 7.7	25.3 ± 5.2	NS
Menstrual cycles (no./yr)	6.2 ± 4.7	6.4 ± 4.8	NS
FG score	14.8 ± 5.9	14.7 ± 7.1	NS
Weight (kg)	112.3 ± 20.6	105.3 ± 20.1	NS
BMI (kg/m^2)	40.8 ± 6.1	38.2 ± 7	NS
WC (cm)	126.6 ± 14.3	123.1 ± 17.5	NS
SBP (mmHg)	122 ± 13.4	129.9 ± 13.2	NS
DBP (mmHg)	76.5 ± 8.5	83.5 ± 11.4	NS
AST (µkat/L)	0.5 ± 0.3	0.7 ± 0.4	NS
ALT (µkat/L)	0.5 ± 0.2	0.6 ± 0.3	NS
GGT (µkat/L)	0.5 ± 0.3	0.4 ± 0.2	NS
LH (IU/L)	4.9 ± 4	7.4 ± 4	NS
FSH (IU/L)	4.8 ± 1.5 [1]	5.3 ± 2.1	NS
DHEA-S (µmol/L)	6.3 ± 2.9	7 ± 2.7	NS
AND (nmol/L)	10.3 ± 4.5	11.7 ± 3.7	NS
Total T (nmol/L)	2.2 ± 0.9	3 ± 0.9	NS
Free T (nmol/L)	6.2 ± 2.6	7.6 ± 2.9	NS
SHBG (nmol/L)	28.2 ± 13.9	23.1 ± 12.1	NS
FAI	10.7 ± 7.9	17.5 ± 13.6	NS
Cholesterol (mmol/L)	4.9 ± 0.9	4.5 ± 0.9	NS
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.2	NS
LDL-C (mmol/L)	3.2 ± 0.8	2.9 ± 0.7	NS
TG (mmol/L)	1.6 ± 0.7	1.4 ± 0.6	NS
Glu 0 min OGTT (mmol/L)	5.5 ± 0.8	5.3 ± 0.5	NS
Glu 30 min OGTT (mmol/L)	8.7 ± 1.9	8.9 ± 1.2	NS
Glu 60 min OGTT (mmol/L)	9.2 ± 2.7	9.2 ± 1.9	NS
Glu 90 min OGTT (mmol/L)	8.4 ± 2.2	8.4 ± 2.4	NS
Glu 120 min OGTT (mmol/L)	7 ± 1.9	7.9 ± 2.4	NS
Insulin 0 min OGTT (pmol/L)	15 ± 11.4	12.3 ± 7.6	NS
Insulin 30 min OGTT (pmol/L)	76.1 ± 40.6	97.1 ± 81.8	NS
Insulin 60 min OGTT (pmol/L)	109.2 ± 62.1	125.9 ± 91.3	NS
Insulin 90 min OGTT (pmol/L)	112.7 ± 91.5	107.6 ± 49.8	NS
Insulin 120 min OGTT (pmol/L)	98.6 ± 95.3	112.4 ± 74.3	NS
HOMA-IR score	3.8 ± 3.6	2.9 ± 1.7	NS
Matsuda index	3.4 ± 2.2	3.5 ± 2.3	NS
FM by DXA (%)	42.8 ± 2.8 [1]	43.3 ± 6.4 [2]	NS

NS = not significant. Means ± SD. Bonferroni-adjusted P values. Number of missing values in square brackets [ ].

RESULTS

Baseline results

Twenty-eight (87.5%) patients (14 on LIRA and 14 on MET) finished the study according to the protocol. One patient was excluded from the MET group due to severe nausea and one from the LIRA group due to a rash at the injection site. Two patients on LIRA were lost due to protocol violation. Baseline characteristics of the study population are provided in Table 1.

Weight change

At 3 months, a significant BMI reduction was noted in both treatment arms compared to baseline

TABLE 2. Baseline and 3-month posttreatment parameters by therapeutic group (evaluable patients)

Parameter	Liraglutide (n = 14) Baseline	Liraglutide (n = 14) After therapy	Metformin (n = 14) Baseline	Metformin (n = 14) After therapy	*P* values
Menstrual cycles (no./yr)	5.4 ± 4.8	5.4 ± 4	6.7 ± 4.8	8.9 ± 4.8	NS
FG score	14.9 ± 6.1	14.2 ± 5.8	14.1 ± 7.1	13.7 ± 7.3	NS
Weight (kg)	113.7 ± 18.7	110.7 ± 18.1	103.6 ± 19.7	101.3 ± 19.8	T <0.001
BMI (kg/m^2)	41.6 ± 5.3	40.5 ± 5.1	37.4 ± 6.4	36.5 ± 6.3	T <0.001
WC (cm)	128.5 ± 13.9	124.1 ± 11.7	121.6 ± 17.1	119 ± 18	T <0.001
SBP (mmHg)	123.6 ± 14.3	122.2 ± 11.6	131 ± 13	127.9 ± 13.9	NS
DBP (mmHg)	77.9 ± 7.9	73.9 ± 9.2	83.7 ± 11.8	80.7 ± 11.7	NS
AST (µkat/L)	0.5 ± 0.3	0.4 ± 0.1	0.7 ± 0.4	0.5 ± 0.2	NS
ALT (µkat/L)	0.5 ± 0.3	0.5 ± 0.2	0.6 ± 0.3	0.7 ± 0.4	NS
GGT (µkat/L)	0.5 ± 0.3	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.3	NS
LH (IU/L)	5.1 ± 4.4	8.9 ± 5.8	7.5 ± 4.1 [1]	5.6 ± 2.9	T = 0.001; I <0.001
FSH (IU/L)	4.6 ± 1.6	5.2 ± 1.8	5.4 ± 2.2 [1]	4.1 ± 2	T = NS; I = 0.030
DHEA-S (µmol/L)	6.3 ± 3 [1]	7.1 ± 2.7	7.2 ± 2.8 [4]	8.5 ± 3.8 [1]	NS
AND (nmol/L)	9.7 ± 4.6	7.8 ± 3.9	11.5 ± 3.7 [3]	8.8 ± 3.3 [1]	T = 0.040
Total T (nmol/L)	2.1 ± 1	2 ± 1.1	3 ± 0.9 [3]	2.1 ± 0.9 [1]	T = NS; I <0,001
Free T (nmol/L)	5.7 ± 2.6	4.6 ± 1.7	7.4 ± 2.8 [3]	4.7 ± 1.9 [1]	NS
SHBG (nmol/L)	30.3 ± 14.5	31.6 ± 12.4	24 ± 12 [3]	26.2 ± 14.3 [1]	NS
FAI	10.1 ± 7.7	9 ± 6.4	16.6 ± 14.1	9.6 ± 6.4	NS
Cholesterol (mmol/L)	4.8 ± 1	4.7 ± 1	4.6 ± 0.9	4.3 ± 0.5	NS
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.2	1.2 ± 0.3	NS
LDL-C (mmol/L)	3.2 ± 0.8	2.9 ± 0.8	2.9 ± 0.8	2.6 ± 0.4	NS
TG (mmol/L)	1.6 ± 0.7	1.4 ± 0.6	1.4 ± 0.6	1.3 ± 0.6	NS
HOMA-IR score	4 ± 4	3.9 ± 2.1	2.7 ± 1.7 [1]	2.8 ± 1.4	NS
Matsuda index	3.7 ± 2.2	3.2 ± 2	3.6 ± 2.3	3.2 ± 2.2	NS
FM by DXA (%)	42.5 ± 2.8	40.8 ± 3.2 [1]	43.3 ± 6.4 [2]	41.1 ± 6.4 [2]	T < 0.001

For *P* values: T = overall effect with both therapies; I = interaction between therapy and time; NS = not significant.
No adjustments for multiple comparisons.
Means ± SD. Number of missing values in square brackets [ ].
FG: Ferriman-Gallwey; BMI: body mass index WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase; LH: luteinizing hormone; FSH: follicle-stimulating hormone; DHEA-S: dehydroepiandrosterone sulfate; AND: androstenedione; Total T: total testosterone; Free T: free testosterone; SHBG: sex hormone-binding globulin; FAI: Free androgen index; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; TG: triglyceride; Glu: glucose; OGTT: oral glucose tolerance test; HOMA-IR: homeostasis model assessment of insulin resistance; DXA: dual-energy X-ray absorptiometry; FM: fat mass.

(P<0.001; Table 2) with no difference with respect to the treatment employed. Comparable results were found for body weight reduction (P=0.003), waist circumference reduction (P=0.003) and whole-body fat mass (P<0.001). Body weight parameters thus decreased significantly with both treatments with no significant difference between treatment arms.

Endocrine changes

Among endocrine parameters there was a significant differential effect of liraglutide compared to metformin with respect to LH (P=0.018), with liraglutide leading to a significant LH increase and metformin leading to a significant LH decrease. There was also a significant differential effect with respect to total testosterone levels (P=0.016), with metformin leading to a significant decrease in total testosterone levels and liraglutide being associated with no significant change (Table 2).

Metabolic changes

Twelve women (42.8%) with PCOS had IGT at the beginning of the study. Fifty percent of these women had normal glucose tolerance at the completion of therapy (four were on LIRA and two were on MET). At baseline 10 patients in the MET group and 12 patients in the LIRA group were insulin resistant according to their $HOMA_{IR}$ score (>2). After 12 weeks of treatment, $HOMA_{IR}$ score >2 was found in 10 patients in the MET group and 10 patients in the LIRA group. Overall, $HOMA_{IR}$ score values did not significantly decrease in either group. Fasting glucose and insulin and glucose and insulin during OGTT did not consistently improve as well (Table 2).

Nine women (60%) of the MET group and nine women (53%) in the LIRA group had metabolic syndrome at the beginning of the study. After 3 months of treatment the metabolic syndrome persisted in seven women (47%) in the MET group and five (29%) women in the LIRA group.

Changes in menstrual pattern

Menstruation frequency (normalized to the number of menstruations per year) was also included as a secondary endpoint. No statistically significant changes were found either when comparing the overall menstruation frequency change irrespective of the therapeutic arm or when analyzing it separately by therapeutic arm.

Subsets – post hoc analysis

Exploratory data analysis suggested two groups, Subset 1 and Subset 2, with significant differences in the following baseline parameter values (Mann-Whitney P values after Bonferroni correction in parentheses): γGT (0.004); OGTT blood glucose after 30 minutes, baseline insulin and insulin after 120 minutes (0.040, 0.007, 0.003, respectively); $HOMA_{IR}$ score (<0.001). The results seem suggestive of certain metabolic differences (i.a. insulin resistance as indicated by $HOMA_{IR}$ score, presence of the metabolic syndrome).

Comparison of HOMA >2 (indicating IR) showed a statistically significant difference (p=0.026, Fisher exact test), with all Subset 2 patients manifesting IR (HOMA >2). In subset 1 HOMA >2 was detected only in 53% of patients (10/19). Analysis with respect to the presence of the metabolic syndrome showed rather high, although not statistically significant, odds of the metabolic syndrome in Subset 2 vs. Subset 1 (OR=3.9). Incidentally, the distribution of therapies between Subset 1 and Subset 2 proved very well balanced (Subset 1: liraglutide n=10, metformin n=9; Subset 2: liraglutide n=4, metformin n=5).

The mixed-model analysis (see section Statistical Analyses) showed a highly significant (P=0.009) three-way interaction suggestive of a heterogenous effect of liraglutide and metformin on BMI decrease/weight reduction among PCOS patients; a significance that could hardly be expected with such a small number of subjects if the inter-subgroup differences were not actually large. The finding is graphically displayed in Figure 1.

Adverse events

Both drugs were generally well tolerated and mild to moderate and transient adverse events did not lead to discontinuation of treatment in the majority of patients. The need for daily subcutaneous injections of liraglutide was generally not less appealing than oral formulation of metformin. In the MET group, nine (out of 14) subjects had temporary mild gastrointestinal (GI) problems (nausea and/or diarrhoea), one of whom discontinued the study. Adverse events

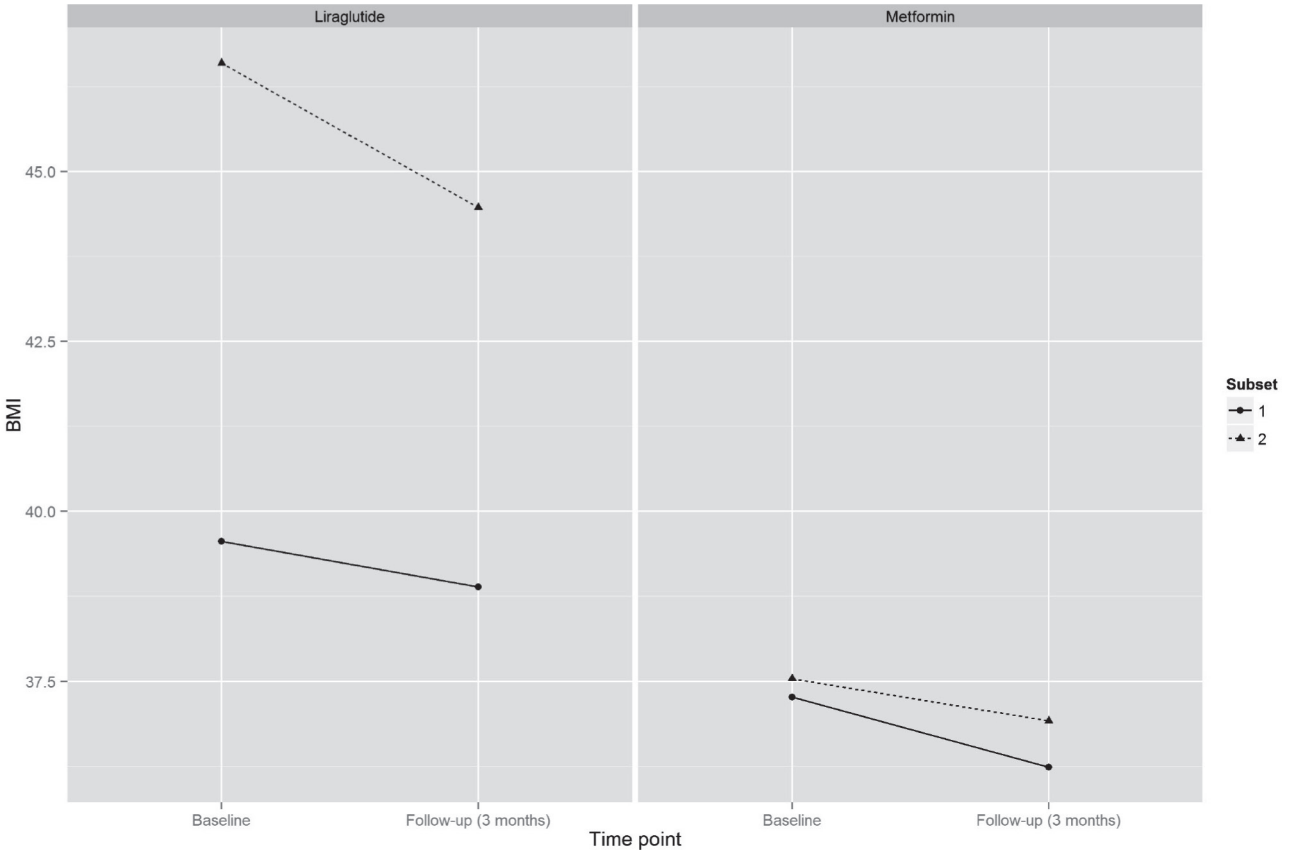

Figure 1. Reduction of BMI from baseline to follow-up visit by treatment group (liraglutide, left; metformin, right) and subset of patients (Subset 1, triangles/dotted lines; Subset 2, points/solid lines). There is a highly significant interaction between treatment and subset (three-way interaction of time point, treatment and subset: p=0.0085), with liraglutide being substantially more advantageous for Subset 2 patients and metformin more advantageous for Subset 1 patients. [Only evaluable patients (liraglutide: n=14, metformin: n=14) are included].

associated with LIRA were nausea (8/14), diarrhoea (3/14), vomiting (1/14), constipation (1/14), stomach ache (1/14), heartburn (1/14), headache (2/14) and dizziness (4/14). Although subjects in general experienced more severe nausea during liraglutide treatment compared with metformin, the severity decreased over time and did not correlate with weight loss. Four patients in the LIRA group reported minor hypoglycemic events. One patient from the LIRA group was excluded because of a rash at the injection site.

DISCUSSION

The potentially beneficial effects of liraglutide in comparison to metformin on weight change have not yet been evaluated in women with PCOS. To our knowledge, this is the first study to date demonstrating that liraglutide was substantially more advantageous than metformin in a subset of patients with insulin resistance, severe obesity and higher odds ratio of the metabolic syndrome.

The effect of metformin on weight reduction and fat distribution in PCOS remains controversial and heterogeneous. While the Cochrane Library Reviews of randomized clinical trials (RTC) could not confirm any weight reducing effect,[19] the results of our study are in agreement with some more recent reports which suggested a dose-dependent effect of metformin on weight reduction, with greater weight loss potentially achievable with higher than 1500 mg/day doses of metformin.[20-22] The magnitude of weight reduction in the present study is comparable with previously reported results. In one of these trials, the weight reduction was 1.5 kg in the 1500 mg/

day treated group compared to 3.6 kg in the 2550mg/day treated group.[20] In another small (n=56) RCT, 6-month treatment with metformin resulted in mean weight reduction of 2.3 kg compared to placebo.[23] Some studies of longer duration where metformin was combined with lifestyle interventions demonstrated a significant reduction in visceral fat mass.[24] Also, this effect seemed to be dose-dependent.[21]

The possible positive impact of metformin on weight loss can be supported by recent data suggesting that metformin may normalize appetite in obese women with PCOS by restoring neuropeptide Y secretion which is impaired in these women.[25,26] In addition, it may also exert its beneficial action in part through the modulation of the incretin axis[27] by the stimulatory effect of GLP-1, leading to enhancement of the expression of GLP-1 receptor and related insulinotropic receptors through a mechanism that is dependent on peroxisome proliferator-activated receptor-alpha (PPAR alpha).[28,29]

As opposed to the inconsistent conclusions about the beneficial effect of metformin on weight reduction, studies consistently linked GLP-1 receptor agonists with progressive and sustained weight loss.[9] A meta-analysis of 25 trials recorded weight loss in the GLP-1 receptor agonist groups in overweight or obese patients with diabetes as well as in patients without diabetes.[10] The participants without diabetes achieved greater reductions in body weight than those with diabetes. A 20-week RCT compared liraglutide to orlistat in obese people without diabetes. It was shown that liraglutide resulted in significant dose related weight loss (mean weight loss 4.8 to 7.2 kg) compared to placebo combined with lifestyle modification.[30] In a LEAD trial programme, placebo-subtracted body weight losses were 0.1 kg, 1.3 kg, 2.6 kg and 1.38 kg with liraglutide.[31-34] Comparator-subtracted weight losses were 2.3 kg versus rosiglitazone ($p<0.001$), 3-3.8 kg versus glimepiride ($p<0.004$) and 3.4 kg versus insulin glargine during 26 weeks.[31-33,35,36] The weight loss in our obese patients with newly diagnosed PCOS treated with liraglutide was in the same range (-3 kg).

As reported, intention-to-treat analysis in our study showed no significant difference in BMI, body weight, waist circumference and whole-body fat mass reductions between therapeutic groups in general. However, with respect to post hoc analysis, a subgroup of our patients with IR, severe obesity and higher odds ratio of the metabolic syndrome fared much better with liraglutide than with metformin. This observation supports the concept that severity of metabolic derangements and the degree of obesity might be influential and serve as predictors of the response to liraglutide. This is in accordance with the analysis of seven phase 3 trials from the liraglutide diabetes development programme reporting that across trials a higher initial BMI was associated with slightly greater weight loss.[37]

By contrast, metformin was more beneficial regarding weight reduction in the subset of patients with lower metabolic risk profile. This observation is in agreement with several studies demonstrating that metformin may be more effective in PCOS patients with lower BMI. On the other hand, there are many studies showing that metformin produces some benefit in women with PCOS irrespective of their body weight or degree of IR.[38]

Further, notwithstanding the comparable effect of both treatments on weight loss in general, metformin-treated subjects in the current study experienced greater LH and testosterone reduction. These superior effects of metformin on the hormonal profile of PCOS might result from its known unique direct effects on LH secretion and on steroidogenesis in ovaries.[38] In contrast, treatment with liraglutide led to a significant LH increase. Due to the small sample size, the pulsatile pattern of LH secretion, blood sampling on a non-specific day of the menstrual cycle and the lack of any data on GLP-1 effects on LH secretion, we cannot provide any firm conclusion about this observation.

The failure to significantly influence the menstruation frequency in our study is in fact not surprising due to the relatively small number of patients and the short observation period. Similarly, the lack of statistically significant difference in IR as assessed by $HOMA_{IR}$ score with both treatments may be due to small sample size and short duration. In addition, a large variability in IR, calculated using the $HOMA_{IR}$ score in women with PCOS and a relatively low sensitivity of the $HOMA_{IR}$ score method in detecting

the specific form of IR that characterizes PCOS, was reported in other trials.[5,11]

In summary, our study is the first to provide preliminary data that short-term liraglutide treatment was associated with significantly greater weight loss in a subset of obese patients with newly diagnosed PCOS and a higher metabolic risk profile when compared to metformin. Although the small sample size and short period of treatment limit the generalizability of our results, we strongly believe that the finding deserves further attention. Larger trials of longer duration are warranted to assess the efficacy and safety of liraglutide in obese women with PCOS.

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