Open Access IMC Journal of Medical Science Original Article

Short-term and low-dose liraglutide plus metformin decreased body mass index and insulin resistance more than metformin alone in obese women with polycystic ovary syndrome: An open-label randomized controlled study

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Abstract

Background and objectives: Reduction of weight improves different manifestations of polycystic ovary syndrome (PCOS). This study compared the effects of liraglutide plus metformin versus metformin alone on weight loss and metabolic profiles in obese women with PCOS.

Methods: This open-label randomized controlled clinical trial consecutively recruited newly-diagnosed PCOS patients of reproductive age with obesity (body mass index ≥ 27.5 kg/m^2). Following randomization into two equal groups, Group-1 received treatment with metformin 1000 mg daily alone while Group-2 was given metformin 1000 mg plus subcutaneous (SC) liraglutide 1.2 mg daily for 12 weeks. Anthropometric, biochemical and hormonal data and ovarian morphology were assessed at baseline and after 12 weeks. Clinical information and side effects were recorded every four weeks after initiation of the treatment. Glucose, lipids, and all hormones were analyzed by glucose oxidase, precipitation method, and chemiluminescent microparticle immunoassay respectively. Insulin resistance was measured by homeostatic model assessment (HOMA-IR).

Results: Study included 30 participants comprising 15 for each group. Among 15 participants, 5 dropped out from the Group-1 and 1 dropped out from the Group-2. The final analysis was done among 24 participants (Gr-1: 10 and Gr-2: 14). Waist and hip circumference (WC, HC) significantly ($p < 0.05$) decreased in patients treated with only metformin. Menstrual irregularity, BMI (body mass index), HC, systolic blood pressure (BP), 2h-OGTT glucose, fasting insulin, and HOMA-IR significantly ($p < 0.05$) decreased in the patients of Group-2 after 12 weeks compared to baseline status. Percentage changes of weight, BMI and HOMA-IR improved significantly ($p < 0.05$) in cases of Group-2 than those in Group-1. Side effects were though numerically higher in the Group-2 patients, but reduced with time.

Conclusions: Addition of liraglutide with metformin was superior to metformin alone for lowering of BMI and insulin resistance among obese PCOS women with acceptable side effects.

IMC J Med Sci. 2024; 18(1):002. DOI: https://doi.org/10.55010/imcjms.18.002

Introduction

Polycystic ovary syndrome is a heterogeneous condition with a combination of reproductive, cutaneous, and metabolic features. Although its pathogenesis is largely unknown, hyperandrogenism and insulin resistance are the main determinants of

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clinical features [1, 2]. According to one hypothesis, PCOS symptoms develop when the body is unable to adjust to excess hepato-visceral fat acquired during the perinatal period. The central fat is pro-inflammatory and promotes both hyperandrogenemia and insulin resistance by secreting several types of adipocytokines. Ultimately, a vicious cycle is created between fat tissues and androgen-producing tissues, which perpetuate the typical features of PCOS [3].

Obesity affects around two-thirds of PCOS patients and is now considered a secondary cause of PCOS [4]. Several studies have shown amelioration of all features of PCOS after weight loss by lifestyle management and bariatric surgery [5,6]. Besides, obesity increases the manifestations of PCOS including hyperandrogenism, and reduces the pregnancy rate [7].

Management of PCOS is essentially symptomatic. Patients having metabolic features are often treated with insulin sensitizers. This use of insulin sensitizers in PCOS is off-level but evidence-based [8]. Metformin is a weight-neutral drug; however, along with the improvement of different manifestations, there is also a reduction of weight especially in patients with obesity [9,10]. Other weight-reducing drugs, especially glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are attractive options. Recent studies have shown a wide spectrum of weight reductions in different obesity-related conditions including diabetes mellitus (DM), nonalcoholic fatty liver disease, obstructive sleep apnea, etc. by different types of GLP-1-RAs [11]. Liraglutide is a once-daily injectable GLP-1-RA that has achieved the approval of the Food and Drug Administration (USA) for the management of DM and obesity [12]. It works through a variety of mechanisms, including inhibiting the hypothalamus appetite center and delaying stomach emptying [13]. Its weight-loss impact is independent of its principal adverse effects, nausea, and vomiting [14]. Patients from South-Asian backgrounds have more metabolic manifestations and may benefit more from GLP-1-RAs [15]. The efficacy and safety of liraglutide in the management of PCOS are not adequately evaluated. This study compared the effects of metformin vs. metformin plus liraglutide in obese PCOS women. Both groups received advice on standard lifestyle management on metabolic and hormonal manifestations of PCOS.

Materials and methods

The study was conducted at the PCOS Clinic of the Department of Endocrinology of Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period of January 2018 to August 2019. The study was conducted according to the World Medical Association' Declaration of Helsinki and the research protocol was approved by the Institutional Review Board (IRB) of BSMMU (No. BSMMU/2018/11032, Dated: 15/09/2018). Informed written consent was taken from all participants.

Study type and population: This open-label randomized controlled clinical trial consecutively recruited newly-diagnosed PCOS patients of reproductive age (15 – 45 years) with obesity (body mass index (BMI) ≥27.5 kg/m^2) [16]. PCOS was diagnosed on the basis of the Revised 2003 Rotterdam criteria [17]. Sample size was calculated by [$n= 2\sigma^2 (Z_\alpha + Z_\beta)^2 / (\mu_1 - \mu_2)^2$] formula where at Z_α = 1.96, Z_β= 0.85 at 80% power, expected mean weight change in metformin plus liraglutide group: μ_1= 6.5, expected mean weight change between groups: μ_2= 1.2 and σ = 6.8 (pooled standard deviation (SD) for each group) [18]. Participants having similar endocrine disorders, DM, chronic kidney disease, chronic liver disease, history of pancreatitis, personal or family history of medullary carcinoma of the thyroid, history of taking metformin, hormonal contraceptive, anti-obesity, or anti-androgen drugs within the last 6 months were excluded.

Intervention: All the study participants were divided into two groups by a computer-generated random number chart. Group-1 (metformin group) was treated with metformin 500 mg twice daily orally and the Group-2 (metformin + liraglutide group) was treated with metformin 500 mg orally twice daily plus subcutaneous injection of liraglutide 1.2 mg once daily for 12 weeks. To reduce the side effects of liraglutide, the participants of Group-2 was given 0.6 mg liraglutide once daily for the first two weeks; then increased to 1.2 mg once daily from the third week onward. Standard lifestyle advice including a weight-based

diet, physical activity, and behavioral modifications was provided to both groups. All patients were educated about symptoms, signs, and management of side effects. Each patient was provided with medication according to her assigned category.

Follow-up and investigations: At the first visit, anthropometric, clinical and biochemical data were recorded in a standard data sheet. The second visit was 2 weeks after the initiation of the study to increase the dose of liraglutide to 1.2 mg. Subsequent visits were made every four weeks from the initiation of the study. Clinical and anthropometric data were taken at every visit. Biochemical and imaging data were taken at the first and final visits. Weight (kilogram) and height (centimeter) were measured by calibrated bathroom scale and mounted measuring tape respectively to calculate BMI (kg/m^2). WC (centimeter) was measured by measuring tape at the level of the umbilicus while HC was measured at the level of the largest lateral extension of the hip, both in a horizontal plane.

Blood pressure was measured by a calibrated sphygmomanometer (mm-Hg). Hirsutism was measured by using the modified Ferriman-Gallwey (mFG) score. Acne was observed over the face. Acanthosis nigricans was checked on the neck, axilla, and groin. Amenorrhea was considered if a women missed at least three menstrual periods in a row while oligomenorrhea was diagnosed when inter-menstrual intervals was greater than 35 days [19,20]. Menstruation occurring for consecutive two months was considered regular menstruation. Tests done in fasting state included: luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), fasting insulin, plasma glucose and lipid profile, followed by a standard 75 g oral glucose tolerance test (OGTT). Blood glucose was measured by the glucose oxidase method and serum LH, FSH, and TT were measured by chemiluminescent microparticle immunoassay at diagnosis during the follicular phase of the menstrual cycle. Total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured by architect Plus Ci4100 automated analyzer. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula = (fasting glucose, mmol/L × fasting insulin, µU/mL) ÷ 22.5 [21].

Data analysis: The statistical analysis was done by SPSS software (version- 22.0). Numerical data were expressed in mean ± SD or median inter-quartile range (IQR) depending on their distribution. Qualitative data were expressed in frequency (%). There were no missing data. The percentage changes were calculated as follows: percentage changes = {(values after 3 months – values at baseline) ÷ values at baseline} × 100. For quantitative variables, comparisons between groups were done by independent samples t-test or Mann-Whitney U test, and within groups were done by paired t-test or Wilcoxon matched-pair signed rank test as appropriate. For qualitative variables, the associations between two groups were analyzed by Fisher's exact test, and within groups were assessed by the McNemar test. Statistical significance for decision-making was set at two-tailed p-values below 0.05.

Results

Study included 30 participants comprising 15 for each group. Among 15 participants, five dropped out from the Group-1 and 1 dropped out from the Group-2. The final analysis was done among 24 participants. The study flow chart is shown in Figure-1.

Table-1 shows that participants from both groups were not significantly ($p>0.05$) different with respect to age, personal history of subfertility, family history of PCOS, subfertility, obesity, hypertension, diabetes as well as thyroid and prolactin statuses.

The anthropometric, clinical, biochemical, hormonal and imaging profiles of the study groups in relation to intervention are shown in Table-2. Patients in Group-2 had significantly higher levels of serum FSH ($p=0.012$) and HOMA-IR ($p=0.042$) levels than patients in the Group-1 before intervention. WC ($p=0.032$) and HC ($p=0.028$) decreased significantly in patients taking only metformin. Menstrual irregularity significantly ($p=0.002$) became regular in patients of Group-2. Also, BMI ($p<0.001$), HC ($p=0.037$), systolic BP ($p=0.043$), 2H-OGTT glucose ($p=0.016$), fasting insulin ($p=0.012$), and HOMA-IR ($p=0.003$) improved significantly in patients of Group-2 after intervention.

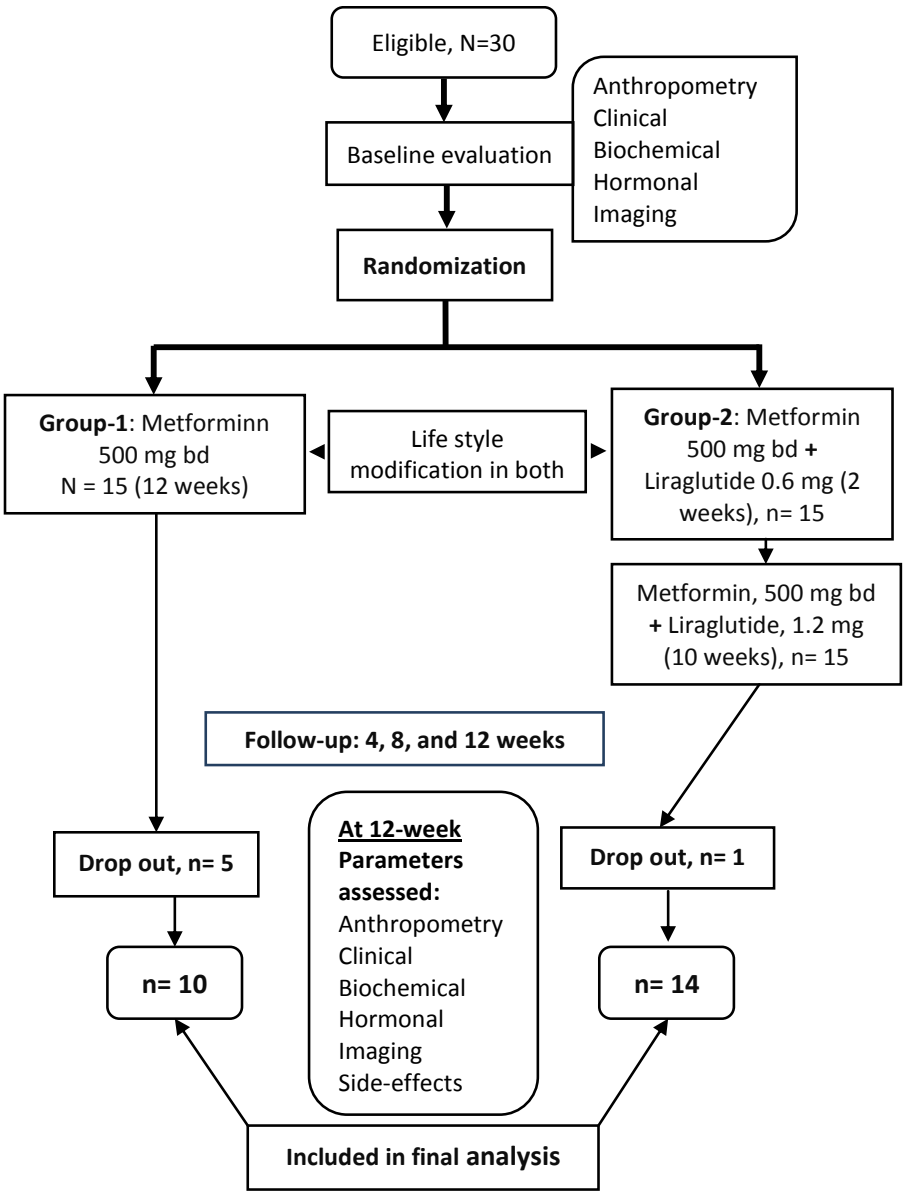

Figure-1: *The study flow chart showing the enrollment, intervention and follow up scheme of the study participants*

Table-1: *Baseline characteristics of the study population (N= 24)*

Variables	Group-1 (n=10)	Group-2 (n=14)	p value
Age, years (mean ± SD)	25.3 ± 4.6	24.1 ±4.3	0.510*
Personal H/O subfertility [9], (n, %)	1 (20.0) [5]	1 (25.0) [4]	1.00†
Family history of (n, %):			
PCOS	3 (30.0)	2 (14.3)	0.615†
Subfertility [9]	2 (20.0)	4 (28.6)	1.00†
Obesity	8 (80.0)	8 (57.1)	0.388†
Hypertension	9 (90.0)	9 (64.3)	0.341†
Diabetes mellitus	8 (80.0)	11 (78.6)	1.00†
TSH, mIU/mL, median IQR	2.3 (1.5 – 3.2)	2.5 (1.5 – 3.9)	0.752‡
FT4, ng/dL, median IQR	1.4 (1.1 – 2.1)	1.3 (1.2 – 1.4)	0.886‡
Prolactin, ng/mL, median IQR	10.9 (8.2 – 14.1)	9.9 (8.9 – 13.6)	0.841‡

*Note: Within parentheses are percentages over column total, [available no.]; *Independent samples t-test or †Fisher's exact test or ‡Mann Whitney U test was done as appropriate*

Table-2: *Anthropometric, Clinical, biochemical, hormonal, and imaging characteristics of Group-1 (n=10) and Group-2 (n=14) study population in relation to intervention (N= 24)*

Variables	Before intervention			After intervention			Gr-1	Gr-2
	Group-1 (n=10)	Group-2 (n=14)	p	Group-1	Group-2	p	p*	p†
Number (%)								
Irregular cycle	8 (80.0)	13 (92.9)	0.550	4 (40.0)	3 (21.4)	0.393	0.219	**0.002**
Significant hirsutism	9 (90.0)	12 (85.7)	1.00	9 (90.0)	11 (78.6)	0.615	1.00	1.00
Acne	5 (50.0)	4 (28.6)	0.403	4 (40.0)	5 (35.7)	1.00	1.00	1.00
Acanthosis nigricans	7 (70.0)	8 (57.1)	0.678	6 (60.0)	5 (35.7)	0.408	1.00	0.250
PCOM	7 (70.0)	11 (78.6)	0.665	7 (70.0)	7 (50.0)	0.421	1.00	0.219
(Mean ± SD								
BMI, kg/m^2	32.8 ± 3.3	34.7 ± 3.7	0.200	32.2 ± 3.7	33.0 ± 3.7	0.617	0.171	**<0.001**
Systolic BP, mm-Hg	105.0 ± 13.5	107.9 ± 13.1	0.609	100 (90 – 112.5)	95 (90 – 110)	0.472	0.257	**0.043**
Diastolic BP, mm-Hg	70.5 ± 8.3	72.5 ± 9.4	0.595	65 (60 – 80)	60 (60 – 80)	0.796	0.581	0.425
TT, ng/dL	46.1 ±15.1	52.2 ±24.8	0.496	48.0 (37.3 – 83.3)	44.8 (32.9 – 58.6)	0.625	0.646	0.925
FSH, IU/mL	3.9 ± 1.6	5.7 ±1.5	**0.012**	4.0 (3.5 – 5.4)	5.2 (4.6 – 6.6)	0.096	0.445	0.683
2H-OGTT, mmol/L	7.1 ± 1.6	7.0 ± 1.6	0.959	6.9 ± 3.3	5.9 ± 1.3	0.300	0.874	**0.016**
TC, mg/dL	204.5 ± 39.7	195.8 ±32.4	0.560	194.6 ± 34.3	195.6 ± 32.4	0.947	0.201	0.970
LDL-C, mg/dL	134.7 ± 41.4	125.1 ± 24.6	0.483	123.5 ± 30.4	123.4 ± 27.5	0.992	0.141	0.728
Median IQR								
WC, cm	96.0 (89.8 – 102.3)	97.0 (94.5 – 102.0)	0.508	93.3 ± 7.2	97.8 ± 8.5	0.189	**0.032**	0.430
HC, cm	112.0 (107.3 – 117.0)	110.0 (106.5 – 116.5)	0.709	106.3 ± 6.0	108.6 ± 7.3	0.415	**0.028**	**0.037**
LH, IU/mL	7.3 (3.6 – 9.6)	6.4 (4.8 – 9.6)	0.931	8.5 (5.2 – 16.5)	8.2 (6.3 – 12.9)	0.977	0.214	0.084
FPG, mmol/L	4.7 (4.6 – 5.2)	5.0 (4.8 – 6.1)	0.056	4.9 ± 0.7	4.9 ± 0.4	0.872	0.550	0.064
HDL-C, mg/dL	40.5 (35.8 – 48.8)	40.5 (36.5 – 42.0)	0.625	45.0 (39.8 – 51.0)	42.0 (39.8 – 47.3)	0.285	0.159	0.073
TG, mg/dL	122.0 (92.0 – 193.3)	149.0 (130.8 – 166.5)	0.285	122.5 (101.8 – 172.5)	131.5 (113.0 – 172.0)	0.666	0.878	0.109
insulin, µIU/mL	17.4 (11.7 – 26.4)	20.8 (18.5 – 25.9)	0.172	16.6 (11.7 – 28.5)	15.4 (10.9 – 22.2)	0.666	0.575	**0.012**
HOMA-IR	3.7 (2.5 – 5.0)	4.9 (3.8 – 6.9)	**0.042**	3.9 (2.4 – 5.2)	3.3 (2.3 – 5.2)	0.886	0.721	**0.003**

*Note: PCOM: polycystic ovary morphology; *between column 2 vs. 5; †between column 3 vs. 6; Independent samples t-test or Mann Whitney U test, or Fisher's exact test was done between the study groups as appropriate; Paired t-test or Wilcoxon matched-pair signed rank test, or McNemar test was done within the study groups as appropriate*

Table-3: *Comparison of the percentage changes of anthropometric, clinical biochemical, and hormonal parameters between the study groups (N= 24)*

Variables	Percentage changes in		P value
	Group-1	Group-2	
	Mean ± SD or Median IQR		
Weight, kg[a]	-2.0±3.1	-5.0±2.5	**0.015**
BMI, kg/m^2	-1.7 ± 3.3	-4.9 ± 3.0	**0.023**
WC, cm	-4.6 ± 5.6	-0.9 ± 6.5	0.160
HC, cm	-3.7 (-7.3 – -1.3)	-3.1 (-5.6 – 0.0)	0.508
Systolic BP, mm-Hg	-2.5 ±7.0	-8.1 ± 14.9	0.233
Diastolic BP, mm-Hg	0.0 (-3.6 – 1.7)	-14.3 (-22.9 – 8.3)	0.259
TT, ng/dL	1.2 (-24.4 – 99.2)	-6.9 (-29.0 – 71.4)	0.625
LH, IU/mL	82.7 (-10.2 – 167.7)	13.1 (-7.3 – 86.4)	0.585
FSH, IU/mL	18.6 (-17.7 – 53.9)	-3.7 (-24.7 – 20.0)	0.212
FPG, mmol/L	-2.4 (-6.4 – 3.2)	-6.0 (-15.4 – 4.7)	0.312
2H-OGTT glucose, mmol/L	-3.4 ± 32.3	-14.0 ± 17.6	0.313
TC, mg/dL	-4.0 ± 11.5	0.4 ± 12.5	0.392
HDL-C, mg/dL	10.7 ± 19.0	9.0 ± 17.6	0.825
LDL-C, mg/dL	-6.1 ± 14.9	-0.2 ± 18.6	0.415
TG, mg/dL	8.7 (-16.7 – 26.9)	-12.8 (-19.4 – 0.7)	0.259
Fasting insulin, µIU/mL	12.5 ± 59.9	-23.2 ± 26.8	**0.061**
HOMA-IR	-5.3 (-31.7 – 37.4)	-25.3 (-54.0 – -10.6)	**0.026**

Note: IQR: interquartile range; Independent samples t-test or Mann Whitney U test was done. a: mean difference = 3.0 kg, 95 confidence interval = 0.6, 5.4.

Table-4: *Adverse effects observed among the study population during the interventions (n= 24)*

Adverse effects	Follow-up	Group-1 (N= 10)	Group-2 (N =14)
Clinical n (%)			
Nausea	1st month	5 (50.0)	10 (71.4)
	2nd month	0 (0.0)	6 (42.9)
	3rd month	0 (0.0)	3 (21.4)
Vomiting	1st month	0 (0.0)	5 (35.7)
	2nd month	0 (0.0)	0 (0.0)
	3rd month	0 (0.0)	0 (0.0)
Loose motion	1st month	4 (40.0)	7 (50.0)
	2nd month	0 (0.0)	4 (28.6)
	3rd month	0 (0.0)	1 (7.1)
Weakness	1st month	0 (0.0)	1 (7.1)
	2nd month	0 (0.0)	1 (7.1)
	3rd month	0 (0.0)	1 (7.1)
Dizziness	1st month	2 (20.0)	4 (28.6)
	2nd month	0 (0.0)	1 (7.1)
	3rd month	1 (10.0)	1 (7.1)
Abdominal pain	1st month	0 (0.0)	3 (21.4)
	2nd month	0 (0.0)	1 (7.1)
	3rd month	0 (0.0)	0 (0.0)
Biochemical (mean ± SD)			
SGPT	Baseline	39.6 ± 27.9	24.5 ± 12.0
	3rd month	45.8 ± 31.8	22.9 ± 8.7
Serum creatinine	Baseline	0.7 ± 0.1	0.7 ± 0.1
	3rd month	0.7 ± 0.1	0.7 ± 0.1

Comparison of percentage changes of different variables shows BMI (p=0.023) and HOMA-IR (p=0.026) significantly decreased in Group-2 than that of Group-1 patients (Table-3). Percentage of weight loss was significantly (p=0.015) higher in the patients of Group-2 compared to Group-1 patients (mean difference 3 kg). Although, at least 5% weight loss was observed in 20% (2/10) and 57.1% (8/14) cases after intervention in Group-1 and Group-2 cases respectively, the p-value did not reach a significant level (p =0.104). Different types of side effects, especially gastrointestinal, were numerically higher in the Group-2 cases than those in Group-1. However, their frequency reduced with time (Table-4).

Discussion

This open-label RCT showed the superiority of short-term (12 weeks) and low-dose of liraglutide (1.2 mg/ day) plus metformin therapy (1 g/day) over metformin (1 g/day) alone, along with lifestyle management, in reduction of BMI, and HOMA-IR among obese patients with PCOS. However, we did not find significant differences in other metabolic as well as hormone profiles between the study groups. Although the gastrointestinal side effects were initially higher in the metformin plus liraglutide group than in the metformin group, they reduced with time.

In our study, when liraglutide was added to metformin, along with improvement of BMI and HC, menstrual irregularity, systolic blood pressure, 2H-OGTT glucose, fasting insulin, and insulin resistance also improved. Several meta-analyses suggest that liraglutide is superior to metformin in the improvement of metabolic manifestations [22,23]. When liraglutide is added to metformin, there is a synergistic effect [24]. Both WC and HC have significantly improved in patients of metformin group and are consistent with the findings of other studies conducted among PCOS patients with a BMI ≥25 kg/m^2 [25]. However, we did not observe improvements in BMI and other endocrine and metabolic abnormalities which could be due to the short duration and lower doses of metformin.

Patients of metformin plus liraglutide group additionally had reduction of weight and BMI by 3% and 1.2% respectively of the baseline than those in metformin group. A meta-analysis comprising three RCTs has reported similar weight loss and reduction of BMI with metformin plus liraglutide compared to metformin alone [26]. Rather than using absolute values, we used percentage changes as our study groups differed by BMI at baseline. Although higher percentages of our Group-2 patients achieved at least 5% weight loss than the Goup-1 cases (57.1% vs. 20.0%), the association was not statistically significant. Study from Slovenia also reported 5% weight loss in 22% cases among their study population receiving liraglutide and metformin [18]. It appears from our findings that people from South Asian backgrounds might respond better than the European population to GLP-1-RA [15]. The Slovenian study group has also shown in other studies that the weight loss response to liraglutide depends on the dose, metabolic status, and genetic polymorphism of GLP-1-RA [27-29].

We also found significant reduction in insulin resistance in patients receiving liraglutide plus metformin than the metformin alone. However, two similar studies did not find significant differences in HOMA-IR levels between cases of liraglutide plus metformin and the metformin groups [8,30]. A meta-analysis which included four RCTs, showed a reduction of both fasting glucose and insulin in patients having metformin plus liraglutide than the metformin alone, however, the values of HOMA-IR were not mentioned [26]. In our study, other metabolic manifestations, including glucose and lipid profile, changed similarly in both the study groups. Jensterle et al. also found similar findings except for a favorable effect on 2H-OGTT glucose levels in cases with metformin plus liraglutide [18]. However, their participants received a double dose of metformin than our study participants. In our study, 2H-OGTT glucose and systolic BP improved only in our Group-2 cases while Jensterle et al. did not find improvement in BP.

We did not find any improvement in hormonal status within or between the study groups. Again, these findings are similar to the study conducted by Jensterle et al [18]. On the other hand, Xing et al.

found significant improvement in free androgen index, LH, and progesterone levels in cases receiving combination of metformin and liraglutide compared to those in metformin group, despite a lack of improvement of any metabolic variables including BMI and HOMA-IR [30]. They also prescribed 2 gm of metformin per day for both groups.

The menstrual cycle significantly improved only in metformin plus liraglutide group. While Xing et al. found improvement in the menstrual cycle in both groups while Jensterle et al. did not find it in any group [30,18]. Hirsutism, acne, acanthosis nigricans and PCOM almost remained similar to baseline indicating the requirement of a longer duration of treatment for significant improvement.

Cases of metformin plus liraglutide group experienced more gastrointestinal side effects than those in metformin group. Nausea, loose motion, and vomiting were the most frequent side effects which were generally mild to moderate and subsided with time. The hypoglycemic events were absent. The short-term safety profile of using liraglutide in obese PCOS patients seemed to be acceptable. However, it is currently impossible to obtain precise estimates of the long-term risk of serious adverse effects such as pancreatitis or precancerous pancreatic lesion that has been claimed by some to be associated with GLP-1 based therapies. Although, a few patients complained of abdominal pain, these were non-specific, not associated with elevated lipase, and improved with symptomatic management. The main limitation of this study was lost to the follow-up of 33% of participants in the metformin group. One participant from both groups became pregnant, and others left the study from the metformin only group which might be due to the open-label nature of the study.

In conclusion, this study demonstrated that when liraglutide was added to metformin, even at low dosages and for a short period of time, coupled with lifestyle management, metabolic parameters such as BMI and insulin resistance decreased significantly in obese PCOS women. Despite high cost and injectable form, liraglutide's effectiveness with acceptable side effects may be explored for the therapy of obesity in PCOS patients. Long-term study and higher dose may be required to ameliorate other metabolic, androgenic and hormonal abnormalities of obese PCOS patients.

Authors' contribution

AH, HB, MAH: Conception and design; AH, MSM, SA: Acquisition, analysis, and interpretation of data; All: Manuscript drafting and revising it critically

Competing interest

The authors have nothing to declare.

Funding

This study was partially supported by a Research grant from Research and Development, BSMMU, Novo Nordisk Pharma, and Beximco Pharmaceuticals Ltd., Bangladesh.

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Cite this article as:
Hossain M, Banu H, Morshed MS, Afrine S, Hasanat MA. Short-term and low-dose liraglutide plus metformin decreased body mass index and insulin resistance more than metformin alone in obese women with polycystic ovary syndrome: An open-label randomized controlled study. *IMC J Med Sci. 2024; 18(1):002*.
DOI: https://doi.org/10.55010/imcjms.18.002