Title: The effects of treatment with liraglutide on quality of life and depression in young obese women with PCOS and controls

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Background: Polycystic ovary syndrome (PCOS) is associated with reduced quality of life (QoL), though the role of associated obesity is unclear. In this study we examined the effects of six months treatment with liraglutide, 1.8mg od, on obesity, depression and QoL in young women with PCOS and obesity compared to age- and weight-matched controls.

Methods: In a cross-sectional study, thirty six women were recruited (19 PCOS, 17 controls), age 33.9 ±6.7 vs. 33.5 ±7.1yr, and weight 102.1 ±17.1 vs. 100.4± 15.1kg, respectively. PCOS was diagnosed according to the Rotterdam criteria. Depression was measured using the Centre for Epidemiologic Studies Depression Scale (CES-D). QoL was measured using the World Health Organisation QoL questionnaire (WHOQOL-BREF).

Results: At baseline there was no difference in QoL or CES-D scores between the two groups. At six months, weight was reduced by 3.0 ±4.2kg, P= 0.01, in the PCOS group and 3.8 ±3.4kg, P= 0.001, in controls. Psychological health improved in the PCOS group (percentage change 11.3%, p<0.02). Combining the two groups revealed significant improvement (P<0.05) in physical (82.6 ±11.2 vs. 78.9 ±13.6), psychological (62.4 ±16.5 vs. 57.5 ±16.4) and social health (76.6 ±15.3 vs. 71 ±16.8) components of the WHOQOL-BREF at 6 months.

Conclusions: Weight loss is associated with an improvement in QoL; and when matched for age and obesity, PCOS was not independently associated with reduced QoL or depression.

Key words: PCOS; Liraglutide; Obesity; Quality of life; Depression.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age [1]. PCOS is associated with conditions that may have a negative impact on quality of life (QoL) including hirsutism, oligomenorrhoea, obesity and sub-fertility. While PCOS has been associated with depression and reduced QoL in several studies [2, 3, 4], it is not yet clear which of its components has the main effect. Obesity is seen in up to 78% of women with PCOS [5] and is associated with reduced Qol [6]. Despite its high prevalence, only a few studies have accounted for obesity when examining the psychological health in women with PCOS and their results are not conclusive [7, 8]. In addition, the effects of weight loss on QoL in women with PCOS and obesity are not yet clear.

Liraglutide is a glucagon like peptide-1 analogue which causes weight loss and it represents an attractive option for the treatment of obesity in women with PCOS [9].

The primary aim of this study was to determine the effect of 6 months treatment of liraglutide on weight loss in PCOS compared to weight matched controls, including an assessment of QoL.

2. Study design

Interventional case-control study of young women with PCOS and obesity, and age- and weight-matched controls. The study was approved by the Leeds (East) Research Ethics Committee and informed consent was given by all study participants before participation; clinical trial registration number: ISRCTN48560305.

3. Methods

Women with PCOS were recruited from the endocrine clinic and controls were recruited through an advertisement in the local newspaper. Women with PCOS and controls were invited for a screening visit if they had a body mass index (BMI) between 30–45 kg/m^2, and were between 18–45 years of age. PCOS was diagnosed according to the Rotterdam criteria [10]. Other endocrine disorders with similar presentation were excluded. Control subjects underwent the same biochemical screening as the PCOS group to exclude any unknown endocrine disorder. Control subjects with a history of clinical or biochemical hyperandrogenism or menstrual irregularities were excluded. Study exclusion criteria included previous history of hypothyroidism, pancreatitis, heart failure, renal failure, type 2 diabetes, alcohol consumption of >14 units/week, and pregnant or breast feeding women.

Participants, PCOS and controls, who fulfilled the study inclusion/exclusion criteria were treated with Liraglutide 0.6 mg od for one week, 1.2mg for one week and then 1.8mg od for six months. Study participants did not receive any special dietary advice and were not advised to change their diet. Study participants were assessed at baseline and six months after treatment with liraglutide.

3.1 Anthropometric measurements

Weight was measured in kilograms, and body mass index (BMI) was calculated as weight (in kg) divided by the square height (in meters).

3.2 Biochemical investigations

Venous blood samples were collected in the morning of study visits after a minimum of 10h fast. Serum testosterone was measured by tandem mass spectrometry and sex hormone binding globulin (SHBG) by an immunometric assay with fluorescence detection on the DPC Immulite 2000 analyzer. Free androgen index (FAI) was calculated as the total testosterone x 100/SHBG. Serum insulin was assayed using a competitive chemiluminescent immunoassay performed on the manufacturer's DPC Immulite 2000 analyzer (Euro/DPC, Llanberis, UK). Fasting plasma glucose (FPG) was measured using a Synchron LX 20 analyzer (Beckman-Coulter). Insulin resistance was measured using the Homeostasis Model Assessment (HOMA) as HOMAIR= (FPG (mmol/L) X fasting insulin (iu/ml))/22.55) [11].

3.1 Quality of life

QoL was measured using the short version of the World Health Organisation QoL questionnaire (WHOQOL-BREF), which includes 26 questions to assess four major domains (subscales): physical, psychological, social and environment [12]. Scores are given out of a hundred and higher scores are better; a score of more than 50% indicates an acceptable to good QoL. The WHOQOL-BREF has been shown to display high internal consistency (0.92); good test-retest reliability (0.66 – 0.72); discriminant validity (discriminating sick from healthy

people), and content validity (correlation with the Short Form 36 Health Survey (SF-36)) [12]. WHOQOL-BREF provides a very good holistic assessment of QoL in the general population and its validation study included a group of women with PCOS [12].

3.2 Depression

Depression was measured using the Centre for Epidemiologic Studies Depression Scale (CES-D), which includes twenty items reflecting six major dimensions of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance experienced in the past week [13]. An average score of ≥16 on this scale suggests a high risk for depression or being in need of treatment. CES-D has been validated and it has an internal consistency ranging from 0.85 to 0.90 [13]. The test-retest reliability was in the moderate range r=0.54 for tests repeated over a three to twelve month time interval [13].

3.3 Statistical analysis

No priori power calculation was undertaken as data presented represent secondary outcomes to another study [14, 15, 16]. Post-hoc power calculations are not recommended [17]. Data were checked for normality using Kolmogorov-Smirnov test. Differences between groups at baseline were analysed using the independent t-test for continuous data (or Mann-Whitney U test for non-normally distributed data). Frequency distributions' were analysed using Chi-square test. Between groups' comparisons after intervention were as follows: for each group (PCOS and controls) a percentage change from baseline to 6 months was calculated. The

between group differences were compared using the independent t-test (or Mann-Whitney U test for non-normally distributed data).

Within groups, and combined groups analyses (baseline vs. six months) were performed using the dependent t-test for continuous data (or Wilcoxon signed-rank test for non-normally distributed data). Data were analysed using intention to treat analysis with missing values for sequential data imputed by carrying the last observation forward [18]. Statistical analysis was performed using the PASW statistics 19 package (SPSS Inc., Chicago, USA). A two tailed P value of <0.05 was considered statistically significant.

4. Results

4.1 Baseline characteristic

Thirty six women were recruited (19 PCOS, 17 controls), age 33.9 ±6.7 vs. 33.5 ±7.1yr, and weight 102.1 ±17.1 vs. 100.4 ±15.1kg, respectively (all P >0.05). The PCOS group, as expected, had higher testosterone 1.3 ±0.4 vs. 0.90 ±0.3nmol/L (P=0.01), free androgen index 4.4 ±2.0 vs. 2.6 ±1.2 (P=0.02), insulin 22.0 ±9.4 vs. 16.1 ±5.6iu/L (P=0.03), and HOMA-IR 5.1 ±2.6 vs. 3.5 ±1.3 (P=0.03), respectively.

There was no significant difference between the PCOS and control groups on the CES-D with six (32%) vs. five (29%), respectively (P=0.8) for women having scores ≥ 16 suggestive of depression. Similarly, there was no difference on the WHOQOL-BREF questionnaire between the two groups (Table 1).

4.2 Intervention with liraglutide

Twenty five women, 69%, completed the study (13 PCOS, and 12 controls). The 11 participants who dropped out during the study were significantly younger than those who completed the study 30.2 ±5.2 vs. 35.2 ±6.9 years (P= 0.04), respectively; but completers and non-completers did not significantly differ in their weight, BMI, QoL or depression scores at baseline, data not presented. Reasons for drop out were: nausea and vomiting with liraglutide (four), loss of follow up (four), frequently missing study drug (one), change in personal circumstances (one), and pregnancy (one). Following six months treatment with liraglutide weight was reduced by 3.0 ±4.2kg (2.8%), P=0.01, in the PCOS group and 3.8 ±3.4kg (3.7%), P=0.001, in controls.

4.3 QoL and depression

There was no significant change at 6 months in the number of women who scored ≥16 on the CES-D questionnaire, suggestive of depression, in the PCOS group (baseline vs. 6-month): 6 (32%) vs. 5 (26%), P=072; and controls: 5 (29%) vs. 3 (18%), P= 0.42, respectively.

The psychological health on the WHOQOL-BREF questionnaire improved in the PCOS group at six months, percentage change 11.2%, P=0.02 (Table 1), however the between groups comparison was not significant: 95% confidence interval= -36.7 – 23.3%, P= 0.40 (Table 1). Scores on other components of the QoL questionnaire did not significantly differ at 6 months compared to baseline in either group (Table 1).

4.4 Combined groups

As both groups responded equally to treatment, and there was no significant difference in QoL or depression scores between the PCOS and control groups at baseline, the effects of treatment were assessed for both groups combined. This showed significant improvement in physical, psychological, and social health on the WHOQOL-BREF questionnaire after 6-month treatment with liraglutide (Table 2). Scores on the CES-D questionnaire did not significantly differ at 6 months from baseline (Table 2).

5. Discussion

There was an improvement in QoL associated with weight loss for both the PCOS and control groups and there was no difference between the groups either at baseline or after 6 months when matched for age and weight. This suggests that obesity rather than the metabolic parameters in PCOS is the main factor driving general wellbeing in young women with PCOS and obesity. Our results are in accord with previous data by Alvarez-Blasco et al. [7] who reported similar QoL for PCOS and controls when obesity was accounted for. Conversely, others have reported that women with PCOS showed significantly lower life satisfaction compared to controls; however, in this study weight was not matched and many of study participants wanted fertility that is a potent cause of reduced QoL [8]. Using the PCOS health-related quality of life questionnaire (PCOSQ) [19], it was reported that menstrual and hirsutism problems were the most serious concerns followed by emotional problems in women with PCOS whereas weight and infertility were the least important; however, this was performed in normal weight women with PCOS [20].

Few studies have examined the impact of weight loss on QoL and depression in women with PCOS. In accord with our study, women with PCOS randomised to one of three 20-week

lifestyle programs all achieved weight loss and an improvement in QoL [21]. A similar finding was reported in overweight and obese women with PCOS who were randomised to low carbohydrate or a conventional diet for 12 months where a 4% weight loss was achieved and a significant improvement in QoL resulted [22]. A low-protein high-carbohydrate diet compared to a high-protein low-carbohydrate diet in overweight women with PCOS showed equal weight loss but only the high-protein diet group improved their depression scores [23].

The improvement in QoL observed in our study may in theory be related to liraglutide treatment rather than the weight loss achieved, especially as our study did not include a placebo treated group. However, the results reported are similar to the improvement seen in diet studies and there are no data to suggest that liraglutide treatment has any neuropsychiatric effects. It is worth noting that none of the participants in our study wanted to conceive and that their average scores on the WHOQOL-BREF were more than 50% indicating at least moderate – good QoL.

6. Study limitations

While many studies examining QoL in women with PCOS have used the PCOSQ [19], we have used the WHOQOL-BREF that provides a very good, more holistic assessment of QoL, and its validation study included women with PCOS [12]. In addition, the PCOSQ may not have reflected QoL well in healthy controls. While the PCOSQ does account for fertility [19], this was not a factor in our study.

A study limitation is the small study sample. Whilst this was a small study there was an overall improvement in the Qol parameters following weight loss arguing against any type 2 error, though larger numbers may have detected small differences between the groups following

weight loss. Combining the two groups was appropriate as there was no difference between the two groups at baseline or at six months in the CES-D and the WHOQOL-BREF scores.

Another limitation is the absence of a control group aiming to achieve similar weight loss through diet or a physical activity; subsequently it is difficult to be sure if the changes in QoL observed in our study were related to Liraglutide, weight loss, or both.

7. Study strengths

We have used a validated questionnaire to assess QoL in women with PCOS and controls. Study participants were well matched for age and obesity, two factors that are known to be associated with reduced QoL [6, 24].

8. Conclusions

PCOS was not independently associated with reduced QoL, and/or depression, in the presence of obesity. Six months treatment with liraglutide resulted in significant reduction in weight and improvement in QoL in young women with PCOS and obesity.

9. Authors' roles

H Kahal contributed to study design, performed experiments, collected, analyzed, and interpreted data and wrote the manuscript; AS Rigby contributed to statistical analysis and writing of the manuscript; AM Coady performed ultrasound scans and contributed to writing of the manuscript; ES Kilpatrick and SL Atkin contributed to design of research, data interpretation and the writing of the manuscript.

10. Acknowledgements

11. Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the paper reported.

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Variable	PCOS (n=19) Baseline mean (SD)	Controls (n=17) Baseline mean (SD)	PCOS Percentage change at 6-month	Controls Percentage change at 6-month	Between groups difference	
					95%CI	P-value
Weight (kg)	102.1 (17.1)	100.4 (15.1)	-2.8%*	-3.7%*	-1.5 – 3.2	0.49
BMI (kg/m^2)	37.9 (5.0)	36.5 (4.6)	-2.6%*	-3.7%*	-1.3 – 3.5	0.27
WHOQOL-BREF:						
Physical health	80.4 (12.8)	77.3 (14.6)	5.4%	7.4%	-13.5 – 9.5	0.49
Psychological health	59.1 (9.7)	55.7 (21.9)	11.3*	18%	-36.7 – 23.3	0.40
Social health	73.7 (12.5)	68 (20.5)	7.4%	15.2%	-24.9 – 9.3	0.85
Environment	71.5 (12.3)	73.3 (16.9)	4.3%	8.0%	-20.4 – 13	0.30

Table 1. Anthropometric measurements and quality of life scores at baseline and after treatment with liraglutide. BMI, body mass index; WHOQOL-BREF, World Health Organisation quality of life questionnaire; PCOS, polycystic ovary syndrome; 95%CI, 95% confidence interval. Data are mean (standard deviation (SD)). 13 women with PCOS and 12 controls completed the study; intention-to-treat analysis was performed, including all study participants, with the last observation carried forward. *Significant within group difference, 6-month vs. baseline, P<0.05.

	Combined groups (n=36)*		
	Baseline	**6-month**	**P**
CES-D ≥16	11 (31%)	8 (22%)	0.42
WHOQOL-BREF			
Physical health	78.9 ±13.6	82.6 ±11.2	0.04
Psychological health	57.5 ±16.4	62.4 ±16.5	0.01
Social health	71 ±16.8	76.6 ±15.3	0.01
Environment	72.3 ±14.5	74.8 ±12.4	0.18

Table 2. The effect of treatment with liraglutide on the CES-D and WHOQOL-BREF questionnaires scores for the combined groups (PCOS and controls). A score of ≥16 on the Centre for Epidemiologic Studies Depression Scale (CES-D) questionnaire is suggestive of depression. WHOQOL-BREF, World Health Organisation Quality of Life Questionnaire. Data presented as mean ±standard deviation (SD) or number (percentage). *25 participants completed the study; intention-to-treat analysis was performed, including all 36 study participants, with the last observation carried forward.