**Low dose of liraglutide combined with metformin leads to a significant weight loss in
Chinese Han women with Polycystic ovary syndrome: a retrospective study**

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Abstract

Background

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder with complex pathophysiological mechanism. It is reported that even a modest weight loss of 5-10% substantially may improve the reproductive and metabolic profile. This study aims to assess the efficacy of the low dose of liraglutide (0.6mg QD) combined with metformin (0.85g BID) in weight loss in Chinese Han women with Polycystic ovary syndrome.

Methods

We included clinical data of 102 obese/overweight (≥ 18 years, body mass index ≥ 28 kg/m² or ≥ 24 kg/m²) women who were diagnosed with PCOS from October 2016 to March 2018 in Wuhan Union Hospital initially. They were treated with Diane-35, low dose of liraglutide (0.6mg QD) and metformin (0.85g BID) for 12 weeks. The demographic and clinical data were retrieved retrospectively, and weight loss was the main outcome measure. Student's paired t-test and Wilcoxon rank sum test were used to compare the differences before and after therapy, $p < 0.05$ was considered statistically significant.

Results

Participants (n=102) had lost a mean of 7.20 (3.42) kg of body weight (95%CI: 6.55-7.86, p<0.001), and the mean reduction of BMI was 2.87 (1.36) kg/m² (95%CI: 0.02-0.27, p<0.001). A total of 88.24% of participants lost more than 5% of their body weight.

Conclusion

The combination of low dose of liraglutide and metformin was associated with significant reduction of body weight in Chinese Han women with PCOS. However, a larger randomized double-blind multicenter controlled clinical trial is needed to confirm it.

Trial registration

The study was registered on <http://www.chictr.org.cn> as ChiCTR1900024384.

Keywords

polycystic ovary syndrome, obesity, overweight, weight loss, metformin, liraglutide

Plain English summary

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, which is characterized by chronic anovulation and hyperandrogenism, among women of reproductive age. Obesity is one of the pathophysiological principles of PCOS, and excess free fatty acids are related with insulin resistance and hyperandrogenemia. And even 5-10% weight loss may improve reproductive and metabolic disorders. Liraglutide, a long acting glucagon-like peptide-1 analogue, is approved by the FDA for weight management, and some researches show there is a synergy between metformin and liraglutide. But for Chinese Han women with PCOS, the dose and effect of combination of metformin and liraglutide in weight loss are worthy of further investigation. In this study, the data of 102 patients in Wuhan Union Hospital who were diagnosed with PCOS were retrospectively analyzed. And even a low dose of liraglutide (0.6mg QD) combined with metformin (0.85g BID)

resulted in a significant weight loss.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder with psychological, reproductive and metabolic features¹. Depending on definitions and populations studied, the prevalence of PCOS is about 8%-13% in reproductive-aged women^{2,3}. According to Rotterdam criteria introduced in 2003, PCOS can be diagnosed with two of three features: clinical or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovaries on ultrasound. Women with PCOS usually present different clinical manifestations including metabolic disorders (obesity, insulin resistance, type 2 diabetes, metabolic syndrome and higher risk for angiocardopathy)^{4,5}, reproductive dysfunctions (hirsutism, irregular menstrual cycles, infertility and pregnancy-related risks)^{6,7} and psychological features (anxiety, depression, and eating disorders)^{8,9}.

The majority of women with PCOS are overweight or obese¹⁰. It is reported that obesity may affect the woman fertility by many processes, such as mitochondrial dynamics derangements, disrupted meiosis, impairment of ovarian follicles development¹¹. For these patients, lipolysis produces more free fatty acid, and cause a toxic effect in reproductive system, which leads to a continuous cell damage and a chronic inflammatory state¹¹.

Moreover, obesity may reduce the utilization of glucose by peripheral tissues and aggravating insulin resistance¹². The excess insulin promotes androgen production in ovarian theca cells as a response to luteinizing hormone stimulation, and result in follicular arrest and anovulation. And hyperinsulinemia presents as a response to insulin resistance and may suppress hepatic production of sex hormone-binding globulin, which is a binding protein for testosterone in the serum. Therefore,

the hyperandrogenemia is aggravated, and leads to follicular dysplasia and persistent anovulation¹³.

Otherwise, the excess fat brings about multiple cardiovascular metabolic risks. It is closely related to nonalcoholic fatty liver disease, atherosclerosis and other diseases. Consequently, losing weight and ameliorating insulin resistance are essential in the treatment of PCOS.

It is reported that even a modest weight loss of 5-10% may improve the reproductive and metabolic profile¹⁴. Nowadays, the common ways to lose weight include lifestyle interventions, medication and bariatric surgery. Lifestyle interventions is considered as the first line of treatments for weight management. However, the choices of diet and exercise still need large-scale evidence, and the treatment goals of lifestyle interventions are usually hard to achieve. It is not sustainable in daily life, many women usually regain their lost weight because of their poor compliance¹⁵. Bariatric surgery is an effective way to help patients lose weight and it is usually reserved for patients with a body mass index (BMI) $>40 \text{ kg/m}^2$ or with BMI $>35 \text{ kg/m}^2$ and one or more significant comorbid conditions, when nonsurgical methods of weight loss have failed. However, it may lead to nutritional deficiencies and other postoperative complications like difficulty swallowing, osteoporosis, kidney stones and dumping syndrome¹⁶. As for pharmacological interventions, many drugs are restricted in pregnant women, and may cause some serious adverse reactions. Metformin is an established treatment for PCOS with good safety and toleration. As an insulin sensitizer, it can not only improve insulin resistance significantly, but also has effects on menstrual disorders, anovulation, metabolic and cardiovascular abnormalities^{17,18}. However, some meta-analyses show its effect on weight loss with lifestyle changes always unsatisfactory¹⁹.

Liraglutide, known as a long acting glucagon-like peptide-1 (GLP-1) analogue, can improve glucose homeostasis by increasing the endogenous secretion of insulin that is induced by glucose ingestion

and inhibiting glucagon secretion²⁰. In addition, it is showed that liraglutide can reduce body weight via delaying gastric emptying and inhibiting appetite²¹. It is proved that liraglutide has significant and sustained effect on weight loss in overweight people with or without diabetes²². As an anti-diabetic therapy is approved at doses up to 1.8mg²³, while higher doses are required for weight loss in many countries. Liraglutide 3mg led to decreases in body weight of more than 5 to as much as 15%²⁴. However, higher doses usually linked potential higher frequency of gastrointestinal side effects like nausea and dyspepsia²⁵.

It is reported metformin combined with liraglutide could enhance weight-lowering capacity. And we wonder whether the combination of metformin (0.85g BID) and a lower dose liraglutide (0.6mg QD) could get weight loss satisfactorily with fewer side effects in Chinese Han women with polycystic ovary syndrome. At the same time, Diane-35 was used to regulate menstrual cycles for all the participants.

Materials and methods

The study population included 102 overweight or obese women who with PCOS between October 2016 and March 2018 in Wuhan Union Hospital (Figure.1).

Figure 1. Overview of women included in the study

According to the guidelines for prevention and control of overweight and obesity in Chinese adults, we define overweight as $24 \leq \text{BMI} < 28 \text{ kg/m}^2$ and obesity as $\text{BMI} \geq 28 \text{ kg/m}^2$. The diagnosis of PCOS was made based on the 2003 Rotterdam criteria with the presence of at least two of the following features: ovulatory dysfunction, clinical and/or biochemical hyperandrogenism and polycystic ovaries on ultrasound (ultrasound shows that the number of follicles with diameters of 2- 9 mm on one side or both sides is equal or greater than 12). We excluded women who were diagnosed with thyroid disease, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome and

androgenic tumor. Furthermore, we excluded pregnant or lactating woman and the patients who had angiocardopathy, severe liver disease and kidney dysfunction. And people who used medicines that affect glucose and lipid metabolism recently were not included.

Participants started with liraglutide 0.6mg once daily and metformin 0.85g twice a day. And Diane-35 was prescribed that taking one pill per day for 21 days, and then stopping for 7days in every menstrual cycle. All patients were treated for 12 weeks.

At baseline and after treatment for 12 weeks, all patients took measurements after an overnight fast for demographic and clinical profile between the second and fifth day of a spontaneous menstrual cycle. The height, weight and waist-hip ratio were measured with light clothes and no shoes. BMI is equal to weight (kg) by the square of the height (m). And visceral fat area and percentage of body fat were measured with bioelectrical impedance analysis. Besides, their blood samples were collected for determination of sex hormone, glucose and lipid metabolism, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), total testosterone (TT), free testosterone (FT), dehydroepiandrosterone (DHEA), sex hormone binding globulin (SHBG), androstenedione, HbA1c, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 and apolipoprotein B. The free androgen index (FAI) is calculated as $TT (nmol/L) \times 100 / SHBG (nmol/L)$, we took 0.7-6.4 as the normal range of FAI²⁶. Then they did a standard 75g oral glucose tolerance test (OGTT) and got glucose and insulin concentration at 0/30/60/120/180 minutes. Insulin resistance was estimated by HOMA-IR score, which was calculated as $(fasting\ glucose [mmol/L] \times fasting\ insulin [mIU/L] / 22.5)$. And $HOMA-IR \geq 2.69$ was the cut off for abnormal values²⁷. As for safety parameters, we concerned about markers of inflammation, hepatic and renal functions like C-

Reactive Protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), serum creatinine (SCR).

Normal data distribution was checked by the Shapiro-Wilk test. We used Student's paired t-test to compare the differences before and after therapy for normally distributed data, and Wilcoxon rank sum test for non-normal distributed data. The parameters are presented as mean (S.D) or median (quartiles), $P < 0.05$ was considered statistically significant. SPSS 23.0 software package was used to do the data analysis.

Result

Weight loss

Mean age of the 102 patients was 25.83(4.20) years. They had a mean body weight at baseline of 70.75(9.09) kg, and a mean BMI at baseline of 28.03(3.18) kg/m² (Table 1). And 57 of them (55.88%) were overweight, while 45(44.12%) of them were obese. After therapy for 12 weeks, we observed significant effects on weight change (Figure 2). The mean weight loss was 7.20(3.42) kg (95%CI: 6.55-7.86, $p < 0.001$), and the mean reduction of BMI was 2.87(1.36) kg/m² (95%CI: 0.02-0.27, $p < 0.001$). Furthermore, there were 19(18.63%) of them got BMI less than 24, and 41(40.20%) of them were overweight, while 42(41.18%) of them were still obese. And no one got a higher BMI. More specifically, 90(88.24%) women lost more than 5% of their baseline of weight, 51(50.00%) women lost more than 10%, and even 3(2.94%) women lost more than 20%. The average percentage of weight loss was 10.24%. In general, the majority of people lost 5%-15% of their baseline body weight. Only 1 person gained 1.1kg in weight, but she had grown by 2cm, that her BMI decreased 0.2kg/m².

Beyond that, we also found there were significant reductions in waist-hip ratio, visceral fat area and

percentage of body fat. The mean reduction of waist-hip ratio was 0.02(0.03) (95%CI: 2.61-3.14, p<0.001), while the mean reduction of visceral fat area was 24.64(14.88) cm² (95%CI: 21.70-27.58, p<0.001), and the mean decrease of body fat decreased was 3.29(3.25) % (95%CI: 2.64-3.93, p<0.001).

Table.1 Characteristics at baseline and after therapy of low dose of liraglutide combined with metformin for 12 weeks

Parameter	Baseline	After therapy	Difference	P
Weight(kg)	70.88(9.19)	63.63(9.00)	-7.25(3.48)	<0.001
BMI(kg/m ²)	28.13(3.23)	25.24(3.21)	-2.89(1.39)	<0.001
waist-hip ratio	0.90(0.04)	0.88(0.04)	-0.02(0.03)	<0.001
visceral fat area(cm ²) [1]	135.37(31.12)	110.74(33.01)	-24.64(14.88)	<0.001
percentage of body fat (%) [1]	39.16(4.76)	35.88(4.91)	-3.29(3.25)	<0.001

Results presented as mean (S.D). P values < 0.05 are in bold. BMI: body mass index. Number of missing values in square brackets [].

Figure 2. Body Weight change at baseline and after therapy

Panel A shows the mean body weight at baseline and after therapy of those patients. Panel B shows the frequency of patients whose weight changed in [-25%, -20%), [-20%, -15%), [-15%, -10%), [-10%, -5%), [-5%, 0), [0, 5%) compared with their baseline. As we can see, almost people got at least 5% weight loss, and a majority of patients had a weight change in -5% to -15%. Panel C shows the cumulative percentage of patients with the change of body weight after 3 months of treatment.

Figure 3. The other characteristics change at baseline and after therapy

Panel A shows body mass index (BMI). Panel B shows waist-hip ratio. Panel C shows visceral fat area. Panel D shows percentage of body fat. All the differences of parameters between baseline and after therapy were analysed by Student's paired t-test. ***for p<0.001.

Endocrine changes

As for endocrine, the total testosterone, free testosterone, androstenedione and FAI decreased significantly after therapy (p<0.05) (Table 2). LH decreased from 10.56(5.99) IU/L to 6.99(3.27)

IU/L ($p<0.001$), and the LH/FSH decreased from 1.74(0.90) to 1.10(0.53). There were 40 women with LH/FSH ≥ 2 at baseline, however after treatment there was only one patient got LH/FSH ≥ 2 . Furthermore, PRL and SHBG increased obviously, while FSH and DHEA had no significant change.

Table.2 Endocrine parameters at baseline and after therapy for 12 weeks

Parameter	Baseline	After therapy	Difference	P
FSH (IU/L) [2]	5.96(5.01,6.90)	6.43(5.45,7.20)	0.47(-0.63,1.63)	0.070
LH (IU/L) [2]	10.67(6.04)	7.00(3.31)	-3.67(6.54)	<0.001
LH/FSH [2]	1.76(0.91)	1.11(0.53)	-0.65(1.04)	<0.001
PRL (ng/ml) [2]	18.03(9.72)	23.23(12.81)	5.21(11.79)	<0.001
SHBG (nmol/L)	57.49(53.31)	159.73(45.07)	102.24(58.1)	<0.001
TT (nmol/L) [4]	1.53(1.07,1.99)	0.95(0.66,1.25)	-0.51(-0.82,0.19)	<0.001
FT (pmol/L)	8.58(3.57)	5.22(3.19)	-3.37(3.98)	<0.001
DHEA (nmol/L)	26.70(17.22,34.74)	21.80(16.12,30.17)	-2.07(12.59,6.30)	0.095
Andro(nmol/L)	8.68(3.54)	6.59(2.60)	-2.09(3.64)	<0.001
FAI [4]	5.29(4.87)	0.87(1.97)	-4.42(4.44)	<0.001

Results presented as mean (S.D) or median (quartiles). P values < 0.05 are in bold. FSH: follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin; T: testosterone; FT: free testosterone; DHEA: dehydroepiandrosterone; Andro: androstenedione; SHBG: sex hormone-binding globulin; FAI: free androgen index. Number of missing values in square brackets [].

Metabolic changes

As for the serum lipid metabolism, the HDL-C and ApoA1 had improved significantly (Table 3) [1.27(0.44) mmol/L to 1.40(0.36) mmol/L, $p<0.001$; 1.15(0.24) mmol/L to 1.45(0.26) mmol/L, $p<0.001$, respectively]. And total cholesterol, triglycerides, LDL-C and ApoB had no significant change. We considered the LDL/HDL ratio and TC/HDL ratio as the parameters for cardiovascular disease risk, and they both had significant decreases [2.33(0.90) to 2.05(0.65), $p<0.001$; 3.96(1.16) to 1.27(0.44), $p<0.001$, respectively].

About glucose metabolism, when we collated the data of OGTT, we found there was one patient's result of OGTT missed. We speculated the side effect of OGTT like nausea and vomiting might be the reason why the patient did not do the test. For the rest 101 patients, the glucose in 120 min during OGTT, fasting insulin, and insulin during OGTT are statistically significant (Figure 4). At baseline,

176 83 women were insulin resistant because their HOMA-IR score ≥ 2.69 . After therapy, 17 of them
 177 (20.48%) had improved their insulin resistant, for HOMA-IR score < 2.69 . And the mean of HbA1c
 178 for all patients decreased from 5.30(0.55) % to 4.93(0.33) %.

Table.3 Metabolic parameters at baseline and after therapy for 12 weeks

Parameter	Baseline	After therapy	Difference	P
TC (mmol/L) [1]	4.49(3.98,5.11)	4.64(4.16,5.17)	0.12(-0.26,0.43)	0.117
TG (mmol/L) [1]	1.55(1.09,2.25)	1.54(1.17,2.15)	0(-0.61,0.36)	0.348
HDL-C(mmol/L) [1]	1.27(0.44)	1.40(0.36)	0.13(0.34)	<0.001
LDL-C(mmol/L) [1]	2.72(0.66)	2.74(0.71)	0.01(0.58)	0.822
LDL-C/HDL-C [1]	2.33(0.90)	2.05(0.65)	-0.28(0.65)	<0.001
TC/HDL-C [1]	3.96(1.16)	1.27(0.44)	-2.69(1.49)	<0.001
ApoA1(mmol/L) [1]	1.15(0.24)	1.45(0.26)	0.30(0.24)	<0.001
ApoB(mmol/L) [1]	0.82(0.21)	0.84(0.26)	0.01(0.25)	0.581
Glu 0 min OGTT (mmol/L) [1]	5.52(0.91)	5.39(0.74)	-0.13(1.07)	0.194
Glu 30 min OGTT (mmol/L) [1]	9.40(8.50,10.70)	9.20(8.40,10.30)	-0.20(-1.30,0.80)	0.145
Glu 60 min OGTT (mmol/L) [1]	10.10(7.80,12.10)	9.50(7.70,11.30)	-0.60(-2.20,1.20)	0.134
Glu 120 min OGTT (mmol/L) [1]	8.48(2.73)	7.53(2.23)	-0.95(2.79)	0.001
Glu 180 min OGTT (mmol/L) [1]	5.32(1.94)	5.05(1.52)	-0.27(2.17)	0.209
AUC _{Glucose} (min* mmol/L) [1]	31.83(6.25)	33.71(7.78)	-1.88(7.31)	0.008
Insulin 0 min OGTT (μ IU/L) [1]	26.82(25.22)	16.91(11.89)	-9.91(23.07)	<0.001
Insulin 30 min OGTT (μ IU/L) [1]	146.81(98.69,201.76)	120.45(82.94,177.47)	-18.69(-58.02,21.42)	0.006
Insulin 60 min OGTT (μ IU/L) [1]	199.48(99.04)	178.65(96.68)	-20.83(80.68)	0.019
Insulin 120 min OGTT (μ IU/L) [1]	186.64(105.86)	134.16(86.13)	-52.47(96.48)	<0.001
Insulin 180 min OGTT (μ IU/L) [1]	77.46(66.14)	46.02(61.26)	-31.44(67.85)	<0.001
AUC _{Insulin} (min* μ IU/L) [1]	596.43(286.95)	484.64(249.32)	-111.79(211.68)	<0.001
HbA1c (%)	5.20(5.00,5.50)	4.90(4.70,5.10)	-0.30(-0.60,-0.03)	<0.001
HOMA-IR [1]	6.94(8.19)	4.16(3.46)	-2.78(7.83)	<0.001

Results presented as mean (S.D) or median(quantiles). P values < 0.05 are in bold. TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Glu: glucose; OGTT: oral glucose tolerance test; HOMA-IR: homeostasis model assessment of insulin resistance; Number of missing values in square brackets [].

Figure 4. The mean glucose, insulin concentration during OGTT at baseline and after therapy.

Panel A shows glucose concentrations during oral glucose tolerance test (OGTT). Panel B shows insulin concentrations during OGTT. Panel C shows the area under the curve (AUC) of glucose during OGTT. Panel D shows the AUC of insulin during OGTT. The data are presented as means (S.D), and calculated with Student's paired T-test. *for $p < 0.05$, ** for $p < 0.01$, *** for $p < 0.001$.

Side effects

During the therapy, no one got hypoglycemia reaction. A few patients had mild transitory headache or gastrointestinal reactions, such as diarrhea and nausea. And these symptoms usually happened at the first 4 weeks and alleviated voluntarily. Nobody dropped out because of these mild symptoms. The parameters of hepatic function had no significant change as a whole, only one patient had aspartate transaminase increased fivefold on the 12th week. C-reactive protein of few patients had increased after 12 weeks of treatment, but we cannot rule out other reasons.

Discussion

The pathophysiological mechanism of PCOS is complex and has not yet been elucidated. Obesity, insulin resistance and hyperinsulinemia are considered to be closely related to PCOS. Most women with PCOS are overweight or obese¹⁰, and obesity plays a key role in the pathophysiological mechanisms of insulin resistance and hyperandrogenism. Too much adipose tissue may cause insulin resistance even hyperinsulinemia and hyperandrogenism, and these will result in acne, hirsutism, menstrual irregularity and infertility. In the other hand, overweight and obesity increase the risks of type II diabetes, coronary heart disease and other metabolic diseases in the long term. Metformin is commonly used in the treatment of PCOS, for reducing insulin resistance and ovulation induction, but its effect on weight loss is often unsatisfactory.

Liraglutide, as an analog of the incretin hormone glucagon-like peptide 1 (GLP-1), has 97% homology with human GLP-1. It is widely used in type 2 diabetes to help control glucose level^{21,22}. Moreover, liraglutide can reduce appetite and caloric intake so it was approved for weight management in many countries. As we known, the maximum dose of liraglutide for weight loss is 3.0mg QD. In 2015, Davies MJ et al²⁵ found 3.0mg of once-daily liraglutide was more effective in

weight loss than 1.8mg once-daily liraglutide, and improved patients' quality of life significantly.

During 56 weeks, among overweight and obese participants with type 2 diabetes, the weight loss was 6.0% (6.4 kg) with liraglutide (3.0mg dose), while 4.7% (5.0 kg) with liraglutide (1.8mg dose).

But patients used liraglutide (3.0mg) had gastrointestinal disorders more frequently.

There were other studies evaluated the effect of the combination of metformin and liraglutide.

Jensterle Sever et al²⁸ reported that in a 12 weeks study of 36 obese women with PCOS, the mean weight loss was 6.5kg with liraglutide 1.2mg plus metformin, 3.8kg with liraglutide 1.2mg alone

and 1.2kg with metformin monotherapy. And no one in the metformin group lost 5% of their initial

weight. Rasmussen CB²⁹ reported that 84 overweight or obese women with PCOS treated with

liraglutide and metformin at least 4 weeks. The dose of liraglutide was started at 0.6mg and

increased to 1.2mg or 1.8mg QD finally if there were no effect on weight and no side effect. And

the dose of metformin was given due to insulin resistance. They found a mean weight loss of 9.0kg

and a mean decrease in BMI of 3.2kg/m². The proportion of women who lost more than 5% of their

baseline was 81.7%.

In the present study, a short-term combination therapy with liraglutide 0.6mg QD and metformin

0.85g BID in overweight or obese women with PCOS result in a mean weight loss of 7.25(3.48) kg

and a reduction of BMI from 28.13(3.24) to 25.24(3.21) kg/m². And 88.24% participants lost at least

5% of their initial body weight. And no one dropped out because of gastrointestinal symptoms or

other side effects. Our results are in accord with these studies in some ways. It seems that a lower

dose of liraglutide (0.6mg) combined with metformin has better effect and less side reactions in

weight loss in Chinese Han women. And we suppose there might be two explanations for this result.

On the one hand, many studies proved metformin might not only enhance the secretion of GLP-1

by regulating multiple components of the incretin axis^{30,31}, but also inhibit the activity of DPP-4 thus increase the active GLP-1 concentrations^{32,33}. And on the other hand, we suspect that the Chinese Han women may be more sensitive to liraglutide. Therefore, metformin can enhance GLP-1 effect of liraglutide and make a lower dose of liraglutide more efficiently in weight loss. Otherwise, Rocha et al³⁴ found that patients with PCOS usually have abnormal lipid metabolism, and their incidence is twice than general population. The incidence of the reduction of HDL(57.60%) and the increase of TG(28.30%) are the most common. Wing RR et al³⁵ showed that weight loss can reduce the risk of cardiovascular disease by improving lipid metabolism and blood pressure. The results of our study suggested there were significant improvements in HDL, ApoA1, LDL/HDL and TC/HDL ratio, while the changes of total cholesterol, TG, LDL, and ApoB were not statistically significant. Combined the obvious reduction in mean of weight loss, the combination of liraglutide and metformin might reduce the risks of cardiovascular disease in overweight or obese women with PCOS. However, the present study has some limitations, including possible selection bias and recall bias. More large randomized double-blind multicenter controlled clinical trials in overweight and obese Chinese Han women with PCOS are needed to assess the optimal dose of liraglutide in weight loss. And we need a longer follow-up period to observe how long the effect of weight loss would last and the reproductive outcome after this treatment.

Conclusions

Above all, in this study, the combination of liraglutide 0.6mg QD and metformin 0.85g BID was associated with reduction of body weight in Chinese Han women with PCOS.

245 **references:**

- 246 1. Azziz R, Carmina E, Dewailly D, et al. Positions statement: criteria for defining polycystic ovary
247 syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin*
248 *Endocrinol Metab* 2006; **91**(11): 4237-45.
- 249 2. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic
250 ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod*
251 2010; **25**(2): 544-51.
- 252 3. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features
253 of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod* 2016; **31**(12): 2841-
254 55.
- 255 4. Apridonidze T, Essah PA, Luorno MJ, Nestler JE. Prevalence and characteristics of the metabolic
256 syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005; **90**(4): 1929-35.
- 257 5. Legro RS, Kusanman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2
258 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective,
259 controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999; **84**(1): 165-9.
- 260 6. Moran L, Gibson-Helm M, Teede H, Deeks A. Polycystic ovary syndrome: a biopsychosocial
261 understanding in young women to improve knowledge and treatment options. *J Psychosom Obstet*
262 *Gynaecol* 2010; **31**(1): 24-31.
- 263 7. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of
264 pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006; **12**(6): 673-
265 83.
- 266 8. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological,

267 reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med* 2010;
268 **8**: 41.

269 9. Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of
270 poor psychological function including anxiety and depression? *Hum Reprod* 2011; **26**(6): 1399-407.

271 10. Hahn S, Tan S, Elsenbruch S, et al. Clinical and biochemical characterization of women with
272 polycystic ovary syndrome in North Rhine-Westphalia. *Horm Metab Res* 2005; **37**(7): 438-44.

273 11. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact.
274 *Fertility and sterility* 2017; **107**(4): 840-7.

275 12. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states.
276 *Cold Spring Harb Perspect Biol* 2014; **6**(1).

277 13. Pasquali R. Obesity and androgens: facts and perspectives. *Fertility and sterility* 2006; **85**(5): 1319-
278 40.

279 14. Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese
280 anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian
281 physiology and fertility rate induced by diet. *Human reproduction (Oxford, England)* 2003; **18**(9): 1928-
282 32.

283 15. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary
284 syndrome. *Cochrane Database Syst Rev* 2011; (7): CD007506.

285 16. Centre NCG. Obesity: Identification, Assessment and Management of Overweight and Obesity in
286 Children, Young People and Adults: Partial Update of CG43. 2014.

287 17. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and
288 meta-analysis. *BMJ* 2003; **327**(7421): 951-3.

289 18. Morin-Papunen L, Rantala AS, Unkila-Kallio L, et al. Metformin improves pregnancy and live-birth
290 rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled
291 randomized trial. *J Clin Endocrinol Metab* 2012; **97**(5): 1492-500.

292 19. Harborne LR, Sattar N, Norman JE, Fleming R. Metformin and weight loss in obese women with
293 polycystic ovary syndrome: comparison of doses. *J Clin Endocrinol Metab* 2005; **90**(8): 4593-8.

294 20. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with
295 liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo
296 and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018; **392**(10148): 637-49.

297 21. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog
298 liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-
299 diabetic adults. *Int J Obes (Lond)* 2014; **38**(6): 784-93.

300 22. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor
301 agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012;
302 **344**: d7771.

303 23. Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic
304 drug therapy in type 2 diabetes: an overview of the LEAD 1-5 studies. *Diabetes Obes Metab* 2009; **11**
305 **Suppl 3**: 26-34.

306 24. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor
307 agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012;
308 **344**: d7771.

309 25. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With
310 Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *JAMA* 2015; **314**(7): 687-99.

- 311 26. Zhou Z, Ni R, Hong Y, et al. Defining hyperandrogenaemia according to the free androgen index in
312 Chinese women: a cross-sectional study. *Clin Endocrinol (Oxf)* 2012; **77**(3): 446-52.
- 313 27. Xing XY, Yang WY. The diagnostic significance of homeostasis model assessment of insulin
314 resistance in metabolic syndrome among subjects with different glucose tolerance. *Chinese Journal of*
315 *Diabetes* 2004.
- 316 28. Jensterle Sever M, Kocjan T, Pfeifer M, Kravos NA, Janez A. Short-term combined treatment with
317 liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary
318 syndrome and previous poor response to metformin. *Eur J Endocrinol* 2014; **170**(3): 451-9.
- 319 29. Rasmussen CB, Lindenberg S. The effect of liraglutide on weight loss in women with polycystic
320 ovary syndrome: an observational study. *Front Endocrinol (Lausanne)* 2014; **5**: 140.
- 321 30. Kappe C, Patrone C, Holst JJ, Zhang Q, Sjöholm A. Metformin protects against lipoapoptosis and
322 enhances GLP-1 secretion from GLP-1-producing cells. *J Gastroenterol* 2013; **48**(3): 322-32.
- 323 31. Maida A, Lamont BJ, Cao X, Drucker DJ. Metformin regulates the incretin receptor axis via a
324 pathway dependent on peroxisome proliferator-activated receptor- α in mice. *Diabetologia* 2011; **54**(2):
325 339-49.
- 326 32. Cuthbertson J, Patterson S, O'Harte FP, Bell PM. Addition of metformin to exogenous glucagon-like
327 peptide-1 results in increased serum glucagon-like peptide-1 concentrations and greater glucose
328 lowering in type 2 diabetes mellitus. *Metabolism* 2011; **60**(1): 52-6.
- 329 33. Green BD, Irwin N, Duffy NA, Gault VA, O'Harte F P, Flatt PR. Inhibition of dipeptidyl peptidase-IV
330 activity by metformin enhances the antidiabetic effects of glucagon-like peptide-1. *Eur J Pharmacol*
331 2006; **547**(1-3): 192-9.
- 332 34. Rocha MP, Marcondes JA, Barcellos CR, et al. Dyslipidemia in women with polycystic ovary

333 syndrome: incidence, pattern and predictors. *Gynecol Endocrinol* 2011; **27**(10): 814-9.

334 35. Wing RR, Tate DF, Garcia KR, et al. Improvements in Cardiovascular Risk Factors in Young Adults in

335 a Randomized Trial of Approaches to Weight Gain Prevention. *Obesity (Silver Spring)* 2017; **25**(10): 1660-

336 6.

337 **Abbreviations**

338 **PCOS:** Polycystic ovary syndrome

339 **BMI:** Body Mass Index

340 **GLP-1:** glucagon-like peptide-1

341 **QD:** quaque die

342 **BID:** bis in die

343 **FSH:** follicle-stimulating hormone

344 **LH:** luteinizing hormone

345 **PRL:** prolactin

346 **TT:** total testosterone

347 **FT:** total testosterone

348 **DHEA:** dehydroepiandrosterone

349 **SHBG:** sex hormone binding globulin

350 **TC:** total cholesterol

351 **TG:** triglycerides

352 **LDL-C:** low-density lipoprotein cholesterol

353 **HDL-C:** high-density lipoprotein cholesterol

354 **FAI:** free androgen index

355 **OGTT:** oral glucose tolerance test

356 **HOMA-IR:** homeostasis model assessment of insulin resistance

357 **CRP:** C-Reactive Protein

358 **AST:** aspartate transaminase

359 **ALT:** alanine transaminase

360 **BUN:** blood urea nitrogen

361 **SCR:** serum creatinine

362 **SD:** standard deviation

363 **ApoA1:** apolipoprotein A1

364 **ApoB:** apolipoprotein B

365 **AUC:** area under the curve

366

367 **Declarations**

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383 **Authors' contributions**

384 Y Liu, C Chen contributed to the design of the study. L Zhang, H Liu, W Xiong, W Li, H He, T Fu,

385 X Li Contributed to the implementation and data entry. X Long analysed the data and wrote the first

386 draft. All authors read and approved the final manuscript.

387 **Ethics declarations**

388 **Ethics approval and consent to participate**

389 The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University

390 of Science and Technology.

391 **Consent for publication**

392 Not applicable.

393 **Availability of data and materials**

394 The data that support the findings of this study are openly available in [ResMan] at

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396 **Competing interest**

397 The authors declare that they have no competing interests.

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