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Original Article

Insulin Resistance in Polycystic Ovary Syndrome Improved by Chinese Medicine Dingkun Pill (定坤丹): A Randomized Controlled Clinical Trial

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ABSTRACT **Objective:** To assess the efficacy and safety of the Chinese medicine Dingkun Pill (定坤丹, DKP) on insulin resistance in women with polycystic ovary syndrome (PCOS). **Methods:** A total of 117 women with PCOS were randomly assigned to Group A (38 women), Group B (40 women), or Group C (39 women) in a randomization sequence with SAS software and a 1:1:1 allocation ratio using random block sizes of 6, and were given 7 g of oral DKP daily (Group A), 1 tablet of Diane-35 orally daily (Group B), or 7 g of oral DKP daily plus 1 tablet of Diane-35 orally daily (Group C). Patients took all drugs cyclically for 21 consecutive days, followed by 7 drug-free days. The treatment course for the 3 groups was continued for 3 consecutive months. Oral glucose tolerance tests (OGTT) were performed before treatment and again after 2 and 3 months of therapy, respectively, and homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were calculated. **Results:** Of 117 women with PCOS, 110 completed the entire course of therapy: 35 in Group A, 36 in Group B, and 39 in Group C. After treatment, all three groups showed significant decreases in fasting glucose: at 1 h glucose decreased significantly in Group A (by 0.5±1.4 mmol/L, P=0.028) and Group C (by 0.5±1.2 mmol/L, P=0.045); while showing a tendency to increase in Group B (by 0.4±1.9 mmol/L, P=0.238). HOMA-IR decreased significantly in Group C [by 0.5 (–2.2 to 0.5) mIU mmol/L^2, P=0.034]. QUICKI was significantly increased in Groups A and C (by 0.009±0.02, P=0.033 and by 0.009±0.027, P=0.049, respectively), while no change was observed in Group B. Repeated-measure ANOVA showed that the absolute changes in all parameters (except for glucose at 1 h), including glucose and insulin levels at all time-points during OGTT and in HbA1c, HOMA-IR, and QUICKI, were not significantly different among the 3 groups after treatment (P>0.05). **Conclusion:** DKP or DKP combined with Diane-35 produce a slight improvement in insulin sensitivity compared with Diane-35 alone in PCOS patients (Trial Registration: ClinicalTrials.gov, NCT03264638).

KEYWORDS Diane-35, Dingkun Pill, Chinese medicine, polycystic ovary syndrome, oral glucose tolerance tests, insulin resistance

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age,[1] and is characterized by a heterogeneous presentation of menstrual irregularity (oligomenorrhea/amenorrhea), hyperandrogenism, and polycystic ovaries.[2] PCOS is associated with a wide arrange of metabolic disorders including insulin resistance, dyslipidemia, and systemic inflammation.[3-5] Effective treatments for PCOS remain a challenge given its complexity and heterogeneity. Dingkun Pill (定坤丹, DKP) is a traditionally formulated Chinese medicine widely used for the treatment of gynecologic diseases, and offers promise for women with PCOS. DKP was invented during the reign of Emperor Qianlong in the Qing Dynasty (1739), and is composed of 30 types of genuine regional drugs. In 1957, DKP was listed by the State Council as a first-class secret prescription of Chinese medicine (one of the 4 secret prescriptions of Chinese medicine), and

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gynecologists are currently increasing its prescription for the treatment of gynecologic endocrine diseases. Although DKP has a history covering several hundred years, its scientific study has only gradually commenced in recent decades. Several Chinese researchers have found that DKP promotes ovulation; decreases serum concentrations of luteinizing hormone, androgens, insulin, and leptin in rats with PCOS; increases menstrual volume; and improves clinical symptoms and hormone levels in PCOS patients.[6] However, there are no published clinical studies depicting the effects of DKP on glucose metabolism in PCOS patients.

Insulin resistance (IR) is proposed to be a key factor in the pathophysiology of PCOS that contributes to both reproductive and metabolic disturbances, and is present in approximately 40% of women with PCOS.[7] Therapeutic strategies that target IR in PCOS ameliorate clinical symptoms and may reduce long-term complications, including diabetes.[8] The present study was conducted to evaluate the efficacy and safety of DKP *vs*. Diane-35 on IR in patients with PCOS.

METHODS

Study Design

The present investigation was a sub-study of a single-center, prospective, open-label, parallel-group, randomized controlled clinical trial. Baseline and follow-up examinations were conducted at the clinics of Peking Union Medical College Hospital in Beijing, China, from December 2016 to September 2017; and participants were recruited by means of advertisement. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Inclusion and Exclusion Criteria

Eligible participants were women aged 18–39 years and diagnosed with PCOS based on the Rotterdam consensus, with 2 of the following 3 criteria: oligo-/anovulation, hyperandrogenemia, and sonographic appearance of polycystic ovaries.[2] Diagnosis of oligo-/anovulation was based upon a menstrual pattern of oligo-/amenorrhea (cycle > 35 days) and/or a low mid-luteal serum progesterone concentration. Hyperandrogenemia was diagnosed either clinically (acne/hirsutism) or biochemically (testosterone ⩾0.75 ng/mL). Ultrasonographic criteria included follicle number ⩾12 (2–9 mm in diameter) and/or an ovarian volume of >10 mL.[9]

Exclusion criteria were medical or surgical treatment for PCOS within the previous 3 months, thyroid disease, hyperprolactinemia, active liver disease, history of cardiac or renal failure, hormone treatment, alcohol use, and tobacco use.

Sample Size Estimation

Sample size was based on primary outcomes of testosterone. From our preliminary experiments we calculated the means and standard deviation of reduced testosterone as, mean (standard) 0.014 (0.20), 0.14 (0.20), and 0.20 (0.20) ng/mL in groups A, B, and C, respectively. With a type Ⅰ error of 5% (2-sided) and a power of 80%, we required 31 patients per group; as considering a compliance rate of 85%, we ultimately needed to enroll at least 110 patients to our study.

Subjects

Of the 123 patients screened for eligibility, 117 were deemed eligible; and we enrolled these in our clinical trial and allocated them to receive DKP (Group A, 38 women), Diane-35 (Group B, 40 women), or DKP plus Diane-35 (Group C, 39 women). Research staff at the study site opened the next sequentially numbered opaque envelope that contained the product assignment, with an individual unassociated with the clinical portion of the study preparing the envelopes. We created a randomization sequence with SAS 9.4 (SAS Institute, Inc., Cary, NC) statistical software and a 1:1:1 allocation ratio using random block sizes of 6.

This trial was approved by the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College, China Academy of Medical Science (No. ZS-1222, dated November 29, 2016) and was registered at U.S. National Library of Medicine (ClinicalTrials.gov, NCT03264638). All participants provided written informed consent.

Interventions

Participants were randomly assigned to one of 3 intervention groups in a 1:1:1 ratio by research nurses: Group A received 7 g of oral DKP (Lot No. 140170207, Shanxi Guangyuyuan Medicine Co., Ltd., China) daily for 21 consecutive days followed by 7 drug-free days; Group B received 1 tablet of Diane-35 (Lot No. 354C2, Bayer Healthcare Co., Ltd., Germany) daily for 21

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consecutive days followed by 7 drug-free days; and Group C took both 7 g of DKP and 1 tablet of Diane-35 orally daily for 21 consecutive days followed by 7 drug-free days. DKP is composed of 30 types of genuine regional drugs, including *Radix Ginseng*, *pilose antler*, *Radix Notoginseng*, *stigma croci*, *Radix Angelica sinensis*, *Radix Rehmannia preparata*, and *Asini Corii Colla*, etc. The course of treatment for the 3 groups was continued for 3 consecutive months.

Participants were supplied with 3 months of study medications at their initial visit and were instructed to visit at 2 and 3 cycles after intervention. Clinical, metabolic, and hormonal parameters were assessed at baseline and at 2 and 3 cycles of treatment.

Clinical Parameters and Biochemical Assays

Clinical parameters were observed and biochemical assays, including oral glucose tolerance test (OGTT), homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), were calculated.

Clinical Parameters

We assessed weight, height, and waist and hip circumferences at each visit, and calculated the body mass index and waist-to-hip ratio (WHR); blood pressure was also measured with an OMRON HBP-1300 sphygmomanometer (Omron Healthcare, China) at each visit. Adverse events were recorded through a patient diary. The total number of menstrual bleeds from baseline to 3 months was calculated. Hyperandrogenism was assessed using the modified Ferriman-Gallwey (mFG)[10] score, and acne severity was graded according to Global Acne Grading System (GAGS)[11] at baseline and at 3 months.

Oral Glucose Tolerance Tests

After an overnight fast of 8–12 h, all subjects underwent an OGTT (with a load of 75 g of glucose in 300 mL of water). Venous blood samples for blood glucose and serum insulin were drawn at 0, 30, 60, and 120 min. Serum insulin concentrations were determined by chemiluminescence immunoassay (Siemens Centaur® XP, Germany), and glucose concentrations were measured using an automated assay (Beckman & Coulter AU automated chemistry analyzer).

HbA1c, HOMA-IR and QUICKI

HbA1c was measured by cation-exchange high-performance liquid chromatography, using a Variant Ⅱ Turbo 2.0 analyzer (HbA1c program, Bio-Rad Laboratories, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as: (fasting insulin mIU/L × fasting glucose mmol/L)/22.5. We evaluated insulin sensitivity using fasting measures with the method described by Katz, et al.[12] Quantitative Insulin Sensitivity Check Index (QUICKI) = 1/(log [fasting insulin] + log [fasting glucose]).

Safety

Adverse events including liver and renal function damage, hematologic toxicities were observed during the course of the study period.

Statistical Analyses

All of the statistical analyses were performed using SPSS software (Version 19.0). All data were normally distributed according to the Shapiro-Wilk test, and are expressed as means ± standard deviation ($\bar{x} \pm s$) except for HOMA-IR, which was described as a median (interquartile range). Differences in primary outcomes from baseline to follow-up at 3 months were examined among treatment groups in an intention-to-treat analysis [one-way analysis of variance (ANOVA), Kruskal-Wallis analysis was used for HOMA-IR]. Comparisons of baseline and follow-up values were performed using a paired *t* test for normally distributed data, and we used a Wilcoxon matched-pairs signed-rank test for HOMA-IR data. We analyzed differences in primary outcomes among treatment groups across study visits by repeated-measures ANOVA. Randomly missing variables were accounted for by the initial analysis that determined no differences between the participants with complete data and those with missing data. Compliance was estimated at every visit by capsule count. Either Chi-square test or Fisher exact-probability test was used at a two-sided significance level of 0.05 to test differences in categorical variables among the three study groups.

RESULTS

Baseline Characteristics

The follow-up rate for the primary outcome was 94.0% (110 of 117). A diagram illustrates the flow of participants through the trial and to 3 months of follow-up, with 110 patients completing the follow-up and included in the final analysis (Figure 1). There were no significant differences in age, BMI, course of PCOS or the oral glucose-tolerance test results among three groups at baseline (Table 1).

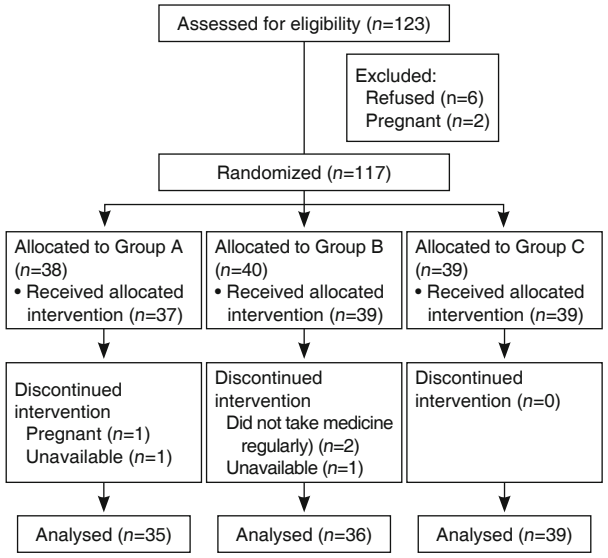

Figure 1. Flow Diagram for Improving Insulin Resistance in POCS Patients with DKP

Table 1. Demographics and Characteristics of Participants at Baseline

Items	Group A (38 cases)	Group B (40 cases)	Group C (39 cases)	P^b
Age (Year)	27.5±3.4	27.2±3.5	26.7±6.4	0.783
BMI (kg/m^2)	26.1±5.4	25.5±5.8	26.4±5.9	0.764
Testosterone (ng/mL)	0.81±0.27	0.72±0.20	0.74±0.24	0.220
Glucose (mmol/L)				
Fasting	5.1±0.4	5.1±0.5	5.2±0.7	0.570
1 h	7.9±2.1	8.2±3.0	8.0±2.5	0.866
2 h	6.6±1.3	7.0±2.3	7.0±2.4	0.700
HbA1c (%)	5.3±0.3	5.3±0.4	5.2±0.4	0.596
Insulin (μIU/mL)				
Fasting	16.32±8.77	18.03±15.82	18.78±13.12	0.703
0.5 h	128.00±64.03	133.05±95.38	112.01±60.05	0.451
1 h	115.70±67.07	124.20±74.41	114.82±76.31	0.860
2 h	94.38±61.67	90.93±77.96	75.869±68.93	0.473
HOMA-IR (mIU•mmol/L^2)^a	3.3 (2.2–4.9)	2.9 (1.6–6.3)	2.9 (2.3–5.4)	0.611^c
QUICKI	0.322±0.025	0.326±0.035	0.319±0.028	0.547

Notes: data are presented as mean±standard deviation ($\bar{x}\pm s$) unless otherwise specified. a: median (interquartile range), comparison among groups using ANOVA unless otherwise specified; b: Kruskal-Wallis analysis; c: Kruskall-wallis analysis

OGTT

After 3 months of treatment, fasting glucose were significantly decreased in 3 groups compared to values at baseline (Figure 2). One-hour glucose decreased by 0.5±1.4 mmol/L in Group A (*P*=0.028) and by 0.5±1.2 mmol/L in Group C (*P*=0.045); while we observed a tendency for an increase in Group B by 0.4±1.9 mmol/L (*P*=0.238).

HbA1c, HOMA-IR and QUICKI

HOMA-IR was significantly decreased in group C (by 0.5 [–2.2 to 0.5] mIU mmol/L^2, *P*=0.034), while remaining unchanged in group A (decreasing by –0.4 [–1.2 to 0.4] mIU mmol/L^2, *P*=0.094) and group B (increasing by 0.0 (–1.0 to 0.6) mIU mmol/L^2, *P*=0.494, Figure 3). QUICKI was significantly increased in groups A and C by 0.009±0.024 and 0.009±0.027, respectively, while remaining unchanged in Group B (Figure 3).

Repeated-measures ANOVA showed that the absolute changes for all parameters except for glucose at 1 h, including glucose and insulin levels at all time-points during OGTT, and also HbA1c (%), HOMA-IR (mIU mmol/L^2), and QUICKI, were not significantly different among the 3 groups after treatment (*P*>0.05).

Safety

No serious adverse events were observed during the course of the study.

DISCUSSION

We demonstrated herein that DKP used alone or in combination with Diane-35 for 3 months exerted a positive effect on insulin sensitivity as observed by a significant increase in the QUICKI index and a reduction in fasting and 1-h glucose levels; and significantly decreased HOMA-IR in Group C. Although fasting glucose was also significantly diminished in Group B, other parameters were not significantly changed; and 1-h glucose levels showed an increasing tendency. Overall our results indicated that DKP exerted a positive effect on glucose metabolism in PCOS patients, and when combined with Diane-35, DKP altered the adverse effects of Diane-35 on 1-h glucose and the QUICKI index.

IR is observed in 60%–80% of women with PCOS,[13-15] and there exist positive correlations between insulin and androgen levels in PCOS.[16-18] Hyperinsulinemia increases androgen production[19] and reduces sex hormone-binding globulin, increasing free androgens.[20] Enhancing insulin sensitivity reduces IR in women with PCOS, and is associated with a diminution in circulating androgen levels, improving ovulation rate and pregnancy.[21,22] DKP alone or in combination with Diane-35 exerted a positive effect on glucose metabolism, indicating that DKP could play a role in the treatment of PCOS. However, the exact mechanisms underlying this effect requires further study.

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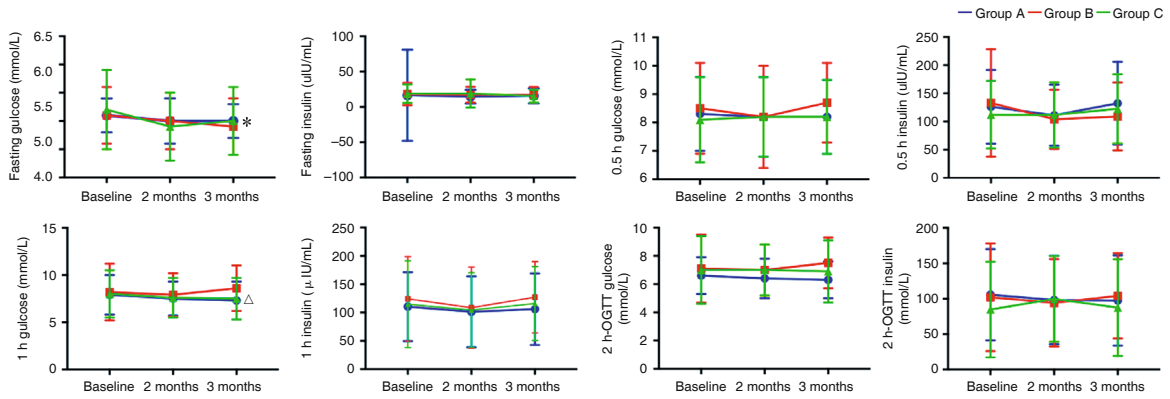

Figure 1. Mean Levels of 2 h-OGTT at Baseline, 2 Months and 3 Months

Notes: *P<0.05, compared with baseline in the same group for the 3 groups; △P<0.05, compared with baseline in the same group for Groups A and C; Group A: 35 cases; Group B: 36 cases; Group C: 39 cases.

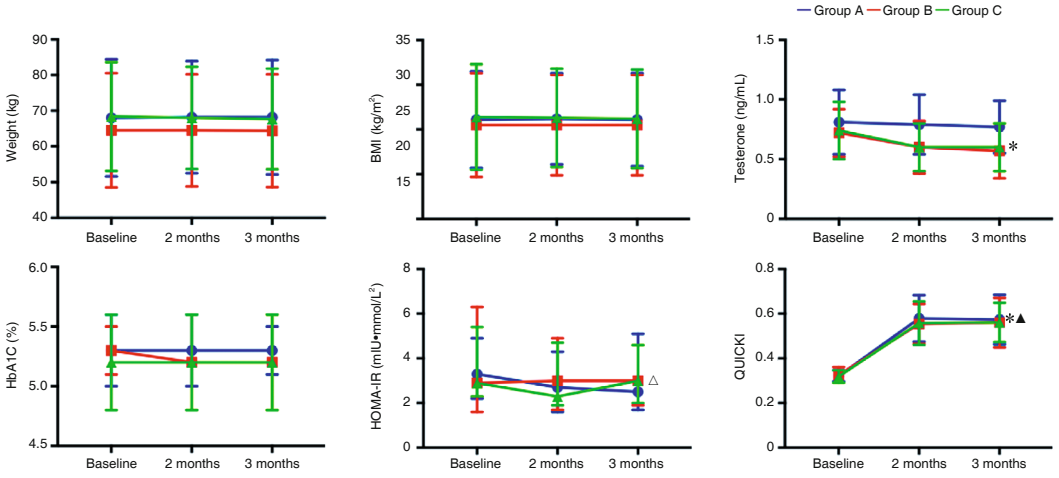

Figure 2. Means Levels of Weight, BMI, HbA1c, QUICKI and Median Levels (Interquartile range) of HOMA-IR at Baseline, 2 Months and 3 Months

Notes: *P<0.05, compared with baseline in the same group for Groups B and C; △P<0.05, compared with baseline in the same group for Group C; ▲P<0.05, compared with baseline in the same group for Groups A and C; Group A: 35 cases; Group B: 36 cases; Group C: 39 cases.

Measuring a 1-h glucose concentration during an OGTT is a good predictor of future dysglycemia among subjects with normal glucose tolerance.[23] In the present study, we observed a tendency for a higher 1-h glucose value during the OGTT after 3 months of treatment with Diane-35, but the differences before and after treatment were not significant. The 1-h glucose value was improved by DKP or DKP combined with Diane-35; but was increased by Diane-35 alone, indicating that DKP may prevent future dysglycemia in patients with PCOS. Previous studies have shown a deterioration in blood glucose concentration after treatment with Diane-35 in patients with PCOS,[24-26] and our results were consistent with these cited studies. QUICK was improved significantly in Groups A and C, while remained unchanged in Group B, indicating that the Chinese medicine DKP may improve insulin sensitivity.

The major drawback to our investigation was that the study duration was only 3 months, and therefore studies of longer duration are needed to evaluate the long-term effects on PCOS patients of DKP or DKP combined with Diane-35. We suggest that one mechanism of action of DKP is via an increase in insulin sensitivity; however, further studies are needed to corroborate this hypothesis.

In conclusion, in this study we demonstrated that taking DKP or DKP combined with Diane-35 produced a slight improvement in insulin sensitivity compared with Diane-35 alone in patients with PCOS.

Conflict of Interest

The authors report no conflict of interest.

Authors Contributions

AJS conceptualized and designed the study, contributed to data collection or interpretation, manuscript writing/editing. YD contributed to study/protocol planning, data analysis and manuscript

writing/editing. WX, YFW, HLZ, JFJ, TPZ and SYZ contributed to data collection. XHL and MX contributed to manuscript editing. All authors read and approved the final version of the paper.

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