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Effect of Metformin on Obesity, Hyperandrogenism and Insulin Resistance in Population with PCOS: A Clinical Analysis

Taiyi Li[1,*] **and Min Zhu**[2]

[1] School of Pharmacy, Fudan University, Shanghai, 200433, China
[2]Faculty of Mathematics, University of Waterloo, Ontario, N2L 3G1, Canada

*Corresponding author: 20301030001@fudan.edu.cn

Abstract:

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder in women, therapeutic methods include reducing obesity, hyperandrogenism and insulin resistance. This paper sorts out data from a clinical study that contains 83 Chinese PCOS patients in Control group, and 87 in Metformin group and analyzes the variation of parameters between baseline and after 4-month treatment. The Wilcoxon signed-rank test shows Metformin has a significant effect on obesity, hyperandrogenism and insulin resistance. They are measured by BMI, FAI and HOMA-IR respectively. The Spearman correlation analysis shows ΔFAI (variation after 4 months) is a mediator that is strongly correlated with ΔBMI and ΔHOMA-IR variation in PCOS patients. Linear regression concludes it as 10.64ΔBMI~ΔFAI~10.20ΔHOMA-IR. Metformin treatment has a stronger effect on decreasing HOMA-IR and BMI than FAI, as the relationship turns to 4.17ΔBMI~ΔFAI~5ΔHOMA-IR. This study fills the gap left by previous research which rarely focused on relationship of characteristic changes in PCOS patients, further explains Metformin treatment mechanism in evidence-based medicine perspective and provides strategy for new use of old medicine.

Keywords: Metformin; obesity; hyperandrogenism; insulin resistance.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine disorders in women with symptoms like hormonal imbalances, irregular periods, hyperandrogenism, and cysts in the ovaries [1]. It also increases the risk of having other health conditions including type 2 diabetes and obesity at least 2- to 3- fold [2]. Although it is a common disease affecting 8-13% reproductive-age

women, it meets with challenges of translation from clinical evidence to evidence-based treatments [3]. One of the reasons is that PCOS is a chronic condition and cannot be cured according to World Health Organization. Therefore, monitoring changes of biochemical characteristics in PCOS patients is essential to stabilize disease progression. Physical and biochemical indicators of patients are always keys in prevention and treatment of PCOS. Studies have tried to control for multiple variables to predict the incidence rate of PCOS or compared the relevance of clinical and hormonal characteristics among PCOS patients [4]. Existing studies mainly observed from a post-event perspective, whereas this study reflects relevance of those factors by examining the changes of parameters in PCOS patients in a dynamic perspective.

The 2023 international PCOS guideline proposed weight management as an initial treatment strategy, since obesity worsens the presentation PCOS symptoms. It also encouraged lifestyle modification for hyperandrogenism besides medical interventions [5]. Metformin, a typical type 2 diabetes medication acting on insulin resistance and weight loss with nebulous biological mechanism, has been found effective also in PCOS treatment with some of the mechanism overlapping [6, 7]. Research has proven that in PCOS patients, hyperandrogenism, obesity, and insulin resistance that occurs in type 2 diabetes are correlated [8]. Traditional studies of clinical data focus on Metformin's therapeutic effect on a specific indicator, like regulating adiponectin in PCOS [9]. Few has focused on the variation of different physical and biochemical characteristics and their correlation. A clear display of Metformin's therapeutic effect on obesity, hyperandrogenism and insulin resistance in population with PCOS is deserved for clinical prescription. Metformin's effect on these factors will be shown by statistical ways in this research.

2. Methods

2.1 Data Source and Description

Research data is from a randomized trial research, containing 342 women with PCOS and IR from three hospitals in China. Participants were aged from 18 to 40 years with BMI $\geq$ 18.5 kg/m^2 [10]. Table 1 summarizes data for following analysis. The Metformin group was treated with Metformin and sham acupuncture (n=114), while the control group was treated with placebo Metformin plus sham acupuncture group (n=114). According to the data source, the oral dose for PCOS patients in Metformin group was 0.5 g three times daily for 4 months, while patients in Control group only received placebo or sham treatment [10]. Participants' physical and biochemical conditions were measured at the time of baseline and after 4 months. After ruling out missing data, sample sizes of Metformin group (n=87) and control group (n=83) decrease. It is necessary for studying the changes in parameters of the same person.

Table 1. Description of the cilinical trial and cleaned dataset

Group name	Treatment	Measured time	Size(n)	Cleaned Size(n)
Metformin	Metformin+ sham acupuncture	baseline after 4-month treatment	114	87
Control	placebo Metformin+ sham acupuncture	baseline after 4-month treatment	114	83

It is noteworthy that the sham acupuncture treatment is a controlled experiment without manual stimulation [11]. Therefore, it is considered not affecting the result.

2.2 Method Introduction

The baseline characteristics of Metformin group and Control group are similar, eliminating the initial effect. The Kolmogorov-Smirnov test shows not all the variables subject to normal distribution, so the method of comparing medians is adopted. Between-group comparisons are carried out by Wilcoxon signed-rank test (or Mann-Whitney U test) as variables are continuous. Spearman correlation analysis is used to study the correlation of changes in specific parameters. Furthermore, linear regression is used to compare these changes between Metformin group and Control group. All p-values are two-sided with no adjustment made for multiple comparisons. A p-value <0.05 is considered to be statistically significant.

2.3 Data Preprocess

Table 2 shows all the 18 characteristics in this research. The medians of each parameter are similar, bringing initial condition of the patients in Metformin group and Control group into correspondence. Parameters can be classified into three categories including obesity (from Weight to WHR), hyperandrogenism (from Total T to LH/FSH) and insulin resistance (from C-peptide to the end). According to authoritative literature, the following data types are rep-

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resentative parameters of these three disorders respectively. The body mass index (BMI) is calculated by dividing weight (kg) by the square of height (m^2). Free androgen index (FAI) is calculated as testosterone (Total T) (nmol/L)/sex hormone–binding globulin (SHBG) (nmol/L) × 100, which is a clinical phenotype of PCOS [12]. Patients with hyperandrogenism are defined with a FAI ≥ 6.1[13]. The homeostasis model assessment of insulin resistance index (HOMA-IR) is calculated as fasting plasma glucose (FPG) (mmol/L) × fasting insulin (FINS) (mU/L)/22.5, and it is associated with the incidence of type 2 diabetes [14].

Table 2. Summary of baseline characteristics

Parameters	Metformin (n=87)	Control (n=83)
Obesity features		
Weight (kg)	65.800(55.3,78.0)	69.700(56.8,77.5)
BMI (kg/m^2), body mass index	25.720(22.8,30.6)	26.810(23.2,29.1)
Waist (cm)	87.000(78.0,97.2)	86.000(78.8,97.0)
WHR, waist-to-hip ratio	0.890(0.8,0.9)	0.880(0.8,0.9)
Androgen levels		
Total T (nmol/L), total testosterone	2.030(1.5,2.7)	2.190(1.8,2.8)
FAI, free androgen index	7.500(4.5,11.1)	7.700(4.6,12.7)
SHBG (nmol/L)	26.030(17.5,39.7)	28.090(20.7,39.3)
FSH (IU/L), follicle-stimulating hormone	5.690(4.9,6.7)	5.710(5.0,6.5)
LH (IU/L), luteinizing hormone	9.235(6.9,12.9)	10.205(6.7,14.0)
LH/FSH, LH to FSH ratio	1.660(1.3,2.2)	1.760(1.2,2.5)
Insulin resistance indicators		
C-Peptide (nmol/L)	0.940(0.8,1.2)	0.900(0.7,1.2)
FPG (mmol/L), fasting plasma glucose	5.230(5.0,5.3)	5.110(4.8,5.4)
FINS (mU/L), fasting insulin	16.800(12.7,24.5)	16.090(12.4,22.9)
Glucose AUC (mmol/L × min)	15.480(13.2,17.3)	14.500(12.6,16.8)
Insulin AUC (mU/L × min)	264.290(165.0,330.8)	223.270(171.7,326.2)
HbA1c (%), glycosylated hemoglobin A1c	5.300(5.1,5.5)	5.300(5.1,5.5)
HOMA-IR	3.870(2.8,6.0)	3.660(2.8,5.0)
HOMA-β (%)	206.790(146.4,295.5)	213.830(143.2,288.8)

Notes: Values are expressed as median (25th percentile, 75th percentile). Glucose AUC and Insulin AUC shows the area under the curve during the oral glucose tolerance test using the trapezoidal rule. HOMA-IR and HOMA-β are homeostatic models for insulin resistance and β-cell function respectively.

3. Results and Discussion

3.1 Changes of Characteristics in PCOS Patients

There are 87 PCOS patients studied in Metformin group. As is shown in Table 3, the Wilcoxon signed-rank test indicates that after 4-month Metformin treatment after baseline visit, many characteristics of PCOS patients change in various degree. Key parameters including obesity features like BMI and Weight, androgen levels like FAI and SHBG, insulin resistance indicators like Insulin AUC and HOMA-IR all have a significant decline. It proves that Metformin plays a significant role in decreasing obesity, relieving hyperandrogenism and reducing insulin resistance.

Changes of characteristics are crucial for evidence-based treatments. To figure out how characteristics of obesity, androgen levels and insulin resistance change, the Spear-

man correlation is used to study the relationship. Since variables of same categories have repetitive functions, a representative indicator needs to be chosen for each type of data to avoid collinearity issue. According to previous research that is elaborated in 2.2 variables selection, the following analysis use BMI to represent obesity, FAI to represent androgen levels, and HOMA-IR to represent insulin resistance.

By subtracting the baseline from the parameters after 4 months of treatment, ΔBMI, ΔFAI and ΔHOMA-IR represent variation of BMI, FAI and HOMA-IR. Since the Control group only receives placebo treatment, changes of characteristics in the Control group can be regarded as the normal fluctuation in PCOS patients.

Table 3. Changes of characteristics in PCOS patients after 4 months of Metformin treatment

Parameters	Baseline	4-month treatment	Δ	p
Obesity features				
Weight	65.800(55.3,78.0)	62.000(52.3,73.9)	-3.8	0.000**
BMI	25.720(22.8,30.6)	24.640(21.3,28.8)	-1.08	0.000**
Waist	87.000(78.0,97.2)	85.000(75.1,94.5)	-2	0.000**
WHR	0.890(0.8,0.9)	0.880(0.8,0.9)	-0.01	0.059
Androgen levels				
Total T	2.030(1.5,2.7)	1.995(1.4,2.6)	-0.035	0.135
FAI	7.500(4.5,11.1)	5.995(4.1,9.6)	-1.505	0.004**
SHBG	26.030(17.5,39.7)	29.120(18.1,43.9)	3.09	0.000**
FSH	5.690(4.9,6.7)	5.880(4.6,7.1)	0.19	0.664
LH	9.235(6.9,12.9)	9.270(5.8,15.7)	0.035	0.742
LH/FSH	1.660(1.3,2.2)	1.745(1.2,2.5)	0.085	0.755
Insulin resistance indicators				
C-Peptide	0.940(0.8,1.2)	0.820(0.7,1.2)	-0.12	0.003**
FPG	5.230(5.0,5.3)	5.060(4.8,5.4)	-0.17	0.034*
FINS	16.800(12.7,24.5)	13.690(9.4,20.6)	-3.11	0.000**
Glucose AUC	15.480(13.2,17.3)	15.650(14.1,17.6)	0.17	0.301
Insulin AUC	264.290(165.0,330.8)	182.660(132.2,267.2)	-81.63	0.000**
HbA1c	5.300(5.1,5.5)	5.300(5.1,5.5)	0	0.034*
HOMA-IR	3.870(2.8,6.0)	3.000(2.2,5.0)	-0.87	0.000**
HOMA-β	206.790(146.4,295.5)	172.100(133.9,266.0)	-34.69	0.016*

Notes: Values are expressed as median (25th percentile, 75th percentile). Comparisons are carried out by Wilcoxon signed-rank test.

3.2 Relationship of Representative Parameters

As is displaced in Table 4, when there is no medical treatment, ΔBMI and ΔFAI, ΔFAI and ΔHOMA-IR show strong correlation respectively, while ΔBMI and ΔHOMA-IR are less correlated. It indicates that ΔBMI and ΔHOMA-IR have an indirect relationship with the mediator of ΔFAI. For Metformin group, relationship of these changes remains the same, but ΔBMI and ΔHOMA-IR shows more correlation because the Metformin treatment amplifies correlation between ΔBMI and ΔFAI as the coefficient value raises. That shows the reduction of obesity features can lead to some extent of decline in androgen levels, which is also correlated with changes of insulin resistance. Patients with different initial characteristics like a FAI $\geq$ 6.1 are also sort out for separate analysis, and the results stay similar.

Table 4. Correlation analysis of parameter variation after 4-month treatment in PCOS patients

Variables	Control(n=83)	p	Metformin (n=87)	p
ΔBMI&ΔFAI	0.306**	0.005	0.408**	0.000

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ΔBMI&ΔHOMA-IR	0.199	0.072	0.251*	0.019
ΔFAI&ΔHOMA-IR	0.350**	0.001	0.313**	0.003

* p<0.05 ** p<0.01. Coefficient value is calculated based on Spearman correlation analysis.

To further explore the relationship of parameter variation when considering ΔFAI as a mediator, Linear regression is done for ΔBMI&ΔFAI and ΔHOMA-IR&ΔFAI. Table 5 concludes equation summaries for linear regression models and Figure 1 is created to show the slope change. Equation for Control group (ΔHOMA-IR = 0.098ΔFAI-3.38, ΔBMI = 0.094ΔFAI-25.64) is shown in green, while equation for Metformin group (ΔHOMA-IR = 0.20ΔFAI-2.76, ΔBMI = 0.24ΔFAI-24.39) is shown in red (Figure 1). Considering ΔFAI as a mediator, the relationship of these parameter changes can be concluded as 10.64ΔBMI~ΔFAI~10.20ΔHOMA-IR for Control group. It means that in PCOS patients, when HOMA-IR has a fluctuation of decreasing by 10.20, FAI may likely to decrease by 1 and BMI may decrease by 10.64. For Metformin group, the relationship changes into 4.17ΔBMI~ΔFAI~5ΔHOMA-IR. Since the equation in Control group shows the relationship of general fluctuation in PCOS patients, factors that cause this pathological parameter fluctuations can be eliminated in comparison. Metformin group has a higher slope than the Control group in ΔHOMA-IR and ΔFAI regression (0.20 > 0.098) as well as ΔBMI and ΔFAI regression (0.24 > 0.094). It indicates that Metformin has a stronger effect on HOMA-IR and BMI decline than that of FAI.

Table 5. Linear regression models of parameter variation in two groups

Group	ΔBMI&ΔFAI	R^2	ΔHOMA-IR&ΔFAI	R^2
Control	-25.64, 0.094	1.2%	-3.38, 0.098	8.0%
Metformin	-24.39, 0.24	10.9%	-2.76, 0.201	37.1%

Values are expressed as intercept, slope. R^2 shows the proportion of variance in the response that can be explained by predictor variables.

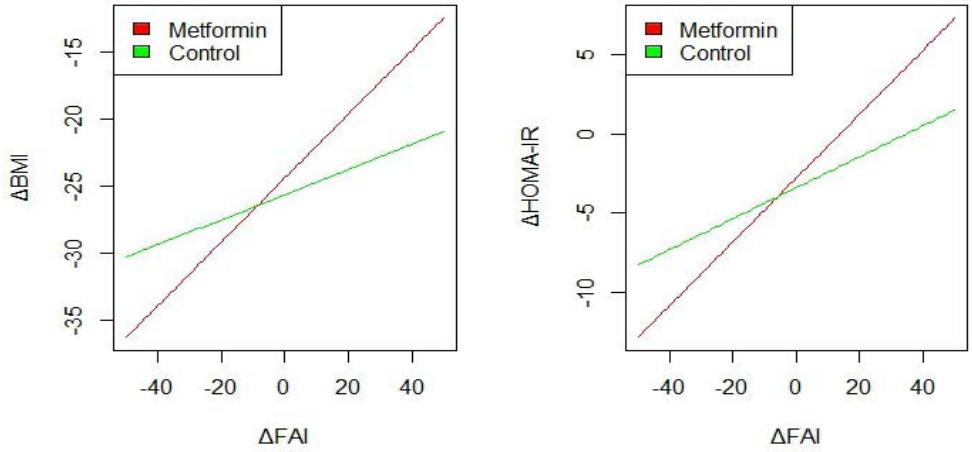

Fig. 1 Linear regression for ΔBMI&ΔFAI and ΔHOMA-IR&ΔFAI.

3.3 Discussion

This study provides a direction for the new use of old medicines in the treatment of PCOS. Another study published recently on Science, shows that Artemisinin, first found as an antimalarial medication, can treat PCOS by inhibiting androgen synthesis [15]. Coincidently, this team has proved Artemisinin can reduce obesity in their previous research [16]. Metformin is also a medication for type 2 diabetes before discovering its effect on PCOS. It confirms that new medication can be found for PCOS in available treatments that are effective for obesity, reducing androgen levels or insulin resistance that also appears in type 2 diabetes.

4. Conclusion

The PCOS is an incurable chronic disease that affects 1-in-10 women. It is essential to focus on the changes of some characteristics that can reflect disease development. Data is from a randomized clinical trial and the initial condition of the patients is similar. Wilcoxon signed-rank test is used to display the general effect of Metformin on various characteristics in PCOS patients.

Metformin can treat PCOS with its therapeutic effect on obesity, hyperandrogenism, and insulin resistance. Metformin has a significant effect on decreasing BMI, FAI and HOMA-IR, representing obesity, androgen levels and insulin resistance respectively. Spearman correlation analysis shows changes of these parameters are correlated. They follow 10.64ΔBMI~ΔFAI~10.20ΔHOMA-IR linear relationship in PCOS patients. The therapeutic effect of Metformin is amplified due to this correlation and its effect on declining BMI and HOMA-IR is stronger than FAI in treating PCOS patients, as the relationship turns to 4.17ΔBMI~ΔFAI~5ΔHOMA-IR.

This study elaborates the relationship of changes in parameters on obesity, hyperandrogenism and insulin resistance. It has rarely been discussed in other studies due to the neglect of relationship in parameter changes. The study further explains Metformin treatment mechanism in evidence-based medicine perspective and helps doctors to analyze clinical characteristics of PCOS patients.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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