Myoinositol Therapy May Adjust the Metabolic Deregulation in Infertile PCOS Women through Modulation of the TyG Index-BMI: A Comparative Study versus Metformin

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Abstract

Background: Polycystic ovary syndrome (PCOS) affects women of childbearing age and is characterized by insulin resistance (IR). Myoinositol has insulin-mimetic, anti-diabetic, and lipid-lowering properties.

Objectives: Evaluating the effect of 6-month insulin sensitizer therapy on IR, glucose tolerance, and hormonal parameters.

Patients and methods: A total of 156 women with PCOS were evaluated to determine their body mass index (BMI) and the homeostatic model assessment of IR (HOMA-IR) index. Blood samples were obtained before and 6 months after treatment to estimate fasting plasma triglycerides to calculate the TyG index and TyG index-BMI and serum total testosterone (TT). Patients received metformin (MET) 500 mg three times/ day or myoinositol/d-chiro-inositol combination (MYO/DCI; 40:1) twice/day for 6 months.

Results: 65 women had regular menstrual patterns, and 15 women seeking pregnancy got pregnant with comparable intergroup differences. BMI, BG, TyG index, and TyG index-BMI measures were significantly ($P<0.001$) decreased in the MYO/DCI arm. Manifestations of hyperandrogenemia (HA) highly improved in both groups. A high percentage of decrease in HOMA-IR ($\beta=0.202$, $P = 0.007$) and serum TT ($\beta=0.287$, $P < 0.001$) were effective factors for resumption of normal menstrual pattern. High percentage of decrease in TyG Index-BMI was valuable predictor ($\beta = 0.447$, $P < 0.001$) for decreased IR.

Conclusion: MYO/DCI is effective therapy for PCOS, especially for those with obese phenotype. MYO/DCI combination provided reductions of HA manifestations and allowed the resumption of regular menstrual patterns and improved fertility. The TyG index-BMI is a good surrogate marker for improved metabolic homeostasis.

Keywords: PCOS; Metformin; Myoinositol; Hyperandrogenemia; TyG Index.

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that affects women of the childbearing period and is characterized by polycystic ovaries, chronic anovulation, hormonal and metabolic aberrations with hyperandrogenemia (HA) **(Sparić et al., 2024)**. Numerous studies have indicated that PCOS often concomitantly occurs with non-alcoholic fatty liver disease (NAFLD), which affects more than 25% of adults and is characterized by steatohepatitis with cardiometabolic derangements **(Xu et al., 2024)**.

Insulin resistance (IR) is the reduction of effective action of insulin on its peripheral target tissues especially muscular and hepatic tissue despite its high plasma levels **(Patel and Goyal, 2019)**, mostly due to masked or endocytosed receptors **(Park et al., 2023)**. Insulin receptors and their downstream signaling proteins show differential expression in ovarian follicles of both healthy women and those with PCOS **(Wang et al., 2023)**. Experimental studies indicate that elevated androgen levels can amplify insulin secretion in response to glucose by upregulating the cystic fibrosis transmembrane conductance regulator protein, thereby increasing insulin levels and perpetuating a vicious cycle **(Sun et al., 2024)**.

Inositol, a six-carbon cyclic sugar alcohol, is an essential constituent of cell membrane phospholipids and plays a vital role in cellular signaling pathways **(Zarezadeh et al., 2022)**. Myoinositol (MYO) demonstrates insulin-like, antidiabetic, lipid-lowering, antioxidant, and anti-inflammatory effects **(Anaforoglu et al., 2011)**, making it beneficial in managing IR and related metabolic disorders **(Rostami et al., 2024)**.

This study suggested a possible role for IR in pathogenesis of PCOS-associated metabolic and endocrinal derangements and improving insulin sensitivity by the use of insulin sensitizers may adjust IR parameters with subsequent improved metabolic and endocrinal milieus in women with POCS. The present study aimed to assess the impact of 6 months of insulin-sensitizer therapy on IR, glucose tolerance (GT), and hormonal parameters of PCOS women.

Patients and methods

Design: The current study was a prospective randomized therapeutic trial.

Setting: Obstetrics and Gynecology Department in conjunction with Clinical Pathology Department at Benha University Hospitals.

Ethical considerations: The study protocol received approval from the Local Ethical Committee (Approval No.: RC 1-11-2024) before participant enrollment and was registered on ClinicalTrials.gov (ID: NCT07058675).

Patients: All women attending the Gynecology outpatient and infertility clinics with manifestations of PCOS irrespective of their fertility status were evaluated for inclusion and exclusion criteria. Before patients' enrolment, the author discussed the study protocol freely with patients, and patients who accepted to participate in the study signed a written fully informed consent.

Randomization: Participants were assigned to two groups in a 1:1 ratio using computer-generated sequences, with odd numbers omitted to finalize allocation. The sequences were printed on cards, sealed in opaque envelopes, and each patient selected an envelope to determine the treatment regimen.

Exclusion criteria: Patients who were maintained on a diet regimen, regular exercise, or medical therapy for PCOS, antidiabetic or antihypertensive therapy, and women who underwent

laparoscopic drilling were excluded from the study. Also, patients with dyslipidemia, hereditary lipoprotein disorders, and chronic liver or kidney diseases were also excluded.

Inclusion criteria: Women presenting manifestations suggestive of having PCOS and were free of exclusion criteria were included in the study.

Treatment Regimens

According to the randomization sequence, patients were divided into two groups:

1. Group I: included patients who received metformin (MET) hydrochloride (Cidophage tab, Chemical Industrial Development, Cairo Egypt) 500 mg three times daily as the standard insulin sensitizer.
2. Group II: encompassed patients who were prescribed tablets containing myoinositol/d-chiro-inositol combination (MYO/DCI) in 40:1 ratio (Viocyst, 2 g tab, Viomix Pharmaceutical Industries, Egypt) twice daily.

Clinical data collection

Information on age, weight, height, and marital, fertility, and menstrual status was recorded. History taking addressed risk factors including sedentary lifestyle, psychological stress, family history of PCOS, obesity-related comorbidities such as diabetes mellitus (DM), and prior PCOS treatments with their outcomes.

Blood sampling

All patients drew 6 ml of fasting venous blood which was divided into three parts. The first part was collected in sodium fluoride-containing tube for determination of BG levels. The second part was put in EDTA-containing tube for estimation of plasma insulin and triglyceride levels. The third part was collected in plain dry tube, allowed to clot and centrifuged at 3000 rpm for 10 minutes to separate serum for estimation of serum insulin and testosterone.

Evaluation tools

1. **Body mass index (BMI)** was determined as weight divided by height in square meters **(Bray, 1992)**. Women were categorized according to BMI as average (BMI < 25 kg/m^2), overweight (BMI = 25-29.9 kg/m^2), obese-I (BMI = 30-34.9 kg/m^2), obese-II (BMI = 35-39.9 kg/m^2) or Obese-III (BMI ≥ 40 kg/m^2) as previously documented by **World Health Organization (WHO), 1995**.
2. **The Rotterdam PCOS diagnostic criteria**: For a woman to be diagnosed as having PCOS, two of the following criteria must be present: 1. Menstrual pattern: amenorrhea which was defined as absence of vaginal bleeding for at least 90 days or oligomenorrhea which was defined as < 8 spontaneous menstrual cycles per year for at least 3 years before enrollment; 2. HA manifested as serum total testosterone (TT) > 0.8 ng/ml; 3. Ovarian US findings as the presence of >12 ovarian follicles of 2–9 mm and/or an ovarian volume of >10 ml per ovary **(Anaforoglu et al., 2011)**.

3. IR indices

- Homeostasis model assessment of IR (HOMA-IR) score: fasting blood glucose (FBG) and fasting plasma insulin (FPI) levels were estimated and applied in Matthews' equation: FPI (µU/ml) x [FBG (mg/ml)/18])/22.5. The cutoff point for diagnosis of IR is a HOMA-IR score of ≥2 **(Matthews et al., 1985)**.
- The triglyceride/ glucose (TyG) index was calculated according to the equation Ln [fasting triglycerides (mg/ml) × FBG (mg/ml)/2] **(Simental-Mendía et al., 2008)**.

4. Glucose tolerance

- 75-g Oral Glucose Tolerance Test (OGTT): after obtaining a fasting blood sample for estimation of FBG, the patient was allowed to take 75-g glucose and to give another blood sample 2 hours later for estimation of postprandial blood glucose (PPBG). Patients were categorized as normal glucose tolerant (NGT) if FBG was <100 mg/dl and PPBG <153 mg/dl or impaired glucose tolerance (IGT) if FBG was >100 and <126 mg/dl with PPBG < 153 mg/dl or if PPBG ≥153 mg/dl. Diabetes was diagnosed if the patient had IGT with PPBG ≥153 mg/dl **(International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010)**.

5. Hyperandrogenemia

- Biochemical HA: serum TT was estimated using Abcam ELISA kit (Abcam Inc., Cambridge, USA; Cat. No ab108666; the Inter assay C.V.% is ≤5.8%; Intra assay C.V. is ≤10.5%). Serum dehydro-epiandrosterone (DHEA) was estimated using Abcam ELISA kit (Abcam Inc., Cambridge, USA; Cat. No ab108669; the Inter assay C.V.% is <10.4%; Intra assay C.V. is <7.9%). Serum level of TT > 0.8 ng/ml indicates biochemical HA **(Anaforoglu et al., 2011)**.
- Clinical HA as judged by

a. The modified Ferriman-Gallwey (FG) map to evaluate the 9 areas and score each area on a 5-point Likert scale with a higher score indicating more extensive hair growth and an FG score of ≥8 indicating HA **(Ferriman and Gallwey, 1961)**.
b. The 4-grade acne scoring system evaluates acne as Grade I if there are—comedones with occasional papules, Grade II if there are papules, comedones with or without pustules, Grade III which is characterized by the presence of predominant pustules, nodules, abscesses, and Grade IV if there cysts, abscesses with widespread scarring **(Adityan et al., 2009)**.

Follow-up protocol

- Treatment has to be continued for six months with no lifestyle changes, dieting regimens, or exercise protocols, and any patient who had stopped treatment through these six months was excluded from the study.
- Clinical and lab evaluations were performed before treatment and at the end of 6 months duration.

Study outcomes

1. The primary outcome of the study was the frequency of women regaining their regular normal menstrual pattern or getting pregnant during the study duration and this was considered the success rate of the provided treatment regimens.
2. The secondary outcomes were the frequency of IS women at the end of therapy and the extent of reduction in biochemical HA and the diminution of clinical HA manifestations

Statistical analysis

Data were coded, organized, and analyzed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA, 2021). Normality of quantitative variables was assessed with the Kolmogorov-Smirnov test, and results were presented as mean ± standard deviation (SD). Between-group comparisons of quantitative data were performed with the independent t-test, while within-group changes were assessed using the paired t-test. Categorical variables were summarized as frequencies and percentages and analyzed using the Chi-square test or

Fisher's Exact test when appropriate. Pearson's correlation analysis was applied to assess the relation between the percentages of change in lab parameters and the resumption of regular menstrual patterns. Univariate Regression analysis was used to confirm the obtained correlated variates. The Receiver Operating Characteristic (ROC) curve analysis was used to determine the significant effectors for the resumption of regular menstrual patterns among the related percentages of change in lab parameters and to determine the predictor for getting insulin sensitivity among IR women as judged by the significance of area under the ROC curve (AUC) relative to the area under the reference line (= 0.05). The Multivariate Regression analysis was performed to determine the persistently significant predictors among those who showed significant AUC. A p-value ≤ 0.050 was considered statistically significant.

Results

During the study duration, 175 PCOS women were evaluated for enrolment criteria, but 19 women were excluded; 7 women were maintained on medical treatment for PCOS, 3 women had previous laparoscopic drilling within three months before enrolment, 4 women had manifest DM, 3 women had morbid obesity and refused to participate in the study. The remaining 156 patients were randomly divided into two groups, but nine patients (11.5%) of Group I stopped MET therapy due to development of gastrointestinal manifestations that patients could not tolerate and were excluded from the statistical analyses and were considered as failure for MET therapy, while no patient in Group II stopped MYO/DCI therapy (**Fig. 1**). The study included 32 single patients (21.8%) and 115 married women (78.2%) within age range of 21-38 (mean age = 28.1±4) with insignificant difference between both groups.

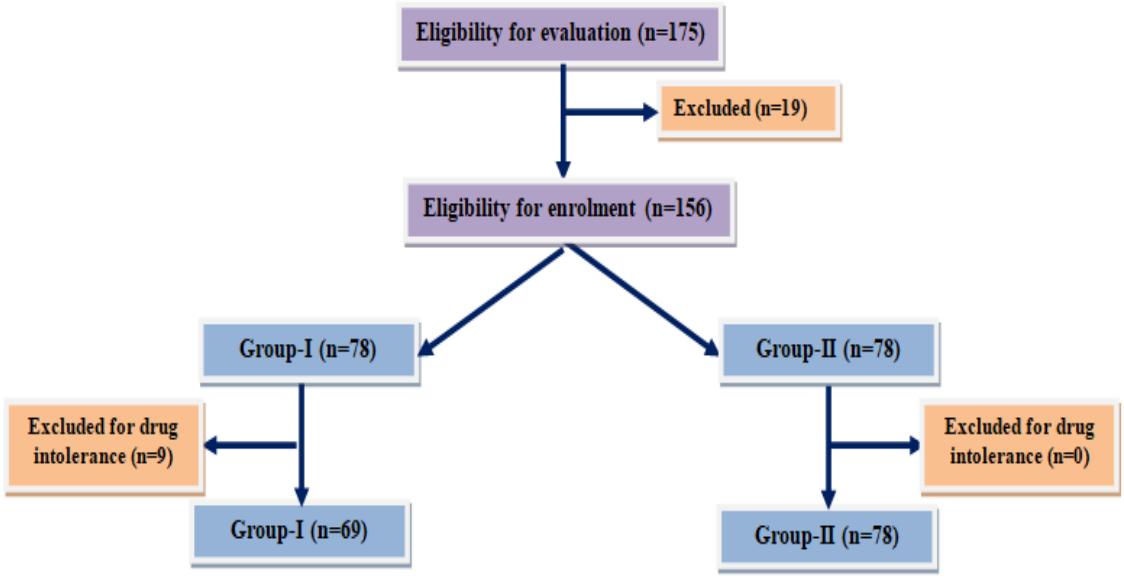

Fig.1. Study flow chart

At the end of 6 months of therapy, both lines of treatment significantly (P < 0.001) reduced the frequency of women who had disturbed menstrual patterns and 65 women (44.2%) got regular menstrual patterns, but 63 patients (42.9%) still had oligomenorrhea and 19 women (12.9%) were still complaining of amenorrhea with insignificant (P

=0.681) intergroup difference. Fortunately, 15 women of those seeking pregnancy got pregnant during the duration of therapy for a pregnancy rate of 13% and 20% among total married women and women seeking pregnancy with non-significant (P = 0.419) difference between both groups (**Table.1**).

Table 1. The effect of therapies on menstrual patterns and pregnancy outcomes

Items				Group I	Group II	P-value
Menstrual pattern	Before the start of therapy	Regular		0	0	0.316‡
		Infrequent		49 (71%)	61 (78.2%)	
		Amenorrhea		20 (29%)	17 (21.8%)	
	after 6 months of therapy	Regular		28 (40.6%)	37 (47.4%)	0.681‡
		Infrequent		31 (44.9%)	32 (41.1%)	
		Amenorrhea		10 (14.5%)	9 (11.5%)	
	Significance versus frequency before therapy			<0.001‡	<0.001‡	
Married women seeking pregnancy		Before		37 (100%)	38 (100%)	0.266
		After	Non-pregnant	31 (83.8%)	31 (76.3%)	0.419†
			Pregnant	6 (16.2%)	9 (23.7%)	

Unpaired t-test*, Fisher's exact test†, and chi-square test‡

Patients' distribution according to BMI grade decreased significantly in both groups after treatment compared to that determined before with significant (P = 0.0029) intergroup difference after treatment in favor of Group II. Additionally, the percentage of decrease in BMI was significantly higher in Group II (**Table.2**).

Table 2.Patients' BMI measures determined before and after treatment

Measures				Group-I	Group-II	P-value
Body weight (kg)		Before		89.6 (±4.6)	91.2 (±5.5)	0.069*
		After		84.3 (±4.1)	85.1 (±5.6)	0.314*
Body height (cm)				165.4 (±3.13)	166.2 (±3.6)	0.175*
Body mass index (kg/m^2)	Grades	Before	Overweight	4 (5.8%)	5 (6.4%)	0.067‡
			Obese-I	60 (87%)	57 (73.1%)	
			Obese-II	5 (7.2%)	16 (20.5%)	
		After	Overweight	21 (30.4%)	35 (44.9%)	0.0029‡
			Obese-I	48 (69.6%)	36 (46.1%)	
			Obese-II	0	7 (9%)	

		Significance of difference	0.0001‡	<0.001‡	
	Average (±SD)	Before	32.76 (±1.65)	33 (±2.48)	0.410*
		After	30.8 (±1.47)	30.73 (±2.4)	0.958*
		Significance of difference	<0.001**	<0.001**	
	Percentage of change		5.92 (±1.6)	6.67 (±1.63)	0.0057*

Unpaired t-test*, paired t-test**, Fisher's exact test†, and chi-square test‡

After treatment 54 patients (36.7%) became glucose tolerant, while 93 patients (63.3%) were still glucose intolerant with significant (P = 0.035) difference in favor of Group II. The estimated FBG did not differ after treatment compared to before, with significant (P < 0.001) intragroup difference with significantly (P = 0.0014) higher percentage of decrease in FBG was in Group II. Contrary to that, the estimated PPBG at the end of therapy was significantly (P < 0.001) lower compared to before treatment with significantly (P = 0.010) lower measures and lower percentage of decrease in Group II than in Group I (**Table.3**).

Table 3.Glucose Homeostasis Data

Measures				Group-I	Group-II	P-value
Fasting blood glucose (mg/dl)	Frequency of glucose tolerance	Before	Intolerant	69 (100%)	78 (100%)	
			Tolerant	0	0	
		After	Intolerant	50 (72.5%)	43 (55.1%)	0.035†
			Tolerant	19 (27.5%)	35 (44.9%)	
	Average (±SD)	Before		120 (±5.1)	121 (±6.1)	0.288*
		After		108 (±10.6)	105 (±9.5)	0.073*
		Significance of difference		<0.001**	<0.001**	
		Percentage of change		10.1 (±6.4)	13.3 (±5.4)	0.0014*
2-h postprandial blood glucose (mg/dl)		Before		148±4.7	147±5.2	0.228*
		After		138±5.2	135.7±5.5	0.010*
		Significance of difference		<0.001**	<0.001**	
		Percentage of change		6.74±2.6	7.65±2.57	0.011*

Unpaired t-test*, Paired t-test**, Fisher's Exact test†, and Chi-square test‡

The frequency of IR was reduced in the studied population by about 65%. Compared to the baseline frequency, at the end of treatments, the frequency of IR women and the HOMA-IR scores were significantly reduced in both groups that showing comparable differences as shown in Table 4. The estimated plasma triglyceride levels and TyG index were decreased significantly (P < 0.001) after the end of 6 months of therapy compared to those obtained before treatment. Additionally, plasma triglycerides and TyG index were significantly (P < 0.001 & 0.0017,

respectively) lower and significantly (P < 0.001) higher percentage of decrease in Group II. Moreover, the calculated TyG Index-BMI was noticeably reduced (P < 0.001) after therapy with an insignificant intergroup difference. However, the decrease in the calculated TyG Index-BMI after therapy was significantly (P < 0.001) higher in Group II than in Group I (**Table.4, Fig. 2**).

Table 4. Insulin Resistance Data

Measures				Group-I	Group-II	P-value
Fasting insulin level		Before		5.42±1.8	5.39±1.9	0.936*
		After		5.13±1.1.69	4.71±1.72	0.139*
		Significance of difference		0.327**	0.021**	
		Percentage of change		5.01±4.7 1	11.93±9.5	<0.001*
HOMA-IR index	Frequency of IR	Before	IR	28 (40.6%)	37 (47.3)	0.511
			IS	41 (59.4%)	41 (52.7%)	
		After	IR	10 (14.5%)	13 (16.7%)	0.717
			IS	59 (85.5%)	65 (83.3%)	
		Significance of difference		0.0006†	0.00004†	
	Average (±SD)	Before		1.63±0.55	1.63±0.6	0.948*
		After		1.39±0.5	1.23±0.47	0.067*
		Significance of difference		0.0073**	0.00001**	
		Percentage of change		24.06±15.84	39.35±25.2	0.00003*
Fasting plasma triglyceride level (mg/dl)		Before		140.5±14.5	145±20.6	0.141*
		After		132.75±14	121.2±13.8	<0.001*
		Significance of difference		<0.001**	<0.001**	
		Percentage of change		5.53±1.5	15.96±4.97	<0.001*
TyG Index		Before		9.03±0.11	9.07±0.16	0.136*
		After		8.87±0.16	8.75±0.15	0.0017*
		Significance of difference		<0.001**	<0.001**	
		Percentage of change		1.85±0.86	3.54±1.06	<0.001*
TyG Index-BMI		Before		295.9±23.6	299.7±23.6	0.263*
		After		273.2±14.8	269.9±22.4	0.294*
		Significance of difference		<0.001**	<0.001**	
		Percentage of change		7.66±1.63	9.96±1.67	<0.001*

Unpaired t-test*, Fisher's Exact test†, and Chi-square test‡

Treatment significantly lowered androgenic hormonal levels than pre-treatment ones with markedly higher percentages of decrease in Group I than in Group II and significantly lower frequency of biochemical HA and mean values of FG hirsutism score in both groups (**Table.5**).

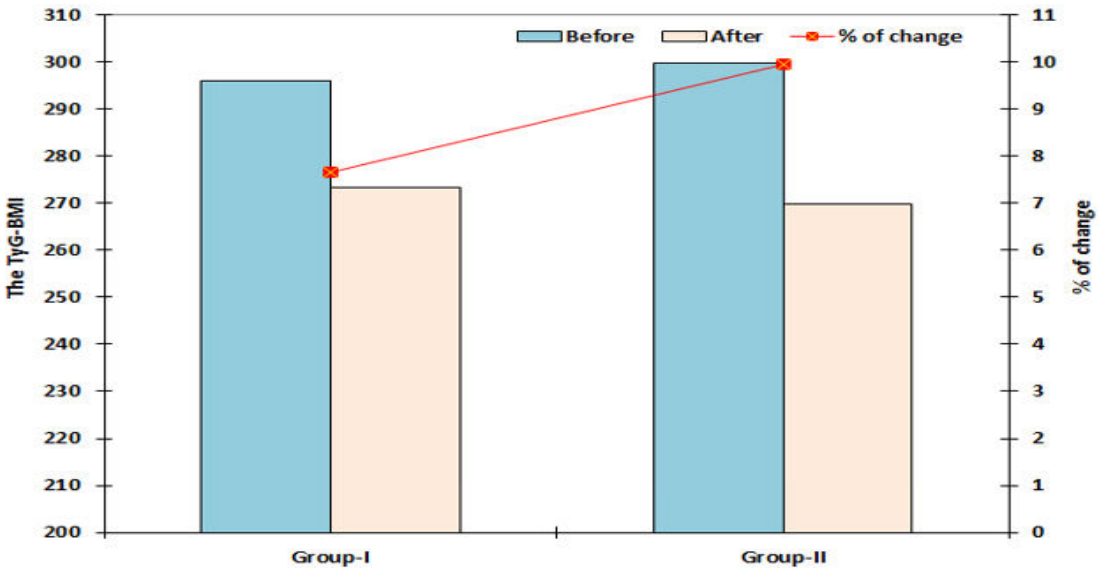

Fig. 2. The mean value of the calculated TyG Index-BMI for women of both groups before and after therapy

Table 5. Hyperandrogenemia

Measures				Group-I	Group-II	P-value
Biochemical	Total testosterone (ng/ml)	Before		0.77±0.1	0.76±0.1	0.324*
		After		0.7±0.09	0.68±0.088	0.096*
		Significance of difference		0.00003**	<0.001**	
		% of change		8.79±4.44	10.3±2.3	0.011*
	DHEA (µg/dl)	Before		296.1±38	286.7±29.7	0.082*
		After		273.8±33.9	260±27.8	0.010*
		Significance of difference		0.0005**	<0.001**	
		% of change		7.45±2.35	9.2±4.88	0.006*
	Frequency of HA	Before	HA	27 (39.1%)	29 (37.2%)	0.808†
			Not HA	42 (60.9%)	49 (62.8%)	
		After	HA	13 (18.8%)	9 (11.5%)	0.216†
			Not HA	56 (81.2%)	69 (88.5%)	
		Significance of difference		0.0086†	0.0002†	
Clinical	Hirsutism	FG score	Before	6.96±1.59	6.9 ±2	0.813*
			After	5.64±1.7	5.96±1.93	0.286*
		Significance of difference		<0.001**	0.004**	
	Acne	Acne score	Before	1.57±0.68	1.52±0.71	0.771*
			After	1.3±0.47	1.33±0.48	0.781*
		Significance of difference		0.081**	0.228**	

The resumption of regular menstrual pattern showed significant positive relation to the percentage of improvement of BMI, HOMA-IR, TyG Index, TyG Index-BMI and serum TT. Univariate Regression analysis assured

the significance of these variates, but ROC curve analysis defined high percentage of change in serum TT, TyG Index-BMI and BMI as the significant effectors for improved menstrual pattern (**Fig.3**). The Multivariate Regression analysis defined high percentage of improvement of serum TT and HOMA-IR score as the persistently significant effectors (**Table.6**).

Table 6. The percentage of change of the studied variates as effectors for resumption of regular menstrual pattern

Analyses	Correlation		Univariate Regression		Receiver Operating Characteristic Curve				Multivariate regression	
Variates	"r"	P	β	P	AUC	Std.	P	95% CI	β	P
BMI	0.231	**0.005***	0.182	**0.017**	0.612	0.047	**0.020**	0.520-0.703	Excluded	
FBG	0.052	0.529	0.167	0.071	Excluded					
PPBG	0.045	0.585	0.131	0.121						
HOMA-IR	0.217	**0.008***	0.261	**0.002**	0.477	0.049	0.627	0.381-0.572	0.202	0.007
Triglycerides	0.135	0.102	0.242	0.108	Excluded				Excluded	
TyG Index	0.181	**0.028***	0.159	**0.041**	0.521	0.048	0.665	0.427-0.614		
TyG Index-BMI	0.252	**0.002***	0.263	**0.002**	0.637	0.047	**0.004**	0.544-0.730		
TT	0.307	**<0.001***	0.283	**<0.001**	0.738	0.041	**<0.001**	0.657-0.819	0.287	<0.001

*Bold: significant

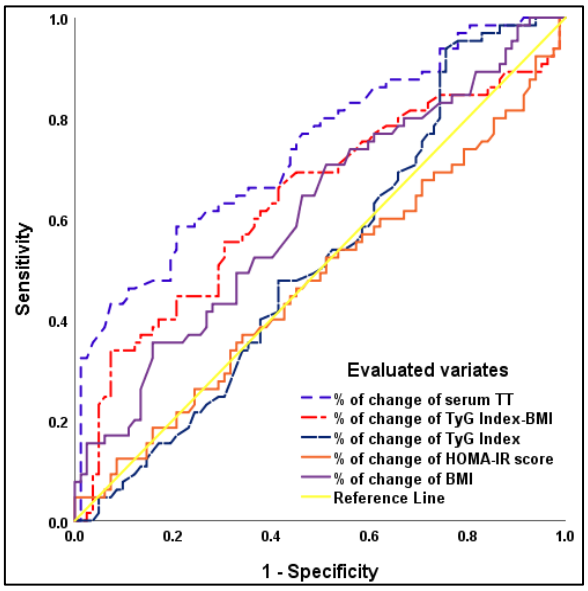

Fig. 3. ROC curve analysis for the positively correlated variates with resumption of regular menstrual pattern to define the effector variate

Table 7. Statistical analyses for the predictors for improved insulin sensitivity

Analyses	Multivariate Regression		Receiver Operating Characteristic Curve			
The % of change of	β	P	AUC	Std.	P	95% CI
PPBG	0.181	0.154	0.387	0.068	0.085	0.253-0.521
TyG Index	0.080	0.421	0.450	0.061	0.451	0.330-0.571
Triglycerides	0.190	0.137	0.521	0.066	0.755	0.392-0.649
TyG Index-BMI	0.447	< 0.001	0.690	0.061	0.004	0.571-0.806

The multivariate regression revealed that high percentage of change in TyG Index-BMI as the only significant predictor for improved insulin sensitivity and this was assured by its high AUC as shown in (**Table.7 , Fig. 4**).

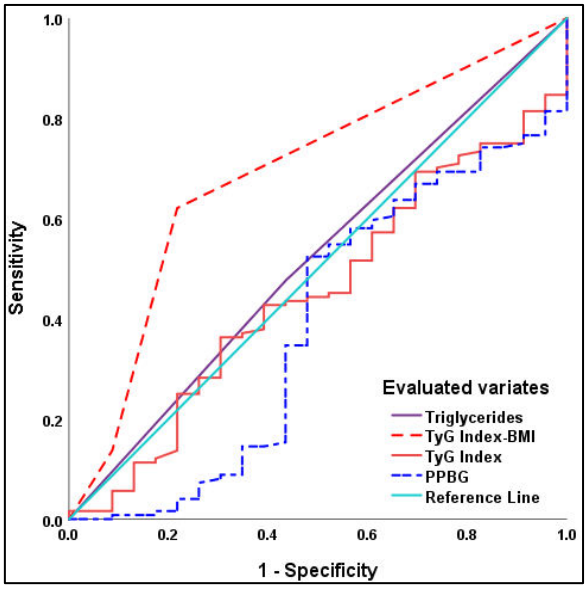

Fig. 4. ROC curve for the percentages of change of lab variates as predictors for improved insulin sensitivity

Discussion

Regarding the metabolic imbalance, both MET and MYO/DCI therapies significantly enhanced body metabolic homeostasis, as shown by the notable reductions in blood glucose, plasma insulin, and triglyceride levels, along with a subsequent decrease in BMI. Additionally, the calculated IR indices improved significantly with both treatments, accompanied by a lower prevalence of IR among these women with PCOS. The TyG Index-BMI emerged as a key predictor for the return of insulin sensitivity, highlighting the connection between high triglyceride and glucose levels, obesity, and their impact on insulin sensitivity. Furthermore, HA improved in both groups on biochemical and clinical levels. Statistical analyses revealed that reductions in HOMA-IR and TyG Index-BMI were major factors driving the restoration of regular menstrual cycles, alongside

biochemical improvements. These metabolic and hormonal changes translated into a significant improvement in menstrual regularity, with 44.6% of women experiencing regular cycles and 20% of women seeking pregnancy becoming pregnant during treatment.

In line with these findings, a recent animal study using a letrozole-induced PCOS model reported the development of IR, abnormal sex and gonadotrophin hormone serum levels, increased cystic follicles, decreased number of the growing follicles and very little or no corpora lutea on microscopic examination and found these effects were reversed by MET and MYO and both drugs were equally effective in improving the reproductive manifestations of PCOS **(Abdelrahman et al., 2024)**.

Also, the obtained results are consistent with the outcomes of systemic reviews for studies that tried MYO, where **Kutenaei et al. (2021)** reported similar effects on PCOS women's hormonal profile and ovarian function with either MYO or MET therapy for PCOS women and attributed improved fertility outcomes with MYO therapy to modulating HA. **Greff et al. (2023)** meta-analysis included 26 randomized controlled studies comparing the effect of MYO versus placebo or MET reported that the risk of having regular menstrual cycle with MYO was 1.79 times higher than placebo and MYO treatment induced greater decrease in BMI, free and total testosterone, androstenedione, glucose and insulin levels with significantly higher levels of sex-hormone-binding globulin (SHBG) compared to placebo and showed non-inferiority compared to MET. Recently, **Lete et al. (2024)** documented the positive results of MYO alone or MYO/DCI combination at a ratio of at least 40:1 for treatment.

In clinical trials, **Hernandez et al. (2021)** using a combination of MYO and α-lactalbumin for PCOS women for 6 months detected a significant effect on HOMA-index, luteinizing hormone (LH), and androstenedione levels in comparison to levels estimated before therapy. Also, **Kachhawa et al. (2022),** in comparison to combined hormonal contraceptives, found MYO/DCI allowed resumption of spontaneous menses in 84.85%, reduction of the mean cycle length with resumption of regular menstrual cycles in 27.27%, and spontaneous cycles continued for three months after stopping the treatment, with reduction of HOMA-IR score with MYO/DCI, but not with contraceptive therapy.

Thereafter, **Nazirudeen et al. (2023)** compared MET as monotherapy versus MET in combination with MYO/DCI for the treatment of PCOS women and reported improved menstrual cycle regularity by both lines of therapy but found the improvement was significantly greater with the combination therapy, while the pregnancy rate showed insignificant difference and concluded that combined MET and MYO/DCI therapy exerts additional benefits in improving menstrual cycle regularity and quality of life of PCOS women. Also, **Unfer et al. (2023)** ensured significant metabolic and endocrine improvements in HA-PCOS women treated with MYO and found that MYO treatment improved endometrial thickness.

Further, **Pustotina et al. (2024)** tried MYO/DCI combination at a 40:1 ratio for the treatment of women who had PCOS phenotype A and reported significant decreases in BMI, HOMA-IR, and numbers of patients who had high plasma insulin levels along with decreased total and free testosterone levels, decreased free androgen index

and LH with increased levels of SHBG and estradiol.

Interestingly, MYO therapy overrides the benefits of MET as an insulin sensitizer as evidenced by the significantly higher percentage of decrease in blood glucose levels and HOMA-IR score. However, its marvelous effect was on the TyG index and the TyG index-BMI combination. Furthermore, these findings indicated a possible role of MYO in the adjustment of lipid metabolism. In line with the effect of MYO on lipid metabolism, **Pan et al. (2022)** detected improved hepatic functions with a reduction of obesity-induced aberrant levels of liver enzymes on MYO supplemental therapy. Also, **Arefhosseini et al. (2023)** found that MYO supplementation could significantly improve anthropometric measures, IR, lipid profile, cardiometabolic factors, and liver function in obese patients with NAFLD.

The effect of MYO on the TyG index and the reported significantly higher percentage of decrease in triglyceride levels after MYO than Met could be attributed to the finding of a previous animal model of PCOS that indicated that MYO therapy most probably reduced weight through increasing serum leptin, which in turn regulated food intake **(Foster et al., 2016)**. Clinically, **Pkhaladze et al. (2021)** reported a significant reduction in weight and BMI in adolescents after three months of MYO therapy, and **Zarezadeh et al. (2022),** in a meta-analysis including 15 controlled clinical trials showed that MYO significantly decreased BMI scores due to improved insulin signaling and sensitivity and found this effect was more clinically pronounced in PCOS participants. Recently, **Rostami et al. (2024)** found MYO therapy significantly reduced the sense of hunger, feeling to eat, and desire to eat sweet and fatty foods with subsequent significant reduction of alteration in lipid profile and BMI.

The beneficial effects of inositol might be attributed, in addition to insulin-sensitizing effects to the improvement of the oxidative milieu with subsequent improved cell vitality **(Pan et al., 2022),** as it was previously documented that MYO plays a role in the activity of the antioxidant system through the PKC/Nrf2 pathways activation in human monocytes **(Jiang et al., 2013)** with significantly increased levels of the antioxidant enzymes and reduction of malondialdehyde and reactive oxygen species production and through increased glucose metabolism through the pentose phosphate pathway with more production of NADPH, which reduces stress in cells, thus maintaining cell health **(Jiang et al., 2014)**.

The reported effect of insulin sensitizers on HA might be attributed to the experimental findings reported by **Zhong et al. (2021),** who using isolated polycystic ovarian thecal tissue, found insulin directly stimulates androgen secretion and induces a greater LH-mediated response than in isolated healthy ovarian tissue and concluded that the coexistence of elevated LH and insulin concentrations leads to a more severe androgen expression, which characterizes PCOS.

Limitations: Estimation of inflammatory biomarkers' serum levels was a limitation of this study to evaluate the effect of the reciprocal relation between obesity and inflammation on ovarian function.

Recommendations: Wider scale studies are required to determine the appropriate cutoff point for TyG index to identify IR patients.

Conclusion

MYO/DCI combination is an effective therapy for PCOS women especially those of obese phenotype. MYO/DCI combination provided a reduction of biochemical and clinical manifestations of HA and allowed the resumption of normal regular menstrual patterns and improved fertility. TyG index-BMI is a good surrogate marker for improved metabolic homeostasis and might be used to assess and follow-up insulin-resistant PCOSs

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