Ameliorative Impact of High Inositol Diet on the Insulin Resistance and Metabolite Hormones among Women with Polycystic Ovary Syndrome

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Abstract:

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy and metabolic condition in women of reproductive age. Inositol was shown to be effective in improving metabolic parameters in PCOS women due to its insulin-sensitizing impact. The current study object to evaluate the impact of high inositol diet to manage insulin resistance of PCOS women. Control clinical trial was conducted on PCOS women that divided into control group (CG) which described for their medication; Inositol diet group (IDG) was preserved on high inositol diet (1500 mg/day per 1800 kcal); Inositol supplement group (ISG) was supplemented with inositol capsule (2 g per day) and kept on high inositol diet. Combined group (IFG) was kept on high inositol diet, inositol capsule supplement and folic acid (400 µg per day), continued for 3 consecutive months. The results indicated that majority of patients had mild degree of hirsutism, and the menstrual cycle occurred three times per year. Androgen hormones decreased significantly at ($P \leq 0.001$) especially in IFG, that have the highest significant ($P \leq 0.001$) impact by means 2.43±0.19 and 56.00±4.27 nmol/L for Total testosterone and sex hormone-binding globulin (SHBG). Luteinising hormone (LH)/follicle stimulating hormone (FSH) ratio was ameliorated significantly ($P \leq 0.001$) that nearest to 1 in IFG, then ISG (1.19±0.18) and IDG (1.36±0.17) compared to CG (2.47±0.34). Glycated hemoglobin A1c (HgA1c) was modulated considerably range between 5.49±0.09 to 4.47±0.36 for IDG and IFG. High density lipoproteins (HDLc) were ameliorated at a high significant value ($P \leq 0.001$) in ISG. In conclusion, the findings proved that dietary management with high inositol

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diet improve insulin resistance and enhanced metabolic hormones of PCOS women.

Key words: hyperandrogenism, folic acid, TSH, lipids, HgAlc.

Introduction

Polycystic ovary syndrome (PCOS) is the most prominent endocrinopathy and metabolic syndrome in premenopausal women of reproductive age, affecting up to 18% of them. (**March *et al*., 2010; Bozdag et al., 2016**). This syndrome should be diagnosed according to the Rotterdam criteria (**NIH, 2012**). "when at least two of the following features are present: I clinical or biochemical hyperandrogenism, (ii) oligo-anovulation, and (iii) polycystic ovaries (**Rotterdam ESHRE/ASRM, 2004**)". PCOS is related to infertility, obesity, dyslipidemia, insulin resistance (IR), hyperinsulinism, and an elevated risk of type 2 diabetes mellites (T2DM), among other reproductive, endocrine, and metabolic characteristics (**Dumesic et al., 2015**). The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) argued that IR is the pathophysiological basis for metabolic syndrome. By the age of 30, 30–50% of obese PCOS women suffer either impaired glucose tolerance (IGT) or (T2DM) (**Diamanti-Kandarakis and Dunaif, 2012; Gambineri et al, 2012**). According to the study of **Apridonidze et al., (2005)** the prevalence of metabolic syndrome in women with PCOS is 2-4 times greater than in the general population, with a prevalence of metabolic syndrome in PCOS women between the ages of 30 and 40 years.

Insulin sensitizing pharmaceuticals like metformin help to normalize the menstrual cycle, which improves hyperandrogenism, resulting the sensitivity to ovulation induction therapy. The efficacy of insulin-sensitizing therapies like metformin, troglitazone, and pioglitazone in enhancing ovulatory function and controlling androgen excess in PCOS supplied more evidence to prove insulin resistance's pathogenic involvement in PCOS. Insulin reduction (**Genazzani et al., 2007**), whether mediated by pancreatic insulin release inhibition (diazoxide or octreotide) or enhanced peripheral insulin sensitivity (metformin, troglitazone, DCI), is proven to reduced

circulating androgens, improved ovulatory function, and increased fertility in women with PCOS. However, adverse effects including as nausea and diarrhea (in the case of metformin) and increased body weight (in the case of pioglitazone) may diminish patient compliance and restrict their usage (**Pasquali and Gambineri, 2006**).

Lifestyle and dietary changes can help to enhance these features to some extent. Inositol, formerly known as vitamin B8, is a vitamin that the human body produces in sufficient amounts from D-glucose. Myo-inositol in its free form, as inositol-containing phospholipids (phosphoinositides), or as phytic acid (inositol hexaphosphate or IP6) can be found in human diets from animal or plant sources (**Holub, 1986**). Myo-Inositol is the most prevalent isomeric form of inositol in living cells and foods, making it a great choice for a dietary approach (**Croze et al., 2013**). Fruits, beans, corn, and nuts are the food groups with the highest content of inositols. Depending on the diet, myoinositol consumption from popular foods can range from 225 to 1500 mg per day per 1800 calories (**Clements and Darnell, 1980**). Furthermore, **Salway et al., (1978)** showed that persistent ingestion of higher levels of myo-inositol would be easier to obtain by food methods than through pharmaceutical administration. In humans, a daily dose of up to 2 g of myo-inositol for a year is safe and well tolerated. When used at doses up to 12 g daily, side effects are modest and mostly gastrointestinal (nausea, flatus and diarrhea) (**Lam et al., 2006; Carlomagno and Unfer, 2011**).

The rationale use of inositols as a therapeutic application in PCOS attribute to the benefits of it as an insulin mimetic (or"insulin sensitizing") agent and their beneficial effects on metabolism, such as lowering postprandial blood glucose levels and stimulating glucose uptake by muscle cells, (**Croze et al., 2015**). Thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and insulin are all tightly controlled by inositol triphosphate, as a second messenger (**Bizzarri and Carlomagno, 2014**). Previous research by **Diamanti-Kandarakis and Dunaif (2012)** evidence that insulin signaling deficit in PCOS might be caused by a malfunction in the inositolphosphate glycan (IPG) insulin second messenger pathway,

which is consistent with IPGs' insulinomimetic role in activating enzymes that govern glucose metabolism (**Cheang et al., 2008**). Also, IPG is involved in several of insulin's activities, and studies have demonstrated that a MYO or DCI deficit can contribute to the development of insulin resistance (**Croze and Soulage, 2013**). Furthermore, inositol administration has been shown to enhance ovulation and spontaneous conception in women with PCOS, as well as lipid profile and body weight (**Minozzi et al., 2013; Unfer et al., 2016**).

There are other interested supplements that support insulin, metabolism and hormones in women with PCOS such as folic acid. Every woman who may get pregnant should take 400 micrograms (400 mcg) of folic acid every day, according to the CDC. Folic acid, a B vitamin, helps to prevent birth abnormalities (**CDC, 2021**). According to **Tafazoli et al., (2016)**, women with functioning ovarian cysts consume much more folate. Furthermore, **Regidor et al. (2018)** shown that daily folic acid supplementation is a potential approach for improving symptoms and infertility in individuals with polycystic ovarian syndrome (PCOS). Therefore, the current study aims to evaluate the effectiveness of high inositol diet and dietary myo-inositol supplementation plus folic acid to manage insulin resistance and improving metabolic hormones of women with PCOS.

2. Patients and Methods

2.1. Ethical approval

This clinical trial was conducted after approval by the Institutional Review Board (IRB) at Imam Abdulrahman Bin Faisal University. All participants signed the informed written consent form before they enroll into the study.

2.2. Recruiting patients

Randomized control clinical trial was conducted on sixty women aged from reproductive age to 45 years suffering from PCOS complicated with insulin resistance. They will be recruited from the Obstetrics and Gynecology Clinic of the Family Medicine and Community Center

(FAMCO), Imam Abdulrahman Bin Faisal University, Eastern Province, Dammam, KSA. The diagnosis of PCOS will be definite under the supervision of consultant according to the revised Rotterdam criteria (**Rotterdam ESHRE/ASRM, 2004**), that require the presence of two of the clinical and biochemical signs of oligo/anovulation, hyperandrogenism, and polycystic ovaries by gynecological ultrasound; and androgen excess and PCOS society in 2009 require that it must be had characteristic A plus either B or C (**Teede, 2012**).

Figure 1. Criteria for diagnosis of PCOS

Clinical finding	National Institutes of Health Criteria, 1990 (must have both of the findings marked below)	Rotterdam criteria, 2003 (must have any two of the findings marked below)	Androgen Excess and PCOS Society, 2009 (must have A plus either B or C)
Hyperandrogenism*	×	×	A
Oligomenorrhea	×	×	B
Polycystic Ovaries		×	C

PCOS = Polycystic Ovary syndrome. *Clinical or Biochemical evidence of excess androgen. Reference of the criteria of diagnosis of PCOS (**Legro et al., 2013**).

Inclusion criteria: PCOS women diagnosed on the basis of the Rotterdam criteria (menses failure "<8 menstrual periods per year", or amenorrhea, hirsutism), laboratory confirmation of excess of androgen, oligo-ovulation and anovulation and polycystic ovaries on sonography, also index of homeostatic model assessment for insulin resistance (HOMA-IR) was less than >2.5 (**Kumarapeli et al., 2008; Balen et al., 2003**).

Exclusion criteria include patients with a past history of thyroid disease (hypothyroidism), diabetes mellitus, or other causes of hyperandrogenism or infertility, such as congenital adrenal hyperplasia, Cushing's syndrome, or other endocrine diseases, and endometriosis, also who using oral contraceptive pills, or any, who exposed lifestyle modification intervention, nutritional supplement and multi vitamin-mineral consumption at least 3 months prior to this study will be excluded.

2.3. Folic acid supplementation

The use of 400 µg folic acid per day is a safe and promising tool in the effective improvement of symptoms and infertility for patients with polycystic ovary syndrome (PCOS) (**Regidor et al., 2018**).

2.4. Protocol of planning high inositol diet

The total myo-inositol content of foodstuffs will be selected from the diabetic exchange lists of the American Diabetes Association that expressed on the basis of weight as well as the amount present in a typical serving of the individual food (**Exchange Lists for Meal Planning, 1976**). The actual determination of the myo-inositol content of these diets was performed by gas-liquid chromatography as described by **Rex et al., (1980)**. The diets will be planned according to the food exchange lists of the American Diabetes Association, and the intake of myo-inositol will be estimated in the present study to achieve 1600 to 2000 mg daily for diet containing 2000 kcal. The greatest amounts of myoinositol in common foods are found in fresh fruits and vegetables, and in all foods containing seeds (beans, grains and nuts), especially high phytic acid contents that found in almonds, walnuts and Brazil nuts (9.4, 6.7 and 6.3% of dry weight, respectively) (**Schlemmer et al., 2009**), also oats and bran contain more myo-inositol than cereals derived from other grains. Among the vegetables, the highest contents were observed in the beans and peas. Fresh vegetables were found to have higher myo-inositol contents than frozen, canned, or salt- products. while leafy vegetables being the poorest vegetable sources. Among the fruits, cantaloupe and the citrus fruits (with the exception of lemons) were found to have extraordinarily high contents of myo-inositol: for example, a portion of grapefruit juice (120 g) contains about 470 mg of myo-inositol. Whole grain breads were found to contain more myo-inositol than refined breads, while among the cereals, oats and bran contained more of this material than did cereals derived from other grains. However, beans and peas tended to be high, whereas carrots and corn were low in their content of this material. It appears that foods consist of seeds (beans, grains, and nuts) provide the most concentrated sources of dietary myo-inositol, while most other foods

contain rather modest amounts of this material (**Clements and Darnell, 1980**).

2.5. Study design

Sixty PCOS women will be divided randomly into four subgroups (fifteen for each):

- **Group 1** (Control group "CG"): PCOS patients was described for their medication "metformin" at dose 500 mg three times daily during the main meal of the day and follow their regular diet without any dietary intervention or supplementation (**Lashen, 2010**).
- **Group 2** (Inositol diet group "IDG"): PCOS patients was modulated their diet to be preserved on high inositol diet (1600 to 2000 mg/day per 1800 kcal) according to Clements and Darnell, (1980).
- **Group 3** (Inositol supplement group "ISG"): PCOS patients was supplemented with inositol capsule (2 g per day) also kept on high inositol diet.
- **Group 4** (Combined group "IFG"): PCOS patients was kept on combined dietary intervention with high inositol diet, inositol supplement and folic acid (400 μg per a day). The study of dietary intervention and supplementation was continued for 3 consecutive months.

2.6. Study parameters

Socio-demographic data will be obtained from the medical records that were systematically recorded at the first clinical visit.

2.6.1. Classification of PCOS symptoms

a. Oligomenorrhea was termed if a woman reports the length of menstrual cycle greater than 35 days or four to nine menstrual cycles in a year as defined by **Riaz and Parekh, (2021)**.

b. The Ferriman-Gallwey scale for hirsutism.

The patients were assessed for the degree of hirsutism using the Ferriman-Gallwey Score>8.

A score is given for nine areas of the body. A total score less than 8 is considered normal, a score of 8 to 15 indicates mild hirsutism, and a score greater than 15 indicates moderate or severe hirsutism. A score of 0 indicates absence of terminal hair (**Martin et al., 2008**).

c. Stage of androgenetic alopecia (AGA)

The Ludwig scale (L) is a method of classifying female pattern of hair loss (FBHL) and severity of androgenic alopecia (AGA) according to **Drake et al., (1996); Piraccini and Alessandrini, (2014)**. It ranges from stages I to III. Stage I begins with thinning on the top of the head. In stage II the scalp starts to show. All of the hair at the crown of the head may be lost when the hair loss progresses to stage III.

d. Degree of Acne

The severity of acne was categorized according to Franik et al., (2018) as:

- **Mild** mostly whiteheads and blackheads, with a few papules and pustules.
- **Moderate** more widespread whiteheads and blackheads, with many papules and pustules.
- **Severe** lots of large, painful papules, pustules, nodules or cysts; might also have some scarring.

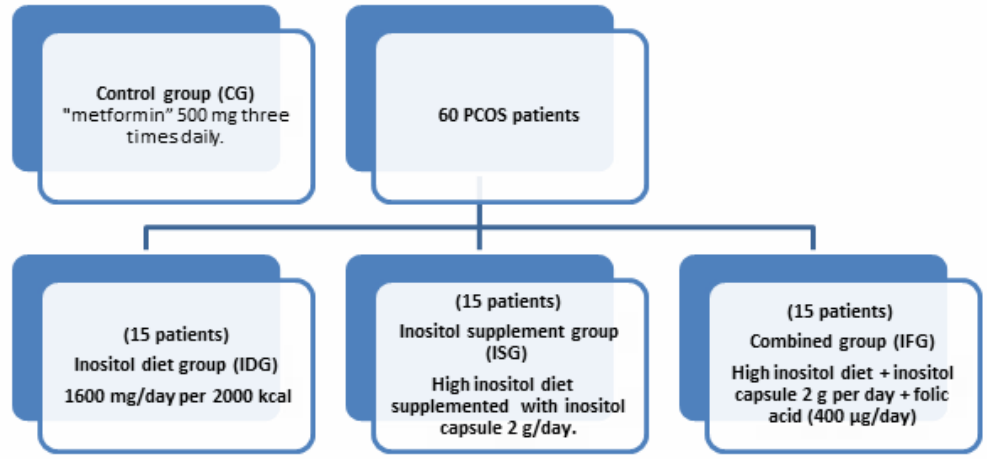

Figure 2. Flow chart of the study design

2.6.2. Anthropometric measurements

Body weight, height, and BMI will be calculated [BMI = body weight (kg)/height (m^2)] **(WHO, 2004).** Waist circumference and waist to hip ratio was estimated at the baseline and after the dietary intervention according to (**WHO, 2008**). Health risks of WHR for female are low (lower than 0.80), moderate (0.81 – 0.85), or high (more than 0.86).

2.6.3. Biochemical indicators

2.6.3.1. Characteristics of menstrual cycles (Hormonal profiles)

PCOS patients' blood samples was collected independent of the day of menses because of irregularity in menstrual cycle. Endocrine and metabolic parameters (LH, FSH), androgens (total testosterone) was estimated in all patients pre and post dietary intervention.

- **Total testosterone** (T.testosterone) was assessed according to **CLIA, (1988)**, the best time to have the test is in the morning when testosterone levels in the blood are usually highest (**CDC, 2012**).
- **Sex hormone-binding globulin (SHBG)** was estimated according to **AACC, (2018)**; the normal value of SHBG for adult premenopausal female is 40–120 nmol/L as referenced in the study of **Zhu et al., (2019)**.
- **Free androgen index (FAI)** is a ratio used to determine abnormal androgen status in humans. The ratio is the total testosterone level divided by the sex hormone binding globulin (SHBG) level, and then multiplying by a constant, usually 100; according to the following equation as mentioned in **Wilke and Utley, (1987)**:

$$\mathrm{FAI} = 100 \times \left(\frac{\text{total testosterone}}{\mathrm{SHBG}} \right)$$

- **Follicle stimulating hormone (FSH) and luteinising hormone (LH)** were determined according to **Pritchard et al., (1995)**. FSH for women who are still menstruating was between (3 to 10 IU/L) (**Jeelani and Bluth, 2022**). Normally this ratio is about 1:1, meaning

the FSH and LH levels in the blood are similar as mentioned by **Saadia, (2020)**.

- **Thyroid-stimulating hormone (TSH)**

Most laboratories classify normal TSH levels equivalent to 0.4 and 4.5 milliunits per liter (mU/L), according to the American Thyroid Association (ATA).

2.6.3.2. Blood glucose and Homeostatic model assessment

Fasting blood glucose (FBG) **Trinder, (1969)** and insulin (FBI) were estimated after 12-hour overnight fasting (**Chevenne et al., 1999**). The following formulae, HOMA-IR = (FBI (mU/l) × FBS (mmol/l))/22.5 was used to determine HOMA IR as a way to assess insulin resistance as another index of insulin sensitivity (**Matthews et al., 1985**). IR was assessed by the homeostasis model assessment score.

HOMA-IR (homeostasis model assessment for insulin resistance) = fasting serum insulin

(microinternational units per mL) × fasting serum glucose (mmole/L) / 22.5 (**Radziuk, 2000**).

Glycosylated hemoglobin HbA1c was assessed using the immunoturbidimetric determination by using Roche Cobas Integra 400 plus autoanalyzer (Roche, Mannheim, Germany) according to the method of **Peacock, (1984)**. The normal range is between 4% and 5.6%. Hemoglobin A1c levels between 5.7% and 6.4% mean you have prediabetes and a higher chance of getting diabetes. Levels of 6.5% or higher means inducing diabetes.

2.6.3.3. Lipid profile

Enzymatic calorimetric determination of triglycerides will be carried out according to **Fossati, (1982).** Total cholesterol will be determined according to **Allain, (1974)**, while HDL according to **Lopez, (1977).** The determination of VLDL (very low density lipoproteins) and LDL were carried out according to the method of **Lee and Nieman, (1996)** as

calculation follows: VLDL (mg/dl) = Triglycerdes/5. LDL (mg/dl) = (Total cholesterol – HDL) – VLDL.

2.6.4. Nutritional assessment

All Participants was interviewed to estimate the dietary intake of the patients, three 24-hour dietary recall form (two weekdays and a weekend) were filled for each patient and control. Nutritive value of the consumed foods and planned high inositol diet were analyzed using computerized software Nutritionist Program, "EISHA software" to assess the intake of dietary inositol and other nutrients **(Magkos et al., 2006)**.

2.7. Statistical analysis

Statistical analysis will be performed using the Statistical Package for Social Sciences Software (SPSS V.23) (IBM.com). Quantitative data will be expressed as mean ± SD, and compared using one-way analysis of variance (ANOVA) (or covariance as appropriate) to detect differences between groups. Pearson correlation test will be conducted among variables for each experimented group. The significance levels will be tested at $p \leq 0.05$.

Results

Clinical features of hyperandrogenism depicts in table 1. In women with PCOS, hyperandrogenism manifests clinically as oligomenorrhea and hirsutism. The menstrual cycle of most women with PCOS occurred three times per year, with 40% in IFG and 33.3 % in CG or ISG. Otherwise, it eventuated four times per year by 33.3% and fifth times by 40% in IDG. The majority of patients had mild degree of hirsutism, with 93.3% to 80% in CG and ISG respectively also 100% existed in IFG. Other manifestations like acne, and androgenic alopecia are signed by increasing androgen excess. Nearly half of PCOS women in CG existed in stage III of androgenetic alopecia by 53.3%, with another 33.3% was situated in each IDG or IFG. Furthermore, 33.3% of participants in IGD, ISG and IFG existed in stage IV. Moreover, most women with PCOS manifested moderate degree of acne by 60% in IFG and 53.5% in CG, IDG or ISG.

Regarding to anthropometric measurements, android obesity is a common feature and this abdominal adiposity may be related to the syndrome's complications in PCOS patients as illustrated in table 2. The mean age of patients with PCOS who participate in the study was ranged between 30.31±4.43 to 31.78±4.67 in ISF and IDG respectively. After nutritional management with inositol and folic supplementation, body weight differed significantly at (P≤0.001) among PCOS patients from 67.20±5.12 to 58.31±3.85 with BMI 27.79±1.44 to 24.11±0.88 (kg/m^2) for IFG, while patients' group who administered high inositol diet only (IDG), the weight was decreased significantly at (P≤0.01) (72.52±5.67 vs. 67.74±4.19 kg) and BMI (31.03±2.35 vs. 28.98±1.61 kg/m^2). furthermore, waist and hip circumference differed significantly at (P≤0.01) after dietary intervention among all experimental groups in particular IFG with mean values ranged (109.83±3.55 vs 92.78±2.29) and (118.50±2.45 vs 109.31±2.05) respectively. For WHR, ISG and IFG decreased significantly (P≤0.01) after dietary supplementation by means 0.83±0.02 and 0.85±0.03 respectively, although it did not change considerably in IDG as well as CG either before or after dietary intervention.

Table 1. Symptoms of PCOS among participants

		CG		IDG		ISG		IFG	
		Freq.	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**
***Oligomenorrhea**	Once	1	6.7	--	--	--	--	1	6.7
	Twice	1	6.7	--	--	4	26.7	2	13.3
	Third times	5	33.3	4	26.7	5	33.3	6	40
	Fourth times	5	33.3	5	33.3	3	20	4	26.7
	Fifth times	3	20	6	40	3	20	2	13.3
	*Sig.	0.255		0.819		0.865		0.255	
Degree of hirsutism (times per year)	Normal= less than 8	--	--	--	--	1	6.7	--	--
	Mild ≤ 8 to ≥ 15	14	93.3	13	86.7	12	80	15	100
	Moderate = More than 15	1	6.7	2	13.3	2	13.3		
	*Sig.	0.001		0.005		0.001		--	
Stage of androgenetic alopecia	Stage II	1	6.7	2	13.3	2	13.3	3	20
	Stage III	8	53.3	5	33.3	4	26.7	5	33.3
	Stage IV	4	26.7	5	33.3	5	33.3	5	33.3
	Stage V	2	13.3	3	20	4	26.7	2	13.3
	*Sig.	0.053		0.616		0.737		0.615	
Degree of acne	Mild	4	26.7	4	26.7	4	26.7	3	20
	Moderate	8	53.3	7	46.64	8	53.3	9	60
	Severe	3	20	4	26.70	3	20	3	20
	*Sig.	0.247		0.236		0.247		0.091	

CG: Control group; IDG: Inositol diet group; ISG: Inositol supplement group; IFG: Inositol and folic acid supplement group. *Oligomenorrhea: when menstruation cycle event four to nine times in a year (**Riaz and Parekh, 2021**).

Table 2. Effect of high inositol diet and dietary supplementation on anthropometric measurements among women with polycystic ovary syndrome

Parameters		CG	IDG	ISG	IFG	P -value
Age		31.27±4.35[a]	31.78±4.67[a]	30.31±4.43[a]	31.05±3.87[a]	0.729
Height (cm)		1.55±0.36[a]	1.52±0.03[a]	1.54±0.04[a]	1.55±0.05[a]	0.162
Weight	Pre	72.75±4.80[a]	72.52±5.67[a]	76.29±2.37[b]	67.20±5.12[c]	0.000***
	Post	73.42±6.98[a]	67.74±4.19[b]	65.71±3.37[b]	58.31±3.85[c]	0.000***
Sig.		0.449	0.001**	0.000***	0.000***	
BMI	Pre	30.07±1.66[a]	31.03±2.35[ab]	32.23±1.44[b]	27.79±1.44[c]	0.000***
(kg/m^2)	Post	30.34±2.61[a]	28.98±1.61[b]	27.74±1.45[b]	24.11±0.88[c]	0.000***
Sig		0.455	0.001**	0.000***	0.000***	
Waist circ.	Pre	108.38±4.12[ab]	108.10±4.14[ab]	106.64±4.02[a]	109.83±3.55[b]	0.194
(cm)	Post	107.96±4.92[a]	101.22±3.59[b]	93.23±1.87[c]	92.78±2.29[c]	0.000***
Sig.		0.322	0.000***	0.000***	0.000***	
Hip Circ.	Pre	120.36±2.91[a]	118.82±2.97[ac]	117.65±3.35[bc]	118.50±2.45[ac]	0.095
(cm)	Post	119.20±2.76[a]	112.24±2.22[b]	111.87±2.33[b]	109.31±2.05[c]	0.000***
Sig.		0.003	0.000***	0.000***	0.000***	
WHR	Pre	0.90±0.03[a]	0.91±0.02[ab]	0.90±0.02[a]	0.92±0.03[b]	0.079
	Post	0.90±0.04[a]	0.90±0.03[a]	0.83±0.02[b]	0.85±0.03[b]	0.000***
Sig.		0.492	0.388	0.000***	0.000***	

CG: Control group; IDG: Inositol diet group; ISG: Inositol supplement group; IFG: Inositol and folic acid supplement group. BMI: Body mass index; WHR: Waist hip ratio. The significant differences are considered at the levels 0.05 (*), 0.01 (**), & 0.001 (***).

The metabolite hormones that benefit for diagnosing if there is hyperandrogenism in women with polycystic ovary syndrome were illustrated in table 3. Total testosterone was elevated among PCOS women's ranged between 4.60±0.48 to 4.84±0.41 (nmol/L) for CG and IDG, while it was decreased significantly at ($P \leq 0.001$) after following high inositol diet and supplements by means 3.03±0.43 and 2.43±0.19 for ISG and IFG, respectively. Other blood tests that can be useful in identifying high androgen levels is sex hormone-binding globulin (SHBG); it was diminished among PCOS women before dietary intervention ranged between 17.26±3.05 in CG, and 19.96±4.57 in IFG, however this group

have the highest significant impact (P≤0.001) after administering inositol and folic acid at mean 56.00±4.27 nmol/L. A ratio used to determine abnormal androgen status in humans is FAI, it was ameliorated significantly (P≤0.001) among experimental groups that followed high inositol diet and supplementation in particular IFG, then ISG and IDG by values 4.36±0.51, 6.98±1.27, and 9.95±1.88 respectively. Regarding to

Table 3. Effect of high inositol diet and dietary supplementation on the metabolite hormones among women with polycystic ovary syndrome

Parameters		**CG**	**IDG**	**ISG**	**IFG**	**P -value**
T.Testosterone	Pre	4.60±0.48^{a}	4.84±0.41^{a}	4.70±0.44^{a}	4.82±0.38^{a}	0.403
(0.5 to 2.4 nmol/L)	Post	4.82±0.38^{a}	3.79±0.58^{b}	3.03±0.43^{c}	2.43±0.19^{d}	0.000
Sig.		0.027	0.000	0.000	0.000	
***SHBG**	Pre	17.26±3.05^{a}	19.29±4.76^{a}	18.03±2.91^{a}	19.96±4.57^{a}	0.238
(40–120 nmol/L)	Post	18.10±3.01^{a}	38.51±3.68^{b}	43.86±2.85^{c}	56.00±4.27^{d}	0.000
Sig.		0.221	0.000***	0.000***	0.000***	
FAI	Pre	27.66±6.68^{a}	26.20±5.33^{a}	26.59±4.18^{a}	25.21±5.43^{a}	0.678
	Post	27.48±5.70^{a}	9.95±1.88^{b}	6.98±1.27^{c}	4.36±0.51^{d}	0.000***
Sig.		0.882	0.000***	0.000***	0.000***	
FSH	Pre	4.85±0.43^{ab}	5.45±0.81^{bc}	5.07±0.70^{abc}	5.40±0.80^{bc}	0.070
(0.3 to 10.0 IU/L)	Post	4.95±0.30^{a}	6.88±0.87^{b}	6.90±1.12^{b}	7.78±0.62^{c}	0.000******
Sig		0.392	0.000***	0.000***	0.000***	
LH	Pre	11.27±1.37^{ac}	12.49±1.34^{bc}	11.45±1.44^{ac}	12.01±1.40^{ac}	0.078
(in midcycle peak)	Post	12.20±1.52^{a}	9.34±1.18^{b}	8.21±1.63^{c}	6.90±0.86^{d}	0.000***
Sig.		0.122	0.000***	0.000***	0.000***	
LH/FSH ratio	Pre	2.33±0.27^{a}	2.31±0.31^{a}	2.27±0.29^{a}	2.25±0.37^{a}	0.905
	Post	2.47±0.34^{a}	1.36±0.17^{b}	1.19±0.18^{c}	0.88±0.09^{d}	0.000***
Sig.		0.284	0.000***	0.000***	0.000***	
****TSH**	Pre	2.38±0.34^{a}	2.91±0.47^{b}	2.51±0.42^{b}	2.80±0.56^{b}	0.007*
(mlU/L)	Post	2.86±0.45^{a}	1.45±0.22^{b}	1.14±0.17^{c}	0.59±0.14^{d}	0.000******
Sig.		0.011	0.000***	0.000***	0.000***	

CG: Control group; IDG: Inositol diet group; ISG: Inositol supplement group; IFG: Inositol and folic acid supplement group. T.Testosterone: total testosterone; SHBG: sex hormone binding globulin; FAI: Free Androgen Index; FSH: follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid Stimulating *Hormone* ; nmol/L: nanomoles per liter; IU/L:international units per liter;

mlU/mL (milli-international units per milliliter. *SHBG for adult premenopausal female is 40–120 nmol/L (**Zhu et al., 2019**), **Target TSH levels accepted from 0.4 to 4.5 mU/L according to **AACE**. The significant differences are considered at the levels 0.05 (*), 0.01 (**), & 0.001 (***).

gonadotropins hormones (FSH and LH) that stimulate the ovaries in females, FSH has slight increase in IFG (7.78±0.62 IU/L), while there was non-significant between IDG and ISG, also LH was decreased significantly (P≤0.001) when compared to CG at values 6.90±0.86 and 12.20±1.52 respectively. LH/FSH ratio was differed significantly among all studied groups after dietary intervention, the best impact was found in IFG that nearest to 1, then ISG (1.19±0.18) and IDG (1.36±0.17) compared to CG (2.47±0.34). Likewise, women with PCOS are more likely to be obese or overweight, which may be due to their higher baseline TSH levels ranged between 2.38±0.34 in CG to 2.91±0.47 in IDG. After therapeutic nutrition, it was diminished at higher significant influence (P≤0.001) in IFG 0.59±0.14 mlU/L, while ISG and IDG were 1.14±0.17 and 1.45±0.22 mlU/L vs to CG (2.86±0.45 mlU/L).

In most, if not all, instances of PCOS, insulin resistance is one of the underlying metabolic abnormalities. The significantly higher prevalence of glucose intolerance in PCOS can be attributed to these anomalies, as well as obesity as revealed in table 4. The results found that blood glucose biomarkers and insulin profiles were differed and modulated considerably. FBG was decreased significantly (P≤0.001) after dietary management, the lowest group is IFG, then ISG and IDG by means 113.42±9.36, 127.86±8.30 and 137.97±17.08 mg/dL. Fasting blood insulin was ameliorated significantly (P≤0.001) from 28.89±2.09 to 17.67±2.01 in IFG compared to CG from 28.21±1.52 to 28.70±2.17. Consequently, HOMA-IR was controlled extremely at (P≤0.001) in all treated groups with high inositol diet and supplementation by means 1.55±0.21, 1.31.27±12.93, and 0.88±0.11 against 2.57±0.51 of CG. Moreover, HgA1c has been modified to normal range between 5.49±0.09 to 4.47±0.36 after dietary management vs 5.81±0.35 to 5.90±0.21 before intervention for IDG and IFG respectively when compared to CG (6.05±0.28 vs 5.99±0.29), with highly significant difference at (P≤0.001).

Table 4. Effect of high inositol diet and dietary supplementation on the insulin resistance among women with polycystic ovary syndrome

Parameters		CG	IDG	ISG	IFG	P -value
***FBG (mg/dL)**	Pre	206.84±47.10[a]	215.93±42.01[a]	202.17±45.90[a]	195.48±34.06[a]	0.611
	Post	202.81±42.24[a]	137.97±17.08[b]	127.86±8.30[bc]	113.42±9.36[c]	0.000***
Sig		0.763	0.000***	0.000***	0.000***	
***Fasting blood insulin** (<25mlU/L)	Pre	28.21±1.52[a]	28.43±1.99[a]	29.06±2.65[a]	28.89±2.09[a]	0.660
	Post	28.70±2.17[a]	25.40±1.12[b]	23.09±1.64[c]	17.67±2.01[d]	0.000***
Sig		0.510	0.000***	0.000***	0.000***	
HOMA-IR (≤2.5)	Pre	2.61±0.67[a]	2.72±0.51[a]	2.60±0.57[a]	2.51±0.48[a]	0.791
	Post	2.57±0.51[a]	1.55±0.21[b]	1.31±0.12[c]	0.88±0.11[d]	0.000***
Sig		0.832	0.000***	0.000***	0.000***	
HgA1c 4-5.6%	Pre	6.05±0.28[a]	5.81±0.35[b]	6.04±0.33[ac]	5.90±0.21[ab]	0.092
	Post	5.99±0.29[a]	5.49±0.09[b]	5.13±0.22[c]	4.47±0.36[d]	0.000***
Sig		0.590	0.003**	0.000***	0.000***	

CG: Control group; IDG: Inositol diet group; ISG: Inositol supplement group; IFG: Inositol and folic acid supplement group. FBG: Fasting Blood glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; HbA1c: Glycated hemoglobin A1c; mcIU/mL: Micro-International Unit per milliliter; *Reference Range of insulin fasting <25 mIU/L (2.6 - 24.9 mcIU/mL). *A HOMA-IR value of 2.5 is taken as an indicator of IR in adults (**Muniyappa et al., 2008**). The significant differences are considered at the levels 0.05 (*), 0.01 (**), & 0.001 (***).

As shown in table 5, there is a significant decline in the lipid profiles of women with polycystic ovarian syndrome. IFG had the greatest influence (P≤0.001) on TG and TC by mean (247.48±8.94 vs 166.94±4.03 mg/dL) and (185.27±8.48 vs 129.76±4.03) before and after dietary intervention respectively. HDLc was ameliorated at a high significant value (P≤0.001) in particular ISG and IFG with no significant difference between them by means of 49.85±4.34 and 52.61±5.72 respectively. There is a significant difference between experimental groups in LDLc and VLDL at (P≤0.001), with IFG having the least means of 95.27±6.44 and 19.05±1.82 mg/dl respectively, compared to CG (175.96±8.91 and 35.93±1.39 mg/dl).

Table 5. Effect of high inositol diet and dietary supplementation on the lipid profiles among women with polycystic ovary syndrome

Parameters		CG	IDG	ISG	IFG	P -value
TC	Pre	247.14±12.19[a]	248.59±7.90a	248.64±8.89[a]	247.48±8.94[a]	0.962
	Post	246.11±7.88[a]	188.48±4.62[b]	181.13±3.62[c]	166.94±4.03[d]	0.000***
Sig.		0.803	0.000***	0.000***	0.000***	
TG (Less than 150 mg/dL)	Pre	190.52±5.25[a]	181.56±5.60[b]	185.27±8.48[b]	181.41±5.94[b]	0.001**
	Post	179.68±6.95[a]	151.92±4.79[b]	129.76±4.03[c]	95.28±9.14[d]	0.000***
Sig.		0.000***	0.000***	0.000***	0.000***	
HDLc (More than 40 mg/dL)	Pre	32.12±3.25[a]	34.45±3.34[b]	32.86±3.02[ab]	32.60±3.07[ab]	0.220
	Post	34.21±2.97[a]	44.70±1.63[b]	49.85±4.34[c]	52.61±5.72[c]	0.000***
Sig.		0.108	0.000***	0.000***	0.000***	
LDL (mg/dL)	Pre	176.91±13.41[a]	177.82±8.60[a]	178.73±8.88[a]	178.59±8.61[a]	0.958
	Post	175.96±8.91[a]	113.40±5.51[b]	105.33±5.75[c]	95.27±6.44[d]	0.000***
Sig		0.836	0.000***	0.000***	0.000***	
VLDLc (mg/dL)	Pre	38.10±1.05[a]	36.31±1.12[b]	37.05±1.69[b]	36.28±1.18[b]	0.001**
	Post	35.93±1.39[a]	30.38±0.95[b]	25.95±0.81[c]	19.05±1.82[d]	0.000***
Sig.		0.000***	0.000***	0.000***	0.000***	

CG: Control group; IDG: Inositol diet group; ISG: Inositol supplement group; IFG: Inositol and folic acid supplement group. TG: Triglycerides; TC: T. Cholesterol; HDLc: High density lipoproteins; LDLc: Low density lipoproteins; VLDLc: Very low density lipoproteins. The significant differences are considered at the levels 0.05 (*), 0.01 (**), & 0.001 (***).

As shown in table 6, the nutritional intake of PCOS women did not differ significantly between the study groups before the dietary intervention, as it is unbalanced and disproportionate. Before dietary intervention, the total energy and fat intake were greater than the nutritional requirements, reach to 2592.40±138.11 kcal/day and 74.08±5.38 in ISG. But the protein intake is less than the daily recommendations range between 49.23±6.41 to 59.24±10.69 in IDG and IFG, respectively. With the nutritional intervention, balanced meals were planned based on the needs of total energy and nutrients of participants, so there are high significant differences ($P \leq 0.001$) between the control group and the study groups, value means was ranged (1966.83±138.2, 73.75±5.18 and 74.08±5.38) for IFG of energy, protein and fat respectively. While the intake of carbohydrates did not differ significantly before and after the dietary intervention, with average values ranging between 295.02±20.74 to 315.42±44.60 for ISG and CG

respectively. Regarding the intake of inositol, less than half of the recommendations among all cases of affected PCOS women, for example, the average intake of the control group was 413.39±123.21 mg/day. On the contrary, after the nutritional intervention, the intake of study groups, especially supplemented groups ISG and IFG, were increased with a high significant difference (P≤0.001) by means 1900.66±187.69 and 1902.81±126.87 mg/day compared to the control group 453.70±160.26 mg/day. Similarly, the intake of folic acid increased after the dietary intervention, especially for group IFG, with an average of 434.40±40.52 mg/day, compared to the control group 241.80±50.34 mg/day.

Table 6. The dietary intake of macronutrients, inositol and folic acid among women with polycystic ovary syndrome

Parameters		**CG**	**IDG**	**ISG**	**IFG**	**P -value**
Energy (kcal/day)	Pre	2548.56±141.19^{ab}	2549.28±93.20^{ab}	2592.40±138.11^{a}	2486.62±130.02^{b}	0.165
	Post	2642.79±115.49^{a}	2069.42±139.68^{b}	1966.83±138.28^{c}	2035.71±159.79^{bc}	0.000***
Sig.		0.131	0.000***	0.000***	0.000***	
Protein (g/day)	Pre	56.05±6.87^{a}	49.23±6.41^{b}	55.01±9.13^{ab}	59.24±10.69^{a}	0.018
	Post	54.85±2.78^{b}	75.85±6.45^{a}	73.75±5.18^{a}	75.84±6.53^{a}	0.000***
Sig.		0.524	0.000***	0.000***	0.000***	
Fat	Pre	70.08±5.32^{a}	68.01±7.61^{b}	74.08±5.38^{a}	72.55±6.03^{a}	0.046
	Post	68.21±4.52^{a}	62.18±5.19^{b}	54.63±3.84^{c}	56.17±4.84^{c}	0.000***
Sig.		0.269	0.007***	0.000***	0.000***	
Carbohydrates	Pre	334.73±36.29^{a}	309.56±36.20 ^{a}	536.07±851.05 ^{a}	316.32±22.42 ^{a}	0.413
	Post	315.42±44.60 ^{a}	303.41±25.81 ^{a}	295.02±20.74 ^{a}	303.35±26.13 ^{a}	0.348
Sig		0.275	0.620	0.287	0.193	
Inositol	Pre	413.39±123.21 ^{a}	456.30±154.18 ^{a}	456.55±147.89 ^{a}	437.67±160.83 ^{a}	0.834
	Post	453.70±160.26^{b}	1876.77±102.43 ^{a}	1900.66±187.69 ^{a}	1902.81±126.87 ^{a}	0.000***
Sig.		0.485	0.000***	0.000***	0.000***	
***Folic acid** (mcg)	Pre	220.12±39.55 ^{a}	216.16±33.08 ^{a}	205.13±39.33 ^{a}	225.40±65.73 ^{a}	0.671
	Post	241.80±50.34^{b}	412.18±33.75 ^{a}	424.57±35.03 ^{a}	434.40±40.52 ^{a}	0.000***
Sig.		0.197	0.000***	0.000***	0.000***	

CG: Control group; IDG: Inositol diet group; ISG: Inositol supplement group; IFG: Inositol and folic acid supplement group.

*The recommended daily amount of folate for adults is 400 micrograms (mcg) according to DRIs, (2005). The significant differences are considered at the levels 0.05 (*), 0.01 (**), & 0.001 (***).

Discussion

The most frequent cause of ovulatory dysfunction is polycystic ovary syndrome (PCOS), which impacts more than 7% of women of reproductive age (**Merviel et al., 2017**). Insulin resistance and hyperandrogenism worsen polycystic ovarian syndrome (PCOS) in 30 to 40% of women (**Chiu et al., 2002**). Hyperglycemia reduces hepatic synthesis of Sex Hormone Binding Globulin (SHBG), resulting in an increase in free androgens in the bloodstream, whereas insulin resistance boosts androgen production by the theca cells. Obesity-related insulin resistance changes the function of the hypothalamus and pituitary gland in the brain, boosting the production of androgenic hormones that contribute to PCOS, according to a review by **Moghetti, (2016)**. The regulation of insulin resistance is therefore essential in the therapy of PCOS, and it is based on dietary changes as well as other molecules like myo-inositol (MI), which is a natural insulin sensitizer. Only in situations of glucose intolerance and type 2 diabetes mellitus can insulin-sensitizing drugs like metformin be prescribed (**Merviel et al., 2021**).

The goal of this study was to see if a high-inositol diet combined with dietary myo-inositol supplementation and folic acid may help women with PCOS regulate their insulin resistance and improve their metabolic hormones.

The results of this study showed the clinical features of PCOS as depicts in table 1, and found that the menstrual cycle of most women with PCOS occurred three times per year, also majority of patients had mild degree of hirsutism, and nearly half of PCOS women in CG existed in stage III of androgenetic alopecia (AGA). In the same pattern the findings of **Kartal et al., 2016** proved a relation between IR and AGA in female patients, who showed that the association of AGA and IR is independent of hyperandroccgenemia.

The findings of present study showed that abdominal adiposity is a common feature in PCOS patients, and this abdominal adiposity may be linked to the syndrome's complications; these findings were consistent with

those of **Yildiz et al., (2008)**, who found that the prevalence of PCOS is higher in overweight and obese women compared to their lean counterparts. Obesity is well recognized as a contributing factor in the development of PCOS, as demonstrated in the research of **Diamanti-Kandarakis, (2007)**. Particularly the abdominal phenotype (central obesity) may be responsible for IR and related hyperinsulinemia in women with PCOS (**Chen et al., 2010; Dudeja et al., 2001**). Insulin resistance might exacerbate hyperandrogenism in the long run; the main characteristics of PCOS listed by (**Mohan and Dasgupta, 2008**).

The results revealed that following nutritional management with a high inositol diet and supplementation, body weight differed considerably at ($P \leq 0.001$), and waist and hip ratio reduced significantly at ($P \leq 0.01$) across all experimental groups, particularly IFG. These findings are the result of the application of new hypotheses and the most recent therapeutic trends in the treatment of obese PCOS patients. Furthermore, **Genazzani et al., (2014)** shown that inositols enhance endocrine and metabolic parameters in overweight and obese PCOS patients and are beneficial in lowering BMI without requiring any lifestyle changes. In this regard, great emphasis is placed on the important role of inositols as insulin action mediators. It was regarded as a novel therapeutic technique in the treatment of obesity and metabolic syndrome linked with PCOS (**Saleem and Rizvi, 2017**). According to the investigations of **Unfer et al., (2016) and Facchinetti et al., (2015)**, a systematic review and an international consensus conference suggested that supplementation with inositol might beneficially alter numerous pathophysiological aspects of obstetrics and gynecology problems.

According to the current findings, total testosterone was elevated in PCOS women, but it was significantly reduced ($P \leq 0.001$) after following a high inositol diet and supplements. Also, sex hormone-binding globulin (SHBG) was decreased in PCOS women before dietary intervention, and IFG had the highest significant impact ($P \leq 0.001$) after administering inositol and folic acid. FAI, or abnormal androgen status in humans, was considerably improved ($P \leq 0.001$) in experimental groups who followed a

high inositol diet and supplementation, in particular IFG. **Manni et al., (1985)** reviewed the same findings, reporting that PCOS is related to insulin resistance, excess insulin, and lower SHBG, all of which increase free testosterone levels. When compared to CG, FSH increased somewhat, while LH dropped significantly ($P \leq 0.001$). After dietary intervention, the LH/FSH ratio changed considerably among all tested groups; the highest impact was reported in IFG, which was the closest to 1. **Regidor et al., (2018)** reported similar results, stating that the myo-inositol group had fewer follicle-stimulating hormone (FSH) units than the placebo group.

According to recent findings, myo-inositol has shown to be a more appealing therapy choice for PCOS patients than metformin as an insulin sensitizer, according to **Laganà et al., (2018) and Regidor et al., (2018)**. For women with PCOS, MI supplementation appears to be a straightforward, safe, and effective first-line therapy (**Marine et al., 2013**). MI was also shown to be beneficial in improving metabolic and hormonal parameters in PCOS women due to its insulin-sensitizing impact. Previous research has shown that MI supplementation can help most women with PCOS regain their fertility by restoring spontaneous ovarian activity (spontaneous ovulation, and menstrual cyclicity). After MI therapy, PCOS women experienced a substantial improvement in typical hormonal parameters, including lower LH, FSH, and testosterone circulating levels and increased SHBG, estrogens, and progesterone circulating levels (**Formuso et al., 2015; Benelli et al., 2016**).

The findings of this study show that women with PCOS are more likely to be obese or overweight, which might be attributed to their higher baseline TSH levels, which were reduced significantly following therapeutic diet ($P \leq 0.001$). According to **Trummer et al., (2015)**, hypothyroid abnormalities and high TSH levels are frequent in PCOS and are correlated to a poor metabolic profile. Thyroid-stimulating hormone (TSH) levels are greater in obese persons. It might be due to the complicated interactions of inflammatory markers and/or the hormone leptin, but they often know that high TSH levels stimulate fat cells to reproduce efficiently (adipocytes). **Mueller et al. (2009)** demonstrated a positive relation between thyroid

function as measured by TSH and IR in women with PCOS, and the correlation appeared to be independent of age and BMI.

In most, if not all, cases of PCOS, insulin resistance is one of the underlying metabolic abnormalities. These anomalies, in combination with obesity, explain why glucose intolerance is so common in people with PCOS. High insulin is both a sign and a cause of PCOS (**PCOS Guideline, 2018; Diamanti-Kandarakis and Papavassiliou, 2006**). Ovulation can be impaired by high insulin levels, which cause the ovaries to produce excessively testosterone (**Corbould et al., 2005**). Insulin resistance and compensatory hyperinsulinemia, as well as central obesity, are common metabolic symptoms of PCOS and are important components in the etiology of anovulation and hyperandrogenism **(Stepto et al., 2013)**. Hyperinsulinemia may cause hyperandrogenism in PCOS women by two different and independent mechanisms: 1) boosting androgen synthesis by the ovary, and 2) directly inhibiting hepatic secretion of the testosterone transporter (Sex Hormon Binding Globulin "SHBG"), depressing its blood level (**Bremer, 2010**). These reactions have the net effect of raising free (active form) testosterone levels in the bloodstream. Hyperinsulinemia may contribute to PCOS anovulation in addition to increasing hyperandrogenism. It may raise the risk of cardiovascular disease and have a deleterious impact on lipid profiles in the long term.

According to the findings of this investigation, blood glucose biomarkers and insulin profiles were significantly different and modulated. After dietary management, FBG was dramatically reduced ($P \leq 0.001$), with the lowest group being IFG. Fasting blood insulin was greatly improved ($P \leq 0.001$), and HOMA-IR was managed extraordinarily well ($P \leq 0.001$) in all treatment groups with high inositol diet and supplementation. Furthermore, HgA1c was changed to the normal range, with a highly significant difference ($P \leq 0.001$).

Inositol is a dietary supplement that is an intracellular transmitter involved in insulin signaling. Inositol improves insulin resistance indicators and "appears to control menstrual cycles, promote ovulation, and generate

metabolic changes in PCOS," according to a 2018 meta-analysis of 10 randomized studies (**Pundir, 2018**). Another study of **Cappelli et al., (2013)** demonstrated that a combination of metformin, myo-inositol leads to an improvement in hyperandrogenism. BMI and insulin resistance improves significantly as compared to treatment with metformin alone. This combination represents an excellent therapeutic choice for those obese women with PCOS who do not want to take hormonal contraceptives. By reducing hyperinsulinemia, insulin-sensitizing agents may improve endocrine and reproductive abnormalities in obese PCOS patients. **Cappelli et al., (2013)** concluded that the association metformin/myo-inositol/alpha-lipoic acid represents an excellent therapy choice to suggest to those obese women affected by PCOS who do not want to take hormones and neither to have any severe side effect.

Regardless of the signal flowing via the insulin receptor, these actions allow for a decline in blood glucose levels (insulin-like effect). Insulin resistance is linked to poor inositol and/or GPI metabolism in women with PCOS, whereas obesity plays a role in aberrant IPG-P production independent of PCOS **(Lagana et al., 2018)**. **Cappelli et al., (2013)** found that a combination of metformin and myo-inositol improves hyperandrogenism. When compared to metformin alone, BMI and insulin resistance improve dramatically. For obese women with PCOS who do not intend to take hormonal contraceptives, this combination is an effective treatment option. Insulin-sensitizing medications may ameliorate endocrine and reproductive problems in obese PCOS patients by lowering hyperinsulinemia. According to **Cappelli et al., (2013)**, the combination of metformin, myo-inositol, and alpha-lipoic acid is a great therapeutic strategy to recommend to obese women with PCOS who do not want to use hormones or have significant adverse effects.

In comparison to metformin, **Shokrpour et al. (2019)** found that giving myo-inositol to women with PCOS for 12 weeks improved glycemic control, triglyceride levels, and VLDL cholesterol levels. According to **Tabrizi et al., (2018)**, inositol optimal threshold value HDL cholesterol levels in PCOS patients and may lower triglycerides, total, and LDL

cholesterol levels in those with metabolic disorders. Myo-inositol therapy can help PCOS women with their dyslipidemia, lowering their cardiovascular risk. According to **Minozzi et al., (2013)**, reducing insulin resistance can enhance lipid metabolism by lowering visceral fat weight, hepatic lipid accumulation, and insulin production, as well as boosting adiponectin levels (Choi et al., 2009). Additionally, considerable weight loss and leptin decrease with MI delivery may result in improved lipid profiles (**Gerli et al., 2007**).

Conclusion

The study concluded that dietary management with high-inositol diet reduced total testosterone, elevated sex hormone-binding globulin (SHBG), and enhanced FAI considerably. The LH/FSH ratio also changed significantly following dietary intervention, with folic acid supplementation having the greatest effect. HOMA-IR was also tightly managed, and HgA1c was brought back to normal levels. So, the study recommend PCOS women to administer high inositol diet and folic acid supplementation for improving insulin resistance and metabolite hormones.

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التأثير التحسيني للنظام الغذائي عالي الإينوسيتول على مقاومة الأنسولين والهرمونات الأيضية بين النساء المصابات بمتلازمة المبيض المتعدد التكيسات

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الملخص العربي:

متلازمة المبيض المتعدد التكيسات (PCOS) هى حالة اعتلال للغدد الصماء و نظام الأيض و هو الأكثر انتشارًا لدى النساء في سن الإنجاب. أثبتت الدراسات أن الإينوسيتول فعال في تحسين معايير التمثيل الغذائي لدى النساء المصابات بمتلازمة تكيس المبايض بسبب تأثيره المحفز للإنسولين. تهدف الدراسة الحالية إلى تقييم تأثير اتباع نظام غذائي عالي الإينوسيتول على مقاومة الأنسولين لدى نساء متلازمة تكيس المبايض. أجريت التجربة الأكلينيكية على نساء متلازمة تكيس المبايض الذين قسموا إلى مجموعة ضابطة (CG) والتي وصفت لأدويتهن ؛ مجموعة حمية الإينوسيتول (IDG) على نظام غذائي عالي الإينوسيتول (١٥٠٠ مجم / يوم لكل ١٨٠٠ كيلو كالوري) ؛ مجموعة المدعمة بكبسولات الإينوسيتول (ISG) بجرعة ٢ جم يوميًا مع اتباع نظام غذائي عالي الإينوسيتول. المجموعة الخليط (IFG) اتبعت نظام غذائي عالي الإينوسيتول ، ومكمل كبسولات إينوسيتول وحمض الفوليك (٤٠٠ ميكروجرام من حمض الفوليك يوميًا) ، واستمرت الوجبة العلاجية لمدة ٣ أشهر متتالية. أشارت النتائج إلى أن غالبية المرضى كانوا يعانون من درجة متوسطة من الشعرانية ، وأن الدورة الشهرية تحدث ثلاث مرات في السنة. بعد التدخل الغذائي، انخفضت هرمونات الأندروجين بشكل ملحوظ عند مستوى معنوية ($P\leq0.001$) خاصة في مجموعة IFG ، بمتوسط ٢,٤٣ ± ٠,١٩ و ٥٦,٠٠ ± ٤,٢٧ نانومول / لتر لإجمالي هرمون التستوستيرون والجلوبيولين المرتبط بالهرمونات الجنسية (SHBG). أيضا تحسن نسبة LH / FSH بشكل ملحوظ ($P\leq0.001$) لما يقرب من ١ في مجموعة IFG ، يليها مجموعة ISG (١,١٩ ± ٠,١٨)، ثم IDG (١,٣٦ ± ٠,١٧) مقارنة بـ CG (٢,٤٧ ± ٠,٣٤). عدلت مستوى الهيموجلوبين السكري HgA1c إلى حد كبير بمعدل يتراوح بين ٥,٤٩ ± ٠,٠٩ إلى ٤,٤٧ ± ٠,٣٦ بمجموعات IDG و IFG. تحسنت معدلات الليبوبروتينات عالية الكثافة (HDLc) عند مستوى عالي الدلالة ($P\leq0.001$) في مجموعة ISG. الخلاصة، أثبتت النتائج أن التدخل الغذائي بنظام غذائي عالي الإينوسيتول يحسن مقاومة الأنسولين ويعزز هرمونات التمثيل الغذائي لدى نساء متلازمة تكيس المبايض.

الكلمات المفتاحية: فرط الأندروجين، حمض الفوليك، TSH، الدهون، الهيموجلوبين السكري.

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