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UNRAVELLING THE IMPACT OF METFORMIN AND LIFESTYLE CHANGES ON SERUM IRISIN AND HEALTH METRICS IN POLYCYSTIC OVARY SYDROME PATIENTS WITH OBESITY

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ABSTRACT **Background:** Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine condition that affects women of reproductive age, often associated with obesity and insulin resistance. Of particular concern is the association between PCOS and obesity, which exacerbates metabolic dysfunction, insulin resistance, and the risk of developing Type 2 diabetes and cardiovascular disease. Irisin, a novel myokine, has garnered significant interest for its potential role in energy metabolism and glucose homeostasis regulation. Metformin, a biguanide derivative has emerged as a cornerstone in the management of PCOS, especially in obese individuals. Therefore, the present study was conducted to know the effect of Metformin and lifestyle modification on certain key metabolic parameters particularly, serum irisin level in obese women with polycystic ovary syndrome. **Material And Methods:** A prospective interventional study was conducted at the Department of Obstetrics & Gynaecology of Dr B.R.A.M. Hospital, Raipur in a span of 1 year, from March 2023 to March 2024. The study was conducted on 52 PCOS women with obesity (BMI >25) coming to the outpatient department. The patients were categorized into two groups. Group A: (26) Subjects receiving metformin therapy along with lifestyle modifications for 12 weeks; and Group B: (26) Subjects not receiving Metformin therapy but only lifestyle modifications for 12 weeks. Irisin levels were assessed using the ELISA kit of Phoenix Pharmaceuticals The statistical analysis was done using MS Excel and SPSS 20. **Results:** Combining Metformin and lifestyle intervention significantly increased serum Irisin levels over 12 weeks (p=0.002) in contrast to lifestyle intervention alone (p=0.286). **Conclusion:** We observed improvement in irisin values in both groups, but the combined approach with Metformin and lifestyle modification shows pronounced improvement in clinical, metabolic, and hormonal profiles in PCOS women with obesity.

KEYWORDS : Metformin, Serum Irisin level, Obese, PCOS

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine condition that affects women of reproductive age, with a prevalence of up to 20%. [1] Biochemical and clinical features of excess androgen, menstrual irregularities, and polycystic ovarian morphology characterize PCOS.[2]

Metformin, a biguanide derivative, has emerged as a cornerstone in the management of PCOS, especially in obese individuals. Beyond its primary role in improving insulin sensitivity and lowering circulating insulin levels, Metformin has been shown to exert pleiotropic effects on various metabolic pathways, including AMP-activated protein kinase (AMPK) activation, mitochondrial function modulation, and inflammatory cytokine regulation. [3] A recent study reported that Metformin increased intramuscular FNDC5 expression and promoted irisin release from murine skeletal muscle into the blood. It is hypothesized that PGC1-α may be a regulator in releasing irisin stimulated by Metformin. The circulating irisin levels and FNDC5 gene expression are lower in type 2 diabetes and obesity subjects. Therefore, irisin is considered to be a potential therapeutic target for obesity and its complications. However, the specific mechanisms underlying its therapeutic benefits in PCOS, particularly in obese patients, remain incompletely understood.[4,5]

Irisin, a novel myokine discovered in 2012, has garnered significant interest for its potential role in energy metabolism and glucose homeostasis regulation. Irisin is released from skeletal muscle in response to exercise and acts on adipose tissue to induce browning, thereby increasing energy expenditure and improving insulin sensitivity. Irisin is derived from the cleavage of fibronectin type III domain-containing protein 5 (FNDC5), which is expressed in muscle tissue.[6,7] Clinical research has demonstrated that circulating levels of irisin are associated with body weight, insulin sensitivity, and hepatic triglyceride, which suggests a potential role in reducing body weight and improving metabolic diseases. Recent studies have reported alterations in irisin levels in women with PCOS, suggesting a potential link between irisin dysregulation and the pathophysiology of the syndrome. [6,7] However, the effects of metformin on irisin levels in PCOS, particularly in the context of obesity, remain unclear.

Hence, the present study was conducted to know the effect of metformin on serum irisin levels in women with obese polycystic ovary syndrome at the tertiary care centre. By elucidating the interplay between metformin treatment, irisin secretion, and metabolic outcomes in this specific population, this study seeks to advance our understanding of the underlying mechanisms contributing to PCOS-associated metabolic dysfunction and optimize therapeutic strategies for its management.

Objective:

- To investigate the impact of metformin treatment and lifestyle intervention on serum irisin levels in patients diagnosed with Polycystic Ovary Syndrome (PCOS) with obesity.

MATERIAL AND METHODS:

This prospective interventional study was conducted from March 2023 to March 2024 at the Department of Obstetrics & Gynaecology and MRU (Multidisciplinary Research Unit) of Dr B.R.A.M. Hospital, Raipur.

A total of 52 patients of PCOS with obesity with BMI >25 kg/m^{2}as per WHO Asian BMI Criteria, coming to the outpatient department were included in the study. Patients aged more than 15 years and less than 45 years, with Pelvic inflammatory disease or any adnexal pathology, diagnosed or suspected malignant neoplastic disease, hyperprolactinemia, adrenal tumor, liver disorder, renal disorder, patients already on Metformin, those who took oral contraceptives in the last 3 months and those having smoking and alcohol habits were excluded from the study. Permission from the Ethical Committee was taken before commencement of the study and informed written consent was taken from the participants of the study who were then randomized into two groups:

Group A: (26) Subjects receiving metformin therapy along with lifestyle modifications for 12 weeks and Group B: (26) Subjects not

receiving Metformin therapy but only lifestyle modifications for 12 weeks. Participants met the diagnostic criteria for PCOS as defined by recognized guidelines of Modified Rotterdam criteria (2003) which was supported in the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS[8]. Patient demographic and medical details and the symptoms preceding the disease were recorded in the proforma sheet. The initial baseline assessment includes the recording of vitals, clinical features/symptoms, general physical examination, systemic examination. Anthropometric measurements (height, weight, BMI, waist circumference, hip circumference) were taken with the participants wearing lightweight clothing without shoes. Body Fat Percentage [15] calculated by suing formula (1.20 x BMI + 0.23 x Age – 5.4). Acne scoring calculation was done using Global Acne Scoring System (GAGS) [16]. Modified Ferriman-Gallwey score (mFG) [17] used for assessing hirsutism. Ultrasonographic assessment of uterine volume, endometrial thickness and ovarian volume is done.

Fasting venous blood sample (3-4 ml) was collected at 9 am in a plain vacutainer between 3rd and 5th day of a spontaneous bleeding episode of the participants. The samples were allowed to clot at room temperature and centrifuged to obtain serum which was stored at -20°C until analysis. The same was repeated after 12 weeks study period.

Estimation of Insulin Resistance (HOMA-IR) [18] index was done with the standard formula: HOMA-IR Index = (Fasting Insulin, uIU/mL) x (Fasting glucose, mg/dL)/ 405

Lifestyle intervention included a low GI diet plan [19] and 45 minutes of moderate-intensity exercise (60-70% of maximum heart rate) done 3 times per week. Individualized calorie requirement was calculated based on Basal Metabolic Rate (BMR) [20] and Total Daily Energy Expenditure (TDEE) [21] and an appropriate calorie deficit (typically 500-750 kcal/day) was applied to promote a weight loss of 0.5-1 Kg per week. A weight loss of approximately 5-10% of their initial body weight was expected over a 12-week study period.

Initiation of Tab Metformin 500 mg twice a day for 12 weeks was done in group A and both groups subjected to lifestyle modification including diet and exercise as described above.

Irisin levels were assessed using the ELISA kit of Phoenix Pharmaceuticals Catalogue No. EK-067-29, Lot No. 610955. Data entry and data analysis was done using MS Excel and Statistics software SPSS 20.0

RESULTS:

In the study, Group A and Group B predominantly consist of participants in the 21-30 age category with a mean age of 24.96 ± 3.85 and 24.88 ± 4.27 years respectively with no statistical significance. In both Group A (88.5%) and Group B (84.6%), the majority of participants reside in urban areas. Group A had higher percentages of cases of menorrhagia (7.6%) and the combination of menstrual abnormalities (5.8%) compared to Group B. Group B had higher instances of oligomenorrhea (46.2%) compared to Group A (30.8%). There were differences in specific types of menstrual abnormalities between the groups, the study did not find these differences to be statistically significant. The data of metabolic and hormonal characteristics of both groups are shown in the table 1.

Table no 1: Comparative analysis of various parameters of Group A (Metformin + Lifestyle) and Group B (Lifestyle)

S. No.	Parameters	Group A (Baseline)	Group A (after 12 weeks)	Group B (Baseline)	Group B after (12 weeks)	T1 value (P1 value) B-B	T2 value (P2 value) 12-12	T3 value (P3 value) Group A	T4 value (P4 value) Group B
1	Age (years)	24.96 ± 3.85		24.88 ± 4.27		0.685 (NS)			
2	Height (cm)	152.38 ± 4.22		152.81 ± 3.43		-0.396 (0.693)			
3	Average cycle length (days)	71.23 ± 20.95	45.31 ± 9.736	72.46 ± 15.72	51.77 ± 7.30	-0.240 (0.812)	-2.708 (0.009)	9.282 (0.001)	8.244 (0.001)
4	Weight (Kg)	73.34 ± 7.30	69.04 ± 7.00	73.73 ± 6.27	70.65 ± 6.58	-0.204 (0.839)	-0.857 (0.395)	2.366 (0.101)	1.507 (0.228)
5	BMI ((kg/m^2)	31.53 ± 2.19	29.68 ± 2.06	31.57 ± 2.43	30.25 ± 2.59	-0.061 (0.952)	-0.867 (0.390)	4.868 (0.010)	1.822 (0.169)
6	Body fat percentage	38.04 ± 2.84	35.83 ± 2.80	37.90 ± 3.32	36.32 ± 3.40	0.164 (0.871)	-0.566 (0.574)	4.004 (0.022)	1.457 (0.239)
7	Body fat mass (Kg)	28.05 ± 4.72	24.88 ± 4.22	28.11 ± 4.82	25.84 ± 4.81	-0.043 (0.966)	-0.766 (0.447)	3.239 (0.045)	1.452 (0.241)
8	Waist circumference (cm)	83.92 ± 5.51	82.19 ± 5.26	83.85 ± 6.93	82.15 ± 6.82	0.044 (0.965)	-0.062 (0.951)	12.184 (0.001)	11.726 (0.001)
9	Hip circumference (cm)	103.96 ± 4.72	103.38 ± 4.92	104.04 ± 6.10	103.12 ± 6.14	-0.051 (0.960)	0.175 (0.862)	1.413 (0.170)	7.50 (0.001)
10	Waist/Hip Ratio	0.80 ± 0.24	0.79 ± 0.27	0.80 ± 0.28	0.79 ± 0.27	0.160 (0.873)	-0.354 (0.725)	3.808 (0.001)	6.356 (0.001)
11	Waist/Height Ratio	0.55 ± 0.36	0.53 ± 0.35	0.54 ± 0.048	0.53 ± 0.046	0.488 (0.628)	0.099 (0.921)	1.257 (0.220)	0.625 (0.538)
12	Hirsutism (mFG-score)	8.12 ± 2.613	7.42 ± 2.194	7.81 ± 2.49	7.46 ± 2.28	0.434 (0.666)	-0.062 (0.951)	4.797 (0.001)	2.560 (0.017)
13	Acne scoring	13.38 ± 7.42	9.46 ± 6.77	13.31 ± 7.51	10.92 ± 6.81	0.037 (0.971)	-0.777 (0.441)	11.800 (0.001)	7.590 (0.001)
14	Fasting blood sugar (mg/dL)	93.96 ± 7.613	84.00 ± 6.164	87.77± 12.56	84.58 ± 11.74	2.150 (0.036)	-0.222 (0.825)	8.396 (0.001)	8.774 (0.001)
15	LH (mIU/mL)	12.88 ± 2.535	12.00 ± 2.668	13.19 ± 3.150	12.50 ± 3.165	-0.239 (0.812)	-0.738 (0.464)	5.892 (0.001)	7.550 (0.001)
16	FSH (mIU/ml)	6.19 ± 1.415	6.15 ± 1.287	6.50 ± 1.393	6.58 ± 1.332	-1.187 (0.241)	-1.407 (0.166)	0.570 (0.574)	-0.811 (0.425)
17	LH - FSH Ratio (mIU/ml).	2.12 ± 0.326	2.04 ± 0.196	2.00 ± 0.01	2.00 ± 0.283	1.619 (0.112)	0.983 (0.331)	1.806 (0.083)	1.00 (0.327)
18	HDL (mg/dl)	48.81 ± 5.706	52.85 ± 5.924	46.54 ± 4.917	48.00 ± 4.89	1.536 (0.131)	3.217 (0.002)	9.687 (0.001)	4.959 (0.001)
19	LDL (mg/dl)	137.50 ± 10.63	128.62 ± 10.60	135.27 ± 9.69	130.42 ± 9.19	0.791 (0.433)	-0.657 (0.514)	11.373 (0.001)	11.707 (0.001)
20	Triglyceride levels (mg/dl)	162.96 ± 10.686	156.19 ± 10.21	162.46 ± 10.478	158.7 ± 10.334	0.170 (0.865)	-0.878 (0.384)	10.414 (0.001)	10.447 (0.001)
21	Total cholesterol levels (mg/dl)	210.12 ± 14.354	204.88 ± 12.691	209.54 ± 13.54	206.5 ± 12.78	0.149 (0.882)	-0.457 (0.649)	10.458 (0.001)	8.830 (0.001)
22	TC/HDL Ratio (mg/dl)	4.46 ± 0.761	3.85 ± 0.675	4.58 ± 0.643	4.35 ± 0.56	-0.972 (0.336)	-2.657 (0.011)	6.325 (0.001)	2.739 (0.011)
23	Testosterone (ng/mL)	1.04 ± 0.196	1.04 ± 0.196	1.04 ± 0.196	1.0 ± 0.01	0.387 (0.700)	-0.033 (0.974)	9.229 (0.000)	9.667 (0.000)
24	Estradiol (pg/mL)	58.92 ± 17.039	53.42 ± 17.086	64.54 ± 19.46	61.58 ± 19.08	-1.120 (0.268)	-1.616 (0.112)	16.942 (0.001)	9.092 (0.001)
25	Progesterone (ng/mL)	0.96 ± 0.599	0.73 ± 0.452	1.08 ± 0.796	0.92 ± 0.744	-0.339 (0.736)	-0.632 (0.530)	2.739 (0.011)	2.132 (0.043)

26	Prolactin (ng/mL)	11.65 ± 5.885	10.46 ± 5.479	12.77 ± 6.250	12.15 ± 6.188	-0.708 (0.483)	-1.090 (0.281)	6.200 (0.001)	5.494 (0.001)
27	AMH (ng/mL)	5.81 ± 1.266	4.50 ± 1.334	5.50 ± 0.812	4.81 ± 0.849	1.239 (0.221)	-1.134 (0.262)	9.815 (0.001)	7.500 (0.001)
28	Fasting Insulin (mIU/mL)	20.58 ± 6.414	18.38 ± 6.034	19.62 ± 5.94	17.77 ± 5.516	0.604 (0.549)	0.332 (0.741)	11.400 (0.001)	2.806 (0.010)
29	HOMA-IR	4.720 ± 1.561	3.81 ± 1.304	4.17 ± 1.31	3.72 ± 1.20	1.368 (0.177)	0.276 (0.783)	10.730 (0.001)	3.432 (0.002)
30	T3 (ng/dL)	117.42 ± 30.40	116.50 ± 29.38	103.23 ± 22.49	103.04 ± 21.99	1.922 (0.060)	1.858 (0.069)	2.168 (0.040)	0.451 (0.656)
31	T4 (ng/dL)	8.54 ± 3.190	8.35 ± 2.870	7.38 ± 3.03	7.35 ± 2.75	1.257 (0.214)	1.416 (0.163)	1.044 (0.306)	0.254 (0.802)
32	TSH (ng/dL)	3.35 ± 1.522	2.73 ± 0.827	3.04 ± 1.280	2.46 ± 0.94	0.964 (0.340)	0.469 (0.641)	3.682 (0.001)	5.091 (0.001)
33	Right Ovary Volume (cc)	11.38 ± 2.513	9.54 ± 2.158	11.62 ± 2.483	10.58 ± 2.335	-0.358 (0.722)	-1.414 (0.163)	10.690 (0.001)	7.997 (0.001)
34	Left Ovary Volume (cc)	11.12 ± 2.703	9.46 ± 2.626	12.96 ± 2.490	11.54 ± 2.68	-2.345 (0.023)	-2.746 (0.008)	7.985 (0.001)	6.018 (0.001)
35	Endometrial Thickness (mm)	4.85 ± 2.33	6.31 ± 1.34	5.31 ± 1.668	6.08 ± 1.598	-0.756 (0.453)	0.801 (0.427)	-5.150 (0.000)	-6.682 (0.001)
36	Serum Irisin (ng/mL)	4.73 ± 1.151	6.08 ± 1.917	6.85 ± 2.525	7.65 ± 2.813	4.244 (0.000)	-2.553 (0.014)	-3.400 (0.002)	-1.091 (0.286)

P1- Group A at baseline v/s Group B at baseline; P2- Group A after 12 weeks v/s Group B after 12 weeks; P3- Group A at baseline v/s Group A after 12 weeks; P4- Group B at baseline v/s Group B after 12 weeks

Combining metformin and lifestyle intervention significantly increased serum Irisin levels over 12 weeks (p=0.002) in contrast to lifestyle intervention alone (p=0.286) as summarised in Table 2 below.

Table no. 2: Distribution of cases according to Serum Irisin levels (ng/mL):

Serum Irisin (ng/mL)	Group A (Metformin + Lifestyle)		Group B (Lifestyle)		T value (P1 Value) B – B	T Value (P2 Value) 12 – 12	T Value (P3 Value) Group A	T Value (P4 Value) Group B
	Baseline Mean ± SD (N, %)	After 12 weeks Mean ± SD (N, %)	Baseline Mean ± SD (N,%)	After 12 weeks Mean ± SD (N, %)				
2.0-3.9	3.58 ± 0.18 (08, 30.8%)	3.21 ± 0.60 (03, 11.5%)	2.06 ± 0.00 (02, 7.7%)	(00, 0.0%)	7.910 (0.000)	----	1.685 (0.126)	----
4.0-5.9	4.92 ± 0.54 (14, 53.8%)	4.85 ± 0.49 (10, 38.5%)	4.74 ± 0.30 (08, 30.8%)	4.97 ± 0.54 (07, 26.9%)	0.860 (0.400)	-0.482 (0.637)	0.325 (0.748)	1.039 (0.318)
6.0-7.9	6.47 ± 0.44 (04, 15.4%)	7.01 ± 0.62 (07, 26.9%)	6.93 ± 0.61 (08, 30.8%)	6.65 ± 0.60 (07, 26.9%)	-1.348 (0.207)	1.112 (0.288)	1.521 (0.163)	0.894 (0.280)
8.0-9.9	(00, 0.0%)	8.27 ± 0.16 (05, 19.2%)	9.05 ± 0.36 (06, 23.1%)	8.71 ± 0.48 (06, 23.1%)	----	-1.933 (0.089)	----	1.388 (0.340)
≥10	(00, 0.0%)	10.83 ± 0.00 (01, 3.8%)	11.38 ± 0.73 (02, 7.7%)	11.90 ± 1.48 (06, 23.1%)	----	-0.671 (0.532)	----	0.460 (0.662)
Total	**4.73 ± 1.151** (26, 100.0%)	**6.08 ± 1.917** (26, 100.0%)	**6.85 ± 2.525** (26, 100.0%)	**7.65 ± 2.813** (26, 100.0%)	**4.244 (0.000)**	**-2.553 (0.014)**	**-3.400 (0.002)**	**-1.091 (0.286)**

P1- Group A at baseline v/s Group B at baseline; P2- Group A after 12 weeks v/s Group B after 12 weeks; P3- Group A at baseline v/s Group A after 12 weeks; P4- Group B at baseline v/s Group B after 12 weeks

Correlation Studies

Correlation values of % change in serum irisin levels with % change in metabolic parameters as presented in table 3 were calculated using Pearson's correlation coefficient, considering P values <0.05 as the level of significance as summarised below:

Table 3: Correlation of % change in serum irisin levels with % change in metabolic parameters:

Metabolic Parameters (% change between baseline and 12 weeks of intervention)	Group A Mean ± SD	Group B Mean ± SD	Pearson r (Group A)	p-value (Group A)	Pearson r (Group B)	p-value (Group B)
Average menstrual cycle length (days)	-33.85 ±12.31	-26.68 ±12.72	-0.100	0.626	-0.321	0.110
FGS (Hirsutism)	-7.42 ± 7.69	-3.58 ± 6.91	-0.691	0.001	-0.869	0.001
Acne scoring (GAGS)	-36.38 ±20.45	-19.38 ±14.77	-0.279	0.167	-0.581	0.002
Weight (Kg)	-5.85 ± 2.20	-4.23 ± 2.32	-0.704	0.001	-0.870	0.001
BMI (Kg/m^2)	-5.81 ± 2.23	-4.20 ± 2.32	-0.722	0.001	-0.867	0.001
Body fat percent	-5.8 ± 2.3	-4.19 ± 2.26	-0.686	0.001	-0.864	0.001
Body fat mass (Kg)	-11.30 ±4.21	-8.17 ± 4.33	-0.704	0.001	-0.867	0.001
Waist Circumference (cm)	-2.00 ± .98	-1.81 ± 0.801	-0.356	0.075	-0.569	0.002
Hip circumference (cm)	-.46 ± 2.04	-0.88 ±0.516	0.139	0.498	-0.286	0.157
Waist/Hip Ratio	-1.51 ± 2.0	-0.99 ± 0.7	-0.282	0.162	-0.388	0.050
FBS (mg/dl)	-10.38 ±5.99	-3.46 ±1.944	-0.009	0.966	-0.523	0.006
HDL (mg/dl)	8.27 ± 4.687	3.23 ± 3.386	0.226	0.267	0.439	0.025
Total cholesterol	-2.46 ± 1.029	-1.46 ± 0.811	-0.503	0.009	-0.352	0.78
Fasting insulin	-10.00 ±5.396	-6.54 ± 11.039	-0.498	0.010	-0.006	0.978
HOMA-IR	-19.31 ±7.396	-10.04 ±10.813	-0.303	0.133	-0.093	0.650

DISCUSSION:

The present study aimed to evaluate the effect of metformin and lifestyle intervention on serum irisin levels and other health parameters in patients with obese polycystic ovary syndrome (PCOS). PCOS is a common endocrine disorder among women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. Obesity exacerbates the clinical manifestations of PCOS, including insulin resistance, which is a core feature of the syndrome. Metformin, an insulin-sensitizing agent, is widely used in the management of PCOS, particularly in obese patients. [9] Irisin, a myokine released during physical exercise, has been shown to play a role in energy homeostasis and insulin sensitivity, making it a molecule of interest in the context of PCOS and obesity.

The present study highlights important findings regarding the effects of

Metformin combined with lifestyle changes (Group A) versus lifestyle changes alone (Group B) on various health outcomes. Both groups share similar demographic characteristics, including age, urban residency, socio-economic status, and family history of health issues like diabetes, hypertension, and obesity. A predominant proportion of participants in both groups also experienced menarche between the ages of 12-13 years.

Notably, both groups demonstrated significant improvements in key health metrics, such as menstrual irregularities, acne, and FGS scores, which were consistent across both interventions. However, the combination of Metformin and lifestyle changes (Group A) showed a more significant impact on parameters like FBS levels, LDL cholesterol, and total cholesterol, indicating a potential added benefit of Metformin alongside lifestyle interventions.

In contrast, Group B, which focused on lifestyle changes alone, showed a more pronounced effect on LH levels, suggesting that lifestyle interventions alone might be sufficient to address specific hormonal imbalances. Additionally, irisin levels, which are associated with metabolic and reproductive health, were notably linked to improvements in weight loss, body fat percentage, and other metabolic markers in both groups. However, the effects of irisin on certain outcomes, such as LH/FSH ratios or thyroid hormones, were minimal. Irisin levels correlated negatively with weight loss, body fat percentage, and waist-to-hip ratio (WHR), suggesting that higher irisin levels are associated with improved body composition and metabolic health.

The data highlights the varied effects of Metformin and lifestyle interventions on serum irisin levels, a marker associated with metabolic health. Studies generally show that Metformin tends to reduce serum irisin levels, as evidenced by significant decreases observed in multiple studies, such as by Minyan Li et al. (22) and Meng-ge et al. (23). These reductions suggest Metformin's role in influencing irisin levels, potentially reflecting its impact on metabolic processes like insulin sensitivity and fat metabolism.

On the other hand, lifestyle interventions alone, such as those examined by Srinivasa et al.(24), did not produce significant changes in serum irisin levels. Interestingly, a combined approach of Metformin and lifestyle changes in the present study (2023-24) resulted in a significant increase in irisin levels ($p = 0.002$), contrasting with previous studies like Srinivasa et al. (2015), which found no significant change in the combined intervention group.

The findings in our study suggest that both treatment approaches lead to significant positive changes in health outcomes, with Metformin and lifestyle changes showing more pronounced effects in some areas, especially in metabolic health. Lifestyle changes alone also proved effective, particularly in improving hormonal balance, offering a feasible alternative for those unable or unwilling to use medication. Further research is needed to explore the long-term effects and potential synergistic impacts of these interventions on reproductive health and metabolic disorders.

CONCLUSION:

The present study concludes that the combined approach with Metformin and lifestyle modification shows pronounced improvement in clinical, metabolic, and hormonal profiles in obese women with PCOS as compared to lifestyle modification alone. This can be attributed to the synergistic effects of combined Metformin and lifestyle interventions, which likely enhance Irisin secretion through improved insulin sensitivity and a well-documented impact of exercise. It signifies that increased levels of Irisin are a marker for improvement in clinical, biochemical, metabolic, and hormonal profiles.

This finding potentially offers a more effective approach for managing obese women with PCOS by integrating pharmacological treatment with lifestyle modifications to achieve optimal therapeutic outcomes in women with PCOS having obesity.

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