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Research Article

Effect of Metformin Monotherapy Versus Omega 3 and Metformin Combination on Ovulatory Dysfunction and Hyperandrogenism State in Iraqi Women With PCOS

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Abstract:
Women with PCOS often have cycles that exceed 35 days in length may indicate persistent an ovulation. Disruptions in ovulation can have detrimental consequences such as infertility, endometrial hyperplasia and endometrial tumor. In PCOS, clinical hyperandrogenism can be differentiated from biochemical hyperandrogenism in females exhibiting symptoms such as acne, alopecia, or hirsutism. To measure the influence of metformin and omega-3 management combination on ovulatory dysfunction and hyperandrogenism state in women with PCOS. The existing interventional prospective training comprised 90 sick with an age range of 18<40 years. Those patients were identified with polycystic ovarian syndrome (PCOS) founded on Rotterdam principles (Rotterdam, 2004) by 2 specialists in obstetrics and gynecology. The patients were recruited from the Maternity and Pediatrics Teaching Hospital in Adiwaniyah Province, Iraq. The training is dated posterior to September the 21st 2023 and extended to March 31st 2024.Following treatment, both metformin+Omega3 and metformin alone were able to reduce mean testosterone considerably (p<0.001 versus p<0.001, separately), however, the amount of reduction caused by combination was more than that caused by metformin alone significantly, 0.8 ng/dl versus 0.7 ng/dl, respectively (p<0.001). Before treatment, there stayed no important variance in mean ovary size among study grouping (p = 0.402), in addition both treatment approaches did not affect mean ovary size significantly (p = 0.302). Both metformin+Omega3 and metformin alone were able to reduce mean AFC significantly (p<0.001 versus p<0.001, separately), however, the amounts of reduction in both grouping stood comparable with no significant difference, 2.22 versus 2.66, respectively (p = 0.112). Both metformin+Omega3 and metformin alone were able to reduce mean hirsutism score considerably (p<0.001 versus p<0.001, separately), however, the amount of reduction caused by combination was > that caused by metformin alone significantly, 1.82 versus 0.4, respectively (p<0.001) The use of Omega3 has an efficient and safe synergistic effect when added to metformin in improving ovarian function and androgen effect in PCOS.

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INTRODUCTION

(PCOS), a common metabolic and endocrine syndrome, affects a significant numeral of premenopausal females. The condition presents a variety of symptoms associated with irregularities in ovarian function and elevated levels of androgens, lacking a definitive additional diagnosis (Escobar-Morreale[1]). In women with PCOS, menstrual cycles longer than 35 days may suggest ongoing an ovulation, while cycles between 32 and 35 days should be assessed for potential ovulatory dysfunction (Dumesic[2]). Ovulatory disruptions can clue to adversative results for instance infertility, endometrial hyperplasia and endometrial tumor (Dumesic *et al.,* 2015). Through transvaginal ultrasonography, the identification of polycystic ovarian morphology (PCOM) is now feasible in affected women with a minimum of 25 small follicles (extending from 2-9 mm) across the complete ovary, with the standard threshold for ovarian volume remaining at 10 ml. According to the 2004 Rotterdam principles, PCOM is considered via the occurrence of at least 12 follicles within the specified size range or an increase in ovarian volume exceeding 10 cc (Rosen field[3]).

Within PCOS, clinical hyperandrogenism can be distinguished from biochemical hyperandrogenism in females displaying symptoms like acne, alopecia, or hirsutism. Nonetheless, in adolescents, hirsutism alone should be considered as a marker for biochemical hyperandrogenism (Wang[4]). Patterns of hair loss can vary, appearing in a diffuse pattern, at the crown, or in the vertex region (Goodman[5]). Hirsutism is characterized by the existence of coarse, dark terminal hairs following a male-like distribution (Spritzer[6]). Elevated androgen levels are identified through increased free testosterone ranks (Lerchbaum[7], French[8]).

Metformin administration in non-obese women with PCOS can ameliorate irregular menstrual cycles, abnormal waist-to-hip ratios and vascular indicators. It is considered a second-line therapy for menstrual irregularities and is frequently prescribed as a monotherapy for adolescents, aiding in the restoration of natural menstruation, enhancement of insulin sensitivity and facilitation of weight loss. While it may alleviate symptoms related to excessive androgen levels, there is no unanimous agreement among researchers (Shah[9]. Omega-3 fatty acids, belonging to the antilipemic class of drugs, are utilized to manage hyperlipidemia and offer subsidiary assistances in the treatment of females with PCOS. Nevertheless, further research is required to establish definitive guidelines regarding dosage and duration of supplementation (Melo[10], Krupa[11]).

MATERIALS AND METHODS

The ongoing experimental investigation involved 90 sick aged among 18 and under 40 years. These individuals stood identified with (PCOS) rendering to Rotterdam principles (Rotterdam, 2004) by 2 experts in obstetrics and gynecology. The recruitment of patients took place at the Maternity and Pediatrics Teaching Hospital in Adiwaniyah Province, Iraq. This research commenced on September 21st, 2023 and continued until March 31st, 2024. Pregnant women, individuals with chronic medical conditions, those with hyperprolactinemia and individuals with thyroid ailments were not part of this study. The women were divided into two categories: the initial group (n = 45) was administered 500 mg of metformin orally (twice daily) for 90 days along with omega 3 for three months, the second group (n = 45) received 500 mg of metformin orally (twice daily) for 90 days. Serum testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) ranks stayed evaluated by means of ELISA (Elabscience, USA), with the procedures and calculations based on the instructions provided by the supplying company. The evaluation of ovarian morphology was conducted through transvaginal ultrasound.

Approval for the training stayed granted via the ethical agreement commission of the College of Medicine/ University of Al-Qadisiyah. All participants were required to provide verbal consent after a comprehensive explanation of the objectives and methods of the current research. The data underwent analysis and presentation using SPSS (version 23, IBM, Chicago, USA) and Microsoft Office Excel 2010. Mean, standard deviation and range were utilized to express quantitative variables. The comparison of means between two independent groups was done by means of an autonomous testers t-test. A paired t-test stayed employed to parallel means among two associated groups pre and post-treatment. Statistical importance stayed recognized at $p = 0.05$.

RESULTS AND DISCUSSIONS

Appraisal of mean levels of serum FSH between the metformin+omega3 group and the metformin Group before and after treatment is illustrated in table 1. Initially, there stayed no notable variance in the mean FSH levels among the groups, with values of 5.58±2.08 mIU/ml and 5.94±0.79 mIU/ml, respectively ($p = 0.288$). Post-treatment, the metformin+Omega3 group showed no significant change in mean serum FSH ($p = 0.126$), while the metformin group experienced a noteworthy increase in mean serum FSH by-0.53 mIU/ml ($p = 0.012$).

This resulted in a significant disparity in the observed changes between the two groups (p = 0.001).

Concerning serum LH levels, before treatment initiation, there stayed no substantial alteration in mean LH among the training groups, 17.74±9.79 mIU/ml and 17.35±6.91 mIU/ml, respectively (p = 0.447). Post-treatment, both metformin+Omega3 and metformin alone led to a important decrease in mean LH ranks (p<0.001 against p<0.001, separately). Nevertheless, the combination therapy resulted in a more pronounced decrease compared to metformin alone, 10.90 mIU/ml versus 8.53 mIU/ml, respectively (p = 0.004). As for the mean LH/FSH ratio, there stayed no important alteration among the groups before treatment, with values of 3.14±1.36 and 3.60±1.08, respectively (p = 0.076). Post-treatment, both metformin+Omega3 and metformin alone significantly reduced the mean LH/FSH ratio (p<0.001 against p<0.001, separately). Nevertheless, the combination therapy induced a larger reduction paralleled to metformin alone, with values of 2.00 versus 1.83, respectively (p = 0.002).

Prior to treatment initiation, there stayed no important alteration in mean serum testosterone ranks between the study groups, 1.18±0.69 ng/dl and 0.94 ±0.53 ng/dl, respectively (p = 0.391). Post-treatment, both metformin+Omega3 and metformin alone led to a important decrease in mean testosterone ranks (p<0.001 versus p<0.001, separately). However, the combination therapy resulted in a more substantial decrease compared to metformin alone, 0.8 ng/dl versus 0.7 ng/dl, respectively (p<0.001).

The comparison of ovary size between the metformin +omega3 group and the metformin Group before and after treatment is displayed in table 2. Prior to treatment, there stayed no important distinction in mean ovary size among the study groups (p = 0.402), and mutually treatment modalities did not notably impact mean ovary size (p = 0.302). Regarding antral follicle count (AFC), before treatment commencement, there stayed no important variance in mean AFC among the study grouping, 25.02±1.85 and 24.64 ±2.32, separately (p = 0.395). Post-treatment, both metformin+Omega3 and metformin alone led to an important decrease in mean AFC (p<0.001 versus p<0.001, respectively). Nevertheless, the reduction quantities in both groups stood comparable, with no significant variance, 2.22 versus 2.66, respectively (p = 0.112).

After receiving the prescribed remedy, the combination of metformin and Omega3 as well as metformin by itself displayed a notable decrease in the average hirsutism score (p<0.001 against p<0.001, separately). Nevertheless, the reduction in hirsutism score was significantly greater with the combined treatment compared to metformin alone, measuring 1.82 versus 0.4, respectively (p<0.001), as exposed in (Table 3).

In this exploration, it was revealed that the combination of metformin and Omega3 did not lead to any notable alteration in the average serum FSH levels. Conversely, metformin by itself demonstrated a noteworthy increase in the mean serum FSH levels. Al-Safi in[12], scrutinized the influence of omega-3 supplemented on women of normal weight and observed a considerable decline in serum FSH levels. It is plausible that omega-3 in this particular investigation induced a decrease in FSH levels, which was counteracted by metformin, resulting in an overall insignificant change in FSH levels in women who received both metformin and omega-3. However, in their controlled clinical trial, Nadjarzadeh[13] did not perceive any important influence on the mean serum LH levels post omega-3 treatment.

Furthermore, as per this research, it was established that both metformin+Omega3 and metformin in isolation were capable of significantly diminishing the mean LH levels, nevertheless, the reduction caused by the combination was notably greater than that caused by metformin alone. Additionally, it was noted that both metformin+Omega3 and metformin alone were able to reduce the mean LH/FSH ratio significantly, however, the reduction induced by the combination was significantly more pronounced than that caused by metformin alone. In the meta-analysis conducted by Guan[14], an overall substantial decrease in FSH and LH levels was observed post metformin administration. Contrarily and in alignment with the current study's results, Nadjarzadeh[13] described a important reduction in LH mean within the omega-3 group.

Curi in[15], documented no significant variations in FSH and LH levels subsequent to metformin treatment in females with PCOS. The precise alterations in FSH and LH from the baseline seem to be contentious, necessitating further extensive research to establish a consensus on these responses. As outlined in the meta-analysis conducted by Yang[16], robust evidence supporting the efficacy of omega-3 fatty acids on FSH and LH levels is lacking, however, this does not negate its medical importance. It might indicate that omega-3 fatty acids could be a harmless or more cost-effective management option. Nevertheless, contradicting Yang[16], the present study demonstrated a important influence of omega-3

Table 1: Appraisal of mean levels of serum FSH between metformin +omega3 group and metformin Group before and after treatment

	Characteristic	Metformin +Omega3 n = 45	Metformin Group n = 45	p
FSH (mIU/ml)	Before			
	Mean±SD	5.58±2.08	5.94±0.79	0.288 I
NS				
	Range	2.76-11.56	4.07-7.05	
	After			
	Mean±SD	4.93±2.39	6.46±1.95	0.001 I
***				
	Range	1.1-9.87	3.24-9.44	
	Difference in mean	0.65	-0.53	
	p	0.126 Pa NS	0.012 Pa *	
LH (mIU/ml)	Before			
	Mean±SD	17.74±9.79	17.35±6.91	0.447 I
NS				
	Range	3.23-32.09	8.6-32.83	
	After			
	Mean±SD	6.85±4.68	8.82±5.57	0.004 I
**				
	Range	1.5-15.06	1.5-19.65	
	Difference in mean	10.90	8.53	
	p	<0.001 Pa ***	<0.001 Pa ***	
LH/FSH	Before			
	Mean±SD	3.14±1.36	3.60 ±1.08	0.076 I
NS				
	Range	0.64-5.6	1.21-4.93	
	After			
	Mean±SD	1.14±0.65	1.77±0.64	0.002 I
***				
	Range	0.3-2.43	0.43-2.82	
	Difference in mean	2.00	1.83	
	p	< 0.001 Pa ***	<0.001 Pa ***	
Testosterone (ng/dl)	Before			
	Mean±SD	1.18 ±0.69	0.94±0.53	0.391 I
NS				
	Range	0.46-2.85	0.2-1.81	
	After			
	Mean±SD	0.38±0.27	0.25±0.11	< 0.001
I				
***				
	Range	0.17-1.09	0.14-0.5	
	Difference in mean	0.80	0.70	
	p	< 0.001 Pa ***	< 0.001 Pa ***	

Table 5: Comparison of ovary size between metformin +omega3 group and metformin Group before and after treatment

	Characteristic	Metformin +Omega3 n = 45	Metformin Group n = 45	P
Ovary Size mm)	Before			
	Mean±SD	17.36±2.15	17.23±1.94	0.402 I
NS				
	Range	14 -22	13.5-19.7	
	After			
	Mean±SD	16.87±1.78	17.09±1.98	0.203 I
NS				
	Range	14 -20	12.8-19.4	
	Difference in mean	0.49	0.13	
	p	0.091 Pa NS	0.181 Pa NS	
Antral follicle count	Before			
	Mean±SD	25.02±1.85	24.64±2.32	0.395 I
NS				
	Range	22-28	22-28	
	After			
	Mean±SD	22.80 ±2.43	21.98±2.43	0.112 I
NS				
	Range	18-26	19-26	
	Difference in mean	2.22	2.66	
	p	< 0.001 Pa ***	< 0.001 Pa ***	

Table 3: Comparison of mean hirsutism mark between metformin +omega3 group and metformin group before and after treatment

	Characteristic	Metformin +Omega3 n = 45	Metformin Group n = 45	P
Hirsutism score	Before			
	Mean±SD	9.22±2.03	9.24±3.90	0.323 I
NS				
	Range	5 -12	6-16	
	After			
	Mean±SD	7.40±1.75	8.84±3.69	< 0.001
I ***				
	Range	5-11	6-16	
	Difference in mean	1.82	0.40	
	p	< 0.001 Pa ***	<0.001 Pa ***	

and metformin on LH levels, an effect that was enhanced by the addition of omega-3 to metformin. This discovery is congruent with the outcomes of the meta-analysis carried out by Yuan[17]. The underlying mechanism of these hormonal changes remains not entirely elucidated, potentially linked to an overall enhancement in ovarian function feedback on the pituitary gland, or a direct influence on the pituitary gland, necessitating further empirical research for validation.

In this research, the combination of metformin+Omega3 and metformin by itself proved effective in significantly reducing mean testosterone levels. Interestingly, the reduction achieved with the combination therapy exceeded that of metformin alone. Supporting these study findings, Kazerooni[18] concluded that metformin treatment in PCOS patients not only decreases testosterone levels but also greatly enhances the clinical manifestation of hyperandrogenism. Back in the 1990s, it was unveiled that metformin brought down testosterone levels in women suffering from PCOS. This result is supposed to stem from the drug's capability to increase insulin sensitivity. All the same, the exact apparatuses through which metformin influences PCOS are quiet a mystery, and the reaction of PCOS patients to this action diverges generally (Sam and Ehrmann[19]).

In a randomized organized medicinal trial attended via (Nadjarzadeh[20]) to explore the influence of omega-3 supplementation on testosterone ranks in PCOS, it was exposed that Omega-3 supplemented could efficiently lower serum testosterone ranks, supporting with the present study's outcomes. Likewise, Amini[21] assumed a randomized double-blind, placebo-controlled trial encompassing 60 PCOS females to evaluate the belongings of Omega-3 supplemented, eventually determining that this involvement led to a important decline in serum testosterone ranks. Therefore, the existing study's outcomes are steady with those of Amini[21]. The deterioration in serum testosterone ranks may be accredited to the stimulus of omega-3 on LH. Overproduction of LH can outcome in raised serum ranks of 17-hydroxy progesterone, testosterone and androstenedione (Demirel[22]). In PCOS patients, heightened serine phosphorylation of the insulin receptor triggers the stimulation of mutually ovarian and adrenal P450c17a enzymes, ultimately fostering androgen production (Allahbadia and Merchant[23]). Phelan *et al* demonstrated that a higher plasma n-6 PUFA absorption and n-6:n-3 PUFA ratio correlated with increased circulating androgens, whereas plasma LC n-3 PUFA position stood linked to a fewer atherogenic lipid profile. Supplementation with LC n-3 PUFA led to a reduction in plasma bioavailable testosterone concentrations, indicating that PUFA intake has the potential to alter the androgen profile (Phelan[24]).

The reasoning behind the enhanced impact of decreasing serum testosterone in women with PCOS after adding omega-3 supplementation is attributed to a synergistic effect achieved through the combined reduction of LH and net LH/FSH ratio by both metformin and omega-3. It has been documented in this research that the combination of metformin+Omega3 and metformin by itself were successful in significantly lowering the mean hirsutism score, nevertheless, the reduction brought about by the combination was greater than that caused by metformin alone. In a training via Kazerooni[18], metformin stayed managed to 40 women with PCOS for 8 weeks resulting in a notable decrease in hirsutism score compared to the baseline score pre-metformin therapy. Therefore, our outcomes support with those of Kazerooni[18] in terms of metformin's efficiency in dropping hirsutism score in females with PCOS. In the examination via Kelly and Gordon[25], sixteen females with PCOS and hirsutism contributed in a 14-month double-blind placebo-controlled cross-over training, viewing a essential enhancement in hirsutism at the finish of the metformin stage against placebo. Thus, the existing study's outcomes parallel with Kelly and Gordon[25] concerning metformin's positive influence on refining hirsutism score in PCOS females.

In a training via Maarouf[26], 67 sick with POS stayed accidentally allocated to two groups: Group I recognized daily 1 gram omega-3 fatty acid capsules, while Group II established no administration for 3 months. The consequences of this study exposed no extensive variation in hirsutism score, which opposes the explanations of the existing study. Khani *et al.* likewise renowned in 2017 that omega-3 supplementation over 6 months did not chief to an development in hirsutism score among females with PCOS, additional conflicting the outcomes of the existing training. The cause behind this spectacle might lie in metformin's capability to weaken testosterone ranks, as demonstrated in the existing research, furthermore, preceding trainings have designated that metformin can decrease ovarian androgen construction via 20%-25% (Shamim[28]). Metformin functions indirectly by hindering CYP17 cytochrome action, which productions a part in androgen synthesis, while likewise improving SHBG ranks, therefore foremost to a drop in free testosterone (Bulsara[20]).

Regarding our discovery of an enhanced impact of metformin when combined with omega-3, it is postulated that omega-3's influence on hirsutism scores may be attributed to the decrease in testosterone ranks,

unlike in the training via Nadjarzadeh *et al.* (2013), where a important decrease in testosterone ranks stayed observed after an 8-week regimen of omega-3 compared to a placebo.

CONCLUSION

The use of Omega3 has an efficient and safe synergistic effect when added to metformin in improving ovarian function and androgen effect in PCOS.

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