Effects of Letrozole And Metformin Versus Metformin alone on incretin in Iraqi patients with PCOS

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KEYWORDS

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ABSTRACT

I Background: The emergence of numerous novel therapeutic agents for managing T2DM has expanded the assortment of tailored therapies available for PCOS sick. One illustration of these is the incretin-based therapeutic agents.

Patients and methods:The extanttrainingcomprised 75 sickthrough an age extent of 18 to less than 40 years. Patients were categorized into three groups: metformin group (positive control group) and they received metformin as 500 mg per-oral (bid); letrozole group who were treated using 2.5 mg per-oral (bid), and combination groups who received both agents with similar doses as above. Each group included 25 females. Informationalmost age and body mass index (BMI) stayed included in the study. Serum measurement of incretin (GLP-1) was done before treatment and 90 days after treatment using Enzyme-Linked Immunosorbent Assay.

Results: There stayed no importantvariance in mean age (p = 0.981) betweentraining groups and means of age were 29.24 ± 6.10 years, 29.56 ± 5.50 years and 29.44± 5.83 years, respectively and the range of age was between 18 and 40 years. In addition, in this training, there stayed no importantalteration in mean BMI (p = 0.534) among study groups and means of BMI were 28.80 ±2.72 kg/m2, 27.53 ±1.95 kg/m2 and 27.07 ±1.99 kg/m2, respectively and the range of BMI was between 21.07 and 31.18 kg/m2. Serum incretin (GLP-1) level showed no significant variation among study groups, the mean levels were in the range of 10.87 -13.79 ng/ml and the range of values was from 9.56 -14.49 ng/ml. Changes in BMI are shown in. Metformin alone caused in more important weight decrease; nevertheless, adding of letrozole caused significant reduction in body mass index, letrozole alone also affect body weight significantly. It was observed that combined use of either drug resulted in more significant change of GLP-1 level at ($p \leq 0.001$).

Conclusion: Combined treatment with letrozole and metformin is safe and efficient in femalesby PCOS resultant in weight decrease, improved insulin sensitivity, increased endogenous GLP-1 secretion and improving overall metabolic derangement.

1. Introduction

An endocrine system disorder known as polycystic ovarian syndrome, or PCOS, affects 4–20 percent of women who are fertile (1-2). The Rotterdam principles for PCOS diagnosis stipulates that two of the subsequent three medical and biochemical indicators must be present at least once: excess androgen levels, anovulation/oligo-ovulation, and ultrasound-confirmed polycystic ovarian morphology (4). Numerous comorbidities, including dyslipidemia, insulin fighting, type 2 diabetes, mood swings, hepatic steatosis, and metabolic disease, are associated with PCOS. infertility, eating disorders, and obesity. Additionally, femalesby PCOS face an elevated possibility of developing hypertension, gestational diabetes, premature delivery, and miscarriages (5-11).

Management strategies for PCOS encompass lifestyle adjustments like dietary changes and physical exercise, which serve as the primary approaches to intervention; nevertheless, their efficacy in weight reduction or alleviating PCOS-related symptoms is reportedly limited (12). Pharmacological interventions are also an option; however, they lack explicit approval for PCOS management, having been predominantly utilized for situationsfor instance T2DM. The emergence of numerous novel healingmediators for management T2DM takes expanded the range of tailored therapies available for PCOS patients. One illustration of these stay the incretin foundedhealingmediators (13).

A notable rise in plasma insulin levels has stood documented following the oral administration of glucose in comparison to intravenous glucose mixture; this occurrence is commonly referred to as the 'incretin effect' and donates to 80% of overall insulin excretion subsequent to oral glucose intake (13). Incretins denote the hormones concealed by the gastrointestinal tract, such as glucose-

dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), mutually of which stay discharged following meal consumption, thereby augmenting insulin secretion triggered by glucose (14).

Incretin hormones production a crucial part in regulating glucose homeostasis through mechanisms such as inhibiting hepatic glucagon secretion, delaying gastric draining, and curbing craving, consequently contributing to the management of body weight and enhancement of glycemic regulation (13). Nevertheless, the majority of investigations conducted on Polycystic Ovary Syndrome (PCOS) have demonstrated compromised incretin secretion and functionality in individuals who are overweight or obese, while smaller-scale research endeavors have documented varied findings on GLP-1 levels in PCOS patients, including reductions, maintenance, or elevations (14, 15).

Next an oral glucose tolerance test (OGTT), femalesthrough PCOS have shown augmented GIP levels and decreased GLP-1 absorptions, as described in a study (17). Another study indicated a decrease in GLP-1 among personsthroughreduced glucose tolerance (IGT) and impaired fasting glucose (IFG), which are initial indicators of pre-diabetes and the development of T2DM (18). Endogenous GLP-1, with a half-life of 1–2 min, is quickly broken down by the proteolytic enzyme DPP-4, faster than GIP, which takes a half-life of 5 min (19). Research in animal prototypes and medicalsituations has shown that both DPP-4 inhibitors and GLP-1 RAs are effective in treating PCOS and preventing its metabolic effects (20). The existing study was aiming at exploring the effects of Letrozole and metformin versus metformin alone on incretin in Iraqi patients with PCOS.

2. Methodology

The existingtrainingcomprised 75 sickthrough an age extent of 20 to less than 40 years. Those patients were analyzedby (PCOS) based on Rotterdam principles (Rotterdam, 2004) by 2 specialists in obstetrics and gynecology. Pregnant women, women with co-morbidities such as diabetes mellitus, essential hypertension, liver disease and kidney disease, women with hyperprolactinemia and women with thyroid disease stoodexceptedas of the training. sickwascharacterized into three groups: metformin group (positive control group) and they received metformin as 500 mg per-oral (bid); letrozole group who were treated using 2.5 mg per-oral (bid), and combination groups who received both agents with similar doses as above. Each group included 25 women. The patients were recruited from the Maternity and Pediatrics Teaching Hospital in Adiwaniyah Province, Iraq. The trainingstayspassérear to October the 21st 2023 and extended to March 31st 2024.

Informationaround age and BMIstood included in the study. Serum measurement of incretin (GLP-1) was done before treatment and 90 days after treatment expending Enzyme-Linked Immunosorbent Assay (ELISA) (BT LAB, China). The trainingstayedacceptedthrough the moralagreementcommission of College of Medicine/ University of Al-Qadisiyah. All participants were informed to give a written consent nextfilleddesign of the aims and the procedures of the existingtraining.

Statistical investigationstayedapproved out by means of (SPSS type 26.0, IBM, Chicago, USA). Numeric data were expressed as range, standard deviation and mean. One way ANOVA checkstayed used to parallel means among study groups, which was followed y least significant difference stake hoc examination. The significance statistical flatstayedfixed at p-value of less than or equaling 0.05.

3. Results and discussion

Comparison of demographic characteristics among training groups stays shown in (table 1). There stayed no importantalteration in mean age (p = 0.981) betweentraining groups and means of age were 29.24 ± 6.10 years, 29.56 ± 5.50 years and 29.44± 5.83 years, respectively and the range of age was between 18 and 39 years. In addition, in this training, there stood no importantvariance in mean BMI (p = 0.534) among study groups and means of BMI were 28.80 ±2.72 kg/m^2, 27.53 ±1.95 kg/m^2 and 27.07 ±1.99 kg/m^2, respectively and the range of BMI was between 21.07 and 31.18 kg/m^2.

Serum incretin (GLP-1) level showed no significant variation among study groups, the mean levels were in the range of 10.87 -13.79 ng/ml and the range of values was from 9.56 -14.49 ng/ml, table 2.Changes in BMI are shown in (table 3). Metformin alone caused in more important weight decrease; nevertheless, adding of letrozole producedimportantdecrease in BMI, letrozole alone also affect body weight significantly. It was observed that combined use of either drug resulted in more significant change of GLP-1 level at ($p \leq 0.001$), table 4.

Table 1: An analysis of the study groups' demographic differences.

Representative	**Grouping M** ***n* = 25**	**Grouping L** ***n* = 25**	**Grouping ML** ***n* = 25**	***P***
Age (years)				
Mean ±SD	29.24 ± 6.10	29.56±5.50	29.44 ± 5.83	0.981 O NS
Assortment	18 - 39	18 - 38	19 - 38	
BMI (kg/m2)				
Mean ±SD	28.80 ± 2.72	27.53 ± 1.95	27.07 ± 1.99	0.534 O NS
Assortment	21.07 – 30.42	24.34 – 31.18	23.82 – 30.81	

Table 2:GLP-1 serum level comparison between research groups.

Characteristic	**Group M** ***n* = 25**	**Grouping L** ***n* = 25**	**Grouping ML** ***n* = 25**	***p***
(GLP-1) ng \ ml				
Mean ±SD	12.24 ± 2.92	13.79 ± 3.11	10.87 ± 2.58	0.358 O NS
Range	11.58 – 13.12	12.68 – 14.49	9.56 – 11.38	

Table 3: Changes in BMI after treatment

Characteristic	**Grouping M** ***n* = 25**	**Grouping L** ***n* = 25**	**Grouping ML** ***n* = 25**	***p***
BMI (kg/m^2) before treatment				
Mean ±SD	28.80± 2.72	27.53 ± 1.95	27.07 ± 1.99	0.534 O NS
Range	21.07 – 30.42	24.34 – 31.18	23.82 – 30.81	
BMI (kg/m^2) after treatment				
Mean ±SD	26.37 ± 3.17	25.39 ± 1.50	24.21 ± 1.15	
Range	23.37 – 35.45	22.86 – 27.58	22.15 – 25.96	< 0.001 O ***
P	<0.001 Pa ***	0.042 Pa *	0.018 Pa*	

Table 4: Changes in serum GLP-1 levels after treatment

Characteristic	**Grouping M** ***n* = 25**	**Grouping L** ***n* = 25**	**Grouping ML** ***n* = 25**	***P***
GLP-1 ng/ml before treatment				
Mean ±SD	12.24 ± 2.92	13.79 ± 3.11	10.37± 2.58	0.358 O NS
Range	11.58 – 13.12	12.68 – 14.49	9.56 – 11.38	
GLP-1 ng/ml after treatment				
Mean ±SD	28.94 ± 5.83	26.28 ± 4.98	25.3 ± 3.92	0.041 O *
Range	27.12 – 29.93	25.53 –27.58	24.93 – 26.4	
P	≤ 0.001 pa ***	≤ 0.001 pa ***	≤ 0.001pa ***	

Discussion

The most important findings in this study were the significant weight reduction using metformin and letrozole and that using both drugs in combination was more effective in this aspect, in addition, the significant improvement in serum GLP-1 levels after using metformin, letrozole or both agents. Regarding the impact of metformin, Vine et al. (21) noted a significant decrease in mean BMI with metformin, a finding consistent with the current study. Another study linked a 5.8% reduction in mean BMI specifically to metformin in women with PCOS (22). Current findings indicate that changes in weight due to metformin are more likely linked to reduced caloric intake rather than increased energy expenses. Metformin is believed to influence craving control mutuallystraight and indirectly through its gastrointestinal lateralproperties (23).

In an experimental investigation concerning the impact of letrozole, the management of letrozole over a period of 21 days led to a notable rise in body weightiness ($p < 0.001$) in the PCOS grouping as paralleled to the controlling rats (24); conversely, Bukke et al. demonstrated that the management of (PCOS) byLetrozole resulted in weight reduction (25). Clinical findings by Vitek et al. presented evidence of elevated BMI subsequent to the administration of letrozole for ovulation induction (26). Hence, the existing data on the influence of letrozole on weight in PCOS patients exhibit discrepancies, necessitating further investigation to achieve consensus; nevertheless, from a clinical standpoint, the combination of metformin with letrozole in PCOS patients is anticipated to lead to weight reduction induced by metformin, thus offering superior metabolic outcomes compared to using letrozole as a standalone treatment. Approximately half of femalesmiseryas of PCOS stay affected by weighty or obesity (27). The presence of additional body weight exacerbates insulin fighting, subsequently triggering metabolic disturbances, inflammation,hyper-androgenism, and sterility in personsthrough PCOS (28).

In relation to GLP-1, subsequent to an extensive exploration of published literature on platforms such as PubMed, ResearchGate, and other medical databases, the investigator encountered a lack of analogous research designs assessing the impact of letrozole or metformin on serum GLP-1 levels in women with PCOS. Consequently, this aspect can be considered a distinctive feature of originality within this particular study. A trainingviaFerjan et al. (29) revealed that the response of GLP-1 to oral glucose stayed diminished in females with both fatness and PCOS along through pre-diabetes, as opposed to females with fatness and PCOS but normal glucose tolerance, in spite ofanalogous BMI, age, and identical sickness characteristics. These outcomesunderline the crucial metabolic function of GLP-1 in females with PCOS, suggesting that weight reduction may underlie the enhancement of GLP-1 serum levels in this population. Regarding the impact of letrozole on endogenous GLP-1 levels, to the finest of our information, this represents the inaugural documentation, demonstrating that the combination of letrozole and metformin led to heightened levels of endogenous GLP-1. Investigations into novel glucose dropping medications, for instance glucagon-like peptide-1 receptor analogs (GLP-1RA) utilized in the management of fatfemalesby PCOS, have exhibited a decrease in body weight, anrise in menstrual regularity, and enhancements in hyperandrogenemia and metabolic irregularities, surpassing the efficacy of metformin (30, 31). The drawback of this particular therapy may involve the subcutaneous route of administration; therefore, the induction of endogenous GLP-1 through oral therapy involving a combination of metformin and letrozole may be more readily embraced from a clinical perspective.

4. Conclusion and future scope

Combined treatment with letrozole and metformin is safe and efficient in femalesby PCOS resultant in weight decrease, improved insulin sensitivity, increased endogenous GLP-1 secretion and improving overall metabolic derangement

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