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Effect of metformin drug on zinc and magnesium levels in women with polycystic ovary syndrome

Efecto del fármaco metformina sobre los niveles de zinc y magnesio en mujeres con síndrome de ovario poliquístico

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Abstract

Background: polycystic ovary syndrome involves oligomenorrhea and/ or anovulation due to excess testosterone or LH, in addition to metabolic disorders that may result in decreased levels of important vitamins and minerals, including Zinc and Magnesium levels. **Aim of the study**: To show if metformin treatment for polycystic ovarian women can change zinc and magnesium levels in those women. **Subjects and methods**: this study involves 23 early-diagnosed polycystic ovarian women not on metformin and 16 polycystic ovarian women on metformin 850 mg twice daily for at least three months. FSH, LH, testosterone, estradiol, prolactin, SHBG, fasting insulin, fasting glucose, magnesium and zinc are measured on the second day of the cycle. **Results**: the patients without metformin showed significant increases in LH, LH: SH ratio, and free testosterone at P-values of 0.03, 0.037 and 0.009 respectively. Zinc showed a direct correlation with estradiol in patients not on metformin and an indirect correlation with body mass index in patients on metformin treatment. **Conclusion**: Zinc is an important element for female fertility as it may enhance estradiol level may be due to its antioxidant activity which decreases the inflammatory reaction in the pelvic region and enhance ovary function. The increase in zinc level has an inverse effect on body mass index. However, metformin treatment in this study showed no effect on the level of magnesium and zinc in polycystic ovarian women.

Keywords: PCOS, Metformin, Zinc, Magnesium, LH: FSH ratio, HOMA-IR

Resumen

Fundamento: el síndrome de ovario poliquístico implica oligomenorrea y/o anovulación por exceso de testosterona o LH, además de trastornos metabólicos que pueden resultar en una disminución de los niveles de vitaminas y minerales importantes, incluidos los niveles de zinc y magnesio. **Objetivo del estudio**: mostrar si el tratamiento con metformina para mujeres de ovario poliquístico puede cambiar los niveles de zinc y magnesio en esas mujeres. **Materiales y métodos**: este estudio involucra a 23 mujeres de ovario poliquístico diagnosticadas temprano que no toman metformina y 16 mujeres ováricas poliquísticas que toman metformina 850 mg dos veces al día durante al menos tres meses. FSH, LH, testosterona, estradiol, prolactina, SHBG, insulina en ayunas, glucosa en ayunas, magnesio y zinc se miden en el segundo día del ciclo. **Resultados**: los pacientes sin metformina mostraron aumentos significativos en la relación LH, FSH y testosterona libre en valores de p de 0,03, 0,037 y 0,009 respectivamente. El zinc mostró una correlación directa con el estradiol en pacientes que no recibieron metformina y una correlación indirecta con el índice de masa corporal en pacientes en tratamiento con metformina. **Conclusión**: el zinc es un elemento importante para la fertilidad femenina, ya que puede mejorar el nivel de estradiol puede deberse a su actividad antioxidante que disminuye la reacción inflamatoria en la región pélvica y mejora la función del ovario. El aumento en el nivel de zinc tiene un efecto inverso en el índice de masa corporal. Sin embargo, el tratamiento con metformina en este estudio no mostró ningún efecto sobre el nivel de magnesio y zinc en mujeres ováricas poliquísticas.

Palabras claves: SOP, metformina, zinc, magnesio, LH:FSH, HOMA-IR

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Metformin is a drug that shows anti-inflammatory activity by decreasing interleukin-1 B and TNF-a[1] and can decrease oxidative stress[2] in addition to its effect of decreasing glucose level[3]. Most polycystic ovarian women suffered from insulin resistance, increased inflammatory reaction as well as high oxidative stress[4-7.]

Low magnesium level is associated with insulin resistance, and it has been detected that low magnesium level can increase polycystic ovary development by 19 times than other causes[8], as magnesium is important for autophosphorylation of insulin receptor[9] while, zinc has antioxidant activity and its deficiency lead to abnormal production of insulin[10], also, low zinc level may have a role in the development of polycystic ovary syndrome[11,12] as it is important for normal insulin activity[13].

It has been found that low zinc level is associated with hirsutism and a high rate of miscarriage, while metformin drug can decrease the rate of these two complications in polycystic ovarian women[14-18]. Moreover, restoration of magnesium levels in polycystic ovarian women can decrease hirsutism and androgenemia and improve sleep[19] which resembles the effect of metformin[20].

Some researchers try to find the effect of metformin on magnesium and zinc in type II diabetes patients[21-23], in chronic kidney disease[24], before and after surgery[25] and one research tries to find the effect of metformin on zinc and magnesium level23 Other type of research try to find the effect of zinc and magnesium as an added complement to metformin treatment[26-29]. The third type of research tries to determine the level of magnesium and zinc in polycystic ovary syndrome[12,16,30].

This research is the first one to try to find the metformin effect on zinc and magnesium level in polycystic ovarian women.

Subjects Materials and Methods

In September 2022, a study was conducted in Mosul, Iraq, where women of childbearing age visited a private clinic for gynaecology and obstetrics. These patients were diagnosed with polycystic ovarian syndrome based on the Rotterdam criteria, and their weight and height were measured to obtain their body mass index (BMI). Patients with diabetes, thyroid problems, or those taking medication other than metformin were excluded from the study. The study consisted of two groups. The first group included 23 women who were diagnosed with polycystic ovarian syndrome for the first time, and they had not taken any medication to treat their condition before. The second group consisted of 16 women who had previously been diagnosed with polycystic ovarian syndrome and were on metformin 850 mg twice daily for at least three months before the study. Both groups provided blood samples after fasting on the second day of menstruation. The blood samples were analyzed for various hormone levels and other factors such as FSH, LH, testosterone, estradiol, prolactin, SHBG, insulin, free testosterone, zinc, magnesium, and glucose. The Cobas technique was used to measure FSH, LH, testosterone, estradiol, prolactin, SHBG, insulin, and glucose, while the ELISA technique was used to measure free testosterone. Zinc was measured spectrophotometrically. This study provides valuable information on the effects of metformin on women with polycystic ovarian syndrome, as well as the hormone levels and other factors that may contribute to the condition.

HOMA-IR measured insulin sensitivity is determined by the formula:

(fasting insulin X fasting glucose)/22.5[31]

Descriptive statistical analysis was used for all the data collected including Mean, Standard deviation, and Median. Mann-Whitney test was used to test the differences between study groups and Spearman correlation coefficient was used to test the relationship between continuous variables. The significance level was set at $p < 0.05$

Results

The table labelled Table(1) depicts a comparison between two distinct groups of women suffering from Polycystic Ovarian Syndrome (PCOS). The first group, referred to as Group 1, consists of patients who have been recently diagnosed with PCOS and have not undergone any treatment using metformin before. The second group, Group 2, comprises women who have been diagnosed with PCOS previously and have been treated using metformin 850mg twice a day for at least three months. The table's findings have shown that there is no significant difference in the measured parameters between Group 1 and Group 2, except for LH, LH: FSH ratio, and free testosterone levels. The p-value for LH, LH: FSH ratio and free testosterone levels were found to be 0.03, 0.037, and 0.009, respectively. This indicates that there is a significant difference in these parameters between the two groups of women. The LH levels were found to be higher in Group 2, which is a significant finding as higher LH levels are typically associated with PCOS. The LH: FSH ratio was also higher in Group 2, which can be attributed to the metformin treatment that they underwent. The free testosterone level is higher in group1, as it is known that PCOS can result in an increase of free and /or total testosterone. This finding could be attributed to the fact that Group 1 patients were recently diagnosed and had not undergone any treatment for PCOS before.

In this study, the correlation of zinc with BMI, estradiol, and HOMA-IR respectively in group 1 of polycystic ovarian women was investigated. The results showed that there were insignificant indirect correlations of zinc with BMI and HOMA-IR, but there was a significant direct correlation of zinc with estradiol at a p-value of 0.029. This suggests that zinc may play a role in regulating estradiol levels in women with PCOS. Additionally, the table in the study exhibited correlations of magnesium with BMI and HOMA-IR in the same group of women. The results showed insignificant indirect correlations between magnesium and both BMI and HOMA-IR. This suggests that magnesium may not play a significant role in regulating these parameters in women with PCOS who are not treated with metformin. Furthermore, the study also found that there was a significant indirect correlation between zinc and BMI at a p-value of 0.001. This suggests that zinc may indirectly influence BMI in women with PCOS. However, there were insignificant indirect correlations of magnesium with both BMI and HOMA-IR. This suggests that magnesium may not play a significant role in regulating these parameters in women with PCOS who are not treated with metformin.

Discussion

The polycystic ovarian women metformin-treated group exhibit a significant decrease in LH, LH: FSH ratio, and free testosterone when compared to polycystic ovarian women, not on metformin (table 1). It is well known that metformin can decrease LH and testosterone by enhancing insulin sensitivity or by neurotransmitter expression that decreases gonadotropin-

Table 1. Comparison between PCOS women not on metformin and PCOS women on metformin treatment

Measured parameters	Metformin-free group (Mean +SD)	Metformin-treated group (Mean +SD)	p-value
Age (Years)	28±5	27±5.7	0.27
BMI	28.6 ± 5.9	28.5 ± 5.07	0.810
FSH (uIU/ml)	6.4 ± 1.7	6.8 ± 3.9	1.000
LH (uIU/ml)	11.1 ± 5.5*	7.7± 3.9	**0.030**
LH: FSH ratio	1.8 ± 1.1*	1.3 ± 0.7	**0.037**
Testosterone (ng/ml)	0.53 ± 0.4	0.32 ± 0.25	0.084
Free testosterone (Pg/ml)	2.8 ± 0.6*	2.24 ± 0.7	**0.009**
Estradiol (Pg/ml)	114 ± 51.6	97.9± 59.5	0.061
Prolactin(ng/ml)	18.7 ± 11.8	24.3 ± 16.7	0.275
SHBG(nmol/L)	27.5 ± 17.3	31.8 ± 14.5	0.228
Fasting insulin (UIu/ml)	16 ± 13.94	15.8 ± 8.8	0.724
sugar Fasting (mg/dl)	111.4 ± 90.7	114.3 ± 55.3	0.251
HOMA-IR	4.3 ± 3.9	4.4 ± 2.8	0.621
Mg (mg/dl)	2.2 ± 0.4	2.0 ± 0.4	0.275
Zn (mg/dl)	84.1 ± 38.9	99.8 ± 44.5	0.101

Independent-Samples Mann-Whitney U Test

releasing hormone[32,33].

But there are no significant differences in zinc and magnesium levels between the two groups. However, untreated PCOS women and those on metformin show an inverse correlation between BMI, HOMA-IR with magnesium and zinc level (table 2), and it is a significant indirect correlation between zinc and BMI in polycystic ovarian women in the metformin group at p-value 0.001(table 2).

This result suggests that metformin will not affect the level of zinc but may enhance its bioavailability and biological activity. A new study found that zinc is an important metal for polycystic ovarian women because it enters the formation of the ZAC protein (zinc-alpha2-glycoprotein). This protein is synthesized by visceral adipose tissue and is decreased in polycystic ovarian women but is increased on metformin intake[34]. ZAC protein has a relation to obesity status, the major complication in polycystic ovarian syndrome[35]. The suggested effect of metformin on the level of ZAC34 may explain the indirect correlation between BMI and zinc in polycystic ovarian women treated with metformin. Therefore, metformin may not affect zinc level but increase zinc that enter the synthesis of ZAC, especially since zinc supplementation has been found to decrease body weight[26].

A study of metformin's effect on zinc and magnesium levels in the rat[23] showed an increase in zinc levels after metformin intake and they suggested that metformin enhances zinc metabolism and absorption. However, the metabolism of zinc in the rat may be different from human metabolism, also the dose used is 50 mg/kg which is too much higher than the human dose in our research

Concerning human studies, one study showed that metformin did not affect on zinc levels but increased intraerythrocytic magnesium levels in type 2 diabetes[21] which is in agreement with our study for zinc levels, but we did not measure magnesium inside erythrocyte

Table 2. Correlation between PCOS women not on metformin and PCOS women on metformin treatment.

		HOMA – IR	Estradiol E2	IMC	
Metformin - Free group	r	-0,15	**0,456**	-0,173	Zn
	p	0,494	**0,029**	0,43	
	r	-0,256		-0,331	Mg
	p	0,239		0,123	
Grupo tratado con metformina	r	-0,390	**0,411**	-0,732	Zn
	p	0,135	0,114	**0,001**	
	r	-0,275		-0,367	Mg
	p	0,302		0,162	

On the other hand, in another study on type 2 diabetes, metformin caused an increase in zinc levels[22] which is not in agreement with our study. They attributed their result that after metformin intake the glycemic index is improved in their patients which may lead to decrease excretion of urinary zinc. However, in our study, the two groups of patients showed no significant difference in insulin sensitivity (HOMA-IR), which may explain the insignificant difference in zinc levels between the two groups

There is a direct correlation between zinc and estrogen in both groups and it is significant in polycystic ovarian patients not on metformin (table2), this may be due to the estrogen decreasing zinc release from the kidney[36], or zinc may increase estrogen secretion from the suprarenal gland[37], another opinion is that zinc may up-regulate ovarian FSH receptors to increase estrogen production[38]. However, the antioxidant activity of zinc may have a role in decreasing inflammatory reactions in pelvic region and enhancing ovarian function

Conclusion

Zinc is an important element for female fertility as it may enhance estradiol level may be due to its antioxidant activity which decreases the inflammatory reaction in the pelvic region and enhance ovary function. Also, an increase in zinc level has an inverse effect on body mass index. However, metformin treatment in this study showed no effect on the level of magnesium and zinc in polycystic ovarian women.

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