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The Effect of Vitamin D3 and Co-enzyme Q10 Supplementation on Metabolic Biomarkers in Women with Clomiphene Citrate Resistant Polycystic Ovary Syndrome

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Abstract:

Polycystic ovary syndrome (PCOS) one of the most common endocrine disorders in women of reproductive age, the pathogenesis of PCOS imitated to be as a vicious cycle involving both hyperandrogenaemia and insulin resistance/hyperinsulinemia. Vitamin D deficiency (VDD) is common among women with PCOS (approximately 67%–85% women with PCOS have VDD). Vitamin D3 and CoQ10 could affect glucose metabolism and insulin sensitivity and improve metabolic abnormalities in PCOS. The study was designed to evaluate the effect of combining oral vitamin D3 tablet or CoQ10 capsule with clomiphene citrate on metabolic biomarkers in women with clomiphene citrate resistance PCOS patients. A prospective interventional randomized-controlled, open-label study include 41 PCOS patients aged range (18-34)years who are clomiphene citrate resistant divided into two groups, group 1 (n=24) whose endogenous vitamin D status less than 20ng/ml receive clomiphene citrate 100mg daily(for 5 days monthly induction) plus vitamin D 10000IU daily (2 months) and group 2 (n=17) whose endogenous vitamin D status equal or more than 20ng/ml receive clomiphene citrate 100mg daily(for 5 days monthly induction) plus CoQ10 200mg daily (2 months). Fasting blood samples were taken at baseline and 2 months after intervention to measure metabolic biomarkers [fasting serum insulin (FSI), fasting blood glucose (FBG), homeostatic model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI)]. After 2 months both interventions result in non-significant change in FSI and FBG while HOMA-IR and QUICKI decreased by both interventions, but the decrease is significant only with CoQ10 supplementations. In conclusion, Vitamin D and CoQ10 supplementation result in improvement in HOMA-IR and QUICKI but the improvement was more obvious in CoQ10 group.

Key words: Polycystic Ovary Syndrome, Vitamin D3 supplementation, Co-enzyme Q10, Homeostatic model assessment of insulin resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI).

تأثير العلاج بالفيتامين دي3 والانزيم المساعد Q10 على العلامات الايضيه لدى النساء المصابات بمتلازمه تكيس المبايض المقوم للعلاج الاحادي بالكلومفين سيترات

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الخلاصة:
متلازمة تكيس المبايض واحدة من أكثر اضطرابات الغدد الصماء شيوعا في النساء في سن الإنجاب ، وان امراضيه تكيس المبايض تبدوا لتكون حلقة مفرغة تنطوي على كل من فرط الأندروجين وفرط الانسولين /مقاومة الأنسولين. نقص فيتامين دي شائع بين النساء المصابات بمتلازمه تكيس المبايض (حوالي 67٪ إلى 85٪ من النساء اللواتي لديهن متلازمة تكيس المبايض لديهن نقص فيتامين دي). فيتامين D3 وCoQ10 يمكن أن يؤثر على استقلاب الجلوكوز وحساسية الأنسولين ويحسنان التغيرات الأيضية في متلازمة تكيس المبايض. صُممت الدراسة لتقييم تأثير اضافه أقراص فيتامين D3 أو كبسولة Co Q10عن طريق الفم على مؤشرات التمثيل الغذائي لمرضى متلازمه تكيس المبايض المقاوم للعلاج الاحادي بالكلومفين سيترات. وهذه الدراسه التوسعية المفتوحة التداخلية العشوائية تشمل 41 مريض تتراوح أعمارهم بين 18-34 عامًا الذين مصابون بمتلازمه تكيس المبايض المقاوم للعلاج الاحادي بالكلومفين سيترات مقسم إلى مجموعتين ، المجموعة 1 (ع= 24) فيها المرضى لديهم حاله الفيتامين دي الداخلي أقل من 20نغ/مل يتلقون كلوميفين سترات 100 ملغ يوميا (لمدة 5 أيام تنشيط) بالإضافة إلى فيتامين D3 10000IU يوميا (شهرين) والمجموعة 2 (ع = 17) فيها المرضى لديهم حالة فيتامين دي الداخلي تتساوى في أو أكثر من20نغ/مل يتلقون كلومفين سيترات 100مغ يوميا (لمدة 5 أيام تنشيط) بالإضافة إلى Co Q10 200mg يوميًا (شهرين). تم أخذ عينات الدم الصائمة في بدايه الدراسه وبعد شهرين من التداخل العلاجي لقياس المؤشرات الحيوية الأيضية (مصل الأنسولين الصائم ، الجلوكوز في الدم الصائم ، HOMA-IR QUICKI). بعد مرور شهرين ، يؤدي كلا التدخلين إلى تغير غير ملحوظ في FSI و FBG بينما انخفض HOMA-IR و QUICKI من خلال كلا التدخلين ، ولكن الانخفاض مهم فقط مع مكملات CoQ10. في الختام ، تؤدي مكملات فيتامين D3 و CoQ10 إلى التحسن في HOMA-IR وQUICKI ولكن التحسن كان أكثر وضوحًا في مجموعة CoQ10.

الكلمات المفتاحية : متلازمه تكيس المبايض، مكملات فيتامين دي 3، كو انزيم Q10، تقييم نموذج التوحيد القياسي لمقاومة الأنسولين، مؤشر فحص التحسس الكمي للإنسولين.

Introduction:

Polycystic ovary syndrome (PCOS) one of the most common endocrine disorders in women of reproductive age and characterized by ovarian dysfunction and characterized by clinical manifestations such as increased insulin resistance, obesity and compensatory hyperinsulinemia, oligo/anovulation and infertility and insulin resistance (IR) is regarded as the core mechanism of PCOS pathogenesis [1]. IR occurred in many PCOS women, and as a result compensatory hyperinsulinemia which thought to contribute to hyperandrogenism [2].

Vitamin D deficiency (VDD) is common among women with PCOS (approximately 67%–85% women with PCOS have VDD) [3]. While the precise mechanism relate vitamin D and insulin resistance is not known, diverse cellular and molecular mechanisms suggested to explain this relationship, also vitamin D mediate insulin sensitivity by improving calcium status, increasing local production of 25OHD, which leads to transcriptional regulation of specific genes and there is evidence that VDR genotype may affect insulin resistance, both in regards to insulin secretion (the Apa1 VDR polymorphism) and insulin resistance (the BsmI VDR polymorphism) or suppressing serum levels of PTH in which VDD associated with increases PTH production, and their level regulated through serum calcium and vitamin D3 level, also PTH may mediate insulin resistance by reducing glucose uptake by liver, muscle and adipose cells, additionally vitamin Dimprove insulin sensitivity indirectly through improving muscle mass, and the reduction in vitamin D status with increased adiposity[4].

Vitamin D can affect glucose metabolism and insulin resistance through direct and indirect actions of vitamin D status through: i) direct stimulation of insulin release through the expression of VDR as well as the enzyme 1 α -hydroxylase in the pancreatic b-cells; ii) binding of the 1,25(OH)2D–VDR complex to the vitamin D response element of the insulin sensitive receptor (INSR) at the tissue level and thereby enhancing insulin responsiveness for glucose transport; and iii) suppression

of proinflammatory cytokines release that thought to mediate IR[5]; iv)vitamin D regulates intracellular and extracellular calcium, which is crucial for insulin-mediated actions in insulin-responsive tissues[6].

CoQ10 is a powerful antioxidant within the mitochondria as well as within other organelle membranes containing CoQ10[7]. Regarding CoQ10 effect on glucose metabolism and insulin sensitivity, CoQ10 intake may improve markers of insulin metabolism by modifying insulin and adiponectin receptors as well as tyrosine kinase (TK), phosphatidyl inositol kinase (PI3K), and glucose transporters[8], also peroxisome proliferated activated receptor-gamma (PPAR-γ) which present primarily in adipocytes, that plays an important function in glucose and insulin metabolism[9]. And CoQ10 intake may induce PPAR-γ expression thorough the calcium-mediated adenosine monophosphate kinase (AMPK) signal pathway and suppressing differentiation-induced adipogenesis [10].

Taken together all the previous evidence, this study was designed to evaluate the potential effect of vitamin D3 and CoQ10 supplementation in women with clomiphene citrate resistance PCOS to improve metabolic abnormalities in PCOS.

Patients and Method

A total of 41 PCOS patients were enrolled in the study during their visit to gynecologic and obstetric of the general hospital and private clinic, patients complete the study are at reproductive aged ranged from 18-40 years and desired to be pregnant.

The patients were under the supervision of specialist gynecologist and were treated according to the practice guidelines and diagnosed according to Rotterdam criteria. All patients were resistant to clomiphene citrate (CC) mono therapy. PCOS patients with vitamin D deficiency (< 20 ng/ml) were enrolled in one group and PCOS patients with insufficient vitamin D (20-30ng/ml) to be enrolled in another group.

The study was approved by the scientific and ethical committee and the agreement of Babylon health directorate was achieved. Patient written consent was taken after full explanation the aim of the study and ensures the reliability of the collected information.

This study is a prospective interventional randomized- controlled, open-label study designed to evaluate the effectiveness of combining oral vitamin D3 tablet or oral Co-enzyme Q10 capsule with clomiphene citrate tablet, on the hormonal profile and response to ovulation stimulation in clomiphene citrate-resistance PCOS patients. The study was conducted during the period from September 2017 to April 2018.

The eligible patients were allocated into two main groups; group 1 include 24 patients assigned to be treated with clomiphene citrate oral tablets 50mg twice daily after meal plus a daily dose of vitamin D3 10000IU oral tablets after meal for two months period. Group 2 include 17 patients assigned to be treated with clomiphene citrate oral tablets 50mg twice daily after meal plus a daily dose of CoQ10 soft gel capsule 200mg after meal for two months period.

Methods

Ten ml of venous blood were collected from each patient and then separated by centrifuge and the serum samples were used in the measurement of Serum Insulin (FSI) using Cobas e411 Sandwich principle [11] and Fasting Blood Glucose (FBG) using ACCU-CHECK Active meter [12]. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated for each patient using their fasting blood glucose in mg/dl and their fasting serum insulin in mIU/ml using the following equation:

HOMA-IR= (Fasting serum insulin) *(Fasting blood glucose) / 405[13]

The quantitative insulin sensitivity check index (QUICKI) was derived using the inverse of the sum of the logarithms of the

fasting insulin in µU/ml and fasting glucose in mg/dl for each patient:
QUICKI = 1 / (log (fasting serum insulin µU/mL) + log (fasting blood glucose mg/dL)) [13]

Statistical Analysis

Statistical analysis was carried out using SPSS version 20. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Fisher exact test were used to find the association between the categorical variables. Independent samples t-test was used to compare means between two groups. Paired t-test was used to compare means for paired reading. A p-value of ≤ 0.05 was considered as significant.

Results

The demographic and disease character-ristics of 41 patients, including 24 patients in group 1 (58.5%) and 17 patients in group 2 (41.5%), the baseline distribu-tion of PCOS patients enrolled in the study groups (Vitamin D3 and CoQ10) accor-ding to the inclusion criteriais shown in Figure (1),The age range for all patients were between 18-34 years with the mean age of 24.71 ± 4.07 years for group 1 patients, and 22.76 ± 3.8 yearsfor group 2 patients. No statistically significant differ-ence found between study groups with respect to age (P>0.05). Considering the patients residence there were (66.7%) of group 1 patients versus (58.8%) of group 2 patients were rural, and (33.3%) of group 1 patients versus (41.2%) of group 2 patients were urban with no significant statistical difference between both groups (P>0.05). The average body mass index (BMI) for group 1 patients and for group 2 patients was 26.46 ± 4.09 kg/m2 and 27.59 ± 4.63 kg/m2, respectively. No statistically sign-ifycant difference was found between the study groups with respect to the BMI (P>0.05). Positive family history was seen in (37.5%) of patients in group 1 and (29.4 %) of patients in group 2, table (1).

Table (1) Demographic data and disease characteristics of PCOS patients

Study variables	Study groups		*P*-value
	Group 1 (n=24)	Group 2 (n=17)	
Age (years) **Range (years)**	(24.71 ± 4.07) (19-34)	(22.76 ± 3.8) (18-31)	0.191^{NS}
	n %	**n %**	
Residence			
Urban	8 (33.3)	7 (41.2)	
Rural	16 (66.7)	10 (58.8)	0.607^{NS}
Total	24 (100.0)	17 (100.0)	
BMI (kg/m^2)	26.46 ± 4.09	27.59 ± 4.63	0.41^{NS}
Normal (18.5-24.9)	9 (37.5)	6 (35.3)	
Overweight (25-29.9)	12 (50.0)	8 (47.1)	1.000^{NS}f
Obese (≥ 30)	3 (12.5)	3 (17.6)	
Total	24 (100.0)	17 (100.0)	
Family history of PCOS			
Yes	9 (37.5)	5 (29.4)	0.591^{NS}
No	15 (62.5)	12 (70.6)	
Total	24 (100.0)	17 (100.0)	

Data presented as mean ± SD, Number of patients (n), Percentage (%), NS: No significant differences (*P*>0.05), f: Fisher exact test.
Independent-sample *t*-test is used for statistical analysis of (age, residence, family history, high diet sugar).

Fisher exact test is used for statistical analysis of (BMI).

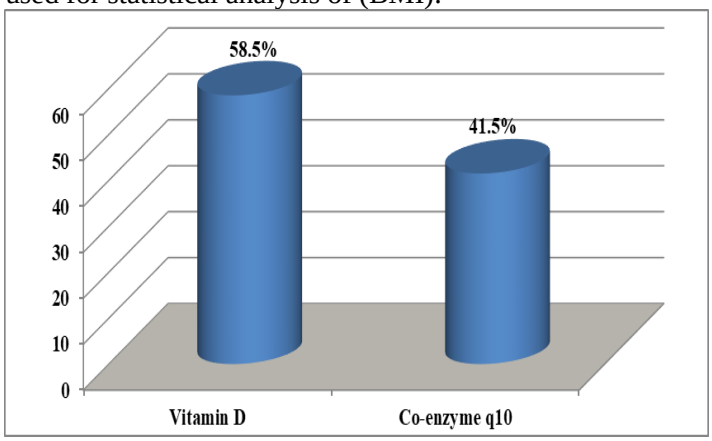

Figure (1) The baseline distribution of PCOS patients

Pretreatment analysis revealed no significant difference in the mean FSL, FBG, and HOMA-IR levels between group 1 and group 2 PCOS patients ($P>0.05$), while pretreatment QUICKI scores between group 1 and group 2 PCOS patients was significant ($P\leq0.05$), moreover, no significant decrease in FSI and FBG level in patients within group 1 and group 2 after treatment when compared to pretreatment level ($P>0.05$). While the decrease in HOMA-IR and QUICKI scoresin group 1 patients after 2 months treatment was non-significant, meanwhile in group 2 patients there is significant decrease in HOMA-IR and QUICKI score when compared to pretreatment ($P\leq0.05$), table (3)

No significant difference in FSI, FBG, HOMA-IR and QUICKI level between both study groups after 2 months of treatment was noticed ($P>0.05$).

Table (2) metabolic parameters (FSI, FBG, HOMA-IR, QUICKI) before and after vitamin D3 and CoQ10 supplementations

Study variable	Study group		*P* value
	Group 1 (n=24)	Group 2 (n=17)	
FSI (µU/ml)	**(Mean ± SD)**	**(Mean ± SD)**	
Pre-treatment	9.49 ± 5.87	13.25 ± 10.52	0.151 NS
Post treatment	7.96 ± 3.01	9.95 ± 6.54	0.197 NS
***P*-value**	0.203 NS	0.102 NS	
Percentage of change (%)	-16.12%	-24.91%	
FBG (mg/dl)			
Pre-treatment	94.58 ± 7.87	99.00 ± 7.65	0.081 NS
Post treatment	95.38 ± 6.30	95.88 ± 5.74	0.794 NS
***P*-value**	0.586 NS	0.102 NS	
Percentage of change (%)	0.85%	-3.15%	
HOMA-IR			
Pre-treatment	2.23 ± 1.31	3.34 ± 2.92	0.109NS
Post treatment	1.87 ± 0.73	2.38 ± 1.66	0.193 NS
***P*-value**	0.193 NS	0.050*	
Percentage of change (%)	-16.14%	-28.74%	
QUICKI			
Pre-treatment	0.351 ± 0.03	0.331 ± 0.02	0.036*
Post treatment	0.353 ± 0.02	0.348 ± 0.03	0.555NS
***P*-value**	0.756 NS	0.017*	

Percentage of change (%)	0.57%	5.14%	

Data presented as mean ± SD, Number of patients (n)
NS: No significant differences ($P>0.05$), *($P\leq0.05$) is considered Significant difference.
Paired *t*-test is statistically used to compare between pre- and post-treatment results in same group. Independent sample *t*-test is used to compare pre or post treatment between group 1 and group 2 patients.

Discussion: -

In the present study, all PCOS patients enrolled in this study are resistance to clomiphene citrate and desired to be pregnant and were at the reproductive aged range from 18-34years and were matched in majority of previous studies [14-17]. Most of them were resident in rural areas than in urban one, willing to have more children.

About (65%) of PCOS patients in both group in this study were overweight and obese, meanwhile only (35%) were normal weight. This finding was consistent with that of Wang et al. (2016) and Gomathi et al. (2011) where (55.65%) of patients were obese[18,19], that weight gain and obesity occur in approximately (61%) and (76%) of women with PCOS[20], mostly central or abdominal obesity in which hyperinsulinemia, insulin resistance (IR), and hyperandrogenemia influence adipocyte function and distribution through inhibition of adipocyte differentiation, which modulates lipolysis and lipogenesis[21]. Moreover, obesity was worsening reproductive and metabolic abnormalities in women with PCOS [22].

Positive family history of PCOS was found in more than (35%) of patients in both groups of the present study Tehrani et al. in (2014) found that about (45%) of patients with PCOS have positive family history of PCOS [23]. Additionally, Begum et al. (2017) reported (60.8%) of patients have positive PCOS family history [24], both studies were consistent with the present one. This is due to the fact presence of a genetic component to PCOS and familial clustering of reproductive and metabolic abnormalities results in increased risk of PCOS among first-degree relatives of PCOS patients [24]. A study found 5 to 6-fold increase in the incidence of PCOS among first-degree female relatives of affected patients when compared with the prevalence of PCOS in general population [25].

In the present study, the treatment with both interventions produced a decrease in fasting serum insulin after two months, though non-significant when compared with pretreatment levels, also the treatment with both intervention produced no significantly change in fasting blood glucose and this was in agreement with Rashidi et al. (2017) who found no significant change in fasting serum insulin and fasting blood glucose after administration of 50000IU vitamin D3 either weekly bases for 8week or monthly bases for 2 months in PCOS patient[26] Another studies by Raja-Khan et al. (2014) the use of a high vitamin D3 dose (12000IU) daily for 12 weeks result in non-significant change in fasting serum insulin and fasting blood glucose[27], Selimoglu et al. (2010) after three weeks of the administration of the single dose of 300,000 units of vitamin D3 orally found no significant change in fasting serum insulin and fasting blood glucose[28], and Garg et al. (2015) also found no significant change in fasting serum insulin and fasting blood glucose after 6 months of daily 400IU vitamin D3 supplementation[29]. Studies by Wehr et al. (2011) and Karadağ et al. (2018) non-significant decrease in fasting serum insulin while significant decrease in fasting blood glucose posttreatment of vitamin D3 for 12 weeks and 24 weeks was noticed [30,31]. Nevertheless, Maktabi et al. (2017) found that vitamin D3(50000 IU orally) every 2 weeks for 12 weeks result in significant decrease in serum insulin and fasting blood glucose [32].

Samimi et al. (2017) study was the first clinical trial evaluating the effects of CoQ10 supplementation on glucose metabolism and lipid profiles among women with PCOS, and he found that CoQ10 supplementation 200mg daily for 12 weeks result in significant decrease in fasting serum insulin and fasting blood glucose[33], in the present study the decrease in fasting serum insulin and fasting blood glucose after CoQ10 supplementation was marked but still non-significant. This result could be affected fasting blood sample less than 8hrs which affect testing of serum insulin and glucose.

The HOMA-IR measurement which reflects insulin resistance in PCOS women was

reduced after both interventions, significantly after CoQ10 treatment. Previous studies stated that vitamin D3 supplementation did not decrease HOMA-IR [27,30,34], which matches the present findings. On the contrary, other studies found significant decrease in HOMA-IR after vitamin D3 supplementation [28,29,31,32]. Jamilian et al. (2017) found that supplementation with 4000 IU/day of vitamin D for 12 weeks to PCOS women resulted in significant decreases in serum insulin, HOMA-IR when compared with 1000 IU/day of vitamin D and placebo [35].

After CoQ10 treatment for 12 weeks, Samimi et al. (2017) found significant decrease in HOMA-IR (-0.3±0.6 vs. +0.2±0.6, P=0.001) [33], which was in agreement with the present study. Insulin sensitivity was measured using QUICKI test which was significantly increased after CoQ10 supplementation in the current study and agreed by Samimi et al. (2017) (+0.006±0.009 vs. -0.006±0.01, P<0.001) [33], and a minimum increase after vitamin D supplementation that was agreed by previous studies [27,36]. Maktabi et al. (2017) and Asemi et al. (2015) also reported significant increase in QUICKI posttreatment with vita-min D or vitamin plus calcium supple-mentation [32,37].

In conclusion, vitamin D 3 and CoQ10 supplementations in clomiphene citrate resistance PCOS result in improvement in HOMA-IR and QUICKI score especially with CoQ10 supplementation.

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