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The role of 25 hydroxycholecalciferol (VITD3) on insulin– Resistance in patients with polycystic ovary syndrome (PCOS)

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the greatest frequent endocrine syndrome in females, giving with numerous likely mixtures of symptoms and signs and a variety of phenotypes, which might contain generative, endocrine, and metabolic modifications. PCOS is characterized by hypothalamic–pituitary– ovary axis dysfunction and anovulation ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured but, unlike other causes of ovulatory disappointment that feature inadequate ovarian follicle development or repressed gonadotropin emission, PCOS typically includes androgen excess and subtle alterations in serum levels of gonadotropins and estrogens.

Objective: demonstrate and compare therapeutic effect of vitamin D; supplementation on the metabolism and endocrine parameters of polycystic ovary syndrome patients with insulin- resistance.

Subjective: The study was carried out on 86 patients, divided into 2 groups, group A treated by vitamin D supplement, while group B treated by placebo.

Results: The fasting blood sugar was significant decreased in the two studied groups. HOMA IR shows a significant decrease in the two studied groups after treatment but in group A "vitamin D supplement" decrease by a highly significant degree than the placebo group. SHBG show a significant increase in both studied groups, after treatment there was a slight increase in group A more than group B in SHBG but this increase was insignificant. Vitamin D induces the transcription of HOXA10 through vitamin D receptors. Managenent with vitamin D rises mRNA and protein appearance of HOXA10. Vitamin D too has a straight influence on the rule of HOXA10, and this has implications for fertility.

Conclusion: A significant effects of vitamin D supplementation on either metabolic or endocrine parameters in our study of PCOS women with insufficient baseline 25(OH)D concentrations.

Keywords: hydroxycholecalciferol (VITD3), PCOS, syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted disorder considered by raised androgen concentration, menstrual indiscretions, and/or small cysts on one or both ovaries [1].

PCOS is a heterogeneous condition that distresses at least 7% of adult femlaes [2]. In one manscripts they proposes that 5.0% -10.0% of women at age 18 to 44 years had pretentious by PCOS making it the greatest public endocrine irregularity amongst females of reproductive age [3].

PCOS is associated with overweightness: among 38 and 88% of females with PCOS are overweight or obese, while PCOS can also obvious in lean patients PCOS also contacts with other topographies of the metabolic I pattern with Type 2 DM (T2DM), high blood pressure, dyslipidemia and insulin resistance, though long-term likely data are missing [4].

Approximations the incidence of metabolic syndrome in patients of PCOS are ranged between 34 - 46%, via the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria. It is also strong that hyperandrogenism is regularly linked with T2DM in females [4].

The syndrome can be morphologic or mostly biochemical (hyperandrogenemia). Hyperandrogenism, a medical stamp of PCOS, it can cause inhibition of follicular development, microcysts in the ovaries, anovulation, and menstrual changes [5]. PCOS can be described as an oligogenic disorder in which the interaction of a number of genetic and environmental factors determine the heterogeneous, clinical, and biochemical phenotype [6].

Although the genettcettology of PCOS remains unknown, a family history of PCOS is relatively common; however, -familial link. to PCOS is unclear.

Environmental influences concerned in PCOS can be worsened by deprived nutritional selections and sedentary lifestyle; infectious agents and toxins may also play a parts. The generative and metabolic topographies of PCOS are occasionally rescindable with lifestyle alterations such as weight loss and exercise [7].

Diabetes Mellitus (DM) is caused by defects in insulin secretion, insulin action or both. The condition is regarded as one of the increasing health problems• in the world. It is estimated that in 2011, a total of 366 million people worldwide had diabetes mellitus, and as many as 4.6 million deaths were attributable to the disease [8].

Insulin is a hormone manufactured by the beta - cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke [9].

The type of DM is based on the presumed etiology. The two most common types of DM are: type l and type 2 DM. Type 1 diabetes (TID) is a syndrome that ' rises subsequent the autoimmune destruction of insulin-producing pancreatic ß cells [10].

The complain often detected in children and adolescents, frequently giving with a classic trio of signs (i.e., polydipsia, polyphagia, polyuria) together with of obvious hyperglycemia, postulating the instant need for exogenous insulin additional - a medicinal introduction to the disorder whose therapeutic practice lasts a lifetime. In type 1 DM, the body does not produce insulin and daily insulin injections are required. The type affects about 1 in every 600 children [11].

Type 2 DM is the result of failure to produce sufficient insulin and insulin resistance. Elevated blood glucose levels are managed with reduced food intake, increased physical activity, and eventually oral medications or insulin [12].

The importance of obesity stems from its association with comorbidities and other obesity-related conditions. Vitamin Dis a steroid derivative, and 25-hydroxy-vitam1n D is a functional. indicator of vitamin D in circulation [13].

According to the last National Diet and Nutrition Survey (NDNS) conducted in the United Kingdom, serum concentration of 25-hydroxy-vitamin D above 30 mg/ml is regarded as: Vitamin D sufficiency, while the concentration below 20 ng/ml is considered as vitamin D deficiency (VDD) [14].

In addition, women with PCOS are more likely to. develop VDD, the prevalence of VDD in PCOS patients is approximately 67-85% which is much higher than the general adults, whose prevalence of VDD is 20-48% Moreover, some articles reported that VDD is associated with some comorbidities, such as T2:0M, insulin resistant syndrome of obesity, metabolism syndrome (MS), and cardiovascular diseases [15].

In T2DM, vitamin D may influence both insulin secretion and sensitivity. A negative association between T2DM and vitamin D is assumed from cross-sectional and prospective manscripts, though decisive resistant is as yet lacking. Obtainable manscripts vary in their project and in the recommended daily budgets (RDA) of vitamin D in non-skeletal diseases and -cell function [16].

The aim of this work was to demonstrate and compare therapeutic effect of vitamin D; supplementation on the metabolism and endocrine parameters of polycystic ovary syndrome patients with insulin-resistance.

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Patients and Methods

This is a randomized clinical trial that was carried out at Al-Azhar University hospital for 12 months from October 2020 till October 2021. It included 86 patients recruited to outpatients of Al-Azhar University hospital. Vit D3 deficiency is associated with insulin resistance (IR) in PCOS women and though supplementation could overcome IR and improve the endocrine dysfunction for those women. Women attending outpatient clinic diagnosed on the basis of Rotterdam criteria for diagnosis of PCOS2004 with proven insulin resistance (HOMA IR). Eligible study subjects were reproductive age women ≥18 years with PCOS according to Rotterdam criteria and 25-hydroxyvitamin D [25(OH) D] serum concentrations 20–30 ng/ml.

History of Hyperandrogenism (Hirsutism)

Hyperandrogenism is a key diagnostic feature of PCOS affecting between 60%-100% with the condition with both clinical and biochemical hyperandrogenism. Equally topographies of hyperandrogenism are inspiring to measure and differ by approaches of assessment, society and confusing factors counting extra weight and life style. Valuation of biochemical hyperandrogenism is disadvantaged by a absence of lucidity on which androgens to quantity.

Examination of Hirsutism: *Clinical need for*

Body image is complex and is influenced by many factors. Body image is defined here as the way a woman may feel, think about and view their body including their appearance. Relevant physical, psychological (self–esteem) and sociocultural factors influence body image. Assessment of body considers body dissatisfaction disorderd eating, body size estimation and weight. Most women from the general population are dissatisfied with their body, yet negative body image appears more prevalent in PCOS and impacts on thoughts and feelings of health, apprerance, QoL, mood and physical fitness. In this context, body image should be considered in PCOS.

Recommendations for screening and assessment that are easy to use and widely applicable are needed and if identified. Addressing negative body and associated mood disorders is important to improve emotional wellbeing and QoL in PCOS.

Investigation of Hirsutism

Signs and symptoms of severe androgen excess can result in virilisation and mansculinisation, Virilisation is rare. Clinical evidence of mild to moderate androgen excess is more common including hirsutism, ocne, and androgen–related alopecia. The interrelationships of these clinical features remains unclear, varies by ethnicitym and requires clinician training, vigilance and skill to assess. These features impact considerably on quality of life in women with PCOS and treatment burden including cosmetic therapies can be significant. Given the fundamental role of hyperandrogenism in diagnosis, and the adverse impact on quality of life, this question was prioritised.

Exclusion criteria

Hormonal contraception within 3 months prior to study inclusion:

1. Use of insulin-sensitizing drugs within 6 months prior to study inclusion.
2. Use of lipid-lowering drugs or serum androgens.
3. Prevalent type 2 diabetes mellitus.
4. Menstrual irregularity.
5. Regular vitamin D supplementation within 3 months prior to study inclusion.

Intervention

1st visit: patients take 1.5 cm vidrops daily for 6 months (30 drops twice daily), following data affected: Age, BMI, Menstruation regulation, Hirsitism, FSB, Fasting insulin, Homa IR, SHBG, Free Testosterone, DHEA, Weight loss and clinical pregnancy, In additional all parpaeite adviced to reduce weight and do some exercise.
2nd visit: 6 months later, we take: FSB, Fasting insulin, Homa IR, SHBG, free testosterone, DHEA and weight loss and clinical pregnancy of the patients (10%)

Statistical analysis of the data: Data were fed to the computer using IBM SPSS software package version 20.0. Qualitative variables was defined with frequent and percentage. Evaluation the difference between studied groups according categorical variable star was verified by Chi-square test.

Results

Table (1) shows that, there was no statistical significant difference among the two studied groups regarding demographic data (P>0.05) while, there was statistical significant difference regarding weight loss (P < 0.05). There was no statistical significant difference between the two studied groups regarding menstruation regulation and presence or absences hirsitism (P > 0.05).

Table (2) showed no statistical significant difference between two studied groups in FBS before treatment (P<0.05), but there was significant decrease in FBS in group A after treatment, both groups showed significant decrease in FBS after 6 months of study. There was no statistical significant difference between both groups before treatment (P1>0.05). Group

(A) showed significant decrease in fasting insulin, both groups showed significant decrease in fasting insulin after 6 months of the study (P2<0.05). There was no statistical significant difference between both groups as regard HOMAS I.R. (P1>0.05). Group (A) showed significant decrease in HOMA IR (P2 < 0.05), both groups showed significant decrease in HOMA IR after 6 months of the study (P1 < 0.05). There was no statistical significant difference between two studied groups before and after SHBG (P1> 0.05), both groups shows significant difference in SBHG after 6 months (P2 < 0.05). There was no statistical significant difference as regard free testosterone (P1 > 0.05). Group (A) showed significant decrease in free testosterone (P2 < 0.05), both groups showed significant decrease in free testosterone after treatment of the study. There was significant difference between groups before treatment (P1< 0.05), but there was no statistical significant difference after treatment as regard DHEA (P1> 0.05). There was significant decrease in DHEA in both groups after 6 months of the study.

Table 1: Comparison between the two studied groups regarding basic demographic data, weight loss and clinical data

Variables	Group A"n=43"					
Age		30.9±3.3	30.2±4.0		0.935	0.352 N.S.
BMI		27.0±2.4	27.2±2.2		0.346	0.730 N.S.
Weight loss in Kg		4.6±1.5	2.4±1.2		7.628	0.001*
Clinical data	No.	%	No.	%	X2	P value
Menstruation regulation Regular Irregular	24 19	55.8 44.2	23 20	19 24	0.047	0.500 N.S.
Hirsitism Negative Positive	24 19	55.8 44.2	19 24	44.2 55.8	1.163	0.194 N.S.

T=student t-test P was significant if ≤ 0.05 N.S. = Not significant

Table 2: Comparison between the two studied groups regarding fasting blood sugar, fasting insulin, HOMA IR, SHBG, free testosterone, DHEA before and after treatment.

	Group A "n=43"	Group B "n=43"	t-test	P1 value1
FBS				
Before treatment FBS	138.5±25.6	134.8±21.7	0.714	0.477 N.S.
After treatment FBS	100.8±20.2	128.2±20.4	-6.237	0.001*
t-test, P2	22.11, 0.001*	8.19, 0.001*		
Fasting insulin				
Before treatment Fasting insulin	31.5±7.8	34.1±8.5	-1.504	0.136
After treatment Fasting insulin	21.9±6.0	27.4±7.3	-3.811	0.001*
t-test, P2	18.76, 0.001*	22.06, 0.001*		
HOMA IR				
Before treatment HOM IR	10.7±3.3	11.3±3.1	-0.803	0.424
After treatment HOM IR	5.4±1.9	8.6±2.4	-6.751	0.001*
t-test, P2	22.10, 0.001*	20.26, 0.001*		
SHBG (nmol/L)				
Before treatment SHBG	36.3±9.3	37.8±9.4	-0.781	0.437
After treatment SHBG	47.1±12.2	44.5±11.3	1.054	0.295
t-test, P2	-20.78, 0.001*	-19.88, 0.001*		
Free testosterone (pg/ml)				
Before treatment free testosterone	5.6±0.8	5.6±0.8	0.426	0.671 N.S.
After treatment free testosterone	3.7±0.6	4.2±0.7	-3.535	0.001*
t-test, P2	27.99, 0.001*	28.75, 0.016*		
DHEA (ng/dl)				
Before treatment DHEA	331.5±108.3	289.4±81.6	2.038	0.045*
After treatment DHEA	230.6±77.1	223.5±64.1	0.460	0.646 N.S.
t-test, P2	16.75, 0.001*	17.67, 0.001*		

P1 comparison between group A and B at the same time P2 comparison between before and after treatment in the same group T=student t-test * Significant at level 0.05 N.S. = not significant

Table 3: Comparison between the two studied groups regarding improvement in hirsutism and clinical pregnancy

	Group A "n=43"		Group "n=43"		χ^2 P value
	No	%	No	%	
Improvement in hirsutism					7.938
-ve	36	83.7	24	55.8	0.005*
+ve	7	16.3	19	44.2	
Clinical pregnancy					
-ve	18	41.9	37	86.0	18.209
+ve	25	58.1	6	14.0	0.001*

T= student t-test P was significant if ≤ 0.05 * Significant at level 0.05

Table (3) showed that, there was statistical significant difference between the two studied groups regarding improvement in hirsutism and clinical pregnancy ($P < 0.05$).

Discussion

In our results, the age, martial stustus, clinical pregnancy, body mass index, Menstruation regulates and Hirsitism show insignificant difference between the two studied groups, this results was important to eliminate the effect of demographic and basic clinical data on the main outcome of the study results.

In our results the fasting blood sugar was significant decreased in the two studied groups, but the decreasing of fasting blood sugar concentration in group was increasing significantly than the non- treated group, also the fasting insulin was significantly decrease in the two studied groups but the decrease in vitamin D treated group was higher than the decrease in group B.

In agreement with our results in change fasting blood sugar level, Trummer *et al*. (2019) [17] study the Properties of vitamin D supplementation on metabolic and endocrine parameters in PCOS, they found that Participants in the vitamin D group were significantly younger and had higher serum glucose concentrations at 60 min during OGTT when compared to the placebo group [17].

Where *et al*. established that vitamin D management at a amount of 20 000 IU weekly for 24 weeks better glucose absorption and menstrual frequency in PCOS women [18].

In contrast to our results, He *et al*., (2015), study the Serum Vitamin D concentration and Polycystic Ovary syndrome, they found in this study that No significant difference effect of vitamin D admission was found in studies reporting on fasting glucose level [15].

Also on the contrary, Ardabili *et al*. observed no significant change in fasting serum insulin and glucose concentrations, insulin sensitivity and homeostasis model assessment of insulin resistance following supplementation with 50,000 IU vitamin D3 for 2 months among patients with PCOS. However, a major drawback of the latter study is the relatively low dose of vitamin D3 treatment which is much lower than the current proposed guidelines [19].

In study carried out by Akl *et al*., (2019), on Role of Vitamin D Supplement Treatment on Ovulation and Insulin Resistance in Women with PCOS: A Randomized Controlled Trial, the results showed that the fasting insulin level was significantly increase in the vitamin D lacking subgroup and the control group related to the normal vitamin D subgroup. Consequently, HOMA2-IR was statistically significantly higher in the vitamin D deficient subgroup and the control group compared to the normal vitamin D subgroup [20].

The results of our study showed that the HOMA IR shows a significant decrease in the two studied groups after treatment but in group A "vitamin D supplement" decrease by a highly significant degree than the placebo group. On the other hand the SHBG show a significant increase in both studied groups, after treatment there was a slight increase in group A more than group B in SHBG but this increase was insignificant. The free testosterone was significantly decrease in the two groups, but the decreasing in patients taken vitamin D was highly significant than the other group.

In agreement with our study, Akl *et al*., (2019), found that the HOMA2-IR stayed significantly increased in the vitamin D lacking subgroup and the control group related to the normal vitamin D subgroup; while no significant differences were found between the vitamin D lacking subgroup and the control group [20].

Many authors have suggested that there is an association between vitamin D status and metabolic dysfunctions—particularly insulin resistance—in women with PCOS. However, the results of randomized controlled study that detect the effect of vitamin D intake of PCOS patients on glucose homeostasis still indecisive [21].

In a earlier meta-analysis that only comprised the results of controlled randomized study, the fasting sugar, fasting insulin, serum HOMA-IR, and QUICKI of PCOS patients show no modification after supplement with vitamin D [22].

Several factors might clarify these conflicting outcomes, counting the changed follow- up duration of vitamin D treatment, or management with vitamin D alone or with other micronutrients. Also, in this meta-analysis, when the vitamin D supplement was measured in the general opinion, the rule did not meaningfully distress fasting sugar, fasting insulin, or HOMA-IR in females with PCOS. Thus they decided to manner a much more thorough examination. It was documented that the amount of vitamin D (low or high), the incidence of supplement (daily or weekly), and the formula in which vitamin D was assumed (alone or as a co-supplement) all held a vital significance for glucose homeostasis. It was also seen that HOMA-IR reduced for low amounts of vitamin D (≤4000 IU/d). This could be the outcome of the more even absorption of vitamin D3 in the gut or well acquiescence [23].

Azadi-Yazdi *et al* suggested that vitamin D supplementation may significantly affect the serum total testosterone, whilst not being effective in improving other markers of the androgenic profile. These results are consistent with the results of the present study [24].

In meta-analysis carried out by Jia *et al*., (2015), they found that Ten studies included in this meta-analysis focused on the correlations between the serum concentration of vitamin D and PCOS. The results of the meta-analysis displayed that 25OHD level and the QUICKI of PCOS females were lesser than those of patients deprived of PCOS and that HOMA-IR was meaningfully more in PCOS women than in females without PCOS, signifying that serum vitamin D level was depressingly related with IR in PCOS [25].

This finding was consistent with previous studies revealing a negative association of 25OHD and HOMA-IR in PCOS women. The 25OHD concentration is an indicator of vitamin D status in the human body, and vitamin D deficiency is a major problem in PCOS because it relates to metabolic syndrome, which includes obesity, IR, and glucose intolerance [26]. Our results indicated that women with PCOS had markedly lower 25OHD concentrations, consistent with the findings of previous studies that reported lower vitamin D levels in PCOS patients than in non- PCOS patients, which may be explained by an association of vitamin D with androgens or sex hormone binding globulin (SHBG). Some authors found a direct relation between hyperandrogenism and vitamin D deficiency, revealing a possible interaction between androgens and vitamin D balance, mediated by a not yet completely known mechanism [27].

Moreover, a previous study also mentioned that androgens and hyperinsulinemia may also play a significant role in vitamin D levels.19 QUICKI is used to assess insulin sensitivity, and low insulin sensitivity can result in IR, which is one of the features of PCOS.44 The results of the metaanalysis revealed that PCOS patients had lower QUICKI, indicating that PCOS patients had lower insulin sensitivity and an elevated risk for IR [28].

In our results the pregnancy rate in treated group with vitamin D was significantly higher than the non-treated.

In agreement with our study, El-Halwagy *et al*., (2015) study the Vitamin D3 Administration in PCO Obese Patients: Effect on the Follicular Fluid Level of Vitamin D3 and Pregnancy Outcome in ICSI, they found that the serum level of vitamin D3 and the pregnancy rate in cases of ICSI were the subject of previous published studies; these studies investigated the role of vitamin D3 in early pregnancy, its expression in the endometrium and it's method of action [29].

Some manscripts strained to examine whether the serum levels of vitamin D3 container be used as a prognostic constraint in the gravidity and implantation rates in females of IVF
e.g. the study was carried out by Garbedian who classified the femles regarding to the vitamin D serum level into females having adequate (≥ 75 nmol/L) or inadequate (< 75 nmol/L) levels of vitamin D3 and he specified that adequate level of vitamin D3 carries improved establishment and gravidity rate than inadequate one [30].

Conclusions

Vitamin D supplementation has a great effect on either metabolic or endocrine parameters in our study of PCOS women with inadequate level of 25(OH)D concentrations. Women with PCOS are diagnosed with a decrease in (25 (OH) D), insufficiency of which is exacerbated as obesity progresses.

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