Benefits of using a microencapsulated vitamin D delivery system in women with polycystic ovary syndrome

Vesselina Yanachkova [1], Radiana Staynova [2], Svetoslav Stoev,[3] Emilia Naseva [4]

[1]Department of Endocrinology, Specialised Hospital for Active Treatment of Obstetrics and Gynecology, Sofia, Bulgaria
[2]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University of Plovdiv, Plovdiv, Bulgaria
[3]Department of Pharmaceutical Sciences and Social Pharmacy, Faculty of Pharmacy, Medical University – Pleven, Pleven, Bulgaria
[4]Faculty of Public Health, Department of Health Economics, Medical University of Sofia, Sofia, Bulgaria

Correspondence to
Dr Vesselina Yanachkova, Department of Endocrinology, Specialised Hospital for Active Treatment of Obstetrics and Gynecology "Dr Shterev", Sofia, Bulgaria; v_ess@abv.bg

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ABSTRACT

Objective To compare and assess the efficacy of two vitamin D delivery systems (oil-based and microencapsulated) on 25-hydroxy-vitamin D (25(OH)D) levels, body mass index (BMI) and insulin resistance (IR) in women with established polycystic ovary syndrome (PCOS) and vitamin D deficiency.

Materials and methods A monocentric, retrospective study was conducted, using the data of 70 female patients, who visited the endocrinology department of the "Dr. Shterev" Hospital, Sofia, Bulgaria between May 2020 and September 2020. The patients were divided into two groups according to the type of vitamin D_3 supplementation: either a microencapsulated liposomal form (n=35), or a conventional oil-based form (n=35). The following clinical measures were analysed and compared: BMI, serum levels of 25(OH)D, fasting plasma glucose levels, fasting immunoreactive insulin (IRI), homeostatic model assessment (HOMA) index, levels of antimullerian hormone (AMH) II generation, and testosterone. In all selected patients, these measurements were performed at baseline and 3 months after initiation of vitamin D supplementation.

Results Significantly increased serum levels of 25(OH)D were observed in patients supplemented with the microencapsulated form of vitamin D_3 in the third month from the beginning of therapy, compared with the control group (p=0.003). In the microencapsulated vitamin D group, there was a decrease in IRI serum levels (p=0.023), HOMA-IR (p=0.021), serum AMH (p=0.010) and testosterone levels (p=0.006). The fasting plasma glucose levels did not change significantly.

Conclusion The results of our study show that the patients supplemented with a microencapsulated form of vitamin D_3 achieved faster compensation of 25(OH)D levels, which in turn, under equal conditions, led to significant improvement in the metabolic profile, in particular insulin sensitivity.

INTRODUCTION

Vitamin D is a fat-soluble vitamin and prohormone that plays a major role in bone metabolism through the regulation of calcium and phosphorus homeostasis.[1–3] Along with this, it has a number of other, extracellular biological actions, which are due to the vitamin D receptors (VDR) located in nearly every tissue and cell in the body, including the ovary, endometrium, mammary glands, pancreatic β-cells, skeletal muscle, adipose tissue, etc.[4] It has been found that in ovarian tissue vitamin D stimulates the production of progesterone by 13%, estradiol by 9%, and estrone by 21%.[5] It is assumed that vitamin D has a physiological role in reproduction, including folliculogenesis and luteinisation, through the effect of the antimullerian hormone (AMH) and progesterone production in human granulosa cells.[6] Vitamin D may play an important role in glucose homeostasis. It stimulates insulin secretion through VDR located in pancreatic β-cells and reduces peripheral insulin resistance through VDR in the skeletal muscles and liver.[7] All this explains the importance of vitamin D in terms of reproduction, insulin secretion, and insulin sensitivity.

The major source of vitamin D for humans is exposure to natural sunlight.[2] Most of the amount of vitamin D_3 in the human body comes from its synthesis in the skin under the action of ultraviolet (UV) rays. Vitamin D_3 is formed when 7-dehydrocholesterol in the skin is exposed to UV irradiation (UVB 290–320 nm), and then converted to previtamin D_3.[8] Only 10–20% of the required amount of vitamin D for the body is obtained through dietary intake.[1] Vitamin D is synthesised under the action of the enzyme 25-hydroxylase in the liver that synthesises 25-hydroxy-vitamin D (25(OH)D), which is currently the main indicator of vitamin D status in the body. Through another metabolic step, under the action of renal 1-α-hydroxylase, 25(OH)D is metabolised to 1,25 dihydroxy-vitamin D—the physiologically active form of vitamin D in the body.[9] The hydroxylation process and the production of 1,25(OH)D depend on several factors, including plasma parathyroid hormone levels, calcium and phosphorus levels, and fibroblast growth factor 23.[4] Due to its binding to tissue receptors, the active form of vitamin D exerts its effects.[1 2]

With an insufficient intake of vitamin D with food, the absence of adequate sun exposure, or when there are disturbances in its synthesis or a defect in VDR, a state of deficiency occurs.[1–3 10]

In recent years, the results of numerous studies show that vitamin D deficiency is associated with a number of metabolic disturbances, including insulin resistance (IR).[11–14] Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and is a major cause of anovulation.[15] PCOS is characterised by the manifestation of moderate to severe IR. Hyperinsulinaemia is one of the main components in the pathogenesis of PCOS and is primarily responsible for hyperandrogenism.[16 17] Hyperinsulinaemia is not just a symptom of PCOS—it is also

Table 1 Baseline characteristics of observed women (p>0.05)

Characteristics	Control group (Oil-based vitamin D_3) n=35	Intervention group (Microencapsulated vitamin D_3) n=35
Age, mean (SD)	26.1 (3.4)	26.4 (3.9)
BMI (kg/m^2), median (IQR)	27.0 (24.0–31.0)	26.0 (21.5–32.0)
25(OH)D (nmol/L), mean (SD)	15.5 (4.4)	15.6 (5.4)
AMH (ng/ml), median (IQR)	8.1 (6.7–11.1)	8.0 (6.9–10.2)
Testosterone (nmol/L), median (IQR)	1.5 (1.1–1.8)	1.4 (1.0–2.0)
Fasting blood glucose (mmol/L), mean (SD)	5.0 (0.5)	5.0 (0.7)
IRI (mU/L), median (IQR)	16.2 (12.0–22.4)	14.2 (10.4–21.3)
HOMA-IR, median (IQR)	3.3 (2.3–4.8)	3.3 (2.3–4.7)

AMH, antimullerian hormone; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; IRI, immunoreactive insulin ; 25(OH)D, 25-hydroxy-vitamin D .

a major driver of the condition. Elevated insulin concentrations can disrupt ovulation and are associated with increased testosterone production.[18]

It has been suggested that vitamin D deficiency plays an important role in the pathogenesis of IR.[4] The prevalence of vitamin D deficiency in women with PCOS is 67–85%.[19] Low levels of 25(OH)D can lead to noticeable symptoms in women with PCOS, including IR, anovulation, menstrual disorders, hyperandrogenism, and obesity.[19–22] A study conducted in Bulgaria aimed to investigate vitamin D levels in 103 women with PCOS and/or obesity. The results showed that almost 2/3 of the observed women with PCOS and/or obesity had vitamin D deficiency.[23]

The aim of our study is to compare and assess the efficacy of two vitamin D delivery systems (oil-based and microencapsulated) on 25(OH)D levels, body mass index (BMI) and IR in women with established PCOS and vitamin D deficiency.

METHODS

Study design and population

A monocentric, retrospective study was performed, using the data of 70 female patients, who visited the endocrinology department of "Dr. Shterev" Hospital, Sofia, Bulgaria between May 2020 and September 2020. The inclusion criteria were women aged up to 35 years with established PCOS (based on the Rotterdam criteria) and vitamin D deficiency (25(OH)D <50 nmol/L).[1 2] Pregnant or breastfeeding women and those with chronic conditions such as diabetes, cardiovascular disease, and malignancies were excluded from the study. The patients were divided into two groups regarding the type of vitamin D_3 supplementation: an intervention group, supplemented with a microencapsulated liposomal form of vitamin D_3 (n=35); and a control group, supplemented with a conventional oil-based form (n=35). The dose administered was consistent with serum 25(OH)D levels and was identical for both groups. The rest of the pharmacotherapy was the same for both groups, including metformin tablets up to 1500 mg daily and myoinositol tablets 2000 mg daily. There were no patients treated with hormonal medications. All patients had received advice regarding a healthy diet (eg, low-calorie diet, reduction of saturated and trans-fatty acids, reduced intake of simple carbs, etc), weight management, and regular physical activity. The patients from both groups were scheduled to attend follow-up visits once a month for monitoring medication and dietary adherence. In every follow-up session, the possible difficulties related to adherence were discussed.

The Ethics Committee of the Specialised Hospital for Active Treatment of Obstetrics and Gynaecology "Dr. Shterev" approved the study. The study was carried out in accordance with the code of ethics of the Declaration of Helsinki.

Laboratory methods

The following anthropometric and clinical measures were analysed and compared: BMI, serum levels of 25(OH)D, fasting plasma glucose levels, fasting immunoreactive insulin (IRI), homeostatic model assessment for insulin resistance (HOMA-IR), levels of the antimullerian hormone (AMH) II generation and testosterone. Baseline measurements were compared with those made 3 months after initiation of supplementation with vitamin D. Fasting plasma glucose concentrations were determined by the hexokinase method (Cobas 6000, Roche, Indianapolis, IN, USA) with a reference interval of 3.9–6.1 mmol /L. 25(OH)D levels were measured by electrochemiluminescence immunoassay (ECLIA). IRI levels were determined by ECLIA (Cobas 6000) with a reference range of 2.6–25.0 mU/L. Insulin resistance was diagnosed using the HOMA-IR: (fasting plasma glucose × fasting IRI)/22.5; reference values: normal HOMA-IR <2.5; risk zone 2.5–5.0; high insulin resistance (HOMA-IR) >5.0. Serum AMH levels were measured using an ELISA kit with a reference range for the laboratory method of 1–6.8 ng/mL, and those of testosterone by ECLIA using Cobas 6000 with a reference range of 0.22–2.90 nmol/L.

Statistical methods

Statistical analysis of the data was performed with the software package IBM SPSS Statistics for Windows, version 19.0 (IBM Corp, Armonk, NY, USA). Continuous variables that followed a normal distribution were presented as mean and SD and those with a non-normal distribution were reported as median and IQR. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Comparison of the mean values between the groups (independent samples) was performed by using the independent samples t-test for normally distributed variables or the Mann-Whitney U-test for variables with a non-normal distribution. The hypothesised difference was 0 and two-sided p values were obtained. The level of significance (type I error) was 0.05 so all values of p<0.05 were considered significant.[24]

RESULTS

The mean age of the observed women, as well as the anthropometric and clinical baseline indicators, were similar in the two groups (p>0.05) (table 1). The mean age was 26.1±3.4 years in the control group taking the oil-based vitamin D3, and 26.4±3.9 years in the intervention group.

Table 2 summarises the results obtained after the 3 month treatment. A decrease in BMI was observed, but there was no statistically significant difference between the two groups. In patients supplemented with the microencapsulated vitamin D3, the serum levels of 25(OH)D increased significantly in the third month from the beginning of therapy compared with the control group (41.6±7.7 nmol/L vs 35.8±7.8 nmol/L, p=0.003). There was a significant decrease in IRI serum levels (p=0.023) and HOMA-IR (p=0.021) in the microencapsulated vitamin D3 group. These patients also had a significant reduction of serum AMH (5.6 ng/mL vs 6.2 ng/mL, p=0.010) and testosterone

Table 2 Measurements after the 3 month therapy

Characteristics	Control group (Oil-based vitamin D_3) n=35	Intervention group (Microencapsulated vitamin D_3) n=35	P value
BMI (kg/m^2), median (IQR)	25.0 (22.0–27.0)	24.0 (20.0–27.0)	0.482
25(OH)D (nmol/L), mean (SD)	35.8 (7.8)	41.6 (7.7)	0.003*
AMH (ng/ml), median (IQR)	6.2 (5.6–8.2)	5.6 (5.1–6.3)	0.010*
Testosterone (nmol/L), median (IQR)	1.2 (1.0–1.5)	1.0 (0.8–1.2)	0.006*
Fasting blood glucose (mmol/L), mean (SD)	5.0 (0.4)	4.9 (0.4)	0.347
IRI (mU/L), median (IQR)	12.3 (9.9–17.5)	10.2 (8.5–14.2)	0.023*
HOMA-IR, median (IQR)	2.7 (2.1–3.7)	2.1 (1.9–3.0)	0.021*

*Statistically significant difference.
AMH, antimullerian hormone; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; IRI, immunoreactive insulin; 25(OH)D, 25-hydroxy-vitamin D.

levels (1.0 nmol/L vs 1.2 nmol/L, p=0.006). The fasting plasma glucose levels did not change significantly.

Discussion

It has been found that vitamin D supplementation may reduce abnormally elevated AMH levels and have a beneficial effect on BMI and insulin sensitivity in patients with PCOS. All this has a positive effect on menstrual disorders and ovulation.[19–22]

Different vitamin D dosage forms are being currently developed.[25] A modern strategy for optimising oral bioavailability is to develop nano-based drug delivery systems, such as liposomes. They have a number of benefits such as biocompatibility, biodegradability, and non-immunogenicity.[26]

Microencapsulated vitamin D_3 used in our study is an oral dosage form containing 2000 IU/mL cholecalciferol and natural lecithin. This is a water-soluble form of vitamin D_3, where the active substance is included in nanocarriers—liposomes. A liposomal drug delivery system provides better and faster absorption.[27] The membranes of liposomes are composed of phospholipids—amphiphilic molecules, similar in structure to the membrane lipids—which makes them easily recognisable by intestinal epithelial cells. Due to the structural similarity, liposomes easily penetrate them.[26] The size of the liposomes is smaller than the intestinal epithelial cells, so the active substance loaded in the nanocarriers is absorbed in the intestinal cells unchanged. The process itself is very fast. Ensuring high bioavailability, the active ingredient is absorbed more efficiently in the intestinal mucosa, which results in faster recovery of normal levels of vitamin D_3. Compared with other forms of vitamin D_3, the microencapsulated drug delivery systems remain active in the blood plasma 2.5 times longer.[27]

Researchers from Lithuania compared the bioavailability of three different vitamin D oral supplements (microencapsulated, micellised, and oil-based) in a laboratory animal model. The results showed that the microencapsulated form of vitamin D was the most bioavailable.[27]

Our study confirms the faster achievement of target levels of 25(OH)D when using a microencapsulated form of vitamin D_3.

What this paper adds

What is already known on this subject

⇒ The microencapsulated form of vitamin D_3 ensures the high bioavailability of the drug.
⇒ Compared with other dosage forms of vitamin D_3, the microencapsulated drug delivery system remains active longer.
⇒ Vitamin D supplementation may reduce abnormally elevated antimullerian hormone levels and have a beneficial effect on body mass index and insulin sensitivity in patients with polycystic ovary syndrome.

What this study adds

⇒ There is currently no comparative analysis between the effects of microencapsulated versus oil-based vitamin D_3 on insulin sensitivity and hormonal levels in women with polycystic ovary syndrome.
⇒ Our results confirm that patients supplemented with a microencapsulated form of vitamin D_3 achieved faster compensation in 25-hydroxy-vitamin D levels.

This supplementation contributes to a faster improvement in insulin sensitivity and reduction of serum AMH and testosterone levels, which has been confirmed in other studies.[28 29] Although some studies have shown an inverse relationship between vitamin D levels and metabolic disorders in PCOS, no definitive conclusions can yet be drawn about this dependence.[30]

CONCLUSION

Our findings show that patients with PCOS supplemented with microencapsulated vitamin D achieved faster compensation in the levels of 25(OH)D, which in turn, under equal conditions, led to a beneficial effect on BMI as well as a significant improvement in the metabolic profile, in particular insulin sensitivity.

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ORCID iDs
Vesselina Yanachkova http://orcid.org/0000-0002-4205-7502
Radiana Staynova http://orcid.org/0000-0002-4025-7502
Emilia Naseva http://orcid.org/0000-0002-1282-8441

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