Original research

Prevalence of hypovitaminosis D, and its association with hypoadiponectinemia and hyperfollistatinemia, in Saudi women with naïve polycystic ovary syndrome

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ABSTRACT

Aims: The association between vitamin D and polycystic ovary syndrome (PCOS) is an active area of growing research. However, data in Saudi Arabia are scarce. This study aimed to define serum 25-hydroxyvitamin D (25(OH)D) levels among Saudi women with naïve PCOS, and to investigate the associations of their 25(OH)D status with their serum adiponectin and follistatin levels, along with indices of insulin resistance and hormonal deteriorations.

Methods: In this case-control observational study, 63 women with PCOS and 65 age- and body mass index (BMI)-matched control women were assessed. PCOS was diagnosed based on the revised criteria of Rotterdam. Fasting serum levels of 25(OH)D, adiponectin, follistatin, insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), androgen (Δ4-androstenedione), estradiol, progesterone, along with fasting plasma glucose (FPG), homeostasis model assessment-insulin resistance (HOMA-IR) index and lipid profile were measured in both groups.

Results: The prevalence of hypovitaminosis D (serum 25(OH)D < 30 ng/ml) was higher in PCOS group than control group (77.8% vs. 12.3%). Serum adiponectin and FSH concentrations were significantly lower, while serum follistatin, LH, TT, Δ4-androstenedione and insulin levels, as well as FPG and HOMA-IR were significantly higher in PCOS group than control group. In addition, 25(OH)D levels of PCOS women were significantly correlated positively with adiponectin and FSH levels, but negatively with follistatin, HOMA-IR, FPG, LH, testosterone, and Δ4-androstenedione levels.

Conclusion: Hypovitaminosis D, coexisted and correlated with hypoadiponectinemia and hyperfollistatinemia, is being an alarming risk factor in Saudi women with PCOS. Further investigational and explanatory studies in large size samples are warranted to realize these findings and to improve both diagnostic and treatment tools in Saudi women with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial, heterogeneous, endocrine-metabolic disorder that commonly affects women at their reproductive age. PCOS is a complex syndrome characterized by chronic oligo-or anovulation, menstrual irregularities, hyperandrogenism, infertility, and polycystic ovarian morphologic features [1–3]. Excess luteinizing hormone (LH) and low follicle stimulating-hormone (FSH) are also common, and approximately 60%–80% of all PCOS cases are more vulnerable to develop insulin resistance (IR) and compensatory hyperinsulinemia, which exacerbates ovarian androgen production and ovulation dysfunction in PCOS patients [1–3].

During the last decade, vitamin D has gained and sustained immense interest in the fields of biomedical and human health research [4,5] including those related to female reproductive-metabolic disorders [6]. At that respect, while the extent of this association remains inconsistent and requires further investigations, there is an increasing evidence that hypovitaminosis D (vitamin D insufficiency/deficiency) is associated with an increased prevalence of PCOS [7–9]. It has been suggested that vitamin D depletion plays a potential role in increasing IR and metabolic abnormalities and in disrupting ovarian folliculogenesis and hormonal secretion in PCOS patients [7–12], and it is therefore essential to screen vitamin D status among all the PCOS patients [13]. Furthermore, some recent interventional trials demonstrated that appropriate supplementation of vitamin D in vitamin D-deficient-PCOS women had resulted in enhancing their insulin sensitivity and improving their deteriorated sex-hormones and metabolic profiles, re-enforcing the importance of vitamin D status in the etiology
Subjects and methods

Subjects

Sixty-three Saudi women with naïve PCOS (case group; mean age: 31.6 ± 6.4 years, and mean body mass index (BMI): 22.2 ± 2.6 kg/m²), along with 65 age- and BMI matched non-PCOS control Saudi women with regular menstrual cycles (control group), who met the inclusion and exclusion criteria listed below, were enrolled and evaluated in this case-control observational study. All participants were outpatients referred to the Gynecology and Endocrinology Clinic of Obstetrics & Gynecology Department, Heraa’ General Hospital, The Western Region of Saudi Arabia. The enrollment process of study subjects was carried out at both the local media and the hospital outpatient’s clinical units by using IRB-approved advertisement materials and notifications, including both electronic and paper advertisements. The advertisement called for young Saudi women with history of irregular menses, infertility, ovary cysts, excess hair, etc., and for healthy volunteers Saudi women who had regular ovulatory cycles and came to the clinic for annual check-up or their partners had male fertility problems. Our plan was to enroll a 1:1 ratio between eligible PCOS and healthy control women matching by age and BMI. Based on available worldwide clinical data examined the prevalence of hypovitaminosis D in women with PCOS [7–11], sample size of 50 women per group was determined according to the following Rotterdam PCOS consensus criteria [27], which referred as the presence of at least two of the following three standard criteria: chronic oligo/amenorrhea and/or chronic anovulation (i.e., having menstruation at longer than 35 days intervals, or ≤9 cycles/year), clinical and/or biochemical signs of hyperandrogenism (i.e., hirsutism and/or excess serum androgens levels), and polycystic ovaries morphological features detected by ultrasound (i.e., having ovarian volume of over 10 cm³ and/or presence of more than 12 ovarian follicles of 2-9 mm in length) [27]. Exclusion criteria of the case group included women with known causes of anovulation, infertility, and hyperandrogenemia; including congenital adrenal hyperplasia, androgen-secreting tumors, Cushing’s syndrome, and hyperprolactinemia, or any disease that could possibly affect reproductive physiology. Women with diabetes, thyroid dysfunction, kidney or liver disease, or pregnancy were also excluded. All enrolled eligible PCOS and control women were not smokers or alcohol or drug abusers, and none of them had received any vitamin D supplement, contraceptives or any other drugs or hormonal treatment known to affect vitamin D metabolism or interfere with metabolic variables and hypothalamic–pituitary–gonadal axis for at least 3 months prior to the study. In addition, according to their ultrasound findings, none of the healthy women in the control group had evidence of polycystic ovaries. Institutional Ethical approval and written informed consent of all participants were obtained before the initiation of the study. The study was conducted according to the principals of the Declaration of Helsinki.

Blood sampling and laboratory parameters measurement

After 12 h fasting, two peripheral blood samples were obtained from each participant. Blood samples of menstruating women were taken during the mid-follicular phase of their menstrual cycle, while those of women with amenorrhea were taken randomly. The first blood sample was collected into a tube contained EDTA-anticoagulant and immediately used to estimate fasting plasma glucose (FPG) level, while the second one was collected into a plain tube without anticoagulant, centrifuged, and aliquots of its corresponding serum were immediately stored at −80 °C until analyzed for serum levels of 25(OH)D, adiponectin, follistatin, insulin, FSH, LH, total testosterone, androgen (Δ₄-androstenedione), estradiol, progesterone, and lipid profile parameters. In addition, insulin resistance (IR) was determined using the homeostasis model assessment of insulin resistance (HOMA-IR) index calculated as FPG (in mg/dL) multiplied by fasting insulin (in μU/mL) divided by 405, and a HOMA-IR value of 2.5 or above was considered as insulin resistant [28].

In the present study, serum levels of 25(OH)D; which is the most widely accepted biomarker for monitoring the overall vitamin D status [29,30], were quantitatively measured by commercially available enzyme-linked immunosorbent assay (ELISA) kit (IDS, Boldon, UK), following the manufacturer’s instructions. Based on the The Endocrine Society Clinical Practice Guidelines, interpretation of vitamin D status among the participants was as follow: 25(OH)D levels of 21–29 ng/mL and ≤20 ng/mL were considered as cases of vitamin D insufficiency and deficiency, respectively, while 25(OH)D of more than 30 ng/mL was regarded as a normal level [29,30]. Commercially available ELISA Kits were also used to determine the serum levels of adiponectin (Mediagnost, Uppsala, Germany), insulin (Monobind, Uppsala, US), and follistatin (R&D Systems, Inc., MN, USA) and following their corresponding manufacturers’ recommendations. As reported by the manufacturers, the intra- and inter-assay coefficients of variation (CVs) for serum 25(OH)D, adiponectin, follistatin and insulin were 5.4, 1.5%, 2.3%, 5.5% and 5.5, 2%, 8%, 5.8%, respectively, while the sensitivity of the assays for 25(OH)D, adiponectin, follistatin and insulin were 2.6 ng/mL, 0.6 ng/mL, 89 pg/mL and 2 μU/mL, respectively. All ELISA assays of 25(OH)D, adiponectin, and follistatin were performed in duplicate on a fully automated ELISA system (DYNEX, Technologies MRX II, VA, USA). The remaining biochemical and hormonal assays, which routinely carried out at Gynecology and Endocrinology Clinic Lab, were performed according to their standard protocols and procedures as described elsewhere.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for quantitative variables, while those for qualitative variables are presented as percentages or numbers. Analyses were performed using the statistical software version 17.0 for windows (SPSS Inc., Chicago, IL, USA). Comparison of mean variables between the two groups was estimated by Student’s t-test, and χ² test was used for frequency analysis. The associations between serum 25(OH)D levels and other measured variables in PCOS group were performed by the Pearson’s correlation test. A
Results

Following inclusion and exclusion criteria, 128 Saudi women, of whom 63 had PCOS (case group) and 65 non-PCOS women served as control group, were assessed in this study. As shown in Fig. 1A, PCOS group had significantly lower serum level of 25(OH)D compared with control group (13.4 ± 5.3 ng/mL vs 28.7 ± 8.5 ng/mL; p < 0.01). Similarly, serum concentration of adiponectin was significantly lower (p < 0.05) in women with PCOS compared with control women (Fig. 1B). However, serum follistatin level was significantly higher (p < 0.01) in PCOS patients compared with non-PCOS controls (Fig. 1C). Women of both groups were sub-categorized based on their vitamin D status (i.e., their serum 25(OH)D levels), and the prevalence of hypovitaminosis D (<30 ng/mL) was significantly (p < 0.01) higher in Saudi women with PCOS than in non-PCOS controls. As shown in Table 1, of the 63 eligible women with PCOS, only 14 cases (22.2%) had a sufficient level of vitamin D, while 49 cases (77.8%) had hypovitaminosis D distributed as follow: 6 cases (25.4%) had vitamin D insufficiency and 33 cases (52.4%) had vitamin deficiency. In contrary, among the eligible 65 non-PCOS controls, 57 women (87.7%) had adequate levels of vitamin D and only 8 women (12.3%) showed a status of hypovitaminosis D (6 women (9.2%) with vitamin D insufficiency and 2 women (3.1%) with vitamin D deficiency) (Table 1).

The characteristic metabolic and hormonal features of the studied PCOS and control groups are summarized in Table 2. The results showed that the levels of serum insulin, HOMA-IR and blood glucose, along with the serum levels of LH, testosterone and androgen (Δ4-androstenedione) hormones were significantly higher, while serum FSH concentrations were significantly lower, in the PCOS group (p < 0.05) compared with non-PCOS control group. Indices of dyslipidemia were higher in women of PCOS group than in the control women; however, this difference was not statistically significant (p > 0.05). Also, there were no significant differences regarding systolic and diastolic blood pressure, and the serum estradiol and progesterone levels between PCOS and control groups (all p not significant) (Table 2).

As demonstrated in Table 3, significant (p < 0.05) positive correlations were observed between the serum 25(OH)D levels of Saudi women with PCOS and their serum adiponectin and FSH levels. By contrary, serum 25(OH)D levels of these PCOS patients were negatively (p < 0.05) correlated with the serum levels of follistatin, LH, testosterone, Δ4-androstenedione, and insulin, as well as with FPG and HOMA-IR levels (Table 3). There were no significant correlations between serum 25(OH)D levels and other measured variables in PCOS group (Table 3).

Discussion

To date, the exact etiology and underlying pathogenic mechanisms of PCOS remain largely elusive. To this end, although its conclusion is still inconsistent and representing an active area of energetic research [31], impaired vitamin D status has been emphasized as an important risk factor in the development of PCOS and increased its metabolic and hormonal abnormalities [6–9]. Nevertheless, whether hypovitaminosis D has a causal association with PCOS among Saudi patients is not known. Data of the present study demonstrated that, besides indices of metabolic and hormonal deteriorations such as insulin resistance (IR), hyperinsulinemia, low circulating FSH, but excess LH testosterone, and

Table 1

Distribution of Vitamin D status among study’s participants. Sixty-three Saudi women with naïve polycystic ovary syndrome (PCOS group) along with 65 age- and body mass index (BMI) matched non-PCOS Saudi women (Control group), were enrolled and studied. After 12 h fasting, peripheral blood samples were obtained, and aliquots of their corresponding serum were used to measure the fasting serum levels of 25(OH)D. Based on the measured value of serum 25(OH)D, interpretations of vitamin D status among all subjects of both groups were as follow: 25(OH)D levels of 21–29 ng/mL and ≤20 ng/mL were considered as cases of vitamin D insufficiency and deficiency, respectively, while 25(OH)D of more than 30 ng/mL was regarded as a normal level.

| Vitamin D status (serum 25(OH)D ng/mL) | Control subjects (n = 65) | PCOS patients (n = 63) | P-value |
|--------------------------------------|-------------------------|-----------------------|---------|
| Adequate (> 30)                      | 57                      | 87.7                  | 14      | 22.2       | < 0.01 |
| Insufficient (20–29)                 | 6                       | 9.2                   | 16      | 25.4       | < 0.01 |
| Deficient (< 20)                     | 2                       | 3.1                   | 33      | 52.4       | < 0.001 |

p-value < 0.05 was considered as statistically significant.
androgen levels [1–3], Saudi women with PCOS had evidence of significant hypovitaminosis D status as indicated by their remarkably decreased serum 25(OH)D levels as compared to healthy controls. Most importantly, serum 25(OH)D levels of these PCOS patients were correlated inversely with IR indices (HOMA-IR and FPG levels) and serum levels of LH, testosterone and androgen, and positively with FSH levels. These findings may coherently support the sustained assumption that hypovitaminosis D is an alarming contributor in prevalence of PCOS and its metabolic and hormonal complications [10–13], and support the raised necessity to monitor PCOS patients for their vitamin D status [13].

Indeed, the mechanisms behind the possible association between vitamin D and pathophysiology of PCOS are not yet covered well; nevertheless, the regulating effects of vitamin D on insulin signaling and sensitivity and expression of its receptors in both classical and non-classical insulin-sensitive tissues, including ovaries [10–13], and vitamin D is a predictor of IR in PCOS [7], should not be neglected. In addition to that, vitamin D receptors (VDR) are existed in the ovarian, fallopian and endometrial cells, and vitamin D may be involved in ovarian physiology and reserve through regulating the activities of genes involved in follicular development, steroidogenesis and androgen production [6], [32]. Low circulating 25(OH)D [6,32], as well as IR and its compensatory hyperinsulinemia [33,34], may lead to over-production of both LH and androgen with consequent aggravation of ovulatory dysfunction in PCOS. Taken together, the aforementioned observations and suggestions can in turn explain, at least in part, the correlations that were reported here between the serum 25(OH)D levels of PCOS patients and their IR indices, serum LH, testosterone and FSH levels. In support, optimized regimens of vitamin D-based therapy in vitamin D-deficient-PCOS women have lately shown to improve their insulin sensitivity and normalize their elevated circulating androgen and other deregulated hormones [14–17].

Disturbed secretions of adipokines have also been accentuated in the pathophysiology of PCOS and its metabolic and reproductive dysfunctions [18,19]. As demonstrated here, Saudi women with PCOS showed lower adiponectin, but higher follistatin, concentrations in their serum compared to control group, and their 25(OH)D levels were correlated positively with adiponectin and negatively with follistatin levels. In constancy with these findings, aberrant hyperfollistatinemia is common in PCOS, in despite of their BMI, and may be involved in induction of ovarian testosterone production and in arresting FSH-o- varian granulosa cell axis and ovarian folliculogenesis [25,26,35,36]. Furthermore, could vitamin D directly reduce the synthesis of follistatin has been previously documented by Woeckel et al. [37] on human oocyte cells; implying the explanation of the negative association between serum levels of 25(OH)D and follistatin that were observed here in PCOS patients. Concerning the current findings related to the lower adiponectin levels in PCOS group, other researchers have also reported the same findings in both obese and non-obese PCOS patients [22–24], including data of a meta-analysis of more than 3500 females of various ages [21]. In addition, circulating adiponectin level was found to be more reduced at lower levels of serum 25(OH)D in women with PCOS [38], and vitamin D supplementation improved serum adiponectin levels in women with PCOS [17]. However, other researchers found no significant difference in the circulating adiponectin concentrations between PCOS and non-PCOS groups [34], and such discrepancy could be related to the ethnic and demographic variations among the studied populations [34]. Toward this latter suggestion, positive correlations of systemic vitamin D status with circulating adiponectin, and hypoadiponectinemia is a link between hypovitaminosis D and IR, have been detected among diabetic Saudi patients [39] and also among African American patients with cardiovascular disease [40].

**Strengths and limitations**

To the best of our knowledge, this study is the first to investigate the
possible association/correlation between hypovitaminosis D and the pathology of PCOS among Saudi women - and highlighted the significant prevalence of vitamin D deficiency and low adiponectin and follistatin levels in their serum. It also suggests the necessity of screening Saudi women with PCOS for their serum 25(OH)D levels. In despite of this, the present study is an observational one with included small sample size and therefore, causation cannot be claimed. Coherently, correction of vitamin D level via a next step clinical trial with vitamin D supplementation therapy in Saudi women with vitamin D-deficiency - and PCOS could provide more knowledge and explore a causal relationship of impaired vitamin D status in etiopathogenesis of PCOS among Saudi women. It has also been reported that vitamin D binding protein (VDBP) levels decrease in PCOS, which may partly account for the reduced 25(OH)D levels and therefore estimation of VDBP with 25(OH)D in a further future study would be more informative. In addition, BMI seems to be an important variable in PCOS, hence the relationship of vitamin D deficiency with increased IR, infertility and hyperandrogenism have been reported to be more intense in obese-PCOS than lean-PCOS patients. However, this variable was not covered here since the BMI of PCOS and control groups were similar and it, in turn, requires further studies with large size samples and variable BMI to be clarified.

Conclusions

Overall, data of the current study indicate, for the first time, that hypovitaminosis D was highly prevalent among the investigated women with naïve PCOS, and significantly coexisted and correlated with hyperadiponectinemia, hyperfollistatinemia, IR and altered sex-hormonal parameters of these PCOS patients. However, in view of using convenience sampling, the present observations cannot be generalized to Saudi population and further studies in large size samples and at different Saudi locations are warranted to realize these findings and to improve the diagnostic and treatment strategies of Saudi women with PCOS.

Conflict of interest

The author declares that there is no conflict of interests.

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