Clinical and Laboratory Pearl

The Association of Oral Contraceptive Use with Plasma 25-hydroxyvitamin D Levels

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Key words: vitamin D, oral contraceptives, 25-hydroxyvitamin D, season

Objective: This analysis was conducted to compare wintertime 25-hydroxyvitamin D (25OHD) levels of young women who did and did not use oral contraceptives (OC).

Methods: The subjects were 66 Caucasian women aged 20 through 40 recruited from the Boston area. Plasma 25OHD was measured in February or March and again 1 year later. Other measurements included height, weight and vitamin D intake from diet and supplements.

Results: The initial mean 25OHD level of the 26 OC users was 41% higher than those of nonusers before adjustment for age and vitamin D intake (83±40 (sd) nmol/L compared with 59±22), and 39% higher after adjustment ($p=0.003$). Five women who discontinued OC use during the year following their initial measurement all had decreases in their 25OHD levels (mean change was −25.5±17.7 (SD) nmol/L), whereas levels in women whose OC use or non-use was constant did not change.

Conclusion: OC use increases circulating levels of 25OHD, and should be considered when interpreting values obtained for clinical evaluation or nutrition research.

INTRODUCTION

Blood levels of 25-hydroxyvitamin D (25OHD) are used both clinically and in research studies as indicators of vitamin D status. Sowers et al [1], who studied women living in rural Iowa, observed higher summertime levels of 25OHD in oral contraceptive (OC) users compared with non-users, and Landin-Wilhelmsen observed higher 25OHD levels in 25 pre- and postmenopausal women consuming any medications containing estrogen [2]. Aarskog et al saw no mean change in 25OHD levels of pubertal girls treated with OC to curtail height gain [3], but 11 of the 16 individuals measured did have increased levels. The purpose of the present analysis was to determine whether or not wintertime levels of 25OHD are similar in premenopausal women who do and do not use oral contraceptives, and to address the potentially confounding effects of age, body size and vitamin D intake on any observed association.

METHODS

We studied 66 Caucasian women aged 20 through 40 who had been recruited from the Boston area for participation in a study of vitamin D and bone mineral density [4]. Recruitment methods consisted of advertisements in local media and direct mailings targeted to women in the appropriate age range. Enrollment criteria included weight less than 113 kg, no use in the past year of drugs known to affect bone metabolism, and no current medical conditions known to affect bone metabolism. The protocol was approved by the Human Investigations Review Committee at Tufts University, and written informed consent was obtained from each participant.

Plasma 25OHD, height, weight, and medication use of all subjects were measured within a two-month period during February or March. Blood for the 25OHD assessment was drawn within 5 days after the start of each subject's last menstrual period, and following an overnight fast. Plasma 25OHD was measured again 1 year later in all but two subjects

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who could not return for measurement. Plasma 25OHD was batch-analyzed by the method of Preece et al [5] with intra-assay and inter-assay coefficients of variation of 5.0% and 7.3%, respectively. Body weight was measured with a digital scale and height was measured with a wall-mounted stadiometer. Use of vitamin D supplements and OC was recorded. Dietary vitamin D over the previous 4 months was estimated by food frequency questionnaire 4 months after other measurements were made. Total intake of vitamin D was computed as the sum of dietary and supplemental intakes. Fisher's exact test was used to compare proportions of smokers and nonsmokers. Two sample t-tests were used to compare other characteristics and laboratory values of women who did and did not use OC. Adjusted means for the two-group comparisons were made with analysis of covariance. All tests used were two-tailed, and analyses were conducted with SYSTAT, version 6.0 (SPSS, Inc., Chicago, IL).

RESULTS

Twenty-six women reported current use of oral contraceptives. All the preparations they used contained ethinyl estradiol and one of five different progestins (norgestrel, levonorgestrel, norethindrone, norethindrone acetate or ethynodiol diacetate). Ethinyl estradiol content of the products was known for 20 of the women and, among them, ranged between 20 and 40 mcg in monophasic (mean±SD: 31±7 mcg, n=12) or triphasic (30/40/30 mcg in all, n=8) preparations. Duration of use ranged from 1 month to 15 years, and averaged 43±28 months.

OC users were an average of 4 years younger, and had slightly higher (though not significantly so) vitamin D intakes than non-users (Table 1). Body size of the two groups was similar (Table 1). Four of the OC users compared with three of the non-users were current smokers (p=0.420).

The mean 25OHD level of OC users was 24.1 nmol/L higher (CI_{95}: 6.9−41.2) than that of non-users before adjustments (Table 1). This 41% difference was reduced only slightly by adjustment for age and vitamin D intake (to a 39% difference, Fig. 1), and remained highly statistically significant. We were able to detect no associations between 25OHD levels and ethinyl estradiol dose, type of OC preparation, or duration of OC use.

Table 1. Subject Characteristics and Vitamin D Metabolite Levels According to Oral Contraceptive (OC) Use[a]

	No OC use	OC user	
n	40	26	p
Age, years	31.6±6.2	27.8±4.3	0.005
Height, cm	166.0±6.0	165.7±6.0	0.808
Weight, kg	62.9±8.4	62.2±9.7	0.745
Vitamin D intake, IU/day[b]	227.9±185.2	291.0±214.0	0.223
Plasma 25OHD (nmol/L)[c]	59.2±21.5	83.2±39.5	0.007

[a] Mean±SD.

[b] Adequate Intake for individuals through age 50 is 200 IU/d [6].

[c] The normal reference range for this assay is 20 to 138 nmol/L.

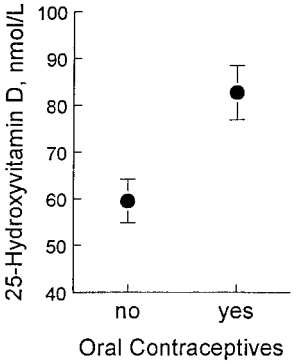

Fig. 1. Mean plasma 25-hydroxyvitamin D levels, adjusted for age and vitamin D intake, according to oral contraceptive use (n=40 non-users and 26 users). The means are significantly different, p=0.003, and the error bars indicate standard errors of the means.

All five of the women who discontinued OC use during the year following their initial measurement (mean 95±41) had decreases in their 25OHD levels (range: −49.9 to −7.5 nmol/L), and the mean decrease was −25.5±17.7 (sd) nmol/L. In contrast, there was almost no change in the mean levels of the 20 women who remained on OC (1.6±15.2) or did not use OC at all during the study (−0.1±19.5).

DISCUSSION

The present study demonstrates that 25OHD levels of OC users may be as much as 24 nmol/L higher than those of women who do not use OC. The magnitude of this difference is substantially greater than that observed by Sowers et al (9 nmol/L) [1]. This may be a chance difference, or it may result from the fact that our measurements were made in winter, when levels are at their lowest, rather than in summer when they are at their highest. The decrease in 25OHD levels of the small number of women in our study who discontinued OC use was similar in magnitude to the difference between our larger groups of OC users and non-users, providing limited supporting evidence of a strong effect.

These results do not provide evidence that OC use improves vitamin D nutrition. Instead, it may alter the relative proportions of free and protein bound 25OHD by influencing levels of vitamin D binding protein [3,7]. The clinical implications of these findings are unclear, but, if the magnitude of the effect on measured 25OHD is as great as that we have observed, OC and related exogenous hormone preparations are likely to be strong confounders in studies of 25OHD that do not take their use into account. In conclusion, OC use increases circulating levels of 25OHD of premenopausal adult women, and should be considered when interpreting values obtained for clinical evaluation or nutrition research.

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REFERENCES

1. Sowers M, Wallace RB, Hollis BW, Lemke JH: Parameters related to 25-OH-D levels in a population-based study of women. Am J Clin Nutr 43:621–628, 1986.
2. Landin-Wilhelmsen K, Wilhelmsen L, Wilske J, Lappas G, Rosén G, Lindstedt G, Lundberg P-A, Bengtsson B-Å: Sunlight increases serum 25(OH) vitamin D concentration whereas $1,25(OH)_2D_3$ is unaffected. Results from a general population study in Göteborg, Sweden (The WHO MONICA Project). Eur J Clin Nutr 49:400–407, 1995.
3. Aarskog D, Aksnes L, Markestad T, Rødland O: Effect of estrogen on vitamin D metabolism in tall girls. J Clin Endocrinol Metab 57:1155–1158, 1983.
4. Harris SS, Wood MJ, Dawson-Hughes B: Bone mineral density of the total body and forearm in premenopausal black and white women. Bone 16:311s–315s, 1995.
5. Preece MA, O'Riordan JL, Lawson DE, Kodicek E: A competitive protein-binding assay for 25-hydroxycholecalciferol and 25-hydroxyergocalciferol in serum. Clin Chem Acta 54:235–242, 1974.
6. Institute of Medicine: Dietary Reference Intakes: "Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride." Washington, D.C.: National Academy Press, 1997.
7. Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK: Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. Am J Clin Nutr 45:755–763, 1987.

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