Improvement of Primary Dysmenorrhea Caused by a Single Oral Dose of Vitamin D: Results of a Randomized, Double-blind, Placebo-Controlled Study

Primary dysmenorrhea is a common disorder characterized by painful uterine cramping, just before or during menstruation, in the absence of any pelvic pathologic conditions. It is frequently accompanied by other symptoms such as nausea, vomiting, diarrhea, asthenia, and insomnia.[1,2] Primary dysmenorrhea affects almost half of menstruating women, often resulting in school and work absenteeism with major educational and economic consequences.[2]

An excessive uterine production of prostaglandins (PGs) is the pathogenetic trigger of dysmenorrhea. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the currently accepted drugs for the management of this disorder.[1,2]

Because the vitamin D receptor is widespread and the mitochondrial cytochrome P450 enzyme 25-hydroxyvitamin D_3 (25[OH]D)-1α-hydroxylase (1α-OHase), which catalyzes the synthesis of 1α,25-dihydroxyvitamin D_3 ($1,25[OH]_2D$) from its precursor 25(OH)D, is expressed in the human uterus and in immune system cells, and because vitamin D reduces the synthesis of PGs, a beneficial effect of vitamin D in the uterus pathophysiology is possible.[3,4]

The aim of this prospective intervention study was to evaluate the effect of a single-loading oral dose of cholecalciferol (300 000 IU) on primary dysmenorrhea.

See Invited Commentary at end of letter

Methods. Forty women aged 18 to 40 years, attending the outpatient clinics of the Department of Internal Medicine of the University of Messina, Messina, Italy, for primary dysmenorrhea were enrolled. Patients were included if (1) their menstrual cycles lasted 21 to 35 days, with menstruation lasting 3 to 7 days; (2) they experienced at least 4 consecutive painful periods in the past 6 months with the pain starting one day before or on the day of onset of bleeding; (3) they showed a 25(OH)D serum level, measured with high-performance liquid chromatography, below the upper limit of the lowest quartile (<45 ng/mL) (to convert to nanomoles per liter, multiply by 2.496) obtained by dividing the normal range of our laboratory (20-120 ng/mL) into 4 parts. Patients had to be in good health and taking no medications including calcium, vitamin D, and oral contraceptives. Previous and current use of intrauterine contraceptive devices within the 6 months prior to enrollment was not permitted. During the observation period, patients used an accepted means of birth control. Use of NSAIDs was permitted and it had to be recorded in a sheet given to each woman.

Women were randomized into 2 groups: 20 women received a single oral dose of cholecalciferol (300 000 IU/1 mL [Abiogen Pharma S.P.A.]) 5 days before the putative beginning of their next menstrual cycle, while another 20 women received placebo.

The primary outcome was the intensity of menstrual pain as measured by a visual analog scale. The secondary outcome was use of NSAIDs during the 2-month duration of the study. The study was performed between October 2009 and May 2010 according to the Principles of the Declaration of Helsinki. Written informed consent was obtained from each woman.

Comparisons between groups were performed by the unpaired *t* test or Mann-Whitney test, and within-group comparisons were determined with the paired *t* test or Wilcoxon matched paired rank sum test for paired data, as appropriate. The Fisher exact test was used to calculate differences in the proportion of categorical variables. Pearson correlation coefficient was calculated to evaluate the correlation between 2 variables. $P<.05$ was considered significant.

Results. The 2 groups did not differ significantly in age, body mass index, severity of pain, and 25(OH)D levels at baseline. There was a negative correlation between the pain score at baseline and the levels of 25(OH)D ($r=-0.36$; $P=.02$). We observed a significant reduction of pain in the vitamin D group compared with the placebo group ($P<.001$) over the 2-month duration of our study (**Figure**). The greatest reduction of pain score was seen in women with severe pain at baseline in vitamin D group ($r=-0.76$; $P<.001$). We recorded no NSAID use in vitamin D group at 1 and 2 months, while 40% of women in placebo group took NSAIDs at least once ($P=.003$).

Calcitriol ($1,25[OH]_2D$) decreases, in vitro, the level of proinflammatory cytokines such as interleukin 6 and tumor necrosis factor[5] and regulates the expression of several key genes involved in the PG pathway causing decreased biological activity of PGs.[6]

Comment. In the present study we used a single high dose of cholecalciferol because it is an inactive and safe precursor of calcitriol and is able to enhance rapidly serum 25(OH)D after 3 days.[7]

Vitamin D insufficiency is rather common in young, otherwise healthy Italian premenopausal women and particularly among those living in the southern part of the country.[8] In our study, low levels of 25(OH)D may in part be justified by the period of sampling (October-May), probably due to reduced sun exposure causing a low endogenous synthesis of vitamin D. To our knowledge, this is the first study investigating the effect of a single high dose of vitamin D in primary dysmenorrhea. Our data support the use of cholecalciferol in these patients, especially when exhibiting low plasmatic levels of 25 (OH)D, and allow these women to limit the use of NSAIDs.

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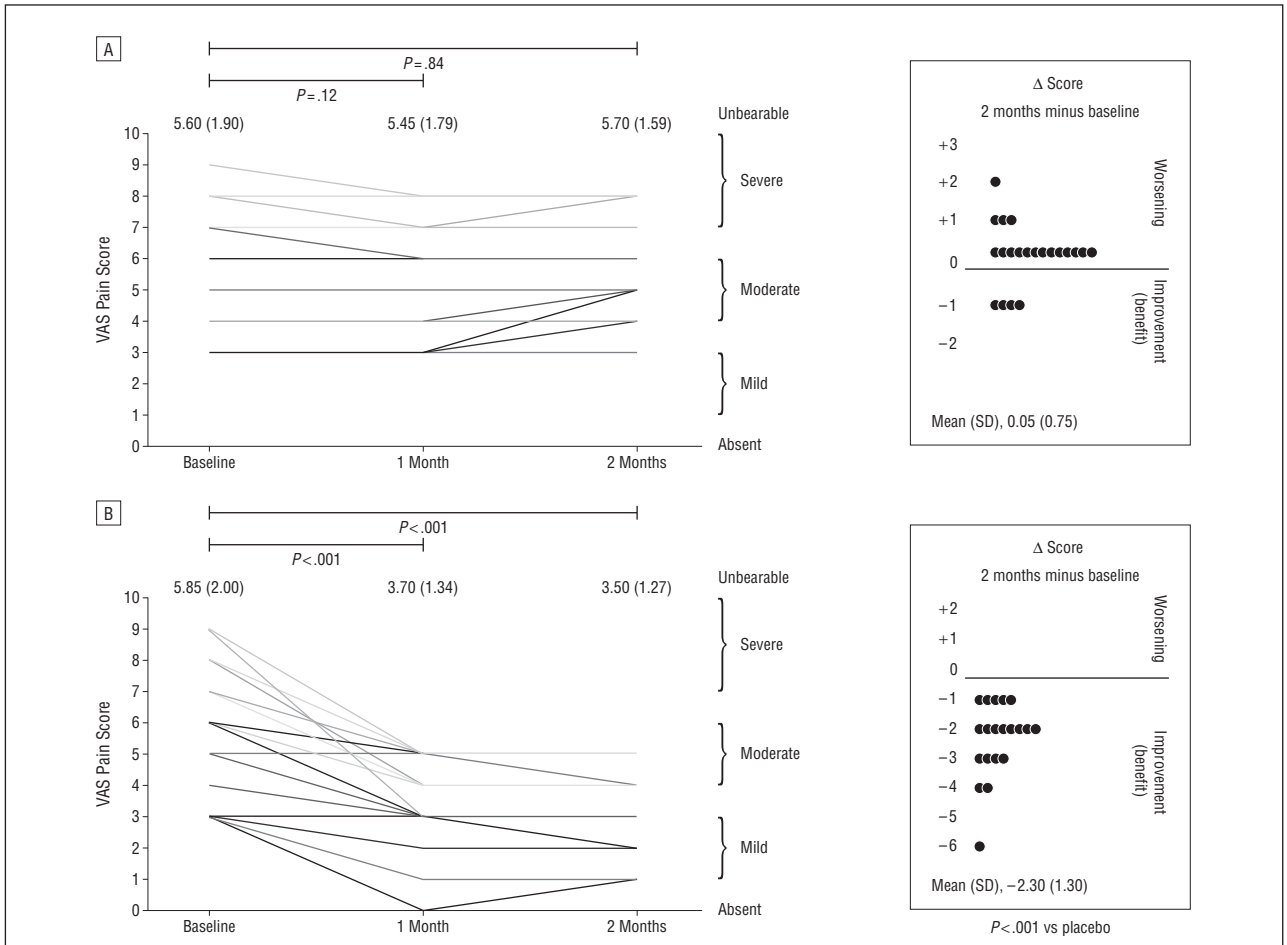

Figure. Changes in mean (SD) pain score in the placebo-treated (A) and vitamin D–treated (B) groups over the 60 days of the study. Eligible women reported intensity of pain on a visual analog scale (VAS) at baseline and then at the end of the first and second month after the dose of placebo or vitamin D. The filled circles in the right panels represent individual changes. Both placebo and vitamin D groups were homogeneous for age (mean [SD], 27 [6.01] y vs 26.3 [6.23] y), body mass index (mean [SD], 21.17 [2.15] vs 21.96 [2.06] [calculated as weight in kilograms divided by height in meters squared]), baseline 25-hydroxyvitamin D_3 levels (mean [SD], 29.97 [7.62] ng/mL vs 27.19 [7.53] ng/mL [to convert to nanomoles per liter, multiply by 2.496]), and baseline VAS pain score (mean [SD], 5.60 [1.90] vs 5.85 [2.00]).

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INVITED COMMENTARY

Vitamin D for Menstrual and Pain-Related Disorders in Women

Primary dysmenorrhea is among the most common menstrual disorders, occurring in at least 50% of reproductive-age women.[1] Dysmenorrhea is characterized by pelvic pain beginning shortly before the onset of menses or at the beginning of menstrual flow and then lasting several days. The disorder results in sub-

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