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Calcium and vitamin D supplementation do not influence menopause-related symptoms: Results of the Women's Health Initiative Trial

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ABSTRACT

Background: It is unknown whether supplementation with calcium and vitamin D has an impact on menopause-related symptoms.
Methods: As part of the Women's Health Initiative Calcium/Vitamin D Supplementation Trial (CaD), women were randomized at 40 clinical sites to elemental calcium carbonate 1000 mg with vitamin D 400 IU daily or placebo. At the CaD baseline visit (year 1 or year 2) and during a mean follow-up of 5.7 years, participants provided data on menopause-related symptoms via questionnaires. Generalized linear mixed effects techniques were used to address research questions.
Results: After excluding participants with missing data ($N = 2125$), we compared menopause-related symptoms at follow-up visits of 17,101 women randomized to CaD with those of 17,056 women given the placebo. Women in the CaD arm did not have a different number of symptoms at follow-up compared to women taking the placebo ($p = 0.702$). Similarly, there was no difference between sleep disturbance, emotional well-being, or energy/fatigue at follow-up in those who were randomized to CaD supplementation compared to those taking the placebo.
Conclusions: Our data suggest that supplementation with 1000 mg of calcium plus 400 IU of vitamin D does not influence menopause-related symptoms over an average of 5.7 years of follow-up among postmenopausal women with an average age of 64 at the WHI baseline visit.

1. Introduction

Most women transitioning through menopause will experience symptoms including hot flashes [1–3], mood disturbances, and muscle aches [4,5]. In many women, these symptoms are severe enough to adversely affect their quality of life, work performance, and personal relationships [6,7]. Current treatments for menopause-related symptoms, such as menopausal hormone therapy, antidepressants, and anticonvulsants, may have significant side effects and serious long-term adverse consequences [8]. In addition, after treatment is discontinued, these symptoms may recur or even develop *de novo* [9,10,3]. It is therefore important to investigate possible determinants of menopause-related symptoms so that new therapies can be developed.

There are several mechanisms whereby vitamin D could potentially improve menopausal symptoms. A menopausal decline in serotonin, a neurotransmitter with known effects on thermoregulation, could contribute to hot flashes [11–13]. In animal models, vitamin D prevents this serotonin decline [14]. Alternatively,

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estrogen increases the activity of the enzyme responsible for activating vitamin D [15]. The fall in estrogen that occurs during the menopausal transition could uncover previously subclinical vitamin D deficiency [16–20]. Vitamin D supplementation can improve mood and muscle aches in nonmenopausal populations [21,22], but its effects on a menopausal population have not been well studied.

Conversely, calcium may stimulate the production of a vasodilator neuropeptide, calcitonin gene-related peptide (CGRP), which has been positively linked to occurrence of menopausal hot flashes [23–27]. Indeed, taking calcium supplements has been linked to a higher likelihood of having hot flashes in breast cancer survivors [28].

We examined the effect of 1000 mg of elemental calcium carbonate plus 400 IU of vitamin D3 (CaD) on menopause-related symptoms in women who participated in the Women's Health Initiative randomized, placebo-controlled Calcium/Vitamin D Supplementation Trial (CaD). We hypothesized that the potential favorable effects of vitamin D on menopause-related symptoms would outweigh the potential negative effects of calcium. Therefore, we believed that women given calcium and vitamin D would experience fewer menopausal symptoms during follow-up than women given the placebo.

2. Materials and methods

2.1. Study population and intervention

The Women's Health Initiative (WHI) Randomized Clinical Trial (CT) enrolled postmenopausal women aged 50–79 years at baseline into a hormone therapy (HT) [29] and/or dietary modification [30] (DM) trial (N = 68,132). Between years 1 and 3, participants in both trials were also asked to join a randomized clinical trial investigating calcium plus vitamin D (CaD) compared with placebo (N = 36,282 women) [31]. Women were randomized at 40 clinical sites to calcium carbonate 1000 mg plus vitamin D 400 IU daily, given as one tablet in two divided doses to be taken two times per day with meals, versus an identical-appearing placebo. Concurrent calcium supplementation was permitted, as was vitamin D supplementation up to 600 IU daily (increased to 1000 IU daily from 1999 through the end of the trial). Details of the study design [32] and baseline characteristics [31] have been presented previously. The primary outcome for the CaD trial was hip fracture. Secondary outcomes included total fractures and colorectal cancer. Included in our final analytic cohort were 34,157 women for whom we had data on menopause-related symptoms at some time point, with 17,101 in the intervention and 17,056 in the control arm (Fig. 1). All participating women provided written informed consent.

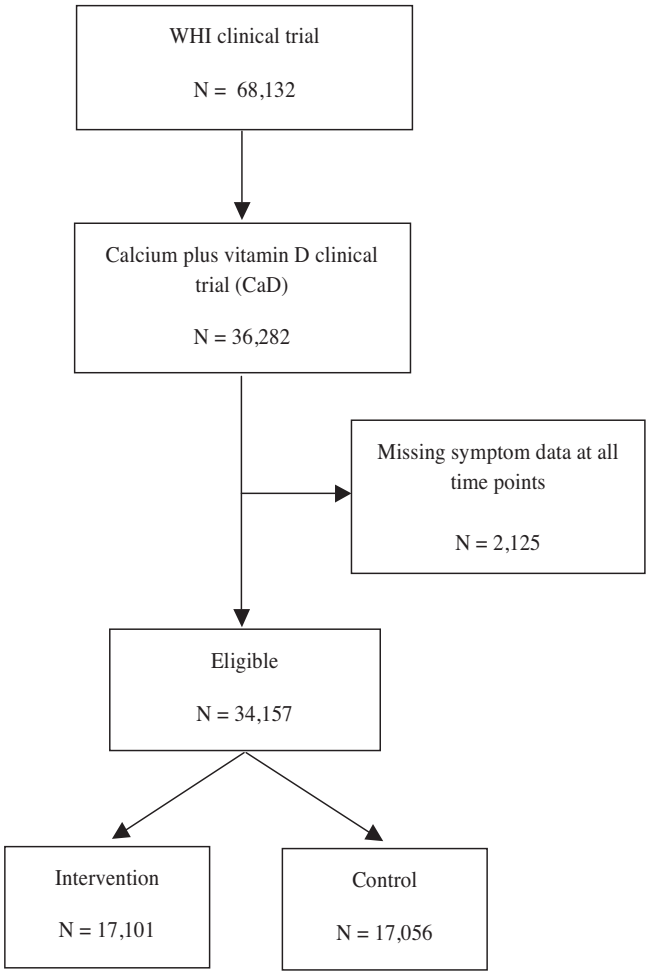

Fig. 1. Flow chart displaying the number of women in eligible and analytic cohorts.

2.2. Data collection

2.2.1. Demographic and health characteristics

Participants self-reported data on demographics (i.e., age, race, education, years since menopause), lifestyle factors (i.e., physical activity, smoking), and UV exposure (i.e., Langley's measure of UV exposure). They underwent physical measurements (i.e., height and weight to calculate BMI) [31]. A standardized, in-person, interviewer-administered form was used to collect information on the dose, frequency, and duration of current supplements (i.e., calcium, vitamin D) and medication use [i.e., menopausal hormone therapy (HT)]. Dietary vitamin D and calcium intakes during the previous 3 months were estimated from a self-administered food-frequency questionnaire (FFQ) specifically designed for WHI [31,33].

2.2.2. Menopausal symptoms

Participants provided data on menopause-related symptoms via self-report questionnaires at the CaD baseline visit (year 1 to year 2 of overall trial) and during follow-up. Questionnaires included a checklist of menopause-related symptoms based on the Postmenopausal Estrogen/Progestin Interventions (PEPI) symptom tool [34] and other national surveys and clinical trials [35,36]. The psychosocial forms containing these symptom items were reviewed for content validity by nationally recognized behavioral and clinical experts and were pretested extensively on age-appropriate women from diverse racial/ethnic groups [10]. For this analysis, the following symptoms were analyzed: hot flashes, night sweats, dizziness, heart racing or skipping beats, tremors, feeling restless or fidgety, feeling tired, difficulty concentrating, forgetfulness, mood swings, vaginal dryness, breast tenderness, headaches or migraines, waking up several times at night, waking earlier than planned, trouble falling back to sleep after waking earlier than planned, overall typical sleep pattern and quality, and loss of energy. Previous research indicates that these are the typical symptoms associated with menopause.

For most of the symptoms, participants rated symptom severity on a 4-point scale: symptom did not occur, mild (did not interfere with usual activities), moderate (interfered somewhat with usual activities), or severe (so bothersome that usual activities could not be performed). For sleep symptoms [37], participants rated how often they had occurred in the previous 4 weeks (from none to five or more times per week).