Impact of vitamin D supplementation on adiposity in African-Americans

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BACKGROUND: African-Americans have higher rates of obesity-associated chronic diseases. Serum 25-hydroxyvitamin D (25(OH)D) shows an inverse association with obesity status. We investigated whether vitamin D supplementation changes body mass index (BMI).

SUBJECTS: In total, 328 overweight African-Americans were enrolled over three consecutive winter periods (2007–2010) into a randomized, double-blind, placebo-controlled trial to receive cholecalciferol supplementation (0, 1000 international units (IU), 2000 IU or 4000 IU per day) for 3 months. Plasma concentrations of 25(OH)D and anthropometric measurements were done at baseline, 3 and 6 months.

RESULTS: At 3 months, vitamin D supplementation in three dose groups (1000 IU, 2000 IU or 4000 IU per day) did not cause any significant changes in BMI as compared with placebo group 3-month change in BMI per 1000 IU per day estimate (SE): 0.01 (0.039); P = 0.78.

CONCLUSIONS: In overweight African-Americans, short-term high-dose vitamin D supplementation did not alter BMI.

INTRODUCTION

An urgent need exists to identify modifiable dietary risk factors for obesity in African-Americans. Human observations since the 1980’s of lower levels of 25-hydroxyvitamin D25(OH)D in obese than in nonobese individuals highlight a possible inverse relation between vitamin D and obesity.1

African-Americans have consistent associations of vitamin D deficiency with obesity and obesity-associated chronic diseases, such as hypertension, coronary heart disease, diabetes and certain cancers,2 although of potentially lower magnitude than Whites.3,4 Furthermore, African-Americans have lower vitamin D and calcium dietary intake.5 The mechanisms underlying this association may include a role for 25(OH)D in regulating lipid metabolism in adipose cells. In vivo studies suggest that vitamin D and calcium administration increase fatty-acid oxidation and decrease lipogenesis.6,7

Results from clinical trials measuring the effect of vitamin D supplementation on obesity are limited and mixed. Some trials show no association of vitamin D supplementation with weight loss.8–10 Other trials show that vitamin D supplementation may be significantly associated with less weight gain but that this association may be dependent on adjunctive calcium supplementation and a particular region of fat.11,12 A recent meta-analysis showed no significant effect of vitamin D supplementation on body mass index (BMI), weight or other adiposity measures.13 This meta-analysis did not assess potential ethnic/racial differences in the effect of vitamin D supplementation on adiposity measures. Studies evaluating the effect of vitamin D supplementation on measures such as insulin resistance in African-Americans14 have not reported on changes in adiposity measures. Thus, this ancillary analysis was undertaken to test the hypothesis that supplementation with vitamin D3 (cholecalciferol) leads to weight loss in African-Americans.

MATERIALS AND METHODS

Study design and participants

This is a prospective, randomized, double-blind, placebo-controlled clinical trial of oral cholecalciferol (vitamin D3) in a community-based overweight African-American population (ClinicalTrials.gov NCT00585637). The protocol has been described in detail elsewhere.15 The primary goal of the trial was to examine the effect of daily supplementation of 1000 international units (IU) of vitamin D3, 2000 IU of vitamin D3 and 4000 IU of vitamin D3 and placebo on plasma 25(OH)D levels. All participants provided written informed consent. This trial focused on African-Americans because African-Americans14 have higher rates of vitamin D deficiency compared with Whites4 or Africans.16 The project was approved by the Institutional Review Boards of Harvard School of Public Health and Dana-Farber Cancer Institute. All procedures were followed in accordance with institutional guidelines.

Recruitment and randomization. Participants in Open Doors to Health, a colorectal cancer prevention intervention study conducted in 12 public housing communities in the Boston metropolitan area,17 were invited to participate if they were 30–80 years old, understood written and spoken English, self-identified as Black18–20 and had permission from their primary care doctors. We also recruited participants from community and faith-based organizations and refer-a-friend program. A total of 328 individuals...
were enrolled into the parent trial (Figure 1). Exclusion criteria included pregnancy, renal disease, pre-existing parathyroid, thyroid, or calcium metabolism disorders, sarcoidosis, requirement for calcium channel blockers, type 1 diabetes and active malignancies (other than non-melanoma skin cancer). Those taking vitamin D supplementation were enrolled if they agreed to discontinue these medications for 6 months prior to enrollment and during the study.

**Treatment.** Participants were assigned to four arms consisting of placebo, 1000 IU per day, 2000 IU per day or 4000 IU per day of vitamin D3 for 3 months in a 1:1:1:1 ratio using block randomization stratified by age, sex and enrollment month. Study statisticians generated the random allocation sequence and subjects were enrolled by research assistants. All capsules also contained 200 mg of calcium carbonate (Pharmavite LLC, Mission Hill, CA, USA). Calcium was included because prior studies have shown that African-Americans have low calcium intake. All capsules were indistinguishable, and both participants and research staff were blinded to treatment assignment. Study medications were started in early winter (November or December) and were taken orally once daily for 3 months (completed in February or March).

**Compliance and safety.** All participants were assessed for adverse events by study staff over the phone at week 2 of each month and in-person at the beginning of each month when the next month’s supply of vitamins was provided. Participants were educated on the warning signs and symptoms of hypercalcemia. Serum calcium was measured in subjects taking hydrochlorothiazide at 1 and 3 months. An additional subset of 44 ‘control’ participants not taking hydrochlorothiazide also underwent calcium assays at 3 months. Electronic pill dispenser systems and pill counts were used to track compliance with study supplementation in addition to biweekly phone calls. Any subject found to have calcium

![Figure 1. Consort diagram.](image-url)
Association of baseline 25(OH)D and BMI and weight
There was no significant association between BMI or weight and 25(OH)D at the beginning of the study. Baseline weight and baseline BMI were not significantly associated with 25(OH)D (estimate (SE), P-value: BMI, −0.04 (0.07), P = 0.55; weight, −0.02 (0.01), P = 0.06). Baseline 25(OH)D was not significantly associated with baseline BMI or baseline weight (BMI, −0.03 (0.05), P = 0.55; weight, −0.56 (0.30), P = 0.06).

Impact of vitamin D supplementation on BMI and weight
The primary efficacy analyses of vitamin D3 supplementation on weight and BMI are shown in Table 2. In linear regression with the dose of vitamin D3 (per 1000 IU per day) as the independent variable and the 3-month change in weight (or 3-month change in BMI) as the dependent variable, no effect of vitamin D3 on change in BMI or weight was observed. For each additional 1000 IU per day of vitamin D3, BMI increased by estimate (SE): 0.01 (0.039); P = 0.78 and weight increased by estimate (SE):0.06 (0.24); P = 0.81. At 6 months, no significant change in BMI or weight was observed (Table 2).

Adverse events
There were five isolated incidences of mild hypercalcemia that were in the reference range on repeated sampling. Vitamin D supplements were discontinued in the four participants with mild hypercalcemia at 1 month. Vitamin D supplementation was discontinued in the participant who had hypercalcemia at month 3. There were no episodes of nephrolithiasis.

DISCUSSION
On the basis of evidence showing that vitamin D deficiency is associated with obesity, we tested the hypothesis that vitamin D supplementation could reduce BMI in a randomized, placebo-controlled trial of African-Americans. Although circulating 25(OH)D increased with vitamin D supplementation, we found that vitamin D supplementation did not lower BMI or weight among healthy African-Americans. Numerous cross-sectional studies have assessed the relationship between vitamin D status and different measures of adiposity.2 These studies found an inverse relationship between vitamin D and total body fat and regional adipose tissue.2 Others have shown an inverse relationship between vitamin D levels and components of metabolic syndrome, including abdominal obesity,25 which is a known risk factor for several chronic conditions. Furthermore, a recent meta-analysis evaluating the effect of vitamin D supplementation on adiposity biomarkers in randomized controlled trials found no significant reduction in adiposity measures in the absence of calorie restriction.13

The lack of effect of vitamin D supplementation on weight may be due to low dietary calcium intake. Heaney et al.26 concluded that vitamin D status and benefits associated with vitamin D supplementation appear to be dependent on calcium intake at or above recommended amounts. The doses of vitamin D tested in this study, as well as the dosing schedule (once per day, rather than intermittent large boluses), may provide an optimal balance of efficacy and safety based on current evidence and the recommended daily allowance and tolerable upper limit set by the Institute of Medicine.27

Although there have been some trials including Whites that suggest that vitamin D supplementation prevents weight gain or promotes weight loss, little is known about African-Americans.28 Some have shown positive effects on weight but these effects may have been due to the adjunctive calcium supplementation. For example, in the Women’s Health Initiative Study,29 women who were randomly assigned to calcium and vitamin D

Impact of vitamin D3 supplementation on plasma 25(OH)D
Among 328 subjects, 25(OH)D level at baseline was median 15.3 ng ml\(^{-1}\) (12.5) with 25(OH)D > 20 ng ml\(^{-1}\) in 34.3% of participants. The effect of the various doses of vitamin D3 supplementation on 25(OH)D levels after 3 months is shown in Table 2. At 3 months, median 25(OH)D levels rose to 29.7, 34.5 and 45.9 ng ml\(^{-1}\), respectively, in participants assigned to 1000, 2000 and 4000 IU per day. After 3 months of vitamin D3 supplementation, 292 subjects (89%) provided plasma for follow-up 25(OH)D determination. The compliance rate with randomized therapy in the whole cohort was 96.6%.

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supplementation arm had significantly less weight gain. Although the overall mean weight change difference between groups was small (~0.13 kg), women in the active intervention who had inadequate baseline calcium intakes (<1200 mg per day) had 11% lower risks for substantial weight gain (1–3 kg) compared to those who had calcium intakes >1200 mg per day. It is possible that among women with calcium intake <800 mg per day, calcium and vitamin D supplementation enhanced the beneficial effect of body weight loss on lipids and lipoprotein profile in overweight and obese women.

In our study, vitamin D supplementation was not associated with any significant adverse effects. This confirms the

### Table 1. Baseline characteristics

| Characteristic                              | Vitamin D3 dose assignment (IU per day) | P-value |
|--------------------------------------------|----------------------------------------|---------|
|                                            | Placebo (n = 81)                        |         |
|                                            | 1000                                   | 2000    | 4000    |
| Age, years, median (IQR)                   | 50.7 (44.1–58.0)                       | 51.1 (43.4–60.1) | 50.3 (43.5–58.3) | 51.3 (44.1–59.7) | 0.98 |
| Sex, No. (%)                               |                                        |         |         |         | 0.72 |
| Male                                       | 27 (33.3)                              | 22 (27.2) | 28 (33.7) | 29 (34.9) |
| Female                                     | 54 (66.7)                              | 59 (72.8) | 55 (66.3) | 54 (65.1) |
| BMI, kg m⁻², median (IQR)                  | 25.1 (23.5–26.8)                       | 25.2 (23.6–26.9) | 25.3 (23.8–26.9) | 25.4 (23.9–27.0) | 0.13 |
| BMI < 25 kg m⁻², mean (s.d.)               | 20.8 (2.2)                             | 23.3 (1.4) | 22.9 (1.4) | 21.9 (3.1) |
| No. (%)                                    | 11 (13.5)                              | 11 (13.5) | 16 (19.2) | 10 (8.3)  |
| BMI 25–29.9 kg m⁻², mean (s.d.)            | 27.0 (1.1)                             | 27.9 (1.5) | 27.6 (1.5) | 27.6 (1.5) |
| No. (%)                                    | 25 (30.8)                              | 24 (29.6) | 21 (25.3) | 25 (30.1) |
| BMI > 30 kg m⁻², mean (s.d.)               | 37.1 (5.9)                             | 37.6 (5.8) | 38.4 (6.2) | 36.6 (5.6) |
| 25(OH)D < 20 ng ml⁻¹, No. (%)              | 53 (65)                                | 50 (62)  | 59 (71)  | 53 (64)  |
| 25(OH)D ng ml⁻¹, median (IQR)              | 15.1 (10.4–23.6)                       | 16.2 (11.0–22.7) | 13.9 (9.5–22.3) | 15.7 (11.0–23.3) | 0.63 |
| Smoking status, No. (%)                    |                                        |         |         |         | 0.26 |
| Never                                      | 33 (40.7)                              | 36 (44.4) | 33 (39.8) | 44 (53.0) |
| Past                                       | 20 (24.7)                              | 16 (19.8) | 27 (32.5) | 20 (24.1) |
| Current                                    | 28 (34.6)                              | 29 (35.8) | 23 (27.7) | 19 (22.9) |
| Frequency of exercise, days per week, median (IQR) | 3.0 (2.5–5.0)                     | 3.0 (2.5–5.0) | 3.0 (2.5–5.0) | 3.0 (2.5–5.0) | 0.99 |
| Diet vitamin D intake, median (IQR)        | 147.3 (71.4–262.8)                     | 162.5 (92.6–295.5) | 144.0 (58.0–265.1) | 198.1 (83.2–306.4) | 0.41 |
| Dietary calcium intake, median (IQR)       | 264.6 (177.7–600.8)                    | 419.4 (233.5–820.3) | 314.4 (178.2–632.0) | 425.0 (203.4–829.0) | 0.11 |
| Regular multivitamin use, No. (%)          | 10 (12)                                | 18 (22)  | 15 (18)  | 22 (27)  |
| Regular vitamin D supplement use, No. (%)  | 8 (10)                                 | 6 (8)    | 2 (2)    | 8 (10)   |
| Food, servings per week (median (IQR))     |                                        |         |         |         | 0.45 |
| Milk                                       | 0.1 (0.1–0.3)                          | 0.1 (0.1–0.3) | 0.3 (0.1–0.6) | 0.3 (0.1–0.6) | 0.9 |
| Soy milk                                   | 0                                     | 0        | 0        | 0        |
| Cheese                                     | 0.3 (0.1–0.3)                          | 0.3 (0.1–0.3) | 0.3 (0.1–0.6) | 0.4 (0.1–0.6) |
| Ice cream                                  | 0.1 (0–0.1)                            | 0        | 0.1 (0.3) | 0.1 (0.3) |
| Yogurt                                     | 0 (0–0.1)                             | 0.1 (0–0.3) | 0.1 (0–0.3) | 0.1 (0–0.3) |
| Green leafy vegetables                     | 0.3 (0.1–0.6)                          | 0.3 (0.1–0.6) | 0.3 (0.1–0.6) | 0.3 (0.1–0.6) |
| Dark fish                                  | 0.1 (0–0.3)                            | 0.1 (0–0.3) | 0.1 (0–0.3) | 0.1 (0–0.3) |
| Orange juice                               | 0.1 (0–0.3)                            | 0.1 (0–0.3) | 0.1 (0–0.3) | 0.1 (0–0.3) |
| Cold cereal                                | 0.1 (0–0.3)                            | 0.1 (0–0.3) | 0.1 (0–0.3) | 0.1 (0–0.3) |
| Post-menopausal hormone use, No. (%)       |                                        |         |         |         | 0.72 |
| Yes                                        | 0                                     | 0        | 0        | 1 (0.5)  |
| Regular calcium supplement use, No. (%)    | 7 (8.7)                                | 9 (11.1) | 7 (8.4)  | 9 (10.8) |
| Regular aspirin use, No. (%)               | 4 (4.9)                                | 10 (12.3) | 5 (6.0)  | 8 (9.6)  |
| Regular NSAID use, No. (%)                 | 6 (7.4)                                | 10 (12.3) | 10 (12.0) | 7 (8.4)  |
| Regular acetaminophen use, No. (%)         | 6 (7.4)                                | 6 (7.4)  | 5 (6.0)  | 5 (6.0)  |
| Marital status, married, No. (%)           | 23 (28.4)                              | 30 (37.0) | 25 (31.7) | 24 (28.9) |
| History of cancer, No. (%)                 | 6 (7.4)                                | 0        | 3 (3.6)  | 15 (4.6) |

Abbreviations: IU, international units; IQR, interquartile range; No., number; NSAID, non-steroidal anti-inflammatory drug. *Data are No. (%) unless otherwise indicated. The numbers do not always sum to group totals owing to missing information for some variables. 25(OH)D conversion to nmol l⁻¹ is 2.49 nmol l⁻¹ for each ng ml⁻¹. The Kruskal–Wallis test was used to calculate P-values for continuous variables. All statistical tests are two-sided. Exercise defined as moderate to vigorous physical activity for at least 30 minutes, resulting in a faster-than-normal heart rate, sweating and deep breathing. Defined as supplement use for 7 days per week during preceding month. Defined as three or more pills per week during the past week. Types of NSAIDs included salicylate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac and oxaprozin. Reported cancers include breast cancer, cervical cancer, uterine cancer, lung cancer, prostate cancer and sarcoma.
Table 2. Effect of vitamin D supplementation on BMI and weight during the treatment (baseline to 3 months, mean (SE)) and 6 months after treatment

| Parameter, mean (SE) | Placebo | 1000 | 2000 | 4000 | 0–3 month change | P-value | 3–6 month change | P-value | 0–6 month change | P-value |
|----------------------|---------|------|------|------|------------------|---------|------------------|---------|------------------|---------|
| n (at baseline)      | 81      | 81   | 83   | 83   |                  |         |                  |         |                  |         |
| BMI, kg m\(^{-2}\)   |         |      |      |      |                  |         |                  |         |                  |         |
| Baseline BMI         | 31.85 (0.9) | 32.46 (0.91) | 32.96 (0.96) | 32.15 (0.81) | 0.01 (0.39) | 0.78 | 0.01 (0.04) | 0.71 | 0.01 (0.05) | 0.87 |
| 3 month BMI          | 32.00 (0.9) | 32.41 (0.93) | 33.11 (0.96) | 32.28 (0.83) |                  |         |                  |         |                  |         |
| 6 month BMI          | 32.14 (0.92) | 32.50 (0.96) | 32.54 (0.96) | 32.02 (0.84) |                  |         |                  |         |                  |         |
| Difference BMI (0–3) | 0.15 (0.09) | –0.04 (0.11) | 0.15 (0.13) | 0.13 (0.12) |                  |         |                  |         |                  |         |
| Difference BMI (3–6) | –0.18 (0.10) | –0.19 (0.10) | 0.01 (0.11) | –0.14 (0.12) |                  |         |                  |         |                  |         |
| Difference BMI (0–6) | 0 (0.11) | –0.17 (0.16) | 0.02 (0.16) | –0.02 (0.15) |                  |         |                  |         |                  |         |
| Weight (wt), kg      |         |      |      |      |                  |         |                  |         |                  |         |
| Baseline weight      | 89.63 (2.44) | 89.40 (2.43) | 92.73 (2.73) | 89.54 (2.44) | 0.06 (0.24) | 0.81 | 0.12 (0.22) | 0.59 | 0.07 (0.29) | 0.80 |
| 3 month weight       | 90.03 (2.50) | 89.29 (2.50) | 93.13 (2.71) | 89.90 (2.49) |                  |         |                  |         |                  |         |
| 6 month weight       | 201.22 (5.63) | 200.02 (5.62) | 203.23 (6.22) | 198.48 (5.71) |                  |         |                  |         |                  |         |
| Difference weight (0–3) | 0.41 (0.27) | –0.11 (0.30) | 0.39 (0.38) | 0.36 (0.36) |                  |         |                  |         |                  |         |
| Difference weight (3–6) | –1.05 (0.62) | –1.37 (0.60) | 0.02 (0.70) | –0.78 (0.73) |                  |         |                  |         |                  |         |
| Difference weight (0–6) | 0.07 (0.67) | –1.37 (0.60) | 0.01 (0.96) | –0.02 (0.94) |                  |         |                  |         |                  |         |
| 25(OH)D, ng ml\(^{-1}\) |         |      |      |      |                  |         |                  |         |                  |         |
| Baseline 25(OH)D     | 17.07 (1.03) | 17.33 (1.00) | 16.12 (0.98) | 17.79 (0.98) | 7.75 (0.39) | <0.0001 | –4.74 (0.32) | <0.0001 | 3.04 (0.31) | <0.0001 |
| 3 month 25(OH)D      | 14.23 (0.96) | 28.12 (1.11) | 35.48 (1.21) | 47.30 (1.22) |                  |         |                  |         |                  |         |
| 6 month 25(OH)D      | 19.07 (1.0) | 22.26 (0.96) | 26.77 (1.02) | 31.48 (0.81) |                  |         |                  |         |                  |         |
| Difference 25(OH)D (0–3) | –2.58 (0.66) | 11.01 (1.22) | 19.21 (1.21) | 29.79 (1.29) |                  |         |                  |         |                  |         |
| Difference 25(OH)D (3–6) | 4.78 (0.77) | –5.80 (1.10) | –9.20 (0.91) | –15.71 (0.93) |                  |         |                  |         |                  |         |
| Difference 25(OH)D (0–6) | 1.83 (0.86) | 5.02 (0.87) | 10.29 (0.95) | 13.81 (0.99) |                  |         |                  |         |                  |         |

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documented by others that even higher doses of vitamin D3 supplements are safe.30 Strengths of our study include its prospective design, the use of a double-blind, randomized placebo-controlled intervention and our adjustment for season. Another strength is the similarity of living environments of these urban African-Americans. Relative homogeneity of the population is likely to reduce the influence of confounding factors on the measurement of the vitamin D effect. We considered seasonal changes in vitamin D and body composition by limiting supplementation of participants to the winter months.

Limitations of our study include the relatively short duration of vitamin D supplementation. Yet, this targeted population of obese African-Americans allowed for short duration and small sample size with adequate power to test the hypothesis that vitamin D supplementation reduces BMI. As this was an ancillary analysis, we did not collect other anthropometric data, such as waist or hip circumference or arm fat thickness. Our primary outcome was change in weight and BMI. These are weaker measures of adiposity than direct measures. Thus, we may be underestimating the association between vitamin D supplementation and adiposity.21 Yet, our finding agree with other published null findings of the effects of vitamin D supplementation on adiposity biomarkers.13 We also recognize that low dietary calcium intake may have contributed to our results. This study is unique in that it evaluates vitamin D supplementation effects in African-Americans with a low intake of calcium.

Other limitations of the trial compared with some trials specifically designed for obesity is the lack of records of energy intake and detailed measurements of physical activity. Small changes in BMI may not be detected because of the small sample size and the measurements of adiposity may not be sufficiently sensitive. BMI includes fat mass, lean mass and bone mass. Furthermore, a variety of hormones including gonadal, thyroidal, adrenal and growth hormones influence adiposity. These hormones are under the influence of the hypothalamic-pituitary axis and have circadian and circannual rhythms in adults.25 Thus, the association between obesity and 25(OH)D status may be related to other hormones that change by season.

In conclusion, supplementation with vitamin D did not significantly alter the weight or the BMI over a relatively short duration in a cohort of overweight or obese African-Americans. It is not known whether the low serum 25(OH)D in African-Americans is due to vitamin D insufficiency secondary to the increase in fat mass or to other factors such as genotype variation in vitamin D binding protein or enzymes involved in vitamin D metabolism. Future trials of longer vitamin D supplementation in African-Americans are needed to examine the biological contributors to the interaction between vitamin D deficiency, obesity, health disparities and obesity-related chronic diseases.

CONFLICT OF INTEREST
Hollis has support from DiaSorin S.p.A for serving as an academic consultant. The remaining authors declare no conflict of interest.

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