Vitamin D_3 supplementation (4000 IU/d for 1 y) eliminates differences in circulating 25-hydroxyvitamin D between African American and white men[1–4]

Elizabeth Garrett-Mayer, Carol L Wagner, Bruce W Hollis, Mark S Kindy, and Sebastiano Gattoni-Celli

ABSTRACT

Background: African Americans suffer disproportionately from diabetes and cardiovascular disease and are significantly more likely to have suboptimal concentrations of circulating 25-hydroxyvitamin D [25(OH)D]. The results of epidemiologic and observational studies suggest that there is a link between vitamin D deficiency and the risk of cardiometabolic disorders, which underscores the importance of maintaining healthy concentrations of 25(OH)D.

Objective: The objective was to investigate whether daily supplementation with 4000 IU vitamin D_3 for 1 y would eliminate any disparities in circulating concentrations of 25(OH)D between African American and white men.

Design: Serum concentrations of 25(OH)D were measured every 2 mo in 47 subjects who received a daily oral dose of 4000 IU vitamin D_3 for 1 y.

Results: More than 90% of African Americans had serum concentrations of 25(OH)D $<$32 ng/mL, and approximately two-thirds had serum concentrations $<$20 ng/mL. Furthermore, there were significant disparities in serum concentrations of 25(OH)D between African American and white men. Supplementation with 4000 IU/d for 1 y eliminated any significant differences in circulating concentrations of 25(OH)D between African American and white men.

Conclusion: The results of this clinical study show the feasibility and efficacy of this approach in the elimination of hypovitaminosis D, which is a widespread health disparity among African Americans. This trial was registered at clinicaltrials.gov as NCT01045109. *Am J Clin Nutr* 2012;96:332–6.

INTRODUCTION

The exposure of skin to sunlight in the UVB range of the spectrum (290–315 nm) results in the photolytic conversion of 7-dehydrocholesterol to previtamin D_3, which is transformed into vitamin D_3 by thermally induced isomerization (1, 2). Vitamin D_3 can be obtained from the diet; however, it is distributed very poorly in natural foodstuffs. Increased skin pigmentation limits one's ability to produce vitamin D_3 (3, 4). According to findings from NHANES 2001–2004, $>$90% of African Americans have serum concentrations of 25-hydroxyvitamin D [25(OH)D] $<$30 ng/mL (5). Furthermore, urban African Americans are 1.7 times more likely than their rural counterparts to exhibit hypovitaminosis D (6). The results of retrospective and interventional studies suggest that to maximize skeletal integrity, circulating 25(OH)D should exceed 80 nmol (32 ng/mL) (7, 8). Some of these data, as well as additional studies, have been summarized in a recent review on the optimization of circulating 25(OH)D concentrations (9), which suggests that the current reference ranges for circulating 25(OH)D are set too low; the desirable range of values for serum 25(OH)D in a sun-rich environment is 54–90 ng/mL (10, 11).

The recent emphasis on the noncalcemic functions of vitamin D concerns the realization that vitamin D deficiency has major implications for human health (12). There is an emerging scientific literature linking impaired vitamin D status with chronic conditions such as diabetes and cardiovascular disease. According to a systematic review of the current literature that screened $>$6000 references on vitamin D and cardiometabolic disorders (13), higher concentrations of circulating vitamin D among middle-age and elderly populations are associated with a substantial decrease in cardiovascular disease, type 2 diabetes, and metabolic syndrome. This association is particularly important for African Americans, who are affected by these pathologies in disproportionate numbers (14, 15). Furthermore, African Americans are significantly more likely to have suboptimal concentrations of circulating 25(OH)D (5).

Several studies suggest that intakes of 1000 IU/d increase serum 25(OH)D values to only slightly above 24 ng/mL (16–18). Vieth et al (19) examined the efficacy and safety of relatively high intakes of vitamin D_3 by assessing the effects of 1000 and 4000 IU/d in 61 adults for $\leq$5 mo. They found that vitamin D_3 at a dose of 4000 IU/d was effective in elevating the serum 25(OH)D concentration to $\geq$40 ng/mL. Until recently, higher-dose

[1] From the Division of Biostatistics and Epidemiology, Department of Medicine (EG-M), and the Departments of Pediatrics (CLW and BWH), Neurosciences (MSK), and Radiation Oncology (SG-C), Medical University of South Carolina, Charleston, SC, and the Ralph H Johnson VA Medical Center, Charleston, SC (MSK and SG-C).

[2] The contents of this article do not represent the views of the Department of Veterans Affairs or the US Government.

[3] Supported in part by grants from the Gateway for Cancer Research, the Health Services Research and Development Program of the Department of Veterans Affairs, the South Carolina Clinical and Translational Research Institute, and the Biostatistics Shared Resource of the Hollings Cancer Center at the Medical University of South Carolina.

[4] Address correspondence to S Gattoni-Celli, Strom Thurmond Biomedical Research Building, Room 338C, 114 Doughty Street, Charleston, SC 29403. E-mail: gattonis@musc.edu.

Received January 7, 2012. Accepted for publication May 30, 2012.

First published online July 3, 2012; doi: 10.3945/ajcn.112.034256.

vitamin D_3 oral supplementation was not viewed as a viable treatment modality because of concerns about potential toxicity. This interventional study was aimed at investigating vitamin D_3 supplementation and its impact on hypovitaminosis D in African American men.

SUBJECTS AND METHODS

Study population

Eligible subjects were enrolled through the Clinical and Translational Research Center at the Medical University of South Carolina. Fifty-two male subjects diagnosed with early-stage, low-risk prostate cancer received vitamin D_3 supplementation at 4000 IU/d for 1 y. Their serum values of 25(OH)D were measured at enrollment and every 2 mo afterward for a total of 7 measurements per enrolled subject. Circulating concentrations of vitamin D [25(OH)D] were measured by radioimmunoassay as previously described (20, 21). BMI was calculated by using the formula weight in kilograms/(height in meters)^2. Information on BMI and 25(OH)D was collected every 2 mo. Forty-seven subjects completed 1 y of supplementation and were included in the analysis. Every 2 mo, we assessed the basic metabolic panel in all subjects enrolled in this interventional study, including calcium and phosphorus, and we measured the urinary calcium: creatinine ratio (in mg/mL:mg/mL, with normal values <0.22 in adult males) to monitor any potential toxicities from vitamin D_3 supplementation. The vitamin D_3 (cholecalciferol) administered for this study was manufactured by JR Carlson Laboratories Inc. This study was conducted under investigational new drug 77,839 (clinicaltrials.gov identifier: NCT01045109) and approved by the institutional review board of the Medical University of South Carolina.

Statistical analyses

Statistical analyses were performed in R version 2.14.2 (22) and in WinBugs version 1.4.3 (23). To be conservative, variance was assumed to be unequal, and Welch's 2-sample *t* tests were used to compare mean age, BMI, and baseline 25(OH)D concentrations across races. Modeling of 25(OH)D over time was performed according to the model proposed by Heaney et al (24), who assumed that there are 2 parameters to define the relation between 25(OH)D concentrations and time since supplementation. Specifically, the exponential model was defined as follows:

$$C(t) = C(0) + a(1 - e^{-kt}) \qquad (1)$$

where t is time, $C(t)$ is the 25(OH)D concentrations at time t [implying that $C(0)$ is the baseline concentration], a is the increment to equilibrium produced by a given constant input, and k is the rate constant representing the proportion of total mass of 25(OH)D metabolized per time unit. This model was generalized to allow for separate a and k parameters for African American and white subjects. The model was estimated in WinBugs, which uses a Bayesian modeling framework and uses Gibbs sampling for generating posterior distributions of parameters. It was assumed that vitamin D concentrations at each time for each individual were normally distributed with mean $C(t)$ and variance σ^2. Prior distributions for parameters were as follows: σ and k were assumed to follow diffuse inverse γ distributions, and a was assumed to follow a diffuse uniform distribution (with limits of 0–100). Five thousand iterations were performed and discarded, followed by 25,000 iterations, every fifth iteration of which was saved. Posterior distributions were based on the 5000 saved iterations. Medians of the posterior distributions served as our point estimates with 95% posterior intervals included to provide precision of estimates. Comparisons of parameters across races are based on the posterior probability estimates of the differences in parameters. Convergence was checked by rerunning the model with different starting values and comparing the resulting posterior distributions. The distribution of residuals was checked to ensure that our assumption of normality of residuals was appropriate. We also used longitudinal linear regression modeling with 3 df for time (ie, we included a linear, quadratic, and cubic term) to more flexibly model the relation between time and 25(OH)D to ensure that the exponential model was appropriate (and not too stringent) for our observed data. The 2 models provided very similar fits, which validates the appropriateness of the exponential model in this setting. Serum values of 25(OH)D were measured in nanograms per milliliter (ng/mL) and expressed as means ± SDs, as appropriate.

RESULTS

Subjects enrolled into the study were followed for 12 mo, and information on BMI and 25(OH)D was collected every 2 mo. Comparisons of age, BMI, and 25(OH)D at baseline and at study exit (12 mo) are provided in **Table 1**, which shows that African American and white subjects had comparable ages, baseline

TABLE 1
Characteristics of subjects[1]

	Values	Minimum, maximum	*P* value
Age (y)			
Whites	65.3 ± 6.4[2]	53, 78	0.43
African Americans	63.2 ± 8.4	49, 74	
BMI (kg/m^2)			
Baseline			
Whites	28.36 ± 5.14	21.4, 43.3	0.98
African Americans	28.40 ± 6.17	18.4, 40.7	
At 12 mo			
Whites	28.20 ± 4.73	21.3, 40.2	0.97
African Americans	28.28 ± 5.38	19.6, 39.0	
25(OH)D (ng/mL)			
Baseline			
Whites	36.73 ± 13.05	12.6, 75.0	<0.0001
African Americans	21.40 ± 7.72	11.7, 34.1	
At 12 mo			
Whites	67.25 ± 13.90	47.1, 95.4	0.93
African Americans	67.68 ± 15.72	35.7, 90.2	
25(OH)D <32 ng/mL (%)			
Whites	34	—	0.0007
African Americans	92	—	
25(OH)D <20 ng/mL (%)			
Whites	11	—	0.01
African Americans	50	—	

[1] $n = 35$ whites, $n = 12$ African Americans. 25(OH)D, 25-hydroxyvitamin D.
[2] Mean ± SD (all such values).

BMI, and exit BMI. Baseline concentrations of serum 25(OH)D (in ng/mL) were significantly different between groups (African American compared with white: 24.1 and 37.2, respectively; $P = 0.01$). Baseline and exit concentrations of 25(OH)D were also different within each group (African American: 24.1 compared with 67.7; $P < 0.0001$; white: 37.2 compared with 67.3; $P < 0.0001$). After only 2 mo of supplementation, differences in circulating concentrations of vitamin D between African American and white subjects became nonsignificant (mean ± SD: 51.43 ± 10.49 ng/mL and 56.25 ± 11.95 ng/mL in African Americans and whites, respectively; $P = 0.20$); As shown in **Figure 1**, subjects with the lowest baseline circulating concentrations of vitamin D had the largest increases by 2 mo. These results are consistent with the concept that the rate of 25-hydroxylation of vitamin D_3 decreases dramatically with higher initial circulating 25(OH)D concentrations. This has been previously reported in 2 recent studies in which production of 25(OH)D decreased when circulating 25(OH)D concentrations approached 40 ng/mL, probably through feedback inhibition (25, 26). The effects over time of 1 y of supplementation on serum concentrations of 25(OH)D in 12 African American and 35 white subjects are shown in **Figure 2**. The 2 groups were essentially indistinguishable after 1 y of vitamin D_3 supplementation (67.7 compared with 67.3 ng/mL in African Americans and whites, respectively; $P = 0.97$). The exponential model for African American and white subjects differed in the increment to equilibrium produced by a given constant input (parameter a: 42.1 compared with 31.7 in African Americans and whites, respectively) but had similar values for the rate constant (parameter k: 0.55 compared with 0.50 in African Americans and whites, respectively) representing the proportion of total mass of 25(OH)D metabolized per day. Model estimates, their estimated dispersion parameter, and 95% credible intervals are provided in **Table 2**. A full representation of the posterior distributions of a and k parameters by race is also provided as supplemental material (*see* Figure S1 under "Supplemental data" in the online issue). These results are consistent with those reported by Heaney et al (24).

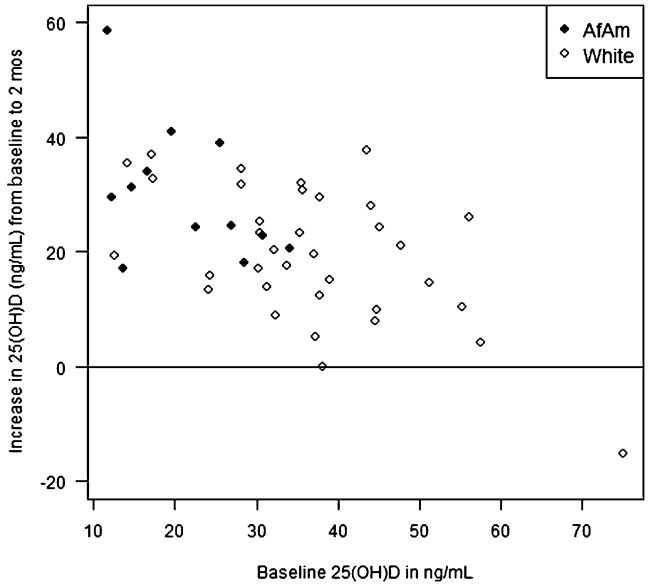

FIGURE 1. Changes in 25(OH)D from baseline to 2 mo after beginning supplementation. African American subjects ($n = 12$) are represented by solid black symbols; white subjects ($n = 35$) are represented by open symbols. AfAm, African American; 25(OH)D, 25-hydroxyvitamin D.

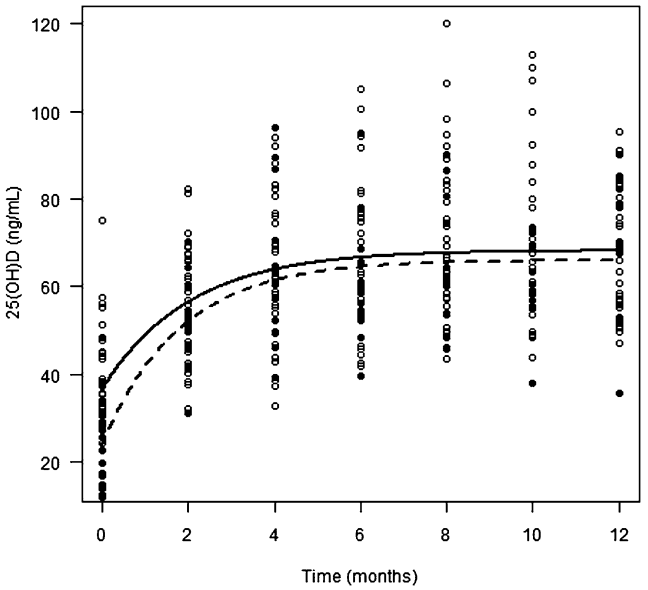

FIGURE 2. Effects of 1 y of vitamin D_3 supplementation at 4000 IU/d on circulating concentrations of 25(OH)D. African American subjects ($n = 12$) are represented by solid black circles; white subjects ($n = 35$) are represented by open circles. Each fitted line is based on the exponential model. The estimated parameter values (95% PI) of the model for African American subjects are $a = 42.1$ (95% PI: 37.2, 48.4) and $k = 0.55$ (95% PI: 0.31, 1.90). The estimated parameter values of the model for white subjects are $a = 31.7$ (95% PI: 28.6, 35.2) and $k = 0.50$ (95% PI: 0.32, 0.85). The a parameter was significantly different between the 2 races (the posterior probability that a in African Americans is less than in whites is 0.008), but the k parameter was not (the posterior probability that k in African Americans is less than in whites is 0.40). PI, posterior interval; 25(OH)D, 25-hydroxyvitamin D.

No adverse events linked to vitamin D_3 supplementation at 4000 IU/d were observed, and no subject reported any symptoms associated with supplementation. Six of 47 subjects had a urinary calcium:creatinine ratio of >0.2 at enrollment before starting supplementation. Five of these 6 subjects had a decrease in the ratio or remained stable after 1 y of supplementation. In one subject who had significant cardiometabolic comorbidities,

TABLE 2
Estimates of exponential model parameters and their dispersion[1]

Parameter and race	Estimate	SD	95% Credible interval
a			
White	31.7	1.64	28.6, 35.2
African American	42.1	2.70	37.2, 48.4
k			
White	0.50	0.25	0.32, 0.85
African American	0.55	0.35	0.31, 1.42

[1] a is defined as the increment to equilibrium produced by a given constant input; k is defined as the rate constant representing the proportion of total mass of 25-hydroxyvitamin D metabolized per unit. Because of the use of Markov-chain Monte Carlo methods, the parameter estimate is the median of the posterior distribution. The SD represents the SD of the posterior distribution of the parameter and can be interpreted similarly to an SE. The 95% credible interval represents the 2.5th and 97.5th percentiles of the posterior distribution of the parameter. These are analogous to frequentist CIs.

the ratio increased from 0.28 to 0.39. This subject expressed no complaints over the time of the study.

DISCUSSION

Our clinical observations of extensive hypovitaminosis D among African American males are entirely consistent with the results of the NHANES 2001–2004, which showed that >90% of African Americans have 25(OH)D serum concentrations <30 ng/mL (5). Supplementation with 4000 IU/d for 1 y elevated circulating 25(OH)D to a range (40–70 ng/mL of serum) that was recently recommended by the Endocrine Society Practice Guidelines (27). The results of this interventional study show the feasibility and efficacy of this approach in eliminating hypovitaminosis D, which is a crucial health disparity among African Americans. In addition, this regimen erased previously significant differences in serum concentrations of 25(OH)D between African American and white subjects. Furthermore, it is important to point out the absence of any significant toxicity of the vitamin D_3 intervention used in this clinical study. The Endocrine Society Practice Guidelines, compared with those of the Food and Nutritional Board of the Institute of Medicine (28, 29), recommend a 2- to 3-fold increase in vitamin D_3 intake, with a tolerable upper intake level of 10,000 IU/d (27). The Institute of Medicine report also concluded that circulating 25(OH)D concentrations were unrelated to various neoplasias, and in fact higher concentrations of circulating 25(OH)D could make the cancer worse. These conclusions of the Institute of Medicine report are not supported by our current data (30).

Although it is possible that optimal concentrations of circulating vitamin D are different between African Americans and whites, the results of our interventional study clearly indicate that after 1 y of vitamin D_3 supplementation at 4000 IU/d the 2 groups were essentially indistinguishable on the basis of serum concentrations of 25(OH)D. These results also suggest that African American men may be able to convert vitamin D_3 into 25(OH)D more rapidly than white men, as originally proposed by Heaney et al (24). However, we acknowledge that the study was not planned with the estimation of the exponential model. As a result, the inferences should be made with caution, with more emphasis provided on the point estimates of the parameters and their interpretation than on statistical significance. In addition, the credible intervals are helpful in obtaining a good understanding of a reasonable range of true values for the parameters based on the data collected in this study.

Vitamin D_3–based interventions targeting adult African Americans could have a beneficial impact on the current epidemics of cardiometabolic disorders in this underserved population, would provide strong evidence for the causal role played by vitamin D deficiency in these pathologies, and could help eliminate well-documented health disparities. Some of the answers will come from prospective, randomized clinical studies.

In the past few years there has been a steady stream of news reports extolling the beneficial effects of the "sunshine vitamin" and the negative health consequences of hypovitaminosis D in the general population. These reports tend to follow the publication of an ever-increasing number of scientific reports showing that hypovitaminosis D has reached epidemic proportions and that lower concentrations of circulating vitamin D have an inverse correlation with the prevalence and severity of a range of diseases including diabetes and cardiovascular disease (13, 31–33). Possible explanations for the higher prevalence of diabetes and cardiovascular disease among African Americans include socioeconomic, genetic, and environmental/dietary factors (34). We propose that these health disparities are also the result of widespread hypovitaminosis D within this population and that, through appropriate vitamin D_3 supplementation, vitamin D deficiency can be easily remedied in African Americans. Through well-designed prospective, randomized clinical trials it will be possible to establish whether, by using an intervention strategy that is extremely cost-effective and easy to implement, vitamin D_3 supplementation has the potential to greatly reduce health disparities among African Americans.

We thank David T Marshall and Stephen J Savage (Departments of Radiation Oncology and Urology, respectively) for helping with the recruitment of eligible subjects.

The authors' responsibilities were as follows—SG-C and MSK: designed the study; EG-M: analyzed the data and performed the statistical analyses; SG-C and EG-M: wrote the manuscript; and CLW and BWH: provided essential reagents and were responsible for measuring circulating vitamin D. All of the authors read and approved the final manuscript. BWH is an academic consultant to the DiaSorin Corporation. The other authors declared no conflicts of interest.

REFERENCES

1. MacLaughlin JA, Holick MF. Biochemistry and physiology of the skin. In: Goldsmith LA, ed. Photobiology of vitamin D_3 in the skin. New York, NY: Oxford University Press, 1983:734–54.
2. Esvelt RP, Schnoes HK, Deluca HF. Vitamin D_3 from rat skins irradiated in vitro with ultraviolet light. Arch Biochem Biophys 1978;188: 282–6.
3. Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW. Racial pigmentation and the cutaneous synthesis of vitamin D. Arch Dermatol 1991;127:536–8.
4. Clemens T, Henderson SL, Adams J, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D_3. Lancet 1982;9:74–6.
5. Ginde AA, Liu MC, Camargo CA. Demographic differences and trends of vitamin D insufficiency in the US population. Arch Intern Med 2009;169:626–32.
6. Nesby-O'Dell S, Scanlon K, Cogswell M, Gillespie C, Hollis B, Looker A, Allen C, Doughertly C, Gunter E, Bowman B. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey: 1988-1994. Am J Clin Nutr 2002;76: 187–92.
7. Bischoff-Ferrari HA, Dietrich T, Orav E, Dawson-Hughes B. Positive association between 25(OH)D levels and bone mineral density: a population-based study of younger and older adults. Am J Med 2004;116: 634–9.
8. Meier C, Woitge H, Witte K, Lemmer B, Seibel M. Supplementation with oral vitamin D_3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. J Bone Miner Res 2004;19:1221–30.
9. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin sufficiency: Implications for establishing a new effective DRI for vitamin D. J Nutr 2005;135:317–22.
10. Haddock L, Corcino J, Vazquez MD. 25(OH)D serum levels in the normal Puerto Rican population and in subjects with tropical sprue and parathyroid disease. P R Health Sci J 1982;1:85–91.
11. Matsuoka LY, Wortsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D: a preliminary study. Arch Dermatol 1988;124:1802–4.
12. Feldman D, Glorieux FH, Pike JW. Vitamin D. Amsterdam, Netherlands: Elsevier Academic Press, 2005.
13. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, Clarke A, Franco OH. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. Maturitas 2010;65:225–36.

14. Pearcy JN, Keppel K. A summary measure of health disparity. Public Health Rep 2002;117:273–80.
15. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. Circulation 2005;111:1233–41.
16. Lips P, Wiersinga A, Van Ginkel FC, Jongen MJ, Netelenbos JC, Hackeng WH, Delmas PD, Van der Vijgh WJ. The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. J Clin Endocrinol Metab 1988;67:644–50.
17. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124:400–6.
18. Sorya A, Risteli J, Risteli L, Valimaki M, Tilvis R. Effects of vitamin D and calcium on markers of bone metabolism in gastric patients with low serum 25(OH)D levels. Calcif Tissue Int 1991;49:588–9.
19. Vieth R, Chan PCR, MacFarlane GD. Efficacy and safety of vitamin D_3 intake exceeding the lowest observed adverse effect level (LOAEL). Am J Clin Nutr 2001;73:288–94.
20. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. Am J Clin Nutr 2008;88:1519–27.
21. Dong Y, Stallman-Jorgensen IS, Pollock NK, Harris RA, Keeton D, Huang Y, Li K, Bassali R, Guo D-h, Thomas J, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D_3 supplementation in blachk youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. J Clin Endocrinol Metab 2010;95:4584–91.
22. The R Project for Statistical Computing. Homepage. Available from: http://www.r-project.org (cited 15 May 2012).
23. The BUGS Project. Homepage. Available from: http://www.mrc-bsu.cam.ac.uk/bugs (cited 15 May 2012).
24. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecaciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204–10.
25. Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW. 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr 2008;87:1738–42.
26. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res 2011;26:2341–57.
27. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96:1911–30.
28. Institute of Medicine. Dietary Reference Intakes for calcium and vitamin D. Washington, DC: National Academy Press, 2011.
29. Ross AC, Manson JA, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
30. Marshall DT, Savage SJ, Garrett-Mayer E, Keane TE, Hollis BW, Horst RL, Ambrose LH, Kindy MS, Gattoni-Celli S. Vitamin D_3 supplementation at 4,000 IU per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. J Clin Endocrinol Metab (Epub ahead of print 16 April 2012).
31. Mainous AG III, King DE, Garr DR, Pearson WS. Race, rural residence, and control of diabetes and hypertension. Ann Fam Med 2004;2:563–8.
32. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol 2009;19:73–8.
33. Artaza JN, Mehrotra R, Norris KC. Vitamin D and the cardiovascular system. Clin J Am Soc Nephrol 2009;4:1515–22.
34. Kuzawa CW, Sweet E. Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. Am J Hum Biol 2009;21:2–15.