Dietary Fat Increases Vitamin D-3 Absorption

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ABSTRACT

Background The plasma 25-hydroxyvitamin D response to supplementation with vitamin D varies widely, but vitamin D absorption differences based on diet composition is poorly understood.

Objectives We tested the hypotheses that absorption of vitamin D-3 is greater when the supplement is taken with a meal containing fat than with a fat-free meal and that absorption is greater when the fat in the meal has a higher monounsaturated-to-polyunsaturated fatty acid ratio (MUFA:PUFA).

Design Open, three-group, single-dose vitamin D-3 comparative absorption experiment.

Participants/setting Our 1-day study was conducted in 50 healthy older men and women who were randomly assigned to one of three meal groups: fat-free meal, and a meal with 30% of calories as fat with a low (1:4) and one with a high (4:1) MUFA:PUFA. After a 12-hour fast, all subjects took a single 50,000 IU vitamin D-3 supplement with their test breakfast meal.

Main outcome measures Plasma vitamin D-3 was measured by liquid chromatography—mass spectrometry before and 10, 12 (the expected peak), and 14 hours after the dose.

Statistical analyses performed Means were compared with two-tailed *t* tests for independent samples. Group differences in vitamin D-3 absorption across the measurement time points were examined by analysis of variance with the repeated measures subcommand of the general linear models procedure.

Results The mean peak (12-hour) plasma vitamin D-3 level after the dose was 32% (95% CI 11% to 52%) greater in subjects consuming fat-containing compared with fat-free meals (P=0.003). Absorption did not differ significantly at any time point in the high and low MUFA and PUFA groups.

Conclusions The presence of fat in a meal with which a vitamin D-3 supplement is taken significantly enhances absorption of the supplement, but the MUFA:PUFA of the fat in that meal does not influence its absorption.
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VITAMIN D SUPPLEMENTS ARE INCREASINGLY RECOMMENDED to curb insufficiency. It is important to understand the determinants of vitamin D absorption to define conditions under which individuals can achieve greater and more consistent improvement in vitamin D status. Several studies have examined the influence of supplementation under various meal conditions on serum 25-hydroxyvitamin D (25[OH]D) levels.[1,2] One found no effect of 600 IU vitamin D-3 in processed cheese daily for 2 months on serum 25(OH)D levels.[1] Raimundo and colleagues[2] reported that the increment in serum 25(OH)D 2 weeks after taking a single 50,000 IU vitamin D-3 dose was greater when the dose was taken with a high-fat meal than with a low-fat meal. We have previously shown that vitamin D-3 supplements taken with a meal resulted in a greater 25(OH)D increment than those taken in the fasting state.[3]

Serum 25(OH)D is neither the most direct nor optimal measure of vitamin D absorption. Serum 25(OH)D levels are influenced by several factors that are at least partially independent of vitamin D supplementation, including genetic regulators of vitamin D binding proteins in the circulation,[4-6] 25(OH)D metabolism,[6,7] and the state of inflammation (increased inflammation is associated with lower 25(OH)D levels,[8,9] possibly as a result of increased urinary losses).[10] The most direct way to assess vitamin D-3 absorption is to measure the peak circulating parent vitamin D-3 level 12 hours after ingestion of the vitamin D dose.[11] Because vitamin D is fat-soluble, it might seem evident that it is the fat component of a meal that enhances absorption, but relatively little evidence is available in human beings. In a small study of eight subjects, Johnson and colleagues[1] found that the peak serum vitamin D-3 increment after taking 10,000 IU vitamin D-3 was greater when the dose was taken with cheese than with water. Although an overall effect of fat vs no fat has not clearly been demonstrated, there is some evidence

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that the type of fat in the meal with which vitamin D is taken may influence its absorption. In rats, absorption was reduced by 30% in the presence of a fourfold increase in luminal fat.[12,13] The polyunsaturated fatty acids (PUFAs), linoleic acid, and linolenic acid decreased vitamin D absorption.[13] Similarly, in human beings, observational data have suggested that the increment in 25(OH)D during supplementation was positively associated with the monounsaturated fatty acid (MUFA)-to-PUFA ratio (MUFA:PUFA).[14] Direct evidence that MUFA:PUFA in a meal alters vitamin D absorption is lacking.

The objectives of this study were to determine whether vitamin D-3 absorption from a supplement taken with a meal was influenced by the presence or absence of fat in that meal and, if so, whether MUFA:PUFA in the meal influenced vitamin D-3 absorption.

MATERIALS AND METHODS

Subjects and Study Design

Healthy white men and white postmenopausal women, all aged 50 years and older, were recruited through mailing lists and local advertisements. They were enrolled between October 1 and May 31, 2011, to reduce sun contribution to plasma vitamin D-3 levels and participated between December 2011 and May 2013.

Inclusion criteria included use of not more than 400 IU vitamin D or 1,000 mg calcium per day, serum 25(OH)D level in the range 20 to 29.5 ng/mL (49.9 to 73.6 nmol/L), and body mass index in the range 20 to 29.5. Exclusion criteria were screening estimated glomerular filtration rate $<$30 mL/minute (calculated by the Modification of Diet in Renal Disease Study equation)[15]; spot urinary calcium:creatinine $>$0.325 mg/mg (corresponding to a 24-hour urine calcium 350 mg); hypercalcemia; malabsorption; Crohn's disease; disorders of bone metabolism; kidney stones in the past 3 years; cancer treatment during the past year; use of proton pump inhibitors, lipid-lowering medications, fish oil, or flaxseed oil; treatment during the past year with hormones (eg, estrogen or testosterone) or osteoporosis medications; high-dose thiazide diuretic therapy; and attendance in tanning salons. The protocol was approved by the Investigational Review Board at Tufts University and written informed consent was obtained from each subject. The protocol is registered at ClinicalTrials.gov as NCT015008845.

Subjects were prescreened by means of a telephone questionnaire. Interested and potentially eligible candidates were invited to the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University for a screening medical history, physical examination, serum 25(OH)D and routine chemical screen, and urine calcium and creatinine measures. Eligible subjects were enrolled.

In this single-blind study, 51 subjects were enrolled; one subject failed to return after the morning visit and was excluded. The subjects were randomly assigned to one of three breakfast meal types: fat-free meal, high MUFA:PUFA meal, or a low MUFA:PUFA meal. Subjects came to the Center after a 12-hour fast and had a blood draw, consumed their test breakfast meal, and took a 50,000 IU vitamin D-3 tablet. They were given a boxed lunch and agreed to eat nothing else until they returned at 6 PM that evening. At 6 PM, they had a blood draw, consumed the provided dinner meal, and remained at the Center for blood draws at 8 and 10 PM. The analyses were carried out in 19 subjects in the fat-free meal group, 11 in the high MUFA:PUFA meal group,* and 20 in the low MUFA:PUFA meal group.

Table 1. Composition of the test breakfast, lunch, and dinner meals, expressed as percent of total energy[a] in a study evaluating the effect of fat quantity and composition on vitamin D-3 absorption in 50 healthy older adults

		Fat-Containing Meal	
Group	**Fat-free meal**	**Low MUFA[b]:PUFA[c]**	**High MUFA:PUFA**
Total fat	0	30	30
MUFA	0	5	20
PUFA	0	20	5
Saturated fatty acid	0	5	5
Protein	15	15	15
Total carbohydrates	85	55	55
Fiber	3	4	3
Other	82	51	52

[a]Weight-based and consumed in three approximately even portions in each of three meals on the test day.
[b]MUFA=monounsaturated fatty acid.
[c]PUFA=polyunsaturated fatty acid.

Meals

The nutrient content of the test meals is shown in Table 1. The total fat content in 2 of the groups was set at the commonly consumed level of 30% of total calories[16]; the third group consumed fat-free meals. Meals were provided by the metabolic kitchen and consisted of real food. For example, breakfast consisted of egg whites flavored with small amounts of onion and tomato, fruit, toast, and cranberry juice. The groups were balanced for energy by adjusting the amount of sugar in the cranberry juice (diet or regular juice or a mixture of the two). Protein and fiber were balanced across all groups. MUFA:PUFA was manipulated by adding varying amounts of MUFA (olive oil) and PUFA (corn oil) to achieve a ratio of 1:4 in the low and 4:1 in the high MUFA:PUFA diets. The boxed lunch and the dinner provided to the study subjects on the test day had fat/protein/carbohydrate content similar to that of the test breakfast meals. Subjects ate all of the food provided but no other food or drink except for water on the study day.

Supplements

The 50,000 IU vitamin D-3 capsules (containing vitamin D-3 powder in microcrystalline cellulose and silica) were purchased as a single lot from BioTech Pharmacal Inc. They were

**This group is smaller because some subjects were part of a different substudy and are not included in this report.*

analyzed by Covance and found to contain 55,906 IU vitamin D-3.

Vitamin D-3 Absorption

Vitamin D absorption was estimated by the method of Lo and colleagues.[11] We assessed plasma parent vitamin D-3 concentration before and 10, 12, and 14 hours after an oral 50,000 IU vitamin D-3 dose.

Total Fat Tissue Mass

Total body fat tissue mass, a potential storage site for vitamin D, was assessed on the first study visit by a GE Lunar Prodigy dual x-ray absorptiometry scanner with acquisition software version 6.1 (2002) and analysis version 12.2 (2008). The precision of this measure in our laboratory is 0.94%.[17]

Diet Assessment

Intake of calcium, macronutrients, and total energy during the past 3 months was assessed on the first study visit with use of a validated Fred Hutchinson food frequency questionnaire.[18]

Biochemical Assays

Blood was drawn in the morning after the subjects had fasted for 12 hours. All samples from individual subjects were batched for analysis. Screening urinary creatinine was measured on an automated clinical chemistry analyzer (Olympus AU400, Olympus America Inc) and urinary calcium was measured by direct-current plasma emission spectroscopy with coefficients of variation (CVs) $<$3.0%. Screening serum creatinine was measured by colorimetry on a Cobas Fara centrifugal analyzer (Roche Instruments). Screening plasma 25(OH)D was measured by radioimmunoassay with commercial kits (Diasorin) with intra- and interassay CVs of 8.6% to 12.5% and 8.2% to 11.0%, respectively.

For the vitamin D-3 assay, 200 μL vitamin D_3-[$^{13}C_5$] internal standard (100 ng/mL) was added to 1 mL plasma, and the vitamin D-3 was extracted twice with hexane-methanol. The extracts were dried, reconstituted in methanol, and purified using a C-18 solid phase extraction column. The eluant was injected into an Agilent 1100 liquid chromatography–mass spectrometry analyzer. Vitamin D-3 was separated from other plasma compounds using a ProntoSiL 200-5-C30, 5 μm (4.6$\times$250 mm) high-performance liquid chromatography column with an isocratic methanol mobile phase (followed by a hexane rinse to remove lipids from the column). The retention time of the vitamin D-3 was 11 minutes. The mass spectrometer atmospheric pressure chemical ionization source was operated in positive ion mode and the vaporizer temperature was set to 350°C. Vitamin D-3 was detected at mass-to-charge ratio (m/z) 385 and the internal standard at m/z 388 using selected ion monitoring. The detection limit of vitamin D-3 is 0.081 pmol injected onto the column. The interassay variation of the liquid chromatography–mass spectrometry method for eight vitamin D-3 standards spiked into a pooled serum sample and measured on 8 different days was 5.3$\pm$0.5 ng/mL (13.8$\pm$1.3 nmol/L) (CV=9.1%).

Randomization and Statistical Analyses

The randomization scheme was generated with use of the scheme described at http://www.randomization.com and administered by one of the coinvestigators (S. S. H.).

All analyses were conducted with SPSS version 21 (2013, IBM-SPSS Inc) Means were compared with two-tailed *t* tests for independent samples. Differences between groups are reported as means and 95% CIs. Distributions of categorical variables were compared with χ^2 tests. Potential influences of covariates and effect modifiers were examined by analysis of covariance using the general linear models procedure. Group differences in vitamin D-3 absorption across the measurement time points were examined with the repeated measures subcommand of the general linear models procedure. P values $<$0.05 were considered to indicate statistical significance. There were no data available upon which to base power calculations.

RESULTS

Fat-Containing vs Fat-Free Meals

The baseline clinical characteristics of the 50 subjects by fat-free (n=19) and fat-containing (n=31) meal groups are reported in Table 2. The fat-free and fat-containing meals were successfully balanced for energy, calcium, and protein content. None of these measures in Table 2 differed significantly in the two groups at baseline ($P \geq 0.140$). In analyses of vitamin D absorption at baseline and the three follow-up time points, there was a significant interaction of fat-free vs fat-containing meal group with time ($P<0.001$). As shown in the Figure, there was no significant difference in plasma vitamin D-3 levels at baseline, but the fat-containing meal group had significantly higher plasma vitamin D-3 concentrations than the fat-free meal group at each time point thereafter. At 12 hours, the fat-containing vs fat-free meal mean difference in plasma D-3 concentration was 26.9 ng/mL (95% CI 9.6 to 44.1 ng/mL) (69.9 nmol/L). Differences at the other time points were for 10 hours, 30.5 ng/mL (95% CI 14.4 to 46.7 ng/mL) (79.3 nmol/L) and for 14 hours, 21.3 ng/mL (95% CI 4.6 to 37.9 ng/mL) (55.4 nmol/L).

Influence of Type of Fat

The baseline characteristics of subjects in the low- and high-MUFA:PUFA meal groups are shown in Table 2. Plasma vitamin D-3 levels did not differ significantly at baseline or at any time point in the two groups ($P \geq 0.254$). Vitamin D-3 levels at 12 hours after the dose were 116.0$\pm$34.6 ng/mL (301.5$\pm$89.9 nmol/L) in the low MUFA:PUFA group and 104.2$\pm$18.9 ng/mL (270.8$\pm$49.1 nmol/L) in the high MUFA:PUFA group.

Potential covariates, body mass index, total body fat mass, and screening plasma 25(OH)D level were not associated with vitamin D absorption and neither modified the effect of fat on vitamin D absorption. There were no serious adverse events during the study. Compliance with the vitamin D supplement was 100%.

DISCUSSION

We recently demonstrated that the increment in serum 25(OH)D after a vitamin D-3 supplement was greater when the supplement was taken with a meal than in the fasting

Table 2. Baseline clinical and biochemical characteristics of the fat-free and fat-containing meal groups in a study evaluating the effect of fat quantity and composition on vitamin D-3 absorption in 50 healthy older adults

		Fat-Containing Meals		
Characteristic	**Fat-free meals[a]**	**All[a]**	**Low MUFA[b]: PUFA[cd]**	**High MUFA: PUFA[d]**
Subjects (n)	19	31	20	11
Female (%)	42.1	45.2	50.0	36.4
	←——— *mean±standard deviation* ———→			
Age (y)	60.1±6.6	62.6±7.0	62.1±7.4	63.6±6.5
Height (cm)	170.1±10.5	169.9±8.6	168.6±8.4	172.3±9.0
Weight (kg)	74.0±9.5	72.1±11.2	70.7±11.7	74.6±10.3
Body mass index	25.4±2.6	24.7±2.5	24.6±2.9	24.9±1.7
Dual x-ray absorptiometry total body fat (kg)	22.6±8.9	21.1±6.6	20.5±6.6	22.0±6.7
Energy (kcal)	1,541±865	1,359±395	1,298±349	1,471±463
Total fat intake (g)	66.3± 45.1	52.7±18.5	49.6±14.5	58.4±23.9
Protein intake (g)	66.1±34.9	56.9±15.9	54.2±12.8	61.9±20.1
Calcium intake from food (mg)	769.0±504.5	724.1±325.6	669.5±333.1	823.5±300.6
Calcium supplements (mg)	185.8±337.2	248.4±287.4	315.0±294.3	127.3±241.2
Plasma vitamin D-3 (ng/mL)[e]	11.0±5.0	11.9±5.1	11.6±4.4	12.4±6.2
Plasma 25(OH)D (ng/mL)[f]	25.1±2.6	25.3±2.5	25.3±2.3	25.3±2.9

[a]The fat-free and fat-containing meal groups did not differ significantly at $P>0.140$.
[b]MUFA=monounsaturated fatty acid.
[c]PUFA=polyunsaturated fatty acid.
[d]The high and low MUFA:PUFA groups did not differ significantly at $P>0.082$.
[e]To convert ng/mL vitamin D-3 to nmol/L, multiply ng/mL by 2.599. To convert nmol/L vitamin D-3 to ng/mL, multiply nmol/L by 0.385. Vitamin D-3 of 11 ng/mL=28.59 nmol/L.
[f]To convert ng/mL 25(OH)D to nmol/L, multiply ng/mL by 2.496. To convert nmol/L 25(OH)D to ng/mL, multiply nmol/L by 0.40. 25(OH)D of 25.1 ng/mL=62.65 nmol/L.

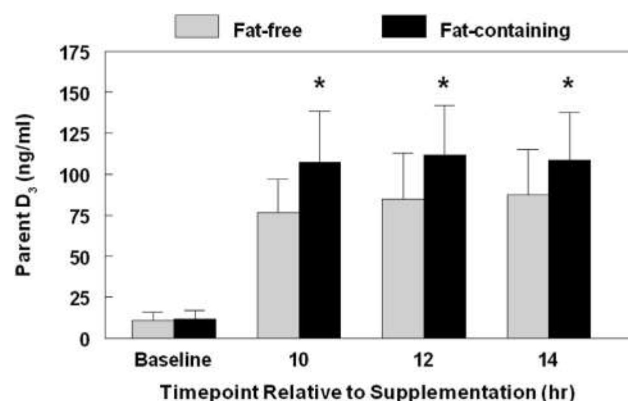

Figure. Effect of meal fat on absorption of vitamin D-3, assessed as serum vitamin D-3 concentration at 10, 12, and 14 hours after a 50,000 IU vitamin D-3 dose given to healthy older adult men and women. Mean±standard deviation plasma vitamin D-3 levels did not differ significantly at baseline ($P=0.544$), but were higher in the 30% kcal fat-containing than the fat-free meal group at 10 hours (107.3±31.2 vs 76.8±20.2 ng/mL [278.9±81.1 vs 199.6±52.5 nmol/L]; $P<0.001$), 12 hours (111.8±30.2 vs 84.9±28.2 [290.6±78.5 vs 220.7±73.3 nmol/L]; $P=0.003$) and 14 hours (108.7±28.9 vs 87.4±27.7 [282.5±75.1 vs 227.2±72.0 nmol/L]; $P=0.013$) after the dose. *$P<0.020$.

state.[3] However, that work did not investigate the specific meal components responsible for the apparently improved absorption. This study extends the earlier finding by determining that taking vitamin D-3 with a meal containing a typically consumed amount of fat, when compared with a fat-free meal, significantly improved its absorption by an average of 32% at the standard peak absorption time 12 hours after the dose. The variability around this estimate is consistent with a difference between groups of 11% to 52%. Even an 11% difference in our view is clinically meaningful. Absorption was also greater at the less frequently measured 10- and 14-hour time points (by averages of 40% and 25%, respectively).

Traub and colleagues[19] recently demonstrated that 25(OH)D increments were greater when vitamin D was provided in an oil droplet compared with a chewable tablet; however, the 25(OH)D increment in response to capsules containing vitamin D as powder, as used in our study, was not significantly different from that observed with the other two matrices. It is unclear what role meal conditions played in the study by Traub and colleagues[19]—subjects were asked to take their supplements five times daily, with no specific regard to meals. In addition, compliance (not reported) may have differed by group in that study. Nonetheless, our findings may not be relevant to oil-based or other vitamin D supplement forms. The long-term effect of supplementation on

serum 25(OH)D levels was not assessed in this study; however, it is well established that the increment in serum 25(OH)D increases with the dose of vitamin D-3.[20] By the same token, increasing absorption of vitamin D-3 by more than 30% would very likely result in higher serum 25(OH)D levels. Presumably, the presence of fat favors absorption of vitamin D-3 by stimulating the secretion of bile and promoting the formation of micelles.

Based on an earlier observation,[14] we had expected that subjects in the low MUFA:PUFA group would have had lower vitamin D absorption than those in the high MUFA:PUFA group. When tested directly, MUFA:PUFA had no significant influence on absorption. MUFA:PUFA tested differed dramatically (1:4 vs 4:1) in an effort to enhance likelihood of detecting a difference in the two MUFA:PUFA groups, if one were present. Smaller differences in MUFA:PUFA commonly present in diets in the general population are not likely to affect the absorption of vitamin D-3. The basis for the discrepancy is unknown but there may have been unidentified enhancers of vitamin D-3 absorption in the self-selected diets of the subjects who reported having higher MUFA:PUFA, enhancers that were balanced in the three groups in this controlled intake study.

Strengths of the study are that the groups were balanced for body fat. Group differences in body fat could have led to different degrees of removal of vitamin D-3 from the circulation because the vitamin is stored in fat tissue. The groups were also balanced for baseline nutrient and energy intake and levels of vitamin D-3 and 25(OH)D. The measurement of serum vitamin D-3 after an oral load is a more direct assessment of absorption than is the often and more readily measured concentration of 25(OH)D, a metabolite of vitamin D. A limitation is that it was a single 50,000 IU dose study. Further work is needed to determine whether absorption of vitamin D from smaller doses is similarly affected by meal content and whether, with repeated dosing, absorption remains the same.

CONCLUSIONS

The peak (12-hour) absorption of vitamin D-3 from a supplement is an average of 32% higher when the supplement is taken with a meal containing a commonly consumed amount of fat than when taken with a fat-free meal. Absorption at 10 and 14 hours was also greater, by means of 40% and 25%, respectively. This study provides the rationale for recommending that vitamin D supplements be taken with a meal containing fat. MUFA:PUFA in the meal does not appear to be important.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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