

The New England Journal of Medicine

©Copyright, 1992, by the Massachusetts Medical Society

Volume 326

APRIL 30, 1992

Number 18

HYPERVITAMINOSIS D ASSOCIATED WITH DRINKING MILK

CLAIRE H. JACOBUS, M.D., MICHAEL F. HOLICK, PH.D., M.D., QING SHAO, M.D., TAI C. CHEN, PH.D.,
INGRID A. HOLM, M.D., JONATHAN M. KOLODNY, M.D., GHADA EL-HAJJ FULEIHAN, M.D.,
AND ELLEN W. SEELY, M.D.

Abstract Background. Vitamin D has been added to milk in the United States since the 1930s to prevent rickets. We report the unusual occurrence of eight cases of vitamin D intoxication that appear to have been caused by excessive vitamin D fortification of dairy milk.

Methods. Medical records were reviewed and a dietary questionnaire was sent to eight patients who had unexplained hypervitaminosis D. Vitamin D analyses with high-performance liquid chromatography were performed on samples of the patients' serum, the dairy milk they drank, and the vitamin D concentrate added to the milk.

Results. All eight patients drank milk produced by a local dairy in amounts ranging from ½ to 3 cups (118 to 710 ml) daily. All had elevated serum 25-hydroxyvitamin D concentrations (mean \pm SD), 731 ± 434 nmol per liter

$[293 \pm 174$ ng per milliliter]). Six of the eight patients had elevated serum vitamin D₃ concentrations. Of the eight patients, seven had hypercalcemia and one had hypercalciuria but normocalcemia (mean serum calcium, 3.14 ± 0.51 mmol per liter [12.6 ± 2.1 mg per deciliter]). Analysis of the dairy's vitamin D-fortified milk revealed concentrations of vitamin D₃ (cholecalciferol) that ranged from undetectable to as high as 232,565 IU per quart (245,840 IU per liter). An analysis of the concentrate that was used to fortify the milk, labeled as containing vitamin D₂ (ergocalciferol), revealed that it contained vitamin D₃.

Conclusions. Hypervitaminosis D may result from drinking milk that is incorrectly and excessively fortified with vitamin D. Milk that is fortified with vitamin D must be carefully monitored. (N Engl J Med 1992;326:1173-7.)

FORTIFICATION of food with vitamin D has dramatically reduced the incidence of rickets. In the United States, milk has been fortified with vitamin D since the 1930s. According to federal regulations, fortified milk should contain 400 IU of vitamin D per quart.¹ We report the unusual occurrence of hypervitaminosis D in eight patients, in whom the intoxication appeared to be due to the sporadic addition of excessive vitamin D₃ to milk during the fortification process by a local dairy. Two patients with unexplained vitamin D intoxication were described independently at a weekly interhospital endocrine conference in the fall of 1990. Six additional patients were then identified by physicians who had attended the conference. This investigation was initiated to deter-

mine the cause of the hypervitaminosis D in these eight patients.

METHODS

All patients had an elevated serum 25-hydroxyvitamin D (25(OH)D) concentration, and none reported taking supplemental vitamin D as either cod-liver oil or a vitamin D supplement. Patients or their guardians signed forms authorizing the release of information and subsequently completed a dietary questionnaire.

Dietary Questionnaire

The questionnaire was designed to obtain information about food intake (including brand names, types of food, and amounts consumed) and the use of vitamin or calcium supplements. Some of the foods asked about may contain vitamin D; they included cod-liver oil, fish oil, eggs, cereals, and milk. Although milk is the only dairy product that is fortified with vitamin D in the United States,² information on the ingestion of other dairy products was sought, since these foods are rich in calcium.

Chart Review

The patients' medical records were reviewed to obtain information on serum levels of calcium, phosphorus, urea nitrogen, creatinine, albumin, and intact parathyroid hormone (normal range, 10 to 65 ng per liter). These components had been measured in several laboratories. Serum 25(OH)D concentrations, representing both 25-hydroxyvitamin D₂ (25(OH)D₂) and 25-hydroxyvitamin D₃ (25(OH)D₃), were determined by competitive protein-binding assays performed by three commercial laboratories — Bioran Labo-

From the Division of Endocrinology, Beth Israel Hospital, Boston (C.H.J.); the Division of Endocrinology, Children's Hospital Medical Center, Boston (I.A.H.); the Division of Endocrinology, Brigham and Women's Hospital, Boston (G.E.-H.F., E.W.S.); Harvard Medical School, Boston (C.H.J., I.A.H., G.E.-H.F., E.W.S.); the Division of Endocrinology, Boston City Hospital and Boston University School of Medicine, Boston (M.F.H., Q.S., T.C.C.); and the Department of Medicine, Norwood Hospital, Norwood, Mass. (J.M.K.). Address reprint requests to Dr. Seely at the Endocrine Hypertension Division, Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115.

Supported by grants (T32DK-07516, RO1-HD244499-04, and AR-36963) from the National Institutes of Health.

ratories, Cambridge, Massachusetts (normal range, 25 to 137 nmol per liter [10 to 55 ng per milliliter]), Mayo Medical Laboratories, Rochester, Minnesota (normal range, 35 to 200 nmol per liter [14 to 80 ng per milliliter]), and the Nichols Institute, San Juan Capistrano, California (normal range, 22 to 130 nmol per liter [9 to 52 ng per milliliter]) — and by Children's Hospital, Boston, with use of a kit from the Nichols Institute (normal range, 22 to 185 nmol per liter [9 to 74 ng per milliliter]). The 25(OH)D levels were fractionated into 25(OH)D₂ and 25(OH)D₃ at the Mayo Medical Laboratories by high-performance liquid chromatography.³ Serum 1,25-dihydroxyvitamin D (1,25(OH)₂D) concentrations (normal range, 36 to 144 pmol per liter [15 to 60 pg per milliliter]) were determined by a radioreceptor assay (performed by Mayo Medical Laboratories in the case of Patients 1 and 4, the Nichols Institute in the case of Patients 3, 7, and 8, and with use of a kit from the Nichols Institute in the case of Patient 2).

Study Analysis

Samples of the vitamin D concentrate and raw milk used by the dairy (before fortification) and of various types of vitamin D-fortified bottled milk were obtained on two occasions directly from the dairy by a Massachusetts Department of Health inspector. The concentrations of vitamin D in serum (normal range, 1.3 to 65 nmol per liter [0.5 to 25 ng per milliliter]), vitamin D concentrate (measured in triplicate), and milk were measured by a procedure described elsewhere.⁴ Analyses by mass spectrometry were performed by eluting the sample from a 3- μ m octadecylsilane column (measuring 4.6 mm by 7.5 cm) with 90 percent aqueous methanol. The effluent was then mixed with 0.1 mol of ammonium acetate per liter, and the mixture was introduced directly into a Vestec (Houston) thermospray mass spectrometer (block, 230°C; vapor, 200°C) under the control of a Teknivent (St. Louis) data system.

CASE REPORTS

Patient 1

A 72-year-old woman presented in March 1990 with anorexia, a 7.7-kg weight loss, and constipation. She drank approximately ½ to 1 cup (118 to 237 ml) of milk daily. Her serum calcium concentration was 2.92 mmol per liter (11.7 mg per deciliter), and her serum 25(OH)D concentration was 774 nmol per liter (310 ng per milliliter), as measured by Mayo Medical Laboratories.

Patient 2

A 15-month-old girl was seen in November 1990 with a history of failure to thrive, anorexia, constipation, irritability, and vomiting; all conditions had been present for several months. She had been breast-fed until the age of nine months, and then she had gradually been weaned to whole milk. By the age of 13 months (August 1990), she was drinking up to 20 oz (591 ml) of whole milk daily. She had a serum calcium level of 3.84 mmol per liter (15.4 mg per deciliter), a carotene level of 0.7 μ mol per liter (36.6 μ g per deciliter; normal, 0.4 to 1.5 μ mol per liter [20 to 80 μ g per deciliter]), and a 25(OH)D level of 1660 nmol per liter (665 ng per milliliter), as measured by the Nichols Institute. The results of renal ultrasonography were compatible with a diagnosis of nephrocalcinosis. Her diet was changed to one that was low in calcium.

Patient 3

A 67-year-old woman with a history of renal calculi, hyperparathyroidism (for which she had undergone parathyroid surgery in 1979), and hypertension was evaluated for osteoporosis in December 1989. The evaluation included the measurement of serum 25(OH)D concentration. The woman drank 2 cups (473 ml) of nonfat milk and 1 cup (237 ml) of whole milk daily. She had a serum calcium level of 2.37 mmol per liter (9.5 mg per deciliter), a serum 25(OH)D level of 507 nmol per liter (203 ng per milliliter), as

measured by Bioran Laboratories, and a ratio of urinary calcium to urinary creatinine of 0.42 (normal, 0.30).

Patient 4

An 82-year-old man with a history of myocardial infarction presented in January 1991 with weakness, fatigue, a change in mental status, and a 6.8-kg weight loss. He drank 1½ cups (355 ml) of nonfat milk daily. He had a serum calcium level of 2.99 mmol per liter (12.0 mg per deciliter) and a 25(OH)D level of 899 nmol per liter (360 ng per milliliter), as measured by Mayo Medical Laboratories.

Patient 5

A 73-year-old woman with a recent history of asthmatic bronchitis and paroxysmal atrial fibrillation and a remote history of renal calculi was seen for bone pain and constipation. The results of a bone scan were compatible with a diagnosis of Paget's disease of the skull and a compression fracture at the level of T7. She drank 2 to 2½ cups (473 to 591 ml) of nonfat milk daily. She had stopped taking an antacid containing calcium carbonate four months earlier when she was found to have hypercalcemia. In August 1990 she had a serum calcium level of 2.67 mmol per liter (10.7 mg per deciliter), a serum 25(OH)D level of 207 nmol per liter (83 ng per milliliter), as measured by Mayo Medical Laboratories, and a urinary calcium:creatinine ratio of 0.35.

Patient 6

A 79-year-old woman with a history of breast cancer in remission presented in June 1990 with weakness, malaise, decreased memory, constipation, and dyspepsia. She drank ½ to 1 cup (118 to 237 ml) of nonfat milk daily and occasionally drank whole milk as well. She had taken a multivitamin sporadically during the preceding winter, but had stopped taking it three months before she was examined. She had also been taking 500 mg of elemental calcium twice a day since November 1987. She had a serum calcium level of 3.17 mmol per liter (12.7 mg per deciliter) and a serum 25(OH)D level of 674 nmol per liter (270 ng per milliliter), as measured by Mayo Medical Laboratories.

Patient 7

A 39-year-old woman with a history of non-insulin-dependent diabetes mellitus was found to have hypercalcemia on routine screening before elective surgery in September 1988. She drank 1 to 2 cups (237 to 473 ml) of lowfat milk daily. She had a serum calcium level of 3.74 mmol per liter (15.0 mg per deciliter), a serum 25(OH)D level of 424 nmol per liter (170 ng per milliliter), as measured by Mayo Medical Laboratories, and a serum carotene level of 1.0 μ mol per liter (56 μ g per deciliter; range, 0.7 to 2.8 μ mol per liter [40 to 150 μ g per deciliter]), as measured by Bioran Laboratories.

Patient 8

An 81-year-old woman presented in April 1990 with progressive weakness, fatigue, a 5.5-kg weight loss, and altered mental status. She drank 2 cups (473 ml) of nonfat milk daily. Her serum calcium level was 3.44 mmol per liter (13.8 mg per deciliter), and her serum 25(OH)D level was 699 nmol per liter (280 ng per milliliter), as measured by Mayo Medical Laboratories.

RESULTS

Patients' Characteristics

Table 1 shows the serum concentrations of 25(OH)D and other substances in these eight patients. All had elevated serum 25(OH)D concentrations (mean [\pm SD], 731 \pm 434 nmol per liter [293 \pm 174 ng per milliliter]). Six of the eight patients had elevat-

Table 1. Laboratory Data on the Eight Patients with Hypervitaminosis D Caused by Drinking Milk.*

PATIENT NO.	SEX/AGE AT PRESENTATION	DATE	SERUM CONCENTRATIONS									
			VITAMIN D ₃	25(OH)D	1,25(OH) ₂ D	25(OH)D ₂	25(OH)D ₃	CALCIUM	ALBUMIN	PHOSPHORUS	CREATININE	PTH
			nmol/liter	nmol/liter	pmol/liter	nmol/liter	nmol/liter	mmol/liter	g/liter	mmol/liter	μmol/liter	ng/liter
1	F/72 yr	3/90	—	774	360	—	—	2.92	43	0.94	159	2
		5/90	—	524	—	20	499	2.59	39	0.77	141	—
		8/90	—	449	—	—	—	3.17	34	1.61	283	—
		9/90	418	519	—	—	—	2.87	37	1.84	239	—
2	F/15 mo	11/90	738	1660	48	—	—	3.84	42	1.91	44	2
		12/90	312	344	—	—	—	2.64	—	—	—	—
		2/91	192	220	—	—	—	—	—	—	—	—
		4/91	125	205	—	—	—	2.64	44	1.84	18	—
3	F/67 yr	12/89	—	507	—	—	—	2.37	42	1.23	80	25
		2/90	—	247	91	—	—	2.30	40	1.29	88	—
		4/90	—	260	—	—	—	—	—	—	—	—
		11/90	—	502	—	—	—	—	—	—	—	—
4	M/82 yr	2/91	185	215	—	—	—	—	—	—	—	—
		4/91	—	352	—	—	—	—	—	—	—	—
		1/91	—	899	336	—	—	2.99	40	1.42	309	8
		1/91	—	624	—	12	599	2.42	39	—	212	—
5	F/73 yr	4/91	—	574	—	5	574	2.62	—	—	203	—
		7/91	159	397	—	—	—	2.52	39	0.87	186	—
		8/90	—	207	—	—	—	2.67	42	1.03	80	46
		9/90	—	250	—	—	—	—	—	—	—	—
6	F/79 yr	1/91	—	197	—	—	—	2.52	—	1.23	80	—
		7/91	52	155	—	—	—	2.50	40	1.00	80	—
		6/90	—	674	—	17	649	3.17	38	1.10	186	21
		7/90	—	524	—	—	—	2.42	—	—	124	—
7	F/39 yr	7/91	179	324	—	—	—	2.40	38	1.29	115	—
		9/88	—	424	—	—	—	3.74	34	1.52	433	—
		10/88	—	267	86	—	—	2.77	—	—	—	12
		12/88	—	187	—	—	—	2.59	38	1.23	168	—
8	F/81 yr	5/89	—	324	—	40	275	2.45	34	1.23	230	—
		6/89	—	449	—	—	—	2.47	35	—	212	—
		8/89	—	250	—	—	—	2.54	38	0.77	230	—
		10/89	—	210	—	—	—	2.57	41	1.36	230	—
		7/91	5	170	—	—	—	2.47	43	1.65	212	—
		4/90	—	699	—	—	—	3.44	42	1.42	380	—
		4/90	—	806	53	—	—	2.72	34	1.37	283	24
7/90	—	938	—	—	—	3.32	48	1.39	336	—		
10/90	—	871	—	—	—	2.87	46	1.29	283	—		
11/90	—	1163	—	—	—	2.99	49	1.61	274	—		
4/91	—	1178	—	—	—	2.74	48	1.16	230	—		
7/91	—	198	612	—	—	2.47	39	1.19	239	—		
Normal range†			1.3–65	22–200	36–144			2.12–2.74	32–55	0.74–1.45	18–150	10–65

*PTH denotes parathyroid hormone. To convert values for vitamin D₃ to nanograms per milliliter, divide by 2.599; to convert values for 25(OH)D, 25(OH)D₂, or 25(OH)D₃ to nanograms per milliliter, divide by 2.496; to convert values for 1,25(OH)₂D to picograms per milliliter, divide by 2.4; to convert values for calcium to milligrams per deciliter, divide by 0.2495; to convert values for phosphorus to milligrams per deciliter, divide by 0.3229; and to convert values for creatinine to milligrams per deciliter, divide by 88.4. The dashes indicate that no measurement was made on the date specified.

†Values are the overall ranges from several laboratories. See the text for results for 25(OH)D from individual laboratories.

ed serum vitamin D₃ concentrations; only vitamin D₃, and not vitamin D₂, was detected in all patients. Of the eight patients, seven had hypercalcemia at presentation and one had hypercalciuria but normocalcemia (mean serum calcium, 3.14±0.51 mmol per liter [12.6±2.1 mg per deciliter]). All had normal serum albumin concentrations and serum phosphorus concentrations that were normal for age. Serum parathyroid hormone concentrations were in the normal range despite concurrent hypercalcemia in four patients (Patients 5, 6, 7, and 8) and were low in three patients (Patients 1, 2, and 4). Patient 3 had a normal serum parathyroid hormone concentration and normocalcemia. Serum 1,25(OH)₂D concentrations were high in two patients (Patients 1 and 4) and normal in four patients (Patients 2, 3, 7, and 8); data were not

available for Patients 5 and 6. Five of the eight patients received glucocorticoid therapy for treatment of their vitamin D intoxication.

Dietary Questionnaire

All patients stated that they drank milk from the same local dairy. None were taking cod-liver oil, fish oil, vitamin D supplements, or health-food supplements. The dairy milk was the sole common vehicle for vitamin D that was identified from the responses to the questionnaires.

Analysis of Milk

The results of the analyses of milk samples obtained from the dairy are shown in Table 2. The bottles of vitamin D–fortified milk contained concentrations of

Table 2. Concentration of Vitamin D₃ in Milk from a Local Dairy.*

TYPE OF MILK	VITAMIN D ₃	
	APRIL 1991	JUNE 1991
	IU/quart	
Raw	49	110
Nonfat	44,576	64,328
Low fat	29,250	795
Nonhomogenized	189	42
Homogenized whole	232,565	<40

*Vitamin D-fortified milk in Massachusetts should contain 400 to 500 IU per quart.⁵ There are 946 ml in 1 quart.

vitamin D that varied greatly. The variability was sporadic: the milk that had the highest vitamin D₃ concentration in April 1991 (232,565 IU per quart) had an undetectable amount in June 1991. Vitamin D was isolated from the milk and purified by high-performance liquid chromatography. Mass spectral analysis revealed that the vitamin D in the milk had a molecular weight of 384 and was therefore vitamin D₃.

Analysis of the Vitamin D Concentrate

The concentrate used to fortify the milk was labeled ergocalciferol (vitamin D₂) containing "400,000 USP per cubic centimeter" (400,000 IU per milliliter) by the manufacturer. High-performance liquid chromatography of the concentrate revealed that it contained cholecalciferol (vitamin D₃). This finding was confirmed by a mass spectrometric analysis that revealed a molecular weight of 384; therefore, the vitamin D used to fortify the milk was vitamin D₃ and not vitamin D₂ (molecular weight, 396), as the label on the container stated. Samples of the concentrate obtained in May and June 1991 had concentrations of 396,400 and 376,800 IU per milliliter, respectively.

DISCUSSION

The cause of the elevated serum 25(OH)D concentrations in the patients was not clear initially. Vitamin D intoxication usually occurs because of the improper use of pharmaceutical preparations of vitamin D that are made from vitamin D₂. Multivitamins and foods fortified with vitamin D may contain either vitamin D₂ or vitamin D₃. No tumors have been reported to make vitamin D₃. Repeated exposure to sunlight can raise serum 25(OH)D concentrations to as high as 197 nmol per liter (79 ng per milliliter),⁶ but there are no documented cases of vitamin D intoxication due to excessive exposure to sunlight. Therefore, when vitamin D intoxication is found in a patient who is not taking a pharmaceutical preparation of vitamin D, a careful search for another exogenous source is warranted. Fractionation of 25(OH)D into 25(OH)D₂ and 25(OH)D₃ can be helpful. Vitamin D₂ is derived from fungi and plants, whereas vitamin D₃ is made in

the skin of vertebrates, including humans, and is found in fish-liver oils.⁷

This study illustrates the importance of discussing cases that do not appear to have an explanation in a hospital or interhospital conference. It is from such a forum that a unifying thread may emerge. The search for a common vehicle in these cases led to a review of each patient's dietary history (with use of a questionnaire) that in no instance revealed the ingestion of an unusual type or amount of food. All patients, however, obtained their milk from the same dairy.

When the serum samples from these patients were analyzed for vitamin D₂ and vitamin D₃, only vitamin D₃ was detected. What was perplexing at first was that the vitamin D concentrate used by the dairy was labeled ergocalciferol (vitamin D₂). However, repeated analyses of the milk from the dairy revealed only vitamin D₃, in concentrations that were up to 580 times the stipulated requirement of 400 IU per quart for vitamin D-fortified milk. The fact that the molecular weight of the vitamin D isolated from both the milk and the concentrate was 384 provided unequivocal proof that the vitamin D was vitamin D₃ and not vitamin D₂.

The serum vitamin D₃ concentrations in the patients varied considerably, as did their serum 25(OH)D concentrations. Analysis of the milk provided a possible explanation for these variations, in that the fortification was apparently sporadic and only at times excessive. The result was that some bottles of milk contained very low or even undetectable concentrations of vitamin D₃ and other bottles contained very high concentrations (Table 2). It is somewhat puzzling that the raw milk contained more vitamin D than the fortified nonhomogenized or the fortified homogenized whole milk in June 1991. These samples probably represent different batches of milk and therefore demonstrate the variability of endogenous vitamin D concentrations in the cows.

Peak serum vitamin D concentrations occur approximately 12 hours after a single oral dose and return to basal levels within 72 hours, whereas the serum half-life of 25(OH)D is 2 to 3 weeks.⁷ Therefore, serum 25(OH)D measurements are a better indicator of exposure to vitamin D from dietary sources and synthesis of the vitamin by the skin.^{8,9} In this regard six patients had elevated serum concentrations of vitamin D₃ at a time when all had elevated serum 25(OH)D concentrations. Four patients (Patients 2, 3, 7, and 8) initially had normal serum 1,25(OH)₂D concentrations. The high serum 1,25(OH)₂D concentrations found in two patients (Patients 1 and 4) may have contributed to their hypercalcemia. Whether these high serum concentrations were due to interference in the assay by another vitamin D metabolite or reflect true elevations is uncertain.^{7,10} Four patients (Patients 5, 6, 7, and 8) had normal serum parathyroid hormone concentrations despite concurrent hy-

percalcemia. The lack of suppression may reflect abnormal parathyroid hormone dynamics and may have contributed to their hypercalcemia. Vitamin A can be added to milk; however, serum carotene concentrations were normal in the two patients (Patients 2 and 7) in whom they were measured.

In 1956, the British Pediatric Association conducted a clinical survey and found that 204 cases of hypercalcemia were reported during a two-year period (1953 through 1955).¹¹ Further analysis indicated that infants may have received up to 4000 IU of vitamin D daily as a result of the excessive ingestion of vitamin D–fortified foods. The sporadic cases of vitamin D intoxication in these infants caused hypercalcemia with failure to thrive¹² and led to the cessation of vitamin D fortification of milk in Great Britain.⁹ This drastic measure, however, has unfortunately led to a high incidence of rickets and osteomalacia in that country.^{8,13}

The fortification of milk with vitamin D has substantial benefits in terms of preventing rickets and osteomalacia, but the potentially toxic side effects of excessive ingestion are equally well established and mandate careful monitoring of vitamin D–fortified foods. In 1938, Jeans and Stearns demonstrated that vitamin D had to be administered cautiously, since infants given more than 1800 units of vitamin D daily did not grow as well as infants given 340 units daily.¹⁴ In adults, it is estimated that continued ingestion of 60,000 units per day may cause intoxication.¹⁵ U.S. federal regulations stipulate that each quart of milk contain 400 IU of vitamin D and be “within limits of good manufacturing practice.”¹ Current regulations for vitamin D fortification in Massachusetts⁵ require that any milk labeled as vitamin D–fortified contain at least 400 and not more than 500 IU of vitamin D₂ or vitamin D₃ per quart. Furthermore, any dairy adding vitamin D to milk is supposed to have the milk analyzed twice a year to ensure that the amount of vitamin D being added falls within the stipulated range.⁵ The occurrence of excessive vitamin D fortification in a state that has an upper limit for the vitamin D supplementation of milk underscores the need for the enforcement of fortification regulations.

When the chromatographic analysis of the vitamin D levels in milk from the dairy was completed, the Department of Public Health halted vitamin D supplementation by the dairy to prevent further vitamin D intoxication. The full extent of intoxication in the population served is being studied by the Centers for Disease Control, and the manner in which the apparent excessive fortification of the dairy’s milk took place is being evaluated by the Massachusetts Department of Health.

We are indebted to Dr. R. Pandian at the Nichols Institute for his help with some of the 25(OH)D assays and to Dr. A. Yergy and Dr. K. O’Brien at the National Institutes of Health for the mass spectrometric analyses.

REFERENCES

1. Department of Health and Human Services. Grade “A” Pasteurized Milk Ordinance. 21 C.F.R. §131.110, 1989:243.
2. Holbrook TL, Barrett-Connor E. Calcium intake: covariates and confounders. *Am J Clin Nutr* 1991;53:741-4.
3. Eisman JA, Shepard RM, DeLuca HF. Determination of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ in human plasma using high-pressure liquid chromatography. *Anal Biochem* 1977;80:298-305.
4. Holick MF, Shao Q, Liu WW, Chen TC. The vitamin D content of fortified milk and infant formula. *N Engl J Med* 1992;326:1178-81.
5. Commonwealth of Massachusetts, Secretary of State. The addition of vitamins and minerals to milk, nonfat milk, skimmed milk, fortified nonfat milk, and fortified skimmed milk (105 CMR 542.000). 12/31/86, revised 10/15/88.
6. Haddad JG, Chyu KJ. Competitive protein-binding radioassay for 25-hydroxycholecalciferol. *J Clin Endocrinol Metab* 1971;33:992-5.
7. Holick MF. Vitamin D: biosynthesis, metabolism, and mode of action. In: DeGroot LJ, Besser GM, Cahill GF Jr, et al., eds. *Endocrinology*. 2nd ed. Vol. 2. Philadelphia: W.B. Saunders, 1989:902-26.
8. *Idem*. Vitamin D requirements for the elderly. *Clin Nutr* 1986;5:121-9.
9. Clemens TL, O’Riordan JLH. Vitamin D. In: Becker KL, ed. *Principles and practice of endocrinology and metabolism*. Philadelphia: J.B. Lippincott, 1990:417-23.
10. Napoli JL, Horst RL. Vitamin D metabolism. In: Kumar R, ed. *Vitamin D, basic and clinical aspects*. The Hague, the Netherlands: Martinus Nijhoff, 1984:91-123.
11. British Pediatric Association. Hypercalcaemia in infants and vitamin D. *BMJ* 1956;2:149.
12. Lightwood R. Idiopathic hypercalcaemia with failure to thrive: nephrocalcinosis. *Proc R Soc Med* 1952;45:401.
13. Stamp TCB, Walker PG, Perry W, Jenkins MV. Nutritional osteomalacia and late rickets in Greater London, 1974–1979: clinical and metabolic studies in 45 patients. *Clin Endocrinol Metab* 1980;9:81-105.
14. Jeans PC, Stearns G. The effect of vitamin D on linear growth in infancy. II. The effect of intakes above 1,800 USP units daily. *J Pediatr* 1938;13:730-40.
15. Haynes RC Jr. Agents affecting calcification: calcium, parathyroid hormone, calcitonin, vitamin D, and other compounds. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman’s the pharmacological basis of therapeutics*. 8th ed. New York: Pergamon Press, 1990:1496-522.