An Outbreak of Hypervitaminosis D Associated with the Overfortification of Milk from a Home-Delivery Dairy

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ABSTRACT

Objectives. The purpose of the study was to identify cases of hypervitaminosis D caused by the inadvertent overfortification of milk from a home-delivery dairy and to identify risk factors for this illness.

Methods. Hospital discharge, laboratory, and state health department data were used to define, identify, and describe cases of hypervitaminosis D diagnosed in the exposed communities between January 1, 1985, and June 30, 1991. To identify disease risk factors, community-based sex- and age-matched controls were used in a case–control study.

Results. Of the 56 case patients identified, at least 41 were hospitalized; 2 died. The study included 33 case patients and 93 control subjects. Nineteen of the 33 case patients had been customers of the implicated dairy. Risk of illness rose with increasing consumption of the dairy's milk and was also associated with vitamin D supplement use, sunburn susceptibility, and cancer history. Accounting for these factors did not alter the association between drinking the dairy's milk and developing hypervitaminosis D.

Conclusions. Overfortification of milk with vitamin D can lead to hypervitaminosis D, manifested by severe illness and death. The episode highlights the need for monitoring the fortification process and enforcing the upper limit for vitamin D addition to milk. (*Am J Public Health.* 1995;85:656–659)

Introduction

Rickets caused by vitamin D deficiency was a major public health problem in the United States until milk fortification was introduced in the 1930s.[1–3] Today, nearly 98% of milk sold in the United States is vitamin D-fortified.[4] Vitamin D is toxic in large doses,[5] and sporadic reports of toxicity (hypervitaminosis D) exist. Clinical symptoms include anorexia, nausea, vomiting, polyuria, polydipsia, constipation, weakness, and changes in mental status. Metabolically, hypervitaminosis D is characterized by high serum levels of 25-hydroxyvitamin D (25[OH]D) and hypercalcemia or hypercalciuria, or both. Prolonged hypervitaminosis D can result in calcium deposition in the soft tissues (especially the kidneys and heart), changes in the central nervous system, and, in severe cases, death.[6–14]

Between October 1988 and January 1991, Boston-area endocrinologists diagnosed nine patients with hypervitaminosis D of uncertain cause. They considered milk from a local home-delivery dairy to be the probable source of excess vitamin D for eight of the nine patients.[15] In April 1991, the Massachusetts Department of Public Health collected milk samples from the implicated dairy for vitamin D analysis. The test results, received in June 1991, revealed the presence of vitamin D at 70 to 600 times the legal limit.[16] On June 28, 1991, the dairy ceased fortification and alerted its customers of the vitamin D excess. At the same time, the state health department requested assistance from the Centers for Disease Control (now the Centers for Disease Control and Prevention).

The implicated dairy delivered milk to approximately 11 000 households in 42 greater Boston communities. From 1987 to 1991, the dairy bought 30 to 35 times the amount of vitamin D concentrate needed to fortify the milk it processed. Dairy inspection revealed that the instrument used to measure vitamin concentrate was broken, implicating the unmeasured addition of vitamin D to the milk as the cause of the excess fortification.

We initiated case finding to determine the extent of clinical illness in the 42 exposed communities and designed a case–control study to identify risk factors for development of clinical illness associated with vitamin D toxicity.

Methods

We used hospital discharge data and laboratory data to identify cases of clinical hypervitaminosis D in the exposed communities diagnosed between January 1, 1985, and June 30, 1991. The Massachusetts Hospital Association provided patient discharge data from all 37 acute care, nonfederal hospitals in the 42 communities served by the dairy. Laboratory data were provided by the seven commercial reference and two local academic laboratories that performed the assay. We

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reviewed medical records to verify discharge diagnoses and reported serum calcium and 25(OH)D values.

A *definite* case of hypervitaminosis D was defined as a hospital discharge diagnosis of vitamin D toxicity (ICD-9-CM code 274.4, 963.5, or E933.5)[17] or laboratory determination of a serum 25(OH)D level of 90 ng/mL or higher. A *possible* case of hypervitaminosis D was defined as hypercalcemia of unknown etiology. Possible cases had a primary or secondary hospital discharge diagnosis of hypercalcemia (ICD-9-CM code 275.4) that could not be explained by other known causes[18] and lacked a serum 25(OH)D determination.

Population-based controls were selected from the 42 communities served by the implicated dairy. A preliminary review showed that case patients' age at diagnosis averaged 69 years and ranged from 5 weeks to 92 years of age. We matched each case patient with three control subjects of similar age and sex for efficiency and because age and sex may be associated with milk intake.[19] Furthermore, women, the very young, and the elderly are most at risk for hypervitaminosis D. We matched case patients and control subjects on telephone area code and exchange and then generated random numbers to complete the telephone numbers to be called. After selection, control subjects were slightly younger than case patients. We included age as a variable in our multivariate models to adjust for the remaining age difference. Thirty-three case patients and 93 control subjects participated in the case–control study. Two case patients were ineligible, 16 were lost to follow-up, and 5 refused to participate. The participation rate for eligible control subjects was 85%.

We interviewed each participant by telephone to solicit information on diet, sun sensitivity, medications, occupation, clinical symptoms, and medical conditions, including self-reported history of cancer. We developed a brief semiquantitative food frequency questionnaire to collect information on the intake of foods and vitamin supplements providing more than 50 IU of vitamin D per 100 g.[20,21] We also sought detailed information on the amount, type, and source of milk consumed. Sun-sensitive persons included those who reported being easily burned when exposed to the sun.

We used conditional logistic regression for the analyses. Each variable was tested in a univariate model. Main effects that were statistically significant, or had an odds ratio (OR) of less than 0.5 or more than 2.0, were included in a multivariate model to derive adjusted odds ratios and corresponding 95% confidence intervals (CIs). All two-factor interactions were tested, but none were found to predict hypervitaminosis D. These analyses were performed with EGRET software.[22] Exact logistic regression for matched data (LogXact software[23]) was used to calculate the exact lower bounds of 95% confidence intervals when maximum-likelihood methods provided indefinite results.

TABLE 1—Risk Factors Associated with Hypervitaminosis D

	No. of Case Patients	No. of Control Subjects	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Use of vitamin D supplements	8	1	23.1 (2.9, 184.8)	15.3 (1.7, 138.5)
Sun sensitivity	16	21	3.4 (1.4, 8.2)	2.9 (0.7, 11.6)
History of cancer	8	5	5.8 (1.5, 22.4)	1.9 (0.2, 18.4)
Daily consumption of milk not from the home-delivery dairy				
None	11	11	1.0	1.0
<8 oz	15	42	0.3 (0.1, 0.9)	0.4 (0.1, 3.0)
≥8 oz	7	40	0.2 (0.0, 0.6)	0.7 (0.1, 5.8)
Customer of the home-delivery dairy	19	8	14.3 (4.2, 49.1)	10.1 (2.7, 37.5)
Daily consumption of milk from the home-delivery dairy				
None	14	85	1.0	1.0
<8 oz	9	6	10.6 (2.3, 48.2)	8.3 (1.5, 44.2)
≥8 oz	10	2	19.4 (3.8, 99.3)	12.9 (1.2, 72.3)
Years' consumption of milk from the home-delivery dairy				
0	14	85	1.0	1.0
<5	5	8	3.5[b] (0.6, 23.2)	NC . . .
≥5	14	0	NC (9.3, NC)	NC . . .

Note. OR = odds ratio; CI = confidence interval; NC = not calculable. Odds ratios of 1.0 indicate that these categories were used as references.
[a]The model includes age, vitamin D supplementation, history of cancer, sun sensitivity, and source of milk.
[b]Exact conditional logistic regression for matched data, unadjusted results only.

Results

We identified a total of 56 cases of hypervitaminosis D: 35 definite and 21 possible cases. The median age of case patients was 68.5 years (range: 1.2–92 years). All case patients were White; 69% were female.

The most frequently noted clinical manifestations of hypervitaminosis D were anorexia (32%), weight loss (27%), weakness (27%), fatigue (21%), disorientation (14%), vomiting (14%), dehydration (14%), polyuria (12%), and constipation (11%). Seven definite case patients were asymptomatic.

Medical records were available for 48 of the 56 case patients, 41 of whom were hospitalized (average stay: 13 days; range: 0–64 days). Of those hospitalized, 24 (59%) had no documented sequelae by the time of discharge; 7 (17%) were discharged with residual renal impairment; 2 (5%) were discharged with metastatic calcification; and 2 (5%) died in hospital. Both deaths were related to a hypercalcemic state. An 86-year-old man died of a fatal cardiac dysrhythmia. A 72-year-old woman died of an opportunistic infection secondary to the use of immunosuppressants for hypercalcemia. Both decedents were home-delivery dairy customers.

The average 25(OH)D level for the 35 definite case patients was 224 ng/mL (range: 56–696 ng/mL; $\text{normal}_{\text{winter}}$: 10–55

TABLE 2—Risk Factors Associated with Hypervitaminosis D, by Definite and Possible Case Status

	Definite Cases			Possible Cases		
	No. of Case Patients	No. of Control Subjects	OR[a] (95% CI)	No. of Case Patients	No. of Control Subjects	OR[a] (95% CI)
Home-delivery dairy customer	15	7	8.6 (1.7, 42.8)	4	1	NC (1.6, NC)
Daily consumption of milk from the home-delivery dairy						
None	9	60	1.0	5	25	1.0
<8 oz	8	5	7.9 (1.3, 49.0)	1	1	NC (0.0, NC)
≥8 oz	7	2	10.0 (1.2, 83.2)	3	0	NC (1.2, NC)
Years' consumption of milk from the home-delivery dairy						
0	9	60	1.0	5	25	1.0
1–4	4	7	2.5 (0.4, 18.5)	1	1	NC (0.1, NC)
≥5	11	0	NC (6.5, NC)	3	0	NC (1.5, NC)
Use of vitamin D supplements	7	0	NC (4.1, NC)	1	1	1.5 (0.1, 38.7)
Sun sensitivity	13	17	7.1 (1.3, 37.5)	3	4	3.4 (0.4, 25.6)
History of cancer	7	3	5.4 (0.8, 38.0)	1	2	1.2 (0.0, 48.9)
Daily consumption of milk not from the home-delivery dairy						
None	9	8	1.0	2	3	1.0
<8 oz	11	31	0.7 (0.1, 4.3)	4	11	0.3 (0.0, 5.0)
≥8 oz	4	28	0.6 (0.1, 4.6)	3	12	0.2 (0.0, 4.5)

Note. OR = odds ratio; CI = confidence interval; NC = not calculable. Odds ratios of 1.0 indicate that these categories were used as references.

[a]Main effects include milk source, cancer history, vitamin D supplementation, and sun sensitivity. When OR was not calculable, univariate exact conditional logistic regression for matched data was used to determine lower bounds.

ng/mL, $\text{normal}_{\text{summer}}$: 15–80 ng/mL[24]). One definite case patient had a discharge diagnosis of hypervitaminosis D with a 25(OH)D level below 90 ng/mL. The serum calcium level of definite case patients at the time of presentation averaged 13.1 mg/dL (range: 8.8–16.4 mg/dL; normal: 9.0–10.8 mg/dL[24]).

The case–control study included 24 of the 35 persons with definite cases of hypervitaminosis D (1 was ineligible and 10 were lost to follow-up) and 9 of the 21 persons with possible cases (1 was ineligible, 6 were lost to follow-up, and 5 refused to participate).

Several factors were associated with hypervitaminosis D (Table 1). Case patients were more likely than control subjects to be taking vitamin D supplements (OR = 23.1, 95% CI = 2.9, 184.8), but only one of the eight supplement users was a dairy customer. Hypervitaminosis D was also related to sun susceptibility (OR = 3.4, 95% CI = 1.4, 8.2) and a history of cancer (OR = 5.8, 95% CI = 1.5, 22.4). Consumption of milk from sources other than the dairy was not associated with an increased risk of hypervitaminosis D.

We observed a strong association between consumption of milk from the implicated dairy and hypervitaminosis D. Nineteen case patients (58%) were customers of the dairy, compared with only 8 control subjects (9%) (crude OR = 14.3, 95% CI = 4.2, 49.1). We also observed a dose–response relationship between hypervitaminosis D and the amount of the dairy's milk consumed per day. Compared with persons who did not consume the dairy's milk, those who consumed less than 8 oz per day were at moderate risk (OR = 10.6, 95% CI = 2.3, 48.2), and those who consumed 8 oz or more per day were at highest risk (OR = 19.4, 95% CI = 3.8, 99.3). Finally, we observed a dose–response relationship between hypervitaminosis D and the number of years a person had consumed the dairy's milk. Persons receiving the dairy's milk for less than 5 years were at moderate risk (crude OR = 3.5, 95% CI = 0.6, 23.2), and those receiving the dairy's milk for 5 years or longer were at the highest risk (crude OR undefined, lower 95% confidence bound 9.3). Adjustments for vitamin D supplementation, cancer history, sunburn susceptibility, and age did not alter the strong association between hypervitaminosis D and consumption of milk from the home-delivery dairy (Table 1), even when the analysis was repeated by definite or possible case status (Table 2).

Discussion

Hypervitaminosis D occurs most frequently in patients taking prescribed vitamin D supplements,[2] and we encourage careful monitoring of such patients. In our study, use of vitamin D supplements was an independent predictor of hypervitaminosis D. Sun sensitivity, a history of cancer, and consumption of milk from sources other than the implicated dairy were also related to the risk of hypervitaminosis D; however, after adjustment for consumption of overfortified milk, these variables were no longer statistically significant.

Our results clearly demonstrate that milk overfortified with vitamin D can lead to hypervitaminosis D, whereas milk that is not overfortified does not present a risk. We estimate that the cumulative incidence rate of hypervitaminosis D for the estimated 33 000 dairy customers was 5.76 cases per 10 000 persons, 96 times the rate for the remainder of the population in the exposed communities.[25] Nevertheless, only 19 dairy customers developed hypervitaminosis D. This suggests a preexisting susceptibility for the development of hypervitaminosis D following exposure to overfortified milk.

Older age was related to the development of hypervitaminosis D. We found that 62% of case patients were older than 60 years, compared with only 17% of the general population.[25] The association of hypervitaminosis D with age may be connected to an age-related decrease in renal function.[26] If so, the elderly persons who consumed excess vitamin D may have been less able to eliminate excess calcium. Among the persons hospitalized, at least 17 had evidence of renal dysfunction (a

creatinine level of 2 mg/dL or higher). It was not possible to determine whether the renal functions of these persons were compromised before, or as a result of, their exposure to excessive amounts of vitamin D.

Our findings confirm those of the initial case series[15]: an outbreak of hypervitaminosis D in Boston resulted from the overfortification of milk. Fifty-six persons met our case definition for hypervitaminosis D. Comparison of 33 case patients with representative control subjects revealed a dose–response relationship between the amount of overfortified milk consumed and the risk of hypervitaminosis D. Adjustment for the effects of other factors associated with serum vitamin D levels did not change this association, nor did analysis by case status.

Hypervitaminosis D caused by overfortification of food is unusual; we could identify only one other occurrence.[27] Nevertheless, the consequences of this episode highlight the importance of enforcing limits of vitamin D addition to milk. The state of Massachusetts requires that vitamin D fortification of milk not exceed 500 IU per quart and that levels be checked biennially.[16] Milk samples from the implicated dairy exceeded state limits by 70 to 600 times.

Our case–control study had several strengths. The community at risk was easily defined and eligibility criteria required that both case patients and their population-based control subjects reside in this community. Hypervitaminosis D is an uncommon illness and very specific diagnostic criteria could be used to define a case. We had access to acute care hospital discharge data and laboratory data enabling us to identify most persons with hypervitaminosis D over a 5½-year period.

Certain limitations should be considered when interpreting the results of this study. Case finding may have been incomplete because not all discharge data of the hospital association were up to date and only one of the nine laboratories provided a full complement of 25(OH)D data. Nonhospitalized patients with hypervitaminosis D were probably underrepresented. By definition, possible cases did not have a 25(OH)D determination and could not be identified without a hospital discharge diagnosis of hypercalcemia. Finally, interview data may be limited by the ability of participants to recall events that occurred several years in the past.

Conclusions

The success of vitamin D fortification as a method for controlling rickets caused by vitamin D deficiency is well established[28] and should be continued. Milk fortification laws were designed primarily to prevent underfortification and fraudulent labeling of underfortified milk. This episode highlights the need for monitoring the fortification process and enforcing an upper limit of vitamin D addition to milk. Furthermore, milk producers should be educated about the risks of vitamin toxicity. □

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