Fluoride exposure and bone status in patients with chronic intestinal failure who are receiving home parenteral nutrition[1–3]

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ABSTRACT

Background and Objective: Metabolic bone disease is frequent in chronic intestinal failure. Because fluoride has a major effect on bones, the status of both fluoride and bone was studied in long-term home parenteral nutrition (HPN) patients.

Design: We studied 31 adults aged ($\bar{x} \pm$ SD) 56.3 ± 15.1 y, mainly patients with short-bowel syndrome, who had been receiving HPN for >1 y. Bone mineral density (BMD) was measured by absorptiometry, and serum fluoride was measured by using a fluoride-sensitive electrode. All patients ate and drank ad libitum. HPN (3.4 ± 1.2 times/wk) complemented oral nutrition. Potential explicative factors were estimated by using a linear regression model (mixed-effects model).

Results: Of 120 fluoride dosages (2–6/patient), 102 were above the upper normal limit (1.58 μmol/L) at the laboratory. Mean (± SD) daily fluoride supply was 8.03 ± 7.71 mg (US adequate intake: 3.1 mg/d for women and 3.8 for men; tolerable upper normal limit: 10 mg/d); intravenous fluoride varied from 0.06 to 1.45 mg, and oral fluoride varied from 0.09 to 27.8 mg. Serum fluoride concentrations were correlated with creatinine clearance and fluoride supply. BMD was significantly lower in the femoral neck than in the spinal area. After adjustment for sex and the duration of HPN, only the effect of serum fluoride on spinal BMD was significant. Two patients had symptoms of fluorosis, eg, calcaneum fissures, interosseous calcifications, or femoral neck osteoporosis.

Conclusions: In chronic intestinal failure, high intakes of fluoride are frequent because of the beverages ingested to compensate for stool losses. Hyperfluoremia has an effect on bone metabolism and may increase skeletal fragility. The consumption of fluoride-rich beverages for extended periods is therefore not advisable. *Am J Clin Nutr* 2006;83:1429–37.

KEY WORDS Fluoride, bone mineral density, fluorosis, home parenteral nutrition, chronic intestinal failure

INTRODUCTION

Metabolic bone disease associated with intestinal resection and long-term home parenteral nutrition (HPN) has been described since 1980 in patients with intestinal failure (1, 2). Three studies (3–5) reported osteoporosis in 41% of patients, bone pain in 35%, and bone fracture in 10%. A state of fluoride deficiency has been related to the pathogenesis of the disease, and serum fluoride concentrations have been shown to correlate significantly with bone mineral density (BMD) in HPN patients (6). Moreover, several years ago, fluoride treatment was studied in cases of osteoporosis, but no evidence of a reduction in fracture risk was seen (7).

The effects of fluoride on bone metabolism are complex: the ingestion of large amounts of fluoride is known to induce fluorosis, a crippling bone and joint disease (8–10), and large epidemiologic studies have shown that the prevalence of bone fracture is associated with prolonged exposure to a low or high concentration of fluoride in drinking water (11). Patients with chronic intestinal failure risk fluoride deficiency (6). Paradoxically, they are often encouraged to drink large amounts of bottled mineral water, which can have varied fluoride concentrations. We conducted this retrospective study to ascertain the fluoride status of long-term HPN patients and the relation of fluoride status with bone status.

SUBJECTS AND METHODS

Subjects

Patients were retrospectively included in the study if, at the time of data collection, all of the following criteria were met: age ≥ 18 y, benign intestinal failure requiring HPN for ≥1 y, ≥2 vertebral and hip BMD evaluations (dual-energy X-ray absorptiometry; Hologic Inc, Waltham, MA), and ≥2 serum fluoride measurements during the period of nutrition. The follow-up period was defined as the interval between the first and last BMD evaluations. All patients were allowed to eat and drink ad libitum, and patients with high-output diarrhea or fistulas were advised to drink high-sodium mineral water, particularly the carbonated water from 2 springs in the vicinity of Vichy, France, which has 1172 (Vichy Célestins, Vichy, France) and 1708 (Vichy St-Yorre, Vichy, France) mg Na/L, respectively. Food intake was complemented by HPN according to patient requirements. All patients underwent infusion for 12 h during the night using 3-in-1

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bags (ie, bags containing glucose, lipids, and proteins; bags produced in the pharmacy of the Hospices Civils, Lyon, France) complemented with Na, K, Ca, and P according to individual requirements and with vitamins (Cernevit; Baxter, Maurepas, France) and micronutrients [Nonan; Aguettant, Lyon, France (providing 1.47 mg fluoride/40 mL solution), and Tracitrans; Fresenius, Sevres, France (providing 0.96 mg fluoride/10 mL solution)] according to the recommendations of the American Medical Association (12).

Data collection

The following data were collected for each subject: sex, age, primary gastrointestinal disease, current intestinal status, duration of HPN, composition of HPN, composition of oral intake, presence of bone and joint pain or fractures, the color of the dental enamel, creatinine clearance calculated from direct urinary creatinine measurement, and biochemical variables related to bone metabolism: ie, serum calcium and phosphorus, 25-hydroxyvitamin [25(OH)D], parathyroid hormone (PTH), osteocalcin, aluminum, and urinary β-isomerized C-terminal telopeptide of collagen type I (collagen cross-laps). A detailed questionnaire concerning diet, the amount and composition of the bottled water consumed, the use of toothpaste, and medications was completed by each patient at the end of the follow-up period.

Radiology, bone mineral density, and metabolism

Vertebral (L2–L4) and hip (femoral neck) BMDs were measured by using dual-energy X-ray absorptiometry conducted with a QDR-1000 (Hologic, Waltham, MA) through 1986 and a QDR-4500 (Hologic) after 1986. The correlation between the 2 machines (measured on 39 standard patients) was excellent: the first lumbar measurement of BMD = the second BMD measurement $\times$ 1.013 $-$ 0.008 (R^2 = 0.98), and the first femoral neck measurement of BMD = the second BMD measurement $\times$ 1.009 $-$ 0.018 (R^2 = 0.95).

BMD (in g/cm^2) was measured by dividing the bone mineral content by the projected area of the region scanned. According to World Health Organization Study Group guidelines (13), the prevalences of osteopenia and osteoporosis were assessed by T score (BMD value of young sex-matched subjects): T score <-1 SD but >-2.5 SD for osteopenia and T score ≤-2.5 SD for osteoporosis. The BMD z score (number of SDs from the mean BMD value of sex- and age-matched healthy controls) was used to evaluate the changes during HPN.

Systematic X-rays of the forearms were made to detect ossification of interosseous membranes. Each X-ray was interpreted by 2 clinicians who did not know the patients.

Biological assays

Serum fluoride was measured by using a specific (fluoride-sensitive) ion electrode (lanthanum fluoride, ISEC 301F; Radiometer Analytic, Lyon, France) in combination with a reference electrode (14–16). The combined electrode was connected to a Tacussel ISIS 20–000 ion analyzer (Radiometer Analytic) that was calibrated by using sodium fluoride solutions containing 0.01, 0.02, 0.05, 0.1, and 0.5 mg flouride/L. Deionized water produced by the hospital was used for the preparation of all solutions. All reagents used were of analytic-reagent grade. A stock solution of 0.1 g fluoride/L (Ref 940907; Orion Research, Cambridge, MA) was used to prepare appropriate concentrations of working standard fluoride solutions on a daily basis. TISAB III buffer with EDTA (Ref 940911; Orion Research) was added to each calibration standard and sample at a concentration of 10%. Plastic material was used because the fluoride contained in glass may constitute a source of contamination. The precision of the procedure was regularly validated by using freeze-dried human serum (Seronorm Trace Elements; SERO AS, Billingstad, Norway). The detection limit was 0.01 mg/L; intraassay and interassay CVs were 5% for a concentration of 0.1 mg/L. Reference values were provided by Torra et al (16). Serum fluoride concentrations were measured in 250 healthy subjects (122 M, 128 F; aged 15–90 y). Mean ($\pm$ SD) serum fluoride concentrations were 0.92 $\pm$ 0.5 μmol/L (0.017 $\pm$ 0.009 mg/L) in the control group. There was no correlation between serum fluoride and age. No sex-related difference was found.

Blood osteocalcin was determined by electrochemoluminescence (Eclia immunoassay, Elecsys N.MID Osteocalcin kit; Roche Diagnostics GmbH, Mannheim, Germany), measurement of collagen-crosslinking amino acids (ie, crosslaps) by enzyme-linked immunosorbent assay (Urine crosslaps ELISA; Nordic Bioscience Diagnostics, Herlev, Denmark), serum 25(OH)D concentrations by the use of a radioimmunoassay (Incstar Corp, Stillwater, MN), and PTH by electroluminescence (Intact-PTH Electroluminescence immunoassay; Roche Diagnostics).

Statistical analysis

Statistical analysis was performed by using SAS software (version 8.02; SAS Institute, Cary, NC). Means and SDs were calculated for each variable. Individual changes in biological variables were calculated. These changes were then compared by using Spearman correlations. Changes in fluoremia and BMD and the potential explicative factors were assessed first by using univariate Spearman correlations and then by using a multilinear regression model for repeated measures (PROC MIXED in SAS). This multilinear regression model acknowledges some similarities among successive measures made for a patient; there is a 2-level hierarchy—several patients and several measures per patient—and thus the data analysis estimates both an overall trend common to all patients and a specific level per patient. Interpatient variance in the effects of fluoride concentrations, age, duration of HPN, and osteocalcin concentrations on BMD was quantified, and its significance was tested. For all tests, $P <$ 0.05 was considered significant.

RESULTS

Patients and HPN

Thirty-one patients (21 M, 10 F) were included in the study. The mean age at which they began HPN was 56.3 $\pm$ 14.3 y. The cause of intestinal failure in 24 patients was short-bowel syndrome resulting from resection for bowel infarction, Crohn's disease, or postoperative complications, and that in 7 patients was medical malabsorption resulting from intestinal pseudoobstruction, visceral myopathy, sclerodermia, and villus atrophy. Of the patients with short bowel syndrome, 6 were type I (jejunostomy or ileostomy) and 18 were type II (with a colon); the mean length of the remaining small bowel was 65 $\pm$ 35 cm (**Table 1**).

TABLE 1
Description of patients included[1]

Patient's number and sex	Cause of intestinal failure[2]	Age	BMI		Length of small intestine
			At beginning of follow-up	2nd assessment	
		y	*kg/m²*		*cm*
1, F	Visceral myopathy	34	15.4	15	N[3]
2, F	Sclerodermia	66	15.4	15.4	N
3, M	Short bowel II	45	17.9	18	90
4, M	Villus atrophy	53	18.8	19	N
5, M	Short bowel II	63	16.3	17.2	80
6, M	Short bowel II	73	20.2	19	35
7, F	Short bowel II	39	19.6	19.6	40
8, M	Short bowel II	63	21.6	21.6	40
9, M	Short bowel II	76	21.9	21.5	40
10, F	Intestinal pseudoobstruction	54	16.7	16.7	N
11, M	Short bowel I	56	19.8	18.9	60
12, M	Short bowel II	44	20.8	19.5	80
13, F	Intestinal pseudoobstruction	78	19.3	19.6	N
14, F	Short bowel II	80	20.2	20	30
15, F	Short bowel I	53	19.4	22	60
16, F	Short bowel II	51	24.6	24.6	45
17, M	Short bowel II	42	19.4	17.5	70
18, M	Short bowel II	53	23.4	23.4	80
19, M	Short bowel I	80	20	21	50
20, M	Short bowel II	37	20.8	18.6	20
21, M	Short bowel II	80	25.6	25.2	70
22, M	Short bowel I	47	36.5	45	100
23, F	Short bowel II	74	21	19.6	70
24, F	Short bowel II	54	18.3	18.3	25
25, F	Short bowel II	66	19.6	16.2	40
26, H	Villus atrophy	42	14.8	16.5	N
27, F	Short bowel II	64	21.9	22	100
28, H	Intestinal pseudoobstruction	43	21.5	22.2	N
29, H	Short bowel I	31	20	20	100
30, F	Short bowel II	67	29	28	80
31, H	Short bowel I	36	18.6	18.6	50
		56.3 ± 14.3[4]	20.6 ± 4.2	20.6 ± 5.4	N

[1] Age and BMI were ascertained at first bone mineral density measurement.
[2] Short bowel type I (jejunostomy) and type II (with a colon).
[3] Normal length (no resection).
[4] $\bar{x}$ ± SD (all such values).

At the beginning of the follow-up period, mean BMI was 20.6 ± 4.2, and 27 patients presented with a mean weight that was 7.9 ± 6.1 kg less than their weight before the illness. During the entire study period (ie, from the initiation of HPN to the last BMD measurement), 17 of 31 patients experienced a weight gain (mean: 5.7 ± 5.3 kg), but only 8 of those 17 gained weight (4.6 ± 4.5 kg) during the follow-up period (ie, from the first to the last BMD measurement).

At the first measurement of vertebral BMD, the mean duration of HPN was 27 ± 36 mo. The mean period between the first and the last BMD evaluation was 39 ± 26 mo (range: 10–99 mo). During this period, patients received 3.5 ± 1.7 infusion bags each week. Each all-in-one bag contained 790 ± 280 (range: 400–1400) kcal as glucose, 527 ± 168 (range: 200–900) kcal as lipids, and 10.3 ± 2.2 (range: 6–15) g N. It also contained 13.6 ± 4.6 (range: 6–20) mmol Ca, 21 ± 9.3 mmol Mg, and 23 ± 9.6 (range: 6–40) mmol P; the ratio of calcium to phosphorus was 0.7 ± 0.36. Whatever the number of bags, each patient received 1540 UI vitamin D (cholecalciferol), supplied by an intravenous polyvitamin solution, each week. In addition, all patients received oral daily doses of 2 g Ca (1–3 g) and 800 IU cholecalciferol (400–1200 IU). There was no significant change in HPN composition during the follow-up period.

Fluoride

Intake and assays

Fluoride was provided both by intravenous and oral routes. The results for each patients are shown in **Table 2**. Intravenous fluoride came exclusively from the micronutrient mixtures added to the nutritional bags. Assays of the bags before addition of the micronutrient mixtures showed no contamination with fluoride. The mean amount of daily intravenous fluoride was 0.74 ± 0.34 (range: 0.06–1.45; median: 0.74) mg.

Oral intake of fluoride could be assessed for 22 patients. The main source of oral fluoride was mineral water, which was drunk

TABLE 2
Mean serum fluoride concentrations, daily fluoride intakes, and creatinine clearance[1]

Patient	Fluoride assays	Serum fluoride	Fluoride intake				Creatinine clearance[4]
			Total intake[2]	Intravenous supply	Intake from water	Other[3]	
	n	*μmol/L*		*mg/d*			*mL/min*
1	5	1.86 ± 0.36[5]	—	1.26	—	2.33	70
2	3	2.63 ± 0.92	—	1.17	—		85
3	3	2.12 ± 0.49	—	0.92	—	—	63
4	4	9.93 ± 2.90	10.14	1.14	9	—	56
5	5	2.51 ± 0.82	0.84	0.42	0.42	—	45
6	5	5.73 ± 1.70	5.15	0.65	4.5	—	86
7	6	2.40 ± 1.19	4.92	0.42	4.5	—	39
8	4	2.59 ± 0.76	0.70	0.42	0.28	—	51
9	3	3.70 ± 0.93	1.35	0.75	0.6	—	50
10	2	1.95 ± 0.37	—	0.56	—		60
11	2	2.55 ± 0.63	3.16	0.91	2.25	—	66
12	6	2.48 ± 0.55	1.12	0.62	0.50	—	46
13	5	2.49 ± 1.09	1.49	0.59	0.9	—	58
14	3	1.21 ± 0.34	0.96	0.87	0.09	—	72
15	3	2.28 ± 1.50	1.31	0.74	0.57	—	85
16	5	1.76 ± 0.66	4.91	0.41	4.50	—	53
17	5	15.66 ± 3.44	18.52	0.42	18.1	—	83
18	6	2.96 ± 0.65	5.18	0.83	2.50	1.85	83
19	4	6.09 ± 3.25	9.66	0.66	9	—	36
20	5	1.84 ± 0.5	—	0.06	—		92
21	2	3.4 ± 2.4	—	1.45	—		33
22	2	2.95 ± 2	18.95	0.95	18	—	92
23	2	4.2 ± 0	3.41	0.41	3		62
24	4	4.2 ± 1.1	9.83	0.83	1	8 (tea)	120
25	3	5.1 ± 1	13.41	0.41	13		55
26	2	1.5 ± 0.6		0.82	—		99
27	2	2.8 ± 0.9	14.41	0.41	12	2 (tea)	62
28	2	1.0 ± 0.5		0.41	—		93
29	2	2.9 ± 1.1		1.24	—		81
30	2	10.0 ± 2.9	27.82	0.82	27		40
31	2	3.5 ± 2.3	19.45	1.45	18		89
Mean ± SD		3.75 ± 3.07	8.03 ± 7.71	0.74 ± 0.34	6.8 ± 7.7		68 ± 15

[1] For all patients, mean (± SD) serum fluoride was 3.75 ± 3.07 μmol/L (median: 2.63; interquartile range: 2.12–4.20); the normal upper limit for the laboratory is 1.58 μmol/L.

[2] Total fluoride intake could be assessed for 22 patients: mean (± SD) intake was 8.03 ± 7.71 mg/d; the US adequate intake is 3.1 mg/d for women and 3.1 for men; the US tolerable upper limit for adults is 10 mg/d.

[3] Medications (sodium fluoride) and tea.

[4] The mean value during the study period.

[5] $\bar{x}$ ± SD (all such values).

in large quantities by several patients. Bottled water (Vichy Célestins and Vichy Saint-Yorre) was the most frequently drunk; it had a fluoride concentration of 6.02 and 9 mg/L, respectively, according to the bottle labels. Fluoride supplied in this way varied from 0.09 to 27.08 mg/d, depending on patient habits. Two patients drank large quantities of tea (estimated fluoride intake: 8 and 2 mg/d, respectively). Two patients received fluoride treatment for osteoporosis; this treatment, a mixture of sodium fluoride and sodium monofluorophosphate, was received either intravenously (6.4 mg/d for 1 y) or orally (19.8 mg fluoride/d for 295 d). The precise amount of fluoride provided by toothpaste could not be determined. For these 22 patients, the mean daily fluoride intake during the follow-up period was 8.03 ± 7.71 (range: 0.7–27.8, median: 5) mg. In 15 patients, the intake was significantly higher than the recommended dietary allowance for fluoride in the French adult population (1.5 mg/d), and, in 14 patients, it was significantly higher than the US adequate intake (3.1 mg/d for females and 3.8 for males); 13 had an intake above the French safety limits for long-term ingestion (4 mg/d) including 7 over 10 mg/d (US tolerable upper limit).

During the follow-up period, 120 serum fluoride assays were conducted (2–6/patient). There were 102 serum fluoride concentrations above the normal limits for the laboratory (1.58 μmol/L). Large intraindividual variability was observed, but the mean serum fluoride concentrations were within the normal range for only 3 patients (patients 14, 26, and 28); they were up to 3 times maximum for 22 patients and 3–10 times maximum for 6 patients (patients 4, 6, 17, 19, 25, and 30).

Factors affecting serum fluoride concentrations

After adjustment of each significant factor for the others, only oral fluoride intake and creatinine clearance had a significant

effect on plasma fluoride concentration: the mean increase in the serum fluoride concentration was 7.12% (95% CI: 4.28%, 10.03%; $P < 0.0001$), for a 1-mg increase in total fluoride intake after adjustment for clearance, and the mean decrease was 0.57% (95% CI: 0.08%, 1.06%; $P = 0.02$), for an decrease of 1 L/min of clearance after adjustment for fluoride intake. Interindividual variability of the increase in concentration linked to clearance was not significant. Age, intravenous supply of fluoride, duration of HPN, and serum creatinine had no significant effect on serum fluoride concentrations.

Fluorosis

Two patients had signs of fluorosis: a high serum fluoride concentration ($> 3\times$ normal) or calcaneum fissures (patient 4) or both and calcification of the forearm interosseous membrane associated with severe osteopenia in the femoral area (patients 4 and 17). Patient 4 had had villous atrophy with high diarrhea output (4–6 L/d) for 13 y, and patient 17 had had pseudoobstruction for 10 y before he underwent a massive small-bowel resection 1 y before the current study. Both patients drank large amounts of Vichy mineral water. Their serum fluoride concentrations and spinal BMD at first measurement were high, and persistent hyperfluoremia was observed during the study period (duration of 24 mo in patient 4 and 99 mo in patient 17). Lumbar BMD was high, and it increased during the study period in both patients. Femoral neck BMD was low, but it rose in patient 4 and decreased in patient 17.

Bone status

Clinical status, bone mineral density, and biochemical measurements

During the follow-up period, 2 patients had fractures that were confirmed by scintigraphy: spinal compression (patient 8) or calcaneum fissures (patient 4). Complaints concerning joints and low back pain were made by 11 patients (patients 1–4, 6, 8, 10, 11, 15, 17, and 18). In these patients, the mean serum fluoride concentration did not differ significantly from that in patients without bone pain (4.57 ± 4.39 and 3.30 ± 2.03 μmol/L, respectively).

Throughout the study period, mean femoral neck BMD was significantly lower than spinal BMD; the mean difference was 0.2874 g/cm^2 (95% CI: 0.3111, 0.2583 g/cm^2; *P* lt] 0.0001; **Table 3** and **Table 4**). The frequency of osteopenia ($-2.5 < T$ score ≤ -1 SD) and osteoporosis (T score ≤ -2.5 SD) at the first and last BMD assessment (mean period 39 ± 26 mo) is provided in **Table 5**. During HPN, the spinal z score was unchanged or improved in 24 patients and worsened in 7 patients, and the femoral neck z score was unchanged or improved in 20 patients and worsened in 8 (a z score variation ≥ 0.3 was considered significant).

In 28 patients, the mean serum osteocalcin concentration was 23.0 ± 17.6 (range: 1.87–88) ng/mL at the time of the first BMD measurement and 27.6 ± 19.3 (8–97) ng/mL at the last measurement (normal values: 10.7–24, 13.5–25.5, and 19.6–41 ng/mL in women, men, and postmenopausal women, respectively). There was no difference between the first and last measurement, but there was a strong correlation between osteocalcin and serum fluoride concentrations. Serum fluoride was the only factor with a significant effect on osteocalcin concentration: a 9.74% (95% CI: 5.22%, 14.46%; $P < 0.0001$) increase in osteocalcin for an increase of 1 μm/L in serum fluoride, and there was no variability between patients.

Urinary collagen crosslaps were measured in 26 patients (1.7 ± 0.9 samples/patient). In 41 samples, the mean $\pm$ SEM was 389 ± 54 μg/mmol creatinine, and the SE of the interpatient variability was 143. These values indicate the frequency and degree of bone resorption (normal values: 140 ± 67 μg/mmol creatinine). For 13 patients, a sample was collected at the time of the first and last BMD evaluations: the mean concentration was 366 ± 213 μg/mmol creatinine for the first dosages and 461 ± 489 μg/mmol creatinine for the last (NS). There was no correlation between crosslaps and fluoremia or serum albumin.

In a subset of 19 patients, the mean serum calcium concentration was 2.24 ± 0.16 mmol/L (median: 2.25 mmol/L; $n = 19$), and the mean serum phosphate concentration was 1.13 ± 0.22 mmol/L (median: 1.08 mmol/L; $n = 19$). Serum concentrations of 25(OH)D were 21 ± 7 (median: 18) ng/L. All patients were within the normal ranges of laboratory values (12–40 ng/L). PTH concentrations were 36 ± 14 pg/L (median: 38 pg/L; normal 10–55 pg/L), which indicated the absence of hyperparathyroidism. Sixty-one analyses of serum aluminum were performed in these 19 patients; 11 samples exceeded the usual concentration of 0.60 μmol/L, and only 2 patients had a mean concentration <0.60 μmol aluminum/L.

Determinants of bone mineral density

Unadjusted regression showed that the serum fluoride concentration, the duration of HPN, the osteocalcin concentration, and sex (whose influence depends on whether the location is spinal or femoral neck) had a significant effect on BMD; age and BMI had no significant effect on BMD. After adjustment for other factors (**Table 6**), spinal BMD increased significantly with serum fluoride and with HPN duration; however, the changes in femoral neck did not differ significantly from zero. Interpatient variability was not significant. The daily supply of calcium, phosphorus, and magnesium had no significant effect on BMD ($P = 0.54$, 0.84, and 0.95, respectively).

The fluoride concentration, duration of HPN, osteocalcin concentration, and age of the patient at the onset of HPN had a significant effect on the z score, and the area—spinal or femoral neck—also had an influence. After adjustment for the duration of HPN, osteocalcin concentration, and age at the beginning of HPN, the spinal BMD z score increased with serum fluoride and HPN duration, and this was significantly different ($P = 0.002$) from femoral neck for which the changes were not significantly different from zero. Interpatient variability was not significant.

DISCUSSION

Of 31 patients receiving prolonged HPN for chronic intestinal failure (mainly short-bowel syndrome), high concentrations of serum fluoride were found in 28 patients, 2 of whom had symptoms of fluorosis. To the best of our knowledge, this disease has not been described in patients on HPN. In the current study, the prevalence of osteoporosis was 45% at the first evaluation, a proportion similar to that found in other studies: 41% from Pironi et al (3), 67% from Cohen-Solal (4) and 33% from Haderslev et al (5).

Bone disease is a common complication in patients on long-term parenteral nutrition for intestinal failure. Several reports

TABLE 3
Spinal bone status[1]

Patient	Mean duration of HPN before study	First measurement			Time between first and last measurements	Last measurement		
		BMD	*T* score	*z* Score		BMD	*T* score	*z* Score
	mo	*g/cm²*			*mo*	*g/cm²*		
1	3	0.667	−3.7	−3.47	33	0.595	−4.4	−4.33
2	39	0.645	−3.9	−2	20	0.617	−4.2	−2.1
3	32	0.909	−1.31	−1.42	60	0.980	−0.79	−0.75
4	156	1.159	0.07	1.06	24	1.208	1.11	1.53
5	24	0.697	−3.15	−2.57	72	0.731	−2.86	−2.08
6	1	0.856	−1.82	−0.85	66	0.886	−1.57	−0.41
7	23	0.96	−0.88	−0.88	36	0.859	−1.36	−1.27
8	16	0.946	−1.06	−0.41	51	1.01	−0.53	0.27
9	24	1.093	0.16	1.41	53	1.085	0.09	1.2
10	13	0.758	−2.25	−1.37	36	0.729	−2.47	−1.40
11	1	0.786	−2.4	−1.92	23	0.775	−2.49	−1.94
12	24	0.919	−1.29	−1.34	60	0.932	−1.19	−1.04
13	63	0.911	−0.77	0.5	25	0.93	−0.7	1.02
14	15	0.774	−2.09	−0.41	29	0.70	−2.86	−1.16
15	1	0.97	−0.67	0.05	60	0.841	−1.53	−0.6
16	13	1.117	0.8	1.37	60	1.109	0.96	1.67
17	11	1.42	2.88	2.76	73	1.54	3.88	3.97
18	37	0.810	−2.20	−1.94	99	0.792	−2.35	−1.92
19	4	0.891	−1.52	−0.28	36	0.935	−1.15	0.20
20	34	0.892	−1.58	−1.52	98	0.882	−1.60	−1.39
21	18	1.027	−0.39	0.99	11	1.029	−0.37	1.03
22	8	0.925	−1.24	−0.97	17	0.960	−0.95	−0.64
23	28	0.895	−1.03	0.73	13	0.942	−0.59	1.15
24	144	0.847	−1.47	−0.17	17	0.804	−1.87	−0.47
25	22	0.852	−1.34	0.19	51	0.969	−0.34	1.41
26	1	0.743	−2.76	−2.64	17	0.703	−3.09	−2.94
27	24	0.790	−2.00	−0.26	13	0.784	−2.06	−0.29
28	53	0.945	−1.07	−0.95	12	1.00	−0.61	−0.46
29	14	0.953	−1.16	−1.43	12	0.909	−1.37	−1.61
30	1	1.00	−0.01	1.76	12	0.971	−0.33	1.43
31	1	1.072	−0.02	−0.15	10	1.061	−0.11	−0.21
Mean ± SD	27 ± 36	0.91 ± 0.16	−1.30 ± 1.35	−0.52 ± 1.55	39 ± 26	0.92 ± 19	−1.29 ± 1.55	−0.39 ± 1.70
Median	18	0.91	−1.31	−0.41	33	0.93	−1.19	−0.47
Interquartile range		0.79–0.97	−2.20–0.67	−1.43–0.5		0.78–1.0	−2.35–0.53	−1.4–1.03

[1] HPN, home parenteral nutrition; BMD, bone mineral density. Changes with time were tested by using a linear regression for repeated measures; changes were significant for spinal bone status ($P = 0.012$).

have suggested that 40% to 100% of these patients have histologic features of low bone density (17). The pathogenesis of this bone disease is still only partially understood, but it probably is related to several factors, such as primary disease and malnutrition (5), medication (corticosteroids), and lifestyle. The role of artificial nutrition has been discussed in earlier studies as being related to either toxicities or deficiencies (17). In studies by Cohen-Solal et al (4) and Pironi et al (3), HPN had no deleterious effect on cortical bone; Cohen-Solal et al even found improved trabecular bone in patients whose intestinal disease started after the age of 26 y (4).

However, our patients differed from other cohorts on 2 points. First, femoral neck BMD, both at first measurement and during the study, was significantly lower than was spine BMD, whereas no differences were reported in the populations studied by Pironi et al, Cohen-Solal et al, and Haderslev et al (total hip). Second, throughout the duration of HPN, femoral BMD remained stable, whereas spinal BMD showed an overall increase. This last finding is in agreement with the findings of Cohen-Solal et al but differs from those of Haderslev et al, who reported lower BMD over the duration of parenteral nutrition at both the femoral and the spinal sites. These differences could be related to the high fluoride concentrations found in the patients in the current study: indeed, there was a strong correlation between serum fluoride concentrations and lumbar BMD and *T* and *z* scores, but there was no correlation with the femoral neck BMD.

The effect of fluoride on osteoporotic bones is complex and depends on its serum concentration. Moderate exposure to fluoride could result in an increase in the density of normal bones (18). Fluoride has been used for the treatment of osteoporosis in postmenopausal patients for >40 y (19). More recently, several clinical trials showed a positive effect of fluoride salts when they were combined with calcium on bone mass in spinal osteoporosis (20, 21). However, the use of fluoride salts to prevent new spinal fractures is controversial: a significant reduction was seen in 2 studies of 200 postmenopausal women and 64 men (20, 21), but no effect was seen in 2 other studies of 202 (7) and 354 (22) postmenopausal women. The incidence of nonspinal fractures

TABLE 4
Femoral neck bone mineral density (BMD)[1]

Patient	Mean duration of HPN before study	First evaluation			Time between first and last evaluations	Last evaluation		
		BMD	*T* score	*z* Score		BMD	*T* score	*z* Score
	mo	*g/cm²*			*mo*	*g/cm²*		
1	3							
2	39							
3	32							
4	81	0.713	−2.42	−1.27	24	0.741	−2.26	−0.94
5	24	0.563	−3.78	−2.38	72	0.605	−3.40	−1.76
6	1	0.590	−3.53	−1.67	66	0.586	−3.57	−1.50
7	23	0.764	−0.78	−.64	36	0.703	−1.09	−1.09
8	16	0.751	−2.07	−0.57	51	0.623	−3.23	−1.58
9	24	0.643	−1.17	−3.06	53	0.580	−3.63	−1.61
10	13	0.523	−2.46	−3.05	36	0.493	−3.06	−2.25
11	1	0.637	−3.11	−1.78	23	0.603	−3.41	−2.05
12	24	0.555	−3.85	−3.17	60	0.580	−3.63	−2.69
13	63	0.566	−2.60	−0.45	25	0.606	−2.00	−0.03
14	15	0.449	−3.81	−1.48	29	0.458	−3.40	−1.29
15	1	0.736	−1.06	−0.25	60	0.598	−2.08	−1.42
16	13	0.690	−1.253	−0.81	60	0.661	−1.48	−1.05
17	11	0.778	−1.83	−1.23	73	.733	−2.23	−1.40
18	37	0.588	−3.55	−2.52	99	0.591	−3.52	−2.29
19	4	0.784	−1.77	0.41	36	0.793	−1.69	0.61
20	35	0.698	−2.56	−1.90	98	0.710	−2.78	−2.23
21	18	0.704	−2.5	−0.17	11	0.660	−2.90	−0.53
22	8	0.758	−2.01	−0.96	17	0.720	−2.35	−1.26
23	28	0.585	−2.19	−0.53	13	0.586	−2.19	−0.46
24	144	0.594	−2.12	−1.09	24	0.576	−2.28	−1.17
25	22	0.551	−2.51	−0.91	49	0.521	−2.80	−1.17
26	0	0.495	−4.40	−3.54	16	0.528	−4.10	−3.18
27	24	0.743	−0.72	0.72	13	0.758	−0.58	0.90
28	53	0.721	−2.35	−1.48	11	0.750	−2.09	−1.18
29	14	0.931	−0.44	−0.01	12	0.902	−0.70	−0.23
30	1	0.734	−0.81	0.71	12	0.737	−0.77	0.77
31	0	0.806	−1.57	−0.99	10	0.804	−1.59	−0.97
Mean ± SD	27 ± 36	0.67 ± 0.11	−2.26 ± 1.07	−1.21 ± 1.15		0.65 ± 0.11	−2.46 ± 0.98	−1.18 ± 0.98
Median		0.69	−2.27	−1.04		0.61	−2.32	−1.22
Interquartile range		0.57–0.75	−2.98–1.33	−1.85–0.47		0.58–0.74	−3.4–1.77	−1.72–0.63

[1] HPN, home parenteral nutrition. Changes with time were tested by using a linear regression for repeated measures; changes were not significant for femoral neck bone status.

was similar in the treated and placebo groups in the study by Meunier et al (7), but it was higher in the treated group in the study by Riggs et al (22). These discrepancies could be explained by a reduction in bone quality: despite the strong enhancement of trabecular bone formation induced by fluoride, mineralization defects have been observed (18).

Thus, the increase in BMD at lumbar sites in patients with bone mineral disease associated with long-term parenteral nutrition could be related to high serum fluoride concentrations and the action of fluoride on trabecular bone formation, which increases cancellous bone density. This possibility is in agreement with the close relation observed between serum fluoride concentrations and the osteocalcin concentration, which is considered a sensitive and specific marker of osteoblastic activity. On the other hand, fluoride concentrations play no role in femoral BMD because fluoride is known to have no effect on cortical bone density.

TABLE 5
Frequency of osteopenia and osteoporosis at the beginning and the end of the survey[1]

	First evaluation	Last evaluation[2]
	n	
Spinal		
Osteopenia[3]	17	12
Osteoporosis[4]	4	5
Femoral neck		
Osteopenia[3]	13	12
Osteoporosis[4]	11	13
Total frequency[5]		
Osteopenia[3]	23	20
Osteoporosis[4]	14	15

[1] $n = 31$.
[2] Time between first and last evaluations was 39 ± 26 mo.
[3] *T* score < -1 SD but > -2.5 SD.
[4] *T* score ≤ -2.5 SD.
[5] Osteopenia and osteoporosis were either spinal or femoral neck.

TABLE 6
Adjusted bone mineral density (BMD)[1]

	Predictor	Effect	*P*
		g/cm²	
BMD			
Spinal	Serum fluoride (+1 μM/L)	0.0177 (0.0102, 0.0252)[2]	< 0.0001
	Duration of HPN (+ 1 y)	0.008 (0.0018, 0.0142)	0.012
Femoral neck	Serum fluoride (+1 μM/L)	−0.0044 (−0.0012, 0.0037)	NS
	Duration of HPN (+ 1 y)	−0.0026 (−0.0091, 0.0039)	NS
z Score			
Spinal	Serum fluoride (+ 1 μM/L)	0.1225 (0.0501, 0.1950)	0.001
	Duration of HPN (+ 1 y)	0.071 (0.0141, 0.1270)	0.015
Femoral neck	Serum fluoride (+ 1 μM/L)	−0.0007 (−0.0812, 0.0957)	NS
	Duration of HPN (+ 1 y)	−0.0033 (−0.0537, 0.0602)	NS

[1] HPN, home parenteral nutrition. Changes in BMD and *z* score with serum fluoride and time were tested by using regressions for repeated measures.
[2] $\bar{x}$; 95% CI in parentheses (all such values).

In the patients in the current study, these effects were in direct relation to the ingestion of large quantities of fluoride-rich mineral water. The same effects were observed in 2 studies by Meunier et al (23, 24) in 23 healthy volunteers who consumed large amounts of Vichy Saint-Yorre mineral water (≥0.75 L/d for ≥5 y): they had higher spinal BMD and higher concentrations of serum osteocalcin and fluoride than did sex- and age-matched control subjects. Because bottled mineral water from Vichy is easily available in France but not in other countries, one may speculate on its role in the differences between the BMD variations observed here and in previously published follow-up studies in patients receiving HPN—ie, an increase in spinal BMD in a French study (4) but not in a Danish study (5).

High concentrations of fluoride were responsible for fluorosis in 2 patients (patients 4 and 17), who had a mean intake of 10.1 and 18.5 mg fluoride/d, respectively, for 13 and 10 y. In most of the other patients in the current study, fluoride intakes were above the safety limits recommended for long-term ingestion to avoid fluorosis. Endemic fluorosis is characterized by dental lesions, periarticular calcifications, and greater bone density, which is associated with greater bone fragility and consequent increases in fracture risk. Different authors have drawn attention to fluorosis induced, on the one hand, by naturally high fluoride concentrations in the drinking water of certain regions such as Turkey, China, India, Kenya, and Tanzania (10, 11, 25) and that induced, on the other hand, by prolonged ingestion of mineral water with high fluoride concentrations (9, 24, 26, 27). Moreover, some foodstuffs such as tea and fish are rich in fluoride: depending on the geographic origin, the content in tea sometimes reaches 5 mg/L.

The risk of fluorosis also depends on the bioavailability of fluoride salts. Intestinal absorption of fluoride occurs in the upper part of the digestive tract and is influenced by the nature of the fluoride source. Chevrel et al (28) showed that the absorption of fluoride supplied by mineral water is high and rapid. This is probably one reason for the high serum fluoride concentrations observed in the patients in the current study, as in healthy people who are heavy drinkers of fluoride-rich mineral water (23, 24). The importance of gastric fluid pH was highlighted by Whitford and Pashley (29), who reported that absorption increased with acidity. In addition, the effect of fluoride is more marked in populations with malnutrition who have low calcium, vitamin D, and protein intakes (30). It is also markedly influenced by renal function: in 7 patients who were heavy drinkers of fluoride-rich mineral water and who had clinical fluorosis, the mean ingestion of mineral water was 2.6 L/d (23.4 mg fluoride) for 20 y for 3 patients with normal renal function, and only 1 L/d (9 mg fluoride) for 20 y in 4 patients with chronic renal failure (23, 24, 27). More generally, the usual period until the appearance of clinical fluorosis, for an ingestion of 20 to 80 mg fluoride/d is 10–20 y in normal subjects. In the patients in the current study, clinical fluorosis appeared after the ingestion of 10 and 18 mg fluoride/d for 13 and 10 y. The period until the appearance of clinical fluorosis is much shorter in patients with renal impairment: 18–27 mg/d for 5 y (9, 31).

Conclusions

In our experience, 28 of 31 patients with chronic intestinal failure on HPN have high serum fluoride concentrations because of high ingestion of bottled mineral water. Even if appropriate fluoride exposure is beneficial to tooth and bone integrity, higher intakes have no beneficial effect on bone status—even if bone densification is observed in the spinal area, no effect is described on the risk of fractures—and they may be deleterious and carry a risk of fluorosis; a cutoff of 10 mg/d for >10 y could be suggested for patients with normal renal function. Therefore, oral fluoride intake must be considered in these patients who require large amounts of water and sodium to compensate for large losses due to diarrhea or stomia outputs and who often are advised to drink large amounts of mineral water. Particular attention should be paid to the composition of the beverages consumed, especially in patients with renal impairment, bearing in mind that beverages that are rich in sodium may also be rich in fluoride. Mineral waters with lower fluoride concentrations should be recommended, but they have to be supplemented by oral absorption of NaCl or $NaHCO_3$.

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All authors helped plan the study, analyzed and discussed the results, and were involved in manuscript revisions. PB undertook most of the practical work in manuscript preparation and interpretation of results. PB, ML, and CC were responsible for the treatment of patients. MB completed the fluoride analysis. EF and PD performed bone mineral density measurements. CG and RE completed the data analysis and statistical procedures. None of the authors had any personal or financial conflict of interest.

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