J Clin Endocrin Metab. First published ahead of print May 18, 2011 as doi:10.1210/jc.2010-2891

Skeletal Fluorosis from Brewed Tea

Kenneth Izuora, Jennifer G. Twombly, Gary M. Whitford, Jennifer Demertzis, Roberto Pacifici, and Michael P. Whyte

Division of Endocrinology, Metabolism, and Lipids (K.I., J.G.T., R.P.), Department of Medicine, Emory University, School of Medicine, Atlanta, Georgia 30322; Department of Oral Biology (G.M.W.), Medical College of Georgia, Augusta, Georgia 30912; Musculoskeletal Disease Section (J.D.), Mallinckrodt Institute of Radiology at Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, Missouri 63110; Center for Metabolic Bone Disease and Molecular Research (M.P.W.), Shriners Hospital for Children, St. Louis, Missouri 63131; and Division of Bone and Mineral Diseases (M.P.W.), Washington University School of Medicine at Barnes-Jewish Hospital, St. Louis, Missouri 63110

Background: High fluoride ion (F^-) levels are found in many surface and well waters. Drinking F^--contaminated water typically explains endemic skeletal fluorosis (SF). In some regions of Asia, however, poor quality "brick tea" also causes this disorder. The plant source of brick, black, green, orange pekoe, and oolong tea, *Camellia sinensis*, can contain substantial amounts of F^-. Exposure to 20 mg F^- per day for 20 yr of adult life is expected to cause symptomatic SF. High F^- levels stimulate osteoblasts and enhance bone apposition but substitute for OH^- groups in hydroxyapatite crystals and thereby result in skeletal fragility and perhaps lead to secondary hyperparathyroidism. Beginning in 2005, we showed that daily consumption of 1–2 gallons of instant tea made from this plant can lead to SF.

Aim: We describe a 48-yr-old American woman who developed SF from brewed tea.

Patient and Methods: Our patient had elevated bone mineral density revealed by dual-energy x-ray absorptiometry (spine Z-score, +9.9), severe chronic bone and joint pain, and kyphosis after consuming 1–2 gallons of brewed orange pekoe tea daily for more than three decades. F^- levels were high in her serum, urine, and clippings of fingernails and toenails, as well as in our reproduction of her beverage. Renal function was normal. She had vitamin D deficiency. Elevated serum PTH levels were unresponsive to adequate vitamin D supplementation. Pain resolved over several months when she stopped drinking tea and continued ergocalciferol.

Conclusion: Our patient shows that SF can result from chronic consumption of large volumes of brewed tea. **(*J Clin Endocrinol Metab* 96: 0000–0000, 2011)**

Skeletal fluorosis (SF) is caused by prolonged ingestion or inhalation of fluoride ion (F^-) (1). Chronic F^- toxicity leads to increased amounts of poor quality bone and painful calcification and ossification of tendons and ligaments (1). Most often, SF is explained by well water containing more than 4 mg/liter F^-; *i.e.* 4 parts per million (ppm) F^- (1, 2). However, SF manifests in some regions of Asia where poor-quality "brick" tea is brewed using the mature leaves, twigs, and berries of the tea plant, *Camellia sinensis* (3). Black tea, also from this plant, can be F^- rich (4, 5), and its preparations (*e.g.* brewed tea, instant tea, or "sun tea" steeped at room temperature) are popular in the United States (6) where SF is rare.

We recently reported SF from chronic consumption of 1–2 gallons of instant tea each day by two unrelated middle-age women living in the Midwest (7, 8). Here, we describe a woman with SF who was an avid drinker of large amounts of brewed tea.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-2891 Received December 8, 2010. Accepted April 29, 2011.

Abbreviations: BMD, Bone mineral density; DXA, dual-energy x-ray absorptiometry; F^-, fluoride ion; HMDS, hexamethyldisiloxane; Nl, normal; 25-OHD, 25-hydroxyvitamin D; ppm, parts per million; SF, skeletal fluorosis.

Case Report

Our patient was a 48-yr-old white woman from Georgia, referred for bone and joint pain, kyphosis, and osteosclerosis documented by dual-energy x-ray absorptiometry (DXA). She reported worsening, throbbing, severe bone and joint discomfort over the previous decade. Painful areas included her elbows, wrists, hips, knees, and ankles. She had increasing difficulty moving around, driving her car, and conducting her activities. Pathological fractures had not occurred. Her physician found serum 25-hydroxyvitamin D (25OHD) below 10 ng/ml, PTH 169 and 196 pg/ml [10–65 normal (Nl)], and TSH 5.1 μIU/ml (0.3–4.2 Nl). She began 50,000 U of ergocalciferol by mouth once weekly, but was not prescribed T_4. She was otherwise well, took no supplemental calcium, had worked in a warehouse packing rubber products, smoked 1½ packs of cigarettes daily for 23 yr, and denied ethanol use. She had not undergone extensive dental F^- treatments or brushed her teeth more than two to three times daily.

Her dietary history disclosed that she imbibed 1–2 gallons of brewed orange-pekoe and pekoe-cut black tea daily since age 12 yr. She purchased the least expensive "store brand" and used seven "twin" bags (3.7 g tea per twin bag) per U.S. gallon of municipal tap water. Water was boiled in a T-Fal pot (coated with polytetrafluoroethylene; *i.e.* Teflon), and then the tea bags were steeped for approximately 25 min. The solution was transferred to a plastic, 1 gallon container for refrigeration. She drank the beverage cold, but without ice, and often consumed a second gallon during the day. The only additive was sugar.

Her paternal grandmother and several paternal aunts were said to be kyphotic, but she had not been given an explanation. All close paternal relatives drank tea daily.

On physical examination, vital signs were normal. She was 58.5 inches tall with severe kyphosis since approximately age 30 yr. Her lowest ribs were within the pelvic brim. Weight was 141 lbs, and body mass index was 29 kg/m^2. Range-of-motion was reduced in her upper extremities, without gross joint deformities. All joints palpated showed tenderness without swelling or warmth.

Biochemical Studies

After the patient took ergocalciferol for 8 wk and was referred to us, serum 25OHD was 11 ng/ml (30–80 Nl) assayed at the Anatomic Research University Pathologists (ARUP) Laboratories (Salt Lake City, UT). Serum calcium was 9.0 mg/dl (8.9–10.3 Nl); phosphorus, 3.8 mg/dl (2.4–4.7 Nl); alkaline phosphatase, 288 IU/liter (32–91 Nl); bone-specific alkaline phosphatase, 96 μg/liter (4.5–16.9 Nl); osteocalcin, 309 ng/ml (11–50 Nl); and PTH, 203 pg/ml (10–65 Nl). Electrolytes, glucose, albumin, blood urea nitrogen, and creatinine levels were normal, as were routine blood counts. Urine N-telopeptide of type I collagen was 519 nM bone collagen equivalents/mM creatinine (21–83 Nl) (ARUP Laboratories). Antibody to hepatitis C viral antigen was negative.

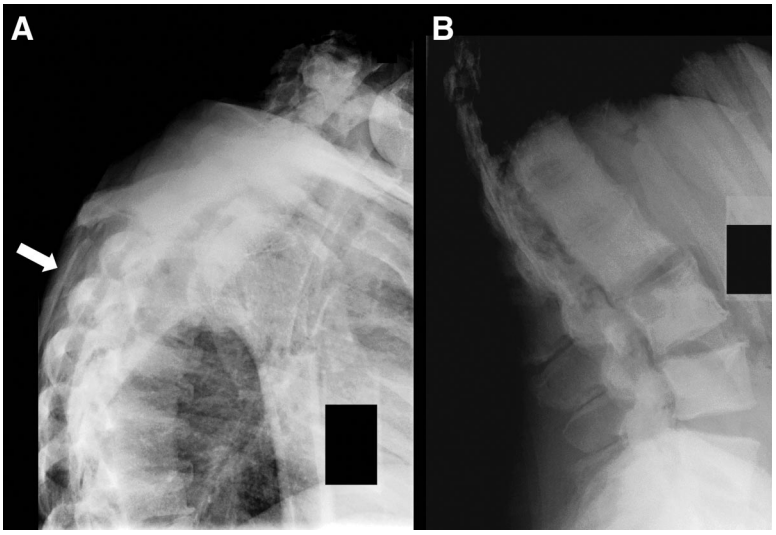

FIG. 1. A, Lateral radiograph of the upper thoracic spine demonstrates diffuse osteosclerosis of the vertebral bodies that obscures the bony trabeculae. There is calcification of the supraspinal ligament (*arrow*) and exaggerated kyphosis. Endplate remodeling with intervertebral disc space narrowing is consistent with moderate degenerative disc disease. B, Lateral radiograph of the lumbar spine demonstrates markedly increased density of the vertebral bodies and posterior elements resulting in a dense, chalky appearance of the bone and loss of the normal trabecular pattern. Increased density of the ribs is also noted. No ligamentous calcification or ossification is identified. There is mild, multilevel, degenerative disc disease with endplate remodeling.

Radiological Studies

DXA (Lunar Prodigy; GE Medical Systems, Waukesha, WI) elsewhere at age 48 yr showed a bone mineral density (BMD) Z-score of +9.9 in the L_1-L_4 spine and +5.0 in the "dual total femurs." The corresponding BMD measurements of 2.342 and 1.586 g/cm^2 were 203 and 165%, respectively, average values for age-matched healthy women. Nevertheless, the DXA software reported normal T-scores and low fracture risk (see *Discussion*).

Radiographs of the patient's skull, hands, thoracic and lumbar spine, pelvis, and knees showed characteristic findings of SF, including diffuse osteosclerosis, sparse and coarsened trabeculae, thoracic kyphosis, as well as soft tissue calcification and ossification (Figs. 1–3). There were no fractures, diaphyseal expan-

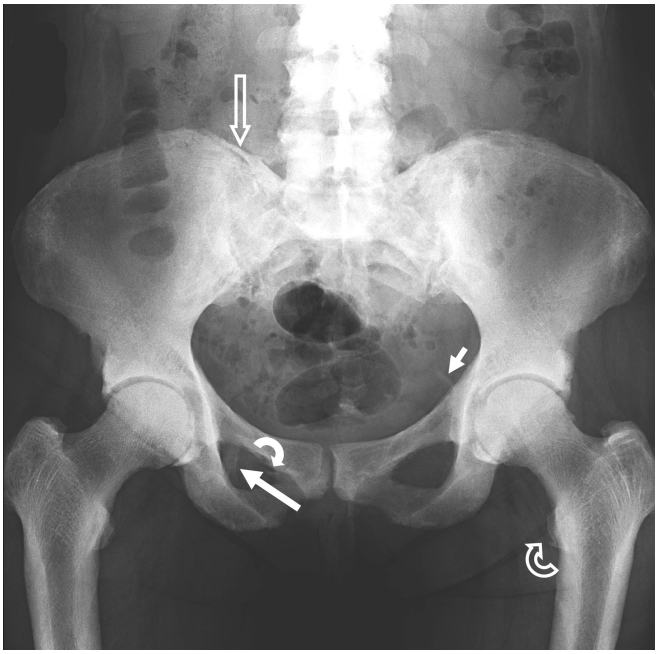

FIG. 2. Anteroposterior radiograph of the pelvis shows diffusely increased bone density in the lower lumbar spine and pelvis, with obscuration of the bony trabeculae in the lower lumbar vertebral bodies and iliac bones. Ossification affects the iliolumbar (*hollow white arrow*), sacrotuberous (*long white arrow*), and sacrospinous (*short white arrow*) ligaments of the pelvis. Calcification involves the obturator membrane (*solid curved arrow*) and attachment of the iliopsoas tendon adjacent to the lesser trochanter (*hollow curved arrow*). Diffuse cortical thickening affects the proximal femoral shafts, with sparse coarse trabeculae best seen in the greater trochanters.

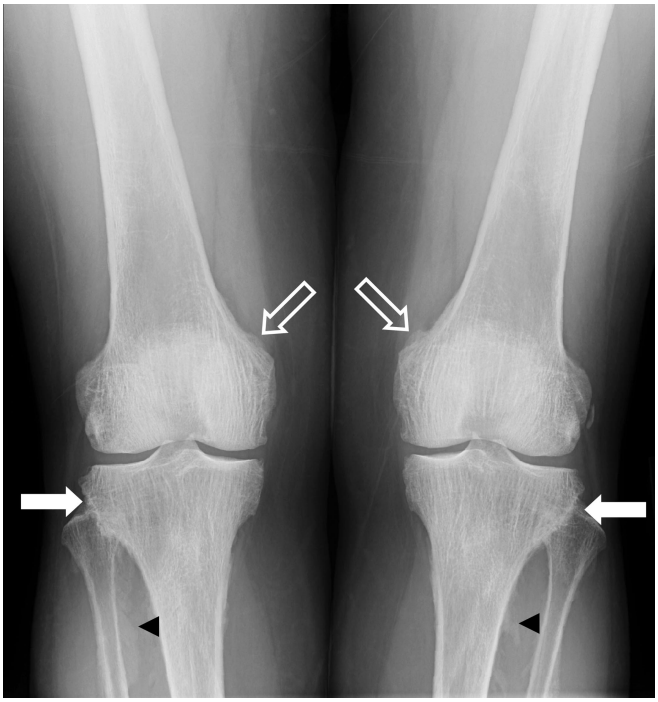

FIG. 3. Anteroposterior weight-bearing radiograph of the knees is remarkable for thick, coarsened trabeculae clustered within cancellous bone of the distal femora, proximal tibiae, and proximal fibulae. Calcification and ossification affects the interosseous membranes (*black arrowheads*). Bony excrescences are present along the proximal lateral tibiae (*solid white arrows*) and medial femoral epicondyles at the site of muscular and ligamentous attachments (*hollow arrows*). There are no fractures, nor is there diaphyseal widening or bone deformity.

sions, or other bone deformities. These observations were typical of phase 3 (crippling) SF, with more advanced ligamentous calcification than we reported for the SF in the two instant tea drinkers who had milder symptoms (7, 8).

Bone scintigraphy demonstrated a "superscan," with increased skeletal radioisotope uptake relative to the soft tissues and absence of activity in the kidneys. Increased uptake in the periarticular regions of the knees and ankles was consistent with active bone remodeling. The findings suggested metabolic bone disease (Fig. 4).

Fluoride Assays

High serum F^- of 220 μg/liter (20–80 Nl), assayed using ion chromatography, was reported by ARUP Laboratories. A reference range for adults exposed to 1 ppm F^- in drinking water is 15–50 μg/liter (9). A 24-h urine collection of 3.5 liters contained 3.5 mg/liter F^-(0.2–3.2 Nl) and 1.2 g creatinine (National Medical Service, Willow Grove, PA). Therefore, our patient excreted a high level of urine F^- of 12.3 mg F^-/d (3.5 mg F^-/liter $\times$ 3.5 liters), or 10 mg F^-/g creatinine (<3 Nl). Renal clearance of F^- (39 ml/min) was normal (30–50 Nl) (10).

To assess further her F^- exposure, F^- levels in her fingernail and toenail clippings obtained before cessation of tea drinking were measured using a F^--selective electrode after hexamethyldisiloxane (HMDS)-facilitated diffusion extraction (11, 12). Control values (8) were derived from clippings of three 46- to 48-yr-old premenopausal women. Their fingernail and toenail F^- levels (mean $\pm$ SE) were 1.61 $\pm$ 0.18 and 2.02 $\pm$ 0.23 mg/kg, respectively (8). The patient's fingernail and toenail specimens were analyzed in triplicate. Her fingernail F^- level (mean $\pm$ SE) of 11.78 $\pm$ 0.33 mg/kg was among the highest we have recorded. Her toenail mean F^- level was much lower (2.76 $\pm$ 0.29 mg/kg) but was elevated compared with controls. We have found differences in fingernail *vs.* toenail F^- levels in other individuals—perhaps a result from less blood flow to the toes.

We also purchased our patient's PriceWise tea and steeped one twin bag in 6 ounces (540 ml) of deionized boiling water for 5 min with occasional swirling to reproduce her beverage. Samples (0.5 ml) at 1.0, 3.0, and 5.0 min were analyzed for F^- using the ion-specific electrode. Two preparatory methods were followed: the direct method that adds an equal volume of buffer solution (Total Ionic Strength Adjustment Buffer) to the sample; and

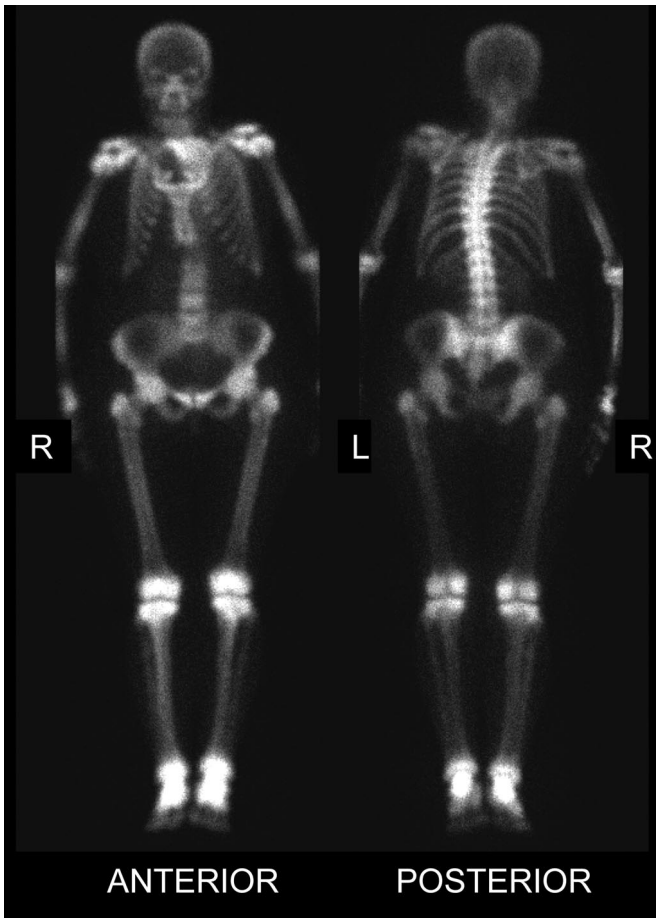

FIG. 4. Whole-body bone scintigraphy demonstrates diffusely increased radionuclide uptake in the axial and appendicular skeleton, with more focal periarticular activity in the knees and ankles, and minimal to absent activity in the soft tissues and kidneys. These findings are suggestive of metabolic bone disease and would be consistent with SF.

the HMDS-facilitated diffusion method (11, 12), which involves adding the sample to 1.5 N sulfuric acid saturated with HMDS in a sealed diffusion dish. Here, one of the acid hydrolysis products from HMDS combines with F^- to form a volatile compound that is captured in an alkaline solution during overnight diffusion. This "trap" is then buffered before analysis for F^- with the ion-specific electrode. F^- is quantitatively captured even from extremely insoluble compounds such as aluminum fluoride and fluorohydroxyapatite (11, 12). The direct method yielded F^- concentrations of 1.36, 1.52, and 1.59 mg/liter (ppm) in the 1.0-, 3.0-, and 5.0-min samples. In contrast, the diffusion method revealed 3.14, 3.55, and 3.87 mg/liter, respectively. These higher F^- levels were likely due to diffusion capture of F^- associated with aluminum in the tea that was not released by the direct method. Tea leaves accumulate high concentrations of aluminum as well as F^- (13, 14). Assuming that the additional 2.28 mg/liter F^- detected in the 5.0-min sample by the diffusion method (3.87 mg/liter − 1.59 mg/liter = 2.28 mg/liter) becomes bioavailable in the acidic environment of the stomach and during transit through the intestines, and that the 5.0 min F^- concentration of 3.87 mg/liter represented a typical preparation of the patient's brewed tea, drinking 1 or 2 U.S. gallons (3.79 or 7.57 liters, respectively) would provide a daily F^- intake of 14.6 or 29.3 mg, respectively. If her tap water was optimally fluoridated (~1.0 mg/liter), the intake would be 18.5 mg or 36.9 mg, respectively. Notably, the lowest value (*i.e.* 14.6 mg, representing 1 gallon of brewed tea), if taken chronically, can cause SF (1–5).

Treatment

Five months after referral, her serum 25OHD level was 62 ng/ml (30–80 Nl), but the PTH level remained elevated at 196 pg/ml, although total calcium was 9.2 mg/dl (8.9–10.3 Nl). A downward trend seemed present for serum osteocalcin, from 309 to 266 ng/ml (10–50 Nl), and for urine N-telopeptide of type I collagen/creatinine, from 519 to 495 nM bone collagen equivalents/mM creatinine (21–83 Nl).

Six months after cessation of tea drinking and while continuing ergocalciferol, our patient reported by telephone nearly complete resolution of her pains. However, she did not return for scheduled follow-up.

Discussion

Prolonged exposure to high levels of F^- increases osteoblast activity and can engender osteosclerosis that does not necessarily signify better bone strength (1). The monovalent anion F^- has close chemical and structural resemblance to the hydroxide (OH^-) group (15), and alteration of hydroxyapatite crystals to denser hydroxyfluorapatite (16) can lead to fracture-prone bone (17) and perhaps to secondary hyperparathyroidism due to skeletal resistance to resorption (18, 19).

Ingestion of more than 10 mg of F^- daily for 10 yr seems necessary for preclinical SF characterized by increased bone mass without symptoms (20). Accordingly, up to this exposure is the "no-observed-adverse-effect level" for adults (20). The lowest effect level for stage 1 or stage 2 SF is 20 mg F^-/d with continuous exposure for at least 20 yr (21). Therefore, in the United States, the highest concentration of F^- permitted by the Environmental Protection Agency (EPA) in drinking water (4 ppm) is the level below which there is no known or expected risk to health (21, 22). The Public Health Service (PHS) optimum level of F^- for community water fluoridation depends on average air temperature and ranges from 0.7–1.2 ppm F^- (20).

Similarly, the Food and Drug Administration (FDA) limit for F^- in bottled water or beverages packaged in the United States, 1.4–2.4 ppm (23), also reflects the annual average maximum daily air temperature where the product is sold (23).

Fluorine is the most reactive element (15). Because F^- is present in minerals, well waters generally have more F^- than surface waters (24). In geographic regions rich in F^--containing minerals, well water may contain 10 ppm F^-, whereas sea water has about 1.3 ppm F^- (25).

F^--rich foods include curly kale, endive, marine fish, and tea (green and black teas especially) (26). High F^- levels in tea are due to selective uptake of F^- by the tea plant, *Camellia sinensis*, particularly in its mature leaves. The F^- levels in tea are conditioned by both the F^- content (13) and the acidity of the soil, according to geographic region (27), season at harvest, tea plant variety (13), age of the leaves, and other factors (28). Reportedly, dry black tea leaves average 100 mg/kg F^-, equivalent to 0.4–0.8 mg in 2–3 cups of tea, and have greater levels where F^- concentrates in ground water (13, 16). Longer brewing time also increases F^- levels in the tea beverage (27). Cookware coated with Teflon releases only small amounts of F^- into boiling water (29, 30).

Beginning in 2005, we reported two unrelated, middle-age, American women living in the Midwest with SF due to several decades of drinking 1–2 gallons of instant tea each day (sometimes prepared "extra strong") (7, 8). Also, we found that some instant teas made according to the manufacturers' recommendations (but using distilled water) exceeded the PHS and FDA limits for F^- in potables (7). One tea sample surpassed the EPA primary standard of 4 ppm (7). In 2006, we reported that F^- levels in several ready-to-drink, bottled teas exceeded the PHS and FDA limits (31). However, these were one-time examinations of various brands. Accordingly, further investigation was necessary.

In 2007, four postmenopausal women with axial osteosclerosis were reported by Hallanger *et al.* (32) to have elevated serum levels of F^- from chronic consumption of various teas, but renal compromise likely impaired their urinary excretion of F^- (10). Our patient with advanced SF had normal renal function but consumed for decades large volumes of brewed tea. Her SF was more severe than our two patients with SF from instant tea (7, 8). Although she has not fractured, her overall clinical picture of prominent symptoms, radiographic osteosclerosis, extensive ligamentous calcification, and numerous bony excrescences was consistent with phase 3 SF (1). This phase can cripple from compressive neurological complications due to calcification (ossification) of tendons and ligaments (33) affecting mainly the axial skeleton.

SF can be revealed by radiographs, but now is more likely in the United States to be discovered by high BMD shown by DXA (7, 8, 34). Unfortunately, despite our caution published in 2005, DXA is still misleading (as exemplified by our current patient) when there is high bone mass (34). DXA software uses the 1994 WHO classification of BMD Z-scores and reports all values above +1 as "normal" with "no increased fracture risk" (35).

If SF seems possible, F^- and creatinine levels in a 24-h collection of urine should be measured to document F^- excess (*i.e.* $>$ 3 mg F^-/g creatinine). Serum F^- levels are assayed for industrial ("shift") F^- exposure and may be more prone to fluctuation. However, the "gold standard" to diagnose chronic F^- toxicity is bone biopsy with quantitation of skeletal F^- (34). This procedure is helpful long after F^- exposure stops (34). Now, we are finding that analysis of fingernail and toenail clippings for F^- is also useful, especially if serum or urine F^- levels recently decreased because F^- exposure ceased (7, 8, 36). In fingernails and toenails, composed primarily of keratin, F^- enters at their growth ends. Hence, F^- levels in clippings reflect average circulating concentrations present 3–4 months previously (37). The mechanism for the F^- accumulation is not known but probably involves diffusion from plasma (11), with levels proportional to, but much higher than, those in the circulation (11).

Of interest, our patient had secondary hyperparathyroidism with symptomatic bone disease which persisted despite correction of her vitamin D deficiency. Secondary hyperparathyroidism is reported for endemic SF (18, 19). It may be that hydroxyfluorapatite crystals are resistant to PTH effects (18).

Treatment of SF involves avoiding F^- and, if necessary, repleting vitamin D levels together with oral calcium supplementation to mineralize excess skeletal osteoid (34). Oral calcium supplementation may also help to bind F^- in the gastrointestinal tract and thereby enhance F^- elimination (34). However, we have recently documented hypercalciuria and kidney stones during skeletal unloading of mineral after F^- cessation in a patient with SF (34). Thus, calcium would be given with caution.

Our previous patients with SF from instant tea were from Missouri and Illinois. The current patient resides in Georgia. Although the Department of Agriculture and the National Health and Nutrition Examination Survey indicate little difference in fluid intake per capita throughout the United States (6), we speculate that SF from drinking large volumes of tea is more prevalent in hot climates (where instant and brewed tea are consumed cold or with ice), especially where F^--containing water is used.

Brewed tea is the most consumed beverage worldwide (7, 8). Recently, there is interest in the potential antioxidant and anticarcinogenic effects of green tea (38). Additionally, antidiabetic effects of black tea have been described in mice (39). SF from chronic ingestion of large volumes of instant or brewed black tea is likely an unrecognized cause of bone and joint pain. Evaluation for SF should be initiated when compatible signs, symptoms, and high BMD (7, 8, 35) accompany a consistent history of tea drinking. DXA may reveal presymptomatic cases where elevated or increasing BMD Z-scores are a key finding (35). SF is both preventable and treatable.

Acknowledgments

Address all correspondence and requests for reprints to: Michael P. Whyte, M.D., Shriners Hospital for Children, 2001 South Lindbergh Boulevard, St. Louis, Missouri 63131. E-mail: mwhyte@shrinenet.org.

This work was supported in part by Shriners Hospitals for Children, The Clark and Mildred Cox Inherited Metabolic Bone Disease Research Fund, and The Barnes-Jewish Hospital Foundation.

Disclosure Summary: There are no disclosures for the authors.

References

1. **Krishnamachari KA** 1986 Skeletal fluorosis in humans: a review of recent progress in the understanding of the disease. Prog Food Nutr Sci 10:279–314
2. **Subcommittee on Health Effects of Ingested Fluoride, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council** 1993 Health effects of ingested fluoride. Washington, DC: National Academies Press
3. **Cao J, Zhao Y, Liu J, Xirao R, Danzeng S, Daji D, Yan Y** 2003 Brick tea fluoride as a main source of adult fluorosis. Food Chem Toxicol 41:535–542
4. **Lung SC, Hsiao PK, Chiang KM** 2003 Fluoride concentrations in three types of commercially packed tea drinks in Taiwan. J Expo Anal Environ Epidemiol 13:66–73
5. **Chan JT, Koh SH** 1996 Fluoride content in caffeinated, decaffeinated and herbal teas. Caries Res 30:88–92
6. **Economic Research Service, U.S. Department of Agriculture** Food availability (per capita) data system. Available at: http://www.ers.usda.gov/data/foodconsumption/spreadsheets/beverage.xls. Accessed: May 5, 2011
7. **Whyte MP, Essmyer K, Gannon FH, Reinus WR** 2005 Skeletal fluorosis and instant tea. Am J Med 118:78–82
8. **Whyte MP, Totty WG, Lim VT, Whitford GM** 2008 Skeletal fluorosis from instant tea. J Bone Miner Res 23:759–769
9. **Sowers M, Whitford GM, Clark MK, Jannausch ML** 2005 Elevated serum fluoride concentrations in women are not related to fractures and bone mineral density. J Nutr 135:2247–2252
10. **Whitford GM** 1996 Renal handling of fluoride. In: Myers HM, ed. The metabolism and toxicity of fluoride. Basel, Switzerland: S Karger AG; 46–48
11. **Whitford GM** 2005 Monitoring fluoride exposure with fingernail clippings. Schweiz Monatsschr Zahnmed 115:685–689
12. **Taves DR** 1968 Determination of submicromolar concentrations of fluoride in biological samples. Talanta 15:1015–1023
13. **Ruan J, Wong MH** 2001 Accumulation of fluoride and aluminum related to different varieties of tea plant. Environ Geochem Health 23:53–63
14. **Matsushima F, Meshitsuka S, Nose T** 1993 Contents of aluminum and manganese in tea leaves and tea infusions. Nippon Eiseigaku Zasshi 48:864–872
15. **Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS** 1998 Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton & Lange; 1410–1414
16. **Friedman PA** 2005 Agents affecting mineral ion homeostasis and bone turnover. In: Shanahan JF, Foltin J, Edmonson K, Brown RY, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 11th ed. Chap 61. New York: McGraw-Hill; 1647–1678
17. **Riggs BL, Hodgson SF, O'Fallon WM, Chao EY, Wahner HW, Muhs JM, Cedel SL, Melton 3rd LJ** 1990 Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 322:802–809
18. **Teotia SP, Teotia M** 1973 Secondary hyperparathyroidism in patients with endemic skeletal fluorosis. Br Med J 1:637–640
19. **Koroglu BK, Ersoy IH, Koroglu M, Balkarli A, Ersoy S, Varol S, Tamer MN** 14 September 2010 Serum parathyroid hormone levels in chronic endemic fluorosis. Biol Trace Elem Res 10.1007/s12011-010-8847-2
20. **Public Health Service, Department of Health and Human Services** 1991 Review of fluoride: benefits and risks. Report of the ad hoc subcommittee on fluoride of the committee to coordinate environmental health and related programs. Washington, DC: U.S. Department of Health and Human Services
21. **U.S. Environmental Protection Agency** 2006 Drinking water contaminants. Available at: http://water.epa.gov/drink/contaminants/index.cfm#List. Accessed November 7, 2010
22. **National Research Council Subcommittee on Health Effects of Ingested Fluoride** 1993 Health effects of ingested fluoride. Washington, DC: National Academies Press
23. 2003 Bottled water (codified at 21CFR§165.110). Washington, DC: U.S. Food and Drug Administration, Department of Health and Human Services
24. **United Nations Children's Fund** 2008 UNICEF handbook on water quality. New York: United Nations Children's Fund (UNICEF)
25. **Fawell J, Bailey K, Chilton J, Dahi E, Fewtrell L, Magara Y** 2006 Fluoride in drinking-water. Geneva: World Health Organization
26. **Chari KV, Rao RJ, Naidu MG,** Fluorine content of some raw vegetable foods available at Podili, Andhra Pradesh. Proceedings of the Indian Academy of Geoscience Symposium on Fluorosis, Hyderabad, India, 1974; 139–144
27. **Malinowska E, Inkielewicz I, Czarnowski W, Szefer P** 2008 Assessment of fluoride concentration and daily intake by human from tea and herbal infusions. Food Chem Toxicol 46:1055–1061
28. **Smid JR, Kruger BJ** 1985 The fluoride content of some teas available in Australia. Aust Dent J 30:25–28
29. **Full CA, Parkins FM** 1975 Effect of cooking vessel composition on fluoride. J Dent Res 54:192
30. **Shannon IL** 1977 Effect of aluminum and Teflon cooking vessels on fluoride content of boiling water. J Mo Dent Assoc 57:26–28
31. **Whyte MP** 2006 Fluoride levels in bottled teas. Am J Med 119:189–190
32. **Hallanger Johnson JE, Kearns AE, Doran PM, Khoo TK, Wermers RA** 2007 Fluoride-related bone disease associated with habitual tea consumption. Mayo Clin Proc 82:719–724
33. **Hafsa C, Zaghouani H, Kriaa S, Salem R, Omezzine SJ, Golli M, Touzi M, Berguaoui N, Gannouni A** 2008 Spinal cord compression revealing fluorosis. Joint Bone Spine 75:91–93

34. **Kurland ES, Schulman RC, Zerwekh JE, Reinus WR, Dempster DW, Whyte MP** 2007 Recovery from skeletal fluorosis (an enigmatic, American case). J Bone Miner Res 22:163–170
35. **Whyte MP** 2005 Misinterpretation of osteodensitometry with high bone density (BMD ≥ + 2.5 is not "normal"). J Clin Densitom 8:1–6
36. **Feskanich D, Owusu W, Hunter DJ, Willett W, Ascherio A, Spiegelman D, Morris S, Spate VL, Colditz G** 1998 Use of toe-nail fluoride levels as an indicator for the risk of hip and fore-arm fractures in women. Epidemiology 9:412–416
37. **Corrêa Rodrigues MH, de Magalhães Bastos JR, Rabelo Buzalaf MA** 2004 Fingernails and toenails as biomarkers of sub-chronic exposure to fluoride from dentifrice in 2-to-3-year-old children. Caries Res 38:109–114
38. **Halder B, Bhattacharya U, Mukhopadhyay S, Giri AK** 2008 Molecular mechanism of black tea polyphenols induced apoptosis in human skin cancer cells: involvement of Bax translocation and mitochondria mediated death cascade. Carcinogenesis 29:129–138
39. **Manikandan R, Sundaram R, Thiagarajan R, Sivakumar MR, Meiyalagan V, Arumugam M** 2009 Effect of black tea on histological and immunohistochemical changes in pancreatic tissues of normal and streptozotocin-induced diabetic mice (*Mus musculus*). Microsc Res Tech 72:723–726