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Gastroduodenal manifestations in patients with skeletal fluorosis

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Abstract: A prospective case-controlled study was performed to evaluate the gastrointestinal symptoms and mucosal abnormalities occurring in patients with osteofluorosis. Ten patients with documented osteofluorosis and ten age- and sex-matched healthy volunteers were included in the study. Clinical evaluation, real-time ultrasound, and upper gastrointestinal endoscopy and biopsy from the gastric antrum and duodenum were performed in all subjects. The biopsies were subjected to a rapid urease test and light and electron microscopic examinations. Ionic fluoride levels were estimated in the drinking water, serum, and urine using an ION 85 ion analyzer. All patients with osteofluorosis had gastrointestinal symptoms, the most common being abdominal pain. Endoscopic abnormalities were found in seven patients with osteofluorosis. In all 7 of these patients, chronic atrophic gastritis was seen on histology. Electron microscopic abnormalities were observed in all 10 patients with osteofluorosis. These included loss of microvilli, cracked-clay appearance, and the presence of surface abrasions on the mucosal cells. None of the control subjects had any clinical symptoms or mucosal abnormalities. It was concluded that gastrointestinal symptoms as well as mucosal abnormalities are common in patients with osteofluorosis.

Key words: osteofluorosis, gastrointestinal symptoms, fluorosis, electron microscopy

Introduction

Osteofluorosis is a major public health problem in India and is caused by the ingestion of drinking water treated with high levels of fluoride.[1,2] To date, the major clinical manifestations of fluorosis have consisted of skeletal and dental involvements.[3,4] Gastrointestinal symptoms have been found in over 45% of the population living in endemic areas of fluorosis.[5] This is much higher than the prevalence of gastrointestinal symptoms reported in the general population (2%).[6] Gastrointestinal symptoms occur in up to 60% of patients treated with sodium fluoride.[7] The present study was undertaken to evaluate prospectively the gastrointestinal symptoms and mucosal abnormalities occurring in patients with skeletal fluorosis.

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Materials and methods

Between June 1988 and December 1989, 10 patients with skeletal fluorosis who were seen at the Department of Orthopedics at the All India Institute of Medical Sciences were included in the study. Ten age- and sex-matched healthy controls were studied during the same period. Fluoride levels in the serum and 24-h urine samples were evaluated in each subject. Fluoride levels in the drinking water sample were estimated on three occasions. An upper gastrointestinal endoscopy was performed and biopsies were obtained from the gastric antrum and duodenum in each subject.

The diagnosis of skeletal fluorosis was made using clinical and radiological criteria.[8] Patients taking nonsteroidal antiinflammatory drugs or any other drugs regularly were excluded. Other causes of dyspepsia including gallstones were excluded by real-time ultrasound using a Toshiba SAL (Toshiba, Tokyo, Japan) with a 3.5-MHz linear array transducer. Upper gastrointestinal endoscopy was performed using an Olympus—GIP Q 10 fiberoptic endoscope (Olympus, Tokyo, Japan). The endoscopist was unaware of the clinical symptoms or the group to which the individual subjects belonged. The biopsies obtained were sub-

jected to a rapid urease test and histological examination for *Helicobacter pylori*.[9] They were also subjected to histological and electron microscopic studies.

For electron microscopy, the biopsy material was washed in 0.1 M phosphate buffer followed by fixation in Karnovsky's fluid for 6 h.[10] The specimens were again washed in 0.1 M phosphate buffer and postfixed in 0.5% osmium tetroxide for 1 h. After four washes in 0.1 M phosphate buffer, the specimen was dehydrated through a graded series of acetone treatments. The tissue was then critical-point dried, sputter-coated with gold, and examined under a scanning electron microscope (Philips 501B Eindoven, Holland) at 15 KV.

Fluoride content was estimated in the drinking water, urine, and serum using an ION 85 Ion Analyser (Radiometer, Copenhagen, Denmark).[11,12]

The correlations between the fluoride levels in drinking water, serum, and urine and the symptoms, endoscopic signs, and microscopic abnormalities were studied. Comparison of qualitative data was performed using the Chi-squared test, and quantitative variables were compared by Student's *t*-test. Skewed data were analysed using Wilcoxon's rank sum test.

Results

The clinical and demographic features of the patients with fluorosis and of the healthy controls are shown in Table 1. All patients with fluorosis had gastrointestinal symptoms. The most common symptoms were abdominal pain and constipation, followed by anorexia and flatulence. None of the control subjects had any such symptoms.

Fluoride levels were abnormal in the drinking water of all the patients with osteofluorosis but in none of the controls. The source of drinking water in patients with osteofluorosis was untreated ground water. In contrast, all the control subjects were using the municipal water supply. The serum and urinary fluoride levels were higher in patients with osteofluorosis than in the control subjects (Table 2).

Table 1. Clinical and demographic characteristics

	Osteofluorosis ($n = 10$)	Controls ($n = 10$)
Male : Female	10:0	7:3
Age (years)[a]	34.6 ± 9.2	25.6 ± 7.3
Range	(19–50)	(15–42)
Clinical symptoms[b]		
Abdominal pain***	10	0
Vomiting*	2	0
Anorexia*	5	0
Flatulence*	5	0
Constipation**	7	0
Source of drinking water[b]		
Hand pump	6	0
Open well	4	0
Municipal supply	0	10

[a] Student's *t*-test
[b] Chi-squared test
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2. Fluoride levels in water and body fluids (ppm)

	Osteofluorosis ($n = 10$)	Controls ($n = 10$)
Drinking water[a]	4.9 ± 4.7*** (1.18–10.2)	0.34 ± 0.10 (0.10–0.54)
Serum[a]	0.12 ± 0.08** (0.02–0.26)	0.04 ± 0.04 (0.01–0.11)
Urine[a]	2.08 ± 2.7*** (0.67–9.1)	0.065 ± 0.023 (0.04–0.109)
Abnormal levels[b]		
Drinking water***	10	0
Serum*	9	3
Urine***	10	0

All values expressed as mean ± standard deviation
Normal fluoride levels: Drinking water <1.00 parts per million (ppm); serum <0.02 ppm; urine <0.10 ppm
[a] Wilcoxon's rank sum test
[b] Chi-squared test
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Upper gastrointestinal endoscopy in patients with osteofluorosis showed multiple gastric erosions in 6 and petechiae in 1 patient. A normal mucosal appearance was found in the remaining 3 patients with osteofluorosis and all 10 control subjects.

Histological evaluation of the gastric and duodenal mucosa showed the presence of chronic atrophic gastritis in 7 patients with osteofluorosis and 1 control subject. The duodenal mucosa bore features of inflammation in 6 patients with osteofluorosis and none of the controls. *H. pylori* was present in the antral biopsy in 1 patient each in the two groups.

On electron microscopic examination, significant cytomorphologic abnormalities were seen. In the gastric antrum and proximal duodenum, the microvilli of the epithelium were scanty and disrupted, giving a bald appearance to the epithelial cells (Fig. 1). The junctions between adjacent epithelial cells were observed to be widened, and in some cases a "cracked clay"-like appearance was noted in the duodenal mucosa (Fig. 2). In addition to the above changes the gastric biopsies revealed more severe structural abnormalities. The epithelium was found to be desquamated in some areas, and the entire surface layer of the gastric mucosa was found to be either severely disrupted or missing (Fig. 3). The biopsies obtained from the control subjects did not demonstrate any of these abnormalities (Figs. 4, 5).

The gastrointestinal symptoms and microscopic patterns were found to be associated with elevated fluoride

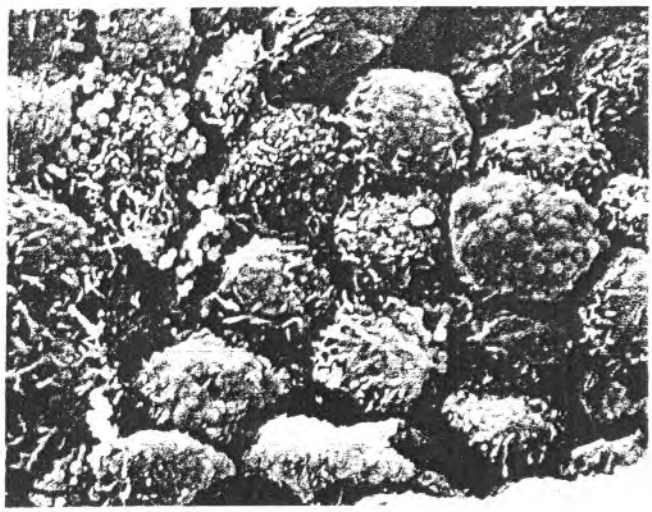

Fig. 1. Epithelium of the gastric mucosa showing loss of microvilli and revealing the bald appearance of the cells in patients afflicted with fluorosis (×5250)

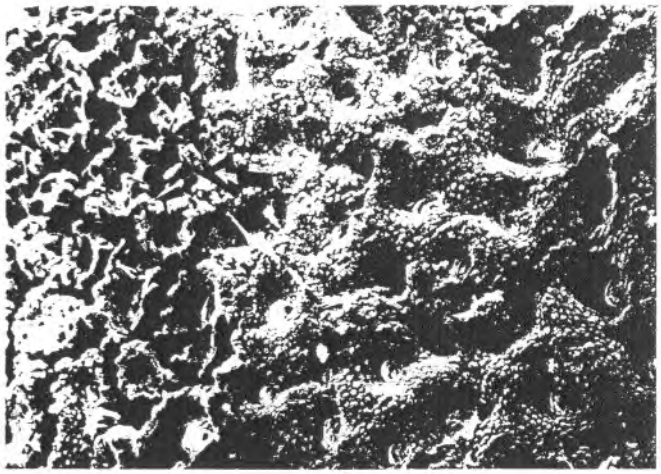

Fig. 3. Scanning electron micrograph of gastric mucosa showing severely disrupted gastric pits with loss of surface epithelium (*arrow*) in patients afflicted with fluorosis (×224)

Fig. 2. Mucosal surfaces of the duodenal villi showing cracked-clay appearance in patients afflicted with fluorosis. (×1750)

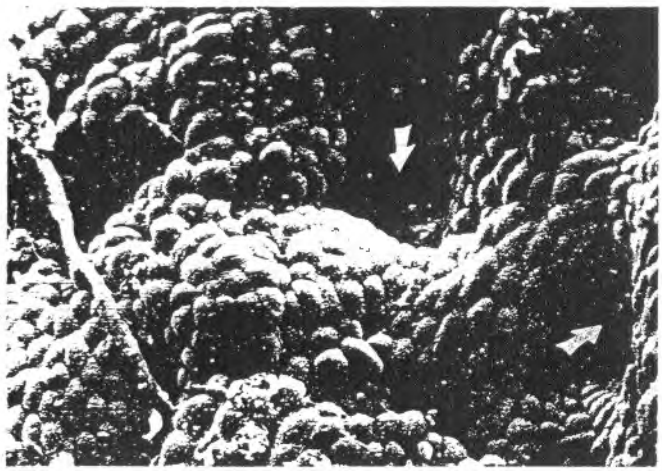

Fig. 4. Gastric mucosa showing normal epithelium with gastric pits (*arrows*) in normal subjects (×896)

Table 3. Fluoride levels, histology and electron microscopy in patients with skeletal fluorosis

			Fluoride levels (ppm)				Histology		Electron microscopy	
S No.	Age	Sex	Water	Serum	Urine	UGIE	Antrum	Duodenum	Antrum	Duodenum
1	50	M	4.91	0.10	1.05	MGE	CAG	Duodenitis	B	A
2	30	M	9.79	0.11	1.15	MGE	CAG	Duodenitis	D	B
3	32	M	1.18	0.10	0.84	Normal	Normal	Normal	D	B
4	24	M	11.36	0.13	9.10	MGE	CAG	Normal	B	A
5	35	M	1.37	0.26	1.09	Normal	Normal	Normal	D	A
6	45	M	10.20	0.14	4.00	MGE	CAG	Duodenitis	A	B
7	36	M	5.62	0.25	1.11	Petechiae	CAG	Duodenitis	A	C
8	19	M	1.96	0.06	1.03	MGE	CAG	Duodenitis	C	C
9	35	M	1.55	0.04	0.81	MGE	CAG	Duodenitis	A	B
10	40	M	1.45	0.02	0.67	Normal	Normal	Normal	B	C

Age in years. Sex: M = male; F = Female. *UGIE*, upper gastrointestinal endoscopy; *MGE*, multiple gastric erosions; *CAG*, chronic atrophic gastritis

Electron microscopic appearances: A, scanty microvilli/bald epithelium; B, cracked clay appearance; C, surface abrasions; D, loss of epithelium (desquamated epithelium)

Acceptable values for fluoride levels: drinking water <1.00 parts per million (ppm); serum <0.02 ppm; urine <0.10 ppm

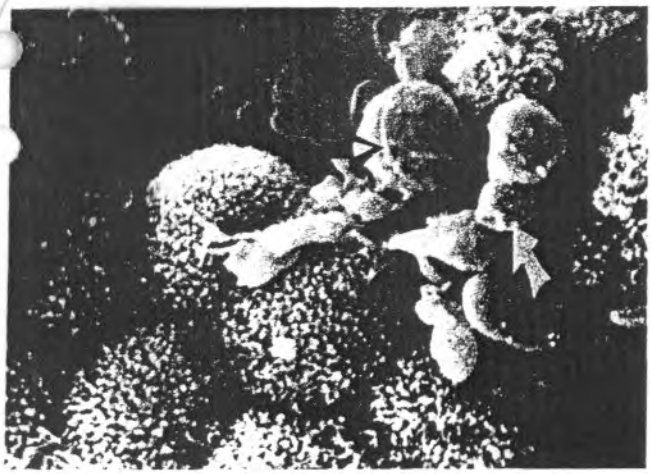

Fig. 5. Gastric mucosa from control subjects showing normal epithelium with microvilli. Mucus droplets can also be seen (*arrows*) (×7000)

levels in patients with osteofluorosis (Tables 1–3). However, no specific symptom or electron microscopic pattern could be correlated with the fluoride levels ($P > 0.1$).

Discussion

The present study showed that gastrointestinal symptoms were common in patients with osteofluorosis. Abnormalities on endoscopy, histology, and electron microscopy were also frequent in these patients.

These observations are in conformity with previous reports on the adverse gastrointestinal effects of fluoride therapy.[13–15] In a prospective study it was demonstrated that fluoride administration caused dyspeptic symptoms.[14] In this study, the authors observed significantly more frequent gastrointestinal symptoms in patients treated with fluoride (17/66) than those treated with a placebo (7/69). Experimental studies have shown electron microscopic abnormalities in rabbits treated with fluoride.[16] It was observed that in the experimental animals, on electron microscopy the duodenal mucosa showed scanty microvilli of the epithelial cells, widening of the intercellular junctions resulting in a cracked clay-like appearance, and the presence of surface abrasions in all animals. In addition, it was observed that the light microscopic findings did not correlate with the type of electron microscopic changes.[16] These observations were similar to those in the present study.

There have been no previous studies of the gastrointestinal symptoms or the mucosa in the stomach and duodenum in patients with skeletal fluorosis. The symptoms of abdominal pain and constipation in these patients were not related to other causes like peptic ulcer, gallstones, or local anorectal pathology. These dyspeptic symptoms were correlated with the presence of elevated urinary and serum fluoride levels and radiological evidence of fluorosis. These suggest that fluoride ingestion results in significant gastrointestinal symptoms.

The electron microscopic changes may also be the result of fluoride toxicity because no such changes were found in the control subjects. The different electron microscopic patterns did not correlate with the light microscopic appearance. In three patients normal histology was associated with abnormalities on electron microscopy. These may suggest that ultrastructural changes occur prior to the microscopic detection of abnormalities, and that these alterations may be enough to result in clinical symptoms of dyspepsia. Since no correlation existed between the electron microscopic patterns and the other variables studied, it was not possible to establish a grading system of the ultrastructural changes. It is possible that a cracked-clay appearance or surface abrasions may represent a more severe injury. This aspect needs to be studied prospectively Furthermore, the specificity of these changes is not known and needs to be studied prospectively in patients with other causes of gastroduodenal mucosal injury.

It is concluded from the observations in the present study that gastrointestinal symptoms and mucosal abnormalities in the stomach and duodenum are common in patients with osteofluorosis. Dyspeptic symptoms in subjects living in an endemic area for fluorosis may warrant investigation for fluorosis before skeletal symptoms become apparent. However, due to the small sample size, a larger number of patients would be required to validate the preliminary observations in the present study.

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