Quantitative Epidemiological Research on the Relationship between Fluoride Content of Drinking Water and Endemic Fluoride Poisoning

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Abstract: The present study analyzes the dose-response relationship that exists between the concentration of fluoride in drinking water and the clinical symptoms of fluoride poisoning. A positive correlation is observed between the fluoride content of water and the rate of dental fluorosis, skeletal x-ray change frequency, skeletal x-ray change index, and the urine fluoride concentration. The skeletal x-ray index of change, which combines information about both the frequency and degree of skeletal x-ray change, reflects an objective law and is shown to have major practical value. This study also investigates the categorization of endemic areas according to severity. There is no clear correlation evidenced between fluoride poisoning and frequency of joint degeneration occurrence, but it may worsen its progress. Periosteal ossification is not an early manifestation of fluoride poisoning.

Keywords: Fluoride Content of Drinking Water;Skeletal X-ray Change;Rate of Dental Fluorosis

When we use single-factor correlation analysis and stepwise regression analysis to investigate the relationship of fluoride poisoning severity to the absorption of fluoride, calcium, and magnesium, and their relative ratios, we find that only the fluoride content of drinking water has an effect on the severity of fluoride poisoning. The current study provides a quantitative analysis of this relationship, with the goal of contributing to a discussion, founded on research establishing the dose-response relationship, which can determine suitable concentrations of drinking water fluoride for such areas, as well as appropriate indices for categorizing afflicted regions.

Method

The targets of our investigation are villages with no fluoride pollution and drinking water either coming from a single well or from multiple sources with relatively little variation in fluoride concentration. The inorganic fluoride concentration of the water and urine samples were determined using the fluoride electrode method. A full survey of fluoride poisoning symptoms was conducted. From age ranges consisting of 10 year spans mixed gender groups of 5 residents were randomly selected (when an age group contained less than 5 residents, all were included) and a skeletal x-ray examination (lumbar spine as well as anteroposterior x-rays of the limbs and pelvis) conducted. See references[1] for standards relevant to determining dental fluorosis and skeletal x-ray changes. Scores were given to the various positive indicators of each subject (changes to bone matter and the periosteum, not including joint degeneration): very light (1 point), light (2-6 points), moderate (8-12 points), serious (14-18 points). The combined score for an entire region is divided by the number of subjects to calculate the skeletal x-ray change index. From regions with a water fluoride concentration of 0.24, 0.80, and 1.00 mg/L, 20 subjects between the ages of 6 and 20 who had already been examined with a standard x-ray were randomly selected for a magnified x-ray with a focal spot of 0.1 mm2 and a magnification factor of 2, in order to examine the trabecular morphology of the pelvis, the lower humerus, the upper ulna, the lower femur, and the upper tibia.

Results

The fluoride concentration of the drinking water in the areas investigated were: Xiaojiabao, Xiuyan County, 0.24 mg/L (0.10-0.30 mg/L); Hejia, Zhangwu county, 0.80 mg/L (0.65-0.88 mg/L); Qiansijianfang, Zhangwu county, 3.12

mg/L (2.50-5.00 mg/L); Xiaowangyedi, Aohan banner, 1.00 mg/L; Mutouyingzi, Aohan banner, 5.60 mg/L (4.00-7.00 mg/L); Hudiegou, Chaoyang county, 1.80 mg/L (1.70-1.90 mg/L); Yihe, Jin county, 4.10 mg/L (3.26-5.00 mg/L); Huojiayingzi, Wengniute banner, 10.27 mg/L (8.40-11.80 mg/L); Panjiawobao, Wengniute banner, 10.81 mg/L (8.40-16.20 mg/L).

I. Relationship between Fluoride Content and Dental Fluorosis

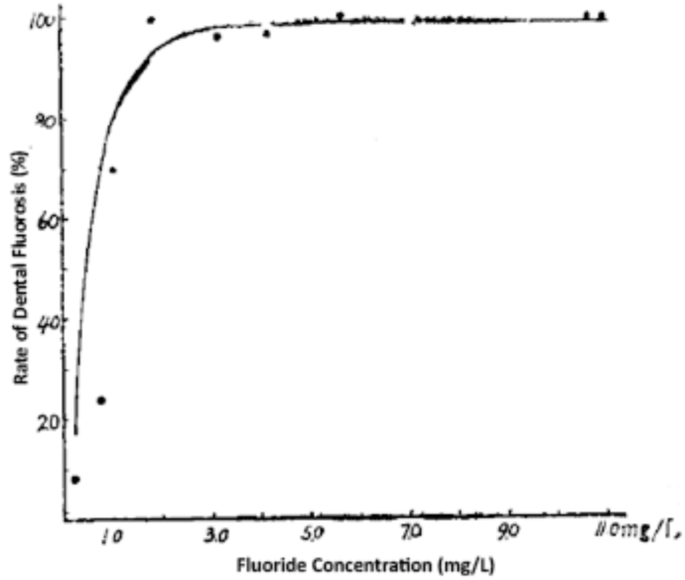
For the relationship between drinking water fluoride content and dental fluorosis of deciduous teeth, see table 1. Most cases of dental fluorosis were of level 1 severity, though at and above 3.14 mg/L a small number of level 2 and 3 cases were observed.

Table 1: Relationship between Fluoride Concentration and Dental Fluorosis of Deciduous Teeth

Fluoride Concentration (mg/L)	No. of Subjects	Subjects with Dental Fluorosis of Deciduous Teeth	
		Number	Percent
0.24	16	1	6.25
0.80	16	1	6.25
1.00	18	2	11.11
1.80	9	3	33.33
3.12	24	8	33.33
4.10	18	7	38.98
5.60	9	2	22.22
10.27	25	9	36.00
10.81	29	14	48.28

For permanent teeth, the rate of dental fluorosis in the area with 0.24 mg/L fluoride concentration was 8.33%, all level 1. For 0.80 mg/L the rate was 23.94%, with some level 2 and 3 cases. At 1.80 mg/L and above, the rate of dental fluorosis is close to or at 100%. The relationship between fluoride concentration and rate of dental fluorosis in permanent teeth is a power function (see Figure 1). The regression equation is log(100.02 – y) = 3.2217 – 4.2104 log(x+ 1.8).

Figure 1: Relationship Between Fluoride Concentration and Dental Fluorosis of Permanent Teeth in Subjects Born in Area



The percentage of level 3 dental fluorosis increases with the fluoride concentration of the water (see Table 2). At 3.12 mg/L it has already reached 69.70%.

Table 2: Relationship between Fluoride Concentration and Dental Fluorosis of Permanent Teeth

Fluoride Concentration (mg/L)	Subjects with Dental Fluorosis		% with Severity Level		
	No.	%	1	2	3
0.24	7	8.33	100.00	0	0
0.80	17	23.94	41.18	29.41	29.41
1.00	58	69.88	48.28	37.93	13.79
1.80	38	100.00	13.16	52.63	34.21
3.12	66	90.41	6.06	24.24	69.70
4.10	103	98.10	0.97	33.98	65.50
5.60	40	100.00	0	10.00	90.00
10.27	82	98.80	4.88	21.95	73.17
10.81	130	100.00	3.85	14.62	81.54

II. Relationship between Fluoride Content and Fluoride Poisoning Symptoms, Reduced Joint Function, Limb Deformities, and Paraplegia

From Tables 3 and 4 we can see that even areas with very low fluoride levels in drinking water have a certain quantity of fluoride poisoning symptoms (bone and joint pain, headache, dizziness, numbness of the extremities, convulsions) and reduced joint function. There is a positive correlation between fluoride concentration and reduced joint function. The rate of occurrence is generally low for the younger age groups, with the rate

Table 3: Relationship between Fluoride Concentration and Fluoride Poisoning Symptoms

Fluoride concentration (mg/L)	No. of Subjects	Symptomatic Subjects		Percent of Symptomatic Subjects by Age Group						
		No.	%	1+	11+	21+	31+	41+	51+	61-83
0.24	127	24	18.90	0	6.45	27.78	35.71	26.67	38.46	33.33
0.80	120	40	33.33	0	13.33	27.27	69.23	70.00	61.54	85.71
1.00	140	84	60.00	3.03	53.33	84.00	76.47	92.86	81.82	84.62
1.80	65	43	66.15	0	68.42	100.00	100.00	100.00	100.00	33.33
3.12	142	71	50.00	3.33	17.95	69.57	95.24	100.00	100.00	87.50
4.10	188	93	47.47	4.28	30.00	64.28	78.37	88.54	100.00	81.25
5.60	93	63	67.74	25.00	53.13	75.00	100.00	100.00	100.00	100.00
10.27	166	125	75.30	28.00	63.46	94.74	93.55	100.00	100.00	83.33
10.81	217	154	70.97	33.33	53.23	88.46	95.00	100.00	94.00	100.00

Table 4: Relationship between Fluoride Concentration and Reduced Joint Function

Fluoride concentration (mg/L)	No. of Subjects	Subjects with Reduced function		Percent of Subjects with Reduced Joint Function by Age Group						
		No.	%	1+	11+	21+	31+	41+	51+	61-83
0.24	127	5	3.94	0	0	0	7.14	6.67	15.39	11.11
0.80	120	7	5.83	0	0	0	7.69	20.00	7.69	42.86
1.00	140	21	15.00	0	0	4.00	17.64	42.86	45.55	46.15
1.80	65	17	26.15	0	5.26	10.00	33.33	71.42	100.00	66.67
3.12	142	24	16.90	0	0	8.70	14.29	54.55	60.00	87.50
4.10	188	49	26.06	0	2.00	21.43	50.00	47.06	75.00	81.25
5.60	93	31	33.33	0	12.50	16.27	70.00	62.50	77.78	100.00
10.27	166	60	36.14	0	7.67	10.53	61.28	94.44	93.33	66.66
10.81	217	94	43.32	9.52	8.06	38.46	75.00	96.00	94.44	100.00

increasing with age; in the high fluoride concentration areas, however, even the younger groups show a relatively high rate of occurrence.

If 5 points are assigned for each joint with reduced function and averaged across all patients in an area to calculate an index for each area, this index also shows a positive correlation with fluoride concentration (see Table 5).

Table 5: Relationship between Fluoride Concentration and Degree of Reduced Joint Function

Fluoride Concentration (mg/L)	Number of Subjects	Reduced Function Points	Reduced Function Index (Reduced Function Points/ Number of Subjects)
0.24	127	120	0.95
0.80	120	105	0.88
1.00	140	295	2.11
1.80	65	435	6.69
3.12	142	495	3.49
4.10	188	1125	5.98
5.60	93	1085	11.54
10.27	166	2035	12.26
10.81	217	3040	14.00

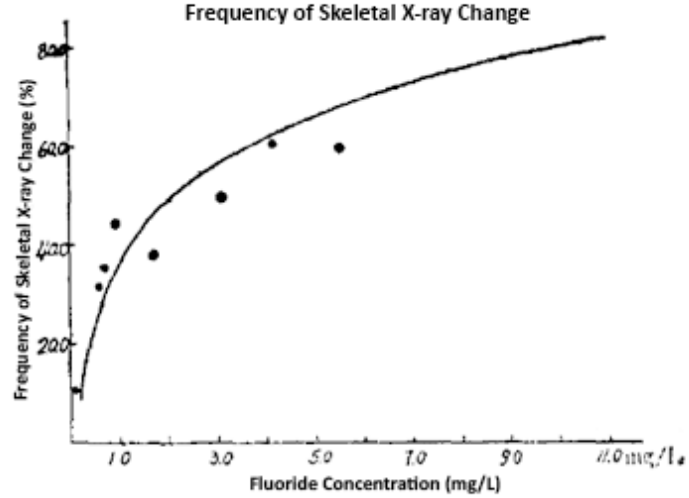
There is a positive correlation between fluoride concentration and limb deformities, but only in areas with 4.10 mg/L fluoride concentration or above does the occurrence rate reach 9.80-25.35%. Most commonly observed was varus and valgus deformities of the knee. Severe deformity of the spinal column was found only in areas with severe fluoride poisoning.

Only one case of paraplegia due to fluoride poisoning was observed in each of the 1.80 mg/L, 3.12 mg/L, 5.60 mg/L, 10.27 mg/L, and 10.81 mg/L areas, resulting in rates of 1.54%, 0.70%, 1.08%, 0.60%, and 0.46%, an irregular distribution. The earliest case occurred at the age of 38, with all other cases occurring over the age of 40. The patient in the 1.80 mg/L area was 75, and had two brothers who also died of the disease in their sixties.

III. Relationship between Fluoride Content and Skeletal X-Ray Change

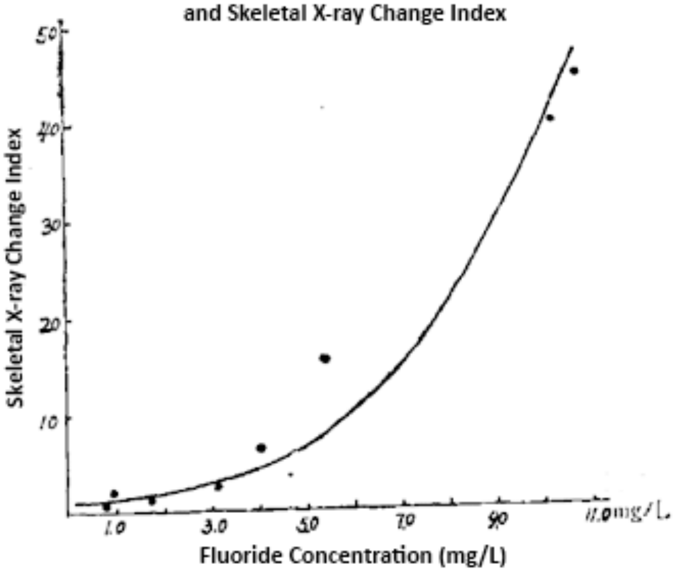
1. Relationship with skeletal x-ray change frequency and severity: There is a positive correlation between the skeletal x-ray change frequency (r = 0.9296, tr = 6.6747, p < 0.001), forming a logarithmic distribution curve with regression function y = 35.7472 + 44.7519 log x, R2 = 0.8967 (Figure 2).

Figure 2: Relationship between Fluoride Concentration and Frequency of Skeletal X-ray Change



However, although there is also a positive correlation between the skeletal x-ray change index and fluoride concentration, (r = 0.9788, t_r = 12.6363, $p < 0.001$), the latter curve is exponential, with a regression equation of y -1 = 1.3857 × 100.1443x, R^2 = 0.9663. The index is relatively steady for areas with less than 4.12 mg/L fluoride concentration, increasing rapidly only at 4.12 mg/L.

Figure 3: Relationship between Fluoride Concentration and Skeletal X-ray Change Index



From Table 6 we see that areas with fluoride concentrations of 1.0 mg/L or less have only light or extremely light changes. Only areas with concentrations greater than 5.60 mg/L have severe skeletal x-ray change.

2. Relationship with skeletal x-ray change of different age groups: There is very little calcium in the bones of one year olds, making x-ray change difficult to diagnose. In children at the age of 2 or above, however, abnormalities in the trabeculae of the pelvis can be observed. From tables 7 and 8 we can see that in each group, there is a clear positive correlation between fluoride concentration and both skeletal x-ray change frequency and skeletal x-ray change index. However, comparing across the different regions, there is no significant correlation between age and skeletal x-ray change frequency and, for relatively low fluoride concentrations, no significant correlation between age and skeletal x-ray change index. Only for extremely high concentrations of fluoride is there a significant positive correlation between age and skeletal x-ray change index.

3. Relationship with type of skeletal x-ray change: The majority of skeletal changes observed in this study were sclerotic in nature; porotic and composite changes were not often observed, and a very small minority of changes were malacic. The majority of porotic and malacic changes all occurred in areas with 4.10 mg/L fluoride concentration or higher; these changes were observed even in the younger age groups for fluoride concentrations of 10.27 mg/L and 10.81 mg/L.

From table 9 we can see that ossification of the periosteum generally occurs after the age of 30; only in areas with extremely high fluoride concentration is it observed in younger age groups. Extreme changes in bone matter are only observed in the 10.27 mg/L and 10.81 mg/L areas. The vast majority of severe skeletal x-ray changes were periosteal ossification. Bone matter

Table 7: Relationship between Fluoride Concentration and the Skeletal X-ray Change Frequency for Various Age Groups

Fluoride Concentration (mg/L)	1+	11+	21+	31+	41+	51+	61-83	r	p
0.24	4.74	5.26	0	9.09	20.00	9.09	37.50	0.7629	<0.05
0.80	45.45	41.18	22.22	16.67	44.44	30.00	33.33	0.2529	>0.05
1.00	33.33	39.13	58.33	22.22	72.73	50.00	40.00	0.2584	>0.05
1.80	12.50	33.33	30.00	66.67	57.14	33.33	66.65	0.7020	>0.05
3.12	45.10	35.00	20.00	60.00	50.00	90.00	85.71	0.8082	<0.05
4.10	55.56	42.10	62.50	50.00	80.00	71.43	100.00	0.8202	>0.05
5.60	43.75	73.68	12.50	60.00	87.50	33.33	100.00	0.3497	>0.05
10.27	81.25	93.44	100.00	100.00	100.00	100.00	100.00	0.7375	>0.05
10.81	56.25	100.00	100.00	100.00	100.00	100.00	100.00	0.6123	>0.05

Table 8: Relationship between Fluoride Concentration and the Skeletal X-ray Change Index for Various Age Groups									
Fluoride Concentration (mg/L)	**1+**	**11+**	**21+**	**31+**	**41+**	**51+**	**61-83**	**r**	**p**
0.24	0.05	0.21	0	0.13	0.40	0.18	1.50	0.1936	>0.05
0.80	0.55	0.50	1.00	0.13	0.56	0.40	1.50	0.3785	>0.05
1.00	0.50	0.73	1.42	0.33	1.91	1.00	1.60	0.5555	>0.05
1.80	0.25	0.83	1.20	1.00	0.86	1.17	6.00	0.6927	>0.05
3.12	0.68	0.55	0.30	1.60	5.25	3.60	12.29	0.8235	<0.05
4.10	0.39	1.21	1.88	0.60	3.40	1.57	39.90	0.6348	>0.05
5.60	1.60	3.95	9.13	16.50	58.38	3.00	59.67	0.6615	>0.05
10.27	6.50	8.00	10.00	30.30	70.33	112.40	101.28	0.9329	<0.05

Table 9: Relationship between Fluoride Concentration and Periosteal Ossification										
Fluoride Concentration (mg/L)	**1+**	**11+**	**21+**	**31+**	**41+**	**51+**	**61-83**	**Totals**		
								Number of Subjects	**Afflicted**	**%**
0.24	0	0	0	0	0	0	37.50	88	4	4.55
0.80	0	0	0	0	22.22	20.00	33.33	68	6	8.82
1.00	0	0	0	0	27.27	0	30.00	86	7	8.14
1.80	0	0	0	16.67	14.29	16.67	33.33	58	4	6.90
3.12	0	0	0	10.00	50.00	50.00	71.42	84	15	17.86
4.10	0	0	0	40.00	50.00	28.57	100.00	82	21	25.61
5.60	0	0	0	50.00	75.00	33.33	100.00	73	19	26.03
10.27	0	0	0	70.00	100.00	100.00	100.00	78	33	42.30
10.81	0	6.66	33.33	80.00	100.00	100.00	100.00	73	35	47.95

changes influences the skeletal x-ray change frequency, while periosteal ossification influenced the skeletal x-ray change index.

There was no statistically significant differences between fluoride concentration and the rate of degenerative conditions such as ossification of the articular capsule, the articular cartilage, or the articular ligaments, changes to articular bone matter, hyperplasia, or articular osteophyte formation ($r = 0.4926$, $t_r = 1.4976$, $p > 0.05$). However, the articular degeneration index is positively correlated with fluoride change ($r = 0.9349$, $t_r = 6.9139$, $p < 0.001$) (Table 10).

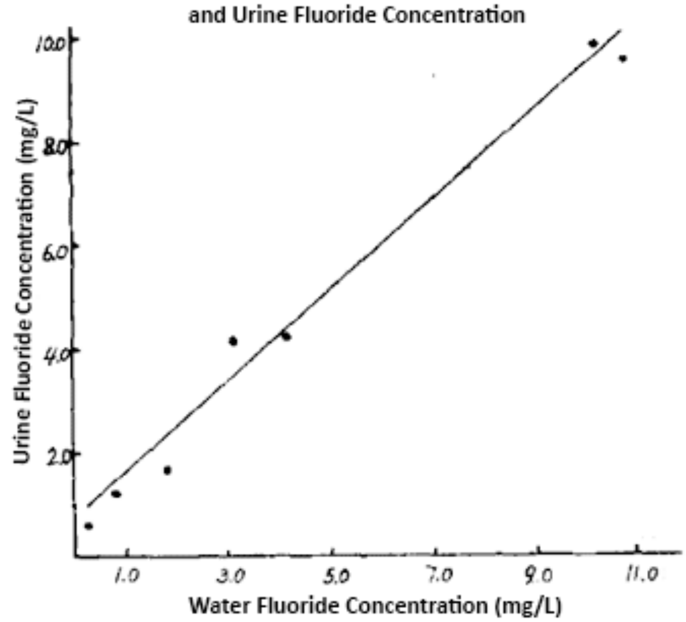
Table 10: Relationship between Fluoride Concentration and Articular Degeneration

Fluoride Conc'n (mg/L)	No. of Subjects	Subjects with Articular Degeneration			
		No.	%	Points	Index
0.24	88	27	30.68	136	1.55
0.80	68	24	35.29	146	2.15
1.00	86	33	30.37	168	1.95
1.80	58	12	20.68	76	1.31
3.12	84	31	36.90	239	2.35
4.10	82	31	37.80	355	4.32
5.60	73	25	34.25	192	2.63
10.27	78	32	41.03	536	6.87
10.81	73	28	38.36	474	6.49

4. Examination of trabeculae with magnified x-ray: In the magnified x-rays the characteristics of normal trabeculae—distinct texture, even thickness, regular structure—are clearly visible. Abnormal trabeculae have an indistinct texture, uneven thickness, and irregular structure, and the difference between the two is very clear. In the 0.24 mg/L area, the rate of trabecular abnormality is 17.65% (3/17), whereas the rate of trabeculae abnormality for the 0.8 mg/L area is 55.00% (11/20) and for the 1.0 mg/L area it is 65% (13/20), there is a statistically significant difference between the former and the latter two areas (χ^2 is 3.98 and 6.58 respectively, $p < 0.05$). Trabecular abnormality is a characteristic sign of osteofluorosis.

5. Relationship with fluoride concentration of urine: In the area with 0.24 mg/L fluoride concentration, the average urinary fluoride concentration of residents was 0.53 mg/L. A positive correlation exists between water fluoride concentration and urinary fluoride concentration ($r = 0.9880$, $t_r = 14.32$, $p < 0.01$). The regression equation is $y = 0.6639 + 0.8705 x$, $R^2 = 0.9772$ (Figure 4).

Figure 4: Relationship between Water Fluoride Concentration and Urine Fluoride Concentration



Discussion

1. Studies both within China and abroad have shown that each day people ingest a certain amount of fluoride from the water they drink, the food they eat, and the air they breathe. Our study is consistent with these findings. Various studies have proven that even people living in areas with relatively small amounts of fluoride in their drinking water have some mottling of the enamel of their teeth, and similarly the group with the 0.24 mg/L fluoride concentration in the present study had some symptoms of fluoride poisoning, including reduced joint function and skeletal x-ray change; we cannot eliminate causes other than fluoride poisoning as possible influences, i.e. these subjects might be suffering from other diseases. This should be viewed as the background prevalence seen in unaffected areas.

In areas with fluoride concentrations of 0.8-1.0 mg/L, the rate of dental fluorosis is already quite high, the skeletal x-ray change frequency is 35.29%-44.19%, and the magnified x-rays demonstrate that clear symptoms of osteofluorosis exist even in these areas. Therefore, in determining a safe level of fluoride for drinking water, dental fluorosis should not be the only indicator, the skeletal x-ray change is also essential evidence, and moreover we should not view areas in the 0.8-1.0 mg/L fluoride concentration range as safe.

2. This study shows that at or below the level of 2.0 mg/L, the rate of dental fluorosis skyrockets as the concentration of fluoride in the water increases, but above 2.0 mg/L the rate of dental fluorosis reaches 100%, it is no longer possible for it to further increase along with the fluoride concentration. Therefore, dental fluorosis is a suitable indicator for determining fluoride poisoning severity at drinking water fluoride concentrations less than 2.0mg/L, but it is not suitable above 2.0 mg/L. Ma et al[2] came to the same conclusion.

3. We are unaware of any research studies conducted outside of China to date which relate water fluoride concentration with skeletal x-rays. Within China, although there are a few studies which use skeletal x-ray change frequency as an indicator[3][4], these studies have not considered the degree of x-ray change. Ours is the first study to use the skeletal x-ray change index, which combines the frequency and degree of change into a single indicator. The resulting distribution curve objectively demonstrates the regular relationship between fluoride concentration and skeletal x-ray change. The first half of the curve is flat, while the second half shows an extreme rise, indicating that there is a clear difference in the degree of disease. The pivot point is at 4.0 mg/L.

Based on these results, we could classify areas with fluoride concentrations of 4.0 mg/L or above as severely afflicted areas, and areas under 4.0 mg/L as a single category. However, since there is a pivot point for dental fluorosis at 2.0 mg/L, we therefore opt to classify 2.1-4.0 mg/L as a moderately afflicted area, and 1.1-2.0 mg/L as a lightly afflicted area. Further research is required for classification under 1.0 mg/L.

4. Articular degeneration is a commonly observed symptom of people living in areas with endemic fluoride poisoning. There is a great deal of divergent opinion on this topic. Huang et al.[5] believe that these articular effects are one manifestation of osteofluorosis. He et al.[5] report that in the vast majority of cases of fluorosis resulting from polluted coal, there is damage to the periosteum and joints but no obvious changes to the bone matter itself. Yang et al.[5] suggest that articular changes should be included in the classification schema. Xu et al.[5], while testing pathological sections from animals, observed damage to the articular and epiphyseal plate cartilage. However, Cheng et al[6] did not observe a statistically significant correlation between water fluoride content and the rate of articular degeneration. Liu et al.[5] conclude that articular degeneration from fluoride poisoning has no particular manifestation in x-ray photography. Li et al.[5] report that coal fluoride poisoning results in much more obvious articular changes than fluoride poisoning from water sources, but this might be related to the different lifestyles, difficulty of labor, and farming techniques in different areas. The current study reports no significant correlation between fluoride concentration and the rate of articular degeneration, but there was a positive correlation between fluoride concentration and the articular degeneration index, indicating that fluoride poisoning increases the degree of articular degeneration. In summary, we believe that there is a certain relationship between fluoride poisoning and articular degeneration, but articular degeneration is not particularly characteristic of fluoride poisoning, and should not be used as diagnostic evidence. The opinion of Li et al should be taken seriously, i.e. further epidemiological studies should be carefully designed and conducted which will serve to clarify the nature of articular changes in patients from areas with endemic coal fluoride poisoning.

Our opinion, based on the present study, is that changes to the periosteum occur much too late to be used as an indicator for early diagnosis.

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