# KIDNEY CHANGES AND KIDNEY STONES IN ENDEMIC FLUOROSIS

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SUMMARY: Urinary tract calculi obtained from 25 patients residing in an endemic fluorotic area revealed a significantly higher fluoride content compared to calculi from 25 persons from a nonendemic area. However the difference in their calcium and phosphate content was not significant. Twenty-four hour urinary fluoride excretion was significantly higher in 10 fluorotic patients than in 10 controls. The incidence of urinary tract calculi was elevated in most of the fluorotic districts of Punjab.

Chronic ingestion of high levels of fluoride is known to produce harmful effects on hard tissues of the body leading to widely recognized clinical manifestations in teeth and bones. The kidneys are the chief organ of the body responsible for excretion of a large portion of ingested fluoride. Patients with endemic fluorosis must excrete excessive amounts of fluoride from the blood into urine. The renal involvement by high doses of fluoride has been described in experimental animals at various concentrations, but no precise studies on humans of the structure and function of the kidneys are available. The present study was undertaken for the purpose of determining the effect of chronic ingestion of high levels of fluoride on the kidneys in humans.

## I. Renal Changes

Complete urine examinations including urea, creatinine and fluoride clearances were carried out on 25 cases of endemic fluorosis. The specific gravity of the urine was measured in all cases after water loading and water deprivation. Successful renal biopsies were possible in 18 fluorotic individuals. In 10 healthy nonfluorotic subjects urea, creatinine and fluoride clearances were measured simultaneously as a control. The following results were obtained:

1. The mean values for maximum urea clearance and standard urea clearance were low compared to mean control values. The decline in creatinine and fluoride clearances compared to the controls was statistically significant, an indication that chronic fluoride intoxication leads to a distinct impairment of glomerular function in human beings.

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2. The renal tubular functions, as determined by water loading and deprivation tests, were found to be normal. Therefore the tubular functions remain unaffected.

3. On histological examination, the sections from the needle biopsy specimens of the kidneys did not reveal any structural change in glomeruli as seen under the light microscope. The only abnormality was the presence of vacuolation in the cells lining the distal convoluted tubules. Thus, a subtle functional impairment of the kidneys is present in chronic fluoride intoxication which requires further investigation.

## II. Urinary Tract Calculi

Fluoride has been demonstrated to be present in almost all body tissues. It is eliminated mainly in the urine (1,2). Its excretion is said to closely parallel its intake from drinking water(3-5). Hence fluoride concentrations are elevated in the urine of subjects residing in endemic areas. Fluoride has been reported to be present in renal tract calculi (6,7).

The presence of fluoride in such calculi combined with excess fluoride in the urine induced us to assess the role of fluoride in the causation of renal calculi. The problem was studied from three different aspects:

1. We estimated the concentration of fluoride, calcium and phosphate in the urinary tract calculi obtained from people residing in endemic fluorotic areas in Punjab compared with calculi obtained in nonendemic areas.

2. Levels of fluoride, calcium and phosphate in 24-hour urinary specimens of fluorotic patients were compared with those of nonfluorotic persons.

3. The records for the past five years of the Rajendra Hospital, Patiala were reviewed to determine the incidence of urinary tract calculi in endemic and nonendemic areas.

### Material and Methods

The kidney stones of 50 patients admitted to the hospital were obtained at surgery. One half of them came from endemic-fluorotic areas, the other half from nonfluorotic areas. The urinary calculi thus obtained were dried overnight at 105° C, weighed and pulverized. They were then extracted with alcohol for 8 hours and with ether for 4 hours, ashed at 550° C for 3 hours and analyzed for calcium, phosphorous and fluoride. The calcium levels in the stone ash were determined according to the method recommended by "Official Methods of Analysis of the Association of Official Agricultural Chemists" (8).

Inorganic phosphorous was estimated according to the method of King and Wooten. Fluoride assays were made by the thorium nitrate titration method.

Ten patients of radiologically proven skeletal fluorosis in the age group of 40 to 70 years were hospitalized. Their 24-hour urine was collected in glass receptacles containing 50 ml of 10% hydrochloric acid. The volume of this urine was measured and analyzed for calcium and phosphorous. Another 24-hour urine specimen was collected in glass containers with a buffer preservative and analyzed for fluoride. The same procedure was carried out in 10 normal subjects from nonendemic areas as controls.

The 1961 to 1965 admission records of Rajendra Hospital, Patiala were examined to ascertain the number of cases with urinary calculi. By charting these records districtwise, the incidence of urinary calculi from the endemic area as outlined by Singh et al. in 1961 (9) was compared with that from the nonendemic areas in the Punjab. In addition, the records of approximately 5000 hospitalized cases during four months in 1963 were reviewed in order to obtain the total number admitted from each district of Punjab.

1. Analysis of Urinary Tract Calculi: The districtwise distribution of the 25 cases from the endemic area is presented in Table 1 and their distribution in terms of age and sex is given in Table 2.

Table 1

Case Distribution from Endemic Area

| Districts | No. of Cases |
|---|---|
| Bhatinda | 14 |
| Sangrur | 5 |
| Ferozepur | 3 |
| Hissar | 3 |
| Total | 25 |

Table 2

Age and Sex of Endemic Group

| Age Group In Years | Sex | |
|---|---|---|
| | Male | Female |
| 0 - 1 | 5 | 1 |
| 11 - 20 | 2 | - |
| 21 - 30 | 2 | 1 |
| 31 - 40 | 5 | - |
| 41 - 50 | 2 | - |
| 51 - 60 | 3 | - |
| 61 - 70 | 3 | - |
| 71 - 80 | 1 | - |
| Total | 23 | 2 |

Of the 25 calculi, 3 were renal stones, 4 ureteric stones and 18 were bladder stones. In two cases multiple calculi were present. The weight of the calculi varied from 0.5 to 13.7 gms.

In the nonendemic districts of Punjab, we had 25 patients, 22 males and 3 females. Their age range and sex ratio was similar to those from fluorotic areas. Nineteen of the 25 calculi were present in the bladder, 4 in the kidneys and 2 in the ureters. The weight varied from 0.5 to 9.2 gms.

Table 3 shows the fluoride, calcium and phosphorous contents of the urinary tract calculi obtained from endemic and nonendemic groups.

Table 3
Analysis of Urinary Tract Calculi

| | | Fluoride mg | Calcium mg | Phosphate mg |
|---|---|---|---|---|
| Endemic Group | Range | 0.84-4.15 | 10.1-31.2 | 1.01-18.2 |
| | Mean | 2.2 | 23.0 | 4.8 |
| | S.D.± | 0.99 | 6.5 | 4.2 |
| Nonendemic Group | Range | 0.03-0.91 | 4.9-30.5 | 1.15-18.2 |
| | Mean | 0.62 | 21.2 | 6.03 |
| | S.D.± | 0.243 | 6.2 | 5.5 |
| Endemic & Nonendemic Group | S.E. + | 0.20 | 1.80 | 1.38 |
| | 't' value | 7.09 | 1.0 | 0.89 |
| | Remarks | Significant | Insignificant | Insignificant |

Significance P = 0.01

The mean fluoride content of stones formed in endemic fluorotic areas was 2.2 mg/100 mg (22,000 ppm) compared to 0.62 mg/100 mg (6200 ppm) stone ash obtained from nonendemic areas. The rise in fluoride levels was statistically significant in the urinary calculi derived from the endemic areas. However no significant change was observed in the calcium and phosphorous content of stones formed in endemic and nonendemic areas.

The calcium/fluoride ratio was 2.8/37.5 in fluorotic calculi and 17.7/840 in control stones. There was no definite correlation between the calcium and the fluoride content of stones. Similarly the calcium/phosphate ratio was 0.9/24.9 in fluorotic calculi and 0.7/22 in control stones. Thus the phosphorous content was also independent of the calcium and fluoride concentrations of the calculi.

2. Analysis of Urine for Fluoride, Calcium and Phosphates:

(a) Fluorotic Group: Ten patients varying in age from 27 to 70 years were hospitalized at Rajendra Hospital, Patiala. Nine of them were males, one was female. Six cases came from District Bhatinda, two from Ferozepur and 2 from Sangrur. All 10 had been residing in the high fluoride areas since birth and calcification of their interosseous membrane was considered proof of skeletal fluorosis.

(b) Control Group: The 10 cases, 9 males and 1 female, of this group came from a nonendemic area. Their ages varied from 30 to 70 years similar to those of the fluorotic group. Eight were residing in the District Patiala, one in Ambala and one in Ludhiana.

The daily excretion of fluoride, calcium and phosphate in the 24-hour urine of both groups is shown in Table 4.

Table 4
Daily Urinary Excretion of Fluoride, Calcium and Phosphate

| | | Fluoride mgs | Calcium mgs | Phosphates mgs |
|---|---|---|---|---|
| Fluorotic | Range | 2.4-12.7 | 70.5-271.5 | 321-853 |
| | Mean | 6.1 | 117.4 | 606.9 |
| | S.D.± | 3.13 | 57.7 | 178.8 |
| Control | Range | 0.21-0.83 | 70.2-249 | 390.1-861 |
| | Mean | 0.54 | 122.9 | 592.3 |
| | S.D.± | 0.20 | 54.8 | 161.9 |
| Fluorotic & Control | S.E.± | 0.99 | 25.16 | 76.28 |
| | 't' value | 5.62 | 0.22 | 0.19 |
| | Remarks | Significant | Insignificant | Insignificant |

Significance P = 0.01

According to Table 4 the daily excretion of fluoride in the urine of fluorotic patients is significantly higher than in the control group. However the daily excretion of calcium and phosphates in urine is almost the same in both groups.

3. Incidence of Urinary Tract Calculi in Endemic and Nonendemic Areas:

The districtwise records of cases with urinary calculi admitted at the Rajendra Hospital, from 1961-1965 and the total number of admissions to this hospital during four consecutive months of the year 1963 are shown in Table 5.

Table 5
Incidence of Calculi in Hospital Admissions

| | District | Total cases with calculi admitted 1961-65 | Total admissions in 4 consecutive months of 1963 | % calculi in 5 yrs. to total no. of admissions in 4 mos. |
|---|---|---|---|---|
| Endemic | Sangrur | 97 | 591 | 16.8 |
| | Hissar | 79 | 228 | 35.1 |
| | Bhatinda | 72 | 301 | 23.7 |
| | Ferozepur | 88 | 212 | 41.1 |
| Nonendemic | Patiala | 284 | 2714 | 10.3 |
| | Karnal | 61 | 249 | 23.0 |
| | Ambala | 61 | 332 | 18.3 |

Table 5 shows a higher percentage of urinary calculi in fluorotic districts than in the nonfluorotic ones.

## Discussion

Fluoride has a pronounced affinity to calcium and combines with it to form insoluble calcium fluoride. It is conceivable that with high concentrations of fluoride in the urine, calcium fluoride may be precipitated and the precipitated particles may form the nucleus around which other salts are laid down to produce the calculi. In areas where the fluoride content of water is high, it is reasonable to assume that it might be responsible for the formation of urinary tract calculi or, at least, that it might accelerate their formation.

Zipkin, Lee and Leone (7) found that the fluoride concentration of calculi was considerably higher than that of bones. They also observed a slightly higher concentration of fluoride in calculi obtained from patients residing in endemic fluorotic areas (0.06 to 1.11%) although the increase was not statistically significant.

In the present series, the mean fluoride content of calculi obtained from patients in endemic fluorotic areas was 2.2 mg% compared to 0.62 mg% in those from nonendemic areas, a statistically significant difference. The discrepancy between our figures and those obtained by Zipkin et al. (7) can be explained on the basis that most of our patients were farmers who work in the scorching heat of summer and drink an average of 8 to 12 liters of water daily compared to people in cooler damp climates where the average intake of water is only 2 to 3 liters daily. Consequently they ingest large amounts of fluoride. Furthermore, the average fluoride concentration of water in the endemic fluorotic areas of India is 16 ppm (10) whereas in the area analyzed by Zipkin et al. (7), it was 2.6 ppm.

No statistically significant difference was observed between the calcium content of the calculi obtained from the endemic fluorotic areas and that from the control group. The calcium content of the calculi in the endemic group was unrelated to the fluoride content of the calculi. The calcium/fluoride ratio varied from 2.8 to 37.5. Zipkin et al. (7) made a similar observation.

The mean phosphate content of calculi from the endemic group (4.84 mg%) was slightly lower than that of the controls (6.03 mg%) although the difference was not statistically significant.

In the ten fluorotic patients in whom fluoride assays of the 24-hour urine were made, the mean value was 6.1 mg as contrasted to 0.54 mg in the controls, a significant difference. Similar observations were made by Largent and Heyroth (11). However, calcium and

phosphorous excretion was similar in the control and fluorotic groups. The difference was not statistically significant.

With respect to the incidence of urinary tract calculi in the endemic and nonendemic areas of Punjab, we observed a higher percentage of urinary calculi in the fluorotic than in the nonfluorotic districts. This technique of calculating the incidence of urinary calculi, however, is approximate and cannot be considered accurate. Nevertheless the data comparing the incidence of urinary calculi in the fluorotic and the nonfluorotic districts as well as our other findings, strongly support our hypothesis that kidney stones are influenced by the level of fluoride in drinking water.

## Bibliography

1. Machle, W., Scott, E.W. and Largent, E.J.: Absorption and Excretion of Fluorides, Part 1 The Normal Balance. J. Ind. Hyg. Toxicol. 24:99-204, 1942.
2. Majumdar, D.B. and Ray, S.N.: Fluorine Intoxication of Cattle in India II. Effect of Fluorosis on Mineral Metabolism. Indian J. Vet. Sci. 16:107-112, 1946.
3. McClure, F.J., and Kinser, C.A.: Fluoride Domestic Waters and Systemic Effects II, Fluorine Content of Urine in Relation to Fluorine in Drinking Water. Publ. Hlth. Rep. 59:1575-1591, 1944.
4. Smith, F.A., Gardner, D.E. and Hodge, C.H.: Investigations on the Metabolism of Fluoride II. Fluoride Content of Blood and Urine as a Function of the Fluorine in Drinking Water. J. Dent. Res. 29:596-600, 1950.
5. Machle, W. and Largent, E.J.: The Absorption and Excretion of Fluoride II. The Metabolism at High Levels of Intake. J. Ind. Hyg. and Toxicol. 25:112-123, 1943.
6. Herman, J.R.: Fluorine in Urinary Tract Calculi. Proc. Soc. Exp. Biol. Med. 91:189-191, 1956.
7. Zipkin, I., Lee, W.A. and Leone, N.C.: Fluoride Content of Urinary and Biliary Tract Calculi. Proc. Soc. of Exp. Biol. Med. 97:650-653, 1958.
8. Official Methods of Analysis of the Association of Official Agricultural Chemists. 8th Ed. 1955, Washington, D.C.
9. Singh, A. and Jolly, S.S.: Endemic Fluorosis with Particular Reference to Fluorotic Radiculo-Myelopathy. Quart. J. Med. 30:357-721, 1961.
10. Singh, A., Dass, R., Hayreh, S.S. and Jolly, S.S.: Skeletal Changes in Endemic Fluorosis. J.Bone Joint Surg. 448:806-815, 1962.
11. Largent, E.J., Bovard, P.G. and Heyroth, F.F.: Am. J. Roentogenol and Radium Therapy. 65:42, 1951.

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