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ORIGINAL ARTICLE

Serpil Savas · Meltem Çetin · Mehmet Akdoğan
Nurettin Heybeli

Endemic fluorosis in Turkish patients: relationship with knee osteoarthritis

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Abstract Fluoride excess primarily effects dental and skeletal tissues, leading to a condition known as endemic fluorosis. The radiological and clinical features of endemic fluorosis vary in different parts of the world. The aim of this study was to investigate the clinical and radiological features of endemic fluorosis in Turkish patients. Physical examination and radiological investigations were performed in 56 patients with endemic fluorosis and 40 age- and sex-matched controls. Knee osteoarthritis (OA) was the main abnormality in both groups, both clinically and radiologically. The radiological severity of knee OA was greater in the endemic fluorosis group than in controls ($P = 0.01$). Osteophytes at the tibial condyles and superior margin of the patellar articular surface of the femur, polyp-like osteophytes on the non-weight-bearing medial side of the femoral condyle, and popliteal loose bodies were detected more frequently in the endemic fluorosis group than in controls ($P = 0.0001$). We suggest that the presence of atypically located osteophytes in the knees may be a feature of endemic fluorosis in Turkish patients and that endemic fluorosis may increase the severity of OA in the knees.

Keywords Bone · Cartilage · Fluoride · Endemic fluorosis · Knee joint

S. Savas (✉)
Süleyman Demirel University Medical School,
Physical Therapy and Rehabilitation Department,
Isparta, Turkey

M. Çetin
Süleyman Demirel University Medical School,
Radiology Department, Isparta, Turkey

M. Akdoğan
Süleyman Demirel University Medical School,
Biochemistry Department, Isparta, Turkey

N. Heybeli
Süleyman Demirel University Medical School,
Orthopaedics and Traumatology Department, Isparta, Turkey

Posta Kutusu 76, 32000, Isparta, Turkey

Introduction

Endemic skeletal fluorosis is a chronic metabolic bone and joint disease caused by ingestion of large amounts of fluoride either through water or rarely from foods of endemic areas [1]. Although the prevalence of this disease has decreased considerably, it still occurs in some parts of the world such as Isparta, an endemic fluorosis area in southern Turkey. A wide range of radiological features have been described in endemic skeletal fluorosis [2, 3, 4, 5, 6, 7, 8]. The main radiological appearances are osteosclerosis, osteopenia, membranous and ligamentous calcification, exostoses, coarse trabecular pattern, diaphyseal widening, and intermittent growth lines. Joint pains, some crippling deformities such as limited spinal movement, thoracic kyphosis and flexion deformities at the hips and knees, bony leg deformities (genu varum, genu valgum, bowing, wind-swept), and spinal cord compression due to the vertebral osteosclerosis have been reported as the clinical findings [4, 5, 6, 7, 9, 10, 11, 12, 13, 14].

To the best of our knowledge, endemic skeletal fluorosis has not been reported previously from Turkey. Observing a high number of female patients with dental fluorosis complaining of knee pain in Isparta led us to investigate the clinical and radiological features of these patients.

Patients and methods

Fifty-six patients with endemic fluorosis who attended the Süleyman Demirel University physical therapy and rehabilitation outpatient clinic for various painful conditions were included in the study. The clinical diagnosis of endemic fluorosis was modified from the criteria of Wang et al. [2]: (1) living in the endemic fluorosis region since birth, (2) having mottled tooth enamel, indicating dental fluorosis, (3) consuming water with fluoride levels above

1.2 ppm (normal 1 ppm), and (4) a urine fluoride level greater than 1.5 mg/l (normal < 1.5 mg/l).

Forty patients living in a nonendemic region who attended the same outpatient clinic and had nontraumatic knee pain were randomly selected as controls. The patients and controls were all urban dwellers and housewives. The medical histories and the main complaint of the groups were recorded. Patients with metabolic bone disease or inflammatory disease in their medical histories were excluded. Physical examination was performed in all groups. The patients' body weight and height were recorded. Body mass index (BMI) was calculated for each patient as weight (kg)/height $(m)^2$. Diagnosis of genu varum or valgum deformity was made using the femorotibial angle. This angle is formed by the intersection at the knee joint of the long axes of the femur and tibia, represented by appropriate lines drawn on the radiograph. Measurements of 175°, or 5° valgus, were accepted as normal [15].

Biochemical investigations

Serum samples were analyzed for calcium, inorganic phosphorus, total alkaline phosphatase, total proteins, albumin, creatinine, and blood urea nitrogen by standard biochemical methods. Patients and controls were asked to bring tap water from their houses in plastic containers. Water, serum, and urine samples were estimated by using an ion-specific electrode (Orion F 94–09).

Radiology

The patients with endemic fluorosis had anteroposterior (AP) radiographs made of the forearm, hands, pelvis with the upper end of the femur, thoracic spine, lumbar spine, knees (anteroposterior, or AP, and lateral views), and tibia and fibula (AP and lateral views). Controls had AP and lateral views of the tibia and fibula only. All radiographs were analyzed by two radiologists who were blinded to each other's findings.

Radiological changes were classified as: (1) existence of radiological knee abnormalities based on the worse knee consisting of femorotibial osteoarthritis (OA) graded according to the Kellgren method using a 5-point scale (0–4), osteophyte formation at the superior and inferior margins of patella, osteophytes on the anterior and posterior parts of the tibial condyles and at the superior margin of the patellar articular surface of the femur, and popliteal loose bodies, (2) osteosclerosis, an overall increase in bone density with thickening of the cortex, and (3) ossification of ligaments, tendons, and interosseous membranes. Definite OA was defined as that with a Kellgren score of 2 [16]. Maximum patellar osteophyte size (grade 3) was determined by measuring with a ruler. Grades 1–2 were calculated as two-thirds and one-third reductions in the area of grade 3 [17].

Statistical analysis

Results were given as mean ± SD. Statistical significance was set at the 0.05 level. Comparison of the groups was performed using Student's-*t* test in parametric values and the chi-squared test in nonparametric values. Correlation analysis was performed to assess the relation between some radiological and the clinical features.

Table 1 The prevalence of symptoms in the 56 patients with endemic fluorosis

Location	*N*
Knee	37 (66.1%)
Hip	2 (3.6%)
Feet	2 (3.6%)
Low back	3 (5.4%)
Low back and knee	5 (8.9%)
Generalised pain	4 (7.1%)
Shoulder	2 (3.6%)
Neck	1(1.8%)

Results

Demographic and clinical features

The endemic fluorosis group consisted of 51 female and five male patients and the control group included 34 females and six males. There was no difference in sex distribution between the groups ($P = 0.36$). The mean age of the endemic fluorosis group and controls was 54.9 ± 11.6 years and 57.45 ± 9.76 years, respectively ($P = 0.26$). The BMI of both groups were 29.75 ± 5.08 and 29.36 ± 4.31, respectively. ($P = 0.69$). The mean numbers of years since menopause were 12.1 ± 6.3 in endemic fluorosis patients and 11.35 ± 6.7 in controls. There was no difference between the groups in the number of mean years since menopause ($P = 0.5$).

The most common complaint of the patients with endemic fluorosis was knee pain (37 patients, 66.1%). The distribution of complaints of the patients with endemic fluorosis is shown in Table 1.

Fig. 1 Radiograph of knee showing osteophytes on the anterior and posterior parts of the tibial condyles (*thin arrows*) and at the superior margin of the patellar articular surface of the femur

None of the patients had thoracal kyphosis, fixed knee, or hip flexion deformities. Seventeen patients (30.4%) with endemic fluorosis and five controls (12.5%) had genu varum deformity ($P=0.05$). The mean femorotibial angle was 184.6±3.9° in the right knee and 184.4±4.2° in the left knee in the endemic fluorosis patients with genu varum deformity. In controls with genu varum deformity, the mean femorotibial angle of the right knee was 183.6±2.6°, and the mean femorotibial angle of the left knee was 183.8±1.3°. Genu varum deformity correlated to age ($P=0.0001$, $r=0.48$) but not to BMI ($P=0.32$, $r=0.13$) in our patients with endemic fluorosis. In controls, genu varum deformity correlated to BMI ($P=0.01$, $r=0.38$) but not to age ($P=0.07$, $r=0.28$). None of the patients in either group had genu valgum deformity.

Biochemical parameters and fluoride levels

Serum total calcium, inorganic phosphorus, and alkaline phosphatase concentrations were normal in all patients.

The mean fluoride level in the drinking water was significantly higher in patients with fluorosis (2.74±0.85 mg/l) than in controls (0.71±0.06 mg/l) ($P<0.0001$). Serum and urine fluoride levels were 0.10±0.04 mg/l and 1.96±0.37 mg/l, respectively, in the patients with endemic fluorosis. These values were significantly higher than in controls, whose mean serum and urine fluoride levels were 0.03±0.01 mg/l and 0.37±0.16 mg/l, respectively ($P=0.0001$).

Radiology

The main radiological features of the patients with endemic fluorosis were degenerative changes including mainly the medial femorotibial and patellofemoral compartments. Twelve patients (21.4%) with endemic fluorosis and eight control patients (20%) had grade 2 OA, 16 patients (28.6%) with endemic fluorosis and three control patients (7.5%) had grade 3 OA, and six patients (10.7%) with endemic fluorosis and one control patient (2.5%) had grade 4 OA. The OA severity was greater in the endemic fluorosis group ($P<0.01$).

Osteophytes at the anterior and posterior parts of the tibial condyles, osteophytes at the superior margin of the patellar articular surface of the femur (Fig. 1), and popliteal loose bodies (Fig. 2) were detected more frequently in the endemic fluorosis group than in controls.

Fig. 2 Popliteal loose bodies

Fig. 3 Large osteophytes located at the superior and inferior parts of the patella

Table 2 Comparison of knee radiographs of the patients with endemic fluorosis and controls

	Fluorosis	Controls	*P*
Grades 2 and 3 osteophytes at the superior and inferior margins of the patella	21 (37.5%)	3 (7.5%)	0.001
Osteophyte at the anterior part of the tibial condyle	29 (51.8%)	3 (7.5%)	0.000
Osteophyte at the posterior part of the tibial condyle	27 (48.2%)	2 (5%)	0.001
Osteophyte at the superior margin of the patellar articular surface of the femur	25 (44.6%)	8 (20%)	0.013
Popliteal loose bodies	20 (35.7%)	4 (10%)	0.004

There was no difference between groups in the existence of osteophytes at superior and inferior margins of the patella ($P = 0.67$). However, these osteophytes were larger in endemic fluorosis patients than in controls ($P = 0.001$) (Fig. 3).

Twenty-five (44.6%) patients with endemic fluorosis had polyp-like osteophytes at the medial non-weight-bearing margin of the femoral condyle (Fig. 4). This kind of osteophyte was not detected in controls. Comparison of the radiological features of the groups are summarized in Table 2.

Two patients (3.6%) with endemic fluorosis had axial osteosclerosis (Fig. 5), and five (8.9%) had interosseous membrane calcification on the forearm (Fig. 6). None of the patients with endemic fluorosis had cartilage calcification or bowing of the tibia or fibula.

Discussion

In our patients with endemic fluorosis, the knee joint was the most commonly involved joint, both radiologically and clinically. In skeletal fluorosis, involvement of the axial skeleton is characteristic, and changes are most marked in the spine, pelvis, and forearm [5, 6, 10, 18, 19]. Knee involvement in endemic fluorosis has been clinically described mainly in children and adolescents as flexion deformities [6, 19] and genu varum or valgum deformities due to the bowing of long bones caused by osteomalacia, secondary hyperparathyroidism, and rickets [4, 9, 10, 11]. Not much is known about the radiological features of the knee involvement in endemic fluorosis.

Fig. 4 Polyp-like osteophytes on the medial non-weight-bearing margin of femoral condyle

Fig. 5 Osteosclerosis of the spine

Fig. 6 Ossification of interosseous membrane

It was surprising to see female dominance in an endemic region. As OA is particularly common in middle-aged/elderly females in this geographic region, it is possible that femorotibial OA was the main problem in both groups; however, the severity of OA was greater in patients with endemic fluorosis than controls, both clinically and radiologically. We thought that endemic fluorosis might be responsible for the increased severity of degenerative features. Some of the osteophytes seen in endemic fluorosis patients were located in unusual sites for OA such as the tibial condyles. Some of the osteophytes were polyp-like and located at the non-weight-bearing medial side of the medial femoral condyle, which is atypical for OA. The osteophytes at the superior and inferior margins of the patella were larger than the patellar osteophytes seen in controls. These atypical osteophytes were not seen in the patients with endemic fluorosis without knee pain, so we decided that they were not incidental findings.

Fluoride is a cumulative poison that increases metabolic turnover of the bone in favor of bone formation [1]. It stimulates bone cell proliferation by directly inhibiting osteoblastic acid phosphatase activity [20] and by prolonging or enhancing the mitogenic signals of growth factors [21, 22]. Histopathological studies of bone in fluorosis have shown osteoid tissue deposited irregularly on the trabeculae and cortex, with extension into muscle attachments [6]. This osteoblastic activity causes a marked increase in bone formation at the organ level, causing the production of exostoses, calcification of tendons and ligaments, and osteosclerosis [22]. The other explanation for the degenerative changes in the knees of our patients with endemic fluorosis may be the chondrotoxic effect of fluoride. Fluoride mainly affects bone metabolism [21]. However, cartilage is one of its deposition areas [22, 23]. In an animal study [9], it was shown that excessive fluoride ingestion caused necrosis of articular chondrocytes, ulcer formation, and articular calcification, which causes a mushroom-like appearance.

Radiological changes in industrial fluorosis suggest that physical strain on bones, ligaments, and joints plays an important role in the development of the lesions [24, 25]. The reason for the selective knee involvement in our patients may be fluoride's selectivity for the most stressed joints [26, 27]. Sitting habits like hyperflexion sitting and ritual worship in our population may stress the knees and cause vulnerability to fluorotic damage.

In our study, some radiological findings such as osteosclerosis, interosseous membrane calcification, or ligament calcification, which were accepted as hallmarks of skeletal fluorosis, were not found as frequently as in the literature [1, 10, 22]. We also did not observe severe crippling deformities. The causes for the clinical and radiological differences may be due to several factors such as the nature, dose, duration of fluoride exposure, age, sex, dietary habits, or their combination [1, 3, 6, 10, 18]. The mean fluoride level in the drinking water of our region was 2.7 ppm. Osteosclerosis and interosseous membrane calcification have usually been reported in levels over 4 ppm [6, 10]. The total quantity of ingested fluoride is reported as the single most important factor determining the clinical course of this disease, which is characterized by immobilization of joints of the axial skeleton and of major joints of the extremities [1, 6]. Jolly [10] suggested that crippling deformities are usually associated with drinking water with a 10 ppm level for 10 to 20 years. However, the concentration of fluoride alone was not found to be responsible for the incidence of skeletal fluorosis. In different areas with similar fluoride content in the drinking water [10, 28] and even in the same endemic area where the source of drinking water was the same, the incidence of the disease and extent of bone changes differed, and X-ray findings of bone fluorosis were significantly different [7, 10]. Arnala suggests the variability of individual susceptibility to fluoride [29]. Another important cause is nutritional status. It is accepted that poor nutrition and low calcium intake enhance the deleterious effects of fluoride [3, 4, 14, 18]. As we did not assess the nutritional status of the patients, we cannot clearly state that poor nutrition is responsible for the abnormal radiological findings in our patients with endemic fluorosis.

We suggest that atypically located osteophytes in the knees may be a feature of endemic skeletal fluorosis in

Turkish patients. We also suggest that endemic fluorosis may increase the severity of knee OA. Further studies are needed in order to understand the exact mechanism of bone and cartilage changes in the knees of patients with endemic fluorosis.

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