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Skeletal Fluorosis: A Risk Factor of Bone Fractures Among Adults in Ethiopia: A Case-Control Study

Heron Gezahegn Gebretsadik*

Abstract

Background: Fluoride is a beneficial trace element. It is contained in the calcified tissues. Fluoride has a prophylactic effect against dental caries when absorbed in doses of less than 1.5 mg/day on the surface of the tooth enamel. It is also used as a therapeutic agent in adults for the treatment of postmenopausal osteoporosis at doses of 15 to 25 mg/day. However, fluoride in high doses can cause skeletal fluorosis, which can lead to bone fractures. The effects of fluoridated water on the skeleton are poorly understood, but there is some evidence that prolonged consumption of highly fluoridated water increases the risk of bone fractures. This case-control study examined the association between skeletal fluorosis and bone fractures among adults living in Ethiopia's Rift Valley (fluoride endemic) region.

Method: A case-control study was conducted among adult Ethiopians in February 2023 to investigate the association between skeletal fluorosis and bone fractures. The study aimed to determine whether skeletal fluorosis poses a risk for bone fractures. Three matched controls were chosen for every case, considering a 1:3 ratio. Spine radiographic investigations were conducted to determine possible skeletal fluorosis-associated morphologic changes among the study participants. Chi-square tests and odds ratios (ORs) were computed. The P-value was also calculated considering a degree of freedom (df) of 1.

Results: Given the 1:3 ratio between cases and controls, the study included 9 cases (6 females and three males) and 27 controls. The cases were diagnosed with femoral neck fractures (n=2), callus fractures (n=2), distal tibial fracture (n=1), lumbar vertebra fractures (n=3), and calcaneal fractures (n=1). The age range of cases and controls was 38 to 69 years. Analysis revealed a statistically (p-value = 0.01) significant association between skeletal fluorosis and bone fractures. Five subjects (4 cases and one control) had a constellation of abnormal bony changes in the spine. The odd ratio (OD) and chi-square ($\chi 2$) were calculated as 20.80 and 6.27, respectively, while the 95% CI was determined as [1.904, 227.274].

Conclusion: This study revealed that skeletal fluorosis is a risk factor for multiple types of bone fractures among adults living in a highly fluoridated area in Ethiopia. However, more thorough studies need to be conducted with a broader study population to further determine the association between skeletal fluorosis and bone fractures.

Keywords: Bone Fractures; Fluorine; Skeletal Fluorosis

Affiliation:

School of Global Health and Bioethics, Euclid University, Banjul, Gambia

***Corresponding Author:**

Heron Gezahegn Gebretsadik, School of Global Health and Bioethics, Euclid University, Banjul, Gambia.

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Introduction

Fluorine is a widespread element in varying concentrations in soils, rocks, and water. Fluorides are substances that contain fluorine, both organic and inorganic [1]. Although fluorine is not a critical trace element for human health, it is beneficial for the integrity of bones and teeth and helps prevent dental caries [2]. Fluorosis is a condition that develops as a result of repeated exposure to high concentrations of fluorine, whether through ingestion or inhalation. Fluorosis primarily affects the nervous system but also the teeth and skeleton. Consumption of drinking water with fluoride concentrations greater than four ppm is the most common cause of fluorosis [3]. In tropical regions of India, China, and some regions of Africa, endemic fluorosis due to fluoride-rich water has been demonstrated [4-6]. Endemic fluorosis associated with indoor coal burning has also been reported in China [7]. Other known sources of fluorosis include excessive consumption of "brick tea," industrial exposure during arc welding, cryolite mining, or aluminum, steel, or glass manufacturing [8]. The dose, duration of consumption, age, sex, meteorological factors, nutritional status, and physical exertion of patients are related to the severity of the disease [2,3,9].

Clinical symptoms of fluorosis include joint pain and limited range of motion, back pain, spinal stiffness, and functional dyspnea caused by restricted respiratory movements [10]. Bony outgrowths are palpable at the anterior tibia and ulna [11]. In severe cases, crippling of the spine and extremities leads to motor and neurological disabilities. Approximately 10% of people with skeletal fluorosis in endemic areas suffer neurologic complications. Due to mechanical compression of the spinal cord and nerve roots by osteophytes and ossification of the posterior longitudinal and flaval ligaments, neurologic symptoms usually manifest as radiculomyelopathy [12]. Dental fluorosis, characterized by discoloration and staining of the enamel of permanent teeth, is caused by exposure to fluoride in children before the age of eight [13]. The main effect of fluoride ions is to promote the growth of new, mostly woven and imperfectly mineralized bone. At the same time, accelerated bone resorption may occur [14]. On X-rays, the pathological changes in bones show up as varying degrees of osteoporosis, osteomalacia, and osteosclerosis [15]. Radiographs of people with skeletal fluorosis, osteosclerosis, increased cortical and trabecular bone volume of the jaw, osteomalacia or rickets, and osteoporosis may show ligament and tendon ossification, growth lines, and periosteal reactions [16].

Littleton [17] thoroughly analyzed the harmful effects of excessive fluoride on physiology and bone. As mentioned earlier, toxic fluoride concentrations can affect bone formation and resorption processes [18]. Osteoclast dysfunction can lead to impaired resorption, or high fluoride concentrations can cause bone minerals to be less quickly resorbed [19]. This results in the formation of abnormal bone that is prone to fractures and other pathologic conditions. Individuals are at risk for developing fractures because the quality of bone formed in fluorosis is reported to be lower than that of bone formed under healthy conditions [20]. Although fluorosis is at least known to cause skeletal changes that can lead to fractures, especially in areas with naturally high fluoride levels [21], little attention has been paid to the issue, and it has been poorly studied [20]. This study examined the association between skeletal fluorosis and bone fractures among adult residents of Ethiopia's highly fluoridated Rift Valley region.

Materials and Methods

Research design

A case-control study was used to investigate the association between skeletal fluorosis and bone fractures among adults living in highly fluoridated areas in Ethiopia. The study matched three controls for each corresponding case in terms of geographic location, source of drinking water, gender, and age.

Sample and setting

The study was conducted in five highly fluoridated cities in Ethiopia, such as Batu, Samiberta, Wonji-Shoa, Gura, and Alemtena. The cases were individuals diagnosed with bone fractures and treated by a senior orthopedic surgeon in a private practice in Addis Abba, Ethiopia. Controls were individuals matched to cases by the village of residence (same neighborhoods as the cases), source of drinking water, age (± 2 years), and sex. However, the control subjects were not diagnosed with bone fractures before the study was conducted.

Inclusion and exclusion criteria

Inclusion criteria

To be included as a case in the study, the volunteer participant should reside since childhood in a fluoride-endemic area (epidemiological data) and be at least 18 years old with a history of dental fluorosis and bone fractures. Control subjects, on the other hand, must be individuals similar to the cases, except that they had no record of bone fractures. Similarity should be based on age, sex, residence area, and drinking water source.

Exclusion criteria

Cases and controls with a history of myelofibrosis, osteoblastic metastases, renal osteodystrophy, ankylosing spondylitis, and/or Paget's disease were excluded to avoid confounding.

Radiologic investigation

A plain radiograph was used to investigate possible

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morphological changes in the spinal vertebrae that can potentially be associated with skeletal fluorosis. The radiographic examination was focused on the bones of the spine, as this is one of the anatomical regions most affected by skeletal fluorosis in humans. An independent radiologist interpreted and reported the findings of the lateral views of the radiographs.

Data analysis

Pearson's chi-square test was used to probe the probability of the association (not causation) between skeletal fluorosis and bone fractures among the study participants. Accordingly, the odds ratio (OD) and the associated confidence interval (CI, 95%) were calculated to discuss the relationship between the variables (skeletal fluorosis and bone fractures) and to describe the range of values within which the OD lies in 95% of instances, respectively. The OD was regarded as the odds of having the disease (i.e., bone fractures) with the exposure (i.e., skeletal fluorosis) versus the odds of having the disease without the exposure. A 2×2 grid table represents the possible inputs (Table 1) for the chi-square test. The degree of freedom for a chi-square grid was 1. A p-value was calculated to test the statistical significance of the associations between the two variables.

Ethical consideration

The Addis Ababa Health Bureau Institutional Review Board (IRB) and the ethics committee reviewed the submitted study proposal and provided ethical assurance (approval number: A/A/H/8415/227). Study participants were adequately informed about the nature of the research project. In addition, each volunteer participant provided verbal informed consent. Care was taken to ensure that study participants had the right to decide. They had the option to terminate the study at any time. The radiographs of the study participants and the various interpretations of the images were kept confidential.

Results

The case-control study investigated the association between skeletal fluorosis and bone fractures. The cases were individuals with different types of fractures treated at a private facility in Addis Ababa between April 2013 and January 2023. Only 9 cases (6 women and three men) that met the inclusion criteria were eligible for selection after a thorough review of all the orthopedic patients' medical records filed in the archive of the practice from April 2013 to January 2023. The selected cases were from Batu (n=2), Samiberta (n=2), Wonji-Shoa (n=1), Gura (n=3), and Alemtena (n=1), cities known for high fluoride concentration in drinking water. They were diagnosed with femoral neck fractures (n=2), callus fractures (n=2), distal tibial fracture (n=1), lumbar vertebra fractures (n=3), and calcaneal fractures (n=1). Their ages varied from 38 to 69 years. The corresponding 27 cohorts were recruited from similar residential areas, using a case-control ratio of 1: 3. Case-control matching also considered similarities in gender, age (± 2), and source of drinking water. Thus, the final analysis included 9 cases with fractures and 27 matched controls. All cases and controls used tap water as their source of drinking water.

After spinal radiographs, 5 participants (4 cases and one control) were found to have various types of morphological changes, including osteomalacia (n=2), abnormal calcifications/hyperostosis lesions (n=2), and osteoporosis (n=1) in the vertebrae of the spine. Of these, 3 were women (all from the case group), and 2 were men from each case and control group. All the radiologically diagnosed subjects with skeletal fluorosis were residents of Samiberta (n=2), Wonji-Shoa (n=2), and Gura (n=1) cities (Table 1 and 2).

On the other hand, analysis of Pearson's test revealed a statistically significant association (p-value = 0.01) between skeletal fluorosis and bone fractures. Five subjects (4 cases and one control) had a constellation of abnormal bony changes in their spine. The odd ratio (OD) and chi-square (χ^2) were calculated to be 20.80 and 6.27, respectively. The measure of association used in the analysis of this case-control study was the odds ratio. Accordingly, the calculated

Table 1: A 2×2 grid table.

Skeletal fluorosis	Cases with bone fractures	Controls	Total
Positives	4	1	5
Negatives	5	26	31
Total	9	27	36

Table 2: Morphologic changes seen on X-rays of the spinal skeleton.

<table>
<tr><th>Study participants who exhibited morphological changes in the spinal vertebrae</th><th>Bone morphologic changes</th><th>Specific anatomic region</th><th>Radiography used</th></tr>
<tr><td rowspan="3">Females (n=3)</td><td>Osteoporosis (1x)</td><td>Sacrum-osteoporosis</td><td rowspan="3">Plain x-ray</td></tr>
<tr><td>Osteomalacia (1x)</td><td>Lumbar vertebrae-osteomalacia</td></tr>
<tr><td>Hyperostosis lesion (1x)</td><td>Cervical vertebrae-hyperostosis lesion</td></tr>
<tr><td rowspan="2">Males (n=2)</td><td>Osteomalacia (1x)</td><td rowspan="2">Lumbar vertebrae-osteomalacia and hyperostosis lesion</td><td rowspan="2">Plain x-ray</td></tr>
<tr><td>Hyperostosis lesion (1x)</td></tr>
</table>

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OD suggests that individuals with skeletal fluorosis are approximately 20.8 times more likely to have fractures than individuals not diagnosed with the condition. The 95% CI was also determined to be [1.904, 227.274]. This was the range in which the researcher could determine the true effect with 95% confidence. This was the case in this study.

Discussion

Fluoride is a naturally occurring mineral found in excessive amounts in many parts of the world, such as groundwater, the workplace, and fallout [9,23]. As a result, residents exposed to it can develop health problems. In some cases, even excessive tea consumption can lead to fluoride poisoning, so dietary fluoride intake should also be considered [24]. The upper limit for drinking water, 1.5 mg/l fluoride, was set by the WHO in 2004 and adopted by the EU in Directive 98/83/EC and the German guidelines [25]. However, it is reported that even in industrialized countries, well over 7 million people are regularly exposed to water containing 2 to 10 mg/l of fluoride, exceeding this limit. Dental and skeletal fluorosis, identified on several continents, are the most commonly cited health problems. Radiological signs and symptoms of skeletal fluorosis have been reported to occur at chronic fluoride intakes of 4 mg/l and above [26,27]. This presumed threshold is based on epidemiologic studies in the United States that found no increase in radiographic bone density in individuals who drank water containing less than four mg/l of fluoride [28-30]. Skeletal fluorosis is described in several stages, including two preclinical, asymptomatic stages characterized by a mild, radiographically detectable increase in bone mass; an early symptomatic stage characterized by intermittent joint pain and stiffness and osteosclerosis of the pelvis and spine; and a second clinical-stage associated with chronic joint pain, arthritic symptoms, and other signs of skeletal fluorosis [31-33]. Adult bone fractures in the Ethiopian Rift Valley correlate with clinical signs of osteoporosis, osteomalacia, and hyperostosis [31-34]. In this study, all patients with skeletal fluorosis diagnosed radiologically were from the towns of Samiberta (n = 2), Wonji-Shoa (n = 2), and Gura (n = 1), which are known for their high fluoride levels in drinking water.

Similarly, Helte et al. [35] demonstrated the association between skeletal fluorosis and the risk of fractures in their cohort of postmenopausal women. According to the research team, fluoride exposure was positively associated with the incidence of hip fractures in the postmenopausal women who participated in their follow-up study. Finally, they concluded that high consumption of drinking water with a fluoride concentration of ~1mg/L~1mg/ may increase both BMD and skeletal fragility in older women. Chemical analysis of a small number of bone and tooth samples confirmed the presence of high fluoride concentrations. The extent of dental fluorosis is comparable to water containing 1-2 ppm of naturally occurring fluoride. However, the prevalence of hyperostosis lesions appears to be higher than expected, for which there are two possible explanations: the inability to distinguish between skeletal fluorosis and diffuse idiopathic skeletal hyperostosis on partially or less affected skeletons, and the presence of risk factors for skeletal fluorosis on the island [22,36].

In another study, Nelson et al. [37] found abnormal bony changes, including osteosclerosis, a high frequency of fractures, and dental abnormalities among the studied population in their first report of skeletal fluorosis from archaeologically recovered human remains from North America. The osteosclerotic changes, along with the naturally high fluoride content of west-central Illinois soil and water, suggested the presence of skeletal fluorosis. A study by Joshi et al. [38] also supports the findings of the current study. In their paper published in the Journal of Osteoporosis International, the researchers described the case of a 53-year-old woman who presented with a metatarsal fracture and was found to have a Bone Mineral Density (BMD) T-score of +11 in the lumbar spine and +7.6 in the hip. Subsequent investigation revealed very high serum, urine, and tissue fluoride levels, associated with excessive tea and toothpaste consumption. In summary, it has shown that chronic environmental fluoride exposure (i) may lead to skeletal fluorosis that presents with increased radiolucency due to a reduction in trabecular and cortical bone, (ii) can cause fragility fractures, at least in sheep, at similar fluoride concentrations to those to which many people worldwide are regularly exposed, (iii) is highly critical when combined with a concurrent calcium deficit and (iv) that the prevalence of human skeletal fluorosis primarily due to groundwater exposure should be reviewed in many areas of the world as low bone mass and absence of osteosclerosis on X-rays does not exclude the diagnosis of skeletal fluorosis [39-44].

Conclusion

The current study shows that excessive fluoride intake leads to skeletal fluorosis and increases the risk of bone fractures. The sclerotic bone changes seen on the X-rays of the diagnosed subjects suggest that chronic fluoride toxicity affects the density of spinal bones. This appears vital in predicting surgical outcomes in orthopedics, neurology, and other related surgical disciplines. Therefore, surgeons should exercise due diligence in treating cases with skeletal fluorosis to ensure the best possible treatment and avoid potential complications. Radiologists should also be familiar with the findings of plain radiographs, Computed Tomography (CT) scans and Magnetic Resonance Imaging (MRI) scans in chronic conditions such as skeletal fluorosis to provide the best possible medical care. In general, policymakers

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and clinicians should collaborate to develop comprehensive guidelines that specifically focus on the diagnosis, management, and treatment options for skeletal fluorosis, with particular emphasis on the prevention and treatment of fractures associated with high tissue fluoride concentrations. It is also important to pay sufficient attention to the condition so that further research and effective preventive measures can be implemented.

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