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| RESEARCH ARTICLE

Effect of Fluoride on Bone Tissues: A Review Article

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| ABSTRACT
The regular functioning of the skeletal system during bone growth, remodeling & even in broken bone healing, as well as maintaining the calcium-phosphorus balance, therefore, regarded bone remodeling was of great importance. The properties of tissues and bone metabolism are affected by trace elements since bones are metabolically active organs. Trace elements act indirectly by regulating the metabolism of major mineral minerals in bones, or directly by influencing the activity or proliferation of osteoclasts or becoming part of the bone mineral matrix. This article discusses the concentration of fluorine and its effect on bone tissue.

| KEYWORDS
Fluorine, bone tissues, fluorosis

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1. Introduction
Fluoride "F" is the most reactive ionic compound derived from fluorine and is among 13th most plentiful elements, constituting about (0.06%–0.09%) of the Earth's crust (Singh et al., 2018).

Because of its presence worldwide, it significantly affects public health, having a useful effect on teeth at low concentrations and leading to many harmful effects at high concentrations or when exposed to excessive low concentrations (Everett, 2011).

All natural geological sources and human activities from which fluoride is formed lead to significant environmental health risks. People in most countries are exposed to fluoride, so there is a global interest in research on this element. Skeletal fluoride poisoning occurs due to strong and irreversible incorporation into deep bone chambers, leading to increased bone mass & density and joint hypertrophy. (Kabir *et al*,2020).

The concentrations of Fluoride up to (1 mg/L^{-1}) are useful in the prevention of dental caries & depending on the degree & duration of exposure, the harmful effect ranges from mild dental fluorosis to severe dental fluorosis, with most people being exposed to fluoride poisoning from drinking water at concentrations exceed the WHO guidelines of (1.5) mg/L (Gupta & Ayub , 2016). Therefore, people with fluorosis suffer from no relief of pain or symptoms because they are not diagnosed with fluorosis or treated with medications for other conditions (Kumar *et al.*, 2016).

Numerous sources of fluoride exposure

It was believed that humans were exposed to fluoride only by drinking water, but different studies have suggested else, Fluoride also enters the human body from other sources around it, including through food, cosmetics, and aerosols (Chowdhury et al., 2019; Kumar et al., 2020 ;Maity et al., 2021). However, the most common cases of excessive exposure to fluoride are in drinking water. (Abouleish, 2016).

There are other ways of exposure to fluoride, which depend on the type of food consumed by the person, as it is found in beverages, vegetables, and grains grown on agricultural grounds, but in small quantities (Kabir *et al*., 2020).

Some foods contain high amounts of fluoride concentration, as shown in Table 1. These are grow in the soil and absorb it easily. These high amounts depend on the concentration of fluoride in soil, fertilizers, pesticides, and water used to grow these products, and the leakage of industrial waste containing a relatively high concentration of this element into the surrounding areas. Tea also contains certain amounts of fluoride and is considered a source of exposure as well (Peng *et al*., 2021).

Infants, The usual diet and fluoride supplements can expose them to large amounts of fluoride, so care must be taken when choosing the appropriate supplements for them because this is an important stage for healthy bone and brain development (Viswanathan, 2018).

Industrial and agricultural workers are exposed to fluoride through their work. In addition, burning coal increases the probability of fluoride poisoning (He *et al*., 2020). The ionized form of (F^-) is less reactive and cannot cause significant harm to humans. (Jha *et al*., 2011). Properly using dental products and n't accidentally swallowing them such as toothpaste and mouthwash, has led to very few reported cases of fluorosis. It has been reported that pesticides and fertilizers contain high amounts of fluoride and are, therefore a means of human exposure to it. Currently, these products are prohibited & do not take into account human exposure to (F^-) (Gan *et al*., 2021; Kabir *et al*., 2020). Drinking water is a major health effect caused by fluoride through its presence in this water, i.e. it is the most common source of total daily fluoride intake among other sources.

Table 1: Some examples of foodstuffs that contain high concentrations of fluoride (Yadav et al.,2019).

Food stuff	Fluoride concentration (ppm)
Cow milk	1.73–6.87
Buffalo milk	3.32–6.85
Fermented milk products	1.76–93.68
Wheat	0.51–14.03
Rice	0.51–5.52
Maize	5.6
Bajra	2.76–3.84
Soybean	4.0
Peas	10.77
Red gram	2.34–4.84
Bengal gram	3.84–4.84
Grape	0.84–1.74
Apple	1.05–2.20
Spinach	9.87–29.15
Cabbage	4.25–11.30
Lettuce	5.7
Green tea leaf	72.62–89.02

2. Effects on bone tissues

Bone tissue consists of (5%-10%) water, (50%-70%) hydroxyapatite, (20%-40%) organic components including (type I collagen), & (10%) non-collagenous proteins involved in bone mineralization (Osterhoff *et al*.,2016).

Based on the porosity and microstructure of bones, they can be classified into two types: compact bone, which is dense bone tissue surrounding the medullary cavity or bone marrow, & spongy bone, which is a dispersed structure in bone marrow, the skeleton of an adult consists (80%) compact bone & (20%) spongy bone, the entire bone structure is filled with blood vessels. (Kini & Nandeesh, 2012).

Bone is constantly being remodeled by alternating absorption and accumulation. Bones are constantly being remodeled, and the balance between these two elements and mechanical and hormonal stimuli is regulated to preserve bone structure. Any imbalance in this balance leads to diseases characterized by low bone density, known as (osteoporosis). (Vidaud et al.,2012).

The modification of bone growth and metabolism is due to the presence of some trace elements as I, Zn, Cu, Ca, P, and Mg. Any deficiency or increased intake of these elements is a risk factor for osteoporosis (Wang et al.,2015; Wang et al.,2020).

The elements interact with the main enzymes and regulate the processes of absorption and cellular formation by incorporating them into the bone matrix. Therefore, these elements have a great impact on bone health. (Gaffney,2019).

Flore, a trace element found in the environment as, form fluoride, essential for humans & widely spread in (soil, rocks, & water) that's mean it's found anywhere in world, fluoride in the environment accumulates as a result of volcanic eruptions, mineral melting, and even human activities (Srivastava & Flora, 2020; Qin *et al*.,2023; Hu *et al*.,2024).

This element tends to accumulate in the bones in large quantities due to its strong affinity with the bones (Veneri *et al*.,2023).

The concentration of the trace element is closely linked to bone development. It promotes the formation of the skeleton when consumed in sufficient quantities and within the permissible limit. Excess accumulation of fluoride leads to skeletal fluorosis (Wang *et al*.,2024; Yu *et al*.,2024; Wu *et al*.,2022).

Skeletal fluorosis is a metabolic disease that commonly affects the joints. Symptoms include diffuse bone sclerosis, skeletal pain, calcification of connective tissue & stiffness of the bone joints. This disease is associated with a disturbance in bone metabolism through an imbalance between bone formation by Osteocytes & bone resorption by Osteoclasts (Park *et al*.,2024; Li *et al*.,2024).

Excess fluoride activates caspase 3, leading to osteoclast apoptosis, an imbalance in bone remodeling &various bone diseases. Excessive osteoclast resorption leads to osteoporosis and autoimmune disease (Bar-Shavit, 2007; Tsukasaki *et al*., 2020).

Bone resorption by Osteoclasts is the main process for normal bone remodeling, so when fluoride is taken in reasonable amounts, it promotes osteoclast proliferation & increased bone mass, alkaline phosphatase, Bone Morphogenetic Protein (BMP) & Glas A levels in the bones (Junrui ET AL., 2016; Tsukasaki & Takayanagi, 2019).

3. **Acceptable & optimal fluoride Intake**

The daily need for the human body fluorine compounds depends mainly on age (Jańczuk et al., 2014).

It should not exceed on average for children nearly (1.2) mg/day, (4.2) mg/day for adult men, & nearly (3.6) mg/day for women. Moreover, others have determined the daily requirement which ranges between (0.01 - 3.0) mg for infants & adults according to age, respectively, as shown in Table 2(Olczak et al.,2016).

Table 2: optimal & acceptable fluoride compounds for the Human body's daily requirements

Age	0–6 months	6–12 months	1–3 years	4–8 years	9–13 years	14–18 years
Recommended Intake of Fluoride mg/day	0.01–0.7	0.5–0.9	0.7–1.3	1.0–2.2	2.0–2.8	3.0–3.6

4. Conclusion

Fluoride is an element that has positive effects on the functioning of living organisms & the appropriate or permissible doses are known , documented & scientifically proven, so the health consequences must be taken into account when consuming products containing fluoride in excessive quantities. These consequences are represented by fluoride poisoning and can damage the integrity of the bones.

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References

[1] Veneri, F., Iamandii, I., Vinceti, M., Birnbaum, L. S., Generali, L., Consolo, U., & Filippini, T. (2023). Fluoride exposure and skeletal fluorosis: a systematic review and dose-response meta-analysis. *Current Environmental Health Reports*, *10*(4), 417-441.

[2] Wang, T., Lv, M., Zhang, Y., Gao, Y., Cai, Z., Zhang, Y., ... & Shang, F. (2024). TDDFT Study on the ESIPT Properties of 2-(2′-Hydroxyphenyl)-Benzothiazole and Sensing Mechanism of a Derived Fluorescent Probe for Fluoride Ion. *Molecules*, *29*(7), 1541.

[3] Yu, F. F., Yu, S. Y., Duan, L. Z., Yang, S., Hou, X. B., Du, Y. H., ... & Ba, Y. (2024). Proteomics Sequencing Reveals the Role of TGF-β Signaling Pathway in the Peripheral Blood of Offspring Rats Exposed to Fluoride. *Biological Trace Element Research*, *202*(5), 2100-2110.

[4] Wu, S., Wang, Y., Iqbal, M., Mehmood, K., Li, Y., Tang, Z., & Zhang, H. (2022). Challenges of fluoride pollution in environment: mechanisms and pathological significance of toxicity–a review. *Environmental Pollution*, *304*, 119241.

[5] Park, Y. A., Plehwe, W. E., Varatharajah, K., Hale, S., Christie, M., & Yates, C. J. (2024). Skeletal fluorosis secondary to methoxyflurane use for chronic pain. *JBMR plus*, *8*(5), ziae032.

[6] Li, Y., Yang, F., Liu, J., Jiang, M., Yu, Y., Zhou, Q., ... & Zhou, L. (2024). Protective effects of sodium butyrate on fluorosis in rats by regulating bone homeostasis and serum metabolism. *Ecotoxicology and Environmental Safety*, *276*, 116284.

[7] Junrui, P., Bingyun, L., Yanhui, G., Xu, J., Darko, G. M., & Dianjun, S. (2016). Relationship between fluoride exposure and osteoclast markers during RANKL-induced osteoclast differentiation. *Environmental toxicology and pharmacology*, *46*, 241-245.

[8] Bar-Shavit, Z. (2007). The osteoclast: a multinucleated, hematopoietic-origin, bone-resorbing osteoimmune cell. *Journal of cellular biochemistry*, *102*(5), 1130-1139.

[9] Tsukasaki, M., & Takayanagi, H. (2019). Osteoimmunology: evolving concepts in bone–immune interactions in health and disease. *Nature Reviews Immunology*, *19*(10), 626-642.

[10] Tsukasaki, M., Huynh, N. C. N., Okamoto, K., Muro, R., Terashima, A., Kurikawa, Y., ... & Takayanagi, H. (2020). Stepwise cell fate decision pathways during osteoclastogenesis at single-cell resolution. *Nature metabolism*, *2*(12), 1382-1390.

[11] Wang, Y., Li, A., Mehmood, K., Hussain, R., Abbas, R. Z., Javed, M. T., ... & Zhang, H. (2021). Long-term exposure to the fluoride blocks the development of chondrocytes in the ducks: the molecular mechanism of fluoride regulating autophagy and apoptosis. *Ecotoxicology and environmental safety*, *217*, 112225.

[12] Osterhoff, G., Morgan, E. F., Shefelbine, S. J., Karim, L., McNamara, L. M., & Augat, P. (2016). Bone mechanical properties and changes with osteoporosis. *Injury*, *47*, S11-S20.

[13] Kini, U., & Nandeesh, B. N. (2012). Physiology of bone formation, remodeling, and metabolism. *Radionuclide and hybrid bone imaging*, 29-57.

[14] Vidaud, C., Bourgeois, D., & Meyer, D. (2012). Bone as target organ for metals: the case of f-elements. *Chemical research in toxicology*, *25*(6), 1161-1175.

[15] Wang, L., Yu, H., Yang, G., Zhang, Y., Wang, W., Su, T., ... & Ma, Y. (2015). Correlation between bone mineral density and serum trace element contents of elderly males in Beijing urban area. *International journal of clinical and experimental medicine*, *8*(10), 19250.

[16] Wang, N., Xie, D., Wu, J., Wu, Z., He, H., Yang, Z., ... & Wang, Y. (2020). Selenium and bone health: a protocol for a systematic review and meta-analysis. *BMJ open*, *10*(10), e036612.

[17] Gaffney-Stomberg, E. (2019). The impact of trace minerals on bone metabolism. *Biological trace element research*, *188*(1), 26-34.

[18] Chowdhury, A., Adak, M., Mukherjee, A., Dhak, P., Khatun, J., Dhak, D., (2019). A critical review on geochemical and geological aspects of fluoride belts, fluorosis and natural materials and other sources for alternatives to fluoride exposure. J. Hydrol. 574, 333–359. https://doi.org/10.1016/j.jhydrol.2019.04.033.

[19] Kumar, M., Goswami, R., Patel, A.K., Srivastava, M., Das, N., (2020). Scenario, perspectives and mechanism of arsenic and fluoride co-occurrence in the groundwater: a review. Chemosphere 249, 126126. https://doi.org/10.1016/j. chemosphere.2020.126126.

[20] Maity, J., Vithanage, M., Kumar, M., Ghosh, A., Mohan, D., Ahmad, A., Bhattacharya, P., (2021). Seven 21st century challenges of arsenic-fluoride contamination and remediation. Groundwater Sustainable Dev. 12, 100538. https://doi.org/10.1016/j. gsd.2020.100538.

[21] Abouleish, M.Y.Z., (2016). Evaluation of fluoride levels in bottled water and their contribution to health and teeth problems in the United Arab Emirates. Saudi Dent. J. 28, 194–202. https://doi.org/10.1016/j.sdentj.2016.08.002.

[22] Kabir, H., Gupta, A.K., Tripathy, S., (2020). Fluoride and human health: systematic appraisal of sources, exposures, metabolism, and toxicity. Crit. Rev. Environ. Sci. Technol. 50, 1116–1193. https://doi.org/10.1080/10643389.2019.1647028.

[23] Peng, C.Y., Xu, X.F., Ren, Y.F., Niu, H.L., Yang, Y.Q., Hou, R.Y., Wan, X.C., Cai, H.M., (2021). Fluoride absorption, transportation and tolerance mechanism in Camellia sinensis, and its bioavailability and health risk assessment: a systematic review. J. Sci. Food Agric. 101, 379–387. https://doi.org/10.1002/jsfa.10640.

[24] Viswanathan, G., (2018). Contribution of infant formula and tea on daily fluoride intake and prevalence of fluorosis among infants and children. Food Qual. 339–363. https://doi.org/10.1016/B978-0-12-811442-1.00011-0.

[25] He, X., Li, P., Ji, Y., Wang, Y., Su, Z., Elumalai, V.,(2020). Groundwater arsenic and fluoride and associated arsenicosis and fluorosis in China: occurrence, distribution and management. Exposure Health 12, 355–368. https://doi.org/10.1007/s12403- 020-00347-8.

[26] Jha, S.K., Mishra, V.K., Sharma, D.K., Damodaran, T.,(2011). Fluoride in the environment and its metabolism in humans. Rev. Environ. Contam. Toxicol. 211, 121–142. https://doi.org/10.1007/978-1-4419-8011-3_4.

[27] Gan, C.D., Gan, Z.W., Cui, S.F., Fan, R.J., Fu, Y.Z., Peng, M.Y., Yang, J.Y.,(2021). Agricultural activities impact on soil and sediment fluorine and perfluorinated compounds in an endemic fluorosis area. Sci. Total Environ. 771, 144809. https:// doi.org/10.1016/j.scitotenv.2020.144809.

[28] Jańczuk, Z., Kaczmarek, U., Lipski, M., & Arabska-Przedpełska, B. (2014). Stomatologia zachowawcza z endodoncją, Wydawnictwo Lekarskie PZWL.

[29] Olczak-Kowalczyk, D., Borysewicz-Lewicka, M., Adamowicz-Klepalska, B., Jackowska, T., & Kaczmarek, U. (2016). Consensus statement of Polish experts on individual caries prevention with fluoride in children and adolescents. *Nowa Stomatologia*.

[30] Yadav, K. K., Kumar, S., Pham, Q. B., Gupta, N., Rezania, S., Kamyab, H., ... & Cho, J. (2019). Fluoride contamination, health problems and remediation methods in Asian groundwater: A comprehensive review. *Ecotoxicology and environmental safety*, *182*, 109362.

[31] Kabir, H., Gupta, A. K., & Tripathy, S. (2020). Fluoride and human health: Systematic appraisal of sources, exposures, metabolism, and toxicity. *Critical Reviews in Environmental Science and Technology*, *50*(11), 1116-1193.

[32] Singh, G., Kumari, B., & Sinam, G. (2018). Fluoride distribution and contamination in the water, soil and plants continuum and its remedial technologies, an Indian perspective – A review. Environmental Pollution, 239, 95–108.

[33] Everett, E. T. (2011). Fluoride's effects on the formation of teeth and bones, and the influence of genetics. Journal of Dental Research, 90(5), 552–560. doi:10.1177/ 0022034510384626.

[34] Gupta, A. K., & Ayoob, S. (2016). Fluoride in drinking water: status, issues and solutions. New York, NY: CRC Press.

[35] Kumar, M., Das, A., Das, N., Goswami, R., & Singh, U. K. (2016). Co-occurrence perspective of arsenic and fluoride in the groundwater of Diphu, Assam, Northeastern India. Chemosphere, 150, 227–238. doi:10.1016/j.chemosphere.2016.02.019.

[36] Srivastava, S., & Flora, S. J. S. (2020). Fluoride in drinking water and skeletal fluorosis: a review of the global impact. *Current environmental health reports*, *7*, 140-146.

[37] Qin, M., Gao, Y., Zhang, M., Wu, J., Liu, Y., Jiang, Y., ... & Gao, Y. (2023). Association between ADAMTS14_rs4747096 gene polymorphism and bone mineral density of Chinese Han population residing in fluorine exposed areas in ShanXi Province, China. *Environmental Science and Pollution Research*, *30*(48), 106059-106067.

[38] Hu, Y., Li, Y., Li, M., Zhao, T., Zhang, W., Wang, Y., ... & Wang, J. (2024). Calcium supplementation attenuates fluoride-induced bone injury via PINK1/Parkin-mediated mitophagy and mitochondrial apoptosis in mice. *Journal of Hazardous Materials*, *465*, 133411.