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ALUMINIUM AND FLUORINE IN DRINKING WATER AS RISK FACTORS FOR HUMAN HEALTH

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ABSTRACT
Drinking water potentially affects a variety of diseases, and their relationship to environmental risk factors is an emerging area that still needs to be clarified. Studies have reported that aluminum and fluoride, elements naturally found in water, have an adverse effect on human health with increasing concentration in drinking water, which is affected by environmental aspects. High aluminum levels in drinking water can cause dementia. Many studies have found an association between the amount of aluminum in drinking water and an increased risk of Alzheimer's. The absorption of aluminum and fluoride is thought to have a positive relationship and together have greater bioavailability. The health effects of aluminum and fluoride can vary depending on the source of the water, the duration of exposure, and the body's detox system. It is crucial to control the content of drinking water in order for humans' vital activities to be healthy. In this review, the general properties and interactions of aluminum and fluoride, which are important for human health, will be discussed. Considering the important toxic effects of these chemicals, the relationship between diseases and health problems will be evaluated.
Keywords: Alzheimer, dementia, drinking water, human health, aluminum, flouride

İNSAN SAĞLIĞI İÇİN RİSK FAKTÖRLERİ OLARAK İÇME SULARINDA ALÜMİNYUM VE FLOR

ÖZ
Su kaynakları ve içme suları çeşitli hastalıkları potansiyel olarak etkilemektedir ve çevresel risk faktörleriyle olan ilişkisi halen aydınlatılması gereken gelişmekte olan bir alandır. Çeşitli araştırmalar, suda doğal olarak bulunan elementler olan alüminyum ve florürün, çevresel yönlerden etkilenen içme suyunda artan konsantrasyonla insan sağlığı üzerinde olumsuz bir etki gösterdiğini bildirmiştir. İçme sularındaki yüksek alüminyum seviyelerinin demansa neden olabileceği düşünülmektedir. Birçok çalışma, içme suyundaki alüminyum miktarı ile artan Alzheimer riski arasında bir ilişki bulmuştur. Ayrıca, alüminyum ve florürün absorpsiyonun pozitif bir ilişkiye sahip olduğu ve birlikte daha fazla biyoyararlanıma sahip olduğu düşünülmektedir. Alüminyum ve florürün sağlık üzerindeki etkileri suyun kaynağına, maruz kalma süresine ve vücudun detoks sistemine göre değişiklik gösterebilir.

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İnsanda yaşamsal faaliyetlerin sağlıklı olması için, içilen içme suyu içeriğinin kontrolünün sağlanması kritik öneme sahiptir. Bu derlemede alüminyum ve florürün insan sağlığı için önemli olan genel özellikleri ve etkileşimleri tartışılacaktır. Bu kimyasalların önemli toksik etkileri göz önünde bulundurularak hastalıklar ve sağlık sorunları arasındaki ilişki değerlendirilecektir.
Anahtar kelimeler: Alzheimer, demans, içme suyu, insan sağlığı, alüminyum, florür

INTRODUCTION

Since the water quality standards recommended by WHO include macro elements and the synergistic effects of trace metals and anions are not taken into account, studies on the effects of these factors on human health are carried out meticulously. The presence of hardness trace elements and synergistic elements should be considered more carefully in water standards (Wasana et al., 2017). In drinking water, there are minerals and elements such as calcium, magnesium, copper, magnesium, iron, fluorine, potassium, lithium, zinc, iodine, selenium, chlorine, bicarbonate, sulfate, and aluminum (Casado et al., 2015). Aluminum (Al^{3+} is the 3rd most found element and is found naturally in water. Only 0.1% of Al^{3+} in food is absorbed from the gastrointestinal tract and is bioavailable (Klotz et al., 2017). Although the source of Al^{3+} in the daily diet is food, water is also one of the minor sources. Al^{3+} absorption in water reaches 0.3%. It has been found that exposure to Al^{3+} and daily intake differ in studies conducted. It is ranged from 1.6 to 13 mg of Al^{3+} per day, this corresponds to 0.2 to 1.5 mg/kg body weight (VW) week for a 60 kg adult (EFSA, 2008). Despite its ubiquitous abundance, Al^{3+} has no crucial biological functions in the human body (Dey and Singh, 2022). It is important in drinking water as the chemical form of Al^{3+} changes its solubility and toxicity. One study showed that the pre-hydrolyzed coagulants changed the amount of Al^{3+} in the water. Al^{3+} compounds show low solubility in the pH range of 6-8, therefore Al^{3+} concentrations in natural source waters are very low and are in the range of 60 to 300 μg/dm^3 (Krupińska, 2020).

Iron affects the absorption of Al^{3+}. Therefore, it has been shown that Al^{3+} absorption is more significant at low iron levels. Since iron can compete with Al^{3+} for binding to transferrin, iron stores needed may reduce the intestinal absorption of Al^{3+}. Like iron, calcium status also affects Al^{3+} absorption and accumulation. Studies have shown that dietary calcium deficiency increases Al^{3+} absorption levels (İnan and Ayaz, 2018).

Aluminum and fluorine in drinking water and Alzheimer's disease

50 million people in the world have Alzheimer's disease, which can result in death 3-9 years after diagnosis, which is indicated and categorized as cognition, memory, and other cognitive, and this burden is a serious global problem (Chen et al., 2021; Sarmadi et al., 2021). Alzheimer's disease is a disease that is increasingly declining with dementia due to the aging world population worldwide. Two potential pathways are known in the formation of this neurodegenerative disease: β-amyloid plaque deposition in the brain and neurofibrillary tangles of hyperphosphorylated tau. (Weller and Budson, 2018). Chronic excess Al^{3+} intake or intravenous exposure increases oxidative stress, and in vivo studies have been found to increase amyloid beta levels (Mc Donald et al., 2021). Alzheimer's disease is a progressive neurological illness that affects the immune system, neurotransmitter system, and vascular system function (Papadimitriou et al., 2018). Aging, hereditary factors, the existence of the apolipoprotein E ε4 allele, high cholesterol, type 2 diabetes, elevated homocysteine levels in plasma, obesity, and depression are all risk factors for Alzheimer's disease (Korabecny et al., 2014). An overview of the pathophysiology of Alzheimer's disease, risk factors for the disease, and treatment approaches can be seen in Figure 1.

There are 2 types of Al^{3+} formation in potable water. Dissolved Al^{3+} passes from the bedrock to the water by rain and mechanical dissolution. Although the solubility of Al^{3+} in water is affected by a variety of circumstances, it can rise with a change in pH value (Farhat et al., 2020). Al^{3+}, a neurotoxic metal, has been shown in studies to take a role in a diversity of diseases, including

Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), encephalopathy, and metabolic bone abnormalities, when it enters the bloodstream and dissolves. (Letzel et al., 2020). At near-neutral pH values, Al^{3+} concentrations are usually much less than 0.1 mg/L. In countries such as Norway, this amount may increase as a result of acid rain. Al^{3+} is widely used in water treatment as a coagulant to remove residual particles and improve the color of the water (Flaten, 2001). A meta-analysis study involving 10567 persons looked at how chronic Al^{3+} intake influences the risk of Alzheimer's disease. Chronic Al^{3+} exposure elevated the possibility of Alzheimer's disease in persons by 71 percent, according to data acquired as a consequence of the study (Wang et al., 2016).

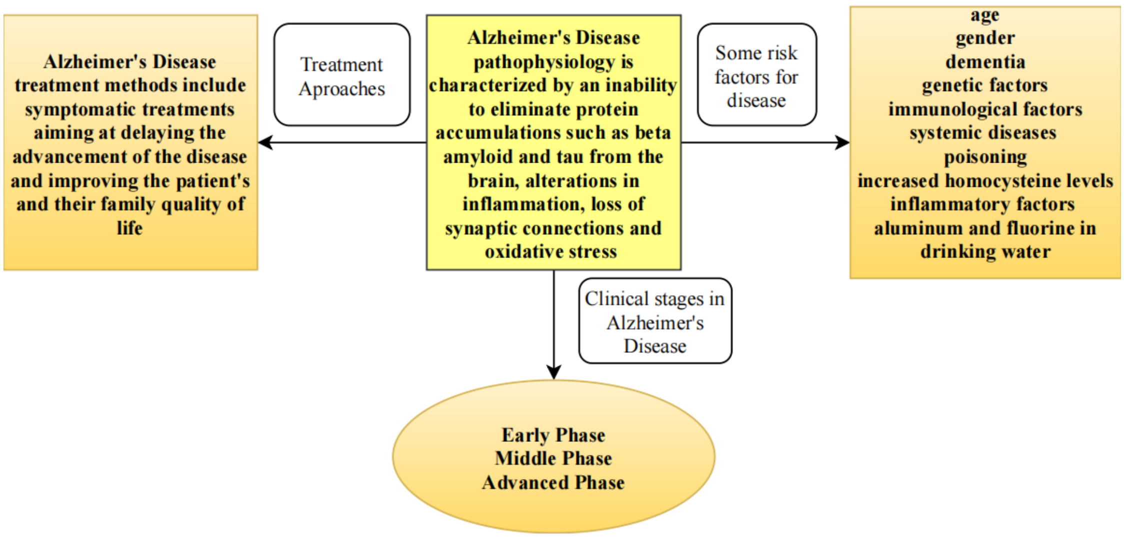

Figure 1. An overview of the pathophysiology of Alzheimer's disease, risk factors for the disease, and treatment approaches (Ahmed Nel. et al., 2016; Ateş, et al., 2016; Salari and Bagheri, 2016; Bobuş et al., 2022)

The safe acceptance level of Al^{3+} in potable water is 200 ppb, which is accepted by the US Environmental Protection Agency (USEPA), WHO (World Health Organization), and European Union (EU). The legally determined level of total Al^{3+} concentration in purified water in America, and Japan is 0.05-0.2 mg/l, 0,1 mg/l. 0.1 mg/l, 0.1 mg/l, and 0.2 mg/l, Sweden, Canada, and China, respectively (Wasana et al., 2017). In the research initiated as a result of increasing studies on the effects of Al intake through potable water in the Langat River Basin in Malaysia; To determine Al^{3+} concentrations by Inductively Coupled Plasma Mass Spectrometry (ICP-MS), water samples from the basin water were examined between 2015 and 2016. It has been stated that the doses of $Al_2(SO_4)_3$ used in water disinfection are very important to protect health (Ahmed et al., 2019; Khairul Zaman et al., 2021).

There are studies, albeit with, a small sample, that Al^{3+} in potable water is associated with Alzheimer's disease. According to the largest cohort study on this subject published in Canada in 2021, Exposure to Al^{3+} in potable water was not significantly associated with an increased risk of Alzheimer's disease. The positive upward trend observed in the subcohort genotyped for apolipoprotein E warrants further investigation (Van Dyke et al., 2021). During the 15-year follow-up period of the Paquid cohort, the relationship of Al^{3+} in potable water with Alzheimer's was evaluated with Mini-Mental State Examination. This analysis suggested that cumulative cognitive decline may be associated with high concentrations of Al^{3+} (>0.1 mg/l) or low concentrations of silica (<11.25 mg/l) in potable water. Another remarkable result of the study was the positive correlation between Al^{3+}

and potable water pH lower than 7.3 (Rondeau et al., 2009). Drinking water distribution systems are also important for Al^{3+} dissolving and also pH fluctuation in 7.8–8.4, which can affect too (He et al., 2021). It has been shown that Al^{3+} exposure accumulated over 10 years increases the risk of Alzheimer's up to 2.5 times. Public health studies have indicated that there may be a relationship between the water consumed and Alzheimer's. In Ontario, it is estimated that 19% of the population was exposed to residual [Al^{3+}] greater than or equal to 100 microgram/L (McLachlan et al., 1996). In a study, drinking water samples taken from a city near the Senegal river did not exceed the Al^{3+} values determined by the World Health Organization (between 0.1 mg/L and 0.2 mg/L) (Dick et al., 2021). In a survey of eighty-eight country districts within England and Wales, the possibility of Alzheimer's disease was 1.5 times higher in areas where the mean Al^{3+} concentration exceeded 0.11 mg/l than in districts where concentrations were less than 0 to 0,1 mg/L (Martyn et al., 1989).

Fluoride (F^-) impacts cellular energy metabolism, the formation of inflammatory factors, and neurotransmitter metabolism when it reaches the brain (Strunecka and Strunecky, 2020). In a study conducted in Scotland from 2005-2012 by the Drinking Water Quality Regulator for Scotland, it was found that F^- and Al^{3+} work with a synergistic effect in potable water also F^- can change the absorption of Al^{3+} (Russ et al., 2020). F^- can create a negative effect on the central nervous system by raising oxidative stress as a result of this ion accumulating in the brain after crossing the blood-brain barrier and the cell plasma membrane (Cao et al., 2019).

Al^{3+} ion, when combined with F^-, obstructs the brain's aerobic metabolism and reduces the efficiency of acetylcholine, activating components involved in the formation of oxidative stress, and speeding up the onset of Alzheimer's disease (George et al., 2009; Jiang et al., 2022). Many studies have shown that fluoride/ aluminofluoride complexes (AlFx) might have a deleterious effect on the brain in animals. Neuronal and cerebrovascular problems, neurotoxic alterations due to oxidative stress, and a significant loss in learning capacity with the effect of fluorine and Al^{3+} ions were detected in animals drinking fluoridated water (Strunecka et al., 2019; Krause et al., 2020). Metals are prevented from entering the brain by a barrier that exists between the body and the brain. Several studies have demonstrated the significance of the interaction between F^- and Al^{3+} in breaking this barrier. In one study, researchers looked at how F^- and Al^{3+} alter neuronal morphology, lysosomal activity, and cell cycle activity. They discovered that these ions altered the enzymatic alkaline phosphatase activity via altering neural histomorphology. At the same time, they observed that inhibiting AChE activity and increasing cathepsin D and cyclin D expression in the brain exacerbated brain neurotoxicity and hastened the development of associated disorders (Ye et al., 2018; Mehany et al., 2022). Prolonged exposure to F^- and Al^{3+} ions is associated with neurological disorders. These ions can bind to proteins interacting with ions similar to them. Such undesirable interactions disrupt the normal biological function of target proteins. In a study, 19 proteins associated with neurodegenerative disorders and bound by these ions were found (Hasan et al., 2018). Endemic fluorosis caused by excessive intake of fluorine is a serious health problem worldwide. A small amount of F^- intake has health effects such as preventing dental caries and supporting bone formation. Excessive F^- also has negative effects on dental and bone health (Everett, 2011). 0.5-1.00 ppm daily intake of F^- has a beneficial effect on dental caries (Srivastava and Flora, 2020). A study investigating the mechanism of neurotoxicity formation of F^-, shows that excess F^- causes morphological changes in NADPH-d/NOS (nitric oxide synthase) positive neurons formed in the brain and increases nitric oxide (NO) synthesis (Bhatnagar et al., 2011). Since it is known that excessive intake of F^- causes neurotoxicity; In 2014, the amount of F^- in table water was investigated in 31 provinces of Iran (KheradPisheh et al., 2016). Studies have shown that F^- increases the absorption of Al^{3+} to cross the blood-brain barrier, thus causing neuronal damage by causing a decrease in neuronal density, and accumulating in the brain tissues, especially the cerebral cortex and hippocampus. In a study on rats; The reduced antioxidant capacity with neuronal degeneration was manifested by a higher malondialdehyde content in most brain tissues of rats, accompanied by decreased glutathione (GSH) content and a reduction in superoxide dismutase (SOD) activity (Kinawy, 2019). In a study on the effects of fluorine and Al^{3+} in potable water on the prefrontal cortex, they discovered that Al^{3+} F^-, which is generated by fluorine and Al^{3+} ions collected in the brain, caused excitotoxicity in the treatment group via oxidative stress. The study's findings are also consistent with the possibility that Al^{3+} and fluorine can induce neurological problems (Akinrinade et al., 2013). Long-term F^- exposure may accelerate neuropathological lesions and related diseases such as Alzheimer's that occur in amyloid precursor protein (APP) mice by increasing oxidative stress and inflammation in the brain, according to a study that examined the effects of low-dose F^- on the brains of mice carrying the APP/ presenilin 1(PS1) mutation (Cao, et al., 2019). In a study of 51 first-year children in Sichuan, southern China; It was found that the F^- concentrations in the morning urine were related to the F^- levels of the well water they consumed and caused neurotoxicity (Choi et al., 2015).

In a study conducted in East Azerbaijan to evaluate the relationship between non-cancer diseases and F^- amounts in potable water and to evaluate the results with ubiquitous standards and health risk assessment; It was observed that the average F^- concentration in potable water in all seasons varied between 0.19-0.65 and 0.18-0.62 mg/L respectively. The F^- concentration was below the standards in 80% of the samples taken for evaluation. The F^- amounts in the potable water of the cities evaluated were lower than the highest concentration calculated by the Galagan and Vermillion equations. Approximative daily fluoride (EDI) intakes for infants, children, teenagers, and adults are shown as 3.06, 2.15, 12, and 12.5 μg/kg/day, respectively (Ashrafi, et al., 2020). A recent study shows that F^- taken through potable water can significantly increase the blood pressure level and the risk of hypertension in the community. Further investigation of the potential cardiovascular disease-causing effects of excessive F^- intake is needed (Davoudi et al., 2021). According to the results of the study conducted in Iran on this issue in 2015. In the superior F^- area, compared to the low F^- area, hypertension, cause unknown was increased (Aghaei et al., 2015).

New studies are carried out to prevent the accumulation of Al^{3+}, iron, copper, and zinc ions in the brain according to their toxic accumulation and to reduce the incidence of Alzheimer's disease (Das et al., 2021).

Solutions and recommendations

The potable water quality includes physical, biological, and components. In the 2030 agenda for Sustainable Development, which is of importance to the whole world, Researchers explained the importance of access to hygienic, healthy, and safe water and the ways to ensure universal access to water (Gara et al., 2018).

Many methods are used to remove F^- and Al^{3+} from the water content. In a study evaluating the coagulant activity of Moringa oleifera seed and Hibiscus esculentus (okra) mucilage, Al^{3+} sulfate, and hydrofluoric acid; The effect of placing these coagulants in a fibrous thin film, as well as their effects on pH and concentration, was also evaluated. As a result of the evaluation; 79.9% Al^{3+} reduction and 91.7% F^- reduction in water were found (Lim et al., 2018). According to the results of another study; Al-alginate particles loaded with hydroxyapatites are good adsorbents. Inexpensive and efficient drinking can be used to reduce F^- concentration (Mılıvojenic et al., 2020).

Because superior F^- ion content in potable water can cause a variety of health concerns, it is critical to diminish F^- levels in water using defluoridation procedures such as membrane and the adsorption technique (such as reverse osmosis, dialysis, electro-dialysis, nanofiltration) and surface assimilation (Indermitte et al., 2014).

Prolonged exposure to F^- damages teeth and skeleton. Therefore, it is absolutory to develop low-cost, locally available, and environmentally safe adsorbents for the removal of excess F^- from contaminated water sources. Researchers have developed an adsorbent that removes fluorine from aqueous solutions (Akafu et al., 2019). Studies show that ozonation and chlorination reduce the amount of dissolved Al^{3+} in drinking water (Li et al., 2021). In future studies, new methods and ways that can be used to control the minerals in the water and to remove harmful substances that may pose a potential disease risk will be investigated.

CONCLUSION

Studies show that excessive intake of Al^{3+} and F^- causes Alzheimer's dementia and dental and skeletal diseases. In light of these studies in the literature, the content of drinking water examined in different countries; been has shown to contain high amounts of F^- and Al^{3+}.

According to the information acquired from many literature studies, Al^{3+} in drinking water reacts with fluorine to form the AlFx complex, which might cause neurotoxicity in the brain. As a result, prolonged exposure to these ions and oxidative stress caused by an increase in free radicals in the body may raise the chance of acquiring diseases such as dementia and Alzheimer's. As a result, in order to interact with these ions in drinking water, it is critical for people's health to perform the necessary water purification and to have these ions in drinking water at a rate that will not pose a health hazard.

It is important to control the content of drinking water, which is necessary for us to continue our vital activities, and to make it balanced and drinkable with various agents and adsorbents.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

This study is designed by Fatma Özsel Özcan Araç. A literature review and critical review of the article were carried out by Fatma Özsel Özcan Araç and Ozan Aldemir. All the authors were involved to wrote the manuscript.

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