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Preclinical and Epidemiological Musculoskeletal Evidence of Aluminium Toxicity: A Systematic Review

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Abstract

Musculoskeletal toxicity refers to the negative effects of medications or chemicals on the composition and/or functionality of the muscles, bones, and joints. Aluminium has been linked to serious health issues such as arthritis, fluorosis, and osteomalacia by altering the structure and/or function of the muscles, bones, and joints. This systematic review was carried out by consulting different databases (Cochrane Library, Medline, the Health Technology Assessment Database (HTA) databases, PubMed central, Biomed central, web of science core collection, and Database of Abstracts of Reviews of Effects (DARE)) using predefined search terms ("Health Risk'' OR ''Effects'' OR ''Risk'' OR "Problems" OR "Adverse Effect" AND 'Musculoskeletal" AND "Epidemiology", AND "Musculoskeletal Clinical Signs", OR "Pathology" AND "Aluminium Poisoning", OR "Preclinical effects of Aluminium". "Musculoskeletal") in order to investigate the preclinical and epidemiological musculoskeletal evidence of aluminium toxicity. Out of six hundred and twenty-one (621) articles identified, eleven (11) were selected based on the inclusion and exclusion criteria. From the study, it was found that the toxic effects of aluminium progress slowly and chronically, causing malformations, disabilities, and, in the most extreme cases, death. It was also found that exposure to aluminium toxicity could lead to neurotoxicity, osteomalacia, fluorosis, and arthritis. This study addressed issues related to the health effects of Al and with possible interventions.

Keywords: *Aluminium, Aluminium toxicity, Health effects, Epidemiology, Preclinical symptoms, Musculoskeletal*

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List of Abbreviations

$AlCl_3$ -Aluminium chloride	CAA- Cerebral amyloid angiopathy	LH- Luteinizing hormone
ALP- Alkaline phosphatase	DARE- Database of abstracts of reviews of effects	LVEF- Low left ventricular ejection fraction
AlP- Aluminium phosphide poisoning	DHA- Dihydroxyacetone	MeSH- Medical subject headings
ALT- Alanine aminotransferase	DNA- Deoxyribonucleic acid	MICU- Medical intensive care unit
ARDS- Acute respiratory distress syndrome.	FSH- Follicle stimulating hormone	PG- Protector and gamble
AST- Aspartate aminotransferase	HCl- Hydrochloric acid	RCT- Randomized controlled trials
	HTA- Health technology assessment database	

1. Introduction

Aluminum toxicity has reportedly occurred in several regions of the world, according to a recent World Health Organization release (2021). It is one of the widespread health issues affecting several organs. Both people and businesses use aluminum frequently on a daily basis. Pieces of equipment, structures, the transportation industry, and aerospace engineering all contain aluminum compound residues (Greger, 2017). Musculoskeletal toxicity refers to the negative effects of medications or chemicals on the composition and/or functionality (Koreti *et al.*, 2014).

With little side effects, employed in medicine as a vaccine adjuvant as a treatment for pathological hyperhidrosis (World Health Organization, 2021). It is crucial to comprehend how aluminum affects preclinical and epidemiological health, especially in groups at risk. Notably, there has been an increased emphasis on the occasionally uncritical public discourse regarding the neurotoxic and perhaps cancerous consequences of aluminum in recent years (Koreti *et al.*, 2014; Mehrpour*et al.*, 2017; Chugh *et al.*, 2019). First proof that aluminium in deodorants can genuinely cause breast cancer, for example, implies that a link has been established. As a result, the scientific question of how serious the risk of negative health effects from aluminium exposure really is arises.

Studies by Lantzy & MacKenzie (2019) and Chugh *et al.* (2019) observed that most healthy adults tolerate comparatively large repeated daily oral Al exposures (up to 3500–7200 mg/day from antacids and buffered aspirin) without any adverse effect, but that other people (notably pre-term infants, young children, and those with reduced kidney function) can be at serious risk for systemic Al intoxication even at much lower daily doses. Because Al gastrointestinal uptake varies from essentially non-detectable for hydrated Al silicates, to 0.1–0.3% for sodium Al phosphates in foods, to 0.2% for $AlCl_3$ to much higher values (> 2.0%) after ingestion of organic Al, exposures expressed as "total Al" are problematic for human health risk assessments (Koreti *et al.*, 2014; Chugh *et al.*, 2019).

Several reports have posited that humans and animals living in environments can be contaminated by industrial and municipal/ domestic wastes which contain high levels of Al (Rashediniaet *al.*, 2016; Lee, 2015; Mehrpour*et al.*, 2017). Numerous AL chemicals and processes are utilized daily by humans and these compounds includes, ammonium sulfate (ammonium alum) and Al silicate (Mehrpour*et al.*, 2017; Gupta, 2015).

Chugh *et al.* (2019) opined that clinical symptoms of poisoning due to aluminium are involved with the cardiovascular, gastrointestinal, nervous, and pulmonary systems. The most common clinical observation of AL poisoning are restlessness, irritability, dizziness, vertigo, tremors, diplopia, imbalance, cough, shortness of breath, abdominal colic, nausea, vomiting, in some cases black vomit, black stools, decreased cardiac output, irregular heartbeat, pulmonary edema, cyanosis, renal impairment, jaundice, enlarged liver and spleen, intestinal paralysis, seizure, and acute respiratory distress syndrome (Klotz, 2017). Tetany, cardiovascular arrhythmia, liver damage, bradycardia, metabolic acidosis, thrombocytopenia, and methemoglobinemia are signs of intoxication. Treatment for AL poisoning is only supportive treatment as there is no known antidote available against it (Lee, 2015; Mehrpour*et al.*, 2012; Klotz, 2017). Despite the several substances that can frequently expose humans to aluminium poisoning, poisoning-related deaths are on the increase (Klotz, 2017).

According to a study, Al's toxic effects can lead to oxidative stress, immune system changes, genotoxicity, pro-inflammatory effects, peptide denaturation or transformation, enzymatic dysfunction, metabolic derangement, amyloidogenesis, membrane perturbation, iron dyshomeostasis, apoptosis, necrosis, and dysplasia (Lantzy & MacKenzie, 2019). The following are likened to aluminium exposure Alzheimer's disease, dementia, sclerosis, autism, macrophagic myofasciitis, osteomalacia, oligospermia and infertility, hepatorenal disease, breast cancer and cyst, pancreatitis, pancreatic necrosis and diabetes mellitus (Lee, 2015; Mehrpour *et al.*, 2012). Another report opined that the impact of Aluminium in the brain which summed up to the conclusion that AL is unsafe to humans after the discovery of increased levels of Al in brain tissues of patients with encephalopathy following exposures to Al accumulation through dialysis (Rashedinia *et al.*, 2016; Bhalla & Singh, 2015).While many AL poisoning; there are few studies summarizing updates on the epidemiological data regarding the musculoskeletal preclinical and epidemiological health effects of aluminium. Therefore, the aim of this systematic study is to provide update on the preclinical and epidemiological musculoskeletal evidence of aluminium toxicity.

2. Methodology

To find evidence to inform this review, a thorough search of literature was carried out in Cochrane Library, Medline, the Health Technology Assessment Database (HTA) databases, PubMed central, Bio-med central, web of science core collection, Database of Abstracts of reviews of Effects (DARE) were searched to identify primary studies of in line with the study objectives. The purpose of this was to detect updated studies on the preclinical and epidemiological musculoskeletal evidence of aluminium toxicity. This provides a detailed discussion of the research perspective, studies selection process, data extraction, quality assessment and synthesis.

This study relies on information gathering from credible and legitimate sources to inform the possible musculoskeletal health effects of Aluminium using both preclinical and epidemiological evidences. In the level of evidence on research design, randomized controlled trials (RCTs) were considered to be the most reliable source of evidence presenting good internal validity in studies relating to effectiveness. Cross sectional studies, cohort studies, case control studies were included for this review on the possible musculoskeletal health effects of Aluminium using both preclinical and epidemiological evidences. Studies were excluded from this review if they were not addressing the primary research question on the possible musculoskeletal health effects of Aluminium using both preclinical and epidemiological evidences.

2.1 Identification of Eligible Studies

To gather evidence on the musculoskeletal health effects of Aluminium using both preclinical and epidemiological evidences, the following electronic databases were searched: Cochrane Library, Medline, Health Technology Assessment Database (HTA), Pub-Med central, Bio-med central, web of Science Core Collection.

These particular databases were chosen because they represent some of the most commonly used databases for identifying data related to the study and were also recommended for searching health professionals' studies.

Keywords and terms were developed. The search process was repeated for the review to identify recent studies published in the last few weeks.

2.2 Search Strategy

The search of electronic databases mentioned above was developed using suitable combinations of keywords. Search terms were used with appropriate Boolean operators. Each search domain was searched separately and Boolean operator 'OR' used to combine related search terms and synonyms within each search domain. The domains were then combined using Boolean operator 'AND'. The specifications of the electronic search involved controlled vocabulary e.g indexing terms used accordingly depending on the database in use. The proximity indicator (N) was used. The asterisk (*) as indicated by Aromataris and Riitano, (2014), was used for truncation to retrieve any alternative endings. Furthermore, wildcards such as question mark (?) and hash (#) were used to replaces one or no characters, or substitute one or more characters respectively, depending on the database functions. Finally, to ensure that only recent reviews were included, publications from the year 2009 to date. Furthermore, only publications in English language were considered for inclusion in this work as it is the only language of communication by the researcher. This step further narrowed down the number of search results.
Search terms related to the population search domain are as follows:
"Health Risk*'' OR ''Effects'' OR ''Risk'' OR "Problems" OR "Adverse Effect" AND 'Musculoskeletal" AND "Epidemiology", AND "Musculoskeletal Clinical Signs", OR "Pathology" AND "Aluminium Poisoning", OR "Preclinical effects of Aluminium". "Muscoskeletal*"

2.3 Selection of Studies

Online search on the databases were conducted and search results from each database were documented. Search results were transferred to electronic reference management end note software). Screening full texts of relevant at stage for eligibility criteria was also implemented. Further search on the reference lists of included studies were screened to identify any other relevant. However, due to the nature of this review being an academic dissertation, the screening process was carried out by one reviewer. This helped reduce the duration of time and resources which would have been used by two reviewers. Data extraction was achieved through reading of the studies included and extracting data/information relevant to the question of interest. Data extraction is very important as it summarizes studies in an objective and accurate information to help in the assessment in the risk of bias. The standardized data extraction form can be in manual form as paper, automated in computerized format, or commercial, or custom built data system and may be as with coding. Information contained in the electronic tool (Excel spreadsheet) created for this review includes name of author and year of publication, study groups (inclusion and exclusion criteria), participant's characteristics, outcomes of significance to the review question and specific objectives.
Synthesis is the process of combining data from reviewed studies to reach a conclusion about answer to a research question (McKenzie *et al.*, 2021). Exploring study findings for heterogeneity is crucial since there may be methodological differences in the details of included studies (CRD, 2009). The methodology in this review is heterogeneous therefore was not subjected to statistical meta-analysis.

3. Results and Discussion

A total of 621 studies were gotten after an electronic search through the various databases (Fig. 1). The studies were saved and imported to the Endnote software. Duplicate studies were removed using the Endnote software to avoid overestimation of effects leaving studies. Then, the criteria were applied. 11 full studies were red and assessed for eligibility. Key elements of the literature were assessed and categorized under various subheadings addressing the risks, harms etc.

3.1 Aluminium Intake

Aluminium (Al) may combine with other elements such as chlorine, sulphur, fluorine, as well as form complexes with organic matter (Jones and Bennet, 2016; Ganrot, 2016; Martin, 2016). Environmental media may be contaminated by Al from anthropogenic sources and through the weathering of rocks and minerals. Weathering processes on rocks release more Al to the environment than human-related activities (Lantzy and MacKenzie, 2019). Exposures to metal recycling, deployment and use of Al-containing compounds and products, and during engagement in Al metal cutting, sawing, filing and welding. Animals and humans living in environments contaminated by industrial wastes may also be exposed to high levels of Al (Sorgdrager *et al.*, 2018; Vandenplas *et al.*, 2018; Boran *et al.*, 2019).

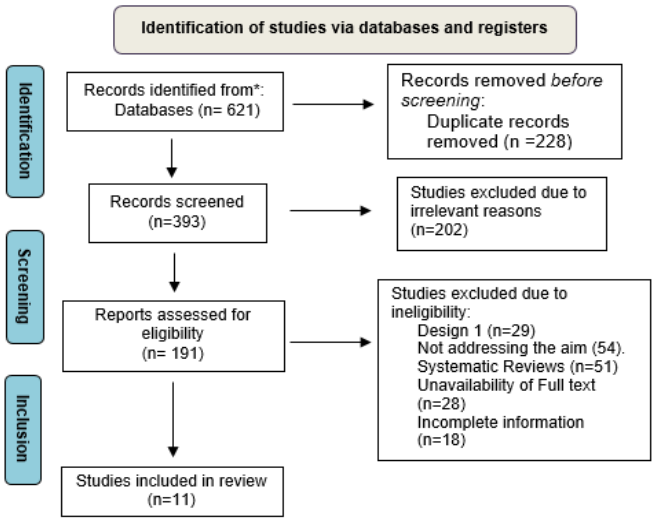

Figure 1: Prisma flowchart

A total of eleven (11) studies were appraised for this review: Chugh *et al.*, 2019; Kerr *et al.*, 2021; Darbre, 2015; Gupta & Ahlawat, 2015; Rashedinia *et al.*, 2016; Bhalla & Singh, 2015; Aggarwal *et al.*, 2019; Kumar *et al.*, 2018; Yadav *et al.*, 2017; Luporsi *et al.*, 2018; Koreti *et al.*, 2014.

Several chemical compounds with Al are in extensive use in various products and processes associated with human activities (Anon, 2018; Lewis, 2021). The compounds are used in crude oil refining and cracking of petroleum; manufacturing of cooking utensils and foils, parchment paper, printing ink, glass, ceramics, pottery, incandescent filaments, fireworks, explosives, photographic flashlight, electric insulators, cement, paints and varnishes, fumigants and pesticides, lubricants, detergents, cosmetics, pharmaceuticals (drugs), vaccines, as well as in water treatment and purification, treating sewage and fur, tanning leather, waterproofing clothes and concretes, industrial filtration, hemodialysis, measuring radiation exposure, in products as flame retardant and fireproofing, anticorrosion agent, food additives to prevent caking as well as components of baking powders and colorants (Anon, 2018, 2018a; Malakoff, 2020; Lewis, 2021; Soni *et al.*, 2021; Saiyed and Yokel, 2015).

The Al ion has no physiological role in metabolic processes (Exley and House, 2021) but it can be a metallic toxicant to humans and animals (Becaria *et al.*, 2018) when there is high body burden of the metal after natural or unnatural exposure (Exley, 2019). Al was considered unsafe to humans after the discovery of increased levels of Al in brain tissues of patients with encephalopathy, having been exposed to Al accumulation through dialysis (Alfrey and Solomons, 2016).

3.1.1 Aluminium in the air

The largest source of airborne Al-containing particles is the dust from soil and rocks (Lee and Von Lehmden, 2019; Sorenson *et al.*, 2020). Human related activities, including mining and agriculture, contribute to the dust in winds (Eisenreich, 2020; Filipek *et al.*, 2017). About 13% of atmospheric Al is attributed to anthropogenic emissions (Lantzy and MacKenzie, 2019). The sources of Al-containing particulate matter include coal combustion, Al production, iron and steel foundries, brass and bronze refineries, motor vehicle emissions and other industrial activities such as smelting, filing, sawing, welding of Al metals (Lee and Von Lehmden, 2019; Ondov *et al.*, 2018; Que Hee *et al.*, 2018, Kazi *et al.*, 2019; Pappas, 2021; Afridi *et al.*, 2015).

3.1.2 Aluminium in drinking water

Al concentrations including surface ruoff can be increased directly or indirectly by human activities through industrial and municipal discharges, surface run-off, tributary inflow, groundwater seepage, and wet and dry atmospheric deposition (Eisenreich, 2020). Industrial release of Al in waste materials into surface waters from processing and manufacturing facilities could be toxic to aquatic life (Filipek *et al.*, 2017; Trieff *et al.*, 2015; His *et al.*, 2016; Gensemer and Playle, 2019, Cronan and Schofield, 2019; Filipek *et al.*, 2017). The appplication of Al compounds as coagulating agents in the treatment of water for drinking could increase its Al content (Qureshi and Malmberg, 2015; Henshaw *et al.*, 2019; Cech and Montera, 2020). In pure water, Al has a minimum solubility in the pH range of 5.5–6.0 and concentrations of dissolved Al increase at higher or lower pH values (Browne *et al.*, 2020). The source of water and the purification process involved may influence the Al content of drinking water as source of exposure.

3.1.3 Aluminium in food

The foods highest in Al are those that contain Al additives (Pennington, 2018; Saiyed and Yokel, 2015; Yokel and Florence, 2016; Yokel, 2018, Liukkonen-Lilja and Piepponen 2018; Pennington and Schoen, 2015, Valkonen and Aitio, 2017; Lin *et al.* 2017, Ranau *et al.*, 2021). Foods found to be naturally high in Al include potatoes, spinach and tea (Pennington and Schoen, 2015; Stahl *et al.*, 2021). Processed dairy products and flour may be high in Al if they contain Al-based food additives (Pennington and Schoen, 2015, Biego *et al.*, 2018; Yang *et al.*, 2014). It is unlikely that Al-containing food additives are intentionally added to the diets of livestock and pets yet, Al contamination of some additives used in livestock and pet food is possible (Burgoin, 2018). Thus, Al contents of harvested food products, processed foods, and cooked, baked or grilled foods may be sources of Al exposure.

3.1.4 Aluminium in pharmaceuticals and agrochemicals

The methoud of contamination can be via inhalation of aerosols, ingestion of medications or by parenteral administration. Humans as well as animals are exposed to Al-containing medications such as phosphate binders, antacids, buffered analgesics, antidiarrheal and antiulcer drugs (Lione, 2019, 2015; Yokel and McNamara, 2021; Krewski *et al.*, 2017). Various intravenously administered pharmaceutical products were reported to contain 684–5977 µg/g of Al (Sedman *et al.*, 2015, Lewis, 2021; Pineau *et al.*, 2014). Al hydroxide, Al phosphate, Al potassium sulfate (alum), and Al silicate (zeolite) are used in the preparation of a number of vaccines to adsorb antigenic components and to serve as adjuvant that enhance immune response (Lione, 2015; Tomljenovic and Shaw, 2021; Issa *et al.*, 2014, Malakoff, 2020; Keith *et al.*, 2018; Mitkus *et al.*, 2021; Glanz *et al.*, 2015) and it is presumed that there could be mistakes in adjusting Al content of vaccines to body weights of neonates who stand the risk of Al toxicity from vaccines (Lyons-Weiler and Ricketson, 2018). It is unlikely that parenteral Al administrations are a major source of Al exposure to livestock or pets (Issa *et al.*, 2014, Moore *et al.*, 2020; Codling *et al.*, 2018). Alum has also been added to dairy slurry to reduce emissions (Lefcourt and Mesinger, 2021). Thus, this section indicates that Al exposure can arise when certain pharmaceutical products are administered orally or parenterally to individuals or when agrochemicals contaminate food/feed and water taken by individuals or those in close proximity inhale aerosols from agrochemical fumigants and sprays.

3.2 Absorption, Distribution and Elimination of Aluminium

Figure 2 depicts the dynamic chain of Al intake, absorption and elimination determines the level of tissue accumulation and development of toxicosis. Inhalation and ingestion (via food and water) are the two main routes through which Al gets into the body (Alfrey, 2020; Teraoka, 2021; Jouhanneau *et al.*, 2017). Following inhalation, Al compounds are deposited in the lungs (Christie *et al.*, 2019; Stone *et al.*, 2019; Thomson *et al.*, 2016). The lungs continually receive Al mostly as particles of Al silicates and other poorly soluble compounds (Thomson *et al.*, 2016). The concentration of Al in the lungs tends to increase with age and may result in respiratory anomalies where the Al is localized (Alfrey, 2020; Teraoka, 2021; Taiwo, 2014). There is no available evidence in literature that particulate or soluble Al gets into the blood circulation from the lungs to be subsequently distributed to other organs of the body.

Gastrointestinal absorption, after ingestion, is the main route through which Al is systemically accumulated in animals and humans, and absorption occurs largely in the duodenum (Feinroth *et al.*, 2014; Steinhausen *et al.*, 2014). The absorption of Al is usually low and varied when compared with the amount ingested (Kawahara *et al.*, 2017). Al absorption from water intake (about 0.3%) is greater than from food (about 0.1%) (Martyn *et al.*, 2019; Steinhausen *et al.*, 2014; Anon, 2018b; Zhou *et al.*, 2018).This was attributed to organic ligands in foods such as phytates and polyphenols that were suggested to form complexes with Al ion and inhibit its absorption (Reto *et al.*, 2017). Absorption of Al via the gastrointestinal tract can be enhanced in the presence of citrate, maltol, lactate and fluoride in water or food, and during chronic renal diseases, while the absorption is reduced in individuals with iron overload, or when ingested with phosphate, silicon, polyphenols and sialic acid (Brown *et al.*, 2017; Edwardson *et al.*, 2019; Anon, 2018c; Zhou *et al.*, 2018). However, there is complete Al uptake from parenteral fluids and vaccines with subsequent distribution to various parts of the body (Tomljenovic and Shaw, 2021). About 90% of the Al circulating in the blood is transported bound to transferrin (iron-transporter protein), while the rest of Al binds to albumin and citrate in the blood (Day *et al.*, 2021; Harris and Messori, 2018; Hemadi *et al.*, 2019; Chen *et al.*, 2020).

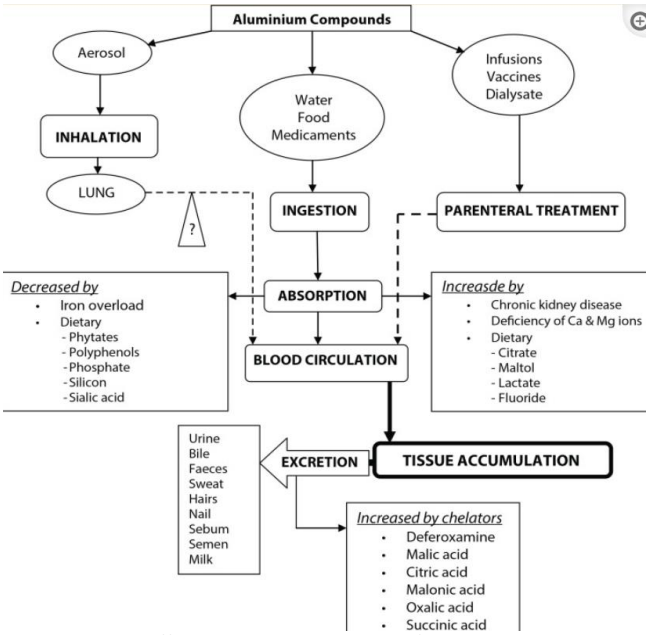

Figure 2: Factors affecting tissue accumulation of aluminium
Source: Alfrey (2020).

Cellular uptake of Al in tissues is relatively slow and is presumed to be mediated by endocytosis and intracellular transfer of the Al bound to transferrin (Hemadi *et al.*, 2019). However, Al-transferrin complex may not bind to the transferrin-receptor (Hemadi *et al.*, 2019; Sakajiri *et al.*, 2020), indicating the existence of an alternative mechanism of cellular uptake of Al (DeVoto and Yokel, 2014; Anon, 2021). The total body burden of Al in healthy humans has been reported to be approximately 30–50 mg/kg body weight and normal levels of Al in serum are approximately 1–3µg/L (Krewski *et al.*, 2017). The mean serum Al level in 44 non-exposed persons who did not use antacids was reported to be 1.6 µg/L (Valkonen and Aitio, 2017) and Chen *et al.* (2020) reported that values in hemodialysis patients were ten-fold higher than the values in unexposed individuals. About one-half of the total body Al is in the skeleton, and the levels in human bone tissue range from 5 to 10 mg/kg (Anon, 2018c). Al has also been found in human skin, lower gastrointestinal tract, lymph nodes, adrenals, parathyroid glands, and in most soft tissue organs (Anon, 2018b). In rats, accumulation of Al after oral exposure was higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lungs (Anon, 2018b). It has also been reported that Al can reach the placenta and fetus and to some extent distribute to the milk of lactating mothers (Anon, 2018b). Al levels increase with age in tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals (Krewski *et al.*, 2017). Moreover, Al has been shown to rapidly enter the brain, extracellular fluid and the cerebrospinal fluid, with smaller concentrations in these organs than in the blood (Martin, 2018; Krewski *et al.*, 2017). The iron status is negatively correlated with Al accumulation in tissues and animal experiments have shown that calcium and magnesium deficiency may contribute to accumulation of Al in the brain and bone (Anon, 2021).

The Al ion in blood circulation is eliminated primarily by the kidneys (about 95%) in the urine, presumably as Al citrate (Shirley and Lote, 2015; Krewski *et al.*, 2017; Anon, 2018c). Tissue accumulation of Al is reduced by citrates and fluorides through renal excretion when the transferrin-Al binding capacity of the blood is exceeded (Anon, 2018b). Al is also excreted in the milk, bile, feces, sweat, hairs, nails, sebum and semen (Gorsky *et al.*, 2019; Greger and Sutherland, 2017; Exley, 2019). Chemical chelators such deferoxamine and malic, malonic, citric, oxalic, and succinic acids, which are discussed in the later section of this text on treatment of Al, increase the excretion of Al through the urine. Overall, it is highlighted that Al exposure and continuous use, as well as increased intestine absorption and decreased metal excretion, all contribute to Al accumulation, which is what causes Al toxicosis.

In most types of animal and plant tissues, as well as in all natural fluids, aluminum is a trivalent cation that is present in its ionic form (Aggarwal, 2019). It makes up about 8% of all mineral components and is the third most common element and most abundant metal in the earth's crust. (Ahmadi, 2018). Due to its reactivity, aluminum in nature is found only in combination with other elements.

Dietary aluminum is pervasive yet in such little amounts that it's anything but a critical wellspring of worry in people with typical disposal limit. Metropolitan water supplies might contain a more noteworthy focus since water is typically treated with aluminum prior to turning out to be essential for the stock. Ensuing decontamination processes that eliminate natural mixtures remove a considerable lot of the very intensifies that tight spot the component in its free state, further expanding aluminum fixation. All metals can cause sickness through overabundance. Furthermore, fundamental metals can influence the human body on account of lack or lopsidedness (Alfrey, 2016). Malabsorption through diarrheal states can bring about fundamental metal and minor component inadequacies. Poisonous impacts are subject to how much metal ingested, section rate, tissue dissemination, fixation accomplished, and discharge rate. Components of poisonousness incorporate hindrance of compound movement and protein amalgamation, adjustments in nucleic corrosive capability, and changes in cell layer porousness.

Approximately 95% of an aluminum load becomes bound to transferrin and albumin intravascularly and is then eliminated renally. Only 0.3% of aluminum taken orally by healthy persons is absorbed by the GI tract, and aluminum is effectively excreted from the body by the kidneys. Aluminum has the ability to accumulate only when the GI barrier is broken, such as during intravenous infusion or when there is significant renal failure. For illustration, with intravenously infused aluminum, 40% is retained in adults and up to 75% is retained in neonates (Bansal, 2015) (Table 1).

Aluminum is retained from the GI plot as oral phosphate-restricting specialists (aluminum hydroxide), parenterally by means of vaccinations. Lactate, citrate, and ascorbate all work with GI ingestion. On the off chance that a critical aluminum load surpasses the body's excretory limit, the overabundance is stored in different tissues, including bone, mind, liver, heart, spleen, and muscle. This amassing causes bleakness and mortality through different systems (Ahmadi, 2018). The harms and risks of Al was summarized in Table 1.
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Table 1: Summary of harms and risks of Aluminum

NEUROTOXICITY	
Type of Study	Seven-week-old male rats were housed in a temperature-controlled room (25 ± 2°C) at a relative humidity (60 ± 5%) with a 12 h dark/light cycle and allowed free access to food and water for 7 days, then randomized into Al-treated group and control group (n = 8 in each group) allowed free access to food and water during the intragastric administration for 6 weeks.
Mechanisms of action	Primary hippocampal neuronal cells cultures were carried on the rats. The hippocampus tissues were then dissected. Based on the principle of fluorescence of Al^{3+}-8-HQ complex, and identify the proteins with specific binding to Al^{3+} in pig hippocampus of the rat.
Results	The location of Al^{3+} in rat hippocampus tissue and primary hippocampal neuronal cells was visualized by 8-HQ staining. The accumulation of Al^{3+} in the neurons was seen around the nuclei (blue fluorescence) with green fluorescence. There was much more abundant accumulation of Al^{3+} in neurons of the Al-exposed rat compared to control rat without exposure to Al.
References	Bhalla & Singh, 2015; Aggarwal et al., 2019; Luporsi et al., 2018; Kumar et al., 2018; Yadav et al., 2017; Kerr et al., 2021; Rashedinia *et al.*, 2016

Table 1: Cont'd

ALUMINIUM PHOSPHIDE POISONING	
Type of Study	7 cases of Aluminium poisoning with severe hemodynamic effects. Presenting complaints, clinical characteristics and laboratory data were recorded at the time of admission.
Mechanisms of action	Gastric lavage was performed with diluted potassium permanganate (1:10000 dilution), coconut oil, sodium-bicarbonate and activated charcoal. Airway protection was given before gastric lavage in required patients. Close monitoring of hemodynamic parameters, urine output, arterial blood pressure and arterial blood gas was regularly done. The primary outcome was categorized as survivor and no survivor.
Results	Totally, 7 cases of aluminium poisoning were managed. Of these, 5 were males, and the mean age of patients was 36.85 years. The mean time lag to MICU transfer was 3 h 50 min. Mean dose of ingested AIP was 5.14 g. Mean systolic blood pressure on presentation was 84 mm Hg. Survivors were 4 (57.14%). Gastric lavage with $KMnO_4$ and sodium-bicarbonate was used in all patients while coconut oil was used in 4 (57.14%). Incidentally all patients with coconut oil use survived. 6 patients were intubated and mechanically ventilated. Two-dimensional echo revealed low left ventricular ejection fraction (LVEF) (mean LVEF of 27.85%) in all patients. Magnesium sulphate was used in all subjects. All survivors had initial electrocardiogram (ECG) of normal sinus rhythm or sinus tachycardia. All non-survivors had cardiac arrhythmias on presentation including ventricular Fibrillation in 2 cases and Atrial Fibrillation in one case. Average Intensive Care Unit stay of survivors was 5 days and in non-survivors was 1.33 days.
References	Rashedinia *et al.*, 2016; Bhalla & Singh, 2015; Dabre, 2015; Yadav *et al.*, 2017; Kerr *et al.*, 2021; Gupta et al., 2015; Luporsi*et al.*, 2018; Aggarwal *et al.*, 2019; Kumar *et al.*, 2018
POSSIBLE RISK OF ALZHEIMER'S DEMENTIA	
Type of Study	A case-control study was carried out to assess exposures from historical measurements of aluminium and silica in water supplies. Cases of Alzheimer's Disease with three sets of controls were compared: patients with other types of dementia, patients with brain cancer and patients with other dieases of the nervous system.
Mechanisms of action	Diagnoses were confirmed by a review of hospital case-notes. All subjects were ensured to be between 42 and 75 years of age.
Results	Al is omnipresent in everyday life and can enter the human body from several sources, most notably from drinking water and food consumption.
References	Kerr et al., 2021; Gupta & Ahlawat, 2015; Aggarwal et al., 2019; Wang *et al.*, 2016; Darbre, 2015; Kumar, 2018
POSSIBLE RISK OF BREAST CANCER	
Type of Study	Mammary epithelial cells from immunodeficient mice were cultured with aluminum chloride ($AlCl_3$).
Mechanisms of action	These mammary epithelial cells were injected into immunocompetent mice.
Results	$AlCl_3$ rapidly increased chromosomal structural abnormalities in these cells. Of the 20 mice injected with the cells cultured in $AlCl_3$, 17 developed tumors at the injection site, whereas none of the 10 mice injected with control cells did. Human bodies also have several defense mechanisms that detect and get rid of cells that aren't quite right, so genomic instability alone may not always be enough to result in cancer.
References	Darbre, 2015; Gupta & Ahlawat, 2015; Rashedinia et al., 2016; Bhalla & Singh, 2015; Aggarwal *et al.*, 2019; Kumar *et al.*, 2018; Yadav *et al.*, 2017; Luporsi*et al.*, 2018; Kerr *et al.*, 2021

According to some of the studies aluminum (Al3+) has a strong affinity for proteins and can cross-link them (Bhalla & Singh, 2015; Aggarwal *et al.*, 2019; Luporsi *et al.*, 2018) In contrast to other commonly found metals such as iron, manganese, and zinc, aluminum is not recognized to have any physiological functions in the human body. Dialysis patients have been shown to have neurotoxic consequences that are clinically meaningful. The causative agents were identified as aluminum salts, which were previously introduced to the dialysate as a phosphate binder (Kumar *et al.*, 2018; Yadav *et al.*, 2017). Aluminium levels in plasma and brain tissue were found to be higher in patients (Kerr *et al.*, 2021). In addition to inducing oxidative stress and binding to negatively charged membrane structures in neurons, aluminium is able to modify hippocampal calcium signal pathways that are crucial to neuronal plasticity and, hence, to memory. Cholinergic neurons are particularly susceptible to aluminium neurotoxicity, which affect synthesis of the neurotransmitter acetyl-choline (Kerr *et al.*, 2021). However, even following aluminium exposure above this threshold, no cases of manifest encephalopathy involving disorientation, impaired memory, and dementia have been reported (Rashedinia *et al.*, 2016; Bhalla & Singh, 2015; Aggarwal *et al.*, 2019).

Poisoning may occur as a result of direct AlP intake or inhalation of phosphine produced by AlP. AlP causes the stomach to produce toxic phosphine gas after consumption (Rashedinia *et al.*, 2016; Bhalla & Singh, 2015). This release is favored by gastric HCl. Phosphine is quickly absorbed throughout the digestive system (GIT). Accidental phosphine exposure is equally fatal to humans since the lungs absorb it quickly. Phosphine has the greatest impact on the heart and vascular tissues. (Darbre, 2015; Rashedinia *et al.*, 2016; Yadav *et al.*, 2017; Kerr *et al.*, 2021).

In the case of shock, plasma renin activity is often observed to be elevated. This correlates with the dose of the poison consumed. Patients show respiratory features such as cough, cyanosis, dyspnea, pulmonary edema and respiratory failure (Kerr *et al.*, 2021). Elevation of blood cortisol with corresponding changes in adrenal gland histopathology is seen (Rashedinia *et al.*, 2016; Bhalla & Singh, 2015). This high suspicion is necessary as there is no established biomarker of AlP poisoning (Kerr *et al.*, 2021; Rashedinia *et al.*, 2016; Bhalla & Singh, 2015). There can be a wide range of complications of AlP poisoning. For example, a patient may have predominantly pleural effusion. Others may present as acute renal failure. Some other patients may develop pancreatitis. The clinical features profoundly differ in these cases. Among them, haemolysis and methemoglobinemia may complicate the course of AlP poisoning. Severe hypoglycaemia may be observed occasionally (Rashedinia *et al.*, 2016; Bhalla & Singh, 2015).

Polyserositis occurred in a case series (Luporsi *et al.*, 2018; Bhalla & Singh, 2015; Aggarwal *et al.*, 2019; Kumar *et al.*, 2018; Yadav *et al.*, 2017; Kerr*et al.*, 2021). The patients developed pleural effusions, pericardial effusion and ascites. Mitochondrial damage in the endothelium leads to capillary leakage syndrome, which accounts for this condition's possible mechanism (Luporsi *et al.*, 2018). The delayed complication of polyserositis has been associated with or without acute respiratory distress syndrome (ARDS). Intravascular hemolysis occurs in patients with glucose-6-phosphate dehydrogenase enzyme deficiency. Methemoglobinemia, acute pancreatitis, esophago bronchial fistula, restlessness, tachypnea, altered sensorium, peripheral cyanosis, and cold sweaty skin may predominate in some cases of AlP poisoning (Aggarwal *et al.*, 2019; Kumar *et al.*, 2018; Yadav *et al.*, 2017; Luporsi *et al.*, 2018). Spontaneous self-ignition is also a rarely observed physical phenomenon in the case of AlP poisoning (Kumar *et al.*, 2018; Yadav *et al.*, 2017).

In the course of the search for the causes of the frequently seen Alzheimer's dementia, the described dementia syndrome following aluminium poisoning was also proposed as an explanation(Kerr *et al.*, 2021; Gupta & Ahlawat, 2015; Aggarwal *et al.*, 2019; Kerr *et al.*, 2021). Dialysis patients exhibited impaired speech, apraxia, and, in the further course, dementia syndrome as well as partly focal, partly generalized seizures
Specific changes in the form of alternating spikes (2–3 c/s) and slow waves have proved to be characteristic and diagnostically significant. Neuropathological investigations revealed minimal changes (mild hydrocephalus, only slight neuronal cell loss in the cortex, hippo campus, or Purkinje cells); mild vascular changes or aluminium detected in tissue have occasionally been reported, without evident changes typical of Alzheimer's disease being identified (amyloid plaques and neurofibrillary tangles).

By contrast, in Alzheimer's patients the characteristic changes typical of aluminum encephalopathy were not observed. The walls of small and very small arteries are often associated with cerebral amyloid angiopathy (CAA) (Wang *et al.*, 2016; Darbre, 2015; Gupta & Ahlawat, 2015), as well as in the central region of senile plaques. The onset of Alzheimer's pathology (bothneuro -fibrillary tangles and amyloid plaques) was observed in animal models following intracranial/intraventricular administration of aluminum compounds. A study by Wang *et al* (2016) found an increased risk for Alzheimer's disease in their meta-analysis of individuals chronically exposed to aluminum in drinking water. In contrast, several studies found no association between aluminum exposure and Alzheimer's disease after significantly higher occupational aluminum exposure (Wang *et al*., 2016)
Presently, the use of aluminium-containing antiperspirants can cause breast cancer (Darbre, 2015; Gupta & Ahlawat, 2015; Rashedinia *et al.*, 2016; Bhalla & Singh, 2015). Although tumors are more frequently diagnosed in the upper outer quadrants of the breast, i.e., in close spatial proximity to where the substances are used, this is also an area with more glandular tissue. Nevertheless, an increase in this localization has been observed in recent decades (Dabre, 2015). However, aluminium does not appear to be the trigger of the tumours, but instead is stored to a greater degree in tumour tissue, much like other minerals. For example, feeding rats with a carcinogenic, non-aluminium-containing substance(2,7-dimethylbenz[a]anthracene) caused mammary gland tumours in which significantly elevated levels of aluminium were measured (Bhalla & Singh, 2015; Aggarwal *et al.*, 2019; Kumar *et al.*, 2018; Yadav *et al.*, 2017; Luporsi *et al.*, 2018). Furthermore, besides aluminium, significantly elevated concentrations of other minerals (e.g., Cd and Ni, as well as Br, Ca, Cl, Co, Cs, Fe, K, Mn, Na, Rb, and Zn) were observed in human breast tumour tissue specimens. In a more recent study, long-term exposure to aluminium chloride transformed breast epithelial cells in vitro in such a way (e.g., by increased DNA synthesis and DNA double-strand breaks) that the cells formed tumours and metastasized in an animal experiment, which can be considered evidence of cell transformation (Kerr *et al.* 2021; Kumar *et al.*, 2018; Yadav *et al.*, 2017).Some studies showed an earlier age of disease onset in breast cancer patients that had used aluminum-containing antiperspirants combined with underarm shaving, whereas case–control studies failed to identify a link between the use of anti-perspirants and the risk of breast cancer (Aggarwal *et al.*, 2019; Kumar *et al.*, 2018; Yadav *et al.*, 2017; Luporsi *et al.*, 2018). Likewise, an analysis of the published literature revealed no increased risk of breast cancer due to antiperspirant use (Kerr *et al.*, 2021).

3.3 Systemic Toxicosis

3.3.1 Musculoskeletal effects

Skeletal muscle necrosis occurred in the diaphragm and abdominal muscles of rats adjacent to the peritoneum after intraperitoneal injection of Al lactate (Levine *et al.*, 2018). Muscle fiber atrophy, with retardation of growth, was reported in growing pigs which was associated with hypophosphatemia induced by dietary Al hydroxide supplementation (Haglin *et al.*, 2014). Smooth muscle contraction induced by K+ ion was inhibited by Al exposure (Nasu *et al.*, 2018). Myocardial function may be altered in diabetic individuals by Al exposure, in as much as Al toxicity potentiates the decline in calcium uptake into the sarcoplasmic reticulum of the myocardial fibers of such individuals (Levine *et al.*, 2020). In individuals where neurodegenerative conditions affect the nerve supply to muscles, the muscles may undergo denervation atrophy and become dysfunctional as in multiple sclerosis or amyotrophic lateral sclerosis.

The bone disorders linked to Al exposure are osteoporosis, osteomalcia, rickets, exostosis, osteodystrophy and osteitis fibrosa (Sherrard *et al.*, 2015; Chappard *et al.*, 2016; Rodríguez and Mandalunis, 2018; Klein, 2019, Cao *et al.*, 2016; Sun *et al.*, 2016) because inhibition of osteoblast proliferation, differentiation and mineralization (Li *et al.*, 2018, 2016; Cao *et al.*, 2016; Sun *et al.*, 2016; Yang *et al.*, 2016; Zhu *et al.*, 2016b; Song *et al.*, 2017; Sun *et al.*, 2017; Huang *et al.*, 2017). In individuals with Al overload, undecalcified bone matrix contains Al and bone conditions like exostosis and osteomalacia may occur in circumstances that increase Al uptake and colocalization as observed in celiac disease, hemochromatosis and sickle cell anemia (Chappard *et al.*, 2016). Osteoclastogenesis is promoted by low-dose exposure while osteoclast apoptosis is caused by high-dose exposure (Yang *et al.*, 2018). There are case reports of osteomalacia and rickets in infants and adults using Al-containing antacids for the treatment of gastrointestinal illnesses (Chines and Pacifici, 2020; Pivnick *et al.*, 2015; Woodson, 2018). The Al in antacids binds with dietary phosphorus and prevents its absorption resulting in hypophosphatemia and phosphate depletion (Woodson, 2018). Osteomalacia, characterized by bone softening, increased spontaneous fractures and pain, has been reported in dialyzed uremic adults and children exposed to Al-contaminated dialysate or orally administered Al-containing phosphate- binding agents (Mayor *et al.*, 2015; Wills and Savory, 2019; Andreoli, 2020). Decreased Al urinary excretion caused by impaired renal function with, possibly, an increase in gastrointestinal absorption of Al results in increased Al load leading to markedly increased bone Al levels and the presence of Al between the junction of calcified and non-calcified bones (Alfrey, 2019). Long-term oral exposure to Al results in an increase in Al levels in the bone (Fig. 3) that is responsible for the bone disease (Ahn *et al.*, 2015; Konishi *et al.*, 2016).

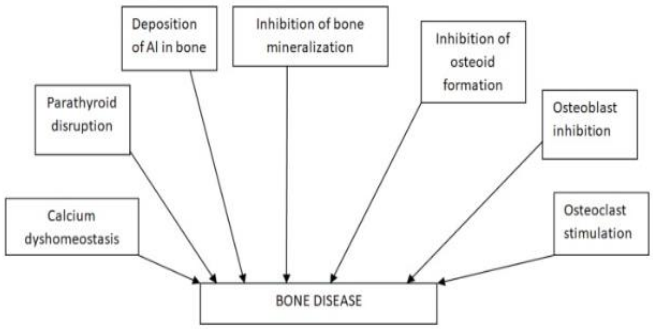

Figure 3: Different bone diseases
Source: Igbokwe *et al.* (2019)

3.3.2 Pulmonary effect

Pulmonary lesions in humans linked to Al exposure during production of Al products include granulomatous pneumonia, pulmonary granulomatosis, pulmonary fibrosis, pulmonary alveolar proteinosis and desquamative interstitial pneumonia (Chen *et al.*, 2018; Herbert *et al.*, 2018; Miller *et al.*, 2014; De Vuyst *et al.*, 2017; Jederlinic *et al.*, 2020; Taiwo, 2014; Iijima *et al.*, 2017). Asthma may be caused by Al exposure (Burge *et al.*, 2020), though the asthma among Al workers may be due to other chemical factors like gases and smoke (Taiwo *et al.*, 2016). Reactive airways dysfunction syndrome was rarely reported among Al smelter workers (Wesdock and Arnold, 2014, Chopra *et al.*, 2016; Khosla *et al.*, 2018, Alter *et al.*, 2021; Kamanyire and Murray, 2019; Moghadamnia, 2018). Intermediate- and chronic-duration studies found no organ weight or histological changes in the lungs of rats exposed to 70 mg Al/kg/day as Al chloride in drinking water for 30, 60 or 90 days (Dixon *et al.*, 2019), rats exposed to 133 mg Al/kg/day as Al nitrate in drinking water for 30 days (Gomez *et al.*, 2016), rats and mice exposed to 0.6 or 1.2 mg Al/kg/day as Al potassium sulfate in drinking water for 24 months (Schroeder and Mitchener, 2015a, b), or mice exposed to 979 mg Al/kg/day as Al potassium sulfate in food for 20 months (Oneda *et al.*, 2014). However,

Hasseeb *et al.* (2021) reported neutrophilic and mononuclear cell infiltrations of lung alveoli of rats administered 37 mg/kg/day of Al chloride in drinking water for 8 weeks. Congested blood vessels in inter-alveolar spaces were reported after administration of different concentrations of Al chloride via gavage for 8 weeks (Buraimoh and Ojo, 2019). Pulmonary lesions are rare and inconsistent in experimental animals where Al exposure is not through aerosol vehicles. Under natural conditions, the vehicular substances and the Al speciation may influence the stimulation of chronic pathologic reactions in the lung.

3.3.3 Cardiovascular effects

Toxic myocarditis, myocardial hypokinesia, left ventricular thrombosis and myocardial dysfunction were reported in a case of Al phosphide intoxication (Hangouche *et al.*, 2017). Ischemic stroke due to thrombosis in the right middle cerebral artery was reported as the delayed complication of Al phosphide poisoning (Abedini *et al.*, 2014). However, other Al compounds may not cause cardiovascular lesion. Cardiac teratogenessis was reported in embryonic chick heart where defects in ventricular septation and ventricular myocardium were reported (El Mazoudy and Bekhet, 2016). There was significant association between increased maternal hair Al contents and risk of total congenital heart defects in offspring, especially in subtypes such as septal defects, conotruncal defects and right ventricular outflow obstruction in female rats (Wang *et al*., 2018). No histological changes were observed in the hearts of rats given 70 mg Al/kg/day as Al chloride in drinking water for 30, 60, or 90 days (Dixon *et al.*, 2019). Similarly, no effect on organ weight nor histological changes were found in the hearts of rats that ingested 133 or 284 mg Al/kg/day as Al nitrate in drinking water or base diet for 30 days (Gomez *et al.*, 2016) or 100 days, respectively (Domingo *et al.*, 2017). Organ weight and histological changes were not observed in the hearts of dogs that consumed 75 mg Al/kg/day (Katz *et al*., 2014) or 88 mg Al/kg/day (Pettersen *et al.*, 2020) as sodium Al phosphate in the diet for 6 months.

3.3.4 Gastrointestinal effects

In horses, Al was found in tissues, blood vessel walls and granulomatous lesions of the intestines associated with equine granulomatous enteritis (Fogarty *et al.*, 2018), and Al was demonstrated to have the capacity to induce granuloma formation in vitro (De Chambrun *et al.*, 2014). Oral intake of Al may affect the intestinal microbiota, permeability and immune response which influence the local inflammatory conditions (Vignal *et al.*, 2016). In individuals that are genetically susceptible to Crohn's disease, Al is linked to the induction and persistence of the chronic relapsing intestinal inflammation (Lerner, 2017). Inflammatory bowl diseases, consisting of disease entities like Crohn's disease and ulcerative colitis, are characterized by excessive intestinal inflammation and experimental evidence in mice indicates that Al promotes intestinal inflammation, thereby implicating Al in the pathogenesis of inflammatory bowl diseases (De Chambrun *et al.*, 2014). Chemically-induced acute colitis and chronic colitis in transgenic mice lacking interleukin 10 were aggravated by oral exposure to Al, because Al increased the intensity and duration of intestinal inflammation and decreased regeneration or renewal of the intestinal epithelial mucosal cells (De Chambrun *et al*., 2014). Furthermore, intestinal barrier function was impaired by Al exposure under basal conditions; and there was a synergistic stimulation of pro-inflammatory cytokine expression by Al and lipopolysaccharides (De Chambrun *et al*., 2014). Oral Al chloride exposure caused epithelial degeneration, goblet cell proliferation and lymphocyte infiltration in the mucosa of the small intestine of Wistar rats (Buraimoh and Ojo). Few experimental studies (Gomez *et al*., 2016; Oneda *et al.*, 2014) did not report intestinal lesions after oral exposure to Al at 133 mg Al/kg/day as Al nitrate in drinking water to rats for 30 days and 979 mg Al/kg/day as Al potassium sulfate in the food of mice for 20 months. The acute and chronic inflammations in the intestine may induce poor intestinal digestion and absorption.

3.3.5 Hematologic effects

Al exposure has been associated with significant inhibition of colony forming units-erythroid (CFU-E) development in the bone marrow of mice exposed to 13 mg Al/kg as Al citrate or chloride administered via gavage for 5 days/week for 22 weeks (Garbossa *et al*., 2016), rats exposed to 27 mg Al/kg as Al citrate administered via gavage 5 days/week for 15 weeks (Garbossa *et al.*, 2018), and rats exposed to 230 mg Al/kg/day as Al citrate in drinking water for 8 months (Vittori *et al.*, 2019). The effect of Al on erythroid progenitor cells and erythrocytes was associated with slow growth and increased degradation of membrane band 3 proteins, respectively (Vittori *et al.*, 2018). The genotoxicity from Al exposure in mice resulted in mitodepressive effect in the bone marrow (D'Souza *et al*., 2014). Anemia caused by Al toxicity is not associated with adequate regenerative activity of the bone marrow and reticulocytosis (Chmielnicka *et al*., 2014; Osman *et al.*, 2018). The additional causes of anaemia appear to be multi-factorial and include defective hemoglobin production due to inhibition of the enzymes of heme synthesis, altered erythrocyte membrane structure and fragility, shortening of red blood cell life span due to eryptotic and oncotic injuries, and inadequate iron utilization (Zatta *et al*., 2019; Perez *et al.*, 2021; Bazzoni *et al.*, 2015; Vittori *et al.*, 2018; Niemoeller *et al.*, 2016; Hernández *et al.*, 2018; Sadhana, 2021; Vota *et al.*, 2018; Lukyanenko *et al.*, 2019; Al-Qayim *et al.*, 2014; Oztürk and Ozdemir, 2015; Zhang *et al.*, 2016; Cheng *et al.*, 2018, Garbossa *et al*., 2016; Garbossa *et al.*, 2018; Vittori *et al*., 2019; Farina *et al.*, 2015). The anemia is characterized by decreases in mean corpuscular volume (microcytosis) and mean corpuscular hemoglobin (hypochromia), but in chronic exposures, the erythrocyte parameters recover with persistence of microcytosis and hypochromia (Mahieu *et al*., 2020, Lin *et al.*, 2019). No alterations in hemoglobin, hematocrit and erythrocyte osmotic fragility were reported in a number of experimental Al exposures (Katz *et al*., 2014; Gomez *et al*., 2016; Domingo *et al.*, 2017; Pettersen *et al.*, 2020; Oteiza *et al*., 2019b; Garbossa *et al.*, 2016 **).** Vittori *et al.* (2019) did not find significant alterations in plasma iron levels or total iron binding capacity in rats exposed to 230 mg Al/kg/day as Al citrate in drinking water for 8 months; however, they reported impaired iron uptake and decreased iron incorporation into heme in the bone marrow. Farina *et al.* (2015) found significant decreases in blood iron concentrations and no change in total iron binding capacity in rats exposed to 54.7 mg Al/kg/day as Al sulfate in a sodium citrate solution in drinking water for 18 months. Florence *et al.* (2014) reported decreases in serum iron levels, total iron binding capacity, and transferrin saturation in rats exposed to 75 mg Al/kg/day as Al citrate in the diet for 6 months. Chronic Al exposure in rats disrupted iron homeostasis (Zhang *et al.*, 2020).

3.3.6 Neurologic effects

In humans, Al accumulation in the brain and scalp hairs has been associated with neurodegenerative diseases such as dialysis-associated encephalopathy, Alzheimer's disease, Parkinson's disease (dementia), amyotropic lateral sclerosis, multiple sclerosis and autism (King *et al.*, 2021; Savory *et al.*, 2016; Kawahara and Kato-Negishi, 2021; Arain *et al.*, 2015; Jones *et al*., 2017; Mirza *et al*., 2017; Mold *et al*., 2018). In autism, Al in parts of the brain was up to 19 µg/g dry weight (Mold *et al.*, 2018). There is a role for Al in multiple sclerosis because patients excrete high amounts of Al in urine, facilitated by drinking silicon-rich mineral water (Jones *et al*., 2017). Sub chronic exposure to Al was associated with reduced population of neural stem cells and hampered cell proliferation and neuroblast differentiation in the brain of mice (Nam *et al.*, 2014, 2016). Injection of Al, especially intra-cisternally, induced neurological changes in animal models (Wisniewski *et al.*, 2020; Anon, 2018c). Rats orally administered Al (100 mg/kg/day) for 90 days accumulated more Al in their brains, had increased brain acetyl cholinesterase activity and had decreased brain choline acetyltransferase activity (Bilkei-Gorzó, 2019). Mice fed high Al levels (1,000 mg/kg diet of Al as Al lactate) were less active, had decreased grip strength, and increased startle responses after 90 days when compared with control (Golub *et al*., 2018). Oteiza *et al.* (2019b) reported that mice fed diets containing 1,000 mg/kg diet of Al (as Al chloride) with sodium citrate accumulated more Al in the brain nuclear fraction and spinal cord, had lower grip strength, and greater startle responsiveness after 5 and 7 weeks. Old (18 months of age) rats exposed to Al (100 mg/kg/day) in drinking water with citrate (356 mg/kg/day of citrate) had decreased numbers of synapses and a greater percentage of perforated synapses than controls, but no changes in behavior (Colomina *et al.*, 2018). Garruto *et al.* (2019) reported that changes that were consistent with early Alzheimer's disease or Parkinson's dementia were in the central nervous system. Golub and Germann (2021) observed growth depression and poorer performance on standardized motor tests in mice off-spring when dams were exposed to Al (1,000 mg/kg diet as Al lactate) with marginal levels of calcium and magnesium during pregnancy and lactation. Mice fed lower rather than recommended levels of calcium (2,500 versus 5,000 mg/kg diet of calcium) with Al (15,600 mg/kg diet as Al hydroxide) for 11 to 25 months accumulated more hyper-phosphorylated tau protein in the cortical neurons and had more atrophic neurons in the central nervous system (Kihira et al., 2018). Transgenic mice with over-expressed human amyloid precursor protein had increased brain isoprostane levels and more amyloid-β peptide formation and deposition when Al was added to their diets, but the effects of Al were reversed by additional dietary vitamin E (Pratico *et al.*, 2018), suggesting that Al could contribute to neurodegeneration by enhancing amyloid deposition and aggravating lesions by oxidative events (Campbell and Bondy, 2020; Chen and Zhong, 2014; Liaquat *et al*., 2019).

3.3.7 Reproductive and developmental effects

Human reproduction may be affected negatively by Al exposure (Klein *et al.*, 2014; Mouro *et al.*, 2017). Human semen and spermatozoa contain Al and

patients with oligospermia had higher Al concentration than healthy individuals (Klein *et al*., 2014). At human dietary level of Al and continuous exposure for 60 days, the rat testes accumulated low Al levels of 3.35 µg/g and it was associated with increased oxidative stress and inflammation, decreased daily sperm production, reduced sperm count and motility and increase in abnormal spermatozoa (Martinez *et al.*, 2017). In male rats, subchronic exposure to Al chloride did not result in elevated Al accumulation in the testes, but toxic effects reported in the testes included impairment of spermatogenesis and increase in sperm malformation rate (Zhu *et al.*, 2014b). Imbalance in trace mineral metabolism occurred in the testis with testicular levels of iron and zinc increasing and that of copper decreasing during exposure (Zhu *et al.*, 2014b). Furthermore, metabolic inhibition in the testis was reported with regard to the functions of acid phosphatase, succinate dehydrogenase, and lactate dehydrogenase and its isoenzymes (Zhu *et al.*, 2014b), alongside with testicular membrane dysfunction due to inhibition of membrane ATPase activities in Al-exposed rats (Sun *et al.*, 2018). The weights of the testes and epididymides were decreased by Al exposure in rats as serum testosterone levels dropped (Mouro *et al*., 2017). In male rats, testicular development was impaired by Al exposure, associated with reduction in serum levels of testosterone and luteinizing hormone (LH) levels and decrease in androgen receptor protein expression without effect on serum follicle stimulating hormone (FSH) (Sun *et al*., 2021, 2018). The offspring of exposed rats (F0) in a three-generation study belonging to F1 and F2 had decreased testosterone and levels, decreased testicular weight, and increase in the production of abnormal immobile spermatozoa, whereas the parental F0 group did not present with such reproductive abnormalities (Muselin *et al.*, 2016). In rats that were injected with Al chloride (4.125 pmole) in artificial cerebrospinal fluid via the lateral ventricle, there were significant decreases in serum FSH, LH and testosterone levels, and reduction in sperm count from the vas deferens and epididymides (Shahraki *et al.*, 2018). Bank voles (*Myodesglareolus*) exposed to Al produced lower quality and quantity of sperm than normal, but reproductive capacity was not significantly affected in females (Miska-Schramm *et al.*, 2017). After intraperitoneal treatment at 50 mg/kg for 20 days, blood testosterone and LH levels were increased in male rats, but FSH level was not affected (Resa and Palan, 2016). Khattab *et al*. (2020) reported that administration of Al chloride (20 mg/kg) to male rats via gavage for 70 days caused fertility disturbances and testicular dysfunction. Other reports showed that Al induced decrease in sperm counts, motility and viability, with increase in dead and abnormal sperm counts (Bataineh *et al*., 2018; Guo *et al*., 2015; Yousef *et al.*, 2017; Yousef and Salama, 2019; D'Souza *et al.*, 2014). Testicular and epididymal weights and serum testosterone and luteinizing hormone levels were reduced by Al exposure (Reza and Palan, 2016; Mouro *et al.*, 2017). In male and female gerbils (*Merionesunguiculatus*), Al exposure disrupted prostate development in neonates, with the consequence of adult off-spring having elevated serum testosterone levels with low androgen receptor frequency associated with increased proliferation of cells of the prostate (Gomes *et al*., 2019).

In adult mice exposed to Al at 1000–1400 ppm in drinking water or 19–39 mg/kg intraperitoneally, pregnancy rate decreased with increased frequency of atretic follicles (Fig. 4); after pregnancy, failure of pregnancy increased with increased rate of uterine resorption and decrease in the number of viable fetuses and implantation sites (Mohammed *et al.*, 2018). Fu *et al.* (2014) reported ovarian ATPases and expressions of androgenic receptors for FSH and LH; and could consequently lead to infertility due to inhibition of ovulation and development of corpus luteum. Exposure to Al during mouse pregnancy resulted in reduced fetal weight and increased frequency of external anomalies in fetuses (Malekshah *et al.*, 2015) and fetal micronucleated erythrocytes (D'Souza *et al*., 2014). Khalaf *et al.* (2017) reported perinatal and postnatal adverse effects of Al exposure on fetuses and neonates during gestation and lactation of female rats (Table 2). The hepatic toxicity of Al chloride was also reported in pregnant rats and their offspring with observation of decreased fetal weight and size (Mestaghanmi *et al.*, 2019, Wang *et al*., 2018; El Mazoudy and Bekhet, 2016).

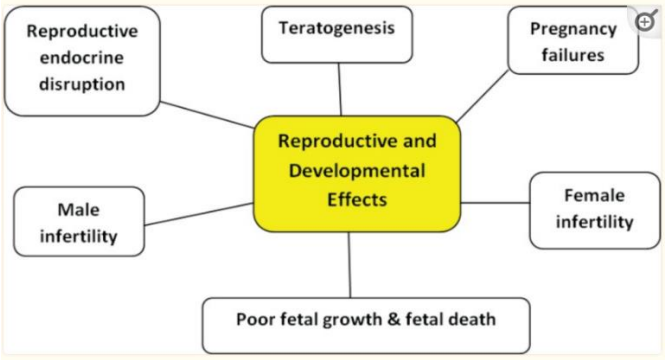

Figure 4: Reproductive and developmental disorders in aluminium toxicosis. Source: El Mazoudy and Bekhet (2016).

Table 2: Muscoskeletal Toxicity Associated with Some Aluminum Exposure Based On Epidemiological Evidences

Aluminum exposures/ effects	Age (years)	Race	Sex	Occupation
Liver steatosis	45-54	Hispanics	Mostly males	None in particular
Nephrotic syndrome	2-7	Asians	Mostly males (boys)	None (occurs mostly in children)
Memory loss	65 and above	African Americans	Mostly females	Retired/ housewives
Tremor	40 and above	African Americans	Mostly males	Laborers (and other physically rigorous jobs)
Jerking	30-50	Europeans	Mostly males	None in particular

Source: Exley (2018).

3.3.8 Hepato-renal and pancreatic effects

Al causes oxidative injuries to the kidney and liver leading to tissue degeneration and necrosis, and associated serum biochemical derangements (Nikolov *et al.*, 2016; Mailloux *et al.*, 2021; Bai *et al.*, 2018; Li *et al.*, 2015; Xu *et al.*, 2017). Abdel-Wahab (2018) reported a significant increase in the activities of alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and total bilirubin, as well as increased serum urea and creatinine levels after oral administration of 20 mg/kg of Al chloride for 30 days in experimental rats. Ingestion of aluminium phosphide pellets was reported to induce acute pancreatitis in one patient (Verma *et al.*, 2017). The hepatic and pancreatic lesions cause changes in metabolism which result in hyperglycaemia, hypoproteinaemia, hyperlipidaemia, hypercholesterolaemia and hypertriglyceridaemia (Omar *et al.*, 2018; Kowalczyk *et al.*, 2014; Türkez *et al.*, 2021; Abdel-Wahab, 2018; Belaïd-Nouira *et al.*, 2019).

3.3.9 Mammary gland or breast effects

Breast cancers and cysts are mammary gland conditions where emerging evidence are suggesting that Al may be involved in their causation (Darbre, 2016, Pineau *et al.*, 2014; Linhart *et al*., 2017). In a case control study (Linhart *et al.*, 2017), the use of underarm cosmetic products containing Al was significantly associated with breast cancer incidence and the Al levels in breast tissues were significantly higher in breast cancer cases than controls (5.8 versus 3.8 nmol/g). Breast cancer patients had higher levels of Al in breast tissues than in blood serum (Darbre *et al.*, 2019b). There were higher levels of Al in nipple aspirates of cancer patients than healthy controls and higher Al levels in breast cyst fluid than serum or milk (Darbre *et al.*, 2021). Current evidence suggests that Al can induce DNA damage in human breast epithelial cells and subsequently induce proliferation of the cells (Darbre *et al.*, 2019a, b). Thus, Al may increase the risk of breast cancer by acting as a metalloestogen (Darbre, 2016). The migratory and invasive properties of oestogen-responsive MCF-7 human breast cancer cells were increased in the presence of Al (Darbre *et al*., 2019a, Bakir and Darbre, 2015).

3.4 Diagnosis and Treatment of Aluminium Intoxication

Accelerator mass spectroscopy, graphite furnace atomic absorption spectrometry, flame atomic absorption spectrometry, electro-thermal atomic absorption spectrometry, neutron activation analysis, inductively coupled plasma atomic emission spectrometry, inductively coupled plasma mass spectrometry, and laser microprobe mass spectrometry are analythical methouds of measuring aluminum (Kumar *et al.*, 2018; Yadav *et al.*, 2017). Contamination is a major problem encountered in theanalysis of Al by all methods except that using radioactive 26Al (Luporsi*et al.*, 2018). When using the other methods, all items used during collection, preparation, and assay should be checked for Al contribution to the procedure (Luporsi*et al.*, 2018).

Treatment of Al intoxication is done with the chelating agent, deferoxamine, which is a colourless crystalline base, produced by the bacterium, Streptomyces pilosus (Kerr *et al.*, 2021). Structurally, it is composed of one molecule of acetic acid, two molecules of succinic acid and three molecules of 1-amino-5 hydroxylamine pentane (Gupta & Ahlawat, 2015; Rashedinia *et al.*, 2016; Bhalla & Singh, 2015; Kerr *et al.*, 2021). But due to the chemical similarity between Al and iron, it can also successfully mop-up excess Al from the body. Deferoxamine administered intravenously has been shown to reduce the body Al load and to ameliorate injury to the bone and brain in patients receiving hemodialysis and peritoneal dialysis. It has also been used successfully to treat Al toxicity in children. Deferoxamine therapy seems beneficial for those with established Al toxicity; however, this therapy is not without hazards. It may cause allergic reactions such as pruritus, wheals and anaphylaxis. Other adverse effects include dysuria, abdominal discomfort, diarrhea, fever, leg cramps, cataract, and tachycardia (Darbre, 2015; Gupta & Ahlawat, 2015).

Other chelating agents such as citric, malonic, oxalic, and succinic acids have been used experimentally to reduce aluminum load in rats and mice (Gupta & Ahlawat, 2015; Rashedinia *et al.*, 2016; Yadav *et al.*, 2017; Luporsi *et al.*, 2018; Kerr *et al.*, 2021). Antioxidants and free radical scavengers such as selenium, melatonin, boric acid and vitamin C have been employed experimentally to ameliorate the deleterious effects of free radicals produced as a result of Al.

Dihydroxyacetone (DHA) has been proposed as another viable treatment for AlP poisoning (Oghabian et al., 2020). Administration of DHA was found to increase the systolic and diastolic BP of AlP poisoned patients. Thus, DHA was found to reduce the impact of low BP in AlP. Furthermore, it was found to increase respiratory rates (Kumar *et al.*, 2018; Yadav *et al.*, 2017). This finding is consistent with animal studies on DHA. Luporsi*etal*, (2018) and Kerr *et al.*, (2021) showed that DHA was used to regulate BP and respiratory rate in rats. DHA has also been observed to play protective role in the acute anoxemia which is present in AlP poisoning and has an effective role in improving metabolic acidosis. Furthermore, studies have shown that, DHA as an ATP supplier increased viability of PH3-treated cells through elevation of ATP production in glycolysis process and through reduction of oxidative damage (Rashedinia *et al.*, 2016; Kumar *et al.*, 2018; Luporsi *et al.*, 2018; Kerr *et al.*, 2021).

3.5 Musculoskeletal Toxicity

The skeleton (which includes bones, ligaments, tendons, and cartilage) and muscles that are attached to it make up the **musculoskeletal system.** It provides the body with its fundamental framework, posture, and range of motion. It gives the muscles and other soft tissues a framework. The larger bones in the body include bone marrow, which is where blood cells are made in addition to their basic structural function. Additionally, calcium and phosphorus are important mineral stores in all bones. To keep the respiratory system running and the body temperature stable, muscles contract. The musculoskeletal system may experience issues as a result of a wide range of illnesses and conditions. Pain and movement restrictions can be brought on by aging, traumas, congenital anomalies (birth defects), and disease.

Musculoskeletal Toxicity refers to the negative effects of medications or chemicals on the composition and/or functionality of the muscles, bones, and joints. Unfortunately, it could result in serious. Based on this study the deleterious effects of drugs or chemicals on the composition and/or functionality of the muscles, bones, and joints are referred to as musculoskeletal toxicity (Bhalla & Singh, 2015; Kerr *et al.*, 2021). Unfortunately, it can lead to serious health problems such as osteomalacia, fluorosis, and arthritis. This study addressed issues related to the health effects of Al. Issues raised by the literature reviewed were based on the neurotoxin effect of Al, possible risks and harms along with the possible interventions. The effect of Al on neurotoxicity in humans remains unclear as studies have found it difficult to prove causality with respect to Al (Bhalla & Singh, 2015; Kerr *et al.*, 2021). This is possibly due to ethical concerns with respect to human studies as humans cannot be injected with Al.

Preclinical investigations with other inhibitors have revealed musculoskeletal effects (Wojtowicz-Praga, 2019). Swelling was detected around the joints of both rats and dogs in preclinical investigations with PG-116800 during chronic toxicity studies (3 and 6 months in rats and 12 months in dogs;, Procter & Gamble Pharmaceuticals, unpublished data) (Bissett *et al.*, 2005). In obvious relation to the swelling, rats and dogs developed collagen buildup connected with joint structures (Sher *et al.*, 2015). Proliferation of periosteal fibrous tissue and bone resorption were seen in the joint of dogs after 12 months of investigation. When the effects were observed at the end of a three-month healing period, they appeared to be reversible (Wojtowicz-Praga, 2019). As a result of the possible musculoskeletal toxicity of inhibitors was recognized prior to the start of the trial, safety procedures. Although a complete hand examination was part of the baseline physical examination, investigators were more aware of hand abnormalities after observing cases with asymptomatic nodules. Withdrawal of patients in the 200-mg dosage group may result in over-reporting of musculoskeletal toxicity upon withdrawal in this group following unblinding. The hand findings were clinically similar to those seen in the early stages of Dupuytren contracture (Bissett *et al.*, 2005; Lehmann *et al.*, 2015).

Furthermore, issues such as enteropathy which is believed to be the result of Al poisoning in humans have not been conclusively proven. However, Kerr *et al.* (2021) blamed the possible neuro-toxic effect of Al on the slow removal of Al from the brain. Furthermore, the study suggested that the impact of Al with respect to neurotoxicity is possibly hinged on dosage as there is the possibility of neurotoxicity when Al levels were around 100µg aluminium/g creatinine. However, there is reason to believe that Al toxicity could predispose an individual to long term risks when it comes to issues such as Alzheimer's or dementia. This is due to the Al content in brain of Alzheimer's patients (Gupta 2015; Rashedinia *et al.*, 2016; Kumar *et al.*, 2018). Al has been shown to slowly leave the brain and as such it can be suggested that the Al present in the brain of Alzheimer's patients accumulated over time. Furthermore, issues related to the use of Al products and possible risk of breast cancer was not observed in this study. Al exposure from antiperspirant use was found to be insignificant according to studies (Bissett *et al.*, 2005; Lehmann *et al.*, 2015). Furthermore, the pathway for development of breast cancer due to Al use is still unclear and unproven.

Treatment of Al exposure involves the use of a chelating agent to mop up excess Al from the body. Deferoxamine was initially used to mop up iron but has been shown to help with Al too due to similarities in both. However, the side effects of deferoxamine use have been shown to be quite severe.

4. Conclusion

The musculoskeletal system is therefore negatively impacted by aluminum, it might be said. Similar negative effects to those reported for other MMP inhibitors were observed in the musculoskeletal system. Given that the majority of MMP inhibitors are now being reported to have these side effects, this is probably due to a class effect. The effectiveness of DHA in treating AlP should be the main topic of future research. It would be wise to look for other, less harmful detoxifying options for aluminium.

Declaration

Competing Interest

The authors declare no competing interest

Authors Contribution

All listed authors contributed equally to the literature writing, review, research process sans editing of article.

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