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REVIEW ARTICLE

Aluminium toxicosis: a review of toxic actions and effects

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ABSTRACT

Aluminium (Al) is frequently accessible to animal and human populations to the extent that intoxications may occur. Intake of Al is by inhalation of aerosols or particles, ingestion of food, water and medicaments, skin contact, vaccination, dialysis and infusions. Toxic actions of Al induce oxidative stress, immunologic alterations, genotoxicity, pro-inflammatory effect, peptide denaturation or transformation, enzymatic dysfunction, metabolic derangement, amyloidogenesis, membrane perturbation, iron dyshomeostasis, apoptosis, necrosis and dysplasia. The pathological conditions associated with Al toxicosis are desquamative interstitial pneumonia, pulmonary alveolar proteinosis, granulomas, granulomatosis and fibrosis, toxic myocarditis, thrombosis and ischemic stroke, granulomatous enteritis, Crohn's disease, inflammatory bowel diseases, anemia, Alzheimer's disease, dementia, sclerosis, autism, macrophagic myofasciitis, osteomalacia, oligospermia and infertility, hepatorenal disease, breast cancer and cyst, pancreatitis, pancreatic necrosis and diabetes mellitus. The review provides a broad overview of Al toxicosis as a background for sustained investigations of the toxicology of Al compounds of public health importance.

KEY WORDS: aluminium; intoxication; pathology; toxicity; toxicosis

Introduction

Aluminium (Al) is the most widely distributed metal in the environment (Delhaize and Ryan, 1995; Ranjbar *et al.*, 2008; Exley and House, 2011) occurring naturally in the trivalent state (Al^{+3}) as silicates, oxides and hydroxides, but may combine with other elements such as chlorine, sulphur, fluorine, as well as form complexes with organic matter (Jones and Bennet, 1986; Ganrot, 1986; Martin, 1992). 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, 1979). Exposures to Al occur in occupations associated with mining and processing of ore, scrap 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.*, 1998; Vandenplas *et al.*, 1998; Boran *et al.*, 2013).

Several chemical compounds with Al are in extensive use in various products and processes associated with human activities. These compounds are Al chloride, Al hydroxide (alumina trihyrate), Al nitrate, Al phosphate, Al sulfate (alum), Al potassium (potash alum), Al ammonium sulfate (ammonium alum) and Al silicate (Anon, 1982; Lewis, 2001). 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, 1982, 2008a; Malakoff, 2000; Lewis, 2001; Soni *et al.*, 2001; Saiyed and Yokel, 2005).

The Al ion has no physiological role in metabolic processes (Exley and House, 2011) but it can be a metallic

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toxicant to humans and animals (Becaria *et al.*, 2002) when there is high body burden of the metal after natural or unnatural exposure (Exley, 2013). 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, 1976). Toxicosis due to Al accumulation in mammalian tissues was associated with various pathologic effects (Wills and Savory, 1983; Kaiser *et al.*, 1984; Boyce *et al.*, 1986; Drüeke *et al.*, 1986; Hewitt *et al.*, 1990; Bushinsky *et al.*, 1995; Reinke *et al.*, 2003; Abubakar *et al.*, 2004; Bogdanović *et al.*, 2008; Yousef and Salama, 2009; Khattab *et al.*, 2010; Blaylock, 2012; Buraimoh and Ojo, 2013; Sumathi *et al.*, 2013). Recent reviews on toxic effects of Al covered reproductive toxicity (Mouro *et al.*, 2017), pulmonary lesions (Kongerud and Søyseth, 2014; Taiwo, 2014), impact on the breast (Darbre, 2016), bone abnormalities (Chappard *et al.*, 2016; Klein, 2019), immunotoxity (Zhu *et al.*, 2014a) and neurologic disorders (Colomina and Peris-Sampedro, 2017; Morris *et al.*, 2017). This review is an abridged and global overview of toxic effects of Al and its compounds, covering some relevant aspects of exposure and updated systemic toxicosis in humans and animals, relevant as background for prospective toxicopathologic studies.

Literature search justification and methods

The initial goal in our study group was to explore the role of the ubiquitous Al ion in erythrocyte membrane dysfunction (Igbokwe, 2016) and metabolic dysregulation (Igwenagu, 2017). With the preliminary literature search starting in 2013 and looking backwards in time, research publications revealed a myriad of toxic actions of Al causing pathological conditions. Several narrative literature reviews, referred to in the introductory section, were discovered to have focused on Al toxicity of one system of the body in each review, covering the scope of nervous, reproductive, respiratory, mammary, skeletal and immune tissue toxicities. One review addressed the toxicities in bone, hematopoietic tissue and kidney (Jeffrey *et al.*, 1996) and another summarized the physiological alterations in the musculoskeletal, respiratory, cardiovascular, hepatobiliary, endocrine, urinary and reproductive systems(Nayak, 2000). Thus the question raised was whether Al toxicosis, as a disease entity, existed in the literature with current research information. The literature search for Al toxicosis as a narrative review (Green *et al.*, 2006) with a broad thematic approach was unproductive and this observation justified the need for the current review.

Toxicosis associated with Al exposure is the pathological condition or disease caused by the toxic actions of Al and its compounds. The literature search was intended to collate, synthesize and integrate the published reports on the subject matter without meta-analysis and critical evaluation of published data. For this review, the major themes for the literature search under the title included exposure modalities, toxic actions and effects in cells, tissues and systems of the body (Figure 1). These themes provided the key words and phrases for the internet search. The initial search platform was usually GOOGLE.COM with the linked GOOGLE SCHOLAR helping to search related articles. Subsequently, the search was extended to MEDLINE, PUBMED, PMC Europe, RESEARCHGATE, SCOPUS, SCIENCEDIRECT, SAGE, TANDFONLINE and SPRINGERLINK. On each platform, an article that was found could also have links to related articles and these links were followed to enrich the search outcomes. Every article was read as an abstract or full article after downloading to the literature bank. At this stage, "backward search" based on references of read articles could be done and "forward search" was required when new themes emerged that needed further exploration. The

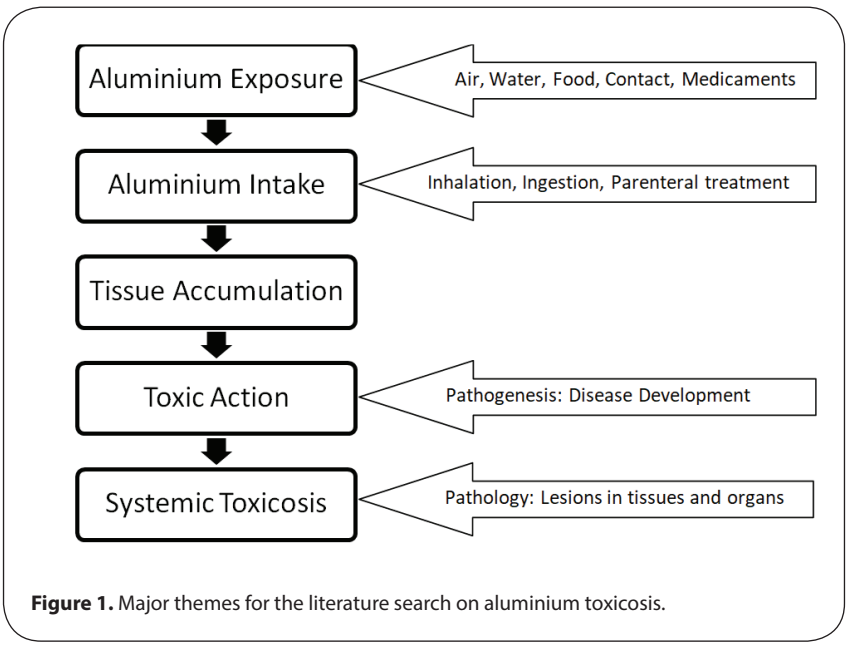

Figure 1. Major themes for the literature search on aluminium toxicosis.

integration of the literature search processes are illustrated in Figure 2. Occasionally, article request options were used to obtain restricted publications and the articles were received from authors. The literature collated from the search was read for content comprehension. The body of knowledge was summarized and narrated after cognitive reflection and integration to represent the current knowledge of the literature on Al toxicosis. The articles with thematic contents were included for the review when they were published in journals with reputable standing. The contents of the excluded articles were peripheral to the themes under review.

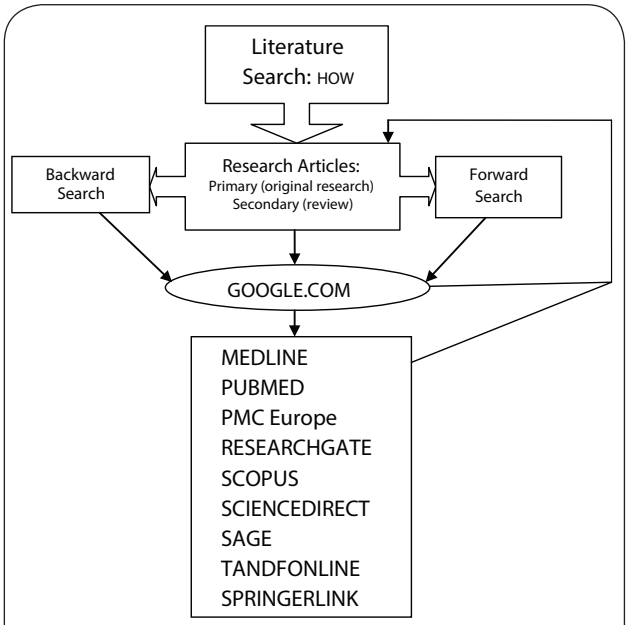

Figure 2. Integrated literature search process.

Exposure to aluminium

Aluminium intake

Aluminium in the air

The largest source of airborne Al-containing particles is the dust from soil and rocks (Lee and Von Lehmden, 1973; Sorenson *et al.*, 1974). Human activities, such as mining and agriculture, contribute to the dust in winds (Eisenreich, 1980; Filipek *et al.*, 1987). About 13% of atmospheric Al is attributed to anthropogenic emissions (Lantzy and MacKenzie, 1979). The major anthropogenic 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, 1973; Ondov *et al.*, 1982; Que Hee *et al.*, 1982). Cigarette smoke may contribute to the concentration of Al in the air (Exley *et al.*, 2006; Kazi *et al.*, 2009; Pappas, 2011; Afridi *et al.*, 2015). The air containing Al particles or droplets becomes the source of Al in inhaled aerosols.

Aluminium in drinking water

Al occurs ubiquitously in natural waters due to weathering of Al-containing rocks and minerals and mobilization from terrestrial to aquatic environment (Campbell *et al.*, 1992). This mobilization of Al is often seasonal in nature and is associated with pH depressions (acidification) occurring during the spring snow melt or associated with erosion from specific storm events (Rosseland *et al.*, 1990; Nelson and Campbell, 1991; Campbell *et al.*, 1992). Al concentrations in surface waters 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, 1980). Industrial release of Al in waste materials into surface waters from processing and manufacturing facilities could be toxic to aquatic life (Filipek *et al.*, 1987; Trieff *et al.*, 1995; His *et al.*, 1996; Gensemer and Playle, 1999). Acidic drainage from mines or acid rain may cause an increase in the dissolved Al content of the surrounding water bodies (Cronan and Schofield, 1979; Filipek *et al.*, 1987). The use of Al compounds as coagulating agents in the treatment of water for drinking could increase its Al content (Qureshi and Malmberg, 1985; Henshaw *et al.*, 1993; Cech and Montera, 2000). 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.*, 1990). The source of water for human and animal consumption and the purification process involved may influence the Al content of drinking water as source of exposure.

Aluminium in food

Al is present in foods naturally or from the use of Al-containing food additives (Sepe *et al.*, 2001; Flaten, 2002; Hayacibara *et al.*, 2004; Yokel *et al.*, 2008). The concentrations in foods and beverages vary widely, depending upon the food product, the type of processing used, and the geographical areas in which the food crops are grown (Sorenson *et al.*, 1974; Pennington and Schoen, 1995). The foods highest in Al are those that contain Al additives (Pennington, 1988; Greger, 1992; Saiyed and Yokel, 2005; Yokel and Florence, 2006; Yokel, 2012). The use of Al cookware, utensils and wrappings can increase the amount of Al in food (Liukkonen-Lilja and Piepponen 1992; Pennington and Schoen, 1995). The migration of Al from cookware into food increases with the acidity of the food and the duration of exposure (Valkonen and Aitio, 1997; Lin *et al.* 1997). Al was also reported to migrate into fish grilled on Al foil and the migration of Al into foods appeared to be dependent on factors such as temperature, duration of cooking, the composition and pH of the food, and the presence of other substances like organic acids and salts (Ranau *et al.*, 2001). Foods found to be naturally high in Al include potatoes, spinach and tea (Pennington and Schoen, 1995; Stahl *et al.*, 2011). Processed dairy products and flour may be high in Al if they contain Al-based food additives (Pennington and Schoen, 1995).

Daily intakes of Al in humans from food range from 3.4 to 9 mg/day (Pennington and Schoen, 1995; Biego *et al.*, 1998; 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, 1992). Thus Al contents of harvested food products, processed foods, and cooked, baked or grilled foods may be sources of Al exposure.

Aluminium in pharmaceuticals and agrochemicals

The route of intoxications with pharmaceuticals and agrochemical sources may be through inhalation of aerosols, ingestion of medications or by parenteral administration. Humans and animals are exposed to Al-containing medications such as phosphate binders, antacids, buffered analgesics, antidiarrheal and antiulcer drugs (Lione, 1983, 1985; Yokel and McNamara, 2001; Krewski *et al.*, 2007). Various intravenously administered pharmaceutical products were reported to contain 684–5977 μg/g of Al (Sedman *et al.*, 1985). Many antacids contain 104–208 mg of Al per tablet, capsule or 5 ml of suspension (Zhou and Yokel, 2005). The use of other consumer items such as dentifrices, disinfectants, fumigants, pesticides, anti-perspirants and some cosmetics are sources of Al exposure (Lewis, 2001; 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, 1985; Tomljenovic and Shaw, 2011; Issa *et al.*, 2014). Adjuvant as a source of Al during vaccinations has been receiving attention in research (Malakoff, 2000; Keith *et al.*, 2002; Mitkus *et al.*, 2011; 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). More Al was absorbed into blood by rabbits after intramuscular injection with adjuvant containing Al phosphate compared to Al hydroxide (Hem, 2002). It is unlikely that parenteral Al administrations are a major source of Al exposure to livestock or pets (Issa *et al.*, 2014).

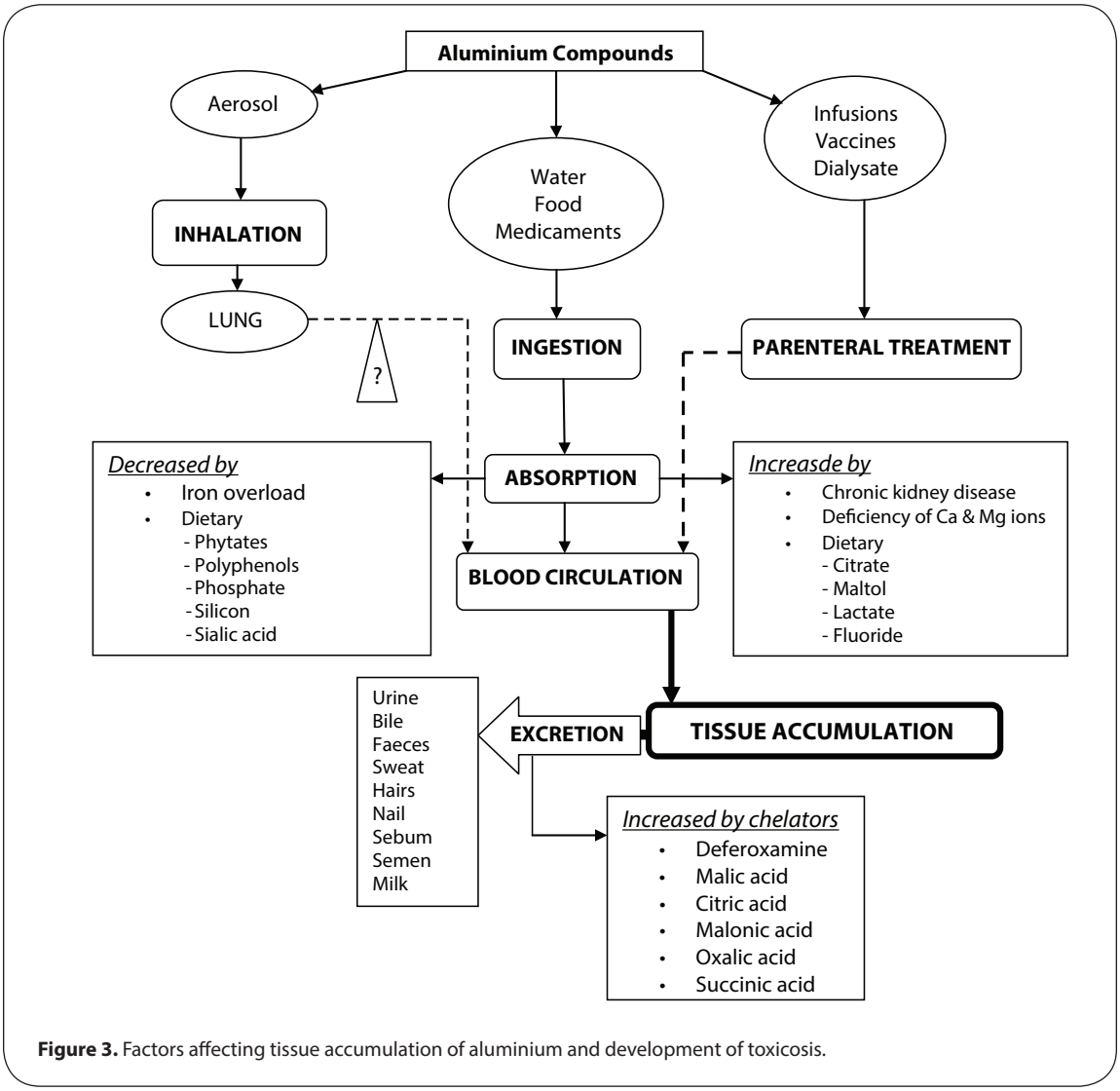

Figure 3. Factors affecting tissue accumulation of aluminium and development of toxicosis.

Food or water for livestock could be contaminated with Al when Al sulfate and zeolite are applied to litter and waste lagoons to reduce phosphorus loss from lands fertilized with the wastes and to reduce ammonia fumes in facilities (Moore *et al.*, 1999; Moore *et al.*, 2000; Codling *et al.*, 2002). Alum has also been added to dairy slurry to reduce ammonia emissions (Lefcourt and Mesinger, 2001). 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.

Absorption, distribution and elimination of aluminium

The dynamic chain of Al intake, absorption and elimination determines the level of tissue accumulation and development of toxicosis (Figure 3). Inhalation and ingestion (via food and water) are the two main routes through which Al gets into the body (Alfrey, 1980; Teraoka, 1981; Jouhanneau *et al.*, 1997). Following inhalation, Al compounds are deposited in the lungs (Christie *et al.*, 1963; Stone *et al.*, 1979; Thomson *et al.*, 1986). The lungs continually receive Al mostly as particles of Al silicates and other poorly soluble compounds (Thomson *et al.*, 1986). The concentration of Al in the lungs tends to increase with age and may result in respiratory anomalies where the Al is localized (Alfrey, 1980; Teraoka, 1981; 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.*, 1984; Steinhausen *et al.*, 2004). The absorption of Al is usually low and varied when compared with the amount ingested (Kawahara *et al.*, 2007). The uptake of Al through gastrointestinal pathway is complex and is influenced by various factors including individual differences, age, pH, stomach contents and type of Al compound (Priest *et al.*, 1996). Al absorption from water intake (about 0.3%) is greater than from food (about 0.1%) (Martyn *et al.*, 1989; Steinhausen *et al.*, 2004; Anon, 2008b; Zhou *et al.*, 2008).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.*, 2007). 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.*, 1987; Edwardson *et al.*, 1993; Anon, 2008c; Zhou *et al.*, 2008). However, there is complete Al uptake from parenteral fluids and vaccines with subsequent distribution to various parts of the body (Tomljenovic and Shaw, 2011).

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.*, 1991; Harris and Messori, 2002; Hemadi *et al.*, 2003; Chen *et al.*, 2010). 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.*, 2003). However, Al-transferrin complex may not bind to the transferrin-receptor (Hemadi *et al.*, 2003; Sakajiri *et al.*, 2010), indicating the existence of an alternative mechanism of cellular uptake of Al (DeVoto and Yokel, 1994; Anon, 2011). 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.*, 2007). 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, 1997) and Chen *et al.* (2010) 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, 2008c). Al has also been found in human skin, lower gastrointestinal tract, lymph nodes, adrenals, parathyroid glands, and in most soft tissue organs (Anon, 2008b). 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, 2008b). 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, 2008b). Al levels increase with age in tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals (Krewski *et al.*, 2007). 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, 1992; Krewski *et al.*, 2007). 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, 2011).

The Al ion in blood circulation is eliminated primarily by the kidneys (about 95%) in the urine, presumably as Al citrate (Shirley and Lote, 2005; Krewski *et al.*, 2007; Anon, 2008c). 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, 2008b). Al is also excreted in the milk, bile, feces, sweat, hairs, nails, sebum and semen (Gorsky *et al.*, 1979; Greger and Sutherland, 1997; Exley, 2013). Urinary excretion of Al is enhanced by chemical chelators such as deferoxamine and malic, malonic, citric, oxalic and succinic acids, as reviewed in the later section on treatment of Al in this document. On the whole, it is noted that Al accumulation, which is responsible for Al toxicosis, is enhanced by exposure to Al and its continuous intake, as well as increased intestinal absorption and decreased excretion of the metal (Figure 3).

Toxic actions of aluminium

The toxic actions of Al responsible for the toxic effects of the toxicities are diverse and capable of causing a multifaceted systemic toxicosis. These toxic actions are summarized in Table 1. The molecular targets of action generate outcomes in the cell and disrupt cellular homeostasis with consequences that lead to lesions in the cell (Figure 4), which are responsible for systemic toxicosis associated with structural and functional abnormalities of organs.

Toxic effects of Al arise mainly from its pro-oxidant activity which results in oxidative stress, free radical attack and oxidation of cellular proteins and lipids (Exley, 2013). Protein polypeptides are transformed to secondary structures when Al ions interact with them through oxygen-containing amino acids, side chains and protein backbone leading to ultimate denaturation (Mujika *et al.*, 2018) or conformational or structural alteration (Exley *et al.*, 1993; Zatta *et al.*, 2005; Exley, 2006) as in β-amyloid. The aggregation and precipitation of β-amyloid is triggered and potentiated by Al exposure which is associated with Alzheimer's disease (Bondy and Truong, 1999; Zatta *et al.*, 2005; Exley, 2006) and this phenomenon may be responsible for neuritic plaque deposition, neuronal death and dysneurogenesis. Fibrillation and aggregation of human islet amyloid polypeptide hormone (amylin) was stimulated by Al exposure leading to formation of β-pleated sheet structure (Mirhashemi and Aarabi, 2011; Mirhashemi and Shahabaddin, 2011; Xu *et al.*, 2016), which may predispose pancreatic β-cell to damage. The proteolytic degradation of the amyloid peptides is also prevented by Al, thereby enhancing the accumulation of the amyloid (Sakamoto *et al.*, 2006). Extracellular surfaces and intracellular ligands may likely associate with Al to induce inhibitory or stimulatory effects (Exley and Birchall, 1992). Interaction of Al with metabolic and other enzymes causes inhibition or activation of the enzymes (Hofstetter *et al.*, 1987; Xu *et al.*, 1990; Exley *et al.*, 1994; Zatta *et al.*, 1999, 2000; Yang *et al.*, 2003; Mailloux *et al.*,

Table 1. Toxic actions associated with aluminium exposure.

Toxic action or effect	Selected references
Oxidative stress, lipid peroxidation	Kattab *et al.*, 2010; Exley, 2013; Abd-Elhady *et al.*, 2013; Zhang *et al.*, 2016; Yang *et al.*, 2018; Yu *et al.*, 2019
Pro-inflammatory: organ inflammation in lung, intestine, heart, and testis	Fogarty *et al.*, 1998; Verma *et al.*, 2007; Lerner, 2007; Exley, 2013; Taiwo, 2014; de Chambrun *et al.*, 2014; Gherardi *et al.*, 2016; Martinez *et al.*, 2017; Hangouche *et al.*, 2017
Immunosupression: induces lymphocyte apoptosis and dysfunction, inhibits lymphocyte proliferation, causes macrophage dysfunction	Nordal and Dahl, 1988; Kammalov *et al.*, 2011; She *et al.*, 2012; Zhu *et al.*, 2014; Zhuang *et al.*, 2016; Xu *et al.*, 2018; Yu *et al.*, 2019
Protein denaturation and transformation	Exley *et al.*, 2006; Mujika *et al.*, 2018
Enzymatic stimulation or inhibition	Ohsaka and Nomura, 2016
Metabolic impairment: impairs glycolysis and Kreb's cycle; promotes lipid and protein oxidation	Xu et al 1990; Mailloux *et al.*, 2006
Genotoxicity: reduced cell proliferation and differentiation, dysneurogenesis	Nam *et al.*, 2014
Amyloidogenic and anti-amyloidolytic	Sakamoto *et al.*, 2006; Xu *et al.*, 2016
Acts as metalloestrogen, promotes proliferation and migration of breast cancer cells	Bakir and Darbre, 2015; Darbre, 2016
Induces teratogenesis causing foetal and neonatal defects	Malekshah *et al.*, 2005; Wang *et al.*, 2012; El Mazoudy and Bekhet, 2016
Disrupts mineral metabolism of Fe, P, Ca, Zn, Cu by altering intestinal absorption and cellular uptake	Jeffery *et al.*, 1996; Contini, 2007; Kell, 2009; Fu *et al.*, 2014; Zhu *et al.*, 2014
Induces apoptosis, eryptosis, tissue necrosis	Niemoeller *et al.*, 2006; Xu *et al.*, 2018; Yang *et al.*, 2018; Yu *et al.*, 2019
Disrupts cell membrane permeability and receptor function, increases osmotic fragility, inhibits membrane ATPases	Fu *et al.*, 2014; Zhang *et al.*, 2016; Sun *et al.*, 2018; Gomes *et al.*, 2019
Endocrine disruption: parathyroid hormone, testosterone, lutenizing hormone, follicle stimulating hormone, estradiol, norepinephrine, cortisol, thyroid hormone, insulin	Díaz-Corte *et al.*, 2001; Chinoy and Patel, 2001; Gonzelez-Suerez *et al.*, 2005; Shahraki *et al.*, 2008; Orihuela, 2011; Sun *et al.*, 2011; Muselin *et al.*, 2016; Zhuang *et al.*, 2016; Mouro *et al.*, 2018; Wei *et al.*, 2018 Gomes *et al.*, 2019
Inhibits cartilage formation	Zhang *et al.*, 2017
Inhibits bone formation and mineralization by increasing osteoclastic activity and reducing osteoblastic activity	Cox and Dunn, 2001; Li *et al.*, 2012; Cao *et al.*, 2016; Song *et al.*, 2016; Sun *et al.*, 2016; Yang *et al.*, 2016; Huang *et al.*, 2017; Yang *et al.*, 2018; Xu *et al.*, 2018
Induces hypertension (systolic and arterial)	Zhang *et al.*, 2016
Causes ischaemic stroke and thrombosis	Abedini *et al.*, 2014
Induces contact allergy	Netterlid *et al.*, 2013
Inhibits the biological function of vitamin D in the intestine linked to calcium absorption	Dunn *et al.*, 1995

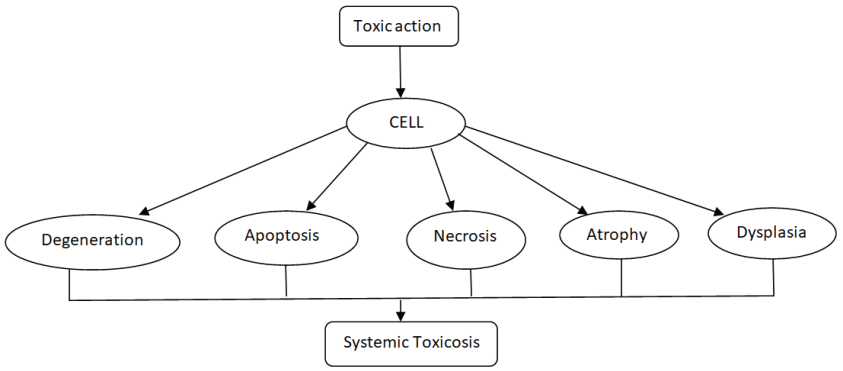

Figure 4. Cellular pathology in the systemic toxicosis of aluminium.

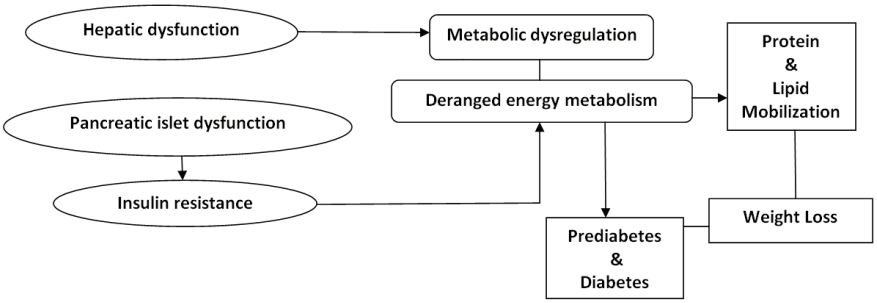

Figure 5. Metabolic abnormalities in aluminium toxicosis.

2006; Sushma *et al.*, 2007; Ohsaka and Nomura, 2016). Al binds to the phosphate groups of nucleotide such as adenosine triphosphate (ATP) and affects energy metabolism (Kawahara *et al.*, 2007). Exposure of hepatocytes to Al impedes ATP production, inhibits glycolysis, impairs the function of tricarboxylic acid (Kreb's) cycle and promotes lipid and protein oxidation (Xu *et al.*, 1990; Mailloux *et al.*, 2006) with a metabolic shift to lipogenesis in tissues (Han *et al.*, 2013). These metabolic perturbations (Figure 5) may be responsible for the reports of body weight loss and decreased production performance (like egg production) in animals exposed to Al (Wisser *et al.*, 1990; Capdevielle and Scanes, 1995; Li *et al.*, 2015).

Al exposure can cause the disruption of iron homeostasis leading to iron overload (Ward *et al.*, 2001; Contini *et al.*, 2007). Oxidative stress and injury, mediated by iron, seems to be facilitated by Al (Xiea *et al.*, 1996). Elevated concentrations of cellular iron can enhance oxidative damage to the cell and are linked to the pathogenesis of neurodegenerative disorders (Jang and Surh, 2002; Toyokuni, 2002; Adzersen *et al.*, 2003; Deugnier, 2003; Ng, 2004). Iron overload due to Al exposure has been shown to result in increased lipid peroxidation, DNA lesions, and apoptosis induced by reactive oxygen species (Bacon *et al.*, 1983; Oteiza, 1994; Kell, 2009). Apoptosis of erythrocytes (eryptosis), lymphocytes and osteoblasts is also stimulated by Al ions (Niemoeller *et al.*, 2006; Li *et al.*, 2012; Xu *et al.*, 2018; Yang *et al.*, 2018; Yu *et al.*, 2019). The oxidative injury was reported to activate the JNK apoptotic pathway in ostoblasts (Yang *et al.*, 2018). In culture, Al induced apoptosis of osteoblasts by inhibiting apoptotic Bcl-2 protein expression and increasing the expression of pro-apoptotic Bax, Bak and Bim proteins (Xu *et al.*, 2018). Al may decrease ferritin synthesis and increase the expression of transferrin receptors, thereby disrupting the normal synthesis of transferrin receptors with ferritin creating increased free iron levels in the cell, resulting in an increase of oxidative damage via the fenton reaction (Yamanaka *et al.*, 1999). The activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione (GSH) are affected by Al exposure because of oxidative stress (Oteiza *et al.*, 1993a; Julka and Gill, 1996; Campbell *et al.*, 1999). Abnormal increases in levels of malondealdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) were reported along with decreased levels of antioxidants such as GSH, GPx, SOD, and CAT in tissue homogenates of rats exposed to Al (Anane and Creppy, 2001; Gonzalez *et al.*, 2007; Newairy *et al.*, 2009; Khattab *et al.*, 2010; Bai *et al.*, 2012; Exley, 2013; Abd-Elhady *et al.*, 2013; Zhang *et al.*, 2016; Yu *et al.*, 2019).

Mutagenesis and alteration of gene function may arise from the toxic action of Al with changes in transcriptional expressions (Exley, 2013). Somatic and germinal

genetoxicity in mice exposed to Al was associated with chromosomal aberrations and depression of mitosis (D'Souza *et al.*, 2014). Neuronal gene expression is influenced by the binding of Al to DNA (Lukiw *et al.*, 1998) predisposing cells to or causing genotoxicity (Pogue and Lukiw, 2016) and thus Al exposure may lead to reduction of cell proliferation and differentiation (Nam *et al.*, 2014, 2016; Sun *et al.*, 2015; Cao *et al.*, 2016; Li *et al.*, 2016; Yang *et al.*, 2016; Sun *et al.*, 2016, 2017; Huang *et al.*, 2017). Neurogenesis was impaired by Al toxicity (Nam *et al.*, 2014, 2016). Osteoblastic proliferation and differentiation were inhibited by Al when there was downregulation and inhibition of Wnt/β-catenin signaling pathway (Sun *et al.*, 2015; Cao *et al.*, 2016; Huang *et al.*, 2017; Sun *et al.*, 2017). Osteoblast differentiation was also inhibited by Al through the inhibition of BMP-2 signaling pathway (Yang *et al.*, 2016). In addition, osteoblast mineralization in vitro was inhibited by Al-induced decline in transforming growth factor (TGF)-β1 expression and action, and upregulation of Smad7 expression (Sun *et al.*, 2016) along with decreased protein expressions of osteopontin, osteocalcin and osteosialoprotein (Song *et al.*, 2017). The mineralization of bone is impaired by decreased calcium absorption (Orihuela, 2007), because Al inhibits the synthesis of calbindin, a calcium-binding protein involved in transcellular transport of calcium in enterocytes and inhibits the stimulation of synthesis of osteocalcin (the bone matrix protein) in osteoblasts by vitamin D via cellular unresponsiveness (Fanti *et al.*, 1992; Jeffery *et al.*, 1996; Cox and Dunn, 2001). The expression of cartilage stimulating growth factors, TGF-β1 and BMP-2, were inhibited by Al, thereby suppressing cartilage growth and disrupting cartilage structure (Zhang *et al.*, 2017). The effects of Al on growth manifested in developmental abnormalities of fetuses due to teratogenesis in pregnant individuals (Malekshah *et al.*, 2005; Wang *et al.*, 2012; El Mazoudy and Bekhet, 2016; Yassa *et al.*, 2017).

The proliferative and migratory characteristics of the human breast cancer cell may be affected by Al when it acts as a metalloestrogen or increases the intracellular secretion of matrix metalloproteinase (MMP9) and levels of activated MMP14 that are involved in migratory and invasive properties of cancerous cells, thereby influencing the metastatic process (Darbre *et al.*, 2013a, b; Bakir and Darbre, 2015; Darbre, 2016). It is unclear whether Al has the capacity to initiate and promote any other carcinogenic process apart from the indirect evidence provided above with regard to breast cancer.

Pro-inflammatory actions of Al have been reported in various tissues (Fogarty *et al.*, 1998; Verma *et al.*, 2007; Lerner, 2007; Exley, 2013; Taiwo, 2014; de Chambrun *et al.*, 2014; Gherardi *et al.*, 2016; Martinez *et al.*, 2017; Hangouche *et al.*, 2017). It is triggered by Al-induced oxidative stress and free radical production (Milnerowicz *et al.*, 2015). Exposure to Al increased pro-inflammatory cytokine (interleukin-1β and tumor necrosis factor alpha) levels (Jangra *et al.*, 2015) and elevated gene expression of tumor necrosis factor alpha (TNFalpha) and macrophage inflammatory protein-1alpha (MIP-1alpha) in concentration-dependent manner (Johnson and Sharma, 2003). Genes that encode pro-inflammatory signaling elements were significantly up-regulated by Al (Lukiw *et al.*, 2005). These cytokines that are released due to Al exposure can recruit leukocytes, which secrete more pro-inflammatory cytokines and other chemokines, to exacerbate the inflammation (Milnerowicz *et al.*, 2015). The inflammation can be a chronic granulomatous type (Chen *et al.*, 1978; de Vuyst *et al.*, 1987; Forgarty *et al.*, 1998; Gherardi and Authier, 2012) and Al has been reported to cause granuloma formation in vitro (de Chambrun *et al.*, 2014). Chronic exposure of mice (5 months) to Al sulfate in drinking water elicited time-dependent systemic inflammation characterized by increased serum interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), C-reactive protein (CRP) and a triad of pro-inflammatory microRNAs (miRNA-9, miRNA-125b and miRNA-146a) and the biomarkers of inflammation indicated progressive chronic inflammation in the exposed animals (Pogue *et al.*, 2017). The inflammatory conditions associated with Al exposure are summarized in Figure 6.

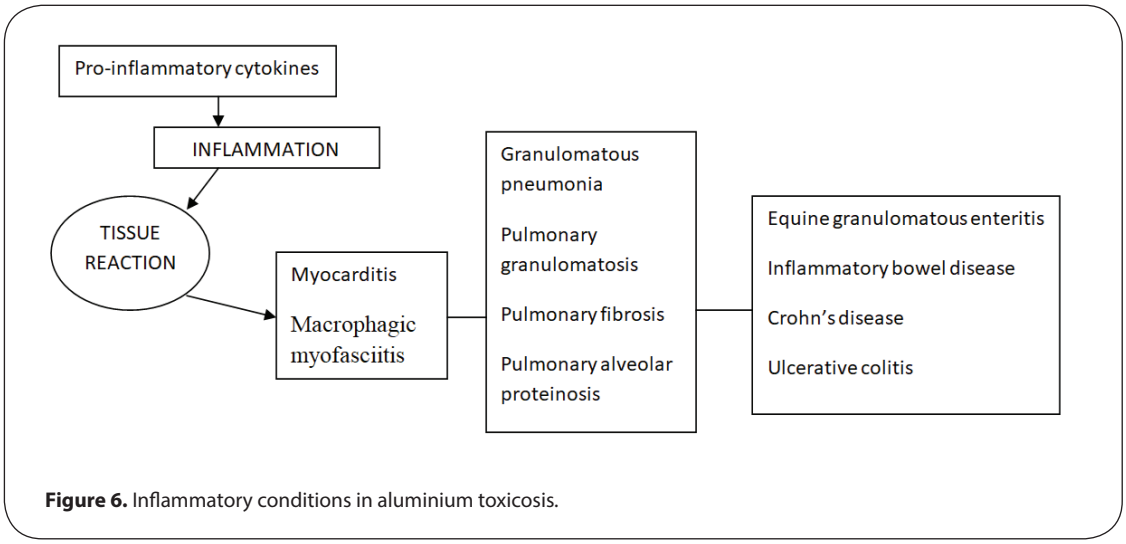

Figure 6. Inflammatory conditions in aluminium toxicosis.

Table 2. Effects of aluminium exposure on endocrine secretions in animals.

Hormone	Animal/human	Increase	Decrease	Normal	Reference
Plasma growth hormone	Duckling			+	Capdevielle *et al.*, 1995
Plasma insulin-like growth factor 1	Duckling			+	Capdevielle *et al.*, 1995
Plasma cortisol	Rat	+			Vasanthan and Joshi, 2018
Blood norepinephrine	Rat	+			Zhuang *et al.*, 2016
Serum estradiol	Mice		+		Chinoy and Patel, 2001
Serum testosterone	Gerbil (*Meriones unguiculatus*)	+			Reza and Palan, 2006; Gomes *et al.*, 2019
	Rat		+		Shahraki *et al.*, 2008; Sun *et al.*, 2011; Muselin *et al.*, 2016; Mouro *et al.*, 2018
Serum luteinizing hormone	Rat		+		Shahraki *et al.*, 2008; Sun *et al.*, 2011; Muselin *et al.*, 2016
	Rat	+			Reza and Palan, 2006
Serum follicule stimulating hormone	Rat			+	Reza and Palan, 2006; Sun *et al.*, 2011
	Rat		+		Shahraki *et al.*, 2008
Serum/plasma parathyroid hormone	Rat		+		Cannata *et al.*, 1983; Díaz-Corte *et al.*, 2001; Gonzelez-Suerez *et al.*, 2005
	Human patient with chronic renal failure, on haemodialysis	+			Sherrard *et al.*, 1985; Cournot-Witmer and Plachott, 1990
Serum thyroid hormone, T4	Rat		+		Orihuela, 2011
Serum thyroid hormone, T3	Rat		+		Orihuela, 2011
Serum thyroid hormone, free T4	Rat			+	Orihuela, 2011
Serum thyrotropin (TSH)	Rat			+	Orihuela, 2011
Insulin	Rat	+ (Acute)	+ (Chronic)		Wei *et al.*, 2018

As an adjuvant, Al in vaccines induces local inflammation that involves the NLRP3 inflammasome and NLRP3-independent pathways where macrophages, B- and T-lymphocytes play important roles in enhancing antigen-specific immune responses and increasing inflammatory cytokine production (Exley *et al.*, 2010; Hogenesch, 2013; Zlatkovic *et al.*, 2013; He *et al.*, 2015). Toxic exposure to Al causes immunotoxicity leading to inhibition of lymphocyte and macrophage functions (Nordal *et al.*, 1988; Zhu *et al.*, 2014a). Immunosuppression arises from oxidative stress which is associated with apoptosis of lymphocytes (Yu *et al.*, 2019) and damage to thymocytes and lymphocytes (Kamalov *et al.*, 2011). Immune functions of splenic B- and T-lymphocytes were inhibited in vitro by reduction of lymphocyte proliferation, cytokine secretion and proportions of CD-3(+) and CD-4(+) lymphocytes (She *et al.*, 2012). LPS-induced NLRP3 inflammasome activation, IL-1β, IL-6 and TNF-α expression and release in peritoneal macrophages were also suppressed by Al exposure (Xu *et al.*, 2018). Norepinerphrine release and activation of β-adenoceotors/cAMP pathway were promoted by Al in vivo, and this endocrine factor suppressed macrophage expressions of MIF and TNF-α (Zhuang *et al.*, 2016). Contact allergy to Al has been reported as an aberrant immune response in those having atopic dermatitis (Netterlid *et al.*, 2013).

The endocrine disruptions or hormonal changes associated with Al exposure are summarized in Table 2. Al accumulates in endocrine glands and causes damage to the glands through oxidative stress, thereby decreasing the level of the hormones secreted (Morrissey *et al.*, 1983) into the bloodstream for action at the target organs, causing organ hypofunction. For instance, there are reports of testicular and ovarian failures (Mohammed *et al.*, 2008; Fu *et al.*, 2014; Miska-Scramm *et al.*, 2017) from inadequate androgenic hormone levels (Chinoy and Patel, 2001; Shahraki *et al.*, 2008; Sun *et al.*, 2011; Muselin *et al.*, 2016; Mouro *et al.*, 2018) and decreased androgen receptor functions (Fu *et al.*, 2014; Sun *et al.*, 2018; Gomes *et al.*, 2019), bone pathology due to dysfunction of parathyroid gland (Cannata *et al.*, 1983; Sherrard *et al.*, 1985; Cournot-Witmer and Plachott, 1990; Díaz-Corte *et al.*, 2001; Gonzelez-Suerez *et al.*, 2005), prediabetes and diabetes due to pancreatic islet damage (Wei *et al.*, 2018). Parathyroid function can be impaired by the Al ion acting on calcium-sensing receptors when calcium level is low, with a higher efficiency than calcium and decreasing the expression of the receptors in the gland (Gonzelez-Suerez *et al.*, 2005). The metabolic effect of some levels of thyroxine (T3 and T4) decline without change in free T4 level is yet to be ascertained (Orihuela, 2011). The secretion of the hormone, sometimes increases when Al ion is stimulatory to the gland or because the target organs are refractory or unresponsive to the hormone when there is receptor depletion or decreased expression of the receptor on the cell membrane. The Al ions act as chemical stressor by promoting the release of norepinerphrine (Zhuang *et al.*, 2016) and cortisol (Vasanthan and Joshi,

2018); and the elevated levels of these hormones can cause increase in blood pressure (Zhang *et al.*, 2016). Elevated blood insulin level is associated with insulin resistance due to depletion of glucose transporter-4 protein expression in skeletal muscles during Al exposure (Wei *et al.*, 2018). Pseudohyperparathyroidism is associated with osteitis fibrosa in human patients with renal failure and hypercalcemia when exposed to Al intoxication (Sherrard *et al.*, 1985).

The cellular membrane is vital for the viability of the cell and Al exposure disrupts membrane activity via oxidative stress in various ways. In Alzheimer's disease associated with Al exposure, membrane fluidity increased in platelets and decreased in erythrocytes; and this observation was corroborated by a study where in vitro exposure of membrane suspensions to Al increased fluidity of platelet membranes and decreased the fluidity of erythrocyte membranes (van Rensburg *et al.*, 1992) with consequent effect on the viability of platelets (Neiva *et al.*, 1997) and erythrocytes (Vittori *et al.*, 2002). Erythrocyte membrane permeability and osmotic fragility are affected by *in vivo* and *in vitro* Al exposures (Igbokwe, 2018). Erythrocyte osmotic fragility decreased (Bazzoni *et al.*, 2005) or increased (Zatta *et al.*, 1989; Hernández *et al.*, 2008; Al-Qayim *et al.*, 2014; Oztürk and Ozdemir, 2015, Zhang *et al.*, 2016; Cheng *et al.*, 2018) depending on the Al speciation and type of erythrocyte injury. Eryptotic (apoptotic) injury reduces the erythrocyte aggregate size (Bazzoni *et al.*, 2005) because of the shrinking effect, thereby increasing osmotic resistance (Igbokwe, 2016). On the other hand, eryptotic injury which progresses to oncotic injury may cause swelling of the erythrocyte and increase osmotic fragility. It is therefore presumed that Al may cause either shrinking or swelling effect when the erythrocyte membrane is destabilized by Al exposure because of altered membrane permeability to intracellular and extracellular ions (Igbokwe, 2016). Cell membrane functions which regulate transmembrane transport of ions are expected to be disrupted when ATPase in cell membrane loses some level of activity during Al exposure. There are reports showing that Al inhibited activities of Na^+K^+-ATPase, Mg^{2+}-ATPase and Ca^{2+}-ATPase in erythrocytes (Zhang *et al.*, 2016), vascular endothelial cells (Vorbrodt *et al.*, 1994), testes (Sun *et al.*, 2018) and ovaries (Fu *et al.*, 2014) of rats. The Al-induced change in erythrocyte size may also be accompanied by change in erythrocyte shape resulting in the formation of echinocytes (Suwalsky *et al.*, 2004), acanthocytes and stomatocytes (Vittori *et al.*, 2002) in vitro, due to altered membrane morphology (Lukyanenko *et al.*, 2013). After long-term oral intake of Al, schistocytes and target cells were observed in stained peripheral blood of rats (Vittori *et al.*, 1999). The lipid bilayer of the plasma and mitochondrial membranes was morphologically altered in lymphocytes (Skarabahatava *et al.*, 2015). The protein components of membranes are degraded or inadequately expressed during Al exposure, as observed in the loss of band 3 protein of erythrocyte membrane (Vittori *et al.*, 2002; Vota *et al.*, 2012; Cheng *et al.*, 2018), inaction of membrane-bound enzymes, inhibition of calbindin protein level in enterocytic membrane (Cox and Dunn, 2001) and downregulation of GLUT4 protein expression in the membrane of skeletal muscle (Wei *et al.*, 2018). The surface of cell membranes could be affected by Al exposure through externalization of phosphatidylserine after apoptosis (Vota *et al.*, 2012), inhibition of membrane receptor protein expression in gonads (Fu *et al.*, 2014; Sun *et al.*, 2018; Gomes *et al.*, 2019), dysregulation of erythropoietin receptor functions on erythroid progenitors (Vittori *et al.*, 2005) and loss of membrane surface sialic acid residues on vascular endothelial tissue with impaired intercellular junctions (Vorbrodt *et al.*, 1994).

Systemic toxicosis

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.*, 1978; Herbert *et al.*, 1982; Miller *et al.*, 1984; De Vuyst *et al.*, 1987; Jederlinic *et al.*, 1990; Taiwo, 2014; Iijima *et al.*, 2017). Asthma may be caused by Al exposure (Burge *et al.*, 2000), though the asthma among Al workers may be due to other chemical factors like gases and smoke (Taiwo *et al.*, 2006). Reactive airways dysfunction syndrome was rarely reported among Al smelter workers (Wesdock and Arnold, 2014). Acute-duration oral exposure to Al phosphide has been reported to cause pulmonary edema in persons following accidental or volitional ingestion (Chopra *et al.*, 1986; Khosla *et al.*, 1988). The toxicity was probably due to the formation of highly toxic phosphine gas rather than to Al exposure (Alter *et al.*, 2001; Kamanyire and Murray, 2003; Moghadamnia, 2012). 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.*, 1979), rats exposed to 133 mg Al/kg/day as Al nitrate in drinking water for 30 days (Gomez *et al.*, 1986), 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, 1975a, b), or mice exposed to 979 mg Al/kg/day as Al potassium sulfate in food for 20 months (Oneda *et al.*, 1994). However, Hasseeb *et al.* (2011) 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, 2013). 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.

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.*, 2012). 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.*, 1979). 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.*, 1986) or 100 days, respectively (Domingo *et al.*, 1987). Organ weight and histological changes were not observed in the hearts of dogs that consumed 75 mg Al/kg/day (Katz *et al.*, 1984) or 88 mg Al/kg/day (Pettersen *et al.*, 1990) as sodium Al phosphate in the diet for 6 months. In summary, cardiovascular effects due to toxicosis are congenital heart defects, inflammation and dysfunction of the myocardium and cardiovascular thrombosis.

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.*, 1998), 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, 2007). 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, 2012). Few experimental studies (Gomez *et al.*, 1986; Oneda *et al.*, 1994) 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.

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.*, 1996), rats exposed to 27 mg Al/kg as Al citrate administered via gavage 5 days/week for 15 weeks (Garbossa *et al.*, 1998), and rats exposed to 230 mg Al/kg/day as Al citrate in drinking water for 8 months (Vittori *et al.*, 1999). 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.*, 2002). 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.*, 1994; Osman *et al.*, 2012). The additional causes of anemia 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.*, 1989; Perez *et al.*, 2001; Bazzoni *et al.*, 2005; Vittori *et al.*, 2002; Niemoeller *et al.*, 2006; Hernández *et al.*, 2008; Sadhana, 2011; Vota *et al.*, 2012; Lukyanenko *et al.*, 2013; Al-Qayim *et al.*, 2014; Oztürk and Ozdemir, 2015; Zhang *et al.*, 2016; Cheng *et al.*, 2018). Significant decreases in hemoglobin, hematocrit (packed cell volume) and erythrocyte osmotic fragility were reported after Al exposure (Garbossa *et al.*, 1996; Garbossa *et al.*, 1998; Vittori *et al.*, 1999; Farina *et al.*, 2005). 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.*, 2000). In rats loaded with Al, heme dyshomeostasis was reported with evidence of decreased activity of aminolevulinic acid dehydratase and increased activity of heme oxygenase in the rat liver associated with activation of JNK pathway, indicating an increase in heme degradation (Lin *et al.*, 2013). No alterations in hemoglobin, hematocrit and erythrocyte osmotic fragility were reported in a number of experimental Al exposures (Katz *et al.*, 1984; Gomez *et al.*, 1986; Domingo *et al.*, 1987; Pettersen *et al.*, 1990;

Table 3. Summary of haematologic effects of aluminium toxicosis.

Toxic effects	Toxic actions
Depressed erythropoiesis	Inhibition of CFU-E
	Slow growth of erythroid cells
	Inhibition of heme synthesis
	Increased heme degradation
	Dysregulated erythropoietin receptor function
Anaemia	Reduced erythrocyte life span
	Erythrocyte apoptosis (eryptosis)
	Altered erythrocyte fragility
	Decreased erythrocyte membrane fluidity
	Inhibition of erythrocyte membrane ATPase
	Altered erythrocyte shape: echinocytes, acanthocytes, stomatocytes, target cells

Oteiza *et al.*, 1993b; Garbossa *et al.*, 1996**).** Vittori *et al.* (1999) 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.* (2005) 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.* (1994) 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.*, 2010). In summary, the hematologic effect of toxicosis consists of anemia due to erythrocyte and erythroid pathology with suppression of erythropoiesis (Table 3)

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.*, 1981; Savory *et al.*, 1996; Kawahara and Kato-Negishi, 2011; Arain *et al.*, 2015; Jones *et al.*, 2017; Mirza *et al.*, 2017; Mold *et al.*, 2018). The Al in brains of 5 out of 12 donors with familial Alzheimer's disease was > 10 μg/g dry weight (Mirza *et al.*, 2017). 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). Subchronic 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.*, 1980; Anon, 2008c). 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, 1993). 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.*, 1992). Oteiza *et al.* (1993b) 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.*, 2002). Garruto *et al.* (1989) reported that cynomolgus monkeys fed a low calcium diet (3,200 mg/kg diet) with Al (125 mg/day) for 41 to 46 months had more degenerative changes that were consistent with early Alzheimer's disease or Parkinson's dementia in the central nervous system than control monkeys. Golub and Germann (2001) observed growth depression and poorer performance on standardized motor tests in mice offspring 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 hyperphosphorylated tau protein in the cortical neurons and had more atrophic neurons in the central nervous system (Kihira et al,. 2002). 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.*, 2002), suggesting that Al could contribute to neurodegeneration by enhancing amyloid deposition and aggravating lesions by oxidative events (Campbell and Bondy, 2000; Yuan *et al.*, 2012; Chen and Zhong, 2014; Liaquat *et al.*, 2019). In a nutshell, Al exposure promotes oxidative stress and amyloid deposition in the nervous tissue which results in neurodegeneration, neuronal necrosis and dysneurogenesis, which constitute the basis for the neurological diseases associated with Al intoxication.

Musculoskeletal effects

The major myopathy induced by Al exposure is macrophagic myofasciitis (aluminic granuloma) associated with chronic arthromyalgia or myalgia and chronic fatigue syndrome (Exley *et al.*, 2009; Gherardi and Authier, 2012; Rigolet *et al.*, 2014; Gherardi *et al.*, 2016; Miller, 2016). 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.*, 1992). 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.*, 1994). Smooth muscle contraction induced by K+ ion was inhibited by Al exposure (Nasu *et al.*, 1998). 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.*, 1990). In individuals where neurodegerative conditions affect the nerve supply to muscles, the muscles may undergo denervation atrophy and become dysfunctional as in multiple sclerosis or amyotropic lateral sclerosis. Taken together, Al toxicosis may cause muscle damage, inflammation and dysfunction

The bone diseases associated with Al exposure are osteoporosis, osteomalcia, rickets, exostosis, osteodystrophy and osteitis fibrosa (Sherrard *et al.*, 1985; Chappard *et al.*, 2016; Rodríguez and Mandalunis, 2018; Klein, 2019). There is increased risk of osteoporosis and low bone mineral density during Al exposure (Cao *et al.*, 2016; Sun *et al.*, 2016) because of disruption of bone formation, and inhibition of osteoblast proliferation, differentiation and mineralization (Li *et al.*, 2012, 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, 1990; Pivnick *et al.*, 1995; Woodson, 1998). The Al in antacids binds with dietary phosphorus and prevents its absorption resulting in hypophosphatemia and phosphate depletion (Woodson, 1998). 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.*, 1985; Wills and Savory, 1989; Andreoli, 1990). Low osseous remodeling rate and peripheral resistance to parathyroid hormone are associated with Al intoxication (Pun *et al.*, 1990). 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, 1993). Long-term oral exposure to Al results in an increase in Al levels in the bone (Ahn *et al.*, 1995; Konishi *et al.*, 1996) that is responsible for the bone disease.

In brief, the review has identified the following events to occur during Al exposure to disrupt bone morphology: (a) interference with the availability of calcium for bone formation at the level of intestinal absorption and hormonal control through parathyroid hormone; (b) inhibition of osteoid formation and mineralization through osteoblast dysregulation; and (c) destabilization of osteoclast functions with alteration in osteoclastogenesis and osteoclast apoptosis (Figure 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

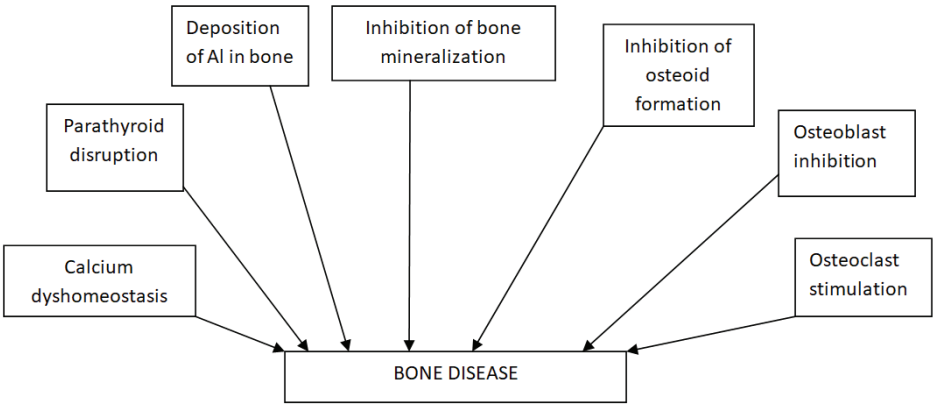

Figure 7. Pathogenesis of bone disease in aluminium toxicosis.

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.*, 2018). 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.*, 2011, 2018). The offspring of exposed rats (F0) in a three-generation study belonging to F1 and F2 had decreased testosterone and LH 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.*, 2008). Bank voles (*Myodes glareolus*) 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, 2006). Khattab *et al.* (2010) 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.*, 1998; Guo *et al.*, 2005; Yousef *et al.*, 2007; Yousef and Salama, 2009; D'Souza *et al.*, 2014). Testicular and epididymal weights and serum testosterone and luteinizing hormone levels were reduced by Al exposure (Reza and Palan, 2006; Mouro *et al.*, 2017). In male and female gerbils (*Meriones unguiculatus*), Al exposure disrupted prostate development in neonates, with the consequence of adult offspring having elevated serum testosterone levels with low androgen receptor frequency associated with increased proliferation of cells of the prostate (Gomes *et al.*, 2019).

Chinoy and Patel (2001) exposed female mice to Al chloride at 200 mg/kg for 30 days and observed decreased steroidogenesis in the ovaries associated with decreased serum estradiol levels. Exposure to Al sulphate during gestation caused reduction in maternal body weight, reduction in fetal weight and crown rump length, and impairment of fetal bone development and preossification (Yassa *et al.*, 2017). 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; 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.*, 2008). Fu *et al.* (2014) reported that Al exposure damaged ovarian structure, disrupted metabolism of iron, zinc and copper in the ovary and decreased the activities of 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.*, 2005) and fetal micronucleated erythrocytes (D'Souza *et al.*, 2014). Khalaf *et al.* (2007) reported perinatal and postnatal adverse effects of Al exposure on fetuses and neonates during gestation and lactation of female rats. 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.*, 2003). Exposed embryonic chicks and rat fetuses developed congenital myocardial defects (Wang *et al.*, 2012; El Mazoudy and Bekhet, 2016).

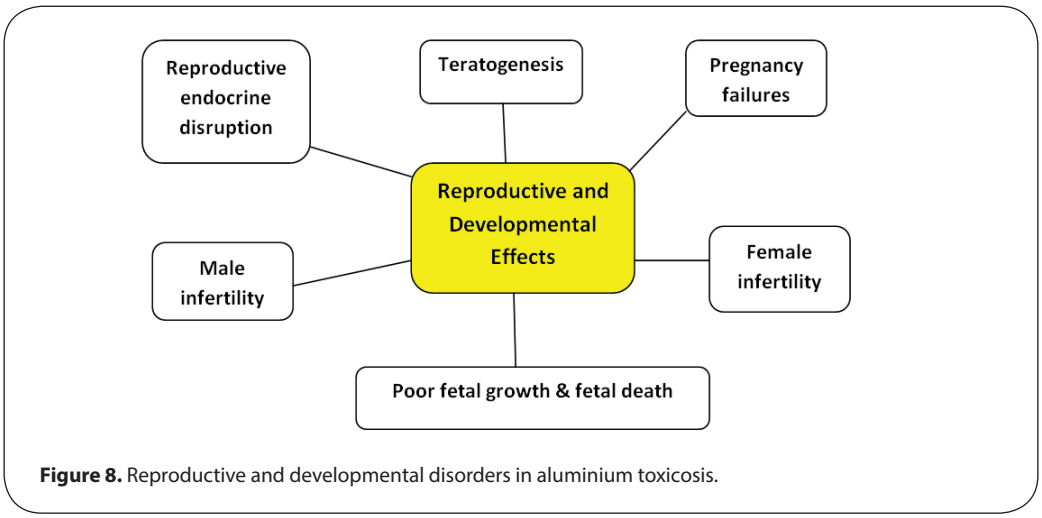

Figure 8. Reproductive and developmental disorders in aluminium toxicosis.

On the whole, Al toxicosis caused lesions in the testes and ovaries resulting in impairment of spermatogenesis and ovarian function related to ovulation, with the consequence of reproductive inefficiency associated with pregnancy failures and poor fetal development (Figure 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.*, 2010; Mailloux *et al.*, 2011; Bai *et al.*, 2012; Li *et al.*, 2015; Xu *et al.*, 2017). Abdel-Wahab (2012) 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.*, 2007). Rats had moderate pancreatic islet necrosis after intermediate oral exposure (50 mg/kg for 28 days) to Al chloride (Figure 9) which was associated with impaired fasting blood glucose and impaired oral glucose tolerance (Igwenagu, 2017; Igwenagu *et al.*, 2019). Rats treated intra-peritoneally with Al chloride at 10 mg/kg for 30 days had significantly increased fasting blood glucose, serum insulin level and insulin resistance index on days 10 and 20 of treatment, but as treatment progressed to day 30, serum insulin level had decreased, indicating that pancreatic β-cell function decreased as pancreatic damage occurred with progression of treatment (Wei *et al.*, 2018). The hepatic and pancreatic lesions cause changes in metabolism (Figure 5) which result in hyperglycaemia, hypoproteinaemia, hyperlipidaemia, hypercholesterolaemia and hypertriglyceridaemia (Omar *et al.*, 2003; Kowalczyk *et al.*, 2004; Türkez *et al.*, 2011; Abdel-Wahab, 2012; Belaïd-Nouira *et al.*, 2013).

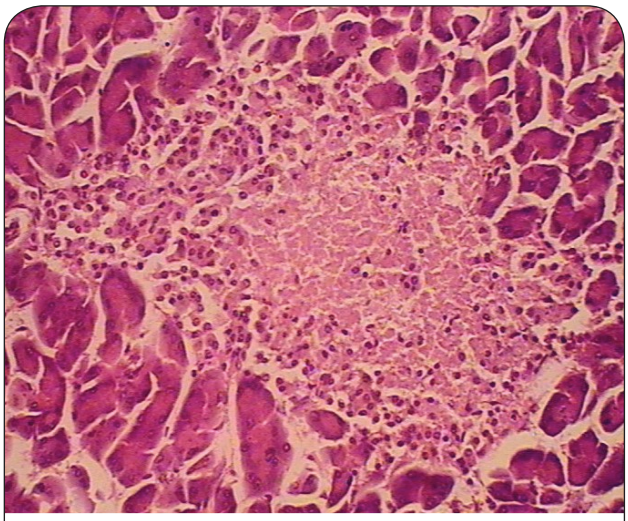

Figure 9. Photomicrograph of pancreas of aluminium chloride-treated rat showing coagulative necrosis of the pancreatic islet tissue with disorganization of its architecture (H & E, x 400) From Igwenagu *et al.* (2019).

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). Al chlorohydrate in antiperspirant cosmetics and other underarm cosmetic products may be an important source of Al exposure (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.*, 2013b). 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.*, 2011). The Al contents of nipple aspirates of breast cancer patients correlated with biomarkers of oxidative stress and inflammation in the breast microenvironment (Mannello *et al.*, 2013). The Al accumulating in the breast tissue may influence the biological characteristics of breast epithelial cells and carcinogenesis is considered a probable outcome (Pineau *et al.*, 2014). The content of Al in breast tissues from mastectomies are being efficiently and accurately estimated in order to properly assess the involvement of Al in the aetiology of breast cancer (House *et al.*, 2013). Current evidence suggests that Al can induce DNA damage in human breast epithelial cells and subsequently induce proliferation of the cells (Darbre *et al.*, 2013a, 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.*, 2013a). Long-term Al exposure also increased the migration of oestrogen-unresponsive MDA-MB-231 human breast cancer cells in culture where their expression of matrix metalloproteinases (MMP9/14) was increased (Bakir and Darbre, 2015).

Diagnosis and treatment of aluminium intoxication

Al can be measured in the blood, bone, urine, and feces to confirm Al load and association with toxicosis. A variety of analytical methods have been used to measure Al levels in biological materials and they include 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 (Maitani *et al.*, 1994; Owen *et al.*, 1994; Van Landeghem *et al.*, 1994; Razniewska and Trzcinka-Ochocka, 2003). Contamination is a major problem encountered in the

analysis of Al by all methods except that using radioactive ^{26}Al. When using the other methods, all items used during collection, preparation, and assay should be checked for Al contribution to the procedure.

Treatment of Al intoxication is done with the chelating agent, deferoxamine, which is a colourless crystalline base, produced by the bacterium, *Streptomyces pilosus*. Structurally, it is composed of one molecule of acetic acid, two molecules of succinic acid and three molecules of 1-amino-5 hydroxylamine pentane (Keberle, 1964). Deferoxamine is mainly used as an iron-chelating agent to treat iron overload. But due to the chemical similarity between Al and iron, it can also successfully mop-up excess Al from the body (Day, 1986; Martin *et al.*, 1987). 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 (Malluche *et al.*, 1984). It has also been used successfully to treat Al toxicity in children (Warady *et al.*, 1986; Ogborn *et al.*, 1991). 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 (Klaassen, 1990).

Malic acid is also a potent chelator of Al used in treatment of Al intoxication (Domingo *et al.*, 1988). Treatment with malic acid has been reported to greatly increase the fecal and urinary excretion of Al and reduce the concentration of Al present in various organs and tissues (Rim, 2007; Crisponi *et al.*, 2012; Al-Qayim *et al.*, 2014). Other chelating agents such as citric, malonic, oxalic, and succinic acids have been used experimentally to reduce aluminum load in rats and mice (Domingo *et al.*, 1988).

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 intoxication (Omar *et al.*, 2003; Abubakar *et al.*, 2004; Fyiad, 2007; Turkez *et al.*, 2011). Other researchers have used plant extracts of fenugreek seed, grape seed, ginger, wheat grass powder, black tea, *Allium cepa, Caesalpinia crista, Arthrophytum* (*Hammada scoparia*), *Moringa oleifera* and *Celastrus paniculatus* to ameliorate the toxicosis caused by Al exposure (Khattab *et al.*, 2010; Hasseeb *et al.*, 2011; Osman *et al.*, 2012; Belaïd-Nouira *et al.*, 2013; Sumathi *et al.*, 2013; Bitra *et al.*, 2014; Osama *et al.*, 2014; Mathiyazahan *et al.*, 2015; Singh and Goel, 2015; Taïr *et al.*, 2016; Ravi *et al.*, 2018). The neuronal death in the hippocampus of the brain associated with neurodegeneration in rats caused by Al exposure was attenuated by quercetin (Sharma *et al.*, 2016). Ginsenoside Rb1 was reported to prevent Al-induced oxidative stress and reverse the osteoblast viability and growth after impairment by Al (Zhu *et al.*, 2016a). Chlorogenic acid was effective as a chelating agent and antioxidant in protection against the toxicity of Al (Wang *et al.*, 2018; Cheng *et al.*, 2017, 2019). Chenodeoxycholic acid ameliorated the neurotoxic effect of Al by improving insulin sensitivity (Bazzari *et al.*, 2019). Türkez *et al.* (2010) reported that propolis prevented the genetic and hepatic damages induced by Al intoxication.

On the whole, the approach to the treatment of Al toxicosis after diagnosis involves strategies that include the following: prevention of Al intake, reduction of Al absorption, increasing Al excretion, maintaining functional kidneys, reducing Al load by chelation with chelating agents and amelioration of toxic effects with antioxidants and other agents that reduce toxicity (Figure 10)

General perspective and conclusion

This review has provided an overview of the pathologic basis of Al toxicosis. The association of Al intoxications with various pathologic syndromes and pathogenic mechanisms linked to toxic actions may provide avenues for strategic interventions. The study of these pathologies

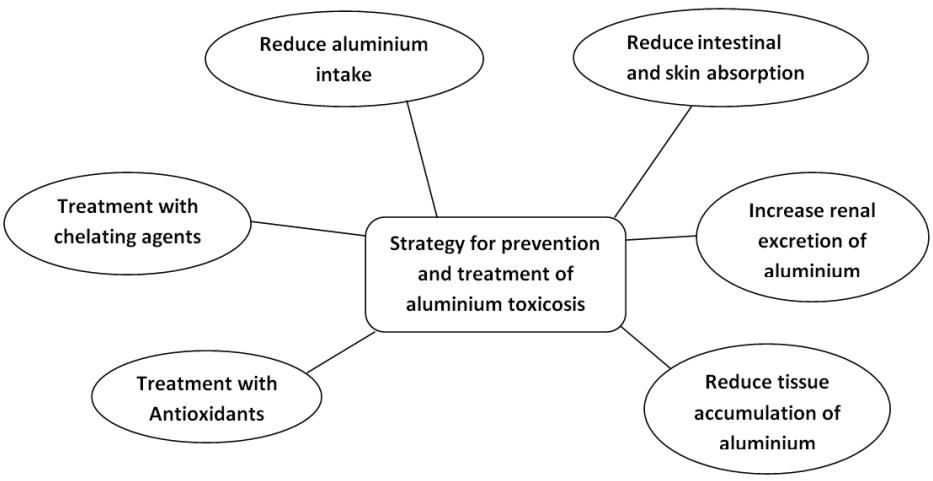

Figure 10. Prevention and treatment of aluminium toxicosis.

have received recent attention in epidemiological surveys in regard to some human diseases such as Alzheimer's disease, autism, osteoporosis, diabetes mellitus, inflammatory bowel disease and others mentioned in the review. We have reviewed the process of Al intoxication, toxic actions and systemic effects with an exploratory approach to provide the subsequent highlights of the review in this section.

After the intake of Al and its deposition in tissues, the cell is the primary target of the toxic action of Al, where the ion interacts with the plasma membrane moieties, cytoplasmic biomolecules, mitochondria and nuclear structures. The major toxic action of Al is to generate oxidative stress by producing reactive free radicals which can overwhelm the antioxidant defenses of the cell to perpetrate cellular injuries. The oxidative injuries emanate from the oxidation of proteins, lipids and nucleotides, which result in generation of altered functional biomolecules with defective operational capabilities towards cellular homeostasis. The disruption of homeostatic environments of the cell has the capacity to change the semi-permeability and receptor functions of the plasma membrane, alter the reactivity of metabolic intermediary molecules and the functions of enzymes and cofactors, and breach the energetic profile and synthetic infrastructure at transcriptional and post-transcriptional stages. In Al toxicosis, we identified the inhibition of cellular viability and function of neurons, osteoblasts, endocrine cells, lymphocytes, macrophages, erythrocytes, erythroid cells, enterocytes, myocytes, germinal cells, and pulmonary alveolar, hepatic, renal and pancreatic islet cells. Progenitor or blast cells were not able to proliferate, differentiate and function in accordance with their genetic resources. The secretory functions of specialized cells were impaired and several signaling pathways were recruited in abnormal chemico-biological settings. Cytokine expression was accelerated by oxidative cellular injuries to initiate inflammatory processes and alter immune responses that support inflammation and immunosuppression, respectively. There were Al-induced endocrine disruptions and altered sensitivities to hormones such as insulin, parathyroid hormone and hormonal vitamin D.

In Al toxicosis, the cellular structures were damaged by molecular mechanisms which cause degenerative changes (from lipid and amyloid depositions), cell death by apoptosis or necrosis, and dysplasia from genetically driven cell growth abnormalities. Cellular degeneration occurred in nervous tissue, liver and kidney. Apoptosis was associated with damage to immune cells, erythroid cells, erythrocytes, osteoblasts and germinal cells. Necrosis was encountered in pancreatic islet, liver, kidney, neurons and muscles. Dysplasia from chromosomal aberrations was associated with developmental defects, teratogenesis and growth abnormalities in fetuses and mammary epithelial cells. Mutagenesis, cell proliferation and impaired mitosis in Al toxicosis are gray areas requiring clarification because of the observed antithesis.

The systemic effects caused by Al toxicosis are diverse and multifaceted, but co-morbidities from multisystemic toxicosis are rarely reported in epidemiological cohorts. The convergence of toxic actions to engage multiple organ systems in an individual is often an observation in experimental animal models and lacks validity in observational studies in human or animal populations. The possible action of Al in the pathogenesis of diabetes mellitus and the concurrence of neurological disorders associated with Alzheimer's disease and other dementias (Arnold *et al.*, 2018) point to the common cellular basis of the pathogenesis of both metabolic and cognitive disorders, which can arise from toxic actions of Al. Longitudinal studies in the future may reveal co-morbidities and multisystemic toxicosis in Al-loaded individuals in locations where there is high risk of Al exposure.

Al-induced oxidative stress with the metabolic defects that accompanies it may incidentally be the crux of the toxicosis, to the extent that the use of antioxidant agents forms the fundamental basis for therapeutic interventions apart from chelating drugs. Chenodeoxycholic acid improved insulin sensitivity to ameliorate the neurotoxic effect of Al (Bazzari *et al.*, 2019). As new researches on the cellular mechanisms in the toxicosis continue to be further elucidated through in vitro and in vivo studies of the metallic toxicant, new therapies against the toxicosis should also focus on alleviating the known aberrations in signaling pathways, synthetic and secretory functions, cellular energetics and membrane integrity.

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