| **Original Article** | **Aluminum Toxicity as aRisk Factor to Osteoporosis in Aging Rats** |
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## ABSTRACT

**Background:** Aluminum has the potential to be cytotoxic for humans and animals. Al absorption is increased with age and bone is considered as its main storage site.

**Aim of the Work:** This study was carried out to investigate the pathological changes in bone of aging rats, treated with aluminum chloride.

**Material and Methods:** Twenty male albino rats (2-years age at the beginning of the experiment) were divided into a control group and an experimental group. The latter subjected to aluminum chloride ingestion for 8 weeks. Plain X-rays as well H&E stain were used to investigate the pathological changes of the femur of the experimental group.

**Results:** In the experimental group, plain x-ray of femurs revealed destruction of medullary bone trabeculae, cortical bone resorption and sclerosis. H&E sections at the proximal end of the shaft of the femur confirmed the gross picture of x-ray and the cortex of the bone appeared thin with erosion cavities leading to fracture in some specimens. The bone cells appeared few or degenerated and the periosteum appeared thin and separated. The inner cancellous bone trabeculae was destroyed and separated by widened bone marrow that may be replaced by fat cells. Ultrastructurally, both osteoblasts and osteocytes showed marked degenerative changes and were surrounded by few irregular collagenous matrix. The degenerative bone changes observed in this study may, in part, be interpreted as a consequence of aluminum administration.

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## INTRODUCTION

Osteoporosis leads to fragility fractures. Fracture incidence increases after the menopause among women and with age in both genders. More than 40 % of women will sustain at least one fragility fracture after the age of 50. Many risk factors have been described, including age, familial history of fracture, low bone mineral density, smoking and low body mass index. Fracture incidence is increasing worldwide, owing to population aging *(Chapurlat, 2008)*

In the past few years there has been an upsurge of interest in aluminum (Al) exposure through diet and environment. Al has a pro-oxidant effect and acts as a neurotoxin *(Nehru and Anand, 2005)*, and subchronic exposure to aluminum chloride in mice diminished motor activity and grip strength suggesting damage to the hippocampus *(Hu, et al. 2005)*. Also, Al salts are known to accumulate with age in a dose-dependent manner in CNS, bone, hematopoietic cells with toxic consequenc-es, even in the absence of renal disease *(Walton, et al. 2009)*. Recently, Al ingestion has been proposed to be a risk factor for development of Alzheimer's disease *(Vasudevaraju, et al. 2008)*.

Although the mature intestine acts as a relatively impermeable barrier, some Al is absorbed and deposited in various tissues. In the pH range of most food (pH 4-8), Al is present predominantly in the form of organic Al-complexes, which is harmful to the human body *(Bi, 1996)*. Al toxicity can induce several clinical disorders and low dose Al exposure for a short-time was responsible for development of anemia in the aluminum-treated animals *(Turgut, et al. 2007)*.

Al in the food supply comes from natural sources including water, food additives, preservatives, coloring agents, and contamination by Al utensils and containers. Most adults consume 1-10 mg Al daily from natural sources. Tea leaves and baking

powder were found to be a rich source of Al while coffee powder has small amount. Toothpaste also contains a significant quantity of Al, more so, when packed in Al tubes *(Greger, 1992; Rajwanshi, et al. 1997)*. Higher amount of Al is found in antacids and some buffered analgesics *(Soni, et al. 2001)*.

Cooking in aluminum containers often results in significant increase in the Al content of foods. NaCl and fluoride were suggested as being able to promote Al leaching. Also, Al levels were higher in an acidified environment due to acid rain or in water treated with Al sulphate for the chemical removal of particles in drinking water. High amounts of Al migrate into acidic products during normal processing in non-coated Al pans; moreover, citric acid is a strong enhancer of gastrointestinal absorption and accumulation of Al *(Muller, et al. 1993; Rao and Rao, 1995; Deng, et al. 2000)*.

Reviewing the literature, many authors studied the adverse effects of Al in uraemic patients *(Moore, et al. 2000; Cannata-Andía and Fernandez-Martin, 2002; Baydar, et al. 2005)*. However, little is known about the long term side effects of Al in normal individuals at advanced age on the bone, the preferred organ of Al accumulation in the body.

## MATERIAL AND METHODS

The present work was carried out on twenty male albino rats at two years of age at the beginning of the experiment. All animals were kept in clean properly ventilated cages under similar environmental conditions and fed the same laboratory diet. Half of the animals are used as control (Control group) while the other half (Experimental group) received, in addition to the usual diet, aluminum chloride dissolved in distilled water for 8 weeks daily in a dose of 100 mg/kg/day via oral intubation. This dose was able to accelerate oxidative damage and induced neurotoxicity in rats *(Nehru and Anand, 2005)*.

At the end of the experiment, the animals were anaesthetized with diethyl ether and the femurs were removed, dissected free of soft tissue, washed with saline and the upper end of the femur of one limb just below the greater trochanter were cut and rapidly immersed in gluteraldehyde as a fixative for 1 day at 4C. All the specimens were then decalcified in daily exchange of EDTA (ethylene-diamine tetra-acetic acid) for 14 days. The femurs of other limbs were rapidly taken to Radiological Department, faculty of Dentistry, Tanta University for plain X-Ray.

Some specimens were processed for preparation of paraffin sections and stained with Haematoxylin & Eosin (H&E). For electron microscopic study, the samples of the decalcified femurs were fixed in 5% phosphate buffered gluteraldehyde (pH 7.3) for two hours at 4ºC and postfixed in 1% osmium tetraoxid for 1-2 hours. Then, they were dehydrated and embedded in epoxy resin. Ultrathin sections were cut with LKB. ultramicrotome and contrasted with uranyl acetate and lead citrate for examination with transmission electron microscope in the Central Lab, Faculty of Science, Ain Shams University.

## RESULTS

**Thymus X-rays:** Plain x-ray to the femur of control rats showed apparently normal bone cortex. It was of regular thickness, straight and continuous with no areas of erosion or expansions. The medullary bone was of normal density with no detectable areas of lysis or sclerosis. However, rats from the experimental group showed the picture of osteoporosis with diffuse cortical thinning associated with cortical erosion cavities and medullary lucency indicating medullary bone trabeculae destruction at the proximal end of the shaft of the femur. There was also cortical expansion with linear sclerotic areas at the distal end of the femur (Figs. 1, 2).

**Light microscopic results:** Sections at the proximal end of the femur of control rats stained with H&E revealed that the external surface of the femur was covered by a dense connective tissue, the periosteum, formed of irregularly arranged collagen fibers and fibroblasts. Under the periosteum, the bone was formed of an outer shell of compact bone and inner trabeculae of cancellous bone. The compact bone was consisted of bone cells (osteocytes) and intercellular calcified matrix. The cancellous bone was formed of network of bone trabeculae composed of irregular and anastomosing bone trabeculae containing osteocytes. The cavities of the cancellous bone were filled by bone marrow formed of haemopoeitic tissue, few fat cells (adipocytes) and blood sinusoids (Figs. 3, 4). The matrix of the compact bone was characterized by regularly arranged collagen fibers in the form of parallel lamellae and Haversian canals. Being formed mainly of collagen, the bony lame-

llae appear highly acidophilic. Within the bone matrix, many osteocytes were easily seen inside lacunae. They were oval in shape and when they were inactive, they became flattened with darker nucleus and less basophilic cytoplasm. A thin layer of cell-rich connective tissue, the endosteum, lines the surface of the bone facing the marrow cavity. This layer was formed of osteogenic layer containing spindle-shaped cells (osteoprogenitor cells) and osteoblasts. Active osteoblasts were cuboidal or columnar in shape with basophilic cytoplasm and rounded eccentric nucleus (Fig. 5).

Examination of sections in the femur of rats received Al showed marked thinning and separation of the periosteum. Apparent thinning of the outer cortical bones was also noticed in all specimens examined and erosion cavities were detected at the endosteal surface of the cortical bones. The inner cancellous bone trabeculae lost their normal architecture and were thin with irregular eroded surfaces. Some trabeculae appeared as discontinuous bony ossicles and separated by widened bone marrow spaces. There were large bony tunnels and resorption cavities in the thinned compact bone. These tunnels were usually invaded by bone marrow cells (Figs. 6-8). Marked thinning of the cortex led to fracture in some specimens (Fig. 8). Bone cells of the cortex appeared few in number, atrophied or degenerated (Fig. 9). In some specimens the bone marrow cells were mostly replaced by increased number of adipocytes (Fig.10).

**Electron microscopic results:** Examination of ultrathin sections in the femur of control rats revealed that the cytoplasm of the osteoblasts was formed of many rER, mitochondria and Golgi apparatus near the almost rounded eccentric nuclei. The collagen fibrils around the cells were either pale (unmineralized matrix or prebone) or dark mineralized matrix (Fig.11). The osteocytes had oval nuclei with prominent nucleoli. They had many cytoplasmic processes extending into canaliculi. Being less active than the osteoblasts, osteocytes have less cytoplasmic organells. They were surrounded by mostly dark mineralized bone matrix formed of collagen fibrils (Fig.12).

In the experimental group, ultrastructure of bone revealed pathological changes affecting the bone cells and matrix. Osteoblasts showed marked degenerative changes. The nuclei were shrunken and irregular. rER appeared highly dilated and

the cytoplasm contained multiple vacuoles. The matrix appeared pale containing few irregularly arranged collagen fibrils (Figs.13-15). Osteocytes contained flat and irregular nuclei with condensed chromatin and vacuolated mitochondria (Fig.16). Most of the osteocytes lost its cytoplasmic processes and the cytoplasm appeared highly vacuolated. Collagen fibrils surrounding the cells were short, degenerated, and irregularly arranged (Fig.17).



**Fig. 1:** A photograph of plain x-ray of the femur of control rat showing the outer bone cortex with straight regular thickness and no erosion cavities or expansions. The medulla also showed the normal bone density with no detectable areas of lysis or sclerosis.



**Fig. 2:** A photograph of plain x-ray of the femur of a rat from the experimental group showing diffuse cortical thinning with an erosion cavity on the lateral aspect of the proximal end of the shaft (arrow). Mottled medullary destruction (medullary lucency) at the proximal end of the shaft of the femur is also seen, while the lower end of the femur shows cortical expansion with linear sclerosis (double arrow).
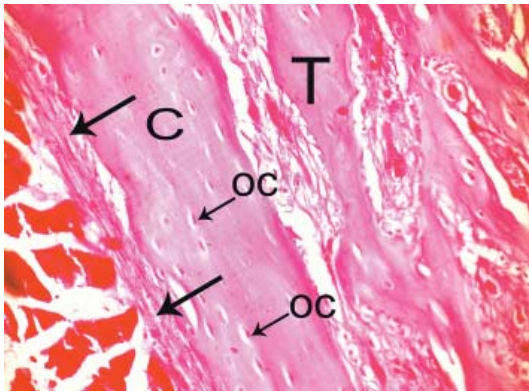
**Fig. 3:** A photomicrograph of a section at the proximal end of the shaft of the femur of a control rat showing the outer compact bone (C) covered with periosteum (arrow) and inner trabecular bone (T) enclosing the bone marrow spaces. Notice the osteocytes (oc) within their lacunae in the matrix of compact bone. H&E; X 200
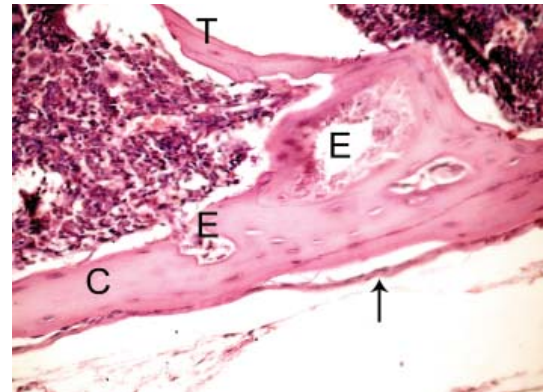


**Fig. 4:** A photomicrograph of a section at the proximal end of the shaft of the femur of a control rat showing thick branching and anastomosing bony trabeculae within which osteocytes (oc) are located in their lacunae. The bone marrow (bm) between the trabeculae is also seen. H&E; X400



**Fig. 5:** A photomicrograph of a section at the proximal end of the shaft of the femur of a control rat showing the endosteum formed of osteogenic layer containing osteoprogenitor cells with elongated nuclei (p) and osteoblasts (ob) with almost rounded nuclei. Notice the Haversian canals (H) within the lamellae (double arrow) of the compact bone. H&E; X 400



**Fig. 6:** A photomicrograph of a section at the proximal end of the shaft of the femur of an experimental rat showing thin and irregular outer compact bone (C) with multiple erosion cavities (E), thin eroded bony trabeculae (T) with widening of bone marrow space and separated periosteum (arrow). H&E; X 200
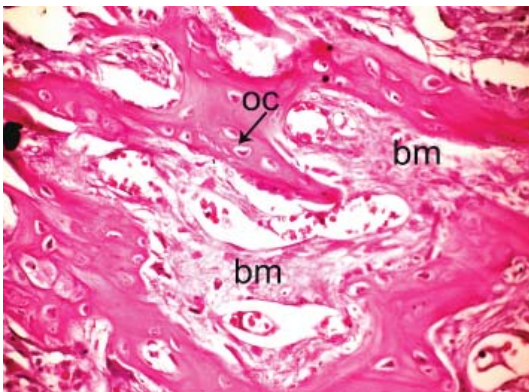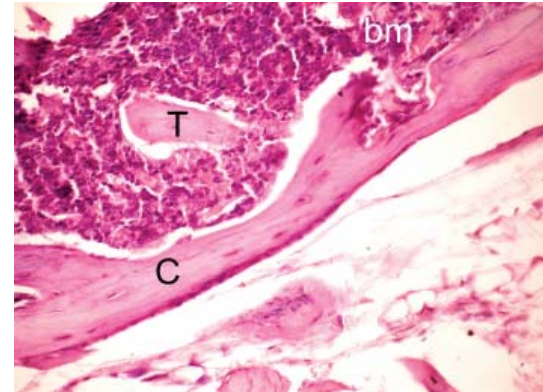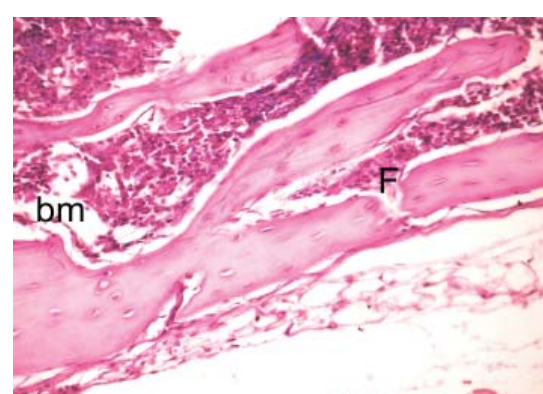


**Fig. 7:** A photomicrograph of a section at the proximal end of the shaft of the femur of an experimental rat showing separated part of trabecular bone (T), marked erosion of the cortex (C) and its invasion with bone marrow (bm). H&E; X 200



**Fig. 8:** A photomicrograph of a section at the proximal end of the shaft of the femur of an experimental rat showing marked erosion of the bony cortex leading to its fracture (F) and invasion with bone marrow (bm). H&E; X 200
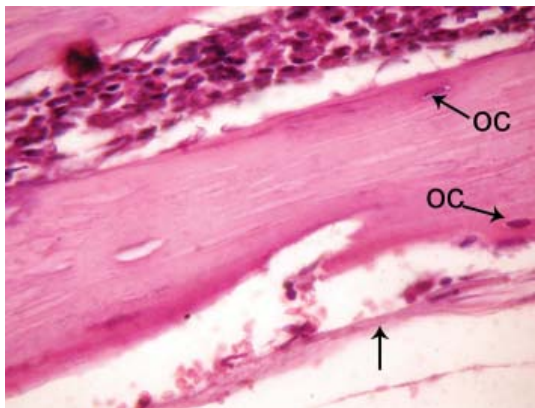
**Fig. 9:** A photomicrograph of a section at the proximal end of the shaft of the femur of an experimental rat showing marked degeneration or atrophy of osteocytes (oc) and thin separated periosteum (arrow).         H&E; X 400
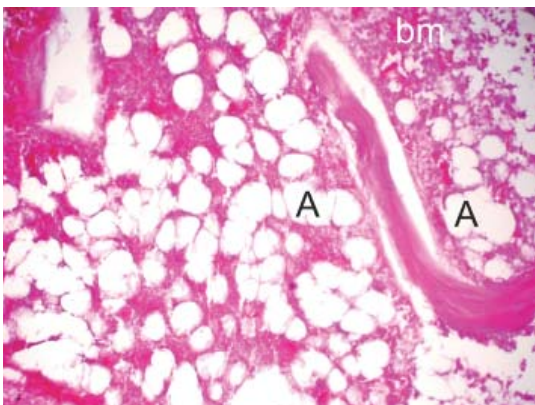


**Fig. 10:** A photomicrograph of a section at the proximal end of the shaft of the femur of an experimental rat showing wide bone marrow space (bm), most of its cells were replaced by adipocytes (A).         H&E; X 200
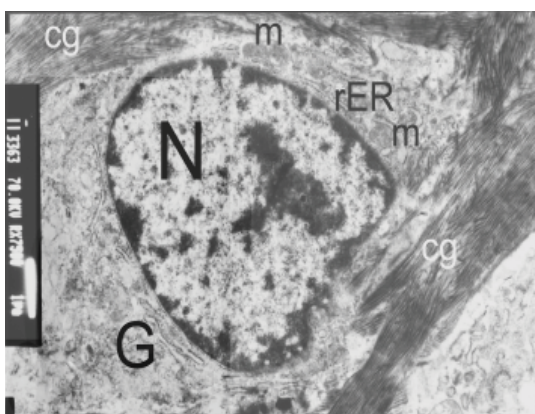


**Fig. 11:** Electron micrograph of a section in a decalcified bone at the proximal end of the shaft of the femur of a control rat showing an osteoblast containing rER, mitochondria (m) and Golgi apparatus (G) near a rounded eccentric nucleus (N). Collagenous fibrils (cg) are seen around the osteoblast.         X 7500
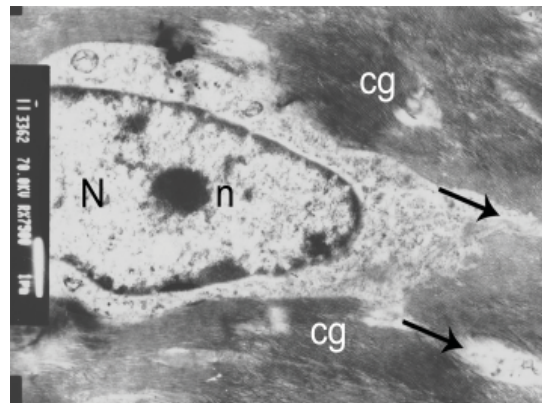


**Fig. 12:** Electron micrograph of a section in a decalcified bone at the proximal end of the shaft of the femur of a control rat showing an osteocyte with oval nucleus (N) and prominent nucleolus (n). It has cytoplasmic processes (arrow) extending into canaliculi. It is surrounded by pale and dark collagenous matrix (cg).         X 7500
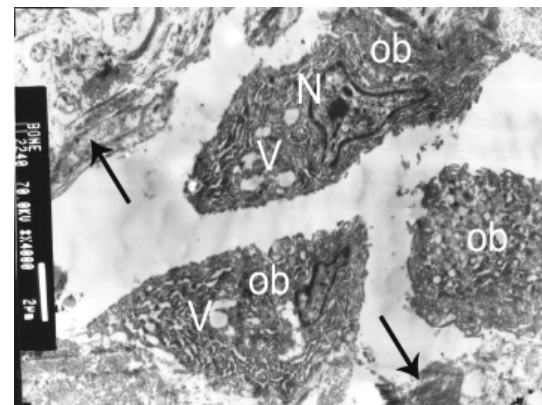


**Fig. 13:** Electron micrograph of a section in a decalcified bone at the proximal end of the shaft of the femur of an experimental rat showing highly degenerated osteoblasts (ob) with irregular nuclei (N) and highly vacuolated cytoplasm (V). The matrix contains few degenerated collagen fibrils (arrow).         X 4000
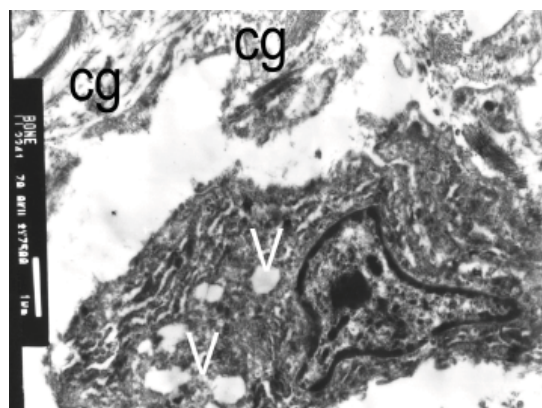


**Fig. 14:** magnification of the previous figure to show an osteoblast with degenerated cytoplasmic contents, vacuoles (V) and shrunken nucleus. Notice the few irregularly arranged collagen fibrils (cg).         X 7500
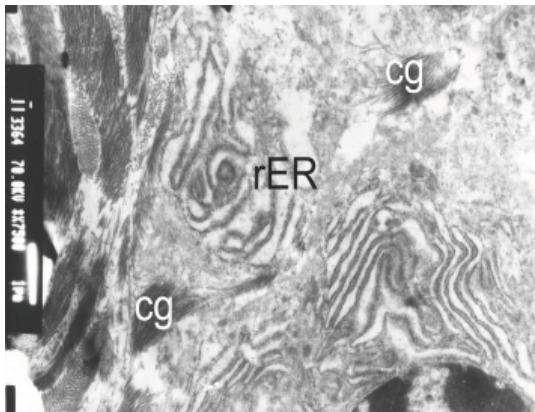
**Fig. 15:** Electron micrograph of a section in a decalcified bone at the proximal end of the shaft of the femur of an experimental rat showing an osteoblast with highly dilated rER and few irregular collagen (cg). X 7500
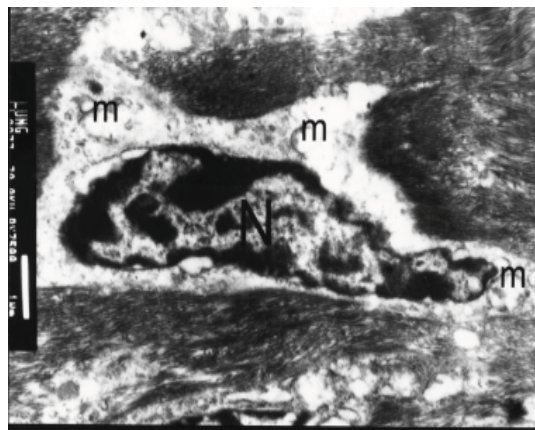
**Fig. 16:** Electron micrograph of a section in a decalcified bone at the proximal end of the shaft of the femur of an experimental rat showing an osteocyte with flat irregular nucleus (N) with condensed chromatin, and vacuolated mitochondria (m) . X 7500
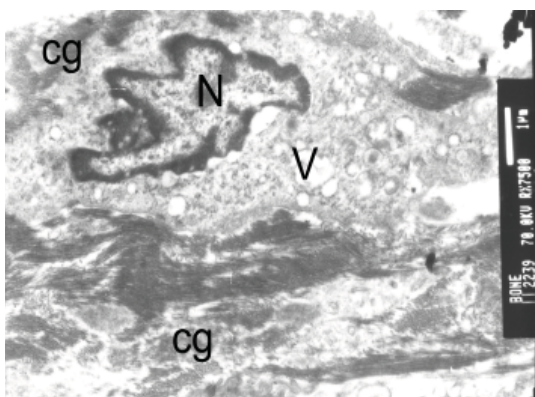
**Fig. 17:** Electron micrograph of a section in a decalcified bone at the proximal end of the shaft of the femur of an experimental rat showing an osteocyte with vacuolated cytoplasmic organelles (V) ,small shrunken nucleus (N) and degenerated collagen fibrils (cg). X 7500

## DISCUSSION

Information concerning Al toxicity is available from clinical studies. Al intoxication was the most likely cause of death in patients treated chronically with haemodialysis. On average, 4% of the Al content of the diet is retained by intestinal absorption, and might partially be accumulated in bone, the main storage site of Al. In the elderly patients the intestinal absorption of Al is increased, thus augmenting the amount of Al stored in bone. Since healthy subjects with normal renal function retain Al, they potentially risk long-term accumulation and low-grade Al intoxication *(Moore, et al. 2000; De Wolff , et al. 2002; Priest, 2004)*

In the present work, Plain x-ray to the femur showed apparent difference in the cortical thickness and medullary bone density between control and experimental groups. Experimental animals showed the picture of osteoporosis with diffuse cortical thinning, erosions and sclerotic areas indicating bone necrosis. There was also medullary lucency indicating medullary bone trabeculae destruction. H&E sections at the proximal end of the femur confirmed the gross picture of x-ray and both cortical and cancellous bone were markedly affected by Aluminum chloride and showed cortical bone resorption cavities and bone trabeculae attenuation. Coinciding with these results, there are previous animal studies in which Al has been proven to inhibit osteoblastic activity and has a negative effect on bone mineralization. *Kidder et al. (1993)* suggested that the bone formation defect associated with Al toxicity in growing rats may be a function of impaired patterns of osteoprogenitor/osteoblast proliferation. *Jeffery et al. (1996)* mentioned that both clinically and experimentally, high doses of Al inhibit bone remodeling, slowing both osteoblast and osteoclast activities and producing osteomalacia. *Bellows et al. (1999)* concluded that although Al accelerates osteoblastic differentiation but is cytotoxic in long-term cultures. More recently, *Cointry et al. (2005)* noticed a relative inhibition of cortical bone formation by Al. Also, *Davis et al. (2008)* mentioned that Al stored in bone or occupational exposure can interfere with normal bone remodeling leading to osteodystrophy or osteomalacia.

There are also, on the contrary, animal studies in which the results were somewhat conflicting, indicating that Al could have negative or positive osteogenic effects. Histomorphometric stu-

dy of *Huang (1993)* on bone of rabbits showed that A1 intake led to increased osteoid formation while mineralization process was inhibited. Also, *Quarles et al. (1994)* mentioned that Al is a potent stimulus for DNA synthesis in osteoblasts in dogs. These findings may represent a different response to aluminum administration in these animal species. It seems also that low doses of Al stimulate bone formation. In osteopenic rats, low Al dose (10 mg/kg/5 days/week) was able to induce bone formation, however, both osteoblastic and osteoclastic activities were increased *(Gomez-Alonso, et al. 1999)*.

The results of the present work revealed apparent thinning and erosions that may lead to fracture in the cortical bones of rats receiving Al. In agreement with this finding, the association between oral ingestion of Al and the risk of hip fracture was examined by *Cumming and Klineberg (1994)* who suggest that long-term use of Al -containing antacids and cooking pots might increase the risk of hip fracture. High dose of Al antacids was also reported to induce osteomalacia in non-uraemic infants *(Golub and Domingo, 1996)*. According to *Malluche (2002)*, Al is absorbed by the intestines and is rapidly transported into bone, where it disrupts mineralization and bone cell growth and activity. Because Al is sequestered in bone for long periods, its toxic effects are cumulative. As a result, even intermittent or low-dose use of Al adds to the total load of this toxin in the bone. Also, *Zhou and Yokel (2005)* found that Al can cause a low-turnover osteomalacia. Recently, The long-term total parenteral nutrition, a procedure commonly applied to patients with advanced forms of intestinal malabsorption, bone metabolic diseases, such as osteoporosis and osteomalacia, are a common finding due to Al toxicity which followed massive contamination of the solutions used with Al from raw materials and injection bags used *(Acca, et al. 2007)*. Furthermore, the relation between Al intoxication and impairment of erythropoiesis and anaemia is well documented in the literature *(Marouani, et al. 2007 and Turgut, et al. 2007)*. The degenerated bone marrow and its replacement by fat cells observed in some specimens of the present work may, in part, explain this clinical state.

Bone cells of the cortex in the present study appeared few in number, atrophied or degenerated. This was in agreement with *Huang and Xu*

*(1991)* who found that osteoblast atrophy tended to increase with increased Al intake in mice. At the level of the electron microscope, ultrastructure of osteoblasts and osteocytes confirmed the current findings and both types of cells showed degenerative changes in the form of shrunken nuclei, degenerated cytoplasmic organelles, highly dilated rER and degeneration of the surrounding collagenous matrix. Going in line with these results, *Rodriguez et al. (1990)* mentioned that aluminum is toxic to osteoblasts and also directly inhibits mineralization. Also, *Niu et al. (2005)* investigated the mitochondrial structure and function in neural cells in vitro and demonstrate that Al may impair the mitochondrial membrane and cristae with decreased enzyme activity. They added that the alteration in the mitochondrial structure and function plays an important role in neurotoxic mechanisms induced by Al as the mitochondria are important organelles involved in maintaining cell function. In addition, *Pan et al. (2008)* found that mitochondrial dysfunction was implicated in the process of neuronal cell death through apoptosis induced by Al chloride exposure. This may explain the markedly degenerated and vacuolated mitochondria observed in the osteocytes of the present work.

The exact mechanism of aluminum toxicity is not known. A number of mechanisms have been proposed for the toxic actions of aluminum, however, no single mechanism emerge to explain these diverse effects. In addition to the suggested direct toxic effect of Al to the osteoblasts *(Rodriguez, et al. 1990; Bellows, et al. 1999)*, indirectly, Al seems to have a negative effect on bone by interfering with parathyroid hormone release and synthesis *(Diaz-Corte, et al. 2001)*. The impairment of intestinal absorption of calcium by Al may also play a pathogenic role in the development of Al osteopathy as it might interfere with Ca uptake by enterocytes through a general effect on cell membrane *(Orihuela, et al. 2005)*.

Bone loss leading to osteoporosis is common in the elderly and Al was included in the list of drugs that considered a risk factor usually associated with osteoporosis *(Tannirandorn and Epstein, 2000)*. Degenerative and osteoporotic changes observed in the results of the present study were only in rats subjected to Al overload and not in the control group leading us to the suggestion that these changes might be due to Al intoxication

supporting the observations of *Lorenzo Sellares and Torregrosa (2008)* who mentioned that osteomalacia is rarely observed in older, diabetic or uraemic patients after the disappearance of aluminum intoxication.

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# سمية معدن الألومينيوم كعامل خطر لهشاشة العظام في الفئران المعمرة

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## ملخص البحث

يتعرض الانسان باستمرار للألومينيوم نتيجة لزيادة التقدم الصناعي والتكنولوجي. وبوسع الألومينيوم أن يكون ساما للخلايا في الانسان والحيوان؛ ويوجد في كثير من الأطعمة المصنعة والأدوية كما أنه يضاف لمياه الشرب لأغراض التنقية. وبما أن العظام هي مكان التخزين الأساسي للألومينيوم كما أن امتصاص الأمعاء للألومينيوم يزداد مع تقدم العمر فقد أجريت هذه الدراسة لفحص التغيرات الباثولوجية في عظام فئران معمرة عولجت بكلوريد الألومينيوم. لقد أجري هذا العمل علي عشرين فأر أبيض ذكر يبلغون من العمر ثمانية عشر شهرا في بداية التجربة. ولقد قسمت الفئران الي مجموعتين احدهما ضابطه والأخري تجريبية تعرضت لابتلاع كلوريد الألومينيوم لمدة ثمانية أسابيع. وقد أظهرت الأشعة السينية لعظمة الفخذ في المجموعة التجريبية ضمور حواجز عظم النخاع ونخر وتصلد عظام القشرة. ولقد أكدت شرائح الهيماتوكسلين والايوسين صور الأشعة وظهرت عظام القشرة في الجزء الأعلي من عظمة الفخذ رفيعة ومتاكلة وبها تجاويف مما أدي الي كسور في بعض العينات. وقد بدت خلايا العظام قليلة أو تالفة وبدا غشاء السمحاق رفيع ومنفصل. لقد كانت حواجز العظام الاسفنجية مدمرة ومنفصلة بنخاع عظمي متسع ربما استبدل بخلايا دهنية. وبالنسبة للتركيب الدقيق فقد أوضحت الخلايا العظمية والخلايا المكونة للعظام تغيرات تلفية وكانت محاطة بألياف كولاجينية قليلة وغير منتظمة. هذه التغيرات التلفية للعظام التي لوحظت في هذه الدراسة ربما تفسر جزئيا أنها حدثت كتداعيات لتعاطي الألومينيوم.