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Effect of Occupational Exposure to Aluminum on Parathyroid Hormone and Calcium Metabolism

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MSS, DAHS and MR designed and performed the study and wrote the first draft of the manuscript. Author MR wrote the protocol. Author LR managed the analyses of the study. Authors MSS and DAHS designed the patient files and managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Aluminum is widely used in industry and it has been associated with several health hazards among exposed workers. To study the effect of aluminum on the parathyroid gland and the disturbance in calcium and phosphorus metabolism among workers exposed to aluminum in aluminum industry.
Methodology: This study was conducted on fifty workers in an aluminum foundry, who were occupationally exposed to aluminum and were compared with fifty non-exposed individuals. Full history was taken, clinical examination and some laboratory investigations were done in the form of: CBC, kidney functions, serum PTH, serum calcium, serum phosphorus and serum aluminum. Plain X-ray was done for workers who were markedly complaining of musculoskeletal symptoms. Environmental measurement of aluminum dusts were carried out in selected workplaces.
Study Design: Case control study of aluminum exposed workers.

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Place and Duration of Study: Aluminum industry in Ain-Helwan, Cairo, Egypt, 2012.
Results: Statistically significant differences were found between exposed and control as regards prevalence of parathyroid and musculoskeletal disorders, serum level of the parathyroid hormone (PTH), serum calcium, serum phosphorus, serum aluminum, creatinine, RBCs count and also there was a statistically significant difference between exposed workers with osteopenia and exposed workers without osteopenia as regards serum aluminum level. The environmental measurements in the workplace were within the permissible limits in Egypt.
Conclusion: The elevation of serum aluminum level in workers exposed to environmental level within the permissible limits was associated with disturbance in PTH, calcium and phosphorus metabolism, so these limits should be revised. Periodic medical examination of workers exposed to aluminum is a must; this should include clinical examination, analysis of aluminum in serum, measurement of serum electrolyte (calcium and phosphorus) and bone imaging.

Keywords: Aluminum; parathyroid hormone; Calcium; Phosphorus; osteopenia; environmental measurements.

1. INTRODUCTION

In the Earth's crust, aluminum is the most abundant (8.3% by weight) metallic element and the third most abundant of all elements (after oxygen and silicon) [1]. Aluminum is the most widely used non-ferrous metal. Global production of aluminum in 2005 was 31.9 million tones. It exceeded that of any other metal except iron (837.5 million tones) [2]. Aluminum metal and its alloys are used extensively in building construction (e.g., siding, roofing, doors and windows), in transportation (in the manufacture of automobiles and aircraft), in packaging (e.g., for beverage cans) and in electrical equipments. Other uses include die-cast motor parts, cooking utensils, decorations, road signs, fencing, coloured kitchenware, food packaging, foil, corrosion-resistant chemical equipments, solid fuel rocket propellants and explosives, dental crowns, jewelers and denture materials. Aluminum is also used for power lines, electrical conductors, insulated cables and wiring [3].

Occupational exposure to aluminum occurs by inhalation of aluminum dusts and fumes during mining, processing, production and recovery of aluminum and its compounds [4].

Aluminum toxicity generally leads to an accelerated cell death due to chronic disruption of cell metabolism. Among the effects, aluminum can lead to an interference with the Glucose transphosphatase cycle, disturbance in parathyroid hormone (PTH), bone metabolism and changes in serum essential elements as calcium and phosphorus [5].

The bone constitutes a primary site for the deposition of aluminum [6]. Elevated aluminum levels in humans, primarily in individuals with impaired renal function and in individuals with long term use of aluminum containing antacid have been associated with several bone disorders [7]. The mechanism by which aluminum exerts its effects on bone tissue has not been fully understood [8]. Aluminum inhibits osteoblast proliferation, function and mineralization of osteoid tissue [7].

Aluminum-induced alterations in the parathyroid hormone-calcium axis have also been extensively investigated with respect to aluminum-induced bone toxicity [6]. It has direct and

indirect effect on the parathyroid gland, acting through different mechanisms. Aluminum accumulation in the parathyroid glands can reduce the parathyroid response to hypocalcaemia and prevents release of PTH [9]. Also it interferes with synthesis of PTH [10] and has an inhibitory effect on parathyroid cell proliferation [11]. Aluminum impairs parathyroid function through a calcium-like mechanism due to the lack of specificity of the calcium-sensing receptor. Also, aluminum decreases parathyroid calcium-sensing receptor mRNA levels through posttranscriptional regulatory mechanism [12]. Uptake of Al by receptors on parathyroid cells reduces the secretion of PTH but not its synthesis [9]. It could indirectly suppress PTH synthesis and release by inducing a state of hypercalcaemia through interference with calcium deposition into bone.

1.1 Aim of the Work

To study the effect of aluminum on the parathyroid gland and the disturbance in calcium and phosphorus metabolism among workers exposed to aluminum in aluminum industry.

2. MATERIALS AND METHODS

This study was performed in a company engaged in the manufacture of aluminum cylinders through smelting and refining of primary aluminum ingots in Ain-Helwan region. There were 3 sections involved in smelting and refining of primary aluminum ingots. The workforce of the three sections in the morning shift consists of 55 workers of whom 50 involved in the study all are males with a mean age (48.10±11.65) and a mean duration of exposure (27±9.92). All workers were exposed directly to aluminum dust.

A control group of 50 subjects was selected from the administrative department in Kasr Al-Ainy hospital of comparable age, gender and socioeconomic status .All workers of control group had no history of aluminum exposure.

Inclusion criteria: eight hours exposure to aluminum dust for six days per week.

Exclusion criteria: Subjects with history of intake of calcium or aluminum containing antacids, laxatives or use of antiperspirants and those who had a history of parathyroidectomy were excluded from the study and their total number was 5 workers.

Prior to this study, approval of the factory manager was obtained. Consent of sharing in this study was voluntarily obtained from each individual after giving an explanation of the aim of the study.

All studied group were subjected to a questionnaire including personal history with emphasis on occupational, present and past history.
Clinical examination and blood sample were taken.

2.1 Bone X-Ray

Plain bone x-ray of hip joint and upper femur was done for workers (16 exposed subjects) who were markedly complaining of musculoskeletal symptoms.

2.2 Laboratory Investigations

2.2.1 Serum aluminum level

Serum aluminum level was determined by Graphite Furnace Atomic Absorption Spectrometry.

2.2.2 Complete blood picture

Complete blood count was performed by an automated analyzer [13].

2.2.3 Kidney function tests

- Blood urea: By the Sclavo diagnostic method.
- Serum creatinine: By Modified Jaffè's Kinetic method.

2.2.4 Serum parathyroid hormone

Total intact PTH Assay by using Immuno-radiometric Assay (IRMA) [14].

2.2.5 Serum calcium

It was measured by Bio-Vision's colorimetric Calcium Assay Kit.

2.2.6 Serum phosphorus

Phosphorus Assay by the ARCHITECT C Systems and the AEROSET system.

2.3 Environmental Monitoring (air sampling)

Dust measurements were carried out in selected workplaces by air sampling from breathing zones. Determination of aluminum in dust samples was carried out by a Graphite Furnace Atomic absorption Spectrophotometer [15].

2.4 Statistical Analysis

Data obtained from the study was coded and entered using the statistical package SPSS version 15. The mean values, standard deviation (SD) and ranges were then estimated for quantitative variable. Qualitative data was expressed as frequency distribution.

Comparisons between exposed and control groups were done using Chi Square (X^2) test for qualitative variables and using the independent simple t-test followed by Post Hoc test for normally distributed quantitative variable. The non parametrical Mann Whitney test was used for quantitative variables not normally distributed.

Correlation "r" was done to test for the presence of linear relations between quantitative variables. P-value less than 0.05 and less than 0.001were considered statistically significant and highly significant, respectively.

3. RESULTS

The results of the present study showed that there were no statistically significant differences between the exposed and the control group as regards age, duration of employment and smoking.

Parathyroid disorders and musculoskeletal symptoms were significantly higher among exposed workers compared to the control group.

The study showed that the levels of serum parathyroid hormone and serum calcium were lower among the exposed group compared to the control and the differences were statistically significant. The levels of serum phosphorus and aluminum were higher among the exposed group when compared to the control with statistically significant difference Table 1.

Also, our study showed statistically significant differences among exposed when compared to the control as regards the level of serum creatinine Table 2, red blood cells and platelet count Table 3. There were statistically significant positive correlations between serum aluminum, duration of exposure and smoking Table 4.

There were negative correlations between serum aluminum level, serum PTH and calcium but did not reach the significant level Table 4.

Also, this work showed that there was a statistically significant difference between exposed symptomatizing workers with osteopenia and exposed workers without osteopenia as regards serum aluminum level Table 5.

Environmental study showed that the measurement of aluminum dusts ranged between 0.33- 3.4 mg/m^3 Table 6. The highest level was 3.4 mg/m^3 in areas of melting of primary aluminum ingots and aluminum scraps with emission of large quantities of aluminum dusts and fumes. The lowest level (0.33 mg/m^3) was recorded in the entrance of the unit which was away from emission.

The previous measurements of aluminum dusts at many sites of the factory were within the permissible levels of exposure which is 10 mg/m^3 according to NIOSH and ACGIH [16] and 15mg/m^3 according to OSHA [17].

There was thinning of bones with increased its radiolucency which indicate decrease in the bone density (osteopenia) in some exposed workers Fig 1.

Table 1. Mean±SD regarding serum PTH, calcium, phosphorus and aluminum among both exposed and control groups

	Exposed (n=50) Mean ± SD	Control (n=50) Mean ± SD	t-test	P value
PTH (pg/ml)	34.31±1.98	47.98±3.26	- 25.328	<.001*
Calcium (mg/dl)	8.92±0.58	9.49±0.47	- 5.349	<.001*
Phosphorus (mg/dl)	4.78±0.49	3.91±0.38	9.875	<.001*
Aluminum (µg/l)	24.46±18.28	0.58±1.2	-7.378	<.001*

**Statistically significant*

Table 2. Mean±SD regarding serum urea and creatinine among exposed and control groups

	Exposed (n=50) Mean ± SD	Control (n=50) Mean ± SD	t-test	P value
Urea(mg/dl)	65.31±11.78	66.09±7.57	-0.397	.120
Creatinine (mg/dl)	0.39±0.24	0.20±0.18	-5.189	<.001*

**Statistically significant*

Table 3. Mean±SD regarding complete blood picture among exposed and control groups.

	Exposed(n=50) Mean ± SD	Control (n=50) Mean ± SD	t-test	P value
HB(gm/dl)	11.78±1.59	12.02±1.05	-0.897	.062
RBCS (million/mm^3)	4.64±0.81	4.07±0.5	4.282	.030*
TLC ($10^3/mm^3$)	9.64±2.84	9.18±1.44	1.023	.065
Platelet ($10^3/mm^3$)	293.12±95.7	216.32±23.54	5.51	.020*

**Statistically significant*

Table 4. Correlation coefficient between serum aluminum and (serum calcium, serum phosphorus, PTH, duration of exposure and smoking index) among the exposed group

	Serum aluminum	
	R	P value
Serum calcium(mg/dl)	-0.048	.105
Serum phosphorus (mg/dl)	0.046	.165
PTH(pg/ml)	-0.108	.067
Duration of exposure	0.471	< .001*
Smoking index	0.327	.032*

**Statistically significant*

Table 5. Comparison between exposed workers with osteopenia and exposed workers without osteopenia regarding serum aluminum, calcium, phosphorus and PTH levels

	Exposed workers		t-test	P value
	Presence of osteopenia Mean±SD n=11	Absence of osteopenia Mean ± SD n=5		
Aluminum (µg/l)	45.81±18.08	16.81±9.66	-2.662	.028*
Calcium (mg/dl)	9.05±0.67	8.94±0.36	-0.355	.105
Phosphorus(mg/dl)	4.67±0.41	4.88±0.61	0.802	.230
PTH (pg/ml)	34.04±1.65	34.04±2	0.004	> .05

**Statistically significant*

Table 6. Environmental measurements of aluminum at different places of exposed group

Points of measurements	Aluminum dust mg/m^3
The melting furnace	3.4
The treating furnace	2.8
Pouring & heating furnace	2.5
Entrance	0.33

Fig. 1. Plain x-ray of hip joint and upper femur of workers who were markedly complaining of musculoskeletal symptoms

4. DISCUSSION

Aluminum (Al) is ubiquitous in the environment and exposure to it is unavoidable [18]. Aluminum is a serious environmental toxicant and included in the priority list of hazardous substances identified by Agency for Toxic Substances and Disease Registry (ATSDR) [19].

A limited number of studies have dealt with the effects of occupational exposure to Al on PTH and essential elements. The few published reports on the interaction between Al and PTH and essential metals were mostly related to patients on heamodialysis, to dietary Alintake in healthy subjects, preterm infants with parental nutrition or experimental animals [20].

By analyzing the clinical findings in the exposed workers in the present study, we found that symptoms of parathyroid dysfunction and musculoskeletal disorders expressed as easy fatigability, loss of concentration, depression, forget simple things, tingling and numbness in the hand, bony pain, muscle cramp, bony tenderness, muscle wasting and tremors were more prevalent among exposed group as compared to the control. Our results were consistent with [21], who studied the effect of aluminum on bone mineralization and parathormone level in aluminum exposed Egyptian workers. They found that the prevalence of musculoskeletal complaints was high among the exposed workers.

Also, these results were in relative resemblance to the results obtained by [22] who studied back pain and widespread pain in relation to sickness absence among aluminum industrial workers. They reported that the prevalence of musculoskeletal disorders in the aluminum industry is high and there is a considerable work-related fraction and that musculoskeletal disorders accounted for 40% of all working days lost the year prior to follow-up.

Our work showed that the level of PTH and calcium were low, while the level of phosphorus and aluminum were high among the exposed group (statistically significant). The lower

levels of serum PTH among the exposed group may be explained by presence of high level of aluminum which inhibits PTH by different mechanisms, such as aluminum accumulation in the parathyroid glands can reduce the parathyroid response to hypocalcaemia and prevents release of PTH [9], interferes with synthesis of PTH [10] and has an inhibitory effect on parathyroid cell proliferation [11].

The current correlated well with results in other studies of the inhibitory effects of high aluminum on parathyroid hormone [23,24]. These results were also in agreement with Ahmed and Ibrahim [21] who studied the effect of aluminum on bone mineralization and parathormone level in occupationally exposed Egyptian workers. They found that serum PTH and serum phosphorus were significantly lower among the exposed group.

Our results were in consistent with Metwally and Mazhar [25] who studied effect of aluminum on the levels of some essential elements in occupationally exposed workers. They found that the mean serum calcium was significantly lower in the exposed group than the controls.

This work was similar to that obtained by Mjoberg et al. [26] who reported that aluminum exposure greatly increased the risk of fragility fractures and bone disorders due to the fact that aluminum decreases serum calcium and inhibits bone mineralization. Orihuela et al. [27] deduced that aluminum might interfere with calcium uptake by enterocytes through a general effect on cell membrane, leading to a reduced transcellular calcium absorption in the small intestine.

Gonalez-Suarez et al. [11] studied the effect of aluminum on calcium sensing receptor expression ,proliferation and apoptosis of parathyroid glands in rats with chronic renal failure .They measured serum phosphorus, PTH and aluminum .They found higher levels of serum phosphorus and lower levels of serum PTH in the aluminum group.

The high serum aluminum levels among the exposed group may be explained by occupational exposure of workers to aluminum dusts and fumes and their inhalation absorption from work environment in addition to lack of ventilation in the factory. Similar results were obtained by Adams [28], who made a study on foundry workers exposed to aluminum dusts and he found that foundry workers had higher blood levels of aluminum compared to controls.

In agreement with our results Bogdanovic and Bulat [29] who studied biliary function among workers occupationally exposed to aluminum dust and fumes, they found that the mean serum aluminum was significantly higher in the exposed workers than controls.

Our work showed higher serum creatinine among the exposed group compared to the control group. This was in agreement with Mahieu et al. [30] who found a significant elevation in serum urea and creatinine due to aluminum overload.

Also, Alkahtani [31] reported an elevation in serum urea and creatinine levels in aluminum treated mice.

These results were also in accordance with Ahmed and Ibrahim [21] who studied the effect of aluminum on bone mineralization, parathormone level and kidney function tests in occupationally exposed Egyptian workers .They found that the mean level of serum creatinine was significantly higher among the exposed workers.

Aluminum nephrotoxic actions arise from its accumulation in the kidneys, with the resultant degeneration of the renal tubular cells [32].

As regards the effect of aluminum exposure on blood picture parameters there was higher levels of serum red blood cells and platelet count in blood among exposed group compared to the controls. These results were in relative resemblance to what obtained by Mahieu et al. [33] who studied the haemotoxic effect of aluminum intoxication in rat over 6 months exposure and they found that at 1st month, there was a decrease in red cell count as compared to control group but at the end of the study there was a significantly increase in red cell count (10±0.3 versus 8.7±0.2 million /ml). Thus, although microcytic anemia constitute an evidence of chronic aluminum exposure , prolonged exposure could lead to a recovery of hematocrit and hemoglobin concentration values with an increase in red cell number.

There were statistically significant correlations between serum aluminum and duration of exposure and smoking. These results may be explained by the fact which establishes that long duration of employment leads to more exposure to aluminum and so its accumulation in tissues and blood with an increase in the total body burden.

In case of cigarette smoking, it was found that aluminum is a major constituent of tobacco [34]. Also, there were negative correlations between the level of serum aluminum and the levels of serum PTH and calcium although it didn't reach the significant level. This agreed with the results obtained by Díaz-Corte et al. [10] who studied the effect of aluminum load on parathyroid hormone synthesis. They found that the serum aluminum levels were correlated with the percentage fall in PTH.

On studying the relation between aluminum exposure and osteopenia, our study showed that there was a statistically significant difference between exposed group with osteopenia and exposed group without osteopenia as regards serum aluminum level with higher level among workers with osteopenia.

Osteopenia may be due to older age and also may be due to exposure to aluminum as aluminum accumulates in bone, disrupts bone mineralization and inhibits osteoblast formation [35]. Similar to our results, Woodson [36] found that high use of aluminum containing antacids is often an important cause of osteomalacia, even in the relatively young persons (40-50 age group).

5. CONCLUSIONS AND RECOMMENDATIONS

In our work, we found a very high prevalence of parathyroid and musculoskeletal disorders among aluminum exposed workers. The evidence of parathyroid and musculoskeletal disorders in the exposed workers is not limited to subjective symptoms but it is supported by low levels of serum PTH, calcium among exposed workers and by the presence of osteopenia among symptomatic workers.

Biological monitoring in the form of serum aluminum was measured and it was elevated in spite of the low level of environmental aluminum. However, this was associated with disturbances in PTH, calcium and phosphorus metabolism which confirms that aluminum had adverse physiological effects on parathyroid gland, calcium, phosphorus and bone mineralization.

From the present work we recommend the use of preventive measures to minimize exposure to aluminum, periodic medical examination of workers exposed to aluminum is a must; this would include clinical examination, analysis of aluminum in serum, measurement of serum electrolyte (calcium and phosphorus) and bone imaging. Encourage the use of personal protective equipments like face masks, respirators and gloves, health and safety education for workers by explaining the hazards of Al exposure and the protective measures should be taken. Stopping smoking should be promoted among workers.

Moreover, we recommend further studies on larger numbers of aluminum exposed workers to support the presence of an association between aluminum exposure, parathyroid disorders and calcium metabolism. Although the environmental measures were within the recommended values in Egypt, still there is a health problem among exposed workers. So these threshold limit values should be further investigated.

CONSENT

All authors declare that “written informed consent” was obtained from the participants of this study.

ETHICAL APPROVAL

Prior permission was sought and obtained from the authorities of the Aluminum industry in Helwan district in Cairo before the study commenced. Recruitment into the study was voluntary and nobody was coerced into participation. Confidentiality was maintained by asking respondent not to write their names.

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COMPETING INTEREST

The authors declare that there are no competing interests.

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