



## Implication of Aluminum in Exerting Some Health Disorders Among Exposed Workers

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### Abstract

The present study aimed to evaluate implication of aluminum in exerting male reproductive and thyroid hormonal disorders and lipid profile changes among aluminum workers. Cross-sectional study was carried on 56 male aluminum workers in aluminum welding factory. Aluminum dust level was measured and questionnaire was conducted for all participants. Urinary aluminum level, serum total cholesterol, triglycerides, high density lipoprotein, high sensitive c-reactive protein, apolipoprotein- E, total antioxidant capacity, malondialdehyde, luteinizing hormone, follicle stimulating hormone, testosterone, 17-beta-estradiol, free triiodothyronine, free thyroxin and thyroid stimulating hormone were measured in both groups. Aluminum dust mean concentration was  $1.6 \pm 0.3 \text{ mg/m}^3$  in the present study. Urinary aluminum, serum triglycerides, very low density lipoprotein cholesterol, high sensitive C-reactive protein and malondialdehyde levels were significantly higher while total antioxidant capacity was significantly lower among the exposed workers compared to controls. Serum follicle stimulating hormone and free triiodothyronine were significantly higher while free thyroxin was significantly lower in the exposed group compared to controls. No effect of smoking on all measured parameters was reported except for luteinizing hormone. Negative correlation was found between duration of exposure and 17-beta-estradiol. Urinary aluminum level was negatively correlated with total antioxidant capacity on one side and positively correlated with malondialdehyde on other side. Induction of oxidative stress and inflammation might be the possible mode of action by which aluminum exert male reproductive hormonal disorders and lipid profile changes. Aluminum may disrupt thyroid hormones. Pro inflammatory effect of aluminum was verified by the inflammatory markers.

**Key words:** Aluminum, oxidative stress; inflammation; male reproductive hormones; thyroid hormones; lipid profile

### 1. Introduction

Aluminum (Al) is the most widely spread metal in the environment. It occurs naturally and is also released due to several activities such as aluminum welding, spraying and polishing. Al particles in air is the source of Al in inhaled sprays [1].

Inhalation, oral, or dermal exposure are the primary routes of Al exposure in humans or animals. Al can be toxic to exposed humans when there is a high body burden of the metal. Excess Al mainly accumulate in bone, liver, testes, kidney, and brain leading to toxicity and organ dysfunction [2].

Inhalation of Al particles results in their retention in the lungs. They are then released to the blood and spread to bones and brain, and excreted in urine. Al can be measured in the blood, urine, and stools to confirm Al load and association with toxicosis. Previous study on Al welders showed that Al

concentration in welding fumes was correlated with Al concentrations in blood and urine [3].

Al toxic effects arise principally from its pro-oxidant activity resulting in oxidative stress. Al through interacting with the essential trace metals Fe, Cu, Se, and Zn may affect the antioxidant enzymes activities [4].

Al toxic action disrupt cellular homeostasis leading to systemic toxicosis with structural and functional abnormalities of organs<sup>1</sup>. Pro-inflammatory actions of Al which is initiated by Al-induced oxidative stress have been reported in heart, and testis [5-6]. Onyegeme and Anacletus [7] provide evidence of adverse effects of Al on reproductive hormones like testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2) and thyroid hormones.

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Despite the increased information nowadays about Al toxicity, very little is known about Al reproductive toxicity in humans. Most information is from animal studies, which is not appropriate to human exposure circumstances. Human male has a relatively low fertility compared to other mammals and is more vulnerable to metal toxicity [8].

Klein et al., [9] suggested that Al exposure negatively affect human reproduction as he found that patients with oligospermia had higher Al levels than healthy persons. Moreover, Berihu [10] added that high Al levels in human testes, blood and urine, were accompanied with worsening in spermatogenesis, free radicals' development with changes in antioxidant enzymes; impaired sperm quality and disruption in sex hormone secretion.

The effect of metals on the human thyroid is still poorly studied. Also, scarce information is found about animal studies on effects of Al on thyroid [11]. Post-mortem enlargement of the thyroid was stated in male workers occupationally exposed to Al powder [12]. DeVito et al., [13] mentioned that FT4 and TSH which are the most sensitive markers of thyroid function in mammals were not affected by Al. Orihuela [14] in his experimental study found that in adult rats Al does not act as a thyroid disruptor.

Previous studies stated that Al may disturb the lipid metabolism causing dyslipidemia. Dyslipidemia is an asymptomatic disorder, but persistently raised serum lipids lead to formation of arterial atheromatous plaques causing stenosis or occlusion [15]. Al toxicity was accused for lipid accumulation intracellularly as a result of induced disturbance in the oxidative-ATP production in the human hepatocytes. Thus, those liver cells secrete lipids and proteins. As such, Al-induced mitochondrial dysfunction stimulates lipogenesis with accumulation of the very low density lipoprotein (VLDL) secondary to decrease in the  $\beta$ -oxidation of fatty acids [16].

Cardiovascular effects due to Al toxicosis are inflammation, myocardial dysfunction and cardiovascular thrombosis [1]. High sensitive c-reactive protein (hs-CRP), a biomarker of inflammation, is an independent predictor for coronary artery disease. Previous studies, showed an association of pro-inflammatory biomarkers with hypertension, coronary and cerebrovascular events. Cardiovascular welfares are more obvious when systemic inflammation is reduced (as verified by declined hs-CRP) [17-18].

Apo lipoprotein E (Apo-E) is a class of apolipoprotein which mediates triglycerides and cholesterol metabolism. It regulates the clearance of

VLDL and high density lipoprotein (HDL) from plasma by interacting with the low-density lipoprotein (LDL) receptor, which is necessary for the catabolism of triglyceride-rich lipoproteins. APO E has pro inflammatory properties and mediates the presentation of lipid antigens to the immune system leading to chronic inflammation [19-20].

The present study aimed to evaluate the implication of aluminum in exerting male reproductive and thyroid hormonal disorders and lipid profile changes among aluminum occupationally exposed workers.

## **2. Subjects and Methods:**

### **2.1 Study design and population**

The present study is a cross-sectional comparative study that included two groups: Al-exposed workers (n=56) and controls (n=38). Controls are clerks from administration jobs with no past or current history of occupational exposure to heavy metals.

This study was carried out on 56 male workers in an aluminum welding factory located in Greater Cairo Governorate, Egypt, with mean duration of exposure ( $22.6 \pm 11.4$ ) years. Their work was 8 hours per day with one day off. None of the workers used any protective equipment (masks, protective goggles and gowns) during working hours. Workers known to be diabetic or hypertensive or with past medical history of reproductive, cardiovascular or thyroid diseases or chronic liver diseases, prior to present job were excluded. Written informed consent was taken from all participants prior to the study. The study was approved by Medical Research Ethics Committee (National Research Centre, Cairo, Egypt) No. (15179).

### **2.2 Methods**

#### **Workplace Al monitoring:**

Air samples to assess total Al dust levels were taken during the shift time from different places in the production unit. Analysis was performed by the atomic absorption spectrophotometry [21].

#### **Questionnaire**

An interview questionnaire was filled by all participants. The questionnaire comprised personal data, smoking habit, occupational history, past and current medical history, types and use of personal protective equipment.

#### **Urine and blood sample**

1- A random morning urine sample was collected from each participant in a plastic container and centrifuged at 4500 rpm for 10 min; then the top 15 ml of the supernatant was stored frozen at  $-20^{\circ}\text{C}$  in aliquots without preservatives until urinary Al was measured. Prior to metal determination, all samples

were digested using nitric acid, where it is an acceptable matrix for flame atomic absorption and it is also used to provide acceptable and consistent recovery compatible with the analytical method [21]. All heavy metal analyses were performed on Agilent 5100 Inductively Coupled Plasma – Optical Emission Spectrometer (ICP-OES) with Synchronous Vertical Dual View (SVDV).

2-Blood sample was collected by venipuncture with 5 ml syringe from each subject. Clotted blood was centrifuged to separate serum to estimate serum total cholesterol (TC), triglycerides (TG), HDL-c, hs-CRP, Human Apo E, total antioxidant capacity (TAC), malondialdehyde (MDA) and hormones including luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, 17-beta-estradiol (E2), free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH). The serum samples were immediately frozen at –20C until analyzed.

### 2.3 Laboratory investigations

- Serum TC was measured by enzymatic colorimetric test-GPO-PAP Method [22].
  - Serum TG was measured by enzymatic colorimetric test-GPO-PAP Method [23].
  - Serum HDL-c was measured using the precipitation with phosphotungstic acid [24].
- All the previous kits were purchased from Centronic GmbH AM Kleinfeld 11, 85456 Wartenberg/Germany
- Serum very low density lipoprotein cholesterol (VLDL-c) was calculated (24).  $VLDL = TG/5$
  - Serum low density lipoprotein cholesterol (LDL-c) was calculated (24).  $LDL-c = TC - (HDL-c + VLDL-c)$
  - Determination of serum hs-CRP by a microplate immunoenzymometric assay Monobind Inc., AccuBind Elisa wells, USA [25].
  - Determination of serum Human Apo E Quantikine ELISA Kit: R&D Systems Inc. Minneapolis, USA
  - Total antioxidant capacity (TAC) was estimated colorimetrically [26].
  - The determination of malondialdehyde (MDA) as a marker for lipid peroxidation using colorimetric method [27].
  - Serum concentrations of LH, FSH, testosterone, free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) were measured using ELISA Kit by DRG International, Inc., (USA) at the research laboratory, 17-beta-estradiol (E2) using kit by Biosource.

### 3. Statistical analysis:

- Data statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 20 for statistical analysis.
- Quantitative normally distributed data is analyzed using independent t-test (comparison of two independent groups),
- Pearson correlation coefficient test is used to test association between variables.

### 4. Results:

The mean of Al dust level in the present study was  $1.6 \pm 0.3 \text{ mg/m}^3$ . These measurements are within the maximum allowable limits according to Egyptian Law ( $3 \text{ mg/m}^3$ ) [28].

Exposed and control groups are all males with comparable ages ( $45.8 \pm 10.1$  vs.  $42.9 \pm 6.9$  years respectively).

Table (1): shows that urinary Al level, serum TG, VLDL, hs-CRP level and MDA were significantly higher, while TAC was significantly lower among Al exposed workers compared to controls.

Table (2): shows that serum FSH and free T3 are significantly higher while free T4 was significantly lower in the Al exposed group compared to the controls.

There was no effect of smoking on all measured parameters except for LH which was  $6.04 \pm 0.24 \text{ mIU/ml}$  in smokers and  $5.68 \pm 0.43 \text{ mIU/ml}$  in non-smokers with t-test = 2.605 and p-value = ( $<0.01$ ).

There was negative correlation between the duration of exposure and E2 [ $r = 0.417$ , p-value =  $0.027$  ( $<0.05$ )].

Also, urinary Al level was negatively correlated with TAC [ $r=0.045$ , (p-value  $<0.05$ )] and positively correlated with MDA [ $r = 0.104$ , p-value  $<0.05$ ].

### 5. Discussion

Wide spread of Al increases the risk of exposure and the consequent health problems in humans. Al is eliminated from the body mainly through the kidneys in urine. Exposure to Al and decreased excretion lead to Al accumulation in body which is responsible for Al toxicosis [1].

The reference value for urinary Al is  $<15 \text{ } \mu\text{g/L}$  in general population (reference values set by the German Federal Environmental Agency) [29]. It is likely to be exceeded in workers with occupational exposure ( $50 \text{ } \mu\text{g}$  of aluminum per gram of creatinine in the urine) [30].

**Table (1): Mean  $\pm$  SD of the investigated parameters among the studied groups**

	Exposed (56)	Control (38)	t-test	P value
	Mean $\pm$ SD	Mean $\pm$ SD		
Urinary Al ( $\mu\text{g/l}$ )	<b>28.03<math>\pm</math>19.89</b>	<b>11.55<math>\pm</math>1.51</b>	<b>3.590</b>	<b>0.001**</b>
TC (mg/dl)	<b>166.77 <math>\pm</math> 65.09</b>	<b>147.98 <math>\pm</math> 34.97</b>	<b>1.152</b>	<b>0.256</b>
TG(mg/dl)	<b>238.01<math>\pm</math>116.07</b>	<b>132.31<math>\pm</math> 80.71</b>	<b>3.371</b>	<b>0.002**</b>
HDL-c(mg/dl)	<b>40.34 <math>\pm</math> 10.95</b>	<b>54.08 <math>\pm</math> 14.13</b>	<b>1.751</b>	<b>0.088</b>
LDL-c(mg/dl)	<b>78.83 <math>\pm</math> 30.93</b>	<b>67.44 <math>\pm</math> 23.10</b>	<b>0.599</b>	<b>0.553</b>
VLDL-c(mg/dl)	<b>47.60 <math>\pm</math> 23.1</b>	<b>26.40 <math>\pm</math> 16.14</b>	<b>3.371</b>	<b>0.002**</b>
Hs-CRP( $\mu\text{g/ml}$ )	<b>8.10 <math>\pm</math> 4.56</b>	<b>4.26 <math>\pm</math> 3.82</b>	<b>2.898</b>	<b>0.006**</b>
ApoE ( $\mu\text{g/ml}$ )	<b>32.86 <math>\pm</math> 33.07</b>	<b>53.22 <math>\pm</math> 72.68</b>	<b>1.119</b>	<b>0.270</b>
TAC (Mm/L)	<b>1.24 <math>\pm</math> 0.3</b>	<b>1.58 <math>\pm</math> 0.42</b>	<b>4.2</b>	<b>0.001**</b>
MDA (nmol/ml)	<b>9.88 <math>\pm</math> 2.2</b>	<b>6.79 <math>\pm</math> 3.49</b>	<b>5.08</b>	<b>0.001**</b>

Al (aluminum), TC (total cholesterol), TG (triglycerides); HDL-c (high density lipoprotein cholesterol); LDL-c (low density lipoprotein cholesterol); VLDL-c (very low density lipoprotein cholesterol); Hs-CRP (high sensitive C-reactive protein); Apo E (apolipoprotein E); TAC (total antioxidants); MDA (malondialdehyde). \*\* $p < 0.01$

**Table (2): Mean levels of investigated hormones among exposed and control groups**

Hormones	Exposed (56)	Control (38)	t-test	P value
	Mean $\pm$ SD	Mean $\pm$ SD		
LH (mIU/ml)	<b>5.84<math>\pm</math>0.40</b>	<b>5.76<math>\pm</math>0.64</b>	<b>0.479</b>	<b>0.634</b>
FSH (mIU/ml)	<b>10.26<math>\pm</math>5.21</b>	<b>6.44<math>\pm</math>1.15</b>	<b>3.132</b>	<b>0.003**</b>
Testosterone (ng/ml)	<b>5.53<math>\pm</math>0.83</b>	<b>6.14<math>\pm</math>1.63</b>	<b>1.501</b>	<b>0.140</b>
E2 (pg/ml)	<b>33.65<math>\pm</math>16.96</b>	<b>29.68<math>\pm</math>8.56</b>	<b>0.940</b>	<b>0.352</b>
fT4 (ng/dl)	<b>1.11<math>\pm</math>0.38</b>	<b>1.39<math>\pm</math>0.33</b>	<b>2.633</b>	<b>0.012*</b>
fT3 (pg/ml)	<b>2.80<math>\pm</math>1.90</b>	<b>1.81<math>\pm</math>0.11</b>	<b>2.264</b>	<b>0.028*</b>
TSH (uIU/ml)	<b>2.11 <math>\pm</math> 0.67</b>	<b>1.89<math>\pm</math> 0.55</b>	<b>1.59</b>	<b>0.117</b>

LH= luteinizing hormone, FSH= follicle stimulating hormone, E2(17-beta-estradiol), fT4= free thyroxin, fT3= free triiodothyronine, TSH= thyroid stimulating hormone. \* $p < 0.05$ ; \*\* $p < 0.01$

The present study showed that urinary Al mean level in the exposed workers was significantly higher (28.03 $\pm$ 19.89 $\mu\text{g/l}$ ) than the control group (11.55 $\pm$ 1.51 $\mu\text{g/l}$ ). This was in agreement with results of previous studies done on workers exposed to Al [31-32].

Al accumulates in endocrine glands causing its damage through oxidative stress, thus decreasing the level of the hormones secreted into blood for action at the target organs, leading to organ hypofunction [33]. Al has the ability to induce male fertility; testicular failures [34], inadequate androgenic hormone [35], decreased androgen receptor functions [36] by prompting oxidative stress in the testes.

In the present study, MDA mean levels were significantly higher, while, TAC mean levels were significantly lower among Al exposed workers compared to controls. Also, there was a statistical positive correlation between urinary Al level and MDA and negative correlation between urinary Al level and TAC. This agree with previous studies done to investigate the relationship between Al levels and oxidative status in workers occupationally exposed to Al [37-38]. Another study done on patients on

hemodialysis with high serum Al level, had significant high MDA and significantly decreased TAC compared to controls [39].

The present study showed significant increase in FSH serum level, increase in LH and decrease in testosterone serum levels but with no significant difference compared to the controls. The Al interference with the reproductive hormones LH, FSH and the testosterone has been observed in studies on laboratory animals [40-36]. These results were partly confirmed also in studies on human subjects exposed to Al. A high concentration of Al in spermatozoa was correlated with decreased sperm motility [41] and declined spermatogenesis [10].

This was explained by Berihu [10]; Al accumulated in the testis, damage Leydig cells, thus reducing testosterone level which in turn increase LH level through a negative feedback function of hypothalamus-pituitary-testis. Al exposure decrease testosterone level and then inhibit testicular development, spermatogenesis and androgenic hormones as it crosses the blood-testis barrier, after inducing oxidative stress that damages the biological

membranes of the testes. This in turn disturbs spermatogenesis.

The current study showed significant decrease in serum fT4 and significant increase in serum fT3 levels with increase in TSH level but with no significance among Al exposed workers compared to the controls. A previous study done on workers occupationally exposed to Al showed TSH level reduction after 1 year of work [42]. Orihuela [14] mentioned that this finding suggest that Al may change the pituitary endocrine regulation of thyroid gland. Orihuela [43] stated that short term oral Al, reduced thyroxin serum levels in rats. However, in his further study which was done to evaluate the effects of Al on thyroid function in adult wistar rats found that fT4 and TSH remain unchanged. He suggested that although Al could indirectly affect thyroid iodide uptake and hormones secretion by induction of an oxidative stress state, however these changes could be managed by the hypothalamus-pituitary-thyroid axis [14].

The current study showed that TG and VLDL-c levels are significantly higher among Al exposed workers compared to controls. Previous studies done on Al workers found significant elevation of serum TC, LDL and TG confirming presence of dyslipidemia as one of the occupational hazards to Al exposure [44-15]. These findings were also supported by other study which suggested that human liver cells exposed to Al were characterized by increased lipid accumulation [45]. This finding was explained by Mailloux et al., [16] who stated that Al affects metabolism by disturbing lipid membrane fluidity and ending in oxidative stress leading to intracellular lipid accumulation as a result of increased lipogenesis and decreased  $\beta$  oxidation of fatty acids. A previous study done to examine the effects of Al oxide in rats found significant elevation in serum levels of TG, TC, LDL, and MDA with significant decreases in serum HDL and myocardial SOD, catalase [46].

Previous study done to find the possible relationship between inhalation of airborne particles as iron, Al and concrete in the work environment and inflammatory markers in blood found that CRP increased by 17% after the second shift [47]. In the present study the hs-CRP mean level in the exposed group was nearly twice that of the controls which confirm the presence of inflammation.

In the present study, Apo E mean level was lower while hs-CRP was significantly higher in the exposed group compared to the controls. Beshir and his colleagues [20] mentioned in their study that Apo E is down regulated by inflammatory cytokines as there is inflammation in the exposed group confirmed by the higher levels of hs-CRP. The role of low grade

systemic inflammation as verified by raised hs-CRP levels in the pathogenesis of cardiovascular diseases (CVD) had been verified in another study who found that mean hs-CRP level was higher in patients with CVD compared with those without CVD [48].

### **6. Conclusion:**

The results of the present study suggested that induction of oxidative stress and inflammation might be the possible mode of action by which Al exert male reproductive hormonal disorders and lipid profile changes. Al may disrupt the thyroid hormones. Pro inflammatory effect of aluminum was verified by the inflammatory markers (hs-CRP and ApoE).

### **Recommendation**

- Administration of exogenous antioxidants to Al occupationally exposed workers to avoid oxidative stress.
- Regular assessment of male reproductive hormones, thyroid function, lipid profile, ApoE and hs-CRP as inflammatory biomarker to AL occupationally exposed workers.

**Conflict of interest:** The authors declare no conflict of interest.

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