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Epidemiology

Aluminium levels in hair and urine are associated with overweight and obesity in a non-occupationally exposed population

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ABSTRACT

Background: Data on the association between aluminium (Al) exposure and obesity and/or metabolic syndrome are insufficient. The objective of the present study was to investigate the association between hair and urine Al levels and obesity.

Methods: A total of 206 lean and 205 obese non-occupationally exposed subjects (30–50 y.o.) were enrolled in the study. Hair and urine Al levels were assessed with ICP-MS. Laboratory quality control was performed using the certified reference materials of human hair, plasma, and urine.

Results: Hair and urinary Al levels in obese subjects were significantly higher by 31% and 46% compared to the control levels, respectively. The presence of hypertension (41% cases), atherosclerosis (8%), type 2 diabetes mellitus (10%), and non-alcoholic fatty liver disease (NAFLD) (53%) in obese patients were not associated with Al levels in the studied subjects. An overall multiple regression model established urinary Al levels ($\beta = 0.395$; $p < 0.001$), hypertension ($\beta = 0.331$; $p < 0.001$) and NAFLD ($\beta = 0.257$; $p = 0.003$) were significantly and directly associated with BMI. Hair Al levels were found to be border-line significantly related to BMI after adjustment for several confounders ($\beta = -0.205$; $p = 0.054$).

Conclusions: Aluminium body burden is associated with increased body weight, although the causal relationship between Al exposure and obesity is not clear. Both clinical and experimental studies are required to further investigate the impact of Al exposure on metabolic parameters in obesity and especially direct effects of Al in adipose tissue.

1. Introduction

The incidence of obesity has significantly increased during the last several decades [1]. Nearly 2 billion people worldwide are overweight, and approximately one third of them are obese [2]. Being initially widespread in developed countries, the incidence of obesity reached a scale of epidemic in developing countries as well [3]. Although some studies indicated a decline in the obesity epidemic [4], such data should be interpreted with caution [5]. Data from 2016 demonstrate that despite the efforts aimed at obesity prevention the incidence of obesity in adults, recently at 37.7%, does not tend to decrease [6].

Although positive caloric balance due to consumption of energy-dense foods and sedentary lifestyle was long considered as the key factor of obesity [7], recent studies demonstrate that obesity results from a complex interplay between genetic, environmental, and behavioral factors [8]. Environmental pollution [9] and especially exposure to persistent organic pollutants was shown to play a significant role in obesity [10,11].

At the same time, recent studies demonstrated the potential impact of toxic metals including mercury [12,13], organotin [14,15], and cadmium [16] on impaired adipogenesis and obesity risk. Particularly, obesity was associated with the levels of mercury, lead, cadmium in various substrates [17–19]. However, existing data are rather contradictory [20,21] and in need for corroboration.

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Aluminium (Al) is considered as a toxic metal being involved in numerous diseases [22–25]. Recent focus has been directed at the potential role of Al in the etiology of various neurodegenerative diseases, including Alzheimer's disease and autism spectrum disorder (ASD) [26,27]. Molecular mechanisms of Al toxicity involve oxidative stress and inflammation [26], as well as interference with essential metal signaling [28]. At the same time, data on the potential association between Al and obesity are very limited. Particularly, in our earlier study, we revealed a significant elevation in hair Al levels in overweight and obese patients, which was also associated with altered lipid profile [29].

Therefore, the objective of the present study was to investigate the association between the level of Al in hair and urine and obesity.

2. Materials and methods

2.1. Subject characteristics

All procedures performed were in agreement with the ethical principles of the Declaration of Helsinki and its later amendments (2013). The protocol of the present study was approved by the Local Ethics Committee. All examinees took part in the present study on a voluntary basis, were informed about the experimental procedures, and signed the informed consent form prior the investigation.

A total of 411 adults aged 30–50 y.o. including 206 lean and 205 obese subjects living in Moscow (Russia) were enrolled in the present study. Only Caucasian subjects living in Moscow for more than last five years were examined. Demographic and anthropometric data are provided in Table 1. The control subjects with normal BMI values (20–25, underweight excluded) were gender-, age-, and height-matched. No significant group difference in age and height values were observed between the control and obese groups. Body weight and body mass index (BMI) in the obese group exceeded the control values by 48%. BMI assessment was used for diagnosis of obesity according to the standard formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$$

Obesity was diagnosed as BMI > 30 kg/m^2. The mean BMI values in the control and obese groups were found to be 33.3 ± 3.2 m^2/kg and 22.5 ± 1.4 m^2/kg ($p < 0.001$).

Data on the presence of metabolic disturbances were obtained from the medical cards of the volunteers based on the results of the last medical examination. The presence of hypertension, atherosclerosis, non-alcoholic fatty-liver disease (NAFLD), and type 2 diabetes mellitus (DM2) was recorded.

In addition, the following exclusion criteria were used during recruitment of the volunteers: smoking (current and former smoker status); excessive alcohol consumption; occupational exposure to environmental inorganic and organic toxins (current and former); living in a proximity to metal emission sources; mineral supplementation; metal implants including dental amalgams; history of acute cardiovascular events; acute inflammatory diseases; menopause (in women); uncommon food habits including vegetarianism. It is also notable that patients suffering from gastrointestinal diseases (gastritis, ulcer) consuming Al-containing antacids were also excluded from the study.

Table 1
Demographic and clinical data from the studied obese patients and lean controls.

Parameter	Control	Obesity	P value
Age, years	43.9 ± 12.1	44.7 ± 11.9	0.087
Weight, kg	64.3 ± 7.6	95.2 ± 12.4	< 0.001 *
Height, cm	168.7 ± 8.1	168.9 ± 9.0	0.895
BMI, kg/m^2	22.5 ± 1.4	33.3 ± 3.2	< 0.001 *
Gender,			
Male	55 (27%)	65 (32%)	0.103
Female	151 (73%)	141 (68%)	
Hypertension	–	84 (41%)	–
Atherosclerosis	–	17 (8%)	–
NAFLD	–	109 (53%)	–
DM2	–	21 (10%)	–

Data expressed as mean ± SD or n (%) (% is indicative of the respective number of subjects with particular characteristics from the total number of examinees); * Significant difference at $p < 0.05$; BMI – body mass index; NAFLD – non-alcoholic fatty liver disease; DM2 – diabetes mellitus type 2.

2.2. Sample collection

Urine samples were collected in the morning after overnight fasting using plastic Vacuette® Urine Collection Cups (Greiner Bio-One International AG, Austria) precleaned with 2% HNO_3. Only the second portion of urine was collected and used for analysis.

Proximal parts of the hair strands (1–2 cm) were collected in a quantity of 0.05 – 0.1 g from the occipital region using ethanol-precleaned stainless-steel scissors. The examinees washed the hair prior to the analysis using their own shampoos that is believed to have no significant impact on hair aluminium content [30]. The obtained hair samples were stored in paper envelopes until analysis.

2.3. Sample preparation

The obtained urine samples were diluted 1:15 with an acidified (pH = 2.0) diluent containing (v/v) 1% 1-Butanol (Merck KGaA, Darmstadt, Germany), 0.1% Triton X-100 (Sigma-Aldrich, Co., St. Louis, MO USA), and 0.07% HNO3 (Sigma-Aldrich, Co., St. Louis, MO USA) in 18.2 MΩ cm distilled deionized water.

The obtained hair samples were washed with acetone and subsequently rinsed three times with 18.2 MΩ cm deionized water (Labconco Corp., Kansas City, MO, USA) in order to remove external mechanical contamination (dust, dirt). The washed hair samples were dried on air at 60 °C till stable weight and subsequently subjected to microwave acid digestion. A quantity of 50 mg dry hair samples was introduced into Teflon tubes containing 5 ml of concentrated (65%) nitric acid (Sigma-Aldrich Co., St. Louis, MO, USA). Berghof SpeedWave-4 DAP-40 (microwave frequency, 2.46 GHz; power, 1450 W) microwave system (Berghof Products + Instruments GmbH, 72,800 Eningen, Germany) was used for microwave digestion. Sample decomposition was performed for 20 min at 170–180 °C. The resulting digests were transferred into polypropylene tubes and adjusted with distilled deionized water to a final volume of 15 ml.

2.4. ICP- MS analysis

Assessment of Al levels in urine and hair of examinees was performed using inductively-coupled plasma mass-spectrometry (ICP-MS) at NexION 300D (PerkinElmer Inc., Shelton, CT, USA) spectrometer equipped with 7-port FAST valve and ESI SC-2 DX4 autosampler (Elemental Scientific Inc., Omaha, NE, USA). Briefly, the system was characterized by: plasma power - 1500 W; Plasma argon flow - 18 l/min; Aux argon flow – 1.6 l/min; Nebulizer argon flow - 0.98 l/min; sample introduction system - ESI ST PFA concentric nebulizer and ESI PFA cyclonic spray chamber (Elemental Scientific Inc., Omaha, NE 68122, USA).

External calibration of the system was performed using Al solutions with a final concentration of 0.5, 5, 10 and 50 μg/l prepared from Universal Data Acquisition Standards Kit (PerkinElmer Inc., Shelton, CT, USA) by dilution with 18.2 MΩ cm distilled deionized water (Labconco Corp., Kansas City, MO, USA) acidified with 1% HNO3 (Sigma-Aldrich Co., St. Louis, MO, USA).

In addition, internal online standardization was used in order to account for different viscosity and acidity of the calibration standards and studied samples. Briefly, 10 μg/l solutions of yttrium-89 and

Table 2
Laboratory quality control of hair, serum, and urine aluminium level analysis.

Level	Certified value, μg/g	Certified range, μg/g	Obtained value, μg/g	Recovery rate, %
GBW09101				
none	23.2	21.2–25.2	23.9 ± 2.0	103
ClinChek® Urine Control				
I	34.0	27.2–40.8	34.7 ± 2.7	102
II	87.1	69.7–105	83.6 ± 3.3	96

The obtained values are expressed as Mean ± SD.

rhodium-103 were prepared from Yttrium (Y) and Rhodium (Rh) Pure Single-Element Standard (PerkinElmer Inc. Shelton, CT, USA) on a matrix containing 8% 1-butanol (Merck KGaA, Gernsheim, Germany), 0.8% Triton X-100 (Sigma-Aldrich Co., St. Louis, MO, USA), 0.02% tetramethylammonium hydroxide (Alfa Aesar, Ward Hill, MA, USA) and 0.02% ethylenediaminetetraacetic acid (Sigma-Aldrich Co., St. Louis, MO, USA).

2.5. Laboratory quality control

Laboratory quality control was performed daily using the certified reference materials (CRMs) of human hair (GBW09101, Shanghai Institute of Nuclear Research, Shanghai, China) and urine (ClinChek® Urine Control, Levels I, II, Lot 1227). Based on the certified values of metal levels and the obtained data the recovery rates (%) were calculated for CRMs of human hair and urine (Table 2). The laboratory of the Center for Biotic Medicine (Moscow, Russia) is also a participant of the Occupational and Environmental Laboratory Medicine External Quality Assessment Schemes (OELM EQAS).

2.6. Statistical analysis

The obtained data were processed Statistica 10.0 (Statsoft, OK, USA). Shapiro-Wilk test was used for data normality assessment. Median and interquartile range (IQR) were used as descriptive statistics due to non-Gaussian data distribution. Paired-group comparisons were performed using Mann-Whitney *U* test False Discovery Rate (FDR) adjustment for p-value was applied due to multiple comparisons. Comparison of categorical parameters was performed using chi-square (χ^2) test. Multiple regression analysis was performed in order to specify the association between Al levels as well as demographic and clinical variables (independent predictors) and BMI (dependent variable). All models were adjusted for variability in age and gender of the examinees. All tests were considered significant at $p < 0.05$.

3. Results

As shown in Fig. 1, obesity was associated with increased Al levels in the studied subjects. Particularly, hair and urinary Al levels in obese subjects were characterized by a significant increase of 31% and 46% as compared to the control levels, respectively. Gender had a significant impact on the observed associations. In particular, hair and urinary Al levels in obese women exceeded those in controls by 28% and 46%, respectively (Fig. 1B). At the same time, the observed 43% increase in hair Al levels in obese men was only nearly significant. However, urinary Al levels in men male obese patients exceeded the control values by a factor of nearly two (Fig. 1C).

Nevertheless, other characteristics of metabolic syndrome (hypertension, atherosclerosis, insulin resistance) as well as NAFLD in patients with obesity were not associated with altered hair or urine Al levels (Table 3). Only urinary Al levels in obese patients with hypertension, NAFLD, and insulin resistance were characterized by a 35%, 25%, and 30% decrease in comparison to obese subjects absent of these comorbidities, although the difference was not significant.

Multiple regression analysis was performed to investigate the association between anthropometric and clinical variables with the level of Al in various biosamples (hair, urine) (Table 4). Particularly, BMI was directly associated with hair and especially urinary Al levels in the studied subjects. It is also noteworthy that hypertension had a negative impact on the level of Al in the urine. At the same time, multiple regression analysis also failed to reveal any significant influence of other metabolic syndrome components on hair Al levels. However, male gender was also considered as a positive predictor of increased hair Al content. Although accounting only for 8% and 3% of variability of Al levels in urine and hair, the regression models significantly predicted the dependent parameter.

Multiple regression analysis was also performed to investigate the association between Al levels and BMI after adjustment for anthropometric and clinical variables (Table 5). Urinary Al levels were found to be independently directly interrelated with BMI in the studied subjects. Hair Al levels were nearly significantly inversely related to BMI after adjustment for other confounders. The presence of hypertension and NAFLD was also associated with elevated BMI. At the same time, the overall model accounted for 41% of BMI variability, being higher as compared to the model not incorporating Al levels in the studied substrates (37%).

Correlation analysis was performed to estimate the relationship between Al levels in different samples in relation to obesity. In the overall cohort of examinees hair Al levels significantly correlated with Al concentration in urine ($r = 0.787$; $p < 0.001$). At the same time, obesity significantly modified the observed correlations. Particularly, in the control group no significant correlations between hair and urine Al levels were observed. Oppositely, a strong association between hair and urinary Al content ($r = 0.849$; $p < 0.001$) was observed in obese subjects.

4. Discussion

Our findings demonstrate that hair and especially urinary Al levels are significantly increased in obesity, being independently associated with body mass index, but not other components of metabolic syndrome (atherosclerosis, hypertension, diabetes, NAFLD).

These findings are generally in agreement with an earlier study demonstrating a direct association between obesity and higher hair Al levels, as well as increased triglyceride levels [28]. However, the causal relationship between Al exposure and obesity has yet to be clarified. On one hand, dietary patterns characteristic for obese patients may also contribute to increased Al intake, whilst on the other hand, increased Al exposure may alter lipid and particularly adipose tissue metabolism, contributing to obesity and metabolic syndrome.

The mechanisms of the potential impact of Al on lipid metabolism and adipogenesis are insufficiently studied. Hypothetically, Al-induced mitochondrial dysfunction may result in increased lipid accumulation in cells thus providing a link between NAFLD and obesity [31,32]. Specifically, it has been proposed that a shift from carbohydrate catabolism to lipid biosynthesis, combined with Al-induced alteration in carnitine shuttle functioning and reduced β-oxidation result in increased lipid accumulation [33]. These mechanisms also explain earlier observations on the association between hair Al levels and triglycerides as well as very low-density lipoprotein cholesterol (VLDL-C) levels [28]. The ability of Al^{3+} to replace other cations and especially magnesium [34] may also contribute to the observed associations. Magnesium is known to have protective effect in obesity and metabolic syndrome [35] due to its structural role in a variety of enzymes involved in carbohydrate and energy metabolism, as well as enhancement of insulin signaling [36]. Hypothetically, Al-induced disruption of Mg homeostasis may impair these processes leading to higher metabolic risk. At the same time, no previous studies were devoted to investigation of direct effects of Al exposure on adipogenesis including PPARγ and its

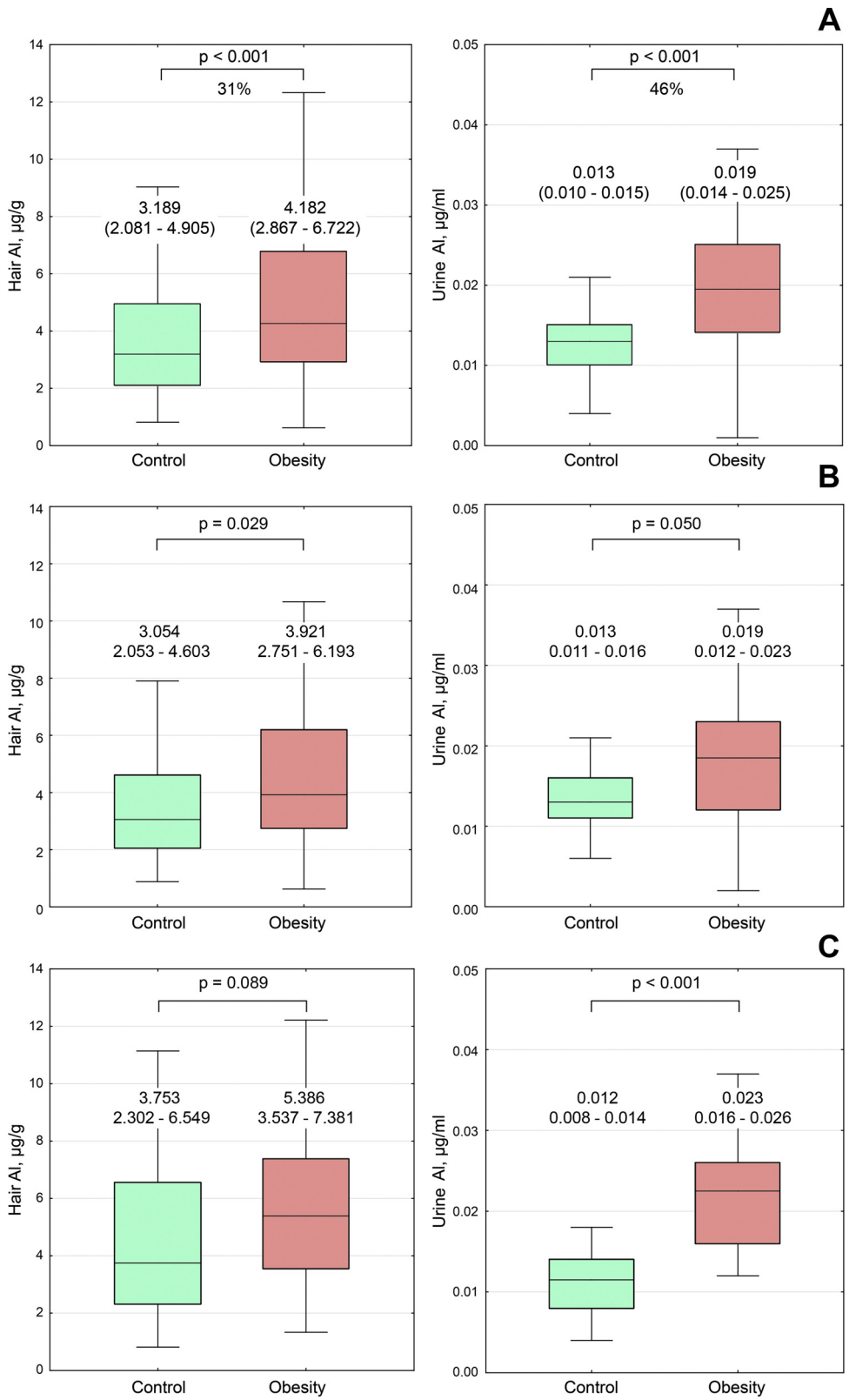

Fig. 1. Hair (µg/g) and urine (µg/ml) Al levels in obese examinees and lean controls in the general sample (A), females (B), and males (C). Data expressed as median (line), interquartile range (IQR), and non-outlier range (whiskers). Significance of group difference assessed using Mann-Whitney *U* test.

target gene expression.

Central effects of Al may also provide an additional link to obesity. Although no direct effect of Al exposure on food intake was demonstrated, the existing data show that Al may interfere with structure and signaling of peptide YY (PYY) and neuropeptide Y (NPY) that are involved in regulation of food behavior [37]. In addition, it has been shown that Al exposure also results in reduced locomotor activity of rats [38] which may also contribute to reduced energy expenditure. However, the occurrence of such effects at low-dose background exposure is yet questionable.

Table 3
Hair and urinary Al levels in obese patients in relation to hypertension, atherosclerosis, DM2, and NAFLD.

Hypertension	No	Yes	P value
Hair Al, μg/g	4.266 (2.784–6.337)	4.287 (2.937–7.088)	0.865
Urine Al, μg/ml	0.020 (0.014-0.026)	0.013 (0.012–0.023)	0.156
Atherosclerosis	No	Yes	P value
Hair Al, μg/g	4.408 (2.886–6.941)	3.284 (2.925–5.491)	0.329
Serum Al, μg/ml	0.019 (0.015–0.024)	0.019 (0.013–0.020)	0.285
NAFLD	No	Yes	P value
Hair Al, μg/g	4.326 (2.623–6.264)	4.189 (3.075–7.207)	0.290
Urine Al, μg/ml	0.020 (0.015–0.026)	0.015 (0.012–0.023)	0.321
DM2	No	Yes	P value
Hair Al, μg/g	4.228 (2.886–6.783)	4.532 (3.284–5.491)	0.852
Urine Al, μg/ml	0.020 (0.014–0.026)	0.014 (0.011–0.016)	0.176

Data expressed as Median (IQR); no significant group difference was revealed using Mann-Whitney U-test; BMI – body mass index; NAFLD – non-alcoholic fatty liver disease; DM2 – diabetes mellitus type 2.

Table 4
Multiple regression analysis of the association between Al levels in hair and urine and anthropometric and clinical variables.

Parameter	Urinary Al, μg/ml		Hair Al, μg/g	
	β	p	β	p
Hypertension, yes/no	−0.233	0.010 *	−0.056	0.429
Atherosclerosis, yes/no	0.029	0.754	0.061	0.266
NAFLD, yes/no	0.048	0.678	0.033	0.636
DM2, yes/no	−0.094	0.297	−0.054	0.315
Age, years	0.104	0.230	0.077	0.139
Gender, M/F	0.110	0.196	0.129	0.011 *
BMI, kg/m^2	0.368	< 0.001 *	0.138	0.026 *
Multiple R	0.364		0.217	
Multiple R^2	0.132		0.047	
Adjusted R^2	0.080		0.028	
P for a model	0.014		0.013	

Data expressed as coefficients of regression (β) and individual p values for a particular association; * - significant association at $p < 0.05$; BMI – body mass index; NAFLD – non-alcoholic fatty liver disease; DM2 – diabetes mellitus type 2.

Table 5
Assessment of the relationship between clinical variables and Al levels in the studied substrates with body mass index as a dependent variable.

Parameter	Model 1		Model 2	
	β	p	β	p
Hypertension, yes/no	0.218	< 0.001 *	0.258	0.004 *
Atherosclerosis, yes/no	−0.039	0.372	−0.034	0.635
NAFLD, yes/no	0.408	< 0.001 *	0.366	< 0.001 *
DM2, yes/no	0.085	0.050	0.097	0.178
Age, years	0.063	0.128	0.028	0.685
Gender, M/F	0.110	0.005 *	0.075	0.258
Hair Al, μg/g	–	–	−0.205	0.054
Urinary Al, μg/ml	–	–	0.380	< 0.001 *
Multiple R	0.617		0.664	
Multiple R^2	0.381		0.441	
Adjusted R^2	0.371		0.407	
P for a model	< 0.001 *		< 0.001 *	

Data expressed as coefficients of regression (β) and individual p values for a particular association; Model 1 – crude model incorporating only metabolic syndrome components as predictors of BMI; Model 2 – adjusted for hair and urinary Al levels; * - significant association at $p < 0.05$; BMI – body mass index; NAFLD – non-alcoholic fatty liver disease; DM2 – diabetes mellitus type 2.

Although no previous studies have addressed the association between Al exposure markers and obesity, recent evidence supports a relationship between Al exposure and metabolic syndrome components. Specifically, a study of Al-exposed workers revealed elevated total cholesterol and triglyceride levels in comparison to controls [39], corroborating our recent findings [28]. Although evidence for the impact of Al on hypertension is scarce [40], the potential mechanisms contributing to Al-induced hypertension may include renal damage [41] and especially up-regulation of renin synthesis [42].

In view of the absence of environmental and occupational Al exposure in the studied subjects, increased dietary Al intake may be considered as the only source of Al. A study in Hong Kong demonstrated that carbohydrate-rich foods including steamed bread/bun/cake and bakery products account for 60% and 23% of total Al intake, respectively [43]. Sweetened beverages [44] and chocolate [45] products also contain significant levels of Al, although their contribution to increased intake of Al is questionable [46]. Consumption of high-carbohydrate foods with high glycemic index is characteristic for obese individuals [47], providing a potential link between increased Al intake in baked goods and obesity. Notably, the use of canned containers for cooking [48] and storage [49] may also significantly increase food Al content.

The obtained data on hair Al content generally correspond to the reference values estimated for Russia [50] and European countries [51], being much lower than that in occupationally and environmentally exposed populations [52]. Urinary Al levels (median) were also lower than the upper reference limits for UK and Italy, although higher as compared to Belgium [53]. Therefore, the observed levels of Al in all studied biosamples support the absence of significant occupational or environmental pollution with Al.

To our knowledge, this is the first large cross-sectional study demonstrating the relationship between markers of aluminium body burden and obesity after adjustment for potential clinical covariates. However, the study has certain limitations. First, an accurate assessment of serum aluminium levels using gel-free monovettes for sampling [54] could be beneficial for analysis of aluminium body burden. Second, monitoring of aluminium intake in control and obese patients could provide an insight whether aluminium intake is higher in obesity or the observed changes occur from altered aluminium handling. Finally, investigation of the association between hair and urinary Al levels and metabolic parameters is required in order to provide a deeper insignt into the potential relationship between Al exposure and metabolic risk.

Taken together, our data demonstrate that the level of Al in urine and hair is significantly increased in obese non-exposed subjects, being also independently associated with BMI values after adjustment for the presence of other components of metabolic syndrome (hypertension, atherosclerosis, diabetes, NAFLD). At the same time, the causal relationship between Al body burden and obesity has yet to be clarified. Both clinical and experimental studies are required to further investigate the impact of Al exposure on metabolic parameters in obesity and especially the direct effects of Al in adipose tissue.

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Declaration of Competing Interest

The authors declare no conflict of interest

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