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## ORIGINAL ARTICLE

# The Relationship of Methylated Arginines with Urine Cadmium Levels

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### SUMMARY

***Background:*** **In this study, we aimed to show that methylated arginines are the predictors of non-clinical atherosclerotic cardiovascular complications in metal workers exposed to Cd.**
***Methods:*** **The 80 Cd-exposed metal workers and 80 non-exposed workers (control) included in the study were available for measuring arginine, ADMA, SDMA, and L-NMMA levels.**
***Results:*** **The average urine Cd levels (CdU) found were 1.03 ± 0.8 µg/g creatinine (0.84 ± 0.65 µg/L) ranging from 0.01 to 3.00 µg/g creatinine in the control group and 5.41 ± 5.2 µg/g creatinine (4.29 ± 3.81 µg/L) ranged from 0.11 to 27.2 µg/g creatinine in metal workers. On the other hand, the median ratios of the different groups (exposed and control) were found to be 449.35 and 483.88 for arginine/ADMA and 1.28 and 1.33 SDMA/ADMA, respectively.**
***Conclusions:*** **The present study was undertaken to investigate the relationship between cadmium exposure and methylated arginines such as ADMA/SDMA/L-NMMA parameters which is important for the early detection atherosclerotic cardiovascular diseases.**
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### KEY WORDS

Cd exposure, CdU, methylated arginines, atherosclerotic cardiovascular diseases

### INTRODUCTION

As a natural compound and an important part of industrial production, cadmium (Cd) is a dangerous contaminant that threatens human health [1]. Cd exerts various toxic effects on many systems of the body including urinary, skeletal, and respiratory organs. The main sources of human exposure are the consumption of contaminated food, industrial activities and tobacco smoke [2-4]. It also has endocrine disrupting and carcinogenic properties [5,6]. There are cellular toxic effects of cadmium with many probable mechanisms, such as oxidative stress, apoptosis, and DNA damage [7]. Cd is known to provoke oxidative damage on DNA indirectly, by inducing cellular proliferation, inhibition of the apoptotic mechanisms, and DNA repair blockage [8]. Cadmium

has been shown to replace iron and copper and increase the concentration of unbound iron and copper ions. This mechanism results in an increase of oxidative stress through the Fenton reaction [9]. Of these, a number of inflammatory mediators including nitric oxide cause the stimulation of cellular and humoral responses leading to inflammation in Cd-induced toxicity [10,11].

Cardiovascular diseases are responsible for 31% of all world-wide deaths and 50% of these are attributed to coronary heart disease [12,13]. Biological monitoring is an assessment of overall systemic exposure to chemicals by measurement of the chemicals, their metabolites, or conjugates in blood, urine or breath [14-17]. In a meta-analysis of epidemiological studies, elevated urinary Cd levels (CdU) were found to be associated with increased mortality in coronary heart disease, stroke, and peripheral artery diseases [18].

The methylated arginines [asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), and N-mono-methylarginine (NMMA)] are the degradation products of arginines and present in all human tissues and biological fluids [19]. At the same time, ADMA and NMMA are competitive inhibitors of nitric oxide synthase (NOS) [20]. Higher blood concentrations of ADMA than NMMA indicate that it is the predominant endogenous NOS inhibitor [21]. Symmetrical and asymmetrical dimethylarginines have been found to be predictors of mortality due to cardiovascular diseases in large patient groups [22]. Cumulative scientific evidence suggests that cadmium exposure initiates and accelerates atherosclerosis and promotes plaque formation, but the exact mechanism is not clear.

In this study, based on the fact that methylated arginines are the predictors of cardiovascular diseases, we investigated the relationship between cadmium exposure and ADMA/SDMA/NMMA levels.

## MATERIALS AND METHODS

### Study Groups

One hundred sixty male subjects (80 controls and 80 Cd-exposed) were included in this study. Control group and study group consist of non-exposed workers and Cd-exposed non-smoker workers of the same metal factory, respectively. Twelve workers with chronic diseases (coronary heart disease, hypertension, diabetes, etc.) and infections were excluded from the study. The study strictly adhered to the principles of the Declaration of Helsinki. Urine for Cd levels and serum samples for ADMA, SDMA, and L-NMMA levels were collected as biological material from the individuals. At the beginning of the shift week, first morning voiding urine samples of participants were collected in sterile polypropylene containers and immediately stored at -20°C until analysis. The samples were transferred in boxes in ice molds to Yozgat Bozok University Science and Technology Application and Research Center (BILTEM) for measuring Cd levels and for analysis arginine, ADMA, SDMA, and L-NMMA. The venous blood samples were collected into tubes (BD Vacutainer, USA), then centrifuged at 3,500 x g for 10 minutes at 4°C. The serum was separated and stored frozen at -80°C until analysis.

### Measurements of CdU with ICP-MS

One milliliter of each urine sample was placed into a high-temperature-resistant Teflon tube in a microwave oven. Then 5 mL Suprapur® (Merck, Darmstadt, Germany) nitric acid ($HNO_3$) and 5 mL ultra-pure water was added. All urine samples were digested using a microwave digestion system (Start D; Milestone, MD, USA). After digestion, each sample was made up to a total volume of 20 mL with 9 mL ultra-pure water in a 50 mL polypropylene tube [23]. Ultra-pure water (Direct-Q®; Millipore, Darmstadt, Germany) was used for dilution of the standard (multi-element standard ChemLab, Zedelgem, Belgium) and sample preparations.

The cadmium was measured using inductively coupled plasma-mass spectrometry (ICP-MS) (Thermo Scientific ICAPQc, USA). The operating parameters were set as follows: radiofrequency power 1,550 W, nebulizer gas 0.97 L/min, plasma gas 0.89 L/min, nebulizer pressure 2.9 bar, dwell time 0.01 milliseconds, and spray chamber temperature 3.5°C. The sampler probe was washed between injections by rinsing with ultrapure water for 30 seconds, followed by washing with 2% $HNO_3$ for 45 seconds, and finally rinsing with ultrapure water for 45 seconds. After the washing step, the instrument automatically ran the next sample. An 11-point calibration curve (0.5 - 500 µg/L) was used to measure the level of each element. The calibration curve of Cd was calculated as f (x) = 14,852.6885* x + 220.0029; r = 0.9999; background equivalent concentration (BEC) = 0.015 µg/L; limit of detection (LoD) = 0.0053 µg/L. To ensure the accuracy of the results, each measurement of the samples and standards was repeated three times. The results of these measurements showed that the relative standard deviation (RSD) did not exceed 5% [24].

### Validation and Optimization of CdU Method

Certified Reference Material (CRM-Seronorm™ Trace Elements Whole Blood L-2, Sero AS, Billingstad, Norway) was used for the validation method. The variation of each measurement of the quality controls was < 15%. The relative percentage differences in replicate analyses were calculated < 5% in the samples and standards.

### Measurements of methylated arginines with ELISA

The serum arginine, ADMA, SDMA, and L-NMMA levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, according to the manufacturer's instructions. Samples were analyzed with the ELISA (BMG LABTECH). Control materials were used for optimization and for validity of the ELISA methods [25].

**Table 1. Comparison of control and exposure groups.**

| | Group" | Mean | Median | SD | Minimum | Maximum | p |
|---|---|---|---|---|---|---|---|
| Age (year) | 1 | 36.48 | 35.00 | 8.15 | 24.00 | 57.00 | 0.585 |
| | 0 | 36.15 | 34.00 | 9.28 | 22.00 | 61.00 | |
| BMI (kg/cm$^2$) | 1 | 26.96 | 27.06 | 2.26 | 22.82 | 33.28 | 0.942 |
| | 0 | 27.07 | 27.10 | 2.77 | 22.64 | 36.80 | |
| Cd (µg/g creatinine) | 1 | 5.41 | 3.17 | 5.20 | 0.11 | 27.20 | 0.001 ** |
| | 0 | 1.03 | 0.99 | 0.80 | 0.01 | 3.00 | |
| Arginine (µmol/L) | 1 | 90.72 | 79.40 | 49.23 | 43.50 | 308.00 | 0.349 |
| | 0 | 87.14 | 78.25 | 52.60 | 33.10 | 315.00 | |
| ADMA (µmol/L) | 1 | 0.17 | 0.17 | 0.03 | 0.11 | 0.27 | 0.001 ** |
| | 0 | 0.16 | 0.15 | 0.03 | 0.11 | 0.26 | |
| SDMA (µmol/L) | 1 | 0.22 | 0.22 | 0.05 | 0.10 | 0.34 | 0.04 * |
| | 0 | 0.21 | 0.21 | 0.04 | 0.10 | 0.32 | |
| L-NMMA (µmol/L) | 1 | 0.03 | 0.02 | 0.01 | 0.01 | 0.05 | 0.017 * |
| | 0 | 0.02 | 0.02 | 0.01 | 0.01 | 0.05 | |
| Arginine/ADMA ratio | 1 | 539.68 | 449.35 | 317.32 | 233.33 | 1,818.18 | 0.446 |
| | 0 | 562.94 | 483.88 | 323.81 | 228.76 | 1,779.66 | |
| SDMA/ADMA ratio | 1 | 1.27 | 1.28 | 0.29 | 0.51 | 1.98 | 0.185 |
| | 0 | 1.33 | 1.33 | 0.28 | 0.61 | 2.01 | |

**" 0 - Control (n = 80), 1 - Exposure (n = 80), * p < 0.05; ** p < 0.01, SD - Standard Deviation.**

**Statistical Analysis**

The data were evaluated in terms of compliance with normal distribution using the Kolmogorov-Smirnov test. Descriptive statistics were presented with mean, standard deviation, median, and minimum-maximum values. Since it was determined that the parameters were not compatible with the normal distribution, the Mann-Whitney U test was used to evaluate the status of two independent variables relative to each other. The relationship between variables was determined by Spearman's correlation analysis.

## RESULTS

The 80 Cd-exposed metal workers and 80 non-exposed workers (control) included in the study were available for measuring arginine, ADMA, SDMA, and L-NMMA levels. Table 1 shows the differences in the main parameters between the study groups. The two groups significantly differed in Cd, ADMA, SDMA, and L-NMMA levels (Table 1, Figure 1) but not in age, body mass index (BMI), arginine, arginine/ADMA ratio, and SDMA/ADMA ratio (Table 1). With a few exceptions, the differences between the control group and the exposure group are shown in Figure 1. The working experience of the exposed and control groups were observed to be similar 9.18 ± 10.24 years and 8.94 ± 9.46 years, respectively ($p > 0.05$). ADMA, SDMA, and L-NMMA levels in exposed groups were found significantly higher than control groups ($p < 0.01$). Also, arginine levels were high in exposed groups ($p > 0.05$). On the other hand, median ratios of the different groups (exposed and control) were found to be 449.35 and 483.88 for arginine/ADMA and 1.28 and 1.33 for SDMA/ADMA, respectively.

Spearman's correlation (Table 2) showed a highly positive relationship between Cd and WBC levels ($r = 0.19$, $p < 0.05$), and a negative correlation was found between SDMA and Cd, AST, PLT levels ($r = -0.20$; $r = -0.19$, $r = -0.17$, respectively, $p < 0.05$). The positive correlations were observed between methylated arginine parameters such as ADMA and SDMA, SDMA and SDMA/ADMA ratio, and ADMA and L-NMMA levels ($r = 0.35$, $r = 0.57$, $r = 0.55$; $p < 0.01$). Negative correlations were determined with arginine/ADMA ratio and ADMA amd SDMA levels ($r = -0.41$, $r = -0.24$; $p < 0.01$). The strongest positive correlation was found between arginine and arginine/ADMA, and the strongest negative relationship was found between L-NMMA and SDMA/ADMA ratio ($r = 0.7$, $r = 0.56$ respectively; $p < 0.01$).

**Table 2. Correlations of parameters of the study.**

| n = 160 | Age | BMI | Cd | Arginine | ADMA | SDMA | L-NMMA | Arginine /ADMA ratio | SDMA/ DMA ratio | WBC | HGB | HCT | PLT | ALT | AST | Creati-nine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1 | 0.30 ** | -0.23 ** | -0.02 | -0.05 | 0.14 | 0.06 | -0.05 | 0.11 | 0.01 | 0.06 | 0.01 | 0.06 | -0.02 | -0.01 | -0.04 |
| BMI | | 1 | -0.23 ** | 0.08 | 0.01 | 0.08 | 0.08 | 0.09 | 0.03 | -0.14 | 0.01 | -0.01 | -0.05 | 0.1 | 0.07 | 0.07 |
| Cd | | | 1 | 0.01 | 0.02 | -0.20 * | -0.05 | -0.01 | -0.14 | 0.19 * | -0.05 | 0.01 | -0.02 | -0.03 | -0.07 | -0.06 |
| Arginine | | | | 1 | 0.22 ** | -0.22 ** | 0.42 ** | 0.87 ** | -0.36 ** | -0.04 | 0.02 | 0.04 | 0.03 | 0.04 | 0.09 | -0.02 |
| ADMA | | | | | 1 | 0.35 ** | 0.55 ** | -0.24 ** | -0.49 ** | 0.09 | 0.19 * | 0.16 * | 0.04 | -0.06 | -0.14 | 0.02 |
| SDMA | | | | | | 1 | -0.11 | -0.41 ** | 0.57 ** | 0.02 | 0.20 * | 0.08 | -0.17 * | -0.15 | -0.19 * | 0.13 |
| L-NMMA | | | | | | | 1 | 0.14 | -0.56 ** | -0.01 | 0.03 | 0.02 | 0.12 | 0.08 | 0.03 | -0.03 |
| Arginine /ADMA ratio | | | | | | | | 1 | -0.13 | -0.06 | -0.08 | -0.03 | 0.02 | 0.07 | 0.15 | -0.05 |
| SDMA/ ADMA ratio | | | | | | | | | 1 | 0.01 | 0.1 | 0.05 | -0.15 | -0.12 | -0.09 | 0.12 |
| WBC | | | | | | | | | | 1 | 0.08 | 0.18 * | 0.19 * | 0.06 | 0.01 | -0.14 |
| HGB | | | | | | | | | | | 1 | 0.79 ** | -0.02 | 0.21 ** | 0.14 | 0.17* |
| HCT | | | | | | | | | | | | 1 | -0.04 | 0.14 | 0.04 | 0.12 |
| PLT | | | | | | | | | | | | | 1 | 0.22 ** | 0.06 | -0.05 |
| ALT | | | | | | | | | | | | | | 1 | 0.71 ** | 0.17 * |
| AST | | | | | | | | | | | | | | | 1 | -0.03 |
| Creati-nine | | | | | | | | | | | | | | | | 1 |

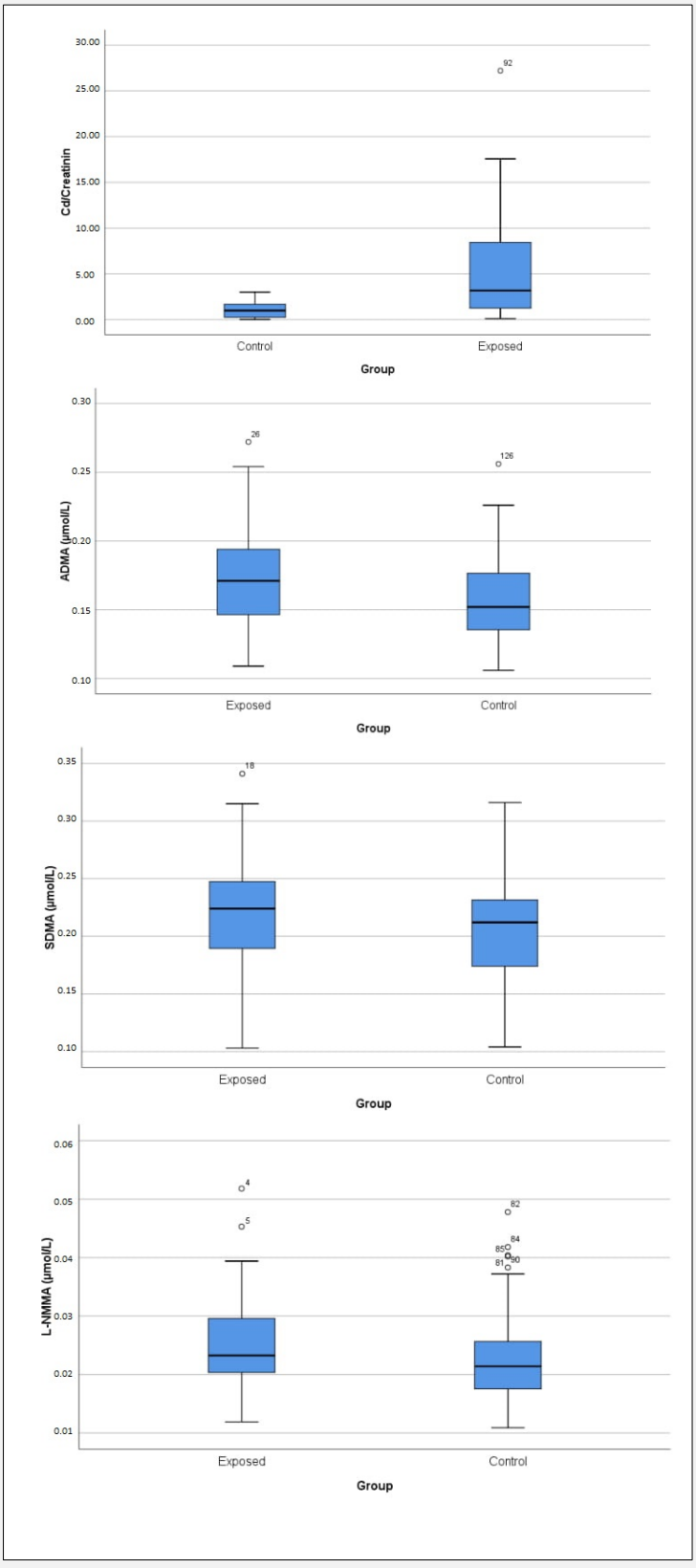


**Figure 1. Graphical comparison of control and exposure groups.**

## DISCUSSION

Cadmium is a widely distributed environmental and industrial pollutant that has a negative impact on human health [26]. With this study we aimed to show that methylated arginines are the predictors of non-clinical atherosclerotic cardiovascular complications in metal workers exposed to cadmium. We proposed to show that Cd measurements in urine can be used in routine periodic examination in detecting Cd exposure and onset of atherosclerosis. The results of this study show a significant increase in ADMA, SDMA, and L-NMMA levels after chronic Cd exposure that decreases over time (Table 1, Figure 1). This and other studies support the evidence that subjects with prolonged heavy metal exposure such as cadmium and lead exhibit endothelial dysfunction mediated by increased ADMA in circulation from clinical observations [27,28]. Occupational cadmium exposure significantly reflected on the increased levels of ADMA, SDMA, and L-NMMA but did not significantly affect ratios of arginine/ADMA and SDMA/ADMA in this study. Both ADMA and SDMA have emerged as strong predictors of cardiovascular events and death in a variety of diseases [29]. Emerging clinical and experimental evidence indicates that ADMA and SDMA are involved in the pathophysiology of several diseases including coronary artery disease, endothelial dysfunction, atherosclerosis, oxidative stress, and inflammation [30-36]. Atherosclerotic coronary heart disease is the leading cause of morbidity and mortality in industrialized countries, and endothelial dysfunction is considered a leading phenomenon [29]. Wang et al. [30] reported ADMA increases in coronary artery disease patients are due to an associated reduction in renal function and to smoking. Holguin et al. [37] reported that obesity, with or without the metabolic syndrome, was associated with higher plasma ADMA levels. In our study, no difference was found between the two groups in terms of BMI, in spite of that a negative correlation was found between BMI and Cd levels ($r = -0.23$; $p < 0.01$).

The average levels of CdU found were 1.03 ± 0.8 µg/g creatinine (0.84 ± 0.65 µg/L) and ranged from 0.01 to 3.00 µg/g creatinine in the control group and 5.41 ± 5.2 µg/g creatinine (4.29 ± 3.81 µg/L) ranged from 0.11 to 27.2 µg/g creatinine in metal workers. Ambient air and dust can also contribute to cadmium exposure in the vicinity of occupational and industrial sources and in certain occupational groups (metal and mining industry, transportation and repairing services) [38]. In contrast, in the Third National Health and Nutrition Examination Survey, urinary cadmium levels ranged from 0.01 to 15.57 µg/L, with a geometric mean of 0.30 µg/L (0.28 µg/g creatinine) for all U.S. workers [14]. Alkhatib et al. [39] reported that exposure to Cd was significantly higher among workers compared with control (12.65 µg/L and 4.66 µg/L; $p < 0.01$). The Occupational Safety and Health Administration (OSHA) acceptable limit for Cd is less than 3.0 µg/g creatinine and the biological exposure index (BEI) is 5 µg/g creatinine in urine samples [40]. This biological monitoring can be done with blood and urine [15-17]. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended BEI acceptable limit for Cd in urine 5 µg/g creatinine [41]. This limit protects against renal dysfunction in nearly all workers. Measurement of Cd in urine is the most widely used biological concentration of chronic exposure to Cd. Most studies with Cd exposure have indicated an increase in excretion of specific proteins in urine when the cadmium excretion exceeded this limit [14-17]. In our study, the metal workers group (5.41 ± 5.2 µg/g creatinine) has been observed to exceed the limits or Cd exposure recommended above. The elevated levels of CdU and methylated arginines such as ADMA/SDMA/L-NMMA in workers may be a cardiovascular risk marker.

The ADMA, which is itself considered a mediator of the vascular effects of several risk factors for atherosclerosis, can be eliminated by renal excretion or by the enzymatic action of the dimethylarginine dimethylaminohydrolases (DDAH). The limitation of our study was that we did not evaluate DDAH activities which metabolize the endogenous nitric oxide synthase (NOS) inhibitors. Maybe these parameters could have helped us to better understand the effects of cadmium on atherosclerotic cardiovascular diseases.

## CONCLUSION

The aim of the present study was to investigate the relationship between cadmium exposure and methylated arginines such as ADMA/SDMA/L-NMMA parameters which is important for the early detection atherosclerotic cardiovascular diseases. At the same time, this study shows that CdU and measurements of methylated arginines can be used in routine periodic examination to detect Cd exposure and onset of atherosclerosis.

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**Declaration of Interest:**
The authors declare that there is no conflict of interest.

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