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ADMA and SDMA levels in healthy men exposed to tobacco smoke

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Dear Editor,

Smoking cigarettes is one of the most important modifiable risk factors for the development of cardiovascular disease (CVD), which includes coronary and cerebrovascular diseases, peripheral arterial diseases and congestive heart failure [1]. Only few reports about the relationship between newly emerging risk factors for CVD and smoking cigarettes exist [2]. These compounds include two biological mediators of interconnected metabolic pathways, namely asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) [3]. ADMA is an endogenous inhibitor of endothelial nitric oxide synthase. When elevated, ADMA plasma levels are associated with an increased risk of atherosclerosis in patients with chronic renal injury [4]. Recent studies also suggest that ADMA may be an independent risk factor of coronary artery disease [5]. In addition, there is evidence that SDMA may be a biomarker of renal disease and useful in the assessment of coronary artery disease risk [6].

We investigated 168 healthy male volunteers aged 18–60 years (mean age 37.9 ± 9.1). They all lived in the city of Katowice (Poland), did not give any history of ischemic heart disease, diabetes mellitus, liver disease, or hypertension. All participants declared alcohol abstinence, practiced a sedentary lifestyle (no daily exercise) and having at least one cup of coffee a day. They also declared that they did not take vitamin supplements during 3 months before examination. Initial plasma lipid levels in most cases were within the reference range used in the laboratory practice. Plasma creatinine levels were measured and found to be <140 μmol/L (no patients with renal impairment). The inclusion criteria were established in order to control confounding variables that influence ADMA or SDMA levels. Men included in the study were classified into three groups based on their plasma cotinine levels (non-smokers <10 ng/mL, passive smokers 10–30 ng/mL and active smokers >30 ng/mL). ADMA and SDMA levels were assessed simultaneously using high-performance liquid chromatography (HPLC) [7].

Our results show that ADMA plasma levels were 15.4% higher in passive smokers (0.45 ± 0.16 μmol/L) than in the control group (0.39 ± 0.16 μmol/L), and 7.7% higher in the active

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smokers group (0.42 ± 0.14 μmol/L) vs. passive smokers. These differences were not statistically significant ($P = 0.110$ and $P = 0.322$, respectively). Among passive smokers, mean plasma SDMA level (0.42 ± 0.14 μmol/L) was insignificantly higher by 13.5% ($P = 0.183$) than in the control group (0.37 ± 0.10 μmol/L), and only by 8.1% ($P = 0.595$) higher than in active smokers (0.40 ± 0.15 μmol/L). There were no statistically significant relationships found between ADMA or SDMA and the tobacco exposure assessed by plasma cotinine for the non-smokers group. In passive and active smokers, the relationships were weak (ADMA: $r = 0.173$ (passive) vs. $r = 0.218$ (active); SMDA: $r = 0.097$ (passive) vs. $r = 0.239$ (active)) and statistically non-significant.

Plasma ADMA and SDMA levels in non-smokers and in passive smokers are highly correlated ($r = 0.671$ and $r = 0.643$, respectively, $P < 0.001$). Strong correlation was also found between plasma ADMA and SDMA levels in active smokers ($r = 0.803$, $P < 0.001$). Multiple regression analysis was used in the case of serum ADMA. Plasma homocysteine (tHcy) and creatinine concentrations were found to be significantly correlated with plasma ADMA concentration in the passive smokers group (Table 1). Although in the active smokers group the β coefficient was the highest for tHcy, it was not significant ($\beta = 0.2810$, $P = 0.090$). Also in the whole examined population tHcy and creatinine concentration were significantly correlated with ADMA ($\beta = 0.2598$, $P = 0.008$ and $\beta = 0.2452$, $P = 0.034$, respectively).

In summary, ADMA levels are not significantly different for active and passive smokers when compared to non-smokers. Our results show that the increased ADMA levels by 7.7% and 15.4% for active and passive smokers, respectively, in comparison with non-smokers, are not significant. The correlation between plasma ADMA level and plasma cotinine in both groups are weak and statistically not significant. Results from this study were compared with published findings of plasma ADMA levels. Table 2 presents the PubMed database papers reporting plasma ADMA levels up to the end of 2007. In most cases, presented data regard patients with some diseases which makes it difficult to compare with our results. Only one study included healthy men [10]. The authors of this study observed highly significant differences (more than 80%) in plasma ADMA levels between smokers and non-smokers. However this result differs significantly from the other studies presented in Table 2. Kielstein et al. [14] pointed to lack of correlation with clinical investigations and a low number of examined persons in the above-citied study. The largest studies to date on plasma ADMA levels were performed by Meinitzer et al. [13]. Multiple regression analysis showed that tHcy is the strongest predictor of plasma ADMA level. In our study, predictive factors for plasma ADMA level were as follows in order of strength of relationship: tHcy > creatinine > age > cotinine > BMI, but they were statistically non-significant. The same order was observed among passive smokers, but in that case the predictive values of tHcy and creatinine were significant. Among the entire examined population, both tHcy and creatinine showed significant predictive value. The other possible risk factors for CVD, such as coexisting diseases, dislipidemias, alcohol and coffee intake, occupational exposures, drugs and renal impairment were not accounted for because those factors were part of our exclusion criteria. Controlling confounding variables improves the internal validity of our results.

Apart from the publications listed in Table 2, there are additional studies on the relationship between ADMA and cigarette smoking; however the studies do not report any exact ADMA levels nor their ranges. A study published by Lu et al. [15] examined the relationship between ADMA as a predictor for the outcomes in patients with angina pectoris who underwent angioplasty ($n = 153$). They found that increases in plasma ADMA levels were independent from other factors, such as age, hypercholesterolemia, application of stents and cigarette smoking. In 2003, Schiel et al. [16] examined 554 patients with type I diabetes mellitus and renal impairment. The obtained results showed higher plasma ADMA and SDMA levels in patients in comparison with the control group, but no significant effect of smoking tobacco on

the examined parameters was observed in any of the groups. In CARDIAC (Coronary Artery Risk Determination Investigating the Influence of ADMA Concentration) study, 816 persons were evaluated for the relationship between plasma ADMA level and the risk of coronary artery disease [17]. Active smokers showed significantly lower plasma ADMA levels than non-smokers. However, in ex-smokers plasma ADMA levels were higher than in non-smokers. Tonstad et al. [18] selected a group of 207 women and men aged 18–39 years with a high risk of coronary artery disease (dyslipidemia, family history of coronary artery disease). They found that ADMA level was related only to BMI but is not related to age, sex, and the number of cigarettes smoked. Wang et al. [11] observed a non-significant increase in plasma SDMA by 2.7% ($P = 0.58$) in smokers in comparison with non-smokers (0.38 μmol/L vs. 0.37 μmol/L, respectively). On the other hand, in human endothelial cell culture, there was an insignificant SDMA level increase (by 43.7%) after supplementing the culture medium with 10% tobacco smoke extract (0.102 nmol/mg protein vs. 0.071 nmol/mg protein, respectively) [10]. Our results showed elevated plasma SDMA levels by 13.5% in passive smokers and only by 8.1% in active smokers relative to control group of non-smokers.

In conclusion, there was no significant effect of tobacco smoke on ADMA and SDMA levels. Therefore, the endothelial dysfunction caused by tobacco smoke is probably not related to the inhibition of nitric oxide synthase by ADMA.

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Table 1

Beta coefficients of the multiple regression analysis for plasma ADMA concentration.

Independent variable	Non-smokers (n = 53)	Passive smokers (n = 48)	Active smokers (n = 67)	Total population (n = 168)
Age	−0.0371	0.2344	−0.1449	−0.0333
BMI	0.0184	−0.0121	−0.0755	0.0485
Creatinine	0.0145	0.2933*	0.2211	0.2152*
tHcy	−0.0062	0.3634*	0.2810	0.2598**
Cotinine	0.0791	0.0522	0.0917	−0.0279

tHcy, total homocysteine; ADMA, asymmetric dimethylarginine; BMI, body mass index.

* $P < 0.05$.

** $P < 0.01$.

Table 2

Literature data on plasma ADMA levels changes in non-smokers and smokers.

First author	Number of study patients (sex, age[a])	ADMA level		Differentiation (%)	*P*	Remarks
		Non-smokers (μmol/L)	Smokers (μmol/L)			
Eid [8]	563 (M, 70)	1.42	1.32	−7.0	0.037	Patients with high risk profile of coronary artery disease; ADMA levels adjusted for blood pressure, BMI, creatinine and insulin $P = 0.14$.
Schnabel [9]	1874 (F/M, 61)	0.61	0.64	4.9	0.002	Patients with coronary artery disease before and after coronary events.
Zhang [10]	22 (M, 39)	0.61	1.10	80.3	0.01	Healthy men; smokers smoked ≥20 cigarettes/day.
Wang [11]	108 (F/M, 62)	0.43	0.47	9.3	0.03	Patients qualified for angioplasty due to a chest pain. Also patients with 3-velssels disease were included in the study.
Mass [12]	88 (M, 61)	0.88	0.69	−21.6	<0.001	Patients with a history of coronary events (heart infarct, and sudden cardiac death).
	254 (M, 62)	0.80	0.74	−7.5	*NS*	Persons with no coronary disease history were the control group.
Meinitzer [13]	3238 (F/M, 63)	0.815	0.840	3.1	0.001	2543 patients with diagnosed cardiovascular disease, 695 with no disease. 1165 never smoked and 632 were active smokers. The rest were former smokers.

[a]Mean age; F, female; M, male; ADMA, asymmetric dimethylarginine; *P*, significance level.