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Elevation of Asymmetrical Dimethylarginine (ADMA) and Coronary Artery Disease in Men with Erectile Dysfunction

Renke Maas[a,*], Sven Wenske[b,c], Marcus Zabel[a], Rodolfo Ventura[d], Edzard Schwedhelm[a], Anna Steenpaß[a], Hanno Klemm[d], Joachim Noldus[b,c], Rainer H. Böger[a]

[a]*Institut für Experimentelle und Klinische Pharmakologie, Universitätsklinikum Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany*
[b]*Klinik und Poliklinik für Urologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany*
[c]*Urologische Universitätsklinik der Ruhr-Universität Bochum, Marienhospital Herne, Herne, Germany*
[d]*Herzzentrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany*

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Abstract

Background: Coronary artery disease (CAD) and erectile dysfunction (ED) of vascular origin are closely related and share common risk factors. The endogenous NO synthase inhibitor asymmetrical dimethylarginine (ADMA) has recently been identified as an independent risk marker for cardiovascular disease and it was the purpose of the present study to investigate the role ADMA in ED with and without underlying CAD.

Methods and results: We determined plasma ADMA levels in 132 men with ED. Patients were divided into a group of 56 men with underlying CAD (ED-CAD) and a group of 76 men without clinical evidence for underlying CAD (ED-No-CAD). Diagnosis of ED was based on the International Index of Erectile Function Score (IIEF-5). Plasma ADMA concentrations in the ED-CAD group were elevated as compared to the ED-No-CAD group, median (IQR): 0.76 (0.65–0.91) μmol/l ADMA vs. 0.49 (0.36–0.71) μmol/l, $p < 0.001$. In a multiple logistic regression analysis adjusting for hypertension, hypercholesterolemia, low HDL cholesterol and diabetes or fasting glucose ≥6.1 mmol/l, ADMA remained a strong and independent predictor for presence of CAD. Odds ratios for second and third tertiles as compared to lowest tertile of plasma ADMA were 3.3 (95%CI, 1.1–10.3; $p = 0.041$) and 8.7 (95%CI, 2.8–27.2; $p < 0.001$), respectively.

Conclusion: As elevation of ADMA has been found to be associated with many risk factors for both CAD and ED, our data provide further strong evidence for the close interrelation of CAD and ED. Determination of ADMA may help to identify underlying cardiovascular disease in men with ED.

Keywords: Coronary artery disease; Erectile dysfunction; Asymmetrical dimethylarginine; ADMA; Risk factor

1. Introduction

Current estimates suggest that worldwide about 152 million men are affected by erectile dysfunction (ED) [1,2], and that the incidence and prevalence of ED will continue to rise [3]. ED and cardiovascular disease (CAD) are closely related [4,5] and share common risk factors such as hypertension, hypercholesterolemia and low HDL cholesterol [1,6–8]. Impaired NO generation has been proposed as major pathophysiological link of erectile dysfunction and cardiovascular disease [9–13]. In recent years the endogenous nitric oxide synthase (NOS) inhibitor asymmetrical dimethylarginine (ADMA) has been identified as an independent risk marker for cardiovascular disease that impairs the L-arginine-NO pathway [14–16]. Surprisingly, in men with ED ADMA levels have not been studied so far. ADMA could be of particular interest in men with ED for two reasons:

* Corresponding author. Tel. +49 40 428033178; Fax: +49 40 428039757.
E-mail address: maas@uke.uni-hamburg.de (R. Maas).

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First, several studies demonstrated that presence of erectile dysfunction identifies men with cardiovascular disease [17,18]. In a majority of cases ED is associated with underlying vascular disease, but other causes such as trauma or psychogenic causes are common as well [1,19]. Here elevation of ADMA could help to distinguish men with ED and underlying CAD from those who only have ED.

Second, being an NOS inhibitor, ADMA itself could be a direct patho-physiological link of ED and CAD [11,10]. It was, therefore, the purpose of the present study to determine the plasma concentration of ADMA and its predictive value for the presence of CAD men in with ED.

2. Methods

Men presenting for diagnostic check up in the Departments of Urology and Cardiology of the University Hospital Hamburg-Eppendorf were approached to participate in the study. The study was approved by the local ethics committee and written informed consent was obtained from all patients and controls. According to the presence or absence of ED of traumatic or non-traumatic origin and cardiovascular disease patients were assigned to the following 4 groups (criteria for ED or cardiovascular disease are described further below):

Patients without ED (Control Groups)
No-CAD: Men without clinical evidence for CAD or ED
CAD: Men with CAD but without ED

Patients with ED
ED-CAD: Men with CAD and non-traumatic ED
ED-No-CAD: Men with ED but without clinical evidence for CAD

General exclusion criteria were age below 18, heart failure (NYHA II or higher), renal failure, anaemia, acute infection or rheumatic disease, and acute coronary syndrome or unstable angina at time of blood sampling.

2.1. Assessment of erectile function and cardiovascular disease

Erectile function was assessed using the abridged 5-item version of the International Index of Erectile Function questionnaire (IIEF-5), a validated, self administered questionnaire [20,21]. Possible scores for the IIEF-5 range from 5 to 25, scores of 22–25 indicate normal erectile function while scores of 21 or below indicate ED [21]. According to the IIEF-5 score ED can be classified as severe (5–7), moderate (8–11) mild to moderate (12–16) or mild (17–21). As it has recently been reported that direct measures of penile function of men with IIEF scores corresponding to only mild ED did not differ from men with score indicating normal erectile function [22], an IIEF-5 score of 16 was used as additional cut off value for the comparison of men with CAD with and without ED. ED of traumatic cause was identified by onset of ED after surgery or accident in men with previously normal erectile function. Men who had both, ED of traumatic cause as well as underlying CAD were excluded.

CAD was identified by stable angina pectoris or a history of myocardial infarction, plus diagnostic criteria for recurrent myocardial ischemia (positive exercise ECG, evidence for myocardial ischemia in thallium scintigraphy, documentation of coronary stenosis by coronary angiography).

Hypercholesterolemia was defined as LDL cholesterol >4.1 mmol/L or ongoing statin treatment. Patients with a blood pressure >140/90 mmHg or when taking antihypertensive drugs based on a previous diagnosis of hypertension were classified as hypertensive.

2.2. Sample handling and clinical chemistry

ADMA and L-arginine were determined by an HPLC method based on a slightly modified standard method [23,24] and validated according to FDA standards. In brief, after adding 10 μM L-homoarginine as internal standard, 500 μl of plasma samples were submitted to solid phase extraction on CBA cartridges. Following two washings steps with water, cationic amino acids (ADMA, SDMA, homoarginine and L-arginine) were eluted by 1 M formic acid, dried, and resuspendend in water. This was followed by online OPA-derivatisation and HPLC with fluorescence detection (excitation $\lambda = 342$ nm, emission $\lambda = 453$ nm). Human reference plasma standards for ADMA (plain and spiked with 1 μmol/l of ADMA and 1 μmol/l SDMA) were included for every 10 samples as quality controls. Within-assay and between-assay variations for ADMA were 1.7% and 2.5%, respectively, the limit of detection was 0.004 μmol/l.

2.3. Statistical analysis

Sample size was based on the comparison of ADMA plasma levels in men with ED and underlying CAD and ED without underlying CAD with subsequent bivariate logistic regression analysis. As it is conventionally estimated that multivariate models require a minimum of 10 patients per variable and modality of the outcome variable, at least 50 patients per group were required to allow inclusion of five variables into the multivariate model. Enrolment of patients and controls was therefore to be stopped once at least 50 patients were reached in both ED groups.

All data were tested for normal distribution with the Kolmogorov-Smirnov test. Continuous variables were expressed as arithmetic mean ± SD if normally distributed or otherwise by median with 25% and 75% percentiles. Parametric (*t*-test) and non parametric tests (Mann-Whitney-*U* (two-sided) and Kruskal-Wallis-H) were used for comparisons, as appropriate. As all analysis except for the prespecified variables were explorative, no correction for the type I error was performed. Unless international references defining cut off values existed continuous variables were split into tertiles for univariate and multivariate analysis. Categorized biochemical characteristics and risk factors of CHD (tertiles of plasma ADMA, diabetes or fasting glucose ≥6.1 mmol/l (110 mg/dl), HDL <1 mmol/l (<40 mg/dl), hypertension, hypercholesterolemia and cigarette smoking) were included into the unconditional logistic regression models. Estimates of risk (odds ratios) and 95% CI were calculated on the basis of coefficients from the logistic regression models. For statistical analyses, SPSS version 11.5 was used.

3. Results

3.1. ADMA, L-arginine and the L-arginine ADMA/ ratio in men with ED

Clinical and biochemical data of 132 patients with ED are presented in Table 1. Differences in baseline