Relationship of Asymmetric Dimethylarginine With Penile Doppler Ultrasound Parameters in Men with Vasculogenic Erectile Dysfunction

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Abstract

Background: Asymmetric dimethylarginine (ADMA), a selective endogenous nitric oxide synthase inhibitor, is elevated in many conditions associated with erectile dysfunction (ED), such as hypertension, diabetes, hyperlipidemia, and renal failure; it is also increased in men with coronary artery disease and ED. The dynamic penile colour Doppler ultrasound is considered the gold standard for the evaluation of penile vascular damage.

Objective: We investigated whether the extent of ultrasonographically documented penile vascular disease is associated with higher ADMA levels.

Design, setting, and participants: One hundred four consecutive ED patients (mean age: 56 ± 9 yr) without manifest cardiovascular/atherosclerotic disease and 31 subjects with normal erectile function matched for age and traditional risk factors were studied.

Measurements: We evaluated penile dynamic colour Doppler parameters of arterial insufficiency (peak systolic velocity) and veno-occlusive dysfunction (end diastolic velocity) and measured systemic inflammatory markers/mediators.

Results and limitations: Compared to men without ED, ED patients had significantly higher ADMA levels (p < 0.001). ADMA was significantly increased in patients with severe arterial insufficiency (PSV < 25 cm/s) compared to subjects with borderline insufficiency and men with normal penile arterial function (p < 0.001, by analysis of variance). Multivariable analysis adjusting for age, mean pressure, other risk factors, high-sensitivity C-reactive protein, testosterone, and treatment showed independent inverse association between ADMA level and peak systolic velocity (p < 0.01). The combination of higher ADMA level with arterial insufficiency showed greater impact on 10-yr risk of a cardiovascular event compared to either parameter alone.

Conclusions: ADMA level is independently associated with ultrasonographically documented poor penile arterial inflow. This finding underlines the important role of ADMA as a marker of penile arterial damage and implies a contribution of this compound to the pathophysiology of generalised vascular disease associated with ED.
1. **Introduction**

Penile erection is a vascular process, and the small vessels of the penis are sensitive to functional and structural changes [1]. Damage to the endothelial lining of the arterial walls impairs the nitric oxide (NO) pathway and the ability for vasodilation. Endothelial dysfunction is an important pathophysiological factor underlying both vasculogenic erectile dysfunction (ED) and atherosclerosis in other vascular beds [2–4]. These two disorders are also linked at the clinical level: ED is common in patients with overt and silent coronary artery disease (CAD) [5–7], and it is increasingly being regarded as the early clinical manifestation of generalised vascular disease [8] and carries an independent risk for future cardiovascular events [9–11].

Increasing attention is focused on the selective endogenous NO synthase (NOS) inhibitor asymmetric dimethylarginine (ADMA) as an important competitive inhibitor of NO formation [12]. Increased ADMA levels have been linked to traditional risk factors [13], preclinical atherosclerotic disease burden [14], and prediction of cardiovascular events [15]. The presence of increased levels of ADMA in many conditions associated with ED [13,16–18] as well as in men with CAD and ED [19,20] has led to the hypothesis that elevated levels of this compound may inhibit penile NO synthesis.

Little and conflicting information is available regarding the association between circulating ADMA levels and questionnaire-based ED severity [17,20,21]. Furthermore, the association of ADMA concentration with functional changes of the penile vascular bed has not been investigated. In the present study, we sought to investigate whether ADMA concentration in blood is higher in men with significantly impaired penile vascular function. For this purpose, we used a thorough penile blood flow approach to evaluate arterial and venous competence.

2. **Methods**

2.1. **Study population**

In this retrospective study, we enrolled 104 consecutive men with vasculogenic ED and no clinical evidence of CAD from June 2005 to January 2007. Thirty-one age-matched control subjects with normal erectile function who had prevalence rates of traditional cardiovascular risk factors similar to that of men with vasculogenic ED were recruited from a large cohort followed in our department for arterial function studies. These subjects were studied in the same period as the ED patients.

All patients were screened for sociodemographic data and cardiovascular risk factors. Diagnosis of hypertension was set if blood pressure was >140/90 mm Hg in three consecutive recordings at rest or when taking antihypertensive drugs. Diagnosis of hypercholesterolemia was set if total cholesterol level was >190 mg/dl (>5 mmol/l) or when taking hypolipidemic drugs and diabetes if fasting plasma glucose level was >125 mg/dl (>7.0 mmol/l) or when using antidiabetic medications. No patient had any bacterial or viral infection or reported regular use of anti-inflammatory or steroid substances during the past 2 mo. We also excluded patients with renal failure (serum creatinine >177 umol/l), which could alter ADMA levels [13].

Using the Framingham-based Adult Treatment Panel III risk assessment tool, an estimate of 10-yr risk for CAD was calculated [22]. These values were further categorised as low (10-yr risk <10%), intermediate (10-yr risk 10–20%), and high (10-yr risk >20%). This study complies with the Declaration of Helsinki; the protocol was approved by our Institutional Research Ethics Committee, and both ED patients and non-ED subjects gave written informed consent.

2.2. **Evaluation of erectile dysfunction**

ED of vasculogenic origin was diagnosed according to comprehensive medical and sexual history, physical examination, score of the five-item form of the International Index of Erectile Function (IIEF), the Sexual Health Inventory for Men (SHIM) score, hormonal testing (measurement of total testosterone), and penile Doppler ultrasonography. In all participants (ED patients and controls), the IIEF-5 questionnaire was used as the first step for evaluation of erectile performance. Men composing the control group had SHIM-5 scores ≥21. Doppler studies were performed only in ED patients by using 20-μg intracavernous prostaglandin E1 and audiovisual stimulation. Vasculogenic ED was diagnosed when the peak systolic velocity (PSV) was <35 cm/s and/or when the end diastolic velocity (EDV) was >5 cm/s [23]. A PSV ≥35 cm/s indicates normal penile arterial function, whereas a PSV ≥35 cm/s indicates arterial insufficiency. A PSV <25 cm/s is diagnostic of severe arterial insufficiency, and a PSV between 25 and 35 cm/s indicates borderline arterial insufficiency. An EDV ≥5 cm/s is accepted as the measurement at which a venous leak is present. In men with arterial insufficiency (borderline and severe), an EDV ≥5 cm/s was considered to indicate mixed-type vascular disease.

2.3. **Measurement of asymmetric dimethylarginine**

In both ED patients and controls, blood samples for measurement of ADMA were drawn at the first visit. Plasma ADMA levels were determined using a gas chromatographic–mass spectrometric (GC–MS)–validated enzyme–linked immunosorbent assay (ELISA) method (microtitre plate format, ADMA-ELISA, DLD Diagnostika GmbH, Hamburg, Germany) according to the manufacturer’s guidelines. The intra- and interassay coefficients of variation were not higher than 7.5% and 10.5%, respectively.

2.4. **Statistical analysis**

2.4.1. **Descriptive statistics**

All continuous variables are presented as means and standard deviations (SDs) if their distribution was normal. The Shapiro–Wilk statistic was used to test for any deviation from normality. If any variable had a skewed distribution, descriptive statistics include medians and interquartile ranges. The categorical variables are described with absolute and relative (percentages) frequencies.

2.4.2. **Univariate and multivariate analysis**

Univariate analysis was performed for determinants of ADMA. Multiple regression models were used to examine the independent significant predictors of Doppler parameters (PSV, EDV). The candidate explanatory (independent) variables for entering in the multiple regression model were age, mean pressure, smoking habits, body mass index (BMI), blood glucose, total triglycerides, high-density lipoprotein (HDL), total testosterone, and use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-II type-1 receptor blockers (ARBs) and statins. Furthermore, because high-sensitivity C-reactive protein (hs-CRP)—an established index of subclinical inflammation—has been shown to correlate with penile vascular dysfunction [24], we introduced hs-CRP as an independent variable in the models to investigate whether ADMA is associated with Doppler parameters beyond the hs-CRP.

Differences between ultrasonographic categories were determined using the student independent-samples t test after checking for equality.
of variances using Levene's test and analysis of variance (ANOVA). Analysis of covariance was performed to detect significant differences in ADMA concentration among study subgroups after adjustment for established confounders. Post hoc (Bonferroni correction) was used for multiple comparisons of the data obtained regarding ADMA.

2.4.3. Diagnostic performance of asymmetric dimethylarginine
A receiver operating characteristic (ROC) curve was generated to evaluate the ability of ADMA to discriminate subjects with and without severe arterial insufficiency (PSV < 25 cm/s).

2.4.4. Estimation of 10-yr risk of a cardiovascular event
On the basis of the median ADMA (0.64 μmol/l), our population was divided into subjects with high and low ADMA concentration, and then further subdivided according to the presence or absence of arterial insufficiency. An analysis of covariance was performed to detect significant differences in the 10-yr risk of a cardiovascular event (%) among the study subgroups after adjustment for established confounders (age, metabolic profile). Statistical significance was defined as \( p < 0.05 \). All statistical analyses were performed using SPSS v.13.0 (IBM Corp., Somers, NY, USA).

3. Results

3.1. Characteristics of erectile dysfunction and the control population
The average age of ED patients was 56 ± 9 yr (range: 36–70). The most common single risk factor in the study population was dyslipidemia (50.9%), followed by hypertension (44%), smoking (38%), and diabetes (23%). The percentage of subjects who had zero, one, or two or more risk factors were 9%, 36%, and 55%, respectively. The mean (±SD) duration of ED was 2.0 ± 1.7 yr. The average age of men without ED was 56 ± 6 yr of age (range: 38–70). In this group, the prevalence of dyslipidemia, hypertension, smoking, and diabetes was 52%, 45%, 35%, and 23%, respectively.

3.2. Correlations between asymmetric dimethylarginine and clinical characteristics in the erectile dysfunction population
ADMA was positively related to BMI (\( r = 0.18; p = 0.045 \)) and mean blood pressure (\( r = 0.19; p = 0.04 \)) and inversely related to total testosterone (\( r = −0.24; p = 0.01 \)). There was no significant correlation between ADMA and total cholesterol (\( r = 0.11; p = 0.27 \)), triglycerides (\( r = −0.14; p = 0.21 \)), and fasting blood glucose (\( r = −0.08; p = 0.74 \)). Men with hypertension (\( n = 46 \)) had a higher ADMA level compared to nonhypertensive patients (0.68 ± 0.13 vs 0.61 ± 0.11 μmol/l; \( p = 0.03 \)). Hypercholesterolemic patients (\( n = 53 \)) had a higher ADMA concentration than did normcholesterolaemic subjects (0.67 ± 0.13 vs 0.61 ± 0.12 μmol/l; \( p = 0.04 \)).

3.3. Correlations between asymmetric dimethylarginine and erectile performance
Compared to men without ED, ED patients had significantly higher ADMA levels (0.65 ± 0.13 vs 0.53 ± 0.11 μmol/l; 0.01). There was no significant correlation between ADMA and total cholesterol (\( n = 46 \)) had a higher ADMA level compared to nonhypertensive patients (0.68 ± 0.13 vs 0.61 ± 0.11 μmol/l; \( p = 0.03 \)). Hypercholesterolemic patients (\( n = 53 \)) had a higher ADMA concentration than did normcholesterolaemic subjects (0.67 ± 0.13 vs 0.61 ± 0.12 μmol/l; \( p = 0.04 \)).

### Table 1 – Clinical and erectile dysfunction characteristics of the study population categorised by peak systolic velocity values

<table>
<thead>
<tr>
<th></th>
<th>NPAF (n = 44)</th>
<th>BAI (n = 39)</th>
<th>SAI (n = 21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>58.0 ± 10</td>
<td>60 ± 8.5</td>
<td>60 ± 9.2</td>
<td>0.165</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.5 ± 4.3</td>
<td>28.7 ± 4.4</td>
<td>28.5 ± 4.5</td>
<td>0.456</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>18 (41)</td>
<td>17 (44)</td>
<td>11 (52)</td>
<td>0.462</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>21 (48)</td>
<td>20 (52)</td>
<td>12 (57)</td>
<td>0.615</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>9 (20)</td>
<td>8 (21)</td>
<td>7 (33)</td>
<td>0.262</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>17 (39)</td>
<td>15 (38)</td>
<td>8 (43)</td>
<td>0.899</td>
</tr>
<tr>
<td>Pack-yr</td>
<td>20.2 ± 26.5</td>
<td>20.7 ± 21.3</td>
<td>25.2 ± 24.2</td>
<td>0.643</td>
</tr>
<tr>
<td>&gt;2 cardiovascular risk factors, no. (%)</td>
<td>22 (50)</td>
<td>21 (53)</td>
<td>12 (57)</td>
<td>0.194</td>
</tr>
<tr>
<td>ACEIs/ARBs, no. (%)</td>
<td>18.7 ± 12.2</td>
<td>21.2 ± 11.5</td>
<td>24.4 ± 13.5</td>
<td>0.357</td>
</tr>
<tr>
<td>Statins, no. (%)</td>
<td>13 (30)</td>
<td>14 (36)</td>
<td>7 (33)</td>
<td>0.752</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>129 ± 14.8</td>
<td>135.6 ± 13.5</td>
<td>134.8 ± 15.2</td>
<td>0.156</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>80.3 ± 8.6</td>
<td>81.3 ± 7.2</td>
<td>81.2 ± 7.3</td>
<td>0.742</td>
</tr>
<tr>
<td>Mean pressure, mm Hg</td>
<td>98.0 ± 9.7</td>
<td>100.6 ± 8.7</td>
<td>100.2 ± 9.5</td>
<td>0.354</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dl (range)</td>
<td>99 (89–115)</td>
<td>101 (92–118)</td>
<td>109 (95–127)</td>
<td>0.209</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>200 ± 39.8</td>
<td>203 ± 41.2</td>
<td>210 ± 37.8</td>
<td>0.187</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>46.1 ± 9.4</td>
<td>45.8 ± 9.7</td>
<td>45.8 ± 9.5</td>
<td>0.353</td>
</tr>
<tr>
<td>Triglycerides, mg/dl (range)</td>
<td>109 (70–148)</td>
<td>112 (87–156)</td>
<td>114 (88–159)</td>
<td>0.895</td>
</tr>
<tr>
<td>hs-CRP, mg/l (range)</td>
<td>1.05 (0.46–1.64)</td>
<td>1.35 (0.57–1.79)</td>
<td>1.44 (0.61–1.85)</td>
<td>0.481</td>
</tr>
<tr>
<td>Total testosterone, ng/ml</td>
<td>4.5 ± 1.2</td>
<td>4.0 ± 1.0</td>
<td>3.5 ± 1.2</td>
<td>0.009</td>
</tr>
<tr>
<td>SHIM-5™</td>
<td>16.4 ± 5.2</td>
<td>14.5 ± 4.8</td>
<td>13.1 ± 5.1</td>
<td>0.038</td>
</tr>
<tr>
<td>Mild, no. (%)</td>
<td>21(48)</td>
<td>15 (38)</td>
<td>5 (24)</td>
<td>0.235</td>
</tr>
<tr>
<td>Moderate, no. (%)</td>
<td>18 (41)</td>
<td>14 (36)</td>
<td>8 (38)</td>
<td>0.735</td>
</tr>
<tr>
<td>Severe, no. (%)</td>
<td>5 (11)</td>
<td>10 (26)</td>
<td>8 (38)</td>
<td>0.030</td>
</tr>
<tr>
<td>ED duration, yr</td>
<td>1.8 ± 1.7</td>
<td>2.0 ± 1.4</td>
<td>2.5 ± 1.6</td>
<td>0.241</td>
</tr>
<tr>
<td>Mixed-type PVD, no. (%)</td>
<td>–</td>
<td>28 (71)</td>
<td>13 (62)</td>
<td>0.215</td>
</tr>
</tbody>
</table>

**NPAF = normal penile arterial function; BAI = borderline arterial insufficiency; SAI = severe arterial insufficiency; BMI = body mass index; ACEI = angiotensinconverting enzyme inhibitor; ARB = angiotensin II type-1 receptor blocker; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; ED = erectile dysfunction; PVD = penile vascular disease; SD = standard deviation.

* Categorical variables are presented as absolute or relative frequencies, while continuous variables are presented as median (±SD) for normally distributed and median value (25–75th percentile) for skewed variables. \( p \) values were obtained by one-way ANOVA or the \( \chi^2 \) test across the three ED groups.

In the whole ED group, ADMA levels were negatively associated with erectile performance as expressed by SHIM-5 score ($r = -0.21; p = 0.03$). ADMA levels of patients whose ED duration was $>2$ yr were significantly higher compared with the levels of subjects whose ED duration was $<2$ yr ($0.69 \pm 0.13$ vs $0.60 \pm 0.11 \, \mu\text{mol/l}; p = 0.03$).

### 3.4. Ultrasonographic evaluation of erectile dysfunction severity

According to PSV measurements, patients were placed into the following categories: (1) normal penile arterial function, (2) borderline arterial insufficiency, and (3) severe arterial insufficiency (Table 1). All patients with normal penile arterial function had venous leakage. No significant association was found between penile arterial disease severity and age or risk factors. There was a stepwise decrease in SHIM-5 score with an increasing severity of penile arterial disease ($p = 0.038$). Testosterone level was significantly associated with progressively increasing penile arterial disease severity ($p = 0.009$).

### 3.5. Correlations between asymmetric dimethylarginine and Doppler parameters of erectile dysfunction severity

#### 3.5.1. Relation to peak systolic velocity and end diastolic velocity

Univariate analysis revealed a significant inverse correlation between ADMA and PSV and a positive correlation between ADMA and EDV (Fig. 1). The significant negative association between PSV and ADMA was retained in multivariate analysis after adjusting for confounders (standardised regression coefficient $[\beta] = -0.224; p < 0.01$; adjusted $R^2$ of model $= 0.233$), indicating a decrease in PSV values in men with higher ADMA concentrations (Table 2). ADMA, when added to the model, explained the variance of PSV by an additional $3.1\%$ (adjusted $R^2$ change). In contrast, in regression model 2, in which EDV was examined, we found that the univariate positive correlation between EDV and ADMA was explained by the covariates, and no independent association existed when confounders were taken into account.

#### 3.5.2. Relation to different types of penile vascular disease

Levels of ADMA were significantly associated with progressively increasing severity of penile arterial disease ($p < 0.001$; Fig. 2). On post hoc analysis, the ADMA levels of patients with severe arterial insufficiency were significantly higher compared to the levels of subjects with either borderline insufficiency or normal penile arterial function ($p = 0.030$ and $p < 0.001$, respectively). Furthermore, ADMA levels of men with borderline arterial insufficiency were significantly higher compared to the levels of subjects with normal penile arterial function ($p = 0.01$). Moreover, men without ED had statistically significantly lower ADMA levels ($0.53 \pm 0.11 \, \mu\text{mol/l}$) compared to all three ED groups (normal penile arterial function, $p = 0.02$; borderline arterial insufficiency, $p < 0.001$; severe arterial insufficiency, $p < 0.001$). In a separate analysis among men with arterial insufficiency (borderline and severe), patients with concomitant venous leakage (mixed-type penile vascular disease; $n = 41$) had significantly higher ADMA levels compared to those men without cavernous failure ($n = 19$; $0.73 \pm 0.12$ vs $0.62 \pm 0.13 \, \mu\text{mol/l}; p = 0.004$).

ROC curve analysis for the prediction of severe arterial insufficiency showed that the area under the curve for ADMA was $76\%$ (95% confidence interval, 67–86). An ADMA

Table 2 – Regression models that evaluated the independent determinants of peak systolic velocity (model 1) and end diastolic velocity (model 2, dependent variable)

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (PSV)</th>
<th>Model 2 (EDV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonstandardised coefficient</td>
<td>Standardised coefficient</td>
</tr>
<tr>
<td>Age</td>
<td>$-0.202$</td>
<td>$-0.216$</td>
</tr>
<tr>
<td>Mean pressure</td>
<td>$-0.209$</td>
<td>$-0.215$</td>
</tr>
<tr>
<td>Glucose</td>
<td>$-0.245$</td>
<td>$-0.210$</td>
</tr>
<tr>
<td>HDL</td>
<td>0.057</td>
<td>0.104</td>
</tr>
<tr>
<td>ADMA</td>
<td>$-13.085$</td>
<td>$-0.224$</td>
</tr>
<tr>
<td>Adjusted $R^2$</td>
<td>0.233</td>
<td></td>
</tr>
</tbody>
</table>

PSV = peak systolic velocity; EDV = end diastolic velocity; HDL = high-density lipoprotein; ADMA = asymmetric dimethylarginine; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II type-1 receptor blocker.

In both models, age, mean blood pressure, smoking habits (packs per year), body mass index, fasting blood glucose, total triglycerides, HDL cholesterol, total testosterone, high-sensitivity C-reactive protein, and use of ACEIs/ARBs and statins were introduced as covariates.
3.6. Cardiovascular risk, arterial insufficiency, and asymmetric dimethylarginine

Fig. 3 shows the impact of high versus low ADMA levels on the basis of median value (0.64 μmol/l) on 10-yr risk of a cardiovascular event (%) according to PSV (cut-off: 35 cm/s; arterial insufficiency [borderline and severe, PSV < 35 cm/s] vs normal penile arterial function [PSV ≥ 35 cm/s]). As shown, the subgroup of patients with high ADMA levels in conjunction with arterial insufficiency (n = 29) exhibits a significantly higher 10-yr risk of a cardiovascular event compared to the subgroups of men with high ADMA levels/normal penile arterial function (n = 23), low ADMA levels/arterial insufficiency (n = 31), and low ADMA levels/normal penile arterial function (n = 21).

4. Discussion

This study is the first to demonstrate that among men with ultrasonographically documented vasculogenic ED, ADMA levels are significantly higher in subjects with arterial insufficiency than in men with venous leakage alone, while there was also an independent inverse association between ADMA level and PSV, a Doppler parameter of cavernosal arterial blood inflow. Our observations highlight the role of ADMA as a marker of penile arterial insufficiency and imply a pathophysiologic contribution of ADMA to processes associated with reduced arterial penile flow and generalised arterial disease associated with ED. However, the cross-sectional nature of this study does not allow inferences on causality, and implications on possible mechanisms should be regarded as hypothesis generating.

4.1. Pathophysiologic considerations

Our findings underscore the involvement of endothelial dysfunction in the pathogenesis of poor penile arterial inflow. Beyond its role as a marker of ED, ADMA may theoretically have a direct involvement in inducing endothelial dysfunction in the penile vasculature. Indeed, accumulation of cavernosal ADMA in animal studies [25,26] suggests that increased levels of local ADMA might directly affect vasorelaxation and erectile function by inhibiting the local NOS system. ADMA can also induce penile atherosclerosis, because it inhibits NO-related antiatherogenic effects of the endothelium [27].

ED is associated with impaired endothelial-dependent flow-mediated vasodilation in the brachial artery [28], suggesting that penile endothelial dysfunction is associated with generalised endothelial dysfunction. Clinical evidence suggests that serum ADMA levels are inversely associated with noninvasively evaluated endothelial function in healthy individuals [29], in patients with coronary atherosclerosis [20,30], and in subjects with multiple risk factors [30,31]. In the present study, blood concentration of ADMA was inversely correlated with pharmacologically stimulated PSV of cavernous arteries, which is an index of endothelial dysfunction confined in the penile vasculature. Taken together, the evidence suggests that this disturbance of the penile vasculature is a part of systemic endothelial dysfunction and indicates the possible role of ADMA as a marker and regulatory link between ED and generalised vascular disease. Interestingly, in our study, ADMA levels were associated with ED duration.

Our finding that the combination of arterial insufficiency and venous leakage is associated with higher levels of ADMA is not surprising. Penile arterial insufficiency results from poor blood inflow due to impaired vasorelaxation and/or luminal atherosclerotic stenosis, with ADMA playing a significant role in both abnormalities [32]. This poor inflow...
may lead to low cavernous pressures and resultant insufficient compression of subtunical venules and ultimately to venous leakage, thus offering a mechanistic explanation for the observed high percentage of veno-occlusive disease among patients with arterial insufficiency.

Endothelial dysfunction associated with NO deficiency as well as low androgen levels are mechanisms involved in the pathophysiology of vasculogenic ED [4,33]. Furthermore, there is indirect evidence from small studies that testosterone supplementation in hypogonadal men is associated with a decrease in ADMA concentration together with an improvement of ED symptoms [34]. Therefore, we introduced total testosterone as an additional parameter in the linear regression model that examines the relationship between ADMA and PSV. The fact that the inverse correlation between PSV and ADMA concentration remained significant even after adjustment for testosterone suggests that men with poor arterial inflow have elevated ADMA plasma concentration independent of testosterone levels.

4.2. Clinical implications

Our findings may have important clinical implications. First, they point out ADMA as a marker of risk beyond traditional cardiovascular factors. Lower Doppler velocities may signal development of atherosclerotic lesions before lesions in other vascular beds, such as carotids. In fact, it is known that clinical manifestations of atherosclerosis in small arteries may appear earlier than those related to atherosclerosis in large vessels [35]. Importantly, ADMA levels correlate with both intermediate end points, such as progression of carotid intima media thickness [36] and degree of coronary artery calcification in young adults [37], and clinical events such as microvascular complications in patients with type 2 diabetes [38], severity of peripheral arterial disease [39], and stroke [14]. Accordingly, measurement of ADMA levels may be useful in the setting of primary prevention to assess a patient’s total cardiovascular risk beyond the information generated by traditional risk factors.

Second, our findings imply that elevation of ADMA may call for more aggressive management of concomitant risk factors, because the combination of penile arterial insufficiency and higher circulating ADMA was associated with a higher cardiovascular risk profile. Furthermore, our findings suggest that an ED patient with elevated ADMA might be a candidate for interventions that, beyond other effects, may also reduce ADMA levels—for example, administration of ACEIs [40]. In addition, supplementation with L-arginine may be of potential value; indeed, recent studies showed that L-arginine not only improves endothelial function in patient populations characterised by elevated ADMA levels but also reduces clinical manifestations of generalised vascular disease, including vasculogenic ED [41]. However, the association between ADMA and penile functional parameters remained significant after adjustment for the use of ACEIs, ARBs, and statins.

Although the SHIM score is a reliable and valid clinical instrument for initial assessment of ED, questionnaire-based evaluation of ED severity does not necessarily correlate with evaluation of ED severity by penile Doppler [43], and our findings are in line with these studies. Nevertheless, in our population, there was a relationship between SHIM score and severity of penile arterial disease in patients with severe ED solely.

5. Conclusions

In conclusion, this is the first study to demonstrate that ADMA, a selective endogenous NOS inhibitor, is associated with poor penile arterial inflow. It points out the important role of ADMA as a marker of arterial damage in the penis and provides mechanistic links for the association between ED and generalised arterial disease. Further investigations are warranted to determine possible causal relationships underlying these associations and to substantiate whether increased ADMA levels should call for more aggressive risk factor management.

References


