Asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and L-arginine in patients with arteriogenic and non-arteriogenic erectile dysfunction

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Introduction

Erectile dysfunction (ED) is highly prevalent and by current estimated, 30 million men in US and 150 million men worldwide are affected and occurs in 19–64% of men aged 40–80 years, both developing and industrialized countries (Benet et al., 1995). Although ED is a multifactorial process, vascular disease of the penile arteries is an
important cause of ED accounting for up to 80% of cases (Kendirici et al., 2007). It has been suggested that endothelial dysfunction is linked to ED as both share a dependence on a common pathway through the nitric oxide (NO) release (Burchardt et al., 2001; Hashimoto et al., 2000; Widlansky et al., 2003; De Angelis et al., 2001). NO is the major endothelium-derived relaxing factor, playing a critical role in the maintenance of vascular tone (Palmer et al., 1988). Penile tumescence and erection is critically reliant on the NO release by both cavernosal nerve terminals and endothelial cells (Saenz de Tajada et al., 2004).

NO is formed from the precursor amino acid, L-arginine, by enzymatic action of nitric oxide synthase (NOS). NO production may be regulated by endogenous NOS competitive inhibitor asymmetric dimethylarginine (ADMA), a L-arginine analogous. The ADMA levels in plasma are a balance between breakdown of proteins containing methylated arginine, renal excretion and the activity of hepatic dimethylarginine dimethylaminohydrolase (DDAH). The L-arginine analogous identified to day, include monomethylarginine (NMMA), symmetric dimethylarginine (SDMA) and ADMA. It was postulated that ADMA, which was identified as circulating in human plasma at a concentration 10 times greater than that of naturally occurring NMMA, might act as an important endogenous regulator of the NO pathway (Vallance et al., 1992).

In view of the apparent role of NO as the key chemical element necessary for penile erection, investigators have begun to explore the incidence of ED in conditions associated with a deregulated ADMA and/or SDMA metabolism as diabetes mellitus, hypercholesterolaemia, renal failure, hypogonadism, ageing and irradiation (Schiel et al., 2003; Maas et al., 2005; Elsberg et al., 2006; Wierzbicki et al., 2006; Kielstein et al., 2005; Lugg et al., 1995; Garban et al., 1995; Carrier et al., 1995). Moreover, over the past decade the interference of these substrates with cardiovascular function has received increasing interest and several lines of evidence suggest that ADMA is involved in the pathogenesis of cardiovascular diseases (Valkonen et al., 2001; Cooke et al., 2004).

As ED may be an early marker for the presence of subclinical atherosclerosis (Solomon et al., 2003) we studied the plasma concentrations of L-arginine, ADMA and SDMA in men with arteriogenic and non-arteriogenic ED, to assess the differences between the two ED subgroups and the healthy subjects, independently by the presence of clinical or subclinical atherosclerosis.

Materials and methods

Investigation protocol

In our centre, patients complaining of ED are currently investigated by careful history-taking and clinical andrological examination; then, a few days later, by a panel of examinations, including blood tests, complete blood picture, haemoglobin, glycated haemoglobin, glycaemia, urea, creatinine, PCR, total and HDL cholesterol, triglycerides, transaminases, testosterone, prolactin, 17-β-estradiol, urine analysis and 24-h urinary albumin excretion (microalbuminuria), the International Index of Erectile Function questionnaire (IIEF) and echo-colour-Doppler of both cavernous arteries.

The IIEF questionnaire (Rosen et al., 1999) is a validated, self-administered tool (Rosen et al., 1999; Rosen et al., 1997), but we only evaluated the answers to the first five (erectile response domain) of the 15 questions (IIEF-15, 1–5). Possible scores for the IIEF-5 range from 5 to 25, scores of 22–25 indicate normal erectile function whereas scores of 21 or below indicate ED (Rosen et al., 1999 Rosen et al., 1999).

Penile echo-colour-Doppler was performed in basal conditions and after intracavernous injection of 10 µg prostaglandin E1 (PgE1) (Aversa et al. 2005), and the peak systolic velocity (PSV) and end-diastolic velocity (EDV) were recorded at 5, 10, 15, 20 and 25 min after the injection in the proximal portion of the penis. Patients were classified as ‘non-arteriogenic’ when their PSV was >35 cm/sec, or ≤35 cm/sec, but >25 cm/sec with concomitant EDV ≤0 cm/sec, and ‘arteriogenic’ when their PSV was ≤20 cm/sec (Barassi A et al., 2009; Barassi et al., 2010). The erection quality was estimated 20 min after each injection. If a patient appeared stressed, he was given a second injection of the same dose of PgE1 and all measurements were repeated. From 30 to 60 min after the penile echo-colour-Doppler, participants were placed in a supine position and blood samples were drawn from a cubital vein into EDTA tubes. Samples were centrifuged at 4000 g for 10 min. The serum was separated and stored at –80 °C until analysis.

Patients and control group

Of a series of 590 filed ED cases studied in the period October 2008–August 2010, we randomly selected 29 arteriogenic ED patients (ED AR) and 32 non-arteriogenic ED patients (ED NON-AR), according to our exclusion criteria for this study, for a total of 61 cases (median age 48.3 years, range 36–53) with a history of at least 3 months, but not more than 1 year of ED. General exclusion criteria were: age below 30 years, congestive heart failure, diabetes, renal failure, anaemia, acute infection or rheumatic disease, evidence from the patient’s clinical history of coronary artery disease, hypertension (>140/90 mm Hg in three consecutive recordings at rest), malignancy, systemic inflammatory disease, hepato-pathies or arrhythmias, current smoking (Tostes et al., 2012 European Academy of Andrology)
2008) and vitamins supplementation. Our patients did not take any therapy.

The 30 healthy controls were all blood donors (median age 45.1 years, range 34–49), and, according to their answers to the first five IIEF-15 questions (erectile response domain), did not suffer from ED. Both healthy controls and the patients of the two ED subgroups declared to develop a normal physical activity.

In accordance with the Declaration of Helsinki II, the design of the study was explained thoroughly to all the participants, and informed consent was obtained for all the test of the study from all ED patients and controls, and for administering the IIEF-15 test to controls. In particular, it was explained to the participants that no additional blood needed for this study.

Assays

From 60 to 90 min before the penile echo-color-Doppler, participants to the study were placed in a supine position and blood samples were drawn from a cubital vein into EDTA tubes. HbA1c was measured using a high performance liquid chromatography (HPLC) method (Bio-Rad). Plasma glucose, creatinine, urea, total cholesterol, HDL-cholesterol, triglycerides, hsCRP, ALT, AST, prolactin, testosterone and 17β-estradiol were analysed with commercially available kits using Modular EVO (Roche). Plasma LDL-cholesterol was calculated with the use of Friedewald’s formula. Urinary microalbumin concentration was measured in duplicate in the morning samples on a Behring Nephelometer II analyser (Siemens).

Plasma concentrations of ADMA, SDMA and L-arginine were determined by the method described by Paroni et al. (Paroni et al., 2005). Briefly, after adding L-homoaarginine as internal standard, 100 µL of plasma samples were submitted to solid phase extraction on SCX cartridges (Phenomenex STRATA SCX, 55 µm, 70 A, 100 mg/1 mL). Following three washing steps with TCA 2%, phosphate buffer pH 8.0 and methanol, respectively, cationic amino acids (ADMA, SDMA, homoarginine and L-arginine) were eluted with 1 mL of a methanol: water solution (70 : 30, v : v) containing 2% triethylamine. The eluate was evaporated to dryness under a gentle nitrogen stream and the residue was resuspended in water. This was followed by online ortho-phthalaldialdehyde derivatisation, HPLC separation (Ultrosphere Beckman ODS, 250 × 4.6 mm, 5 µm) and fluorimetric detection (λex= 340 nm, λem = 455 nm). The liquid chromatographic system included an Agilent 1200 Series Rapid Resolution chromatograph equipped with binary pump SL, thermostatted column compartment SL, high performance autosampler SL plus and a 1260 Infinity Fluorescence Detector. Within-assay and between-assay variations for all the analytes were <3.0% and <6.0%, respectively; the detection limit of the assay was 1.5 pmol injected at a signal-to-noise ratio of 3 : 1. The total run time was 32 min.

Statistical analysis

All the variables were expressed as median and range (or 25% and 75% percentiles). Normal distribution of the data was tested by the Kolmogorov–Smirnov test. The significance of differences between controls, ED AR and ED non-AR was assessed by the non-parametric test Mann–Whitney Rank sum test. Spearman correlation was used to assess the strength of association between variables. Probabilities ≤0.05 were considered to be statistically significant. All analyses were performed using the statistical software package Sigma Stat (Statistical Analysis System, version 3.0) (Jandel Scientific GmbH, Erkrath, Germany).

Results

Of the 61 men included in the study, 29 (47.5%) were classified as having ED AR and 32 (52.5%) as having ED NON-AR. Clinical and laboratory features of 30 controls and 61 patients with ED are presented in Table 1. In ED AR (median age 49.2 years, range 42–52) and ED NON-AR (median age 47.5 years, range 36–53) the median of IIEF values were 10.5 (range 5–19) and 12.8 (range 7–20) respectively. There were no significant differences between the two ED subgroups (p > 0.05). There were no differences neither between ED patients and controls nor between the two ED subgroups regarding all the laboratory tests (p > 0.05). Hormonal status of all patients was in the normal range (Table 1).

The ADMA concentration (median and range in µmol/L) in ED AR [0.682 (0.536–0.811)] and in ED NON-AR [0.554 (0.492–0.722)] was significantly higher (p = 0.003) compared with controls [0.445 (0.380 –0.570)]; in ED AR it was also significantly higher (p = 0.038) than in ED NON-AR.

The SDMA concentration in ED AR [0.746 (0.613–0.808)] and in ED NON-AR [0.592 (0.528–0.751)] was significantly higher (p = 0.003 and ≤0.001 respectively) compared with controls [0.465 (0.425–0.529)]; in ED AR it was also significantly higher (p = 0.030) than in ED NON-AR. The results are reported in Fig. 1.

Spearman correlation analysis demonstrated a negative correlation between serum ADMA levels and IIEF score that reached the significance in ED AR (r = −0.396; p < 0.01) but without reaching the significance in ED NON-AR (r = −0.03; p < 0.20).

The L-arginine plasma concentration (median and range in µmol/L) did not differ significantly (p > 0.05)
Table 1 Clinical and laboratory features of controls and patients with erectile dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 30)</th>
<th>ED (n = 61)</th>
<th>ED-AR (n = 29)</th>
<th>ED-NON AR (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.1 (34–49)</td>
<td>48.3 (36–53)</td>
<td>49.2 (42–52)</td>
<td>47.5 (36–53)</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>125 (118–137)</td>
<td>128 (116–138)</td>
<td>130 (118–138)</td>
<td>127 (116–135)</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>82 (75–86)</td>
<td>85 (72–88)</td>
<td>87 (80–88)</td>
<td>83 (72–86)</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>72 (65–81)</td>
<td>75 (63–88)</td>
<td>77 (65–88)</td>
<td>73 (63–85)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 (22.3–27.4)</td>
<td>27.3 (21.8–28.2)</td>
<td>27.5 (22.5–28.2)</td>
<td>26.8 (21.8–27.7)</td>
</tr>
<tr>
<td>Diuresis (L)</td>
<td>1.6 (1.3–2.0)</td>
<td>1.7 (1.2–2.1)</td>
<td>1.8 (1.4–2.3)</td>
<td>1.5 (1.2–1.99)</td>
</tr>
<tr>
<td>Microalbuminuria (mg/L)</td>
<td>11 (11–14)</td>
<td>11 (11–13)</td>
<td>11 (11–13)</td>
<td>11 (11–12)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>90.2 (80–96)</td>
<td>94.1 (85–99)</td>
<td>95.9 (89–102)</td>
<td>93.3 (84–95)</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>69.0 (5.8–8.5)</td>
<td>7.5 (6.1–9.1)</td>
<td>7.4 (6.6–8.4)</td>
<td>7.9 (6.0–9.9)</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>4.9 (3.9–5.3)</td>
<td>4.6 (3.8–5.1)</td>
<td>4.5 (3.8–4.8)</td>
<td>4.7 (3.8–5.5)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.81 (0.75–0.88)</td>
<td>0.85 (0.79–1.00)</td>
<td>0.82 (0.73–0.89)</td>
<td>0.85 (0.78–0.92)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>37 (32–45)</td>
<td>38 (33–45)</td>
<td>37 (32–46)</td>
<td>39 (34–45)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>25 (20–32)</td>
<td>26 (19–39)</td>
<td>29 (22–43)</td>
<td>26 (19–34)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>28 (20–34)</td>
<td>27 (22–31)</td>
<td>29 (23–32)</td>
<td>26 (22–31)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>196 (159–220)</td>
<td>208 (177–226)</td>
<td>198 (175–213)</td>
<td>211 (186–227)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>118 (92–140)</td>
<td>112 (89–144)</td>
<td>116 (94–161)</td>
<td>112 (84–131)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53 (45–63)</td>
<td>55 (46–64)</td>
<td>52 (46–61)</td>
<td>57 (50–64)</td>
</tr>
<tr>
<td>IIEF-5 score</td>
<td>23 (22–25)</td>
<td>11.6 (5–20)</td>
<td>10.5 (5–19)</td>
<td>12.8 (7–20)</td>
</tr>
</tbody>
</table>

Values are reported as median and range.

*p < 0.001 vs. Controls.

neither between ED AR [54.10 (46.67–65.57)] or between ED NON-AR [53.80 (40.23–62.30)] and controls [47.15 (36.20–60.50)] nor between the two ED subgroups.

The L-arginine/ADMA ratio [66.50 (52.17–90.95)] and L-arginine/SDMA ratio [72.10 (59.37–82.7)] in ED AR were significantly lower (p = 0.002) than in controls [100 (85.5–136.5) and 105.5 (78–144)] and than in ED NON-AR [87.70 (82.40–116.70) p = 0.004 and 82.90 (78–114) p = 0.029]; the two ratios in ED NON-AR did not differ (p > 0.05) from the controls (Fig. 2).

Discussion and conclusions

Cells regulate NO homeostasis by different mechanisms. eNOS (type 3) and nNOS (type 1) are constitutively expressed low output enzymes whose enzymatic activity depends on Ca²⁺ levels, protein myristilation, phosphorylation and protein/protein interactions. By contrast, iNOS (type 2) is an inducible NO synthase not normally expressed in resting cells, and upon stimulation by various cytokines or bacterial lipopolysaccharide its transcription can be induced within several hours. The discovery of ADMA and demonstration of in vivo and in vitro effects on inhibiting NO synthesis has led to a large body of work attempting to discover its role in a wide range of different clinical conditions which share endothelial dysfunction as a common feature. After proteolysis of methylated proteins, ADMA is released within cells where can concur to regulate excessive iNOS activity, as well as the other NOS isoforms by competing with the NOS natural substrate arginine (Vallance et al, 1992; Ueda et al, 2003). The local concentrations of substrate and inhibitors, i.e. the L-arginine/ADMA concentration ratio, may be therefore an important factor, although not the only, in the pathogenesis of ED in various disease states. Presumably, the state of activation or inhibition of NOS will depend on ADMA exported from the site of origin by cationic amino acid transporter, the same used by L-arginine (CAT) (Baylis 2006; Welch et al, 1997). The majority of ADMA is metabolized by the enzyme DDAH to yield citrulline and dimethyl-amine (Achan et al, 2003; Tsuji et al, 1986; Palm et al, 2007). Intracellular ADMA that escapes metabolism by DDAH, besides to inhibit NOS, may also reduce NO generation by competing with L-arginine for cellular uptake by CAT transporter. Thus, ADMA not only blocks NOS activity but also limits the cellular uptake of L-arginine, thereby contributing to oxidative stress that further inhibits NO biogenesis (Böger et al, 2009). SDMA, in contrast, has no direct effect on NOS. However, it may still be important by competing with L-arginine for transport across the CAT (Closs et al, 1997; Bode- Böger et al, 2006). Thus, also SDMA may indirectly limit NO generation.

The populations studied, ED and controls, were homogeneous with similar patterns of metabolic and inflammatory variables. It is generally accepted that ED has been...
associated with advanced atherosclerotic CAD (Solomon et al., 2003; Feldman et al., 2000; Takiuchi et al., 2004): then, the subjects with clinical history of CAD and/or with atherosclerotic risk factors were excluded from the study. As ADMA has been associated with characteristics of the metabolic syndrome only subjects without those characteristics were included in our study.

In this study of well-characterized patients, in particular as regards the penile arteriogenic and non-arteriogenic aetiology of ED, we found a significant increase of ADMA and SDMA concentrations in both the ED subgroups compared with healthy controls and in ED AR compared with ED NON-AR. Our findings confirm recent data of Ioakeimidis et al. that found ADMA levels significantly higher in ED AR than in ED NON-AR patients with an independent inverse association between ADMA and PSV (Ioakeimidis et al. 2011).

Although elevated ADMA levels in patients with renal failure could be attributed, at least in part, to reduced

![Figure 1](image1.png)

![Figure 2](image2.png)
renal excretion, the precise cause of elevated ADMA levels in ED has not been identified yet. One cause could be a reduced activity of DDHA, highly expressed in the liver (Nijveldt et al., 2003), whose activity may be inhibited by a large series of traditional (hypercholesterolaemia, diabetes, smoking), non-traditional (hyperhomocysteinaemia, inflammation, oestrogen deficiency, insulin resistance, hypothyroidism) risk factors and finally by oxidative stress. A fairly recent study showed that plasma reactive oxygen metabolite (ROS) concentrations were higher and plasma total antioxidant status (TAS) was lower in ED AR patients in comparison with ED NON-AR patients and in controls (Barassi et al., 2009). Furthermore, through uncoupling of NOS, increased production of superoxide could further impair DDAH, leading to a perpetuating increase in ADMA concentration (Sydow et al., 2003).

There were no significant differences neither between ED patients and controls nor between the two ED subgroups regarding L-arginine concentration. L-arginine/ADMA ratio and L-arginine/SDMA ratio were significantly lower in ED AR in comparison with those in the controls and in ED NON-AR. In ED NON-AR, the two ratios were not different from those in the controls. A low L-arginine/ADMA ratio (i.e. the ratio of NOS substrate and its endogenous inhibitor concentrations) is compatible with ADMA acting as a competitive inhibitor of NOS, resulting in a reduced NO synthesis. It is more difficult to explain the increased level of SDMA and the decreased L-arginine/SDMA ratio in ED patients. In fact, the role of SDMA in these pathologies is not yet completely clear. Nevertheless, the decrease of the ratio only in ED AR can contribute to limit NO generation by reducing the availability of L-arginine, the NOS substrate.

The HPLC method used for quantification is characterized by a very low imprecision, allowing reliable determination also in the presence of small concentration differences between groups. Nevertheless, we found near borderline significant differences in ADMA and L-arginine/ADMA levels between AR and NON-AR patients; then, from a diagnostic standpoint it needs caution in discriminating between AR and NON-AR patients from levels near the limit of reference ranges. The concentrations of both ADMA and SDMA are tightly controlled in health, with intraindividual variations (CVi) of 7.4% and 5.8% respectively (Blackwell et al., 2007). Based on a desirable imprecision of no more than 0.5 times CVi (Fraser et al., 1999), our method meet this goal. In addition, both the generation of NO and the formation of the L-arginine analogues, by the sequence of protein methylation and proteolysis, are intracellular processes. ADMA and SDMA in plasma probably originate from cellular spillover. A limited increase in the plasma concentration may thus reflect a much larger increase of their intracellular concentration, which may be sufficient to substantially inhibit NO production. In fact, cells can concentrate L-arginine analogous up to 5–10 times than that in plasma.

This study supports the hypothesis that elevated ADMA and normal-low or low L-arginine levels may contribute, either directly or through NOS uncoupling, to the inhibition of penile NO synthesis (Maas et al., 2002). In fact, also L-arginine/ADMA ratio in ED AR is significantly lower than in ED NON-AR and controls. Furthermore, the increased SDMA competes with the L-arginine entrance in the cells reducing the availability for NO synthesis. ED, but only ED AR, may be the earliest manifestation of a generalized vascular disease and only these patients may be at risk of later developing CAD.

Recently, Elesber (Elesber et al., 2006) and Aktoz (Aktoz et al., 2010), comparing plasma ADMA concentration and severity of ED and coronary artery disease, demonstrated a significantly negative correlation between IIEF score and ADMA levels, but none of the two studies split the ED patients in relation to the different aetiology (AR and NON-AR) according to the penile echo-colour-Doppler after intracavernous injection of prostaglandin E1. Our results showed a significantly negative correlation between serum ADMA levels and IIEF score but only in ED AR subgroup confirming the role of ADMA in ED but only in those patients with ED of arteriogenic origin.

Chen et al. (Chen et al., 1999) reported significant improvement in sexual function when ED patients characterized by relative L-arginine deficiency (L-arginine/ADMA elevated), were treated with L-arginine supplementation in combination with phosphodiesterase type s (PDE-5) inhibitors. Quite recently, the oral supplementation with arginine or citrulline (which escapes intestinal or liver metabolism, enters the kidneys and is rapidly converted into L-arginine) has been also proposed to patients with mild ED and in heart failure (Cormio et al., 2011; Orozco-Gutierrez et al., 2010), thus providing the rationale for oral L-citrulline supplementation as a donor for the L-arginine/NO pathway in patients with endothelial dysfunction. From the results of our study, we can speculate that only a subgroup of ED patients, ED AR with elevated ADMA, might benefit from L-arginine or L-citrulline supplementation. For this reason, we think advisable to recognize between the ED patients those with arteriogenic aetiology.

In conclusion, NO pathway is of critical importance in the physiological regulation of erection. Elevated endogenous NOS inhibitor, like ADMA, not balanced by and increased L-arginine concentration, contributes to NO deficiency, leading impaired NO-mediated relaxation in the lower urinary tracts and corpus cavernosum. Moreover, our observations could be also interpreted as
evidence for a reduced systemic availability of L-arginine in men with ED; but only in men with ED AR, ADMA appears to be preferentially elevated and both L-arginine/ADMA ratio and L-arginine/SDMA ratio decreased; thus, confirming in this subgroup the diagnosis of vascular origin of ED obtained with the penile echo-colour-Doppler procedure. Nevertheless, the levels of ADMA and of L-arginine/ADMA are not sufficiently different to accurately discern between AR and NON-AR patients. Probably because the precise aetiology of NON-AR ED can be difficult to elucidate and may be because of a combination of organic as well as psychological factors. Taken together with the relatively small number of samples in this study, this may account for the fact that levels of ADMA and L-arginine/ADMA, even though a statistically significant difference was shown between AR and NON-AR patients, can not accurately differentiate a single patient presenting with ED in clinical setting.

Additional studies are required to define the importance of ADMA in ED, but the results demonstrate that future research should investigate separately AR from ED NON-AR patients, because they belongs to different populations and according to severity of arteriogenic status by using PSV values (Ioakeimidis et al., 2011). This will increase understanding of the role of ADMA in the mechanisms that lead to ED and potentially provide therapeutic targets.

Finally, our results point out the importance of the determination of ADMA, SDMA and L-arginine concentration that we suggest to insert in the list of the tests for an early screening of ED patients.

References


ADMA and SDMA in erectile dysfunction

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