

1224

## ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

---

### Evaluation of Microalbuminuria in Patients with Erectile Dysfunction

Alessandra Barassi, MD,\* Raffaele Pezzilli, MD,<sup>†</sup> Antonio Maria Morselli-Labate, MD,<sup>†</sup> Wanda Porreca, MD,<sup>‡</sup> Guido Piediferro, MD,<sup>§</sup> Francesco Ciociola,<sup>§</sup> Giovanni Colpi, MD,<sup>§</sup> and GianVico Melzi d'Eril, MD\*

\*Università degli Studi di Milano—Dipartimento di Medicina, Chirurgia e Odontoiatria, Milano, Italy; <sup>†</sup>Ospedale S.Orsola-Malpighi—Dipartimento di Medicina Interna e Gastroenterologia, Università degli Studi di Bologna, Bologna, Italy; <sup>‡</sup>Ospedale San Paolo—Laboratorio di Analisi, Milano, Italy; <sup>§</sup>Ospedale San Paolo—Unità di Urologia Andrologica, Milano, Italy

DOI: 10.1111/j.1743-6109.2009.01503.x

#### ABSTRACT

---

**Introduction.** The recent sophisticated diagnostic procedures aimed at identifying the exact cause of erectile dysfunction (ED) are often complicated in clinical application, invasive, or highly expensive. Microalbuminuria, a test easy to perform and of low cost, is a marker of extensive endothelial dysfunction, and it has been suggested to be linked to ED.

**Aim.** The aim of this study was to investigate the eventual role of microalbuminuria in differentiating patients with arteriogenic and non arteriogenic ED.

**Methods.** The diagnosis of ED was based on the International Index of Erectile Function 5-questionnaire, and patients were classified as arteriogenic (N = 29) and non-arteriogenic (N = 49) in relation to the results of echo-color-doppler examination of cavernosal arteries in basal conditions and after intracavernous injection of 10 µg prostaglandin E<sub>1</sub>.

**Main Outcome Measures.** The microalbuminuria of 78 males without the most common atherosclerotic risks and with ED was measured.

**Results.** Microalbuminuria, defined as urinary albumin/creatinine ratio, was not significantly ( $P > 0.05$ ) different between patients of the two groups.

**Conclusions.** Our data show that in ED patients the cavernosal arteries damage, as assessed by dynamic echo-color-doppler, may be independent on or precede extensive endothelial dysfunction, and that microalbuminuria cannot be predictive of penile arteriogenic etiology. **Barassi A, Pezzilli R, Morselli-Labate AM, Porreca W, Piediferro G, Ciociola F, Colpi G, and Melzi d'Eril G. Evaluation of microalbuminuria in patients with erectile dysfunction. J Sex Med 2010;7:1224–1228.**

**Key Words.** Erectile Dysfunction; Microalbuminuria; Endothelial Function; Cardiovascular Risk for Erectile Dysfunction

---

#### Introduction

Erectile dysfunction (ED) has been defined by the National Institute of Health as the inability to achieve and/or to maintain penile erection of sufficient quality to allow a satisfactory sexual intercourse [1]. It has been estimated to affect 20

million to 30 million men in the United States, and that approximately 5–20% of men, complain of moderate to severe ED [2]. Although penile erection is the result of a complex and coordinated series of events involving vascular response, neuronal pathways, and psychosomatic stimulation, the proper function of the vascular endothelium is

essential to achieving and maintaining penile erection. In fact, recent data reveal more than 80% of ED has an organic basis, with vascular disease being the most common etiology [3,4]. A functioning NO pathway is a primary determinant of smooth muscle tone, arterial inflow, and restricted venous outflow in the physiology of erection. Disruption of any of these factors can lead to ED. Endothelial dysfunction, which is associated with impaired release and activity of nitric oxide (NO), underlies the pathophysiology of vascular ED [5,6]. The small diameter of the cavernosal arteries and the high content of endothelium and smooth muscle on a per-gram tissue basis, compared with other organs, may make penile vascular bed a sensitive indicator of systemic vascular disease [7]. It follows that ED can be a result of any number of structural, like minimal occlusion of cavernosal arteries, or functional, like impaired smooth muscle relaxation, abnormalities in the penile vascular bed [8].

The study by Nathan et al. [9] illustrates the relation of microalbuminuria to vascular complications such as intima-media thickening. The validity of microalbuminuria as an index is further addressed by Perkins et al. [10]. The amount of albumin excreted in the urine over a 24-h period was once considered the "gold standard" for defining microalbuminuria. However, 24-h urine collections are cumbersome and subject to error because of inaccurate timing and/or incompleteness. To avoid these adverse influences, 24-h urinary albumin excretion is replaced by the ratio of urinary albumin concentration to urinary creatinine concentration (UACR) [11]. Hence, microalbuminuria was defined as UACR cutoff of 30–299 mg/g according to the criteria of the American Diabetes Association [12]. Assessment of microalbuminuria is particularly important in diagnosing diabetes kidney disease because low levels of albuminuria are an early clinical manifestation of diabetic nephropathy that may present several years before development of a diminished glomerular filtration rate [13]. Furthermore, microalbuminuria alone has been associated with an increased risk of cardiovascular disease, both in patients with and without diabetes mellitus [14–16]; moreover, microalbuminuria is a significant risk factor for cardiovascular mortality in type 1 [17] and 2 diabetes [18], as well as in the non-diabetic population [19]. Accordingly, microalbuminuria can be considered a marker of extensive endothelial dysfunction and plays a key role as a potential cardiovascular and atherosclerotic risk factor [20].

The coincidence of microalbuminuria and extrarenal vascular damage in diabetic patients led to the hypothesis that albuminuria does not only reflect a state of glomerular, but also generalized endothelial dysfunction [21]. Many recent studies [22] demonstrate the usefulness of microalbuminuria as a valuable and clinically relevant tool for the identification of individual patients at risk for the development of end-organ damage, for example, systemic cardiovascular disease. Therefore, the endothelium appears to be the link between metabolic changes and physiological dysfunction. In accordance with the aforementioned data, we hypothesized that microalbuminuria could be a marker of vascular ED in a population free of the most common atherosclerotic risks. The benefits of using microalbuminuria to screen for endothelial injury are that it is inexpensive and the results are available rapidly.

The aim of this study was to investigate the relationship between arteriogenic ED and microalbuminuria, as a marker of endothelial dysfunction, in a group of patients without known clinical risk factors for vascular pathology.

### Materials and Methods

Erectile function was assessed on an appropriate clinical work-up study and by using the abridged five-item version of the International Index of Erectile Function questionnaire (IIEF-5), a validated, self administered questionnaire [23,24]. Seventy-eight men (mean age 44.1 years, range 24–62 years) underwent echo-color-doppler examination of cavernosal arteries in basal conditions and after intracavernous injection of 10 µg prostaglandin E<sub>1</sub>, and the peak systolic velocity (PSV) and end-diastolic velocity (EDV) were recorded 5, 10, 15, 20, and 25 minutes after the drug injection into the proximal portion of the penis. PSV and EDV are reported as the mean of the values measured in both cavernosal arteries. Patients were classified as non-arteriogenic when their PSV was  $\geq 35$  cm/sec, or  $< 35$  cm/sec but  $> 25$  cm/sec with concomitant EDV  $\leq 0$  cm/sec, and arteriogenic when their PSV was  $\leq 20$  cm/sec [25]. Resistance index (RI)  $> 0.80$  is considered normal. The erection quality was estimated 20 minutes after each injection. If a patient appeared stressed, he was given a second injection of the same dose of prostaglandin E<sub>1</sub> and all measurements were repeated. The procedure was repeated in one non-arteriogenic and two arteriogenic patients without changing the outcomes.

None of the patients had clinical evidence of coronary artery disease, diabetes mellitus, hypertension, malignancy, renal failure, congestive heart failure, systemic inflammatory disease, or arrhythmias. In all patients, we measured the testosterone and prolactin serum levels, and only patients without endocrine risk factors were considered in the present study. In accordance with Helsinki Declaration II, the design and execution of the experiment were explained thoroughly to the participants, and informed consent was obtained. The Mann-Whitney and the Fisher's exact tests were applied to analyze data by running the SPSS (Version 12.0 for Windows) statistical package. Urinary microalbumin concentration was measured in duplicate in the morning samples on a Behring Nephelometer II analyzer (Dade Behring). The within-run ( $N = 40$ ) and the between-run coefficient of variation (CV) ( $N = 15$ ) of the determination were 4.1% and 5.0% at 49.2 g/L, respectively. The detection limit was 11 mg/L. Urinary creatinine in the same morning samples was measured in duplicate by a modified Jaffe's reaction (Crea, Roche) on a Modular analyzer (Roche) and the within-run ( $N = 40$ ) and the between-run CV ( $N = 15$ ) of the determination were 1.2 and 2.3% at 0.6 g/L, respectively. The detection limit was 0.040 g/L. Both determinations were performed on the same day of the sample collection. The UACR (mg/g) was calculated by dividing the mean of the urinary albumin values by the mean of the urinary creatinine concentration. The body mass index (BMI) of all patients has been calculated because the population with higher muscle mass have higher levels of creatinine excretion [26].

## Results

The characteristics of the arteriogenic and non-arteriogenic ED patients are summarized in Table 1. Out of the 78 males, based on the echocolor-doppler examination results, 29 patients had

arteriogenic ED (mean age 42.1 years, range 26–62 years; mean BMI 23.4 Kg/m<sup>2</sup>, range 20.9–25.6 Kg/m<sup>2</sup>) and 49 patients had non-arteriogenic ED (mean age 45.0 years, range 24–61 years; mean BMI 23.0 Kg/m<sup>2</sup>, range 20.2–25.5 Kg/m<sup>2</sup>). The age and the BMI of the two groups were not significantly different ( $P = 0.213$  and  $P = 0.312$ , respectively). Mean PSV was 16.2 cm/sec (range 9–19 cm/sec) and 46.4 cm/sec (range 32–79 cm/sec) in patients with arteriogenic and with non-arteriogenic ED ( $P = 0.001$ ), respectively. Mean EDV was 4.11 cm/sec (range 0–6 cm/sec) and 2.18 cm/sec (range from –6 to +12 cm/sec) in patients with arteriogenic and with non-arteriogenic ED ( $P = 0.002$ ), respectively. Mean RI was 0.72 (range 0.63–0.79) and 0.95 (range 0.73–1.2) in patients with arteriogenic and with non-arteriogenic ED ( $P = 0.001$ ), respectively. In the first group, IIEF values were: mean 11.20 (range 0–22); in the second group the respective figures were 12.9 (range 0–21). There were no significant differences between the two groups ( $P = 0.289$ ). Undetectable levels of albuminuria in at least one of the two determination were present in 20 (69.0%) patients with arteriogenic ED and in 40 (81.6%) of those with non-arteriogenic ED ( $P = 0.267$ ). In the 18 patients with detectable UACR concentrations, the mean  $\pm$  SD UACR was 38.6  $\pm$  27.9 mg/g (range 8–95 mg/g) and 52.2  $\pm$  41.8 mg/g (range 10–143 mg/g) in the first (9 patients) and in the second (9 patients) group, respectively. UACR of arteriogenic ED patients were not significantly different from UACR of non-arteriogenic ED patients ( $P = 0.429$ ). Even in the patients with detectable UACR concentrations, there was no correlation with IIEF scores in both groups ( $P = 0.05$ ).

## Discussion

The small diameter of the cavernosal arteries and the high content of endothelium and smooth muscle on a per-gram tissue basis (compared with

**Table 1** Characteristics of study participants on the basis of ED status

Characteristics	Arteriogenic ED (n 29)	Non-arteriogenic ED (n 49)	P
Age, years	42.1 (26–62)	45.0 (24–61)	0.213
BMI, kg/m <sup>2</sup>	23.4 (20.9–25.6)	23.0 (20.2–25.5)	0.312
PSV, cm/sec	21.0 (10–25)	48.3 (36–79)	0.001
EDV, cm/sec	3.3 (0–9)	5.1 (–6+12)	0.039
RI	0.84 (0.63–0.89)	0.86 (0.73–0.90)	0.570
IIEF	11.2 (0–22)	12.9 (0–21)	0.289

Data are expressed as means (range). A value of  $P < 0.05$  was considered significant.

other organs) may make the penile vascular bed a sensitive indicator of systemic vascular disease [27]. A normal erectile function requires a healthy endothelial function [28]. Endothelial dysfunction, which is associated with impaired release and activity of NO, therefore, can be a cause of vascular ED [29,30]; through the same system, endothelial dysfunction is the physiologic connection between ED and systemic vascular disease [31,32]. As previously mentioned, microalbuminuria is considered as a marker of extensive endothelial dysfunction. In the Steno hypothesis put forward by Deckert [21], albumin leakage into the urine is a reflection of widespread vascular damage. In a sense, the kidney is the window of the vasculature. In view of these considerations, endothelial function and chronic inflammation have been suggested as possible candidates to explain the association between microalbuminuria and cardiovascular diseases [33,34]. However, other studies indicate that although microalbuminuria, endothelial dysfunction, and low-grade inflammation are linked, they all are independently associated with risk for cardiovascular death [35,36].

In our present search for a sensitive marker of endothelial dysfunction in ED patients, the aim of our study was to check if a simple examination like microalbuminuria could replace the dynamic echo-color-doppler evaluation of the cavernosal arteries in discriminating the arteriogenic from the non-arteriogenic ED subjects. Our results do not support a role of microalbuminuria as a screening method. In line with this evidence, recently conducted studies that measured early markers of cardiovascular diseases and endothelial dysfunction (flow mediated-vasodilation and soluble P-selectine), demonstrated that damage to the penile vascular bed occurs before systemic vascular illness becomes clinically apparent [37–39].

## Conclusion

Our study shows that in ED patients without clinical evidence of atherosclerotic diseases, and free of the common risk factors associated with generalized penile arterial insufficiency, the cavernosal arteries damage, as assessed by dynamic echo-color-doppler, may be independent on or may precede extensive endothelial dysfunction. In addition, in this kind of ED patients microalbuminuria expressed as UACR cannot be predictive of pure penile arteriogenic etiology, at least in our experimental conditions. In general, no relation-

ship was shown between ED and microalbuminuria in patients without any other known clinical pathology.

This preliminary study shows that urinary microalbumin expressed as UACR would be unsatisfactory for the prediction of ED of arteriogenic etiology, at least in our experimental conditions.

**Corresponding Author:** Alessandra Barassi, MD, University of Milan, Via Di Rudini, Milan, 20142, Italy. Tel: +393923325300; Fax: +90281844027; E-mail: alessandra.barassi@unimi.it

*Conflict of Interest:* None.

## Statement of Authorship

### Category 1

#### (a) Conception and Design

Alessandra Barassi; GianVico Melzi d'Eril; Raffaele Pezzilli

#### (b) Acquisition of Data

Antonio Maria Morselli-Labate; Wanda Porreca; Guido Piediferro; Alessandra Barassi; Giovanni Colpi

#### (c) Analysis and Interpretation of Data

Guido Piediferro; Francesco Ciociola; Giovanni Colpi; Alessandra Barassi; GianVico Melzi d'Eril

### Category 2

#### (a) Drafting the Article

Alessandra Barassi; GianVico Melzi d'Eril; Wanda Porreca; Raffaele Pezzilli; Antonio Maria Morselli-Labate

#### (b) Revising It for Intellectual Content

Alessandra Barassi; GianVico Melzi d'Eril; Raffaele Pezzilli; Francesco Ciociola; Giovanni Colpi; Guido Piediferro

### Category 3

#### (a) Final Approval of the Completed Article

Alessandra Barassi; Raffaele Pezzilli; Antonio Maria Morselli-Labate; Wanda Porreca; Guido Piediferro; Francesco Ciociola; Giovanni Colpi; GianVico Melzi d'Eril

## References

- 1 NIH Consensus Conference. Impotence. NIH consensus development panel on impotence. *JAMA* 1993;270:83.
- 2 Kubin M, Wagner G, Fugi-Meyer AR. Epidemiology and erectile dysfunction. *Int J Impot Res* 2003;15:63–71.
- 3 O'Kane PD, Jackson G. Erectile dysfunction: Is there silent obstructive coronary artery disease? *Int J Clin Pract* 2001; 55:219–20.
- 4 Kendirci M, Trost L, Sikka S, Hellstrom WJ. The effect of vascular risk factors on penile vascular status in men with erectile dysfunction. *J Urol* 2007;178:2516–20.

- 5 Jeremy JY, Angelini GD, Khan M, Mikhailidis DP, Morgan RJ, Thompson CS, Bruckdorfer KR, Naseem KM. Platelets, oxidant stress and erectile dysfunction: An hypothesis. *Cardiovasc Res* 2000;46:50–4.
- 6 Feldt-Rasmussen B. Microalbuminuria, endothelial dysfunction and cardiovascular risk. *Diabetes Metab* 2000;26(Suppl 4):64–6.
- 7 Bookstein JJ, Vandeberg J, Machado T. The cavernosal acetylcholine/papaverine response. A practical in vivo method for quantification of endothelium-dependent relaxation. Rationale and experimental validation. *Invest Radiol* 1990;25:1168–74.
- 8 Billups KL. Sexual dysfunction and cardiovascular disease: Integrative concepts and strategies. *Am J Cardiol*. 2005; 26;96(12B):57M–61M. Epub 2005 Nov 15.
- 9 The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003;348:2294–303.
- 10 Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 2003;384:2285–93.
- 11 Romundstad S, Holmen J, Kvenild K, Hallan H, Ellekjaer H. Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: A 4.4-year follow-up study. The Nord-Trøndelag Health Study (HUNT), Norway. *Am J Kidney Dis* 2003;42:466–73.
- 12 American Diabetic Association. Diabetes nephropathy. *Diabetes Care* 2002;25(Suppl.):S85–9.
- 13 Radbill B, Murphy B, LeRoith D. Rationale and strategies for early detection and management of diabetic kidney disease. *Mayo Clin Proc*. 2008;83:1373–81.
- 14 Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension and diabetes. *Circulation* 2004;6:32–5. Epub 2004 Jun 21.
- 15 Gerstein HC, Mann JFE, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;286:421–6.
- 16 Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: A systematic overview of the literature. *Arch Intern Med* 1997;157:1413–8.
- 17 Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 years observational follow up study. *BMJ* 1996;313:779–84.
- 18 Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: A systematic overview of the literature. *Arch Intern Med* 1997;157:1413–8.
- 19 Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion. An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 1999;19:1992–7.
- 20 Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 2003;42:149–60.
- 21 Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989;32:219–26.
- 22 Ochodnický P, Henning RH, van Dokkum RP, de Zeeuw D. Microalbuminuria and endothelial dysfunction: Emerging targets for primary prevention of end-organ damage. *J Cardiovasc Pharmacol* 2006;47(suppl 2):S151–62.
- 23 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822–30.
- 24 Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11:319–26.
- 25 Pickard RS, Oates CP, Sethia KK, Powell PH. The role of colour duplex ultrasonography in the diagnosis of vasculogenic impotence. *Br J Urol* 1991;68:537–40.
- 26 Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. *J Am Soc Nephrol* 2002;13:1034–9.
- 27 Bookstein JJ, Vandeberg J, Machado T. The cavernosal acetylcholine/papaverine response. A practical in vivo method for quantification of endothelium-dependent relaxation. Rationale and experimental validation. *Invest Radiol* 1990; 25:1168–74.
- 28 Costa C, Virag R. The endothelial-erectile dysfunction connection: An essential update. *J Sex Med* 2009;6:2445–54.
- 29 Jeremy JY, Angelini GD, Khan M, Mikhailidis DP, Morgan RJ, Thompson CS, Bruckdorfer KR, Naseem KM. Platelets, oxidant stress and erectile dysfunction: An hypothesis. *Cardiovasc Res* 2000;46:50–4.
- 30 Feldt-Rasmussen B. Microalbuminuria, endothelial dysfunction and cardiovascular risk. *Diabetes Metab* 2000;26(suppl 4):64–6.
- 31 Solomon H, Man J, Wierzbicki AS, O'Brien T, Jackson G. Erectile dysfunction: Cardiovascular risk and the role of the cardiologist. *Int J Clin Pract* 2003;57:96–9.
- 32 Jones RWA, Rees RW, Minhas S, Ralph D, Persad RA, Jeremy JY. Oxygen free radicals and the penis. *Expert Opin Pharmacother* 2002;3:889–97.
- 33 Stehouwer CD, Henry RM, Dekker JM, Nijpels G, Heine RJ, Bouter LM. Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: Further evidence for a link between microalbuminuria and endothelial dysfunction—The Hoorn Study. *Kidney Int* 2004;92:S42–4.
- 34 Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. *J Am Soc Nephrol* 2006;17:2106–11.
- 35 Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects. *Clin Sci (Lond)* 1995; 88:629–33.
- 36 Nosadini R, Velussi M, Brocco E, Abaterusso C, Piarulli F, Morgia G, Satta A, Faedda R, Abhyankar A, Luthman H, Tonolo G. Altered transcapillary escape of albumin and microalbuminuria reflects two different pathogenetic mechanisms. *Diabetes* 2005;54:228–33.
- 37 Kaiser DR, Billups K, Mason C, Wetterling R, Lundeberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 2004;43:179–84.
- 38 Bocchio M, Desideri G, Scarpelli P, Necozone S, Properzi G, Spartera C, Francavilla F, Ferri C, Francavilla S. Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol* 2004;171:1601–4.
- 39 Araujo AB, Travison TG, Ganz P, Chiu GR, Kupelian V, Rosen RC, Hall SA, McKinlay JB. Erectile dysfunction and mortality. *J Sex Med* 2009;6:2390–404.