ELSEVIER

SEMINARS IN
NEPHROLOGY

Ultrastructural Changes of Corpora Cavernosa in Men With Erectile Dysfunction and Chronic Renal Failure

Guido Bellinghieri,* Giuseppe Santoro,† Domenico Santoro,* Bruno Lo Forti,‡ Vincenzo Savica,* Pietro Favazzi,§ Ludovico Magaudda,† and Arthur H. Cohen‖

Erectile dysfunction (ED) is a common and often distressing side effect of renal failure. Uremic men of different ages report a high variety of sexual problems, including sexual hormonal pattern alterations, reduced or loss of libido, infertility, and impotence, thereby influencing their well-being. The pathogenic mechanisms include physiologic, psychologic, and organic causes. To determine the contribution of morphologic factors to impotence we studied the ultrastructure of the corpora cavernosa in 20 patients with end-stage renal disease who were treated with chronic dialysis and compared the findings with 6 individuals with no clinical history of impotence. Our results indicated that in male uremic patients with sexual disturbances there were major changes in smooth muscle cells. This was characterized by reduction of dense bodies in the cytoplasm, thick basement membranes, and increased interstitial collagen fibers with resultant reduction of cell-to-cell contact. In addition, there was thickening and lamination of basement membranes of endothelial cells and increased accumulation of collagen between nerve fibers. These alterations were more evident in patients with longer time on dialysis and were independent of type of primary renal disease. We hypothesize that ED in dialysis patients is not related to the primary disease but to the uremic state.

KEYWORDS corpora carvernosa, smooth muscle cells, dialysis, impotence, biopsy

Erectile dysfunction (ED) has been defined as the inability to achieve or maintain an erection sufficient to allow satisfactory sexual intercourse.[1] Erection is the result of neurovascular and hormonal mechanisms and is related to the integrity of penile tissue.[2] The vascular mechanism is well understood and surgical revascularization procedures for the treatment of impotence are well established. Because 50% of the patients who undergo penile vascular surgery do not experience improvement in symptoms, it has been postulated that factors other than those of vascular origin might have an important role in the pathophysiology of impotence.[3] Indeed, in patients with vasculogenic (severe arterial and venous dysfunction) impotence, the prominent ultrastructural finding was a decrease in and deterioration of smooth muscle cells.[4]

The corpora cavernosa are a sponge-like system of irregularly shaped vascular spaces fed by afferent arteries and drained by efferent veins; they are composed of smooth muscle cells, interstitial matrix, and numerous nonmyelinated and preterminal autonomic nerves. An appropriate orientation of the smooth muscle cells with respect to blood vessels and a proper molecular association of cells and the extracellular matrix are necessary for adequate corporeal smooth muscle cell function and proper cell-to-cell and cell-to-matrix association for transfer of metabolites.

In patients with ED, there is a progressive quantitative decrease of smooth muscle that results from degenerative changes and atrophy of smooth muscle cells with gradual replacement by collagen.[5] The introduction of sildenafil for therapy of ED has completely changed the approach to evaluating these patients.[6] However, it should be appreciated that sildenafil requires structurally intact penile tissue to cause a satisfactory erection.

*Division of Nephrology.
†Department of Biomorphology.
‡Division of Surgery, University of Messina, Messina, Italy.
§Dottorato Scienze Nefrologiche, Seconda Università di Napoli, Napoli, Italy.
‖Department of Pathology, Cedars Sinai Medical Center, Los Angeles, CA.
Address reprint requests to Guido Bellinghieri, University of Messina, Division of Nephrology, Viale regina margherita, 69, Messina, I-98122, Italy.

 0270-9295/04/$-see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.semnephrol.2004.06.002

ED is common in patients with uremia; it is present in 30% of patients with chronic renal failure and in 50% of patients undergoing dialytic treatment.[8] Recent studies have documented that sildenafil is an effective and safe treatment for ED in most patients on chronic dialysis.[7-9] Consequently, we proposed a new algorithm for the evaluation and treatment of impotence.[10] ED has been related to several disturbances common in uremic patients; these include peripheral neuropathy, autonomic nervous system dysfunction, peripheral vascular disease, drug toxicity, and psychologic factors.[11,12] Although many of these problems have been investigated, the role of corpora cavernosa structure in determining abnormal function remains unclear. We hypothesize that sexual dysfunction, in patients with ED and end-stage renal disease, could be related in part to the structural changes in the corpora cavernosa; we therefore conducted an electron microscope study in men with ED on chronic hemodialysis to investigate the contribution of structural abnormalities of the corpora cavernosa.

Materials and Methods

We evaluated the prevalence of ED in a group of 180 patients treated with chronic bicarbonate dialysis 3 times weekly. This evaluation was performed using a 15-item sexual function questionnaire: the international index of erectile function.[13] The international index of erectile function represents a brief and reliable measure of erectile function. The sexual function questionnaire was self-administered to all uremic patients. Responses to the score questions of the international index of erectile function were recorded using 5-point categoric scales, with high scores indicating more favorable outcomes. The mean scores of patients with ED were significantly lower than the mean scores for healthy controls for all 15 questions (all P values $< .01$). According to the score of this test we selected 20 patients with ED, mean age 43 years old ($\pm$ 8 y), who were treated with chronic dialysis for a mean period of 6.5 years ($\pm$ 5 y). The patients had been treated unsuccessfully with sildenafil and intracavernous prostaglandin E_1. Our standard investigation included detailed sexual histories, physical examination, measurement of the biochemical and hormonal profile (prolactin, leuteinizing hormone, follicle stimulating hormone, progesterone, and testosterone), pharmacologic color Doppler ultrasound investigation of the cavernous arteries, and nocturnal penile tumescence (NPT) rigidity monitoring with the Rigi Scan Device (Dacromed, Minneapolis, MN). All these investigations were unrelated to the development of ED. The primary diseases leading to end-stage renal disease were diabetes (7 patients), hypertension (5 patients), chronic glomerulonephritis (4 patients), autosomal-dominant polycystic kidney disease (2 patients), urinary tract infection (1 patient), and chronic interstitial nephritis (1 patient).

After informed consent, fine-needle biopsy examination of the corpora cavernosa was performed. Control penile tissue was obtained from 6 individuals with a mean age of 46 years old ($\pm$7 y) who had no clinical history of ED, diabetes, hypertension, renal dysfunction, or any surgical intervention (Nesbit procedure) for correction of congenital or acquired penile curvature.

The standard biopsy technique included superficial anesthesia by infiltrating the skin of the penis with 1 mL of lidocaine 2%. The needle (tru-cut type) G21 was introduced through the albuginea in the right cavernous body and pulled proximally. A specimen of 1.5 $\times$ 12 mm was obtained. Biopsy specimens were processed for transmission electron microscopy; fixation was in 4% glutaraldehyde in phosphate buffer 0.2 mol/L, pH 7.4, at 4°C for 3 hours. After rinsing in buffer, the tissue was postfixed in 1% OsO4 in 0.2 mol/L phosphate buffer with a pH level of 7.2 to 7.4, dehydrated in graded alcohol and acetone, and flat embedded in Durcupan. Ultrathin sections were cut on a LKB Ultratome V (LKB, Washington, DC) and stained with uranyl acetate and lead citrate.

Results

In the control group, the smooth muscle cells of the corpora cavernosa had normally distributed intracellular filaments, dense bodies, peripherally located vesicles, and were surrounded by intact basal lamina of normal thickness. The basement membrane of capillaries were thin and single layered (Fig 1A). In contrast, capillaries from patients with ED showed basement membranes considerably thickened and with multiple layers (Fig 1B). Moreover, there were decreased numbers of smooth muscle cells with an increase in intervening connective tissue, predominantly collagen. Basement membranes surrounding these cells were greatly and uniformly thickened (Fig 2). The sarcoplasma had reduced electron-opaque contractile myofilaments and lacked dense bodies; there was a marked decrease in or absence of glycogen. The cytoplasm contained numerous vacuoles. Abundant collagen fibrils interposed between the smooth muscle cells were orientated randomly. The increase in the interstitial component resulted in a marked decrease in cell-to-cell contacts. The diabetic patients showed the most pronounced basement membrane changes in vessels; they were characterized by greatly thickened and multilayered basement membranes of capillaries. Patients of different ages showed almost similar changes, but in a subgroup of patients with a longer time on dialysis we observed a greater degree of damage in all tissue elements of the corpora cavernosa.

Discussion

Human corpora cavernosa are constituted by abundant smooth muscle cells embedded in a collagenous extracellular matrix with a rich blood supply and relatively sparse neuronal components. The corporeal extracellular matrix consists mainly of an abundance of type I and type IV collagen, with a lesser amount of type III as well as laminin; type I and type III collagen are characteristic of the interstitial connective tissue, whereas type IV collagen and laminin are components of the basal lamina of basement membrane.[14]

Erection and detumescence of human corpora cavernosa are hemodynamic events regulated by alternating relaxation

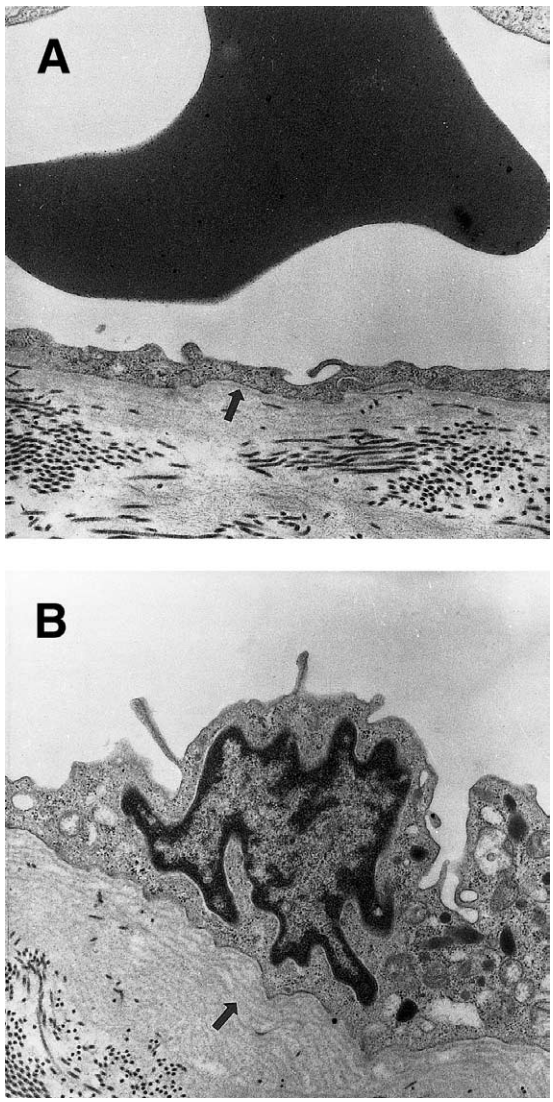

Figure 1 (A) Normal capillary. The basement membrane is thin and single layered (arrow) (magnification, ×12,500). (B) Capillary from patient with ED. The basement membrane is thickened considerably and has multiple layers (arrow) (magnification, ×11,500).

and contraction of the smooth muscle cells and to the alternate dilatation and contraction of the penile arteries.[2] It has been suggested that the smooth muscle cell relaxation is determined by decreased adrenergic tone together with increased release of cholinergic and/or nonadrenergic/noncholinergic neurotransmitters, neuromodulators, or hormones. On the other hand, detumescence is achieved by the opposite events: contraction of the corporeal smooth muscle cells, decrease in arterial blood flow, and return of normal venous outflow.[15] To achieve adequate corporeal smooth muscle cell function and proper cell-to-cell and cell-to-matrix association for transfer of metabolites, appropriate orientation of the smooth muscle cells with respect to blood vessels and proper molecular association of cells and the extracellular matrix are necessary. Alterations of any of these components may lead to ED.

Ultrastructural studies previously have documented that different behavioral (smoking, alcoholism) and/or medical conditions (hypertension, diabetes, and so forth) produce similar degenerative tissue responses.[5] Investigators assessing amount of muscle, presence of myofilaments, lipid droplets, pseudovacuoles, mitochondrial aggregation, external lamina thickening, and cell-to-cell separation by collagen did not observe any consistent changes that could be related to a single or specific cause of impotence. Similarly, in another study performed on 29 impotent patients it was not possible to determine the relationship between the ultrastructural appearances and the causes of impotence.[16]

It has been suggested that smooth muscle cells and other structural components of the erectile tissue such as collagen and elastin can be injured by renal failure–associated hypoxia.[17] Indeed, we previously had observed subjective and objective improvements in sexual function during recombinant human erythropoietin therapy.[18] We postulated that correction of anemia, through an improvement of hypoxia, increase of blood viscosity, and general well-being, would improve sexual function.

Many investigators believe that primary ED represents abnormal smooth muscle function rather than a consequence of collagen content or distribution.[4,19] Our findings of abnormal smooth muscle cell morphology including increased density of cytoplasmic inclusions, decreased filaments, and decreased dense bodies indicate that these cells would be incapable of the relaxing-contractile process and are in agreement with the previously mentioned observation.[4,19] We also documented thickening of the basement membranes of smooth muscle cells with resultant separation of these cells by increased collagen, features that lead to a decrease in the cell-to-cell contact, an important component of the process leading to ED.

The value of a small biopsy examination in establishing the pathologic process has been discussed previously in the literature. Some investigators observed that the degree of the pathology is not site-dependent, whereas others described differences between right and left corpora cavernosa.[5,19,20]

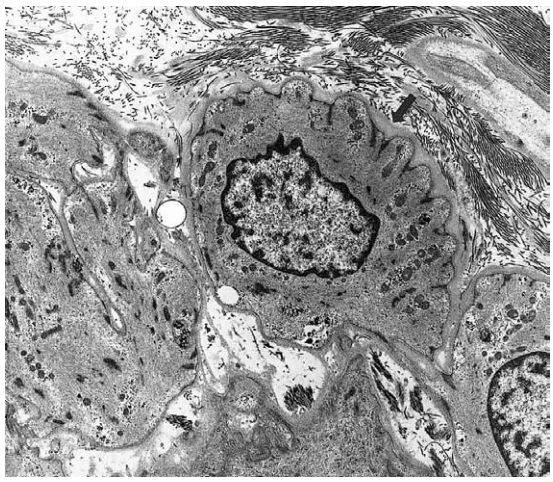

Figure 2 Portion of artery. The smooth muscle cells are surrounded by very thick basement membranes (arrow) (magnification, ×6,750).

Wespes et al,[21] analyzing the percentage of smooth muscle cells in biopsy specimens taken at different sites of corpora cavernosa, affirmed that vascular impotence is a diffuse penile disease and that quantification of these cells at any site can be used to select patients for vascular reconstructive surgery.

Our patients represent a select group of uremic subjects affected by ED, despite the primary process leading to uremia. The diabetic group also may have changes consequent to major larger vessel damage, although the abnormalities that we observed in all groups were the same. This suggests to us that impotence in uremic patients is not related to the primary process but to some manifestation of the uremic states. Further studies on uremic patients or animal models will perhaps assist us to understand better the effects of uremia on the corpora cavernosa, to establish the value of intracorporeal biopsy examination in selecting treatment for impotent patients, and, possibly, how to prevent or symptomatically treat these changes.

Acknowledgment

The authors are grateful to Kai Chien for technical assistance.

References

1. NIH Consensus Development Panel on Impotence: Impotence. JAMA 270:83-90, 1993
2. Wagner G, Tejeda S: Update on male erectile dysfunction. BMJ 316: 678-82, 1998
3. Levine FJ, Goldstein I: Vascular reconstruction surgery in the management of erectile dysfunction. Int J Impot Res 2:59-64, 1990
4. Karademiz T, Topsakal M, Ayodogmus A, et al: Correlation of ultrastructural alterations in cavernous tissue with the clinical diagnosis vasculogenic impotence. Urol Int 57:58-61, 1996
5. Mesdorf A, Goldsmith PC, Diederchs W, et al: Ultrastructural changes in impotent penile tissue. A comparison of 65 patients. J Urol 145:749-58, 1991
6. Goldstein I, Lue TF, Padma-Nathan H, et al, for the Sildenafil Study Group: Oral Sildenafil in the treatment of erectile dysfunction. N Engl J Med 338:1397-404, 1998
7. Punzo G, Maggi S, Ponzio R, et al: Use of sildenafil in the chronic uremic patient. Minerva Urol Nefrol 53:39-43, 2001
8. Chen J, Mabjeesh NJ, Greenstein A, et al: Clinical efficacy of sildenafil in patients on chronic dialysis. J Urol 165:819-21, 2001
9. Rosas SE, Wasserstein A, Kobrin S, et al: Preliminary observations of sildenafil treatment for erectile dysfunction in dialysis patients. Am J Kidney Dis 37:134-7, 2001
10. Bellinghieri G, Santoro D, Lo Forti B, et al: Erectile dysfunction (Ed) in uremic dialysis patients: Diagnostic evaluation in the Sildenafil era. Am J Kidney Dis 38:S115-7, 2001
11. Massry SG, Bellinghieri G, Savica V, et al: Sexual dysfunction in Massry and Glassock's Textbook of Nephrology (ed 4, chap 74, part 6). Philadelphia: Lippincott Williams and Wilkins, 2001, pp 1371-1376
12. Palmer BF: Sexual dysfunction in uremia. J Am Soc Nephrol 10:1381-8, 1999
13. Rosen R, Riley A, Wagner G, et al: The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology 49:822-30, 1997
14. Raviv G, Kiss R, Vanegas JP, et al: Objective measurement of the different collagen types in the corpus cavernosum of potent and impotent men: an immunohistochemical staining with computerized-image analysis. World J Urol 15:50-5, 1997
15. Bosh RJLH, Bernard F, Aboseif SR, et al: Penile detumescence: Characterization of three phases. J Urol 146:867-71, 1991
16. Liu LC, Huang CH, Huang YL, et al: Ultrastructural features of penile tissue in impotent men. Br J Urol 72:635-42, 1993
17. Kaufman JM, Hatzichristolou DG, Mulhall JP, et al: Impotence and chronic renal failure: A study of the hemodynamic pathophysiology. J Urol 151:612-8, 1994
18. Bellinghieri G, Santoro D, Savica V: Eritropoietina e funzione sessuale. Haematologica 84:30-5, 1999
19. Jevtich MJ, Khawand NY, Vidic B: Clinical significance of ultrastructural findings in the corpora cavernosa of normal and impotent men. J Urol 143:289-93, 1990
20. Meuleman EJH, Ten Cate LN, De Wilde PCM, et al: The use of penile biopsies in the detection of end-organ disease: A histomorphometric study of the human cavernous body. Int J Impot Res 2:161-5, 1990
21. Wespes E, Moreira De Goes P, Schulman C: Vascular impotence: Focal or diffuse penile disease. J Urol 148:1435-6, 1992