Comparative analysis of the penis corpora cavernosa in controls and patients with erectile dysfunction

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OBJECTIVE

To evaluate the presence of structural disorders of the corpora cavernosa in patients with erectile dysfunction (ED), as despite new drugs being effective in many men with ED, some aspects of structural disorders of the corpora cavernosa remain unknown.

MATERIALS AND METHODS

Biopsy specimens were taken from the corpora cavernosa of seven patients (mean age 57.8 years, range 51–72) with severe ED who had a penile prosthesis implanted. The controls tissues were fragments of corpora cavernosa obtained from autopsies of six men (mean age 52.3 years, range 40–66) who died from causes unrelated to the urogenital system. For light microscopy, the specimens were processed routinely to paraffin wax, and by immunohistochemistry to evaluate elastic fibres, and by Masson's trichrome to analyse collagen and smooth muscle fibres. Stereological methods were used to quantitatively evaluate the different elements (as a percentage).

RESULTS

The percentages of the different elements in the human penis of controls and men with ED, respectively, were: elastic fibres 13.2% and 9.1%; collagen fibres 40.8% and 41.6%; and smooth muscle, 40.4% and 42%.

CONCLUSIONS

In patients with ED there was a statistically significant reduction in the percentage of elastic fibres, but no statistically significant difference in collagen and smooth muscle fibres, and no appreciable differences in collagen distribution between the groups.

KEYWORDS

penile erection, corpora cavernosa, corpus spongiosum, extracellular matrix, erectile dysfunction, quantitative evaluation

INTRODUCTION

Erectile dysfunction (ED) is estimated to affect >150 million men worldwide. Erection involves the coordination of three haemodynamic events; increased arterial inflow, sinusoidal smooth muscle relaxation and decreased venous outflow. Erection also involves the interaction of brain, nerves, neurotransmitters, and smooth and striated muscles. The effect of ageing on erectile function and the cause of age-related ED are also unknown. Alterations in any of the components noted above may affect the functional response of the penile tissues and would cause ED. An understanding of the different morphological components of the penis might improve basic scientific knowledge of the disease processes and provide a background for rational therapy [1].

Penile erection is related to the integrity of penile tissue. The mechanism of penile erection includes haemodynamic and complex physiological process. Besides the well-known vascular problems, other alterations could play a significant role in ED [2,3]. Penile tissue is composed of smooth muscle cells resting on collagen and elastic system fibres. The corpus cavernosum is the main structure involved in erection and is composed of smooth-muscle fibres, interstitial matrix, blood vessels, vascular lamina and numerous unmyelinated and pre-terminal autonomic nerves. The main interstitial matrix components are collagen and elastic system fibres. They must allow for elongation and increase in rigidity during erection, while providing adequate resilience to return rapidly to the relaxed flaccid state after detumescence [4–6].

The role played by smooth muscle cells is to maintain the erection by increasing the intracavernosal pressure during erection, which could not achieved by vascular mechanisms alone. The smooth muscle cells, as the main contractile-relaxing component of the corpora cavernosa, has numerous intracytoplasmic contractile filaments and dense bodies that serve as anchoring sites for the filaments. Indeed, to reach penile tumescence and maintain rigidity, an adequate percentage of smooth muscle cells is required [7,8].

The composition and organization of the corpora cavernosal structures are thought to have a key role in the mechanism of erection. Indeed, ED has been associated with qualitative and quantitative changes in these structures as a consequence of ageing, pathological conditions and social habits [9]. In the present study we characterized and quantified the different structural components of the corpora cavernosa in controls and patients with ED, focusing on smooth muscle cells, collagen and elastic fibres.

MATERIALS AND METHODS

Biopsies of the corpora cavernosa were collected from seven patients (mean age 57.8 years, range 51–72) with severe ED of any cause who had a penile prosthesis implanted. The controls comprised fragments of corpora cavernosa obtained from autopsies of six men (mean age 52.3 years, range 40–66) with no clinical manifestation of ED, and died from causes unrelated to the urogenital system. The time elapsed between death and fixation of the material was <12 h. The local committee on human research approved the study.

FIG. 1. *Photomicrographs of the corpus cavernosum:* **a**, *in the control group; and* **b**, *in the ED group; note the collagen fibres (blue) and smooth muscle (red). Masson's trichrome, ×200.*
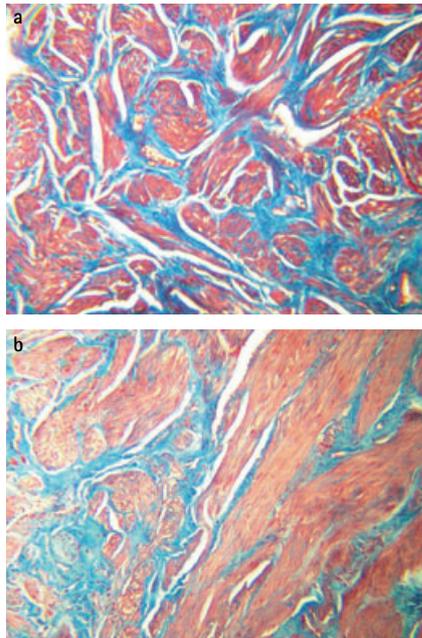

FIG. 2. *Photomicrographs of corpus cavernous in:* **a**, *the control group; and* **b**, *the ED group. Note the elastic fibres. Anti-human elastin antibody, ×200*
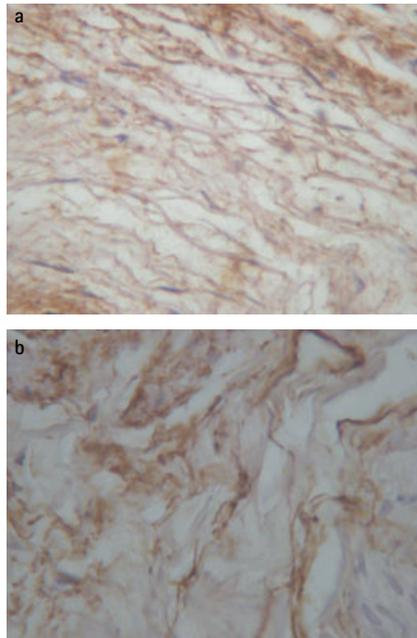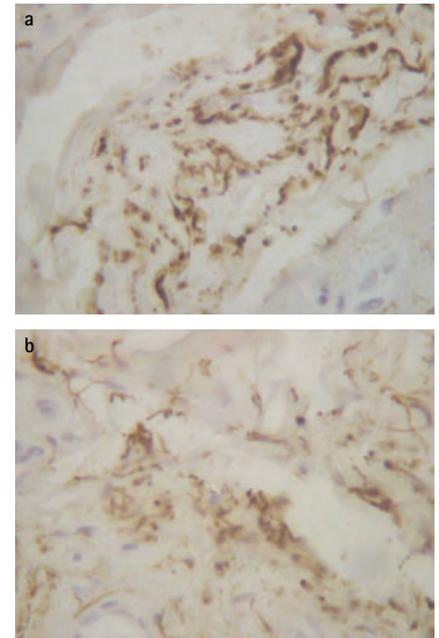

FIG. 3. *Photomicrographs of corpus cavernous in:* **a**, *the control group; and* **b**, *the ED group. Anti-fibrilin antibody, ×200.*

For light microscopy, the specimens were fixed in formalin 10% (pH 7.2), processed according to routine histological methods, and embedded in paraffin wax. From the paraffin-embedded samples, 5-μm thick sections were initially stained with haematoxylin and eosin and were examined by a pathologist to exclude samples with artefacts. Masson's trichrome technique was used to detect collagen and muscle fibres. The elastic fibres were detected using immunohistochemistry.

From each penis, two samples were excised from the corpora cavernosa and from every sample we selected five different sections. From every section, five random fields were evaluated, therefore analysing 25 test areas of each section. For the stereological analysis, the 5-μm thick sections were stained by Masson's trichrome to show collagen fibres (stained blue), promoting a sharp contrast with smooth muscle fibres (stained red). The elastic system fibres were detected by immunolabelling with anti-serum monoclonal antibody for anti-elastin and anti-fibrilin. The analysed fields were digitized with a final magnification of ×400 using a video camera (DXC 151-A model, Sony Corp, Japan) coupled to a light microscope.

Distributions were quantified using a test grid system on the digitized fields in the screen of a colour monitor. According to stereological principles, in isotropic tissue, the area distribution of a given structure, as determined on a two-dimensional section of the structure, is proportional to the volume distribution of this structure. The volume density of the histological components was calculated as $Vv = Pp/Pt$, where Vv is the volume density, p is the tissue component under consideration, Pp is the number of test points associated with p, and Pt the number of points of the test system. The stereological methods were described in detail elsewhere [5,10].

RESULTS

Masson's trichrome showed that the corpora cavernosa were arranged into trabeculae composed of collagen fibres intertwined with smooth muscle, blood vessels and nerves, and separated by endothelial-lined cavernosal spaces (Fig. 1). There were similar amounts of collagen and smooth muscle in the tissues, and there were no appreciable differences in collagen distribution and architecture. The immunohistochemistry for elastin and fibrilin

TABLE 1 *Stereological analysis of the different elements of corpora cavernosa in men. Values are mean (SD)*

Stain for:	Controls, %	ED, %
Collagen	40.7 (4.6)	41.5 (4.1)
Smooth muscle	40.4 (3.6)	41.9 (5.7)
Elastic fibres	12.8 (3.3)	7.9 (1.5)

(Fig. 2 and Fig. 3) showed a significant decrease of the elastic system fibres in patients with ED. The stereological analysis of the different components of the corpora cavernosa of the penis is shown in Table 1.

DISCUSSION

Penile erection is a complex neurovascular process whereby corpora cavernosa connective tissue, elastic system fibres and smooth muscle cells can be affected by poorly organized, overgrowth or decrease of one or all of these elements, resulting in trabecular stiffness and, eventually, alteration in the mechanical properties of erectile tissue. It is well known that in elderly men there are

changes, as in other organs, in the cellular and extracellular components of the penis [11,12].

In the present study we attempted to minimize the effects of ageing on the statistical evaluation by choosing a control group of similar age to those with ED. There were no significant differences between controls and men with ED in collagen and muscle fibres. According to Luangkhot *et al.* [13], a quantitative analysis of erectile tissue showed no correlation between collagen content and erectile failure. The present results are in accord with Jevtich *et al.* [14] who reported no statistically significant difference between controls and ED in smooth muscle cell content.

According to Iacono *et al.* [15], a lower concentration of elastic fibres in the tunica albuginea and in penile corpora cavernosa was detected in patients with ED caused by several factors. In the present study there was also a statistically lower concentration of elastic fibres in the penile corpora cavernosa in men with ED, which could lead to a loss of elastic capacity. According to Sattar *et al.* [16] the elastic fibres are important in achieving firmness of the corpora cavernosa during erection. Any loss could make the penis less resistant to dilatation during erection, with a consequent pressure decrease and thus ED. However, the disposition of these fibres remains the same, i.e. more numerous in the corpus spongiosum and around blood vessels of the corpora cavernosa [16,17]. These observations suggest that changes in elastic fibres might be one of the important factors in developing ED. Changes in the content of these fibres may alter the relaxation properties of cavernosal tissue and would play a role in the pathophysiology of ED.

In addition, in conditions associated with reduced functions of nerves and endothelium, e.g. ageing, hypertension, smoking, hypercholesterolaemia and diabetes, circulatory and structural changes in the penile tissues can result in arterial insufficiency and defective muscle relaxation [18]. Despite new drugs being effective for some types of ED, the answer to all changes involving ED remain unknown. Elucidating the structure and function of the different components of the penis is an essential step in answering many questions about erectile pathophysiology and eventually could be help to resolve some forms of ED.

CONFLICT OF INTEREST

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Abbreviations: **ED**, erectile dysfunction.