Prostatic epithelial and luminal area in the transition zone acini: morphometric analysis in normal and hyperplastic human prostate

M.A. BABINSKI, M.A. CHAGAS, W.S. COSTA and F.J. SAMPAIO

Urogenital Research Unit, State University of Rio de Janeiro (UERJ), and Sections of Histology and Anatomy, Fluminense Federal University (UFF), Rio de Janeiro, Brazil

Accepted for publication 8 May 2003

OBJECTIVE

To analyse quantitatively the acini and changes in the acinar epithelium and lumen in the transitional zone of normal and hyperplastic human prostates.

PATIENTS AND METHODS

Tissue samples of the transitional zone were taken from prostates with benign prostatic hyperplasia (BPH) obtained from 20 patients with clinical symptoms of bladder outlet obstruction who underwent open prostatectomy. The control tissue comprised 20 transitional zones of prostates obtained during autopsy of adults aged <30 years (killed in accidents). The following variables were measured; the number of acini, total acinar area, area of the lumen, epithelial area, and the median (range) epithelial height, using computerized histomorphometric techniques.

RESULTS

The total area of the acini and the luminal area was statistically significantly greater in BPH. In normal and hyperplastic prostates, respectively, the total mean (SD) area (mm^2) of the acini was 0.041 (0.007) and 0.056 (0.016), of the lumen was 0.016 (0.003) and 0.036 (0.013), and of the epithelium was 0.025 (0.004) and 0.019 (0.003) (all $P < 0.001$). There was no statistically significant difference in the number of acini between controls and BPH. The area and the height of the acinar epithelium was statistically significantly greater in BPH; for epithelial height (μm) in normal and BPH tissue, respectively the minimum height was 9.92 (1.67) and 6.45 (1.14), the maximum 54.38 (4.09) and 41.52 (4.51) and the median 27.89 (2.48) and 19.96 (2.20) (all $P < 0.001$).

CONCLUSIONS

There was no significant difference in the number of acini between control and BPH tissue, but the area and the height of the acinar epithelium was significantly lower in BPH.

KEYWORDS

prostate, BPH, morphometry, acini, epithelium

INTRODUCTION

The histological architecture of the human prostate is organized into two main components, the fibromuscular stroma and the glandular or epithelial component [1]. BPH is a hyperplastic process involving these components, which leads to major changes in prostatic organization [2], resulting in the formation of nodules, which in >70% of cases are in the transition zone and compress the periurethral glands [3]. BPH is strongly associated with ageing, as histological evidence of BPH is present in ≈90% of men aged >80 years and is rare in men aged <50 years [4,5]. Recently there has been increasing interest in minimally invasive therapies for BPH, the target of these therapies being the different histological prostatic elements [1,6]. Further knowledge of these elements and the changes in BPH might contribute to understanding the genesis of this pathological condition, and help to choose better therapies, among the several alternatives available [1].

Histomorphometry provides numerical objective data on the histological architecture and changes in structure [7]. There are few reports of the use of histomorphometric methods for analysing the different histological components in the human prostate [8–12]. Also, these studies compare BPH and prostate carcinoma [13], or different samples of BPH [8,10,14], or even BPH and fetal prostate [15].

Currently there is still controversy about the main elements involved in prostate enlargement, i.e. whether there is an epithelial origin (ducts or acini) [2,16,17], or a proliferation of stromal elements, the last being a more accepted view [18,19]. Our recent stereological analysis [19] corroborated the findings of others [5,11,18,20] of a significant stromal increase in BPH. Nevertheless, to date there are few quantitative studies of the changes in the glandular components in BPH [5,8,12,17]. Thus the present study aimed to determine and quantify changes in the acini of the hyperplastic prostate and compare it with the transitional zone acini of control tissues.

PATIENTS AND METHODS

Samples of prostatic tissue from the transition zone of prostates with BPH were collected from 20 men (mean age 73 years, range 63–79) who had not been previously treated for symptomatic BPH, and who underwent open prostatectomy (retropubic or transvesical). All patients presented symptoms of BOO and the analysis of surgical specimens confirmed the diagnosis of BPH with no focus of prostatic carcinoma.

© 2003 BJU INTERNATIONAL | 92, 592–596 | doi:10.1046/j.1464-410X.2003.04433.x

Variable	Control	BPH	P
Mean (SD):			
Acini/prostate	183.9 (47.9)	215.1 (60.1)	0.115
Acini/mm^2	3.9 (0.9)	4.5 (1.1)	0.082
Acinar area, mm^2			
total	0.041 (0.007)	0.056 (0.016)	< 0.001
luminal	0.016 (0.003)	0.036 (0.013)	< 0.001
epithelium	0.025 (0.004)	0.019 (0.003)	< 0.001
Epithelial height, μm			
median	27.89 (2.48)	19.96 (2.20)	< 0.001
minimum	9.92 (1.67)	6.45 (1.14)	< 0.001
maximum	54.38 (4.09)	41.52 (4.51)	< 0.001

TABLE 1
The number of acini evaluated per mm^2 in each prostate, in the transition zone of the control and BPH samples, and the epithelial height

The control samples comprised the transition zone of 20 prostates obtained from autopsies of young men (mean age 24 years, range 18–30) who died from causes unrelated to the urogenital system. To be sure that only the transitional zone was analysed, one fragment was taken from each side, close to the angle of the proximal urethra (verumontanum), as described previously [3] and elsewhere [12,19]. The time elapsed between death and the fixation of the prostate was <6 h. The local committee on human research approved the study.

The prostatic tissue was obtained following the anatomical orientation proposed by McNeal [3]. The fragments were then analysed morphometrically by isotropic and random orthogonal triplet probe sections ('orthrip method') [21], which consists of making the material uniformly isotropic by dividing the fragment three times consecutively; the first section is random, the second is orthogonal to the first and the third orthogonal to the second. This allows random sections to be obtained that are uniformly isotropic [7,21]. The material was fixed in Bouin's solution, processed using routine histological methods, paraffin-embedded and sectioned at 5 μm. The samples were stained with haematoxylin and eosin (H&E), and examined by a pathologist to detect any focus of carcinoma and exclude inadequate samples with inflammation or cellular changes which could affect the results.

From each prostate five samples were randomly excised from the transition zone and from each sample five different sections were cut. The sections were then stained using Gomori trichrome and H&E. From each section, all acini of five different random fields were analysed and quantified, totalling 25 test areas in each prostate and 500 fields in each group (controls and BPH). The analysed images were obtained with at ×40 using a video camera coupled to a light microscope. The images were converted to digital signals and transferred to a computer, where software was used (Image Pro-plus, Media Cybernetics, USA) to delineate the basal and luminal limits of the epithelium, providing data on epithelial height and area (Fig. 1A–C). The morphometric features assessed were the delineation of the luminal surface of the acini, providing the total area of the lumen, and of the basal limit of the acini, providing the total acinar area From these two measurements the software was used to estimate the total area of the epithelium and the median (range) epithelial height.

The data were analysed using the Kolmogorov-Smirnov test to verify a normal distribution and groups compared using Student's *t*-test, with $P < 0.05$ considered to indicate statistically significant differences.

RESULTS

In the transition zone of the control group the acinar epithelium was composed of cuboid epithelial cells with a basal layer and a columnar apical layer. The epithelium projected inside the acinar lumen, with a papillary aspect (Fig. 1D). In the BPH group the epithelium was reduced to low cuboid cells which did not project inside the lumen; the epithelial height was less and consequently the luminal area was greater and had a cystic aspect (Fig. 1E). In the BPH group there were numerous eosinophilic granule (at the apex of the columnar cells) projecting inside the acinar lumen and condensed as prostatic concretions (corpora amylacea).

In all, 3743 acinar units were measured (morphometrically) in the control and 4317 in the BPH group (8060 acinar units in total), giving a mean number of acini evaluated in each prostate of 184 and 215, respectively; the mean number of acini per mm_2 between the groups was not significantly different (Table 1). The morphometric results of the acinar total, luminal and epithelial area in both groups are shown in Table 1, with the median (range) epithelial heights; the minimum, maximum and median epithelial height was 35%, 24% and 28% less in the BPH samples than in the controls.

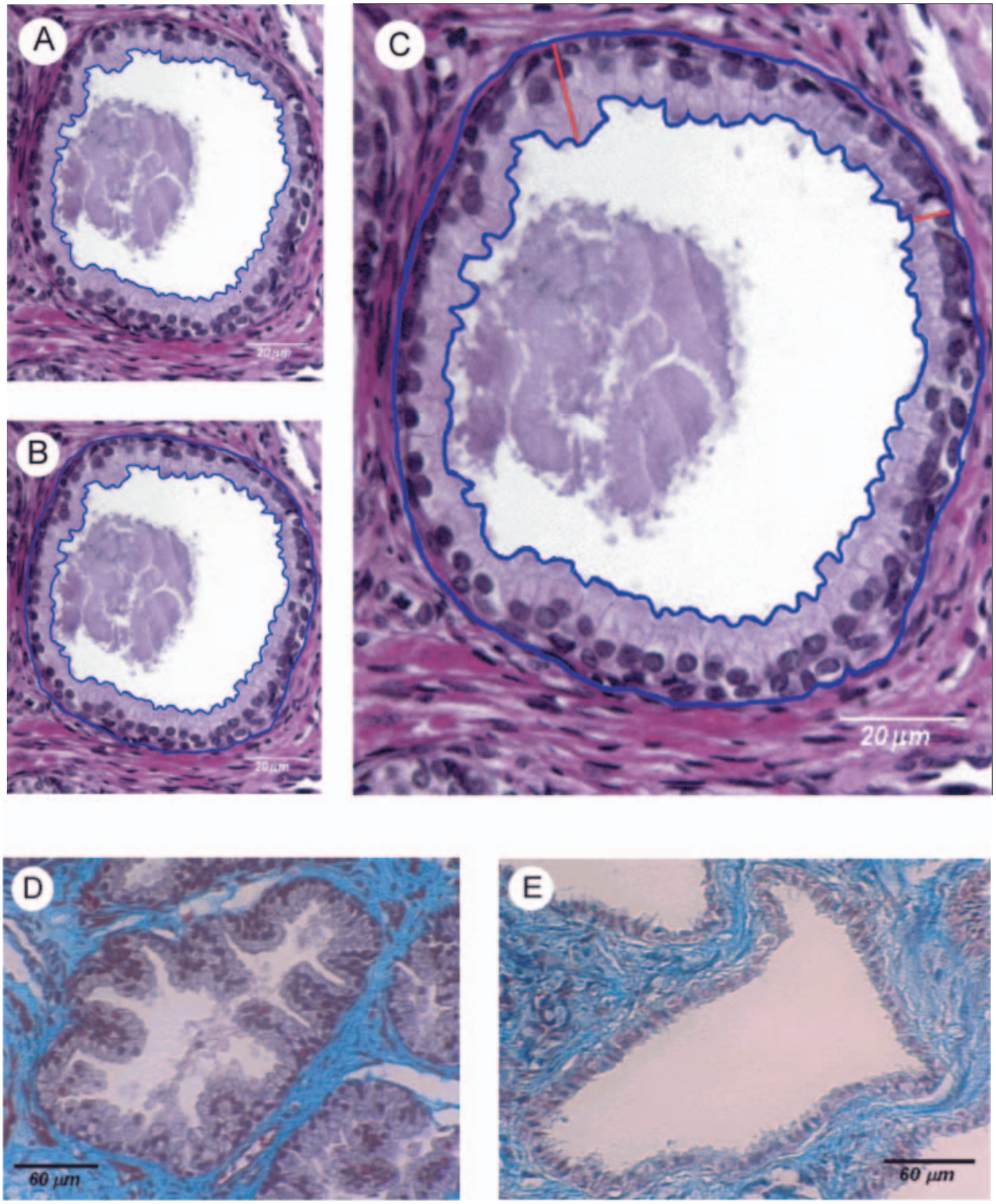
DISCUSSION

According to the 'orthrip method' for sectioning the samples, the prostate is cut into three or more sequential sections [21], ensuring that they are random sections and uniformly isotropic for the histomorphometry of the acini. The use of a semiautomatic histomorphometric method with software support was useful in previous analyses of prostatic stroma and epithelium [12,19], and for evaluating the prostatic acini in the present study. The specimens were evaluated by bi-dimensional measurements (surface area) of all acinar units of the glandular prostatic component, in random histological fields from the transition zone.

Some of the changes in BPH are caused by ageing, but a comparison with prostates of young adults with no BPH might be useful for establishing the pattern of histomorphometric changes in BPH. In the present study we did not consider weight variations in BPH samples or in the total prostate. All patients providing samples had undergone open prostatectomy, which is indicated at our institution only for prostates of > 40 g.

Some previous qualitative and quantitative studies of BPH did not consider that the prostate is a histologically heterogeneous organ [5,18] and compared prostatic regions that have distinct morphological characteristics; this probably explains the variability in previously published data. The present analysis refers only to the transition zone. Although quantitative data previously published agree that the stroma is the major component involved in BPH [8,11,14,19], studies focusing on stromal growth did not refer to simultaneous or secondary changes in the number and form of the hyperplastic acini

*FIG. 1. Photomicrographs of: prostatic acini (**A–E**, all H&E × 400) showing the different steps of the computerized image analysis; **A,** The acinar luminal surface was delineated (blue line), providing the total area of the lumen; **B,** The basal limit of the acini was delineated (second blue line), providing the epithelial area and the total acinar area; **C,** The maximum and minimum epithelial heights were measured (red lines); **D,** prostatic acini from the control group, showing the irregular aspect of the acini with papillae and folds projecting inside the lumen (Gomori trichrome, ×200); **E,** prostatic acini from the BPH group showing the cystic dilatation and a decrease in the epithelial height (Gomori trichrome, × 200).*



[8,11,14,19]. Few studies have assessed the glandular component [9,12,16,17,22], although in some there were comparisons between the epithelial and prostatic volume [9,17], and between the epithelial volume and pharmacological response [8,17,22].

Despite the morphological changes in the epithelial component in BPH being well known [1,3,6,23,24] data on the transition zone of normal prostates are scant [12,19]. Shapiro *et al.* [5] quantitatively analysed the glandular component in normal prostates, but the precise regional orientation of the prostatic tissues was unknown, as the specimens were obtained from pathological records.

The present findings showed a significant decrease (24%) in the acinar epithelial area in BPH, and in epithelial height (Table 1). These data appear to confirm that in BPH there are simultaneous changes in the stromal and glandular components [12,16,25]. In our previous report [12], in eight patients with BPH there was a significant decrease in epithelial height, findings confirmed by the present study.

The present results (Table 1) did not refer specifically to the number of acinar units of the glandular component, which was not statistically significant between the groups and supports the possibility that the formation of new acini, if any, is minimal and occurs as consequence of BPH and/or ageing.

There was an increase of 125% in the area of the lumen in BPH; this increase is the result of a decrease in the epithelial area and a simultaneous increase in the total acinar volume. The luminal changes in BPH may be related to ductal obstruction secondary to enlargement of the hyperplastic nodules, which determines the secretory stasis and congestion. Consequently the area and height of the acinar epithelium was significantly greater in BPH. These variations are apparent in acinar BPH as cystic alterations secondary to obstruction [23].

The decrease in epithelial area, with the cells becoming cuboid or even flattened in some acini, may be related to compression and may progress to significant atrophy of the glandular component [23]. The presence of prostatic concretions (corpora amylacea; Fig. 1C) is probably a consequence of congestion and secretory stasis [24]. These concretions are present in most hyperplastic acini [6,23,24]. The cellular profile in the hyperplastic acini is similar to a regressive or atrophic process, and could lead to a condition of BPH with atrophy [6]. These data correspond with the obstructive symptoms and the age of the patients studied.

In conclusion, there was no statistically significant difference in the total number of acini between control and BPH tissues, suggesting no evidence for the formation of new acini. Nevertheless, the total area of the acini and the area of the lumen was significantly greater in BPH tissue.

ACKNOWLEDGEMENTS

This work was supported by Grants from the National Council of Scientific and Technological Development (CNPq-Brazil), and from the Foundation for Research Support of Rio de Janeiro (FAPERJ)

REFERENCES

1 **Cadeddu JA, Pearson JD, Lee BR *et al.*** Relationship between changes in prostate-specific antigen and the percent of prostatic epithelium in men with benign prostatic hyperplasia. *Urology* 1995; **45**: 795–800
2 **Price H, McNeal JE, Stamey TA.** Evolving patterns of tissue composition in benign prostate hyperplasia as a function of specimen size. *Hum Pathol* 1990; **21**: 578–85
3 **McNeal JE.** Prostate. In Sterenberg SS ed. *Histology for Pathologists*, 2nd edn. Chapt 42. Philadelphia: Lippincott-Raven Publishers, 1997: 997–1017
4 **Walden PD, Leftkwitz GK, Ficazzola M *et al.*** Identification of genes associated with stromal hyperplasia and glandular atrophy of the prostate by mRNA differential display. *Exp Cell Res* 1998; **245**: 19–26
5 **Shapiro E, Hartanto V, Perlman EJ *et al.*** Morphometric analysis of pediatric and nonhyperplastic prostate glands: evidence that BPH is not a unique stromal process. *Prostate* 1997; **33**: 177–82
6 **Iczowsky KA, Bostwick DG.** Prostate biopsy interpretation. Current concepts 1999. *Urol Clin North Am* 1999; **26**: 435–52
7 **Gundersen HJG, Bendtsen TF, Korbo L *et al.*** Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. *APMIS* 1988; **96**: 379–94
8 **Marks LS, Treiger B, Dorey FJ *et al.*** Morphometry of the prostate. I. Distribution of tissue components in hyperplastic glands. *Urology* 1994; **44**: 486–92
9 **Schuster GA, Schuster TG.** The relative amount of epithelium, muscle, connective tissue and lumen in prostatic hyperplasia as a function of the mass of tissue resected. *J Urol* 1999; **161**: 1168–73
10 **Ichiyanagi O, Sasagawa I, Ishigooka M *et al.*** Morphometric analysis of symptomatic benign prostatic hyperplasia with and without bladder outlet obstruction. *Urol Res* 2000; **28**: 29–32
11 **Deering RE, Choongkittaworn M, Bigler SA *et al.*** Morphometric quantitation of stroma in human benign prostatic hyperplasia. *Urology* 1994; **44**: 64–70
12 **Babinski MA, Chagas MA, Luz HP, Pereira MJ, Costa WS, Sampaio FJB.** Quantitative morphological changes in the prostate epithelium of patients with benign prostatic hyperplasia. *Braz J Urol* 2001; **27**: 348–52
13 **Nakada T, Kubota Y.** Connective tissue protein in the prostate gland. *Int Urol Nephrol* 1994; **26**: 183–7
14 **Shapiro E, Becich MJ, Hartanto V *et al.*** The relative proportion of stromal and epithelial hyperplasia is related to the development of symptomatic benign prostate hyperplasia. *J Urol* 1992; **147**: 1293–7
15 **Bierhoff E, Walljasper U, Hofmann D *et al.*** Morphological analogies of fetal prostate stroma and stromal nodules in BPH. *Prostate* 1997; **31**: 234–40
16 **McNeal JE.** Origin and evolution of benign prostatic enlargement. *Invest Urol* 1978; **15**: 340–5
17 **Eri LM, Svindland A.** Can prostate epithelial content predict response to hormonal treatment of patients with benign prostatic hyperplasia? *Urology* 2000; **56**: 261–6
18 **Barstch G, Muller HR, Oberholzer M *et al.*** Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. *J Urol* 1979; **122**: 487–91
19 **Chagas MA, Babinski MA, Costa WS, Sampaio FJB.** Stromal and acinar components of the transition zone in normal and hyperplastic human prostate. *BJU Int* 2002; **89**: 699–702
20 **Ishigooka M, Hayami S, Hashimoto T**

et al. The relative and total volume of histological components in benign prostatic hyperplasia: relationships between histological components and clinical findings. *Prostate* 1996; **29**: 77–82

21 **Mattfeldt T, Mobius HJ, Mall G.** Orthogonal triplet probes: an efficient method for unbiased estimation of length and surface of objects with unknown orientation in space. *J Microsc* 1985; **139**: 279–89

22 **Lepor H, Wang B, Shapiro E.** Relationship between prostatic epithelial volume and serum prostate specific antigen levels. *Urology* 1994; **44**: 199–205

23 **Narayan P, Pateli M, Rice L *et al.*** Histopathology of benign prostatic hyperplasia. In Narayan P ed. *Benign Prostatic Hyperplasia.* London: Churchill Livingstone, 2000: 19–22

24 **Cohen RJ, McNeal JE, Redmond SI *et al.*** Luminal contents of benign and malignant prostatic glands: Correspondence altered secretory mechanisms. *Hum Pathol* 2000; **31**: 94–100

25 **Aumüller G.** Morphologic and regulatory aspects of prostatic function. *Anat Embryol* 1989; **179**: 519–31

Correspondence: F.J. Sampaio, Urogenital Research Unit, UERJ, Avenue 28 de Setembro, 87 – fundos – FCM – térreo, Rio de Janeiro, RJ, 20551–030, Brazil.
e-mail: sampaio@uerj.br

Abbreviation: **H&E**, haematoxylin and eosin.