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COMPARATIVE ANALYSIS OF THE RESULTS OF MORPHOLOGICAL EXAMINATION OF HYPERPLASTIC PROSTATE TISSUE IN PATIENTS WITH AND WITHOUT TESTOSTERONE DEFICIENCY

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Introduction. Benign prostatic hyperplasia (BPH) is an important and urgent public health problem. Prostatic hyperplasia is characterized by epithelial, stromal, and muscular proliferation.
Objective. To conduct a comparative analysis of the results of morphological examination of resected prostate tissue in patients with prostatic hyperplasia with and without testosterone deficiency.
Materials and methods. The results of morphological examination of the resected prostate tissue of 188 men with BPH were analyzed, who were divided into two groups: Group I – 71 patients with testosterone deficiency, group II (control) – 117 patients with testosterone levels above 12.1 nmol/L.
Results. In patients with testosterone deficiency, during morphological examination of resected pancreatic tissue samples, prostate hyperplasia had a diffuse stromal character, combined with cystic deformity of the acinuses, with flattened and unclassifying epithelium, against the background of basal cell hyperplasia. In patients with normal Tc levels during morphological examination, during morphological examination of resected pancreatic tissue samples, the hyperplasia in all patients was glandular (epithelial), and the epithelial cells of the acinuses were tall cylindrical, with signs of active secretion.
Conclusion. In hypogonadal men, stromal hyperplasia was detected in most cases (76.1%) in the resected prostate tissue, and in normogonadal patients, hyperplasia was glandular in all cases.

K e y w o r d s: prostate hyperplasia, proliferation, testosterone deficiency, hypogonadism

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Introduction. Benign prostatic hyperplasia (BPH) is an important and relevant healthcare problem [1–3]. According to most definitions, BPH is an age-associated, progressive chronic condition characterized by an increase in prostate volume due to the proliferation of its glandular and/or stromal components and clinically manifested in most cases by lower urinary tract symptoms (LUTS) [1, 4, 5].

BPH may present with epithelial (consisting mainly of prostate epithelial cells), stromal (consisting exclusively of stromal cells), or muscular proliferation (containing smooth-muscle elements). Pure muscular hyperplasia is extremely rare and is usually observed as part of a mixed pattern containing stromal, epithelial, and muscular cells. In any morphological variant of BPH, the dominant compartment is either epithelial or stromal hyperplasia [6, 7].

During male development, androgens stimulate the differentiation and proliferation of epithelial, muscular, and stromal components of the prostate [8].

The predominance of a particular tissue compartment in the prostate or in hyperplastic prostate tissue depends on multiple factors, including serum total testosterone (TT) levels and the presence of chronic persistent inflammatory or infectious processes, among others [9–11].

Normal interactions between the epithelial and fibromuscular–stromal components of the transition zone tissue vary depending on the serum TT level, leading to a decrease in the epithelium-to-stroma ratio and, consequently, to remodeling of micronodules. This remodeling determines the pattern of BPH growth and the development of associated LUTS [12]. An especially interesting area of research is the evaluation of the type of BPH in hypogonadal versus eugonadal men, which is the focus of the present study.

Aim. To perform a comparative analysis of the morphological characteristics of resected prostate tissue in patients with BPH depending on TT level (low vs. normal)

Materials and methods. We analyzed resected prostate tissue from 188 men with BPH, divided into Group I (71 patients with testosterone deficiency) and Group II (control, 117 patients with serum testosterone levels >12.1 nmol/L).

The study was carried put using specimens obtained during transurethral resection of the prostate (TURP). The initial fixation of prostate tissue was performed in buffered 10% formalin solution (HistoSafe®, BioVitrum LLC, St. Petersburg, Russia) for 24 hours. Tissue processing was carried out automatically in an open-type tissue processor (LEICA ASP 300S) using "Isoprep Plus" dehydrating reagent (BioVitrum LLC, St. Petersburg, Russia), followed by embedding in homogenized paraffin medium "Histomix" (BioVitrum LLC, St. Petersburg, Russia).

From the paraffin blocks prepared using the standard protocol on the modular embedding station MPS/P2 (BioVitrum), 5-μm paraffin sections were obtained with a semi-automatic rotary microtome CUT 5062 (BioVitrum).

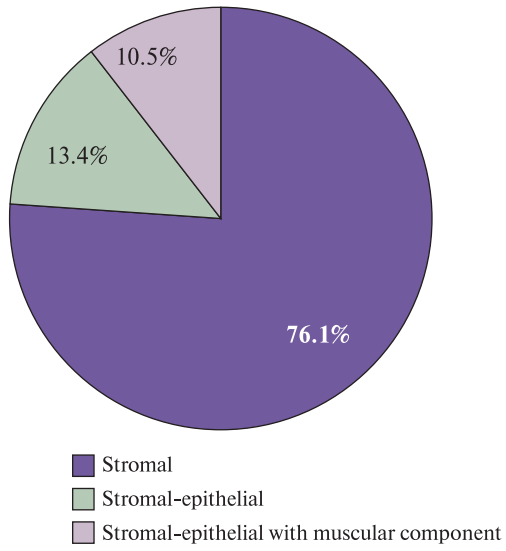


Figure 1. Type of benign prostate hyperplasia in patients of Group I.

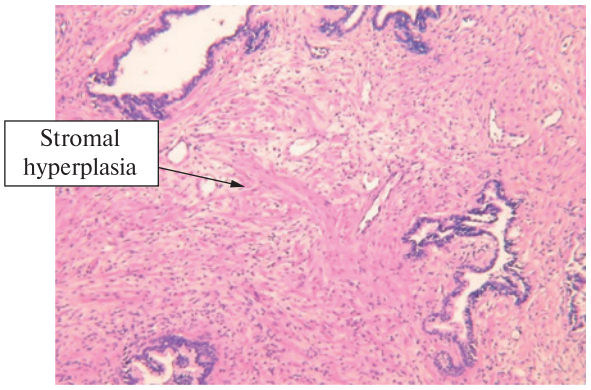


Figure 2. Benign prostate hyperplasia with predominance of the stromal component. Hematoxylin and eosin staining. Magnification ×100. (Group I)

The sections were stained with hematoxylin and eosin (H&E) in automatic mode using the Autostainer XL (ST5010, Leica).

The stained histological slides were mounted under coverslips using "Vitrogel" mounting medium (BioVitrum LLC, St. Petersburg, Russia). Microscopic examination and microphotography were performed using a Nikon Eclipse Ci light microscope (eyepiece ×10; objectives ×5, ×10, ×20, ×40, ×100) equipped with a Nikon DS-Ri2 digital color camera.

A detailed assessment of the glandular and stromal components of the prostate was carried out. The areas of glands and interstitial tissue were measured using the "VideoTest 4.0. Morphology" software (St. Petersburg). The area of each microscopic field at ×400 magnification (objective ×40, eyepiece ×10) was 96,238 μm2.

Morphological analysis included detailed evaluation of the type of hyperplasia (proliferation), as well as the features of epithelial cells (atrophy, secretory activity).

The results were processed using Microsoft Excel (Microsoft Office 2007). Statistical analysis was performed with STATISTICA 6.1 (StatSoft Inc., USA).

The study was carried out as part of a dissertation ("Characteristics of benign prostatic hyperplasia and its management in testosterone deficiency") approved by the Local Independent Ethics Committee of Rostov State Medical University, Ministry of Health of Russia (No. 16/21, dated October 21, 2021). The study received no external funding.

Results. In the assessment of morphological findings in resected prostate tissue from patients in Group I, most cases (76.1%) demonstrated diffuse stromal hyperplasia, whereas stromal hyperplasia combined with glandular or muscular proliferation was observed less frequently (*Fig. 1*).

In all cases, the stromal component was pronounced and represented by fibrous connective tissue with hypertrophied smooth-muscle fibers in combination with a dominant fibrotic process in the prostate. Disruption of the normal lobular architecture was evident (*Fig. 2*).

Notably, avascular zones were identified within areas of sclerosis. This contributes to the development and progression of prostatic ischemia and further activation of fibrosis. In addition, sclerotic changes and single smooth-muscle elements, disturbances in vascular architecture were observed, while the connective-tissue pseudocapsule responsible for the nodular pattern of the gland was poorly developed (*Fig. 3*).

Stromal hyperplasia was also characterized by a marked distortion of the normal lobular structure and the presence of avascular ischemic areas. Cystically deformed and dilated acinar structures with epithelial atrophy predominated (*Fig. 4*).

In all cases, acinar epithelium was atrophic and flattened. All patients demonstrated lobular distortion and cystic transformation of acini. The internal surface of the glands was usually smooth, without pronounced folding or secretory activity. Moreover, in 57 patients (85.1%), the glandular lumen was widened due to cystic dilatation, and the inner surface remained smooth; thick, dense fibrous septa with reduced microcirculation were observed between glands.

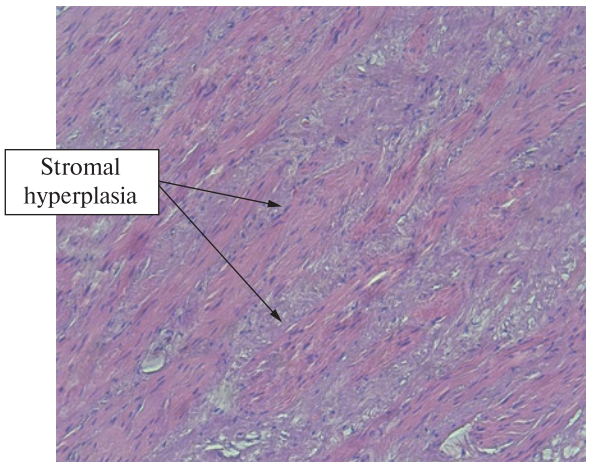


Figure 3. Stromal hyperplasia of the prostate. Marked fibrosis. Absence of vascular structures. Hematoxylin and eosin staining. Magnification ×100. (Group I)

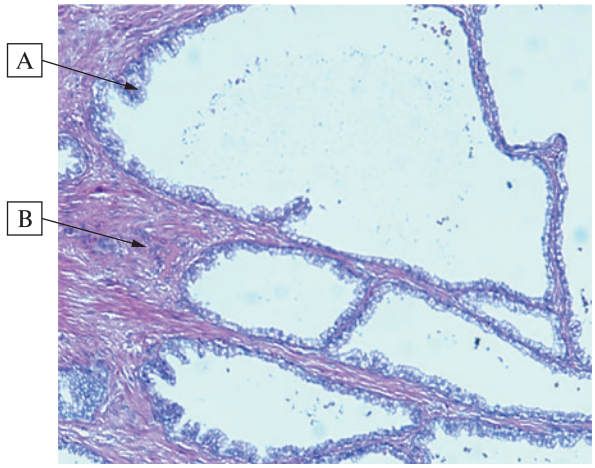


Figure 4. Histological pattern of benign prostate hyperplasia (Group I). Acinar epithelium is atrophic (A). Stromal component is prominent (B). No glandular proliferation. Single smooth-muscle elements. Hematoxylin and eosin staining. Magnification ×100. (Group I)

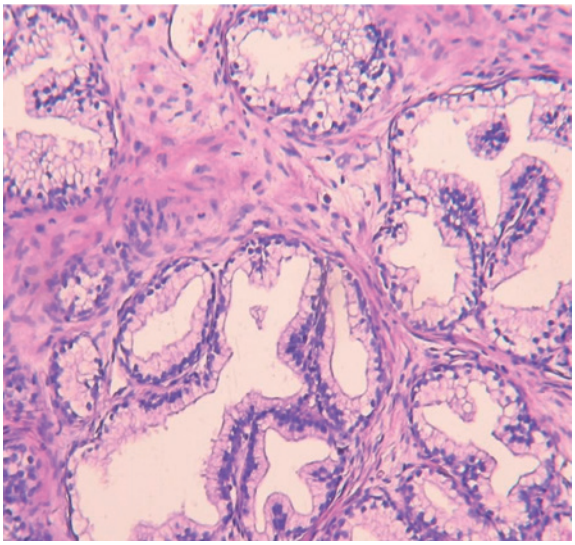


Figure 5. Histological pattern of glandular prostate hyperplasia (Group II). Marked hyperplasia of acinar structures (A); pronounced glandular component (B). Secretory epithelial cells are tall. Hematoxylin and eosin staining. Magnification ×200. (Group II)

In Group II, all patients (100%) demonstrated glandular-type hyperplasia, while the stromal component accounted for only a small proportion (*Fig. 5*). The proliferative activity of the glandular component varied. The most intensive proliferation was observed in acinar cells of mucous glands, whereas moderate proliferation occurred in acinar cells of transitional (submucosal) glands, and the lowest proliferative activity was found in acinar cells of the main glands. In all cases, stromal component fixation was minimal. In 62 patients (92.5%), the acinar structures, predominantly of medium diameter, were located closely adjacent to each other. Signs of cystic degeneration were minimal. The internal glandular surface demonstrated folding due to numerous finger-like epithelial projections (*Fig. 6*).

The stroma appeared as thin fibrous strands. Stromal elements were organized, sparse, and compacted. The myofibrillar stromal framework, normally characteristic of prostate tissue, was transformed together with other stromal structures into coarse, loose fibrous connective tissue, while smooth-muscle cells were almost absent. Serial sectioning revealed well-defined radial proliferative foci resembling proliferative centers. Around some nodules of

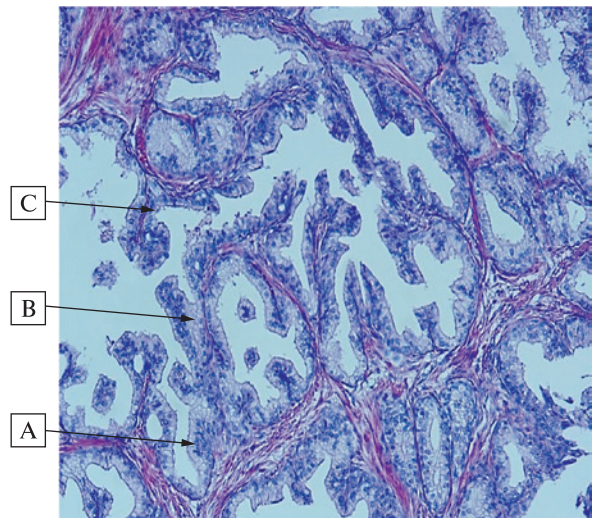


Figure 6. Histological pattern of benign prostate hyperplasia (Group II). Marked hyperplasia of acinar structures (A), glandular component (B) predominates over the stromal component. Stromal elements are scarce. Secretory epithelial cells are tall (C). Hematoxylin and eosin staining. Magnification ×400. (Group II)

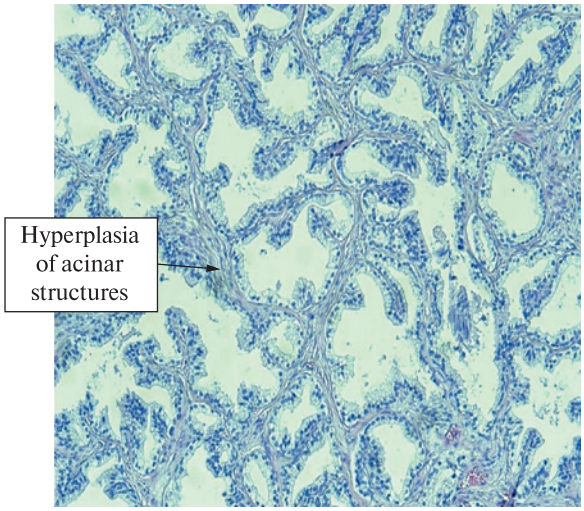


Figure 7. Histological features of benign prostate hyperplasia in patients of Group II. Glandular hyperplasia. Hyperplasia of acinar structures and glandular component. Tall secretory epithelial cells. Hematoxylin and eosin staining. Magnification ×100. (Group II)

hyperplastic tissue, a connective-tissue pseudocapsule was formed, closely associated with the fibrous scaffold of the glandular prostate architecture (*Fig. 7*).

Discussion. Androgens, particularly testosterone derivatives, play a central and determinative role in the normal anatomical and functional development of the prostate. The primary mechanism of androgen action is mediated by the androgen receptor, which is a transcription factor predominantly localized in luminal epithelial cells, almost absent in basal cells, and present in lower concentrations within certain stromal cells of the prostate [6, 13].

It is believed that normal interactions between epithelial and stromal components of the transition zone change with age or decreasing serum TT levels, leading to a reduced epithelium-to-stroma ratio. This shift determines the morphological architecture of the prostate and subsequently influences the pattern of BPH growth [13–15]. In hypogonadal men, stromal elements may initially predominate, and during pathological proliferation they determine both the pattern of hyperplasia and the severity of clinical symptoms [12].

In our study, morphological examination of resected prostate tissue in patients with testosterone deficiency revealed diffuse stromal hyperplasia with cystic deformation of acini, flattened non-secretory epithelial cells, and basal-cell hyperplasia. In contrast, patients with normal TT levels demonstrated exclusively glandular (epithelial) hyperplasia, characterized by tall cylindrical acinar epithelial cells with signs of active secretion.

Conclusion. Significant differences in the morphological structure of hyperplastic prostate tissue were identified depending on TT levels. In hypogonadal men, stromal hyperplasia was found in most cases (76.1%), whereas in eugonadal patients, hyperplasia was glandular in all specimens.

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