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REVIEW ARTICLE



Benign prostatic hyperplasia - etiology, clinical features and management. Historical and contemporary aspects

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ABSTRACT

Introduction. Benign prostatic hyperplasia and chronic prostatitis are the most common conditions in men, the frequency of which varies with age. Chronic prostatitis (infectious or inflammatory) has a frequency of 8-35% in patients aged 20-50 years, reaching a maximum of 60-70% in those aged over 50 years.

Materials and methods. Materials for the study served the medical literature regarding benign prostatic hyperplasia and chronic inflammation, published in the local and international scientific journals. Scientific databases like *Cochrane Library, Medline, Scopus, Medicus, NCBI, PubMed, Google Scholar* were used to find the necessary articles. Research methods – analysis, synthesis, systematization, and description.

Results. After analyzing the available data, a review of the literature was conducted which highlighted both the strong and weak points of the historical medical approaches to addressing benign prostatic hyperplasia, as well as the ontogenetics and anatomical characteristics of the prostate gland. This included examining the incidence rates, concepts of causation and development, principles of diagnosis and classification of benign prostatic hyperplasia. The review also revealed the pros and cons of using mini-invasive treatment strategies versus traditional transvesical approaches in treating this condition, as well as the ongoing and significant socioeconomic impact in underdeveloped countries.

Conclusions. There remains the issue of reducing intra- and post-operative complications after benign prostatic hyperplasia surgery, especially a voluminous one, which imposes itself as a very critical problem in the development of an effective treatment strategy. For the first time, a problem was described by assessing the particularities of some biochemical criteria at local surgical site and in blood serum, histological - at the level of nodular prostatic hyperplasia and at the border of the surgical site. This requires a complex correlational study to assess the biochemical, histological and immunohistochemical parameters, including the evaluation of the associations or coexistence of benign prostatic hyperplasia and chronic prostatitis.

Keywords: urology, benign prostatic hyperplasia, prostatitis, etiology, morphogenesis, treatment, advantages and disadvantages.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

In order to develop an effective medical and surgical approach for reducing the risk of complications during and after the removal of a large benign prostate gland growth, known as nodular hyperplasia, it is crucial to have a thorough understanding.

The research hypothesis

There is needed an effective treatment approach that can decrease

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postoperative complications and improve monitoring of general hemostasis and inflammation at the surgical site.

The novelty added by manuscript to the already published scientific literature

A systematic study of the specialized literature was carried out, in order to highlight the etiological, clinical and diagnostic features and the impact to obtain an effective hemostasis after enucleation of benign prostate nodular hyperplasia and define criteria for local surgical site monitoring in reducing the postoperative complications. Due to limited data, there is a need for a comprehensive examination using biochemical, histological, and immunohistochemical methods. This includes evaluating the potential relationship or simultaneous occurrence of both benign prostatic hyperplasia and chronic prostatitis.

Introduction

The prostate is a small gland with an anatomically important role and is part of the male reproductive system. Various changes in the prostate cause serious problems with the lower urinary tract. Among the most common prostate pathologies that induce micturition disorders, has an impact on the quality of life, starts from the working age, but with a major impact in old age, are benign prostatic hyperplasia (BPH), chronic prostatitis (PCr) and prostate carcinoma (CP). However, the most important is BPH [1-4].

Benign prostatic hyperplasia and chronic prostatitis are the most common conditions in men, the frequency of which varies with age. Chronic prostatitis (infectious or inflammatory) has a frequency of 8-35% in patients aged 20-50 years, reaching a maximum of 60-70% in those aged over 50 years. BPH has a significant frequency after the age of 50-60 years with a maximum of 76.3-81.4% in the elderly population (75-90 years) [3, 5]. In the last 2-3 decades, BPH became a modern problem due to affecting younger population (35-40 years), being placed fourth after arteriosclerosis, hypertension and diabetes, having a significant social-economic impact, the etiology being still enigmatic and questionable [3, 6-8].

In the literature there are various opinions on the etiology of BPH, which are determined by the totality of the diseases characteristic of this organ (atrophy, inflammation, hyperplasia and neoplasia) which are contradictory despite the fact that they have the same pathogenetic substrate [1, 9-11].

Advances in diagnostic technologies, pharmacological and surgical treatment in recent years have greatly contributed to the optimization of diagnosis and treatment by mini-invasive surgical resolution of obstructive syndrome in BPH [6, 12, 13]. However, the individualized approach to treatment allows to achieve the optimal result of treatment and improve postoperative quality of life [4, 12, 14]. The optimization of treatment in BPH and the reduction of the intraoperative and postoperative complication risks remains open, being an ongoing problem, which requires further research.

The purpose of the study is to review and analyze medical literature on the aspects of etiology, clinical picture, diagnosis, treatment, and social-economic impact of BPH, in order to determine the optimal tactics and the risks of intra- and postoperative complications especially in voluminous BPH.

Materials and methods

Materials for the study served the medical literature of various lengths – monographic, scientific, randomized, and non-randomized clinical trials, reports of clinical cases and case series, national and international guidelines about BPH and chronic prostatitis published in the national and international journals. The articles were searched using the following databases – *Cochrane Library*, *Medline*, *Scopus*, *Medicus*, *NCBI*, *PubMed*, *Google Scholar*. In parallel, a literature search was performed to identify meta-analysis, randomized controlled trial and reviews articles related to „benign prostate hyperplasia“, „prostatitis“, „etiology“, „morphogenesis“, „adenomatous hyperplasia“, „adenomectomy“ in the PubMed, MEDLINE, ISI Web of Science, Cochrane databases. There were selected only the most relevant and recent articles. Research methods - analysis, synthesis, systematization, and description.

Ninety-one primary sources that were relevant were chosen based on their impact score, and the selection criteria included a scientific, reproducible, and transparent approach to the subject under discussion, as well as subsequent data extraction and analysis. To ensure varied conclusions, the research findings from foreign studies were supplemented by published research data from the Republic of Moldova. A narrative synthesis of the data was performed as part of the qualitative research process.

Results and discussions

As a result of the literature analysis, there were selected 91 articles scientifically important. Based on the analyzed data, the synthesis of literature revealed the aspects of historical, medical approaches to the problem of BPH, ontogenetic and topographical aspects of the prostate; incidence

and concepts of etiology and morphogenesis, diagnosis and classification principles of BPH, and especially on advantages and disadvantages of different treatment strategies in BPH, from classical to mini-invasive methods as well as the socio-economic impact of BPH.

Historical approaches to benign prostatic hyperplasia. BPH, a term widely used in recent decades, is a benign hypertrophic-hyperplastic benign pathological formation, known in the past as „prostatic hypertrophy”, „adenomatous hyperplasia”, „chronic lobular prostatitis”, „benign nodular hypertrophy”, „adenoma of the paraurethral glands” and/or „prostate adeno-fibro-leiomyomatous”. For the first time, Goldberg V. (1960) introduced the term of prostate adenoma, and the surgery to treat the nodular tumor – adenectomy, a notion successfully used until the last decade [7, 15, 16]. Based on the fact that prostate adenoma implies both, BPH and a nodular hypertrophic-hyperplastic process, the Consensus Conference on Benign Prostate Hyperplasia (Monaco, 1995) established the final term to be BPH [17].

Over decades, research has been carried out to determine the etiology and pathological processes that induce hyperplasia of the prostate, invoking various factors, such as: pelvic venous stasis, aging, atherosclerosis and vascular atheromatosis, hormonal theory (androgens, estrogens), oxidoreductase, hormonal disbalance – mediated hormonal feedback etc. [18]. The role of infection and chronic inflammation as a predictive factor of hypertrophy in the prostate was proposed by Tsekhanovskii G. (1901). Later Vertkin I. (1931) provided results that proved the infectious-inflammatory role as controversial and proved that inflammation is a consequence of nodular hyperplasia (cited by Aivazean A, 1957) [19]. However, McNeal (1968) reported a 44% incidence of prostate inflammation in BPH based on autopsy findings in older men, while the role of chronic inflammation has been supported by many other researchers in the following decades [20, 21]. However, the infectious-inflammatory role as a predictive factor as well as the cause of prostate inflammation has remained a subject of heated debate for a significant period [22].

Over decades, the hormonal theory has been reinforced as an important etiological factor in the evolution of BPH. The theory was described by exposed by Dunaevskii L. (1935), Topchanov A. (1949) and many others (quoted by Aivazean A, 1957). Dunaevskii L. marks the role of testicular hyperfunction in prostatic hypertrophy, associated with advanced age, which induces hyperplasia of the periurethral glands with the formation of nodular hyperplasia [19]. Peterman N. (1939) states that in prostatic hypertrophy the prostatic parenchyma evolves to hyperplasia and adenomatosis, and it is impossible to distinguish the origin of the periurethral glands from the prostate glands, while the remaining tissue after adenectomy is nothing but the residual peripheral area of the prostate [23].

Another important issue of BPH from a historical perspective is about the treatment, conservative and surgical. The first stage includes the use of various bimanual methods, therapeutic procedures that declined with the emer-

gence in the 20th century of α -adrenergic antagonists, the 5-alpha reductase inhibitor, phytotherapeutic preparations, which are recognized as one of the most effective therapeutic treatments and relieve the symptoms of the lower urinary tract (LUTS) [24-26].

Surgical prostatectomy was first introduced by Eugene Fuller (1895) according to some sources. Fuller’s approach was associated with a considerable mortality rate of approximately 18%, and as a result, it faced several objections. Later, the technique was improved and adopted in 1900 by Peter Freyer, who despite a 5% mortality rate had a great success [27, 28].

A remarkable advance in BPH surgery is considered the elaboration of the technique of retropubic extravasal “prostatectomy” conceived by Terrence Milin (1945), which achieved significant reduction of mortality [29]. In this context, Aivazean A. (1957), mentions the significance of radical adenectomy in BPH introduced by Russian surgeons: Podrez F. (1887) – adenectomy by suprapubic approach, Druzhinin M. (1889) – by perineal approach, Fedorov S. (1899) performed transvesical scraping of the prostate, Kholtsev B. (1906) – two-step adenectomy by transvesical approach, Lidinskii A. (1922) – by extravasical retropubic approach [19].

The beginning of a true revolution in the surgical treatment of BPH is considered the first transurethral resection surgery performed by Maximilian Stern and Joseph McCarthy (1932) using a wire loop under visual control, this being an instrument developed by the authors that later became the precursor of the current resectoscopy – TURP (transurethral resection of the prostate) [29].

Also, BPH surgery in recent decades has benefited from mini invasive surgical techniques such as: transurethral vaporization – TUVP being an alternative to TURP/TUIP; Laser enucleation: Nd:YAG, KTP:YAG, with diode, Holmium: YAG; HoLEP; Cryosurgery - bipolar electrocoagulation, intermittent coagulation resection, rotoresection. A dynamic evaluation study 5 years after the application of HoLEP and open transvesical prostatectomy established a promising evolution with the need for follow-up surgeries at a low rate [4, 30-32]. However, for prostates with nodules larger than 80-100 g, TURP had a rate of re-surgery rate of 55% and mortality rates of 6% [33, 34]. In this context, Novikov I, et al. (2001), Shakhmachev V. (2010) emphasize that mini-invasive treatment is promising, but still requires confirmation in large clinical trials, because the remaining tissue fragments after coagulation not always can be easily handled, and urinary infections or secondary interventions in connection with complications, as well as some in the result of long-term hospitalizations have made these methods less preferable [35].

Ontogenetic aspects, topographic and zonal anatomy of the prostate. Morphologically, the prostate consists of a glandular and fibro-muscular component, surrounded by a capsule. Prostate growth manifestations occur throughout life, much faster in the puberty period. At the age of 15-16 years, the division into acinar or alveolar structures with ep-

ithelial-papilliform cellular projections takes place, with the formation of glandular prostatic parenchyma and opening of the ducts [36]. Structural differentiation of the prostate is considered when the glandular epithelium manifests secretory characteristics, with basal, neuroendocrine cells and immunoreactivity maximum values of secretion reaching at 20-21 years. With the differentiation and organization of the prostate parenchyma occurs the maturation of glandular secretory cells. During this period, the secretory cells become mature expressing the secretory form of both the acid phosphatase isoenzyme (ALK-P) and the prostate-specific antigen (PAS) [37, 38].

From the puberty period, the prostate enlarges 10 times in volume, reaching maximum functionality at the age of 30-45 years, and then gradually atrophies. From the age of 45-60 years, atrophy of glandular tissue occurs. With age, both atrophy and prostatic hyperplasia can occur, which can be correlated with the androgenic hormonal status, otherwise nodular hyperplasia of the prostate (BPH) can occur, with significant frequencies at the age of 61-75 years [39].

From an anatomical-topographic point of view with improvement of imaging techniques and regarding surgical topography, 4 surfaces of the prostate have been described – anterior, posterior and two inferior-lateral, a base projected upwards to the bottom of the urocyt and a lower-facing apex, which has a fibro-muscular casing that externally envelops the prostate through the sphincter of the urethra, and inside it, urethra is surrounded by the urocytic sphincter. Outside the external sphincter, we can distinguish the periprostatic capsule, which originates from the visceral pelvic fascia, while in the inside the fibro-muscular layer can be identified. The fibro-muscular layer is a real capsule of the prostate. Towards the centripetal prostatic parenchyma from the internal surface of the fibro-muscular capsule are divided septa that compete in a central area being crossed by the ejaculatory ducts and the prostate utricle, the urethra being located anterior [20, 39].

The anatomical-functional features of the prostate are also dependent on the anatomy of the neuro-vascular system, the architectonic-functional being stacked in the plexus: related and efferent, superficial (at the capsule level) and profound (septa, glandular-muscular structures). Arterial blood originates from the lower urocytic arteries (*a. visceralis inferior*), the middle rectal arteries (*a. rectalis media*) and internal pudendal arteries [40].

Of significant importance for the surgical diagnostic and interventional orientation are the knowledge of the anatomical-topographic landmarks of the prostate based on the studies carried out by McNeal J. (1968-1978) and Sampaio F. (1992) which divided the prostate into areas. Anatomically quantifying with clinical importance 4 distinct areas at the level of the prostate: frontal, peripheral, central and transition area [20, 41]. Of the most important in the clinical-diagnostic and surgical perspective is the peripheral and transition area.

According to some biopsy studies, the transition zone in 70% is the site of BPH and only in about 10-20% of ma-

lignant neoplasms. In hyperplastic processes, including in BPH, the central and partially peripheral areas are considerably compressed, becoming a thin layer with the appearance of a surgical pseudocapsule after enucleation of nodules in BPH [42, 43]. However, the central area, which includes about 20% of the prostate volume, is less susceptible to inflammatory processes and can be the site of about 5% to 10% of accidentally detected malignant tumors. This area may play an important role in the development of BPH [36, 44].

The zonal division of prostate has a valuable practical and predictive importance due to the knowledge of the risk of preferential distribution and the prostate structural contribution in the evolution of specific lesions such as prostatitis, BPH, and prostate carcinomatous neoplasia [36, 43].

The incidence and concepts of etiology and morphogenesis of BPH. Equal prevalence of BPH between European and African countries is noted in the literature. However, if talking about disease progression, authors Handisuriya A., et al. (2001) noticed a more severe course of BPH in the African population. The incidence of statistical prostate adenoma also varies from country to country due to both the lack of data as well as overlap of clinical picture with other nodular processes such as fibroid – 11.3%, myoma – 0.3%, fibromiomyoma – 1.2% [45, 46].

The etiology of BPH at the current stage remains incompletely elucidated and contradictory. Such an opinion is also determined by the totality of diseases characteristic of this organ such as infections, inflammation, hyperplasia, and neoplasia that often counter or have the same etiopathogenetic factors [10, 11].

Currently, the following etiopathogenetic factors of BPH are old age, excesses or sexual abstinence, liver cirrhosis, but also some life-style habits such as smoking, alcoholism, obesity, hyperglycemia and diabetes. The key role according to most experts is hormonal disorders (androgens and estrogens) associated with aging [47].

The effect of androgens in BPH is mediated by cellular interaction, based on androgen receptors (ARs) by stimulating stromal and epithelial cell growth with intensified epithelial-mesenchymal transition [48]. According to Nickel J. (2008), the primary role in the evolution of BPH is due to estrogens more than due to androgens, which would explain the incidence of nodular hyperplasia in the transitional area on the one hand and on the other hand by converting testosterone into estrogen under the action of aromatase [49]. According to studies by Peehl D., et al. (1998) and Coppe J. (2010) in 50% of men who underwent adenectomy up to the age of 60 years old and in 9% after 60 years old, genetics has a predictive role [50, 51].

An important role is given to oxidative stress. The role of free radicals such as RLO, OPL, and SAO in the pathogenic mechanisms of prostate adenoma evolution has been described. The evolution of prostate adenoma may be an alternative pathway of prostate carcinogenesis due to disorders of prostate growth promoted by oxidative stress and inflammatory mediators [52]. Majority of experts state that

aging, significant imbalance of the free radicals, infections and inflammation are recognized as predictive factors of BPH and prostate cancer [11].

Therefore, it is worth mentioning that androgens, estrogens, disorders of epithelial-cellular interactions, growth factors, neuroreceptors and infections can play a pathogenetic role in prostatic tissue hyperplastic processes and induce the formation of a chronic heterogeneous prostatitis underlying BPH morphogenesis [53].

BPH morphogenesis evolves through two main stages. The first stage is the proliferative process of fibromuscular stroma, which includes important changes in fibroblasts, capillaries, fibromuscular stroma, and the composition of glycosaminoglycan that induce the formation of primordial stromal nodule (NSP) or more commonly called early nodules. In about 70% of cases, nodules in the transition zone can be found [54, 55].

According to structural morphological changes, NSPs are divided into immature mesenchymal nodules (NMIm), fibroblastic stromal nodule (NSFB), fibromuscular stromal nodules (NSFM) and muscular stromal nodules (NSM). Under the interaction between cellular-stromal and acinar-epithelial relationship, proliferation of glandular structures occurs, thus forming the proliferative center. In the second stage, when the nodules are growing with advancing age, the stromal component in the nodules is reduced quantitatively. Simultaneously with the proliferation of the adjacent nodule, other proliferative outbreaks occur. It should be noted that the incidence of histopathological changes in BPH precedes clinical symptoms [43].

Diagnosis and principles of classification of prostate adenoma. The clinical and diagnostic features of prostate pathology are viewed from three etiopathogenetic directions: infectious-inflammatory (prostatitis), BPH and prostate cancer. Prostate cancer (PC), a diagnosis that is based on clinical symptoms, paraclinical, imaging, histology, and cytopathology. The most common conditions are prostatitis and BPH and both pathologies represent a reactive and symptomatic pattern of the lower urinary tract requiring a diagnosis of prevention and control [56].

Depending on the clinical disorders in BPH, they are divided into irritative and obstructive manifestations. In the course of the disease, three stages have been identified: the prostatism – or compensatory stage, the incomplete retention stage without dystonia of the urocyt and the incomplete retention stage with dystonia of the urocyt [17].

From the point of view of clinical symptoms, BPH is manifested by symptoms of the lower urinary tract (LUTS), and prostatitis with predilection of pain syndrome and painful ejaculatory dysfunction. Some comparative studies show that painful ejaculation may be present in 5–31% in men with AP-driven LUTS [57, 58]. Currently both pathologies benefit from modern sophisticated diagnosis and treatment, which is based on national and international guidelines. Chronic prostatitis in medical history can be an early sign in the development of BPH [59, 60].

BPH is a nodular process with dimensions between 27–

50 mm³ and/or greater than 80 mm³. Prostate adenoma has a clinical picture of lower urinary tract symptoms (LUTS) associated with benign enlargement of the prostate (BPR) leading to bladder outlet obstruction (BoO) which is assessed by quantifying the international score of symptoms caused by prostate adenoma (IPSS) as well as assessing the quality-of-life index (QoL) [3, 13, 60].

The diagnosis of BPH is based on history, rectal digital exam, laboratory investigations, imaging methods such as intravenous urography, cysto-urethrography, ultrasound (USG), computed tomography (CT), magnetic resonance imaging (MRI), uroflowmetry, international prostate symptom score (IPSS), prostate-specific antigen (PSA), hemostasis and rheological features of the blood serum, renography, cystoscopy, BPH biopsy [60, 61].

Determination of PSA levels according to some studies in BPH is welcomed. Bhat A. mentions that the persistence of PSA after prostatectomy is a warning signal for the doctor [62]. However, in this context, a correlation study of the PSA level in the blood serum and the histological peculiarities is welcomed.

The dimensions of the nodules in BPH correlate with the weight, which frequently reaches the dimensions of an apricot (50-100 g.), but much more voluminous forms have been described, up to 250-400 g. With reference to the dynamism of the annual progress of BPH, according to some studies in recent years it has an evolution of about 0.6 mm per year. Depending on size, BPH is divided into small nodular hyperplasia ≤25-30 mm³, medium nodular hyperplasia – 30-80 mm³, large nodular hyperplasia ≥80 mm³, giant nodular hyperplasia >250 mm³.

Depending on the configuration, BPH can evolve in aspect of spherical solitary node, or in the form of two to three nodules and in shape of grape. Taking into account the nature of the growth, the following forms have been described: BPH intraurocystic (intravesical), preurocystic (retrotrigonal), suburocystic (intraticgonial) and mixed nodular form due to the presence of a diffuse growth [60].

Aleksandrov V. (2007) describes five stages of morphogenesis of BPH [46]:

- Stage I – formation of immature adenoma consisting of 2-3 reinforced acinar structures;
- Stage II – quantitative enlargement of the glandular structures that form proliferative centers;
- Stage III – emergence in peripheral areas of new proliferative centers/outbreaks;
- Stage IV – retention of secretion of the acini of proliferative centers with cystic dilation;
- Stage V – all acini forming proliferative centers or most of them are cystic dilated with epithelium atrophy.

Histological examinations have shown that the presence of inflammatory processes has an etiopathogenetically predictive role and is significant for the postoperative period [63]. Epithelial-muscular nodules in BPH are frequently associated with chronic inflammatory processes [64]. Kohnen P. et al. (1979) reported an inflammatory process prevalence of 98% in 162 examined cases, Kramer G. (2006) states that

chronic inflammation is frequently present in BPH, predilection in lumpy nodular BPH, with higher PSA levels and a higher risk of acute urinary retention [65-67].

Currently, BPH, especially the voluminous form, is a contemporary problem, due to both high incidence and prevalence, its evolution and serious complications that is associated with, as well as due to the shortcomings of pharmacological and surgical techniques used by modern medicine [3, 14].

Surgical treatment strategies in prostate adenoma, advantages, and disadvantages. For many years, managing BPH has had its pros and cons as efforts have been made to refine non-invasive treatments, surgical interventions, and adenectomy hemostasis techniques. Komlev D.L (2004) notes that the surgical procedure in treating BPH, a major share 75.7% belongs to the transurethral adenectomy (TUR) compared to the open transvesical method – 24.3% [69]. It is remarkable that due to the technological potential from the last decades, the medical and surgical management in BPH has improved and the patients' outcome has improved [68, 69].

Today, the gold standard is transurethral endoscopic method (TUR) [29, 32], which is performed in many countries, including for BPH ≥ 80 mm³. Similar opinions can be found in the local literature [31, 70]. However, we must mention that in lumpy nodular BPH, open adenectomy interventions are preferred, partly due to the difficulty of making a long resection, but also due to the high risk of larger postoperative complications.

Notwithstanding that endoscopic, transurethral resection of the prostate (TUR-P) in BPH is considered "gold standard", medical practice demonstrates that in voluminous nodule BPH the surgical treatment remains a valid option to this day. In this regard, Lopatkin N. et al. (2009), Martov A. et al. (2006), state that approximately 7-30% of surgical maneuvers for the treatment of BPH are performed with open surgery, with preferred surgical techniques described by Fedorov-Freyer [17, 71]. In addition, a good part of foreign authors from high-income countries mention the advantageous clinical efficiency of open transverse approaches compared to the TUR in cases of high risk of interventions, in particular, in voluminous nodular hyperplasia [2, 72].

Tiktinskii O. (2006) states that transurethral resection is welcomed in BPH with nodules up to 50 mm³, maximum size – 70 mm³ [73]. Later, Vasilchenko M. et al. (2012) mention that open transvesical prostatectomy remains will remain for a long time as one of the approaches of choice despite the advantages of unquestionably proposed medicinal and interventional mini-invasive treatment in recent years [74].

On this subject, many authors in recent years have focused on comparing between transurethral and open transvesical method. The latter being described as an intervention with major complications, such as: hemorrhage from the adenoma site from 250-2500 ml, intensive hematuria, inflammatory processes (urethritis, prostatitis, cystitis) including at the level of residual prostate, urinary infiltration,

obstructive processes (urocystic cervical sclerosis, urethral stricture), urinary incontinence, as well as high mortality $\geq 2.2\%$ [75, 76]. At the same time, the authors mention that open method transvesical adenectomy is accessible in different prostate adenoma volumes, including especially those complicated with diverticulum, concretions, tumors, etc., with excellent results characterized by minimal bleeding and in patients with heart failure and other comorbidities, but some disadvantages in the evolution of complications in the intra- and early and late postoperative period are also accentuated.

Among the most common complications are: hemorrhage and inflammation of the prostate adenoma site, such as urethritis, urethral fever, bacteriotoxic shock, thromboembolic syndrome, and at a distance the formation of bladder lesions, stenosis and structures of the urocyst cervix and prostate urethra, the prevention of which is a serious problem, being insufficiently solved so far [77, 78]. In this respect, we note that complications in open adenectomies has a frequency from 12.5 to 30.9% based on multiple factors [79, 80].

All factors that can induce complications can be divided into two categories: general factors that are evaluated and corrected preoperatively and local factors, which are dependent on the urinary tract and some unforeseen complications that can occur during the enucleation process, non-effective intraoperative hemostasis, urine infiltration, parallels of the neuro-muscular component especially in the voluminous adenoma and others such as insufficient drainage of the surgical site, etc. Prevention of intraoperative and postoperative complications to date is determined by the features of hemostasis performed both locally, at the level of the surgical adenoma removal and regionally [81].

The lack of a unified vision on the causes and nature of complications after transvesical prostatectomy in order to improve hemostasis has been proposed several methods both transvesical and extravescical directed to stop bleeding as one of the major complications. Depending on the methods used for hemostasis, they are currently divided into mechanical-thermal, surgical and chemical. The extravescical ones included various mechanical-thermal actions (compression by transrectal balloon); suturing with vessel embolization, hypothermia, monitored hypotonia, which has become a thing of the past in BPH surgery. Ineffective mechanical-thermal methods include the use of electric current (electrocoagulation), which is unreasonable because causes deep necrolytic processes, the progression and persistence of cystitis, the formation of scars and strictures [78, 82].

To avoid bleeding from the surgical site, it is recommended to process it with hot 0.9% NaCl solution, or with ice (hypothermia), including with 3% H₂O₂ solution or 6%, buffering the box with gauze and by various changes of suturing the box with over 200 procedures. Relatively effective is also considered electrical stimulation of the surgical site using the transurethral electric catheter proposed by Shumakova E. (2000), which currently is being used for insignificant intra-operative hemorrhage [83, 84].

In contradictory discussions so far are also transvesical surgical methods such as draining the bladder using the Foley catheter, as well as methods of suturing the box and permanent or remove hemostatic connections [17]. Regarding the application of sutures, the data from the specialized literature prove that in the most common cases, they do not lead to an effective stop of complications during surgery or postoperative, which induce the emergence of favorable conditions for the development of acute or chronic inflammatory processes, including the sclerosis in the urocystic cervix and the prostate urethra [46, 72].

In the handling of intraoperative hemostasis at the surgical site after prostatectomy, the chemical method based on the use of hemostatic materials in the form of adhesives, collagen plasters containing fibrinous substances, which contribute to coagulation, is widely used, and the collagen substrate forms an impermeable barrier for air, deterring removal in regenerative processes. These are used as a method of choice [17].

To achieve a hemostatic effect with better visualization of the operating field, scientific research has been undertaken that is directed towards achieving perfect hemostasis. Recent studies conducted by Nazarov E. (2009) dedicated to the effectiveness of the use of absorbent hemostatic plasters at the level of the surgical site applied on the entire surface with the fixation of the hemostatic plaster through the Foley catheter balloon and using the closed irrigation system of the urocyst with antiseptics [83].

Another study carried out by Vitruk Iu. (2010) in the decompensated cases of the diverter consists of the application of temporary sutures on the cervix of the urocyst and the concomitant separate drainage of the urocyst and the surgical site after open adenectomy [85]. The authors note that due to the methodologies used, the reduction of complications in the postoperative period as well as the reduction of obstructive processes and bed day was achieved. In this respect, the majority opinion with reference to the proposed methods for the improvement of the lodge hemostasis after adenectomy and the reduction of inflammatory processes are estimated to be ineffective further. In this context, Komlev D.L (2004) noted that the particularities of management to improve hemostasis in the surgical site after the removal of benign nodular hyperplasia of the prostate is the "golden dream" of urologists and the effectiveness of innovative technologies used [69].

However, so far the majority of opinions referring to the priority of endoscopic versus classical transvesical interventions are diverse and sometimes contradictory, because, with the significant increase in the dynamism of the expenses of endoscopic interventions, they constitute an impressive medical-social and economic impact. Some sources mention that this impact is determined by the increase in the number of the population of advanced age relative to the working-age population [86].

Joseph E. (1992) mentions that in the US about 400,000 men manifest the symptoms of BPH. Speakman V. et al. (2004) also warned that referring patients to a doctor with

diagnosis symptoms of BPH in recent years marks an incidence of 113-125 cases per 100,000 men. In the US direct expenditure on surgical assistance alone in BPH annually averages about \$1.1-1.5 billion, and conservative treatment with alpha blocker inhibitors reached the limit of \$800 million [3, 86-88], and this fact differs greatly from the economic possibilities of many European states, including Moldova.

At the same time, some authors mention that the increased level of morbidity and the high costs of transurethral interventions have favored the use of various alternative conservative treatments in BPH. Mini-invasive interventions are successfully applied in many economically developed countries, as a rule in small- and medium-volume BPHs, while for voluminous BPHs they are often unsuccessful, so transvesical open interventions have remained up-to-date to this day [89]. It is worth mentioning that the mortality rate in transvesical interventions is on average 3.3% in different countries with various public health systems, it is variable and dependent on the economic level - financial allocations and innovative technological resources available [29, 69, 75].

The data from the specialized literature in the last decades demonstrate the presence and persistence of advantages and disadvantages to the problem of BPH treatment, their basis is the diversity of surgical and conservative therapy approaches, the incidence of intra- and postoperative complications, especially the ineffectiveness of hemostasis methods after adenectomy, the increasing incidence of patients with voluminous BPH (≥ 80 and 100 cm^3), the economic-financial impact in medicine [77, 90]. Voluminous adenomas and mini-invasive technologies are also a significant burden for private medicine. According to Saigal C. (2005), the medical costs for treating BPH, direct and indirect, are estimated to be \$3.9 billion annually. Thus, the findings in terms of cost-effectiveness meanings provide convincing evidence for clinicians, financiers, and policy makers to help differentiate minimally invasive surgical treatment and transverse open interventions in BPH [91].

Therefore, in conclusion, it is worth mentioning that the evolution of BPH is a complex and integrated process, with a heterogeneous etiology and involves a number of mediators and factors with mutual interactions, which with age induce an increase in the frequency of complications from the lower urinary tract (prostate, urethra, urocyst) and postoperatively with significant repercussions at a distance in the use of open transvesical adenectomy or by mini-invasive methods as methods of selection; and especially in voluminous BPH. It remains questionable the infectious-inflammatory factor as the etiopathogenetic predictive moment of the prostate adenoma were secondary in the pathogenesis of intra- and postoperative complications in voluminous BPH which is imposed as a problem of great topicality with an obvious impact in the development of an effective therapeutic and medical-surgical treatment strategy at the level of the lodge. A problem for the first time is the study of inflammatory histomorphological peculiarities in prostate adenoma as well as at the limit of enucleation

and lodge after enucleation of the hyperplastic pathological process, which motivates the need to conduct a complex correlational histomorphological and immunohistochemical study in assessing the associations or coexistence of BPH and prostatitis.

An important aspect in the effective implementation of open transvesical interventions is the need to perform an effective hemostasis during surgery and the postoperative period that will allow monitoring of the activity of proteolytic processes at the level of the prostate adenoma and blood serum, PSA and alkaline phosphatase, the assembly of which will allow the definite optimization of therapeutic, medical-surgical treatment with significant reductions in postoperative complications. The lack of a real method that would diminish postoperative complications and raise the possibilities of monitoring and evaluating the general homeostasis and at the surgical site is a desideratum of research for the first time.

Conclusions

There remains the issue of reducing intra- and post-operative complications in BPH, especially the voluminous one, which imposes itself as a very topical problem in the development of an effective treatment strategy. For the first time a problem is the study of the particularities of some biochemical criteria at surgical site and in blood serum, histological - at the level of nodular prostatic hyperplasia and at the border of the prostate adenoma, which motivates the need for a complex correlational of biochemical, histological and immunohistochemical facts, including in the evaluation of the associations or coexistence of BPH and chronic prostatitis.

Competing interests

None declared.

Author's contribution

All the authors have contributed equally at the results presentation in the paper, approved the „ready for print” version of the manuscript.

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