CHRONIC PROSTATITIS AND FIBROSIS OF PROSTATE. PREDISPOSING FACTORS FOR SURGICAL COMPLICATIONS

Abstract. Prostatitis is an inflammatory process of the prostate, which continues to be considered one of the most common urological diseases in men under 45. Predisposing factors as trophic, microcirculatory and congestive disorders, contributes to the onset and development of the inflammatory process in the prostate and risk factors as urethral catheter, urethrocystoscopy, endoscopic surgery for infection and deterioration of the integrity of the urethral epithelium. The purpose of this study was to determine the impact of chronic inflammation and fibrosis of prostate on urodynamics and local prostatic microcirculation and to evaluate the efficacy of medicamentous treatment. In the study were included 58 patients (with pronounced clinical
symptoms as dysuria, stranguria, nocturnal pollakuria 2-4 times per night and residual urine about 50ml) that followed a course of treatment with Adenosprosin 250 mg. According to the study results, we can outline that the level of microcirculation and urodynamics impairment indicates the level of prostate fibrosis. This process in chronic prostatitis is reversible by using antifibrotic and anti-inflammatory treatment supplemented with Adenoprosin 250 mg.

**Keywords:** Prostatic sclerosis, chronic prostatitis, fibrose, prostate, adenoprosin

**Résumé**

L'inflammation chronique comme un facteur de risque des complications chirurgicales de la prostatite chronique.

La prostatite est un processus inflammatoire de la prostate qui continue à être considérée l'une de plus fréquentes maladies parmi les hommes âgés de moins de 45 ans. Les facteurs prédisposants, tels que les troubles trophiques, les maladies congestives et de la microcirculation, contribuent à l’apparition et au développement du processus inflammatoire de la prostate ; et aussi des facteurs de risque comme le cathétér urétral, urétrocystoscopie, chirurgie endoscopique pour l’infection et la détérioration de l’intégrité de l’epithélium urinaire.

Cette étude vise à déterminer l’impact de l’inflammation chronique et de la fibrose de la prostate sur la microcirculation locale dans la prostate et sur l’urodynamique, et à évaluer l’efficacité du traitement médicamenteux.

Les 58 patients visés par l’étude (présentant des symptômes cliniques prononcés comme dysurie, strangurie, pollakiurie nocturne 2-4 fois par nuit et urine résiduelle d’environ 50ml) ont suivi un traitement avec des suppositoires Adenoprosin 250 mg.

Selon les résultats de l’étude, on peut souligner que le niveau de microcirculation et de la détérioration de l’urodynamique indique le niveau de fibrose de la prostate. Ce processus dans la prostatite chronique est réversible en cas d’utilisation du traitement anti-fibrosant et anti-inflammatoire complété par Adenoprosin 250 mg.

**Mots-clés:** Prostatite chronique, sclérose, fibrose, prostate, adenoprosin

**Introduction**

Prostatitis is an inflammatory process of the prostate of unknown etiology, which methods of diagnosis and treatment have not been sufficiently highlighted [1,5,10]. However, prostatitis is still considered one of the most common urological
diseases in men aged under 45 and the third most common urological diagnosis in
men aged over 45, following a benign hyperplasia (BPH) and prostate cancer, and
accounting for 14 -18% of outpatient visits [2, 4]. According to various literature
data, the incidence of prostatitis ranges from 25-35% to 60-80% of cases. The
frequency of the disease increases with age, viz. 35% of men under the age of 40
suffer from prostatitis, 45% of men over 40 years, and 55% - over 50 years old, etc.
[6,9,12]. The early mean age of the patients, the decrease in the reproductive
function, the persistent disease evolution the treatment approaches, as well as the
frequent recurrences are reasons to consider this pathology both a medical and social
problem [7]. The most common pathogens of bacterial prostatitis are the
microorganisms of the family Enterobacteriaceae, namely, E. fecalis, P. aeruginosa,
P. mirabilis [1, 15], however, over the last decade, there is a marked tendency to
involve both atypical microorganisms (chlamydia, mycoplasma, and ureaplasma),
as well as staphylococci [11, 14, 15]. The role of anaerobes, gonococci,
trichomonads in the development of prostatitis has not been sufficiently studied. The
anterior and posterior urethra, as well as other parts of the urinary tract might be a
source of infection. Predisposing factors contribute to the development of
inflammatory changes (trophic, microcirculatory and congestive disorders) within
the prostate, whereas the risk factors lead to infection of the prostate gland and
damaged bladder epithelial integrity (urethral catheterization, use of urethral plugs,
urethral instillation, and urethrocystoscopy). Chronic prostatitis is characterized by
less severe clinical symptoms, which last for more than 3 months including
perineum pain and discomfort, supravesical pain, difficulty urinating, frequent
urination, a reduced potency and poor life quality. However, acute prostatitis differs
in its clinical symptoms from the chronic one, being much more pronounced and
causing the patient to visit the urologist immediately.

The pathogenesis of chronic prostatitis has not been definitively highlighted;
however, prostate inflammation has been determined to a greater extent due to the
pathomorphological studies of surgical or biopsy samples retrieved from benign
prostatic hyperplasia or cancer. There has been found a correlation between the
inflammation degree and LUTS severity (lower urinary tract symptoms) [1-4]. It has
been assumed that the main reason is a reduced tissue elasticity due to excessive sclerosis that is the final stage of a chronic inflammatory process [5, 6]. The development of inflammatory processes involves the physiological healing response due to an excessive production of fibrosis and damage or degradation of collagen, unless the inflammation is treated within the acute phase [9, 14]. Collagen is a major component of a large group of extracellular matrix proteins and a subtype that is mostly involved in fiber formation [13]. These, in turn, play an essential role in formation of "tissue skeleton", which provides tissue strength and extensibility, cell migration and adhesion, tissue regeneration after damage [14, 15, 16]. There are two balanced multidirectional processes of collagen synthesis and degradation, whereas the imbalance results in excessive fibrous (scar) tissue formation that might disrupt the proper function of the target organ [3, 4].

Fibrosis caused by chronic inflammatory disease of the prostate is one of the major complications or causes of subsequent urinary disorders [8, 9, 10], which has been proven experimentally to contribute to its spread on the bladder neck [14]. A retrospective case study in men who underwent surgical intervention for benign prostatic hyperplasia and prostate cancer showed a significant correlation between the fibrosis degree and malignant prostate tumor development, whereas the tumor was more aggressive in inflammatory processes [10, 13]. It should be noted that prostate fibrosis not only affects the process of urination, but also might exacerbate the surgery outcomes. The literature data have reported a potential regression of inflammatory consequences due to the enzymatic effect of drugs that might reduce collagen biodegradation and stromal fibrosis by decreasing the periglandular and perivascular sclerosis process and enhancing blood vessel network and vessel lumen in the prostate [7, 16, 17, 18].

A series of studies have proven the successful use of conservative treatment in acute bacterial prostatitis, leading to regression of inflammatory changes, as well as to insignificant denaturation of collagen [11, 17, 18]. Thus, the experimental studies have found that acute prostatic inflammation might cause minimal fibrosis, when chronic inflammation, followed by the development of sclerotic changes leads to a complete healing of the prostate parenchyma, whereas early treatment of
inflammation increases its effectiveness. An individual treatment approach for patients with prostate sclerosis is possible due to the emergence and development of ultrasound diagnostic techniques that diagnose the disease, assess the prostatic blood flow, monitor its dynamics, identify the prognosis of blood flow disorders within the impaired prostatic vessels via Doppler ultrasound and predict possible postoperative complications [3, 7, 18]. A range of quantitative indicators of regional blood flow of the prostate allows identifying qualitative indicators that might determine the nature of regional blood flow of the impaired organ, such as the pulse rate and venous flow velocity, which reveal the venous tone status, as well as the presence of pelvic venous disease, including that of the prostate gland [4, 11, 17].

**Material and methods**

The purpose of this study was to determine the degree of impact of chronic inflammation and prostate fibrosis on urodynamics and local prostate microcirculation, as well as to identify possibilities for their correction and improvement via drug therapy.

The mandatory diagnostic investigations include laboratory tests that should be carried out in the primary health care (complete blood count and urinalysis, three-glass test (an increase in the number of WBCs in the third portion of urine is characteristic for chronic prostatitis), and a microbiological urine test), as well as instrumental methods, including transrectal ultrasound of the prostate and digital rectal examination. Additional diagnostic assessment includes serological methods, PCR diagnostic test (for detection of mycoplasma and chlamydia), uroflowmetry, and prostate biopsy (if necessary).

Blood flow assessment was carried out via transrectal ultrasound doplerography with General Electric LOGiQP9 equipment, using a sensor at a frequency of 4-10 MHz and which determines the following indicators: maximum systolic blood flow rate, minimum diastolic blood flow rate, resistance and pulsation indices, vein lumen size of the periprostatic venous plexus and the venous blood flow.

A direct relation to the severity degree of blood flow disorder in the prostate vessels was assessed both in the pre- and post-treatment period. Thus, patients with
prostate and bladder neck fibrosis exhibited blood flow disorders in the prostatic tissues, which produces favorable conditions for complications during different periods of treatment. A retrospective, comparative study was carried out to confirm the correlation between chronic inflammation and prostate fibrosis on urodynamics and microcirculation in the prostate. The study included 58 patients with pronounced clinical symptoms (dysuria, stranguria, 2-4 times nocturnal pollakiuria, post-void residual volume, on average 50ml), which are characteristic of prostate sclerosis, resulting from chronic prostatitis.

A transrectal ultrasound was initially performed to determine the prostate structure and volume and presence of prostate fibrosis with or without signs of acute or chronic inflammation. At the same time, patients diagnosed with formations characteristic of benign prostatic hyperplasia or suspected prostate cancer were excluded from the study. All patients underwent uroflowmetry, including the assessment of maximum flow rate (Qmax), average flow rate (Qmed) and speed of urine flow over time. According to the study findings, the patients were divided into two groups viz. group I included 26 patients with inflammation and severe fibrosis of prostate tissue and group II - 32 patients with inflammation and a less marked fibrosis, which based on ultrasound and clinical data, were assessed from 0 points (no changes) to 3 points (pronounced changes).

Subsequently, all patients were given a course of treatment with Adenoprosine 250 mg (as suppositories) for three weeks. The complaints decreased in 21 patients at the end of treatment and they ceased it. These patients (6 (23.1%) from the group with severe inflammation and fibrosis and 15 (46.9%) from the group with inflammation and initial fibrosis) were recommended dynamic outpatient care visits to the urologist. Despite an improvement in the condition of the other 37 patients, characterized by reduced complaints and better clinical and paraclinical parameters, they were recommended to continue administering conservative Adenoprosine suppositories for 30 days more, followed by subsequent follow-up investigations. Three patients from the study (2 from group I and 1 from group II, respectively) underwent endoscopic bipolar transurethral incision of the bladder neck and prostate.
CURRENT ISSUES AND PROSPECTS FOR THE DEVELOPMENT OF SCIENTIFIC RESEARCH

(TURP) under spinal anesthesia, followed by the retrieval of biopsy material for pathomorphological examination.

**Research results**

A comparative study of the obtained data was performed on the pre- and post-treatment investigations with Adenoprosine 250 mg suppositories, thus determining the correlation between urodynamic and microcirculation disorders depending on the degree of inflammation and prostate fibrosis.

The fibrosis degree in patients from group I (with severe prostate fibrosis) decreased insignificantly by 0.1 points compared to 0.4 points in the group with milder sclerosis. The degree of inflammation was significantly lower in both groups, namely, 0.8 and 1.0 points, respectively, which proves the effectiveness of anti-inflammatory treatment with Adenoprosine 150 mg suppositories. These very results were confirmed by the pathomorphological assessment (in three patients), characterized by a more reduced fibrous tissue areas in patients from group II and lack of acute inflammatory areas in the histological samples from both groups. All 37 patients from both groups exhibited an improvement in the maximum and average flow rate at the end of treatment and an insignificant decrease in prostate volume, resulting from a reduced inflammatory process in the prostate following treatment with Adenoprosine.

According to ultrasound findings, all 37 patients undergoing an additional treatment approach showed some structural changes of the prostate: inhomogeneous echogenic tissue and increased and decreased foci of echo density. Patients from group I had only a 0.1-point decrease in the degree of fibrosis, whereas the degree of inflammation decreased by 0.8 points. The second group showed more significant alterations of fibrosis and inflammation degree viz. 0.4 and 1.0 points, respectively. Qmax increased by 1.5 ml/s and Qmed -by only 0.5 ml/s in patients from the 1st group with severe prostate fibrosis. The 2nd group (patients with minimal prostate fibrosis) had significantly better uroflowmetry values viz. 3.9-4.0 and 4 ml/s, respectively. Microcirculatory disorders were also more pronounced in patients from group I compared to those with moderate fibrotic changes from group II. The indices of microcirculatory disorders were 3 times higher in group I compared to
group II. Prior to treatment, 17 (46.0%) patients out of the 37 patients exhibited vein dilation of the periprostatic venous plexus up to 3.5 ± 0.6 mm and a blood flow rate of up to 6.2 ± 1.3 cm/s. The post-treatment indices showed a reduced vein dilation of the periprostatic venous plexus up to 2.5 ± 0.2 mm in 9 (24.3%) patients and a better blood flow rate up to 9.1 ± 0.3 cm/s. Comparative data analysis in patients before and after treatment are presented in Table 1.

Ultrasound investigations with the transrectal sensor recorded an irrelevant decrease in the mean volume of the prostate due to a reduced prostate edema and a decreased inflammatory process. The pathomorphological study of biopsy sample obtained via endoscopy in 3 patients confirmed a stromal fibrosis with elements of paravascular sclerosis, which was more severe in two patients from group I.

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Indices</th>
<th>Qmax ml/s</th>
<th>Qmed ml/s</th>
<th>Degree of fibrosis</th>
<th>Degree of inflammation</th>
<th>Fibrosis stage (ultrasound-based)</th>
<th>Prostate volume cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grou p I</td>
<td>Before therapy</td>
<td>10,8±2,5</td>
<td>6,3±0,4</td>
<td>2,5±0,2</td>
<td>2,6±0,25</td>
<td>Advanced&gt;70%</td>
<td>36±0,2cm³</td>
</tr>
<tr>
<td>After therapy</td>
<td>12,3±2,3</td>
<td>6,8±0,1</td>
<td>2,4±0,1</td>
<td>1,8±2,3</td>
<td>&gt;60%</td>
<td>35,5±0,03 cm³</td>
<td></td>
</tr>
<tr>
<td>Grou p II</td>
<td>Before therapy</td>
<td>15,6±1,2</td>
<td>9,4±1,5</td>
<td>0,6±0,01</td>
<td>2,2±0,15</td>
<td>Moderate 50-70%</td>
<td>37,6±0,52 cm³</td>
</tr>
<tr>
<td>After therapy</td>
<td>19,5±1,5</td>
<td>13,4±1,5</td>
<td>0,2±0,15</td>
<td>0,2±0,13</td>
<td>&gt;30%</td>
<td>36,4±0,01 cm³</td>
<td></td>
</tr>
</tbody>
</table>

Note: Statistically significant values after treatment compared to initial ones:
± p <0.05; xx p <0.01; xxx-p <0.001

Therefore, it has been found that chronic inflammation associated with fibrosis, might exacerbate the local microcirculation and the urodynamic. Chronic prostatitis, complicated by advanced fibrous tissue, leads to major irreversible damages of the prostate parenchyma and local blood flow. However, moderate
impairment of the prostate parenchyma is likely to partially restore and improve the urodynamics and microcirculation. Thus, the conservative treatment with Adenoprosine 250 mg suppositories used to prevent fibrosis formation and regression has a good pathogenetical rationale.

**Conclusion**

In conclusion, the study results proved that the impaired microcirculation and urodynamics indirectly indicate the stage of prostate fibrosis. This process is reversible in chronic prostatitis, unless anti-fibrotic and anti-inflammatory drugs are administered, supplemented with Adenoprosine 250 mg suppositories.

**Compliance with Ethics Requirements:**

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

"All institutional and national guidelines for the care and use of laboratory animals were followed"

"No funding for this study"

**Acknowledgements:**

None

**References:**


17. Думбравяну И., Банов П., Ариан Ю., Тэнасе А. Применение энтомологических препаратов в комплексном лечении больных хроническим простатитом и эректильной дисфункцией. 18 Конгресс ассоциации андрологов России. Дагомыс 23-25 мая 2019.
18. Думбрэвяну И., Гикавый В., Чебан Е., Тэнасе А. Лечение доброкачественной гиперплазии предстательной железы и воспалительных процессов простаты препаратом Аденопросин. В: Андрология и генитальная хирургия. 2010, 2, с. 136-137, ISSN 2070 -9781.