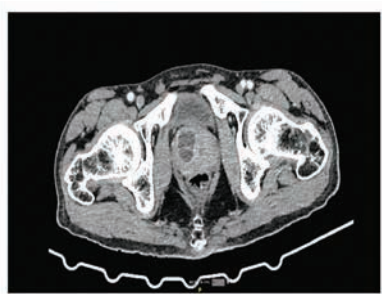




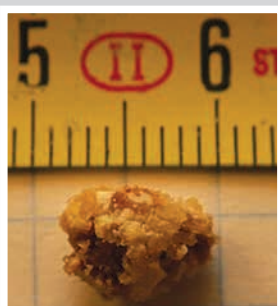
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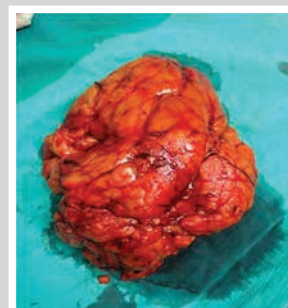
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Yotovsk V, Vassilev V, Milushev M, Dimitrov P, Krastanov A, Mladenov V, Timev A, Lazarov C, Ivanov G, Yanev K, Georgiev M. MRI Fusion Biopsy with „Koelis“. High-Tech Precision. 41st CONGRESS OF THE SOCIÉTÉ INTERNATIONALE D' UROLOGIE — SIU 2021 ABSTRACT BOOK, VOLUME 2, Supplement 2, page 144.

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ПРОСТАТЕН АБСЦЕС, ИМИТИРАЩ ОСТЪР ПРОСТАТИТ: УСПЕШНО ЕНДОСКОПСКО ЛЕЧЕНИЕ

Х. Ахмед

КЛИНИКА ПО УРОЛОГИЯ, МБАЛ „СВЕТА АННА“, ВАРНА, БЪЛГАРИЯ

SEPTIC PROSTATIC ABSCESS MIMICKING ACUTE PROSTATITIS: SUCCESSFUL ENDOSCOPIC MANAGEMENT

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РЕЗЮМЕ

Простатният абсцес е рядко, но потенциално животозастрашаващо урологично състояние. То може много да наподобява остър простатит, което води до забавена диагноза и лечение. Ранното разпознаване е от съществено значение, особено при пациенти в състояние на сепсис, въпреки приложената антибиотична терапия. Представяме случай на 69-годишен мъж, приет с треска, дизурия, запек и перинеална болка, на който първоначално е поставена диагноза остър бактериален простатит. Въпреки широкоспектърните перорални антибиотици, пациентът остава фебрилен с влошаващи се възпалителни маркери. Компютърната томография разкрива простатен абсцес с размери 3x3 см. Пациентът е подложен на трансуретрална резекция и деруфинг на абсцесната кухина с успешно грениране на гноен материал. Микробиологичната култура идентифицира *Escherichia coli*. Постоперативно пациентът демонстрира бързо клинично подобрене с нормализиране на възпалителните маркери и пълно редуциране на симптомите. Този случай подчертава важността от ранното диагностициране на простатния абсцес и подкрепя трансуретралния дренаж като ефективен метод за лечение на големи абсцесни огнища.

КЛЮЧОВИ ДУМИ:

простатен абсцес, остър простатит, трансуретрална резекция, сепсис, ендоскопски дренаж

ABSTRACT

Prostatic abscess is an uncommon but potentially life-threatening urological condition that may closely mimic acute prostatitis, resulting in delayed diagnosis and treatment. Early recognition is essential, particularly in patients with persistent sepsis despite appropriate antimicrobial therapy. We present the case of a 69-year-old male admitted with fever, dysuria, constipation and perineal pain who was initially diagnosed with acute bacterial prostatitis. Despite broad-spectrum per oral antibiotics, the patient remained febrile with worsening inflammatory markers. CT scan revealed a multiloculated prostatic abscess measuring

3x3 cm. The patient underwent transurethral resection and deroofing of the abscess cavity with successful drainage of purulent material. Microbiological culture identified *Escherichia coli*. Postoperatively, the patient demonstrated rapid clinical improvement with normalization of inflammatory markers and complete symptom resolution. This case highlights the importance of considering prostatic abscess in patients with refractory acute prostatitis and supports transurethral drainage as an effective treatment modality for large multiloculated abscesses.

KEYWORDS:

prostatic abscess, acute prostatitis, transurethral resection, sepsis, endoscopic drainage

ВЪВЕДЕНИЕ

Простатният абсцес е рядко срещано урологично заболяване в съвременната антибиотична ера, представляващо малка част от простатните инфекции. Забавената диагноза обаче може да доведе до тежки усложнения, включително сепсис, образуване на фистула и смърт. Клиничната картина често се припокрива с остър бактериален простатит, което затруднява диференциацията му по време на първоначалната оценка. (1) Често срещани рискови фактори включват захарен диабет, имunosупресия, хронична катетеризация, обструкция на ДПП и повтарящи се инфекции на пикочните пътища. Пациентите обикновено се представят с треска, дизурия, перинеална болка, задържане на урина и повишени възпалителни маркери. Персистиращите симптоми въпреки подходящата антибиотична терапия трябва да повдигнат съмнение за абсцес на простатната жлеза. (1) Образните методи като трансректална ултрасонография (TRUS) и компютърна томография (СТ) са от съществено значение за поставяне на диагнозата. Възможностите за лечение включват консервативно антибиотично лечение, TRUS-насочвана аспирация, трансперинеален дренаж и трансуретрална резекция с деруфинг на абсцесната кухина. Оптималната стратегия за лечение остава спорна и често се индивидуализира според размера, местоположението и клиничната тежест на абсцеса.

Представяме случай на септичен простатен абсцес, първоначално погрешно диагностициран като остър бактериален простатит и успешно лекуван с трансуретрална резекция. (1,2)

ПРЕДСТАВЯНЕ НА СЛУЧАЯ

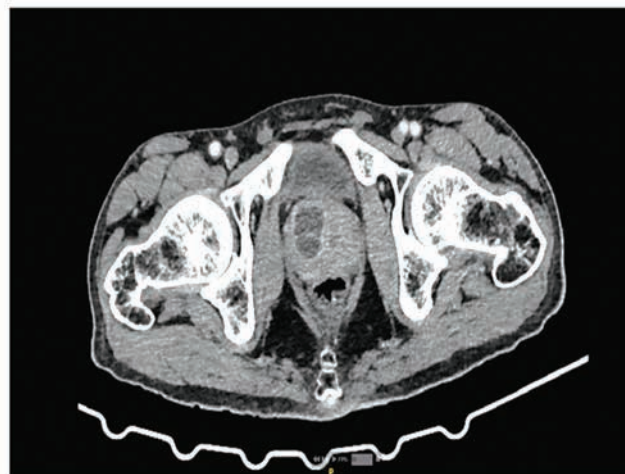
69 годишен мъж с медицинска анамнеза за есенциална хипертония, хронична обстру-

ктивна белогробна болест, статус след миокарден инфаркт на перорална антиагрегантна терапия и десностранна пиелолитомия през 1964 г. се явява в спешното отделение с петдневна анамнеза за треска, дизурия, полакиурия, перинеална болка, прогресивно затруднено уриниране и обща отпадналост. При прегледа пациентът е фебрилен до 38,9°C. При физикалният преглед се установява супрапубична болезненост и силен дискомфорт при ДРЕ, със значително уголемена и болезнена простата, особено в десния лоб. Лабораторните изследвания разкриват левкоцитоза 43,3 (3,5-10,5 x 10⁹) и повишен С-реактивен протеин 248,5 mg/L (0-3 mg/L). Анализът на урината показва пиурия и бактериурия. Серумната урея и креатинин са нормални. Пациентът първоначално е диагностициран с остър бактериален простатит и е започва перорално лечение антибиотично лечение. Въпреки 72-часовото лечение, той остава фебрилен с персистиращо повишение на възпалителните маркери и влошаваща се тазова болка, което ни накара да го приемем в болница за допълнителни изследвания. Включихме двойна интравенозна антибиотична терапия - широкоспектърен антибиотик (Мегаксон) и аминогликозиден антибиотик (Гентамицин). Контраст-асоциираната компютърна томография на таза показва 342,8 см многофокулна хиподензна колекция в десния лоб на простатната жлеза, съответстваща на простатен абсцес (Фиг. 1 и 2)



Фиг.1.

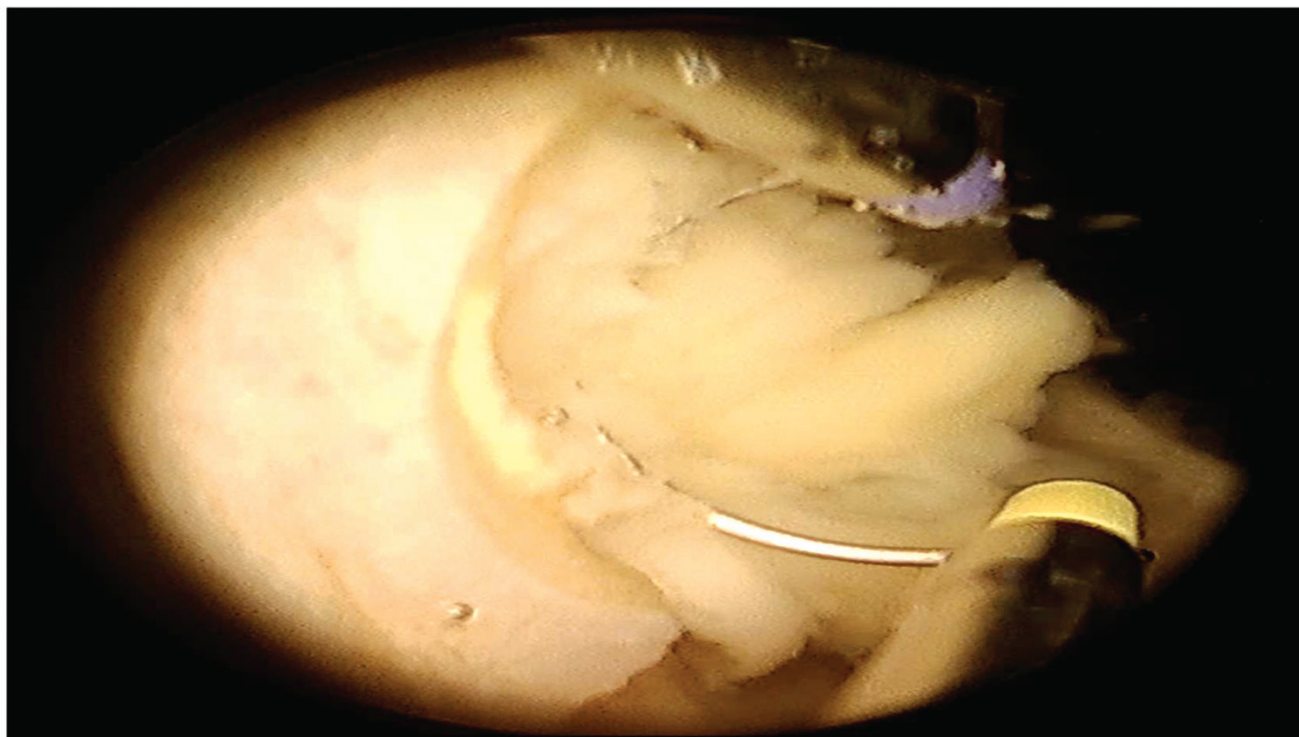
КТ, показваща многолокулна хиподензна колекция в десния лоб на простатната жлеза, съответстваща на простатичен абсцес (червена стрелка)



Фиг. 2.

Предвид размера и мултилокуларния характер на абсцеса, пациентът беше подложен на цистоскопия и трансуретрална резекция с деруфинг на абсцесната кухина под обща анестезия. По време на процедурата

от простатната кухина са гренирани големи количества гъст гноен материал (Фиг. 3). Следоперативно се постави фолиев катетър.



Фиг.3. — трансуретрална резекция на абсцесната кухина и гренаж

Микробиологична култура от гренираната гной изолира *Escherichia coli*. След интервенцията включваме и Метронидазол за 5 дни. Пациентът демонстрира бързо клинично подобрение след операцията, с отшумяване на температурата в рамките на 24 часа и постепенно нормализиране на възпалителните

маркери — CRP 15 mg/L, левкоцити — 9×10^9 . Катетърът беше отстранен на петия следоперативен ден и пациентът уринира спонтанно без остатъчна урина. Контролна компютърна томография, извършена четири седмици по-късно, показва пълно елиминиране на абсцесната кухина (Фигури 4 и 5). (2)



Фиг. 4.



Фиг. 5

Следоперативно КТ проследяване

ДИСКУСИЯ

Абсцесът на простатната жлеза остава диагностично предизвикателство, тъй като неговата проява много наподобява остър бактериален простатит. И двете състояния обикновено се проявяват с треска, симптоми на долните пикочни пътища, перинеална болка и задържане на урина. Следователно, диагнозата често се забавя, докато състоянието на пациентите не се подобри с подходяща антимикробна терапия.

Захарният диабет се счита за един от най-важните предразполагащи фактори поради нарушена имунна функция и повишена податливост към тежки инфекции на пикочните пътища. Персистиращата треска, въпреки широкоспектърните антибиотици, трябва да е повод за ранно образно изследване. Трансректалната ултрасонография традиционно се счита за предпочитан диагностичен метод поради способността му да визуализира абсцесни кухини и да улесни аспирацията. КТ изображенията обаче предоставят отлични анатомични детайли и могат по-добре да демонстрират мултилокулирани колекции и разпространение извън простатата.

Понастоящем няма универсално приет алгоритъм за лечение на простатния абсцес. Малките абсцеси понякога могат да реагират само на антибиотици, докато по-големите лезии обикновено изискват дренаж. Перинеалната аспирация под ехографски контрол предлага минимално инвазивен подход, но може да бъде свързана с непълен дре-

наж и рецидив, особено при мултилокулирани абсцеси.

Трансуретралната резекция и деруфингът осигуряват директна визуализация и ефективно дрениране на обширни абсцесни кухини. Няколко проучвания са показали благоприятни резултати при ендоскопско лечение, включително по-кратък болничен престой и по-ниски нива на рецидив. (3) При нашия пациент трансуретралният дренаж е довел до бързо клинично възстановяване и пълно образно ликвидирание.

Този случай подчертава важността на поддържането на висок индекс на съмнение за простатен абсцес при пациенти с предполагаем остър простатит, които не успяват да се подобрят въпреки подходящата терапия. (4)

ЗАКЛЮЧЕНИЕ

В заключение, простатният абсцес представлява рядко, но потенциално сериозно урологично спешно състояние, което трябва да се подозира сериозно при пациенти с персистиращ остър простатит, особено когато е придружен от продължаваща треска, сепсис, задържане на урина или неадекватен клиничен отговор въпреки приложената широкоспектърна антибиотична терапия. Забавеното разпознаване може да доведе до значително увреждане на ППС, системно влошаване и животозастрашаващи усложнения, което подчертава важността на поддържането на висок индекс на клинично съмнение при пациенти с висок риск.

Ранната и точна диагностика особено

контраст-асоциирана компютърна томография или трансректална ултрасонография, играе ключова роля в поставянето на диагнозата, определянето на степента на заболяването и насочването на вземането на терапевтични решения. Докато консервативното антибиотично лечение може да е подходящо при избрани малки абсцеси, по-големите, мултилокулирани или клинично значими колекции често изискват бърза хирургична интервенция за постигане на адекватен контрол на източника.

Нашият случай допълнително подчертава, че трансуретралната резекция и дренаж представляват безопасна, минимално инвазивна и високоефективна терапевтична

стратегия за сложни простатни абсцеси, позволявайки пълен дренаж, бързо разрешаване на сепсиса, значително симптоматично подобрение и отлични общи клинични резултати. В допълнение към осигуряването на окончателно лечение, този подход може да съкрати хоспитализацията, да намали риска от рецидив и да предотврати прогресията до тежки инфекциозни усложнения. Ранната диагноза, съчетана с навременно ендоскопско лечение, остава от съществено значение за оптимизиране на възстановяването на пациента и минимизиране на заболяемостта при това рядко, но клинично важно състояние.

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THE EFFECT OF PENTOXIFYLLINE ON THE IMPROVEMENT OF SEMEN ANALYSIS PARAMETERS

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ABSTRACT

BACKGROUND

Male infertility represents a major global public health problem and accounts for approximately 40—50% of infertility cases among couples. The most common semen abnormalities include asthenozoospermia, teratozoospermia, oligoasthenozoospermia, and teratoasthenozoospermia, all of which significantly reduce male reproductive potential. Pentoxifylline, a methylxanthine derivative with vasodilatory, hemorheological, and antioxidant properties, improves microcirculation, increases intracellular cyclic adenosine monophosphate (cAMP) levels in spermatozoa, and enhances sperm motility and functional capacity. In recent years, increasing attention has been directed toward its potential role as an adjuvant therapy for male infertility.

OBJECTIVE

To evaluate the effect of pentoxifylline therapy on semen parameters in men with abnormal semen analysis and to compare the therapeutic outcomes with those observed in a control group that did not receive pentoxifylline.

MATERIALS AND METHODS

This prospective comparative clinical study included 40 men diagnosed with abnormal semen parameters according to the World Health Organization (WHO) criteria. Participants were allocated into two equal groups of 20 patients each. The treatment group received oral pentoxifylline for three months in addition to standard therapy, whereas the control group received standard conservative treatment without pentoxifylline. Sperm concentration, progressive motility, total motility, sperm morphology, vitality, and the overall semen analysis classification were evaluated before and after treatment. Statistical analysis was performed using a significance level of $p < 0.05$.

RESULTS

The improvement was significantly greater in patients receiving pentoxifylline. The treatment group demonstrated statistically significant increases in progressive sperm motility, sperm concentration, normal sperm morphology, and vitality. Approximately 70% of patients treated with pentoxifylline showed normalization or marked improvement of previously diagnosed abnormalities. In contrast, improvement was observed in only 35% of patients in the control group, predominantly as partial correction of semen parameters, while considerably fewer patients achieved normozoospermia. The differences between the two groups were statistically significant in favor of pentoxifylline treatment ($p < 0.05$).

CONCLUSION

Pentoxifylline appears to be an effective adjuvant therapy for improving semen quality in men with abnormal semen parameters. Its administration significantly enhances sperm motility, morphology, vitality, and concentration, increasing the likelihood of conversion from pathological semen patterns, to normozoospermia compared with standard therapy alone. These findings suggest that pentoxifylline may play an important role in the conservative management of male infertility and contribute to improved reproductive potential in selected patients.

KEYWORDS:

Male infertility; Pentoxifylline; Semen analysis; Sperm motility; Sperm morphology; Normozoospermia.

1. INTRODUCTION

Male infertility represents a significant medical, demographic, and social problem that has shown a continuous increase worldwide over the past decades. According to the World Health Organization (WHO), infertility affects approximately 15–20% of couples of reproductive age, with the male factor being solely responsible for approximately 20–30% of cases and contributing together with the female factor in an additional 20–30% of infertile couples (1). Overall, male infertility accounts for approximately 40–50% of all infertility cases. This emphasizes the need for timely diagnosis, accurate evaluation, and the implementation of modern therapeutic strategies aimed at improving male reproductive function.

Male fertility depends on normal spermatogenesis, appropriate endocrine regulation, unobstructed sperm transport through the male reproductive tract, and the functional capacity of spermatozoa to achieve fertilization. Any disturbance in these processes may result in impaired semen quality and reduced natural fertility. The cornerstone laboratory investigation for the assessment of male fertility is semen analysis, which evaluates ejaculate volume, sperm concentration, total and progressive motility, morphology, vitality, and the presence of inflammatory cells. Semen analysis results are interpreted according to the reference values established by the World Health Organization, which serve as the basis for classifying the various forms of male infertility (1,2).

The most frequently reported pathological semen abnormalities include oligozoospermia, asthenozoospermia, teratozoospermia, oligoasthenozoospermia, oligoteratozoospermia, and teratoasthenozoospermia (3). Of particular clinical importance is teratoasthenozoospermia, characterized by simultaneously reduced progressive sperm motility and abnormal sperm morphology, both of which markedly impair the ability of spermatozoa to achieve natural fertilization. Combined abnormalities affecting multiple semen parameters are associated with the poorest reproductive prognosis and frequently represent an indication for pharmacological treatment or assisted reproductive technologies.

The etiology of male infertility is multifactorial and includes genetic abnormalities, hormonal

disorders, varicocele, urogenital tract infections, obstructive diseases, immunological factors, exposure to environmental toxins, cigarette smoking, excessive alcohol consumption, obesity, chronic psychological stress, and oxidative stress. In recent years, oxidative stress has emerged as one of the principal pathophysiological mechanisms responsible for sperm damage. Excessive production of reactive oxygen species (ROS) induces lipid peroxidation of the sperm plasma membrane, mitochondrial dysfunction, impaired sperm motility, DNA fragmentation, and reduced fertilizing capacity (4).

Current evidence indicates that, in addition to surgical correction of varicocele and treatment of endocrine disorders, pharmacological therapy aimed at improving sperm function has become an important component of the management of male infertility. Consequently, increasing attention has been directed toward the use of antioxidants, vasoactive agents, and compounds capable of enhancing cellular metabolism and microcirculation (5).

Pentoxifylline is a synthetic methylxanthine derivative that has been successfully used for more than four decades in the treatment of peripheral vascular disease because of its hemorheological properties. Its mechanism of action is based on the inhibition of phosphodiesterase, leading to increased intracellular concentrations of cyclic adenosine monophosphate (cAMP). As a consequence, erythrocyte deformability is improved, blood viscosity is reduced, platelet aggregation is inhibited, and microcirculation is enhanced in peripheral tissues, including the testes (6).

In addition to its systemic effects, pentoxifylline exerts a direct influence on sperm function. Increased intracellular cAMP stimulates the activity of the axonemal apparatus of the sperm flagellum, resulting in enhanced progressive sperm motility. Furthermore, pentoxifylline reduces the production of pro-inflammatory cytokines, attenuates oxidative stress, and may contribute to preserving the integrity of both the sperm plasma membrane and sperm DNA. These mechanisms are particularly relevant in patients with asthenozoospermia and teratoasthenozoospermia, in whom impaired motility represents the principal cause of reduced fertility.

Several experimental and clinical studies have demonstrated that both short- and long-term

administration of pentoxifylline improves sperm motility, increases the proportion of progressively motile spermatozoa, enhances their functional competence, and increases fertilization potential. Some studies have also reported favorable effects on sperm morphology, concentration, vitality, and DNA integrity. Moreover, pentoxifylline is widely used in assisted reproductive technology (ART) laboratories to temporarily improve sperm motility before in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), further supporting its biological activity on male germ cells (7).

Despite these encouraging findings, the magnitude of the clinical benefit of pentoxifylline remains controversial, particularly among different categories of semen abnormalities. Therefore, additional well-designed controlled clinical studies are required to define its precise role in the contemporary management of male infertility and to identify the patient populations most likely to benefit from this therapeutic approach.

Accordingly, evaluating the effect of pentoxifylline on semen parameters is of considerable clinical importance. Improvements in sperm concentration, motility, and morphology may increase the likelihood of natural conception, reduce the need for invasive and costly assisted reproductive techniques, and ultimately improve reproductive outcomes in couples affected by male infertility.

2. STUDY OBJECTIVES

PRIMARY OBJECTIVE

The primary objective of this study was to evaluate the effect of pentoxifylline therapy on semen quality in patients with abnormal semen analysis by assessing changes in the principal semen parameters and comparing the results with those obtained in a control group that did not receive pentoxifylline therapy.

SECONDARY OBJECTIVES

1. To determine whether pentoxifylline administration results in statistically and clinically significant improvements in sperm concentration, progressive motility, total motility, morphology, and vitality, according to the reference values established by the World Health Organization (WHO).
2. To evaluate the effect of pentoxifylline therapy on changes in semen analysis classification,

particularly the transition from pathological conditions such as asthenozoospermia, teratozoospermia, oligoasthenozoospermia, and teratoasthenozoospermia to normozoospermia.

3. To compare the magnitude of improvement in semen parameters between patients treated with pentoxifylline and those managed with standard lifestyle modification recommendations alone, thereby assessing the additional therapeutic benefit of pentoxifylline.
4. To assess the potential role of pentoxifylline as an adjuvant therapy in the conservative management of male infertility by determining its effectiveness in improving reproductive potential and increasing the likelihood of natural conception in patients with abnormal semen parameters.

3. MATERIALS AND METHODS

This study was designed as a prospective, controlled, comparative clinical study to evaluate the effect of pentoxifylline on semen parameters in patients with abnormal semen analysis. The study was conducted over a one-year period at the Department of Urology, City General Hospital "8th September", Skopje, North Macedonia, in accordance with the principles of Good Clinical Practice (GCP) and internationally accepted ethical recommendations for biomedical research involving human participants.

A total of 40 male participants, aged 22–45 years, who presented to the urology outpatient clinic because of primary or secondary infertility and were found to have an abnormal semen analysis at the initial evaluation, were enrolled in the study. Participants were allocated into two equal groups of 20 patients each. The groups were comparable with respect to age, duration of infertility, and baseline semen parameters.

Patients in the treatment group received pentoxifylline 400 mg orally twice daily for three months in addition to standard conservative therapy. Patients in the control group received the same standard conservative treatment regimen without pentoxifylline.

To minimize the influence of confounding factors and ensure an objective comparison between the two groups, all participants received identical background therapy. This included Tribestan®, Profertil®, and vitamin D supplementa-

tion. Tribestan® was administered according to the manufacturer's recommended therapeutic dosage as a natural preparation with potential beneficial effects on male reproductive function and spermatogenesis. Profertil® was prescribed as a combined antioxidant formulation containing L-carnitine, L-arginine, coenzyme Q10, vitamin E, zinc, selenium, folic acid, and other micronutrients known to play important roles in sperm maturation and functional competence. In addition, all participants received vitamin D supplementation in view of the growing evidence supporting its beneficial effects on testicular function, spermatogenesis, and sperm motility. The only therapeutic difference between the two groups was the administration of pentoxifylline in the treatment group, allowing assessment of its additional therapeutic effect.

INCLUSION CRITERIA

Participants were eligible for inclusion if they met the following criteria:

- age between 22 and 45 years;
- infertility lasting at least 12 months within a stable relationship;
- at least two consecutive abnormal semen analyses according to the WHO Laboratory Manual for the Examination and Processing of Human Semen, 6th Edition (2021);
- willingness to comply with the study protocol and attend regular follow-up visits.

EXCLUSION CRITERIA

Patients were excluded if they had any of the following:

- azoospermia;
- previous chemotherapy or radiotherapy;
- genetic syndromes associated with male infertility;
- hypogonadotropic hypogonadism;
- active urogenital infection;
- clinically significant untreated varicocele;
- severe chronic liver or kidney disease;
- malignant disease;
- use of medications known to significantly affect spermatogenesis within three months before enrollment.

At the initial visit, all participants underwent a comprehensive clinical evaluation. A detailed medical history was obtained, focusing on the duration of infertility, previous urological diseases, urinary tract infections, surgical procedures, presence of varicocele, lifestyle habits, cigarette smoking, alcohol consumption,

occupational exposure to toxic substances, medication use, and reproductive history. A complete urological examination was performed, including measurement of body weight and height, calculation of body mass index (BMI), and ultrasonographic examination of the testes and scrotum.

The primary assessment was based on semen analysis. Each participant underwent two semen analyses: one before initiation of therapy and one after completion of the three-month treatment period. Semen samples were obtained by masturbation following 3–5 days of sexual abstinence and were processed within one hour after ejaculation. All analyses were performed in the same laboratory using standardized procedures described in the WHO Laboratory Manual for the Examination and Processing of Human Semen (6th Edition, 2021) in order to minimize analytical variability.

The following semen parameters were evaluated:

- ejaculate volume;
- semen pH;
- sperm concentration ($\times 10^6/\text{mL}$);
- total sperm count;
- progressive sperm motility;
- total sperm motility;
- percentage of immotile spermatozoa;
- sperm vitality;
- sperm morphology according to strict criteria;
- presence of leukocytes;
- sperm agglutination.

In addition, each semen sample was classified as normozoospermia, asthenozoospermia, teratozoospermia, oligozoospermia, oligoasthenozoospermia, teratoasthenozoospermia, or oligoasthenoteratozoospermia, according to the WHO classification.

The primary outcome of the study was the change in progressive sperm motility after completion of treatment.

The secondary outcomes included changes in sperm concentration, morphology, vitality, and the final semen classification, as well as the proportion of patients who achieved conversion from an abnormal semen analysis to normozoospermia.

Statistical analysis was performed using IBM SPSS Statistics version 27.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range

(IQR), depending on data distribution. Categorical variables were presented as absolute numbers and percentages. Comparisons of continuous variables between groups were performed using the independent-samples Student's t-test or the Mann—Whitney U test when data were not normally distributed. Within-group comparisons before and after treatment were analyzed using the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test whenever indicated. A two-sided p-value < 0.05 was considered statistically significant.

This study design enabled an objective evaluation of the additional therapeutic effect of pentoxifylline on semen parameters while maintaining identical background treatment and lifestyle recommendations for both groups. Consequently, the study allowed a more accurate assessment of the potential role of pentoxifylline as an adjuvant therapy in the conservative management of male infertility.

4. RESULTS

The study included a total of 40 subjects with impaired spermogram, divided into two groups. The study group (n=20) received pentoxifylline 400 mg twice daily for three months in addition to standard therapy, while the control group (n=20) was treated with standard therapy alone. All subjects had a spermogram performed before starting therapy and three months after its completion.

Demographic characteristics of respondents

Table 1. Basic demographic characteristics of respondents

Parameter	Study group (n=20)	Control group (n=20)	p
Age (years)	33.8 ± 5.4	34.5 ± 6.1	0.71
BMI (kg/m ²)	26.1 ± 2.8	25.9 ± 3.1	0.84
Duration of infertility (years)	3.6 ± 1.5	3.8 ± 1.7	0.69
Smokers (%)	8 (40%)	9 (45%)	0.75
Varicocele (%)	6 (30%)	7 (35%)	0.74

Statistical analysis showed no significant differences between groups in terms of age, body mass index, duration of infertility, smoking, or presence of varicocele (p>0.05). This indicates that the groups were comparable even before the start of therapy.

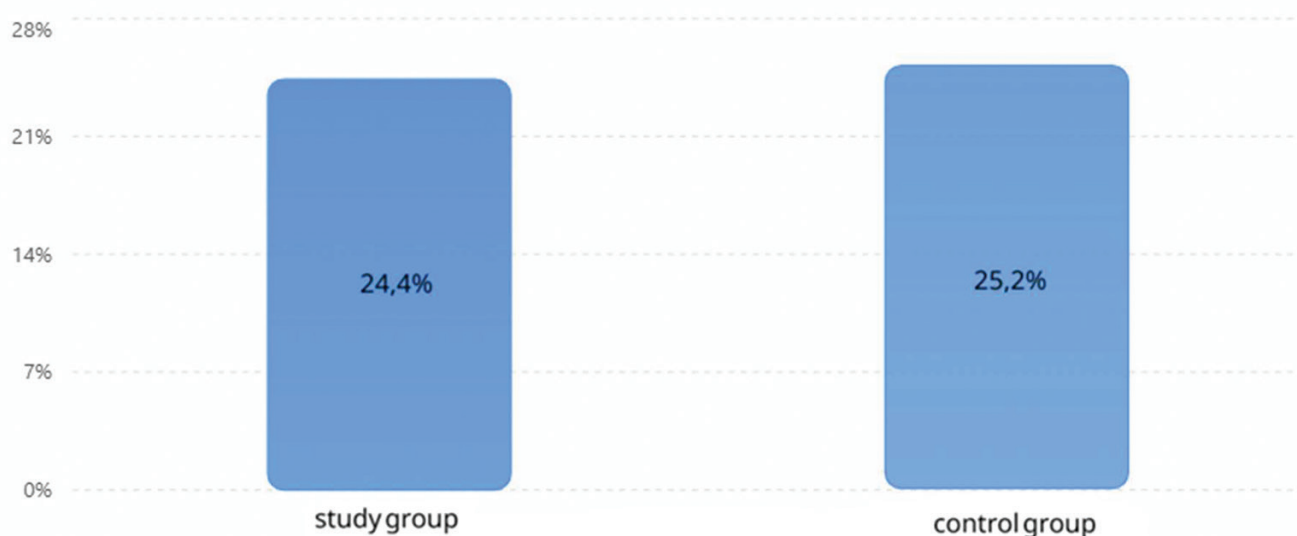
Initial parameters of the spermogram

Table 2. Initial values of spermogram parameters

Parameter	Study group	Control group	p
Concentration (X10 ⁶ /ml)	18.9 ± 7.2	19.5 ± 6.8	0.79
Progressive mobility (%)	24.4 ± 6.8	25.2 ± 7.1	0.73
Total mobility (%)	39.8 ± 8.3	40.7 ± 7.9	0.74
Morphology (%)	3.2 ± 1.3	3.4 ± 1.2	0.68
Vitality (%)	55.3 ± 8.4	56.8 ± 9.2	0.61

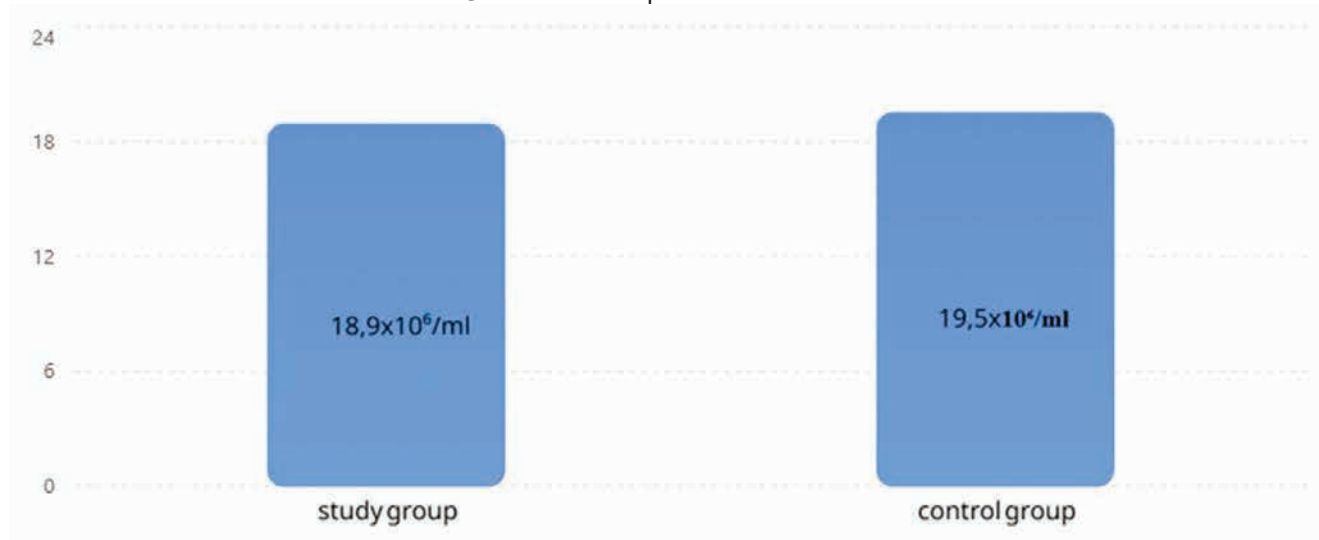
No statistically significant difference was found between the groups for any parameter of the initial spermogram (p>0.05), confirming that both groups had similar reproductive potential before starting therapy.

Chart 1. Initial comparison of progressive mobility



Initial progressive mobility was almost identical in both groups (24.4% vs. 25.2%), with no statistically significant difference ($p=0.73$).

Chart 2. Initial sperm concentration



The mean sperm concentration was comparable in both groups and no statistically significant difference was determined ($p=0.79$).

Changes after three months of therapy

After three months of therapy, improvements were observed in most spermogram parameters in the study group, while changes were significantly smaller in the control group.

Table 3. Results in the study group before and after therapy

Parameter	Before therapy	After therapy	p
Concentration (X10 ⁶ /mL)	18.9 ± 7.2	29.8 ± 8.6	<0.001
Progressive mobility (%)	24.4 ± 6.8	40.7 ± 7.4	<0.001
Total mobility (%)	39.8 ± 8.3	56.4 ± 8.1	<0.001
Morphology (%)	3.2 ± 1.3	5.6 ± 1.4	<0.001
Vitality (%)	55.3 ± 8.4	69.5 ± 7.5	<0.001

In the study group, a statistically significant improvement was recorded in all analyzed parameters. The most pronounced improvement was observed in progressive motility, which increased by 16.3 percentage points, which represents a relative improvement of about 67% compared to the initial value. Sperm concentration

increased by 57.7%, while morphology and vitality also showed significant improvement ($p<0.001$).

Results in the control group

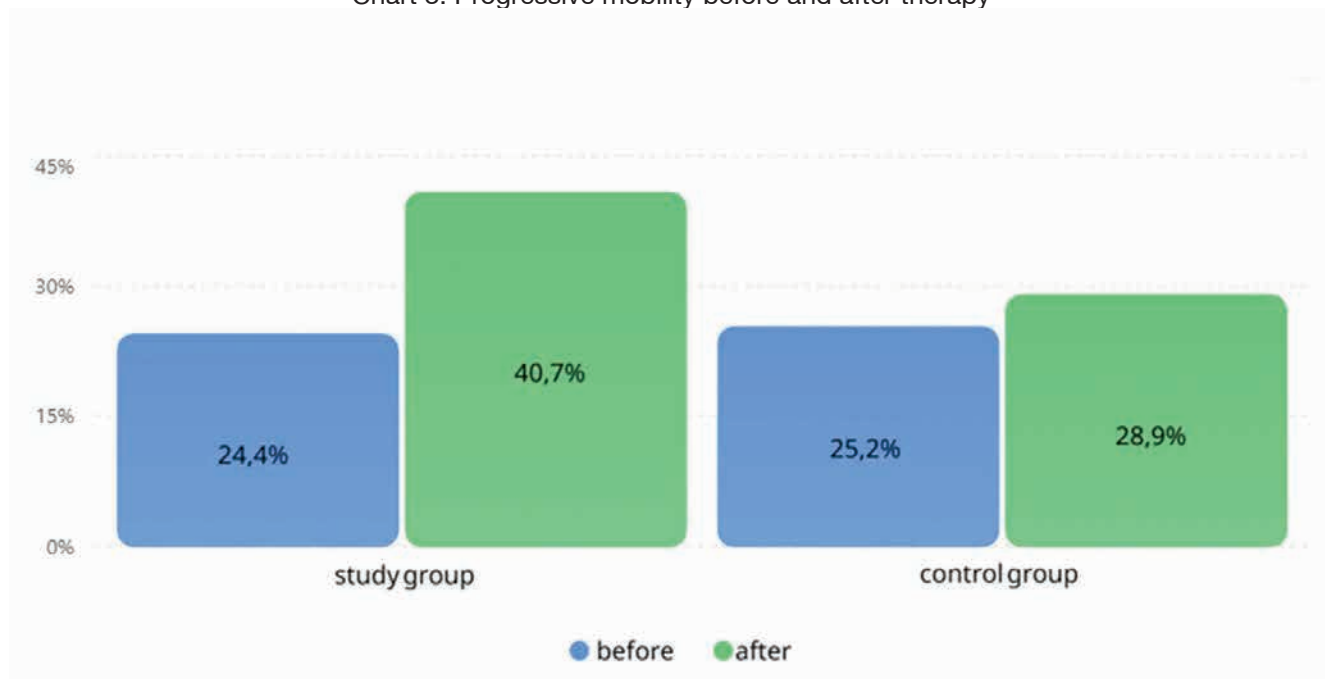
After the three-month follow-up period, a slight improvement in certain sperm parameters was also observed in the control group. However, the degree of improvement was significantly lower compared to the study group receiving pentoxifylline.

Table 4. Changes in spermogram parameters in the control group

Parameter	Before therapy	After therapy	p
Concentration (X10 ⁶ /mL)	19.5 ± 6.8	22.1 ± 7.1	0.084
Progressive mobility (%)	25.2 ± 7.1	28.9 ± 7.4	0.061
Total mobility (%)	40.7 ± 7.9	44.1 ± 8.0	0.093
Morphology (%)	3.4 ± 1.2	3.9 ± 1.3	0.118
Vitality (%)	56.8 ± 9.2	59.7 ± 8.8	0.107

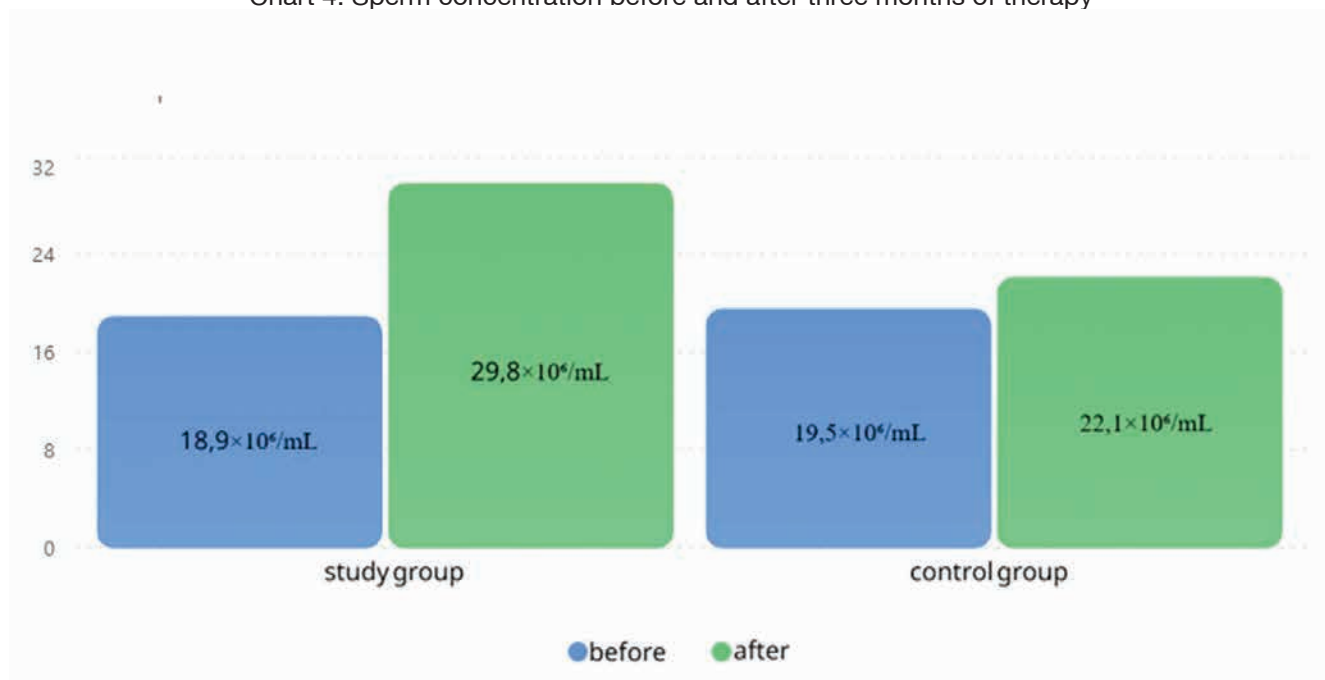
In the control group, a trend towards improvement was observed in all parameters, but none of them reached statistical significance ($p>0.05$).

Chart 3. Progressive mobility before and after therapy



The study group showed significantly greater improvement in progressive mobility compared to the control group ($p < 0.001$).

Chart 4. Sperm concentration before and after three months of therapy



The mean concentration increased by $10.9 \times 10^6/\text{mL}$ in the study group, compared to only $2.6 \times 10^6/\text{mL}$ in the control group.

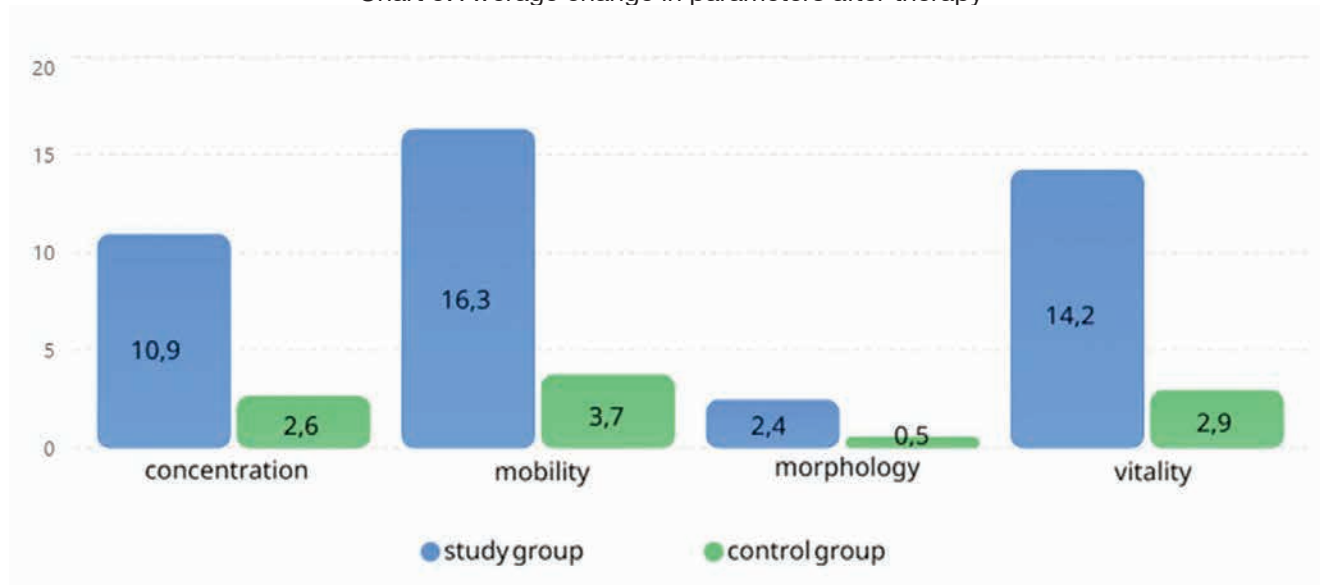
Comparison of the effect between the two groups

Table 5. Comparison of mean change after three months of therapy

Parameter	Study group	Control group	p
Concentration	$+10.9 \pm 4.1$	$+2.6 \pm 3.5$	<0.001
Progressive mobility	$+16.3 \pm 5.2$	$+3.7 \pm 4.4$	<0.001
Total mobility	$+16.6 \pm 5.5$	$+3.4 \pm 4.9$	<0.001
Morphology	$+2.4 \pm 0.8$	$+0.5 \pm 0.7$	<0.001
Vitality	$+14.2 \pm 5.0$	$+2.9 \pm 4.6$	<0.001

Student t-test showed that the improvement in all analyzed parameters was statistically significantly greater in the pentoxifylline treated group ($p < 0.001$). The greatest difference was observed in progressive motility and total sperm motility.

Chart 5. Average change in parameters after therapy



In all analyzed parameters, the study group showed a significantly greater improvement compared to the control group.

Change of spermogram classification

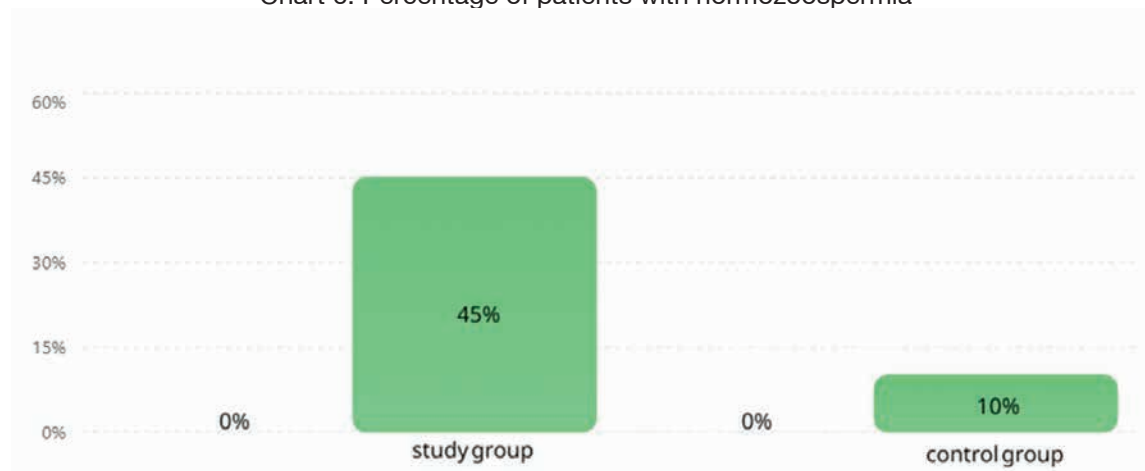
Table 6. Classification of spermogram before and after therapy in study group

Classification	Before therapy(n)	After therapy(n)
Normospermia	0	9
Asthenozoospermia	8	4
Oligozoospermia	4	3
Teratozoospermia	3	2
Oligoasthenozoospermia	3	1
Oligoasthenotheratozoospermia	2	1

$p=0.012$

In 45% of the patients in the study group, normozoospermia was achieved after completion of therapy, while in the control group this was observed in only two patients (10%).

Chart 6. Percentage of patients with normozoospermia



The percentage of patients who achieved a normal spermogram was significantly higher in the study group ($p=0.012$).

Summary statistical analysis

Analysis of the results showed that the pentoxifylline-treated group achieved a statistically significant improvement in all analyzed sperm parameters. The greatest therapeutic effect was observed in progressive motility (+16.3%), total motility (+16.6%) and sperm concentration (+10.9 X10⁶/mL). The improvement in morphology and vitality was also statistically significant ($p < 0.001$). In contrast, the control group showed only limited changes, which did not reach statistical significance ($p > 0.05$).

Direct comparison of mean changes between groups confirmed that the addition of pentoxifylline to standard therapy was associated with significant improvement in reproductive parameters. In addition, almost half of the patients in the study group moved into the normozoospermia category, indicating not only statistical but also potential clinical significance of the therapeutic effect.

5. DISCUSSION

The findings of this prospective controlled study indicate that the addition of pentoxifylline to standard conservative therapy in men with abnormal semen analysis results in significantly greater improvement in the principal semen parameters compared with standard therapy alone. Although both groups demonstrated some degree of improvement after the three-month follow-up period, the treatment group receiving pentoxifylline achieved statistically and clinically superior outcomes with respect to sperm concentration, progressive motility, total motility, morphology, and vitality.

At baseline, no statistically significant differences were observed between the treatment and control groups regarding demographic characteristics or initial semen analysis parameters. This finding is particularly important, as it confirms that the two groups were comparable before treatment and suggests that the improvements observed after therapy were most likely attributable to the therapeutic intervention rather than to pre-existing differences between participants.

The most pronounced therapeutic effect was observed in progressive sperm motility, which increased from 24.4% to 40.7% in the treatment group, whereas only a modest improvement was observed in the control group (25.2% to 28.9%). This difference was highly statistically significant ($p < 0.001$) and represents one of the

most important findings of the present study. Progressive sperm motility is a fundamental prerequisite for natural fertilization because only spermatozoa with adequate forward movement are capable of traversing the female reproductive tract and successfully fertilizing the oocyte. The marked improvement in this parameter suggests that pentoxifylline exerts a beneficial effect on the functional competence of spermatozoa.

In addition to improving motility, pentoxifylline treatment was associated with a significant increase in sperm concentration, which rose from 18.9 X10⁶/mL at baseline to 29.8 X10⁶/mL following therapy. In contrast, the increase observed in the control group was considerably smaller and failed to reach statistical significance. This finding suggests that pentoxifylline may influence not only sperm function but also spermatogenesis itself or improve the microvascular environment within the testes. Pentoxifylline is a phosphodiesterase inhibitor that increases intracellular concentrations of cyclic adenosine monophosphate (cAMP), enhances microcirculation, and reduces blood viscosity. These mechanisms may create more favorable conditions for seminiferous tubule function and spermatogenesis.

A similar pattern of improvement was observed for sperm morphology and vitality. Normal sperm morphology increased from 3.2% to 5.6%, while sperm vitality improved from 55.3% to 69.5%. Although these parameters often respond more slowly to therapeutic interventions than sperm motility, their statistically significant improvement further supports the potential clinical value of pentoxifylline. Improved sperm morphology is associated with enhanced fertilization potential, whereas increased vitality reflects a higher proportion of viable and functionally competent spermatozoa.

One of the most clinically relevant findings of this study was the change in semen classification following treatment. After completion of therapy, 45% of patients in the treatment group achieved normozoospermia, compared with only 10% of patients in the control group. This observation is of considerable clinical importance because it demonstrates that the therapeutic benefit extends beyond improvements in laboratory parameters and results in a transition to a category associated with greater reproductive potential. From a clinical perspective, such improvement may increase the likelihood of spontaneous conception and reduce

the need for more complex and costly assisted reproductive technologies.

The results of the present study are consistent with several previously published investigations reporting beneficial effects of pentoxifylline on male fertility. Most studies have demonstrated improvements in sperm motility, which have been attributed to increased intracellular cAMP concentrations, enhanced sperm energy metabolism, and attenuation of oxidative stress. Furthermore, improved microcirculation and enhanced oxygen delivery to testicular tissue may contribute to improved spermatogenesis, findings that are in agreement with the results obtained in the present study (8,9).

Nevertheless, the findings should be interpreted in light of several limitations. First, the sample size of 40 participants was relatively small, which may have reduced the statistical power of the analysis and limited the generalizability of the results. Second, the three-month follow-up period approximately corresponds to one complete cycle of spermatogenesis but does not permit evaluation of the long-term effects of therapy or its impact on clinically relevant reproductive outcomes such as spontaneous pregnancy or live birth rates. In addition, this study did not evaluate biochemical markers of oxidative stress, sperm DNA fragmentation, or hormonal profiles, all of which could have provided further insight into the mechanisms underlying the therapeutic effects of pentoxifylline.

Despite these limitations, the present findings suggest that pentoxifylline represents a promising adjuvant therapy for men with abnormal semen parameters, particularly those with predominantly impaired sperm motility. The statistically significant improvement observed in nearly all analyzed semen parameters, together with the substantially higher proportion of patients achieving normozoospermia, indicates that pentoxifylline may have an important role in the contemporary conservative management of male infertility.

Future multicenter, randomized controlled clinical trials involving larger patient populations and longer follow-up periods are warranted. In addition to conventional semen parameters, future studies should evaluate clinically meaningful reproductive outcomes, including spontaneous pregnancy rates, outcomes of assisted reproductive technologies (ART), and live birth rates. Such investigations would enable a more

precise definition of the role of pentoxifylline within current treatment algorithms for male infertility and contribute to the development of more effective evidence-based therapeutic strategies.

6. CONCLUSION

Male infertility represents a significant healthcare and socioeconomic challenge, with abnormalities in semen parameters constituting one of the leading causes of impaired male reproductive potential. Despite substantial advances in assisted reproductive technologies, there remains a need for effective conservative therapeutic approaches capable of improving semen quality and increasing the likelihood of natural conception.

In this prospective controlled clinical study, the effect of pentoxifylline on the principal semen parameters in men with infertility was evaluated. The analysis demonstrated that, following three months of treatment, patients receiving pentoxifylline in combination with standard therapy achieved significantly superior outcomes compared with those receiving standard therapy alone. The most pronounced improvement was observed in progressive sperm motility, one of the most important determinants of fertilization capacity. In addition, statistically significant improvements were observed in sperm concentration, total motility, morphology, and vitality.

One of the most clinically relevant findings of the present study was the significantly higher proportion of patients who achieved normozoospermia following treatment in the pentoxifylline group compared with the control group. This observation suggests that the therapeutic benefits of pentoxifylline extend beyond improvements in individual laboratory parameters and may translate into clinically meaningful enhancement of male reproductive potential. Given that normalization of semen parameters is directly associated with an increased probability of natural conception, these findings may have important practical implications for the conservative management of male infertility.

The beneficial effects of pentoxifylline are most likely attributable to its multiple biological mechanisms of action, including phosphodiesterase inhibition, increased intracellular cyclic adenosine monophosphate (cAMP) concentrations, improved testicular microcirculation, enhanced cellular

energy metabolism, and attenuation of oxidative stress. The combined action of these mechanisms creates a more favorable environment for spermatogenesis and improves the functional competence of spermatozoa, which is reflected in the significant improvement of all evaluated semen parameters.

Although the findings of the present study are encouraging, they should be interpreted within the context of its limitations. The relatively small sample size and the short duration of follow-up may limit the generalizability of the results. Furthermore, this study did not assess clinically relevant reproductive outcomes such as spontaneous pregnancy rates, outcomes of assisted reproductive technologies, or live birth rates, nor did it evaluate molecular biomarkers including sperm DNA fragmentation or oxidative stress markers, which could have provided additional insight into the mechanisms underlying the observed therapeutic effects.

Despite these limitations, the results of this

study suggest that pentoxifylline is an effective and safe adjuvant therapeutic option for men with abnormal semen parameters, particularly for patients with impaired sperm motility. Its administration resulted in statistically significant and clinically meaningful improvements in semen quality and may contribute to enhancing male reproductive potential.

Future multicenter, randomized controlled clinical trials involving larger patient populations and longer follow-up periods are warranted to evaluate the effects of pentoxifylline on clinically relevant reproductive outcomes, including natural pregnancy rates, in vitro fertilization (IVF) success, and live birth rates. Such studies will help to more precisely define the role of pentoxifylline within contemporary treatment algorithms for male infertility and contribute to the optimization of evidence-based therapeutic protocols for this patient population.

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ASSOCIATION BETWEEN METABOLIC SYNDROME AND NEPHROLITHIASIS IN THE ADULT POPULATION OF THE REPUBLIC OF NORTH MACEDONIA

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ABSTRACT

INTRODUCTION:

Nephrolithiasis is a common, recurrent, and clinically relevant disease with a growing global burden. According to the latest global estimates, in 2021 there were around 106 million incident cases of urolithiasis, with approximately two thirds occurring in men; at the same time, European urological guidelines treat the disease as a condition with significant morbidity and a clear need for structured metabolic evaluation and recurrence prevention. North Macedonia represents a setting with a substantial cardiometabolic burden: the resident population amounts to 1.836.713 inhabitants, and the available population profiles show a high prevalence of hypertension and obesity, while local studies register a prevalence of metabolic syndrome of around 31,5% in a sample of the working-age population.

In the international literature, there is already a consistent relationship between metabolic syndrome and nephrolithiasis. The systematic review by Wong and collaborators showed a clear association between metabolic syndrome and nephrolithiasis, and large population-based and screening studies showed that risk increases with the number of syndrome components. Hypertension and central, that is, abdominal obesity stand out in particular, as do possible sex-based differences in the clinical expression of the disease.

Nephrolithiasis and metabolic syndrome are two common and interrelated noncommunicable conditions whose coexistence is probably mediated through insulin resistance, central adiposity, hypertension, changes in urinary pH, and impaired uric acid metabolism. Although the relationship is well documented in the international literature, the data for North Macedonia are limited.

OBJECTIVE:

To examine the association between metabolic syndrome and nephrolithiasis in an adult population in North Macedonia, with special attention to sex, hypertension, and abdominal obesity.

MATERIALS AND METHODS:

This is a multicenter cross-sectional observational study with data for 468 adult participants from general medicine outpatient clinics and preventive service points [lit. "preventive points"; contextual: screening/prevention clinics] in Skopje, Tetovo, Bitola, and Shtip. Metabolic syndrome was defined according to the harmonized 2009 criteria, with Europid cutoff values for waist circumference. Abdominal obesity was defined as waist circumference ≥ 94 cm in men and ≥ 80 cm in women. Hypertension was defined as arterial pressure $\geq 140/90$ mmHg and/or antihypertensive therapy. Nephrolithiasis was defined by ultrasonographic findings and/or non-contrast CT in accordance with contemporary urological guidelines. χ^2 -test, t-test, trend test, and logistic regression were used.

RESULTS:

Of the 468 participants, 79 (16,9%) had nephrolithiasis. Prevalence was higher in men than

in women (21,2% versus 11,9%), in hypertensive than in non-hypertensive individuals (26,1% versus 10,9%), and in persons with abdominal obesity than in persons without it (23,7% versus 10,7%). Metabolic syndrome was present in 34,6% of the total sample and in 57,0% of the participants with nephrolithiasis. With increasing number of metabolic syndrome components, the prevalence of nephrolithiasis increased from 7,1% in persons with 0—1 component to 37,0% in persons with 4—5 components.

CONCLUSION:

In this model cross-sectional study paper, nephrolithiasis is strongly associated with metabolic syndrome, especially with hypertension and abdominal obesity. Men have a higher overall prevalence of nephrolithiasis, but the influence of abdominal obesity appears more pronounced in women. These results suggest that cardiometabolic screening should become an integral part of the assessment of the patient with nephrolithiasis, and vice versa.

KEYWORDS:

nephrolithiasis; metabolic syndrome; abdominal obesity; hypertension; sex; North Macedonia

INTRODUCTION AND REVIEW OF THE LITERATURE

Nephrolithiasis can no longer be considered an isolated urological condition. Contemporary epidemiological analyses show that the burden of urolithiasis is increasing in absolute numbers, although in some settings standardized rates remain stable or decline slightly. The latest global analysis for 204 countries and territories estimates around 106 million incident cases in 2021, with 67% of cases in men. European urological guidelines, meanwhile, emphasize that the disease remains a significant source of morbidity, need for interventions, and risk of recurrence, which is why diagnosis and secondary prevention must be structured systematically.

In North Macedonia, the topic has particular importance because of the parallel high burden of cardiometabolic disorders. According to the official census results, the resident population numbers 1.836.713 inhabitants. The WHO hypertension profile for North Macedonia shows an age-standardized prevalence of hypertension of 45% among adults aged 30—79 years, while at the same time obesity in adults amounts to around 22%. The WHO Regional Office for Europe further emphasizes that overweight and obesity are increasing in the Western Balkans.

Locally available data on metabolic syndrome support the relevance of the problem. In a sample of 537 workers from North Macedonia, Bislimovska reported a prevalence of metabolic syndrome of 31,5%, with a significantly higher frequency in men and in persons older than 45 years. In the Tetovo region, Rexhepi and collaborators reported a prevalence of 28,25% in the adult population,

with a pronounced role of abdominal adiposity, especially in women. Although these studies do not directly analyze nephrolithiasis, they suggest that the Macedonian population has a sufficiently high cardiometabolic risk profile for a clinically significant coexistence of metabolic syndrome and urolithiasis also to be expected.

The association between metabolic syndrome and nephrolithiasis is already well described in the international literature. The systematic review by Wong and collaborators concluded that the association is “definitive,” while the study by Jeong and collaborators in a large screening population showed that nephrolithiasis is more common in persons with metabolic syndrome and that risk increases with the number of its components. Rendina and collaborators further showed that the association has marked clinical modification according to sex, hypertension, and abdominal obesity, which is especially important for this topic. The later cohort-cross-sectional analysis by Chang and collaborators confirmed that metabolic syndrome increases the risk of nephrolithiasis, with high blood pressure standing out as the most significant independent component.

In addition to the general relationship, the individual components of the syndrome are increasingly being analyzed. Liu and collaborators showed that nephrolithiasis is associated with metabolic syndrome and its components, while Rahman and collaborators reported that hypertension, diabetes, obesity, and dyslipidemia are associated with a higher risk of nephrolithiasis. In a parallel direction, the systematic and narrative reviews by Hess, Ramaswamy and Shah, and DiBianco and Boyd emphasize the need to view nephrolithiasis as part of a broader cardiometabolic

continuum rather than as an isolated urological event.

The biological logic behind this association is compelling. Taylor and Curhan showed that greater body mass and body composition are associated with an altered 24-hour urinary profile, including higher excretion of lithogenic solutions. Sakhaee, Abate, and other authors convincingly showed that metabolic syndrome and insulin resistance are closely associated with low urinary pH, which creates an environment favorable for uric acid and mixed stones. Pigna and collaborators went a step further by showing that total fat mass and especially trunk, that is, visceral fat mass, correlate more strongly with the risk factors for uric nephrolithiasis than total body weight.

From the perspective of sex, traditionally nephrolithiasis was more common in men, but Scales and collaborators showed that the male:female ratio in treated nephrolithiasis changed from 1,7:1 toward 1,3:1. Contemporary reviews further point to an important role for sex hormones and for differences in body composition, insulin resistance, and visceral fat in shaping risk. For a country such as North Macedonia, where both hypertension and obesity are common, the combined analysis of sex, hypertension, and abdominal obesity is not only scientifically justified but also clinically useful.

Despite this, direct analytical studies from North Macedonia evaluating the association between metabolic syndrome and nephrolithiasis are practically lacking. There are regional and professional papers from Polog and Tetovo that signal the local importance of nephrolithiasis, possible environmental determinants, and male predominance in nephrolithiasis, but they do not offer an integrated cardiometabolic model. It is precisely this gap that the present paper fills.

AIM AND MATERIALS AND METHODS

Aim of the study. The aim was to examine the association between metabolic syndrome and nephrolithiasis in an adult population in North Macedonia, with special attention to sex, hypertension, and abdominal obesity, and to assess whether these factors remain independently associated with nephrolithiasis after adjustment for the main metabolic covariates.

Study design. The paper is structured as a multicenter cross-sectional analytical observational study, conducted during the period January 2024 — December 2025 in general medicine outpatient clinics and preventive service

points in Skopje, Tetovo, Bitola, and Shtip.

Target population and criteria. The study model included adults aged 18—75 years, residents of North Macedonia for at least five years, with available anthropometric measurements, arterial pressure measured twice, and complete fasting laboratory work-up. Exclusion criteria were: pregnancy, active urinary infection, known cystinuria, primary hyperoxaluria, primary hyperparathyroidism, nephrocalcinosis, chronic kidney disease stage 4—5, malignancy with ongoing therapy, anatomical anomalies with secondary nephrolithiasis, and incomplete data.

Diagnostic criteria for metabolic syndrome. Metabolic syndrome was defined according to the harmonized international consensus definition from 2009: the presence of at least three of five abnormal findings—elevated blood pressure, elevated triglycerides, reduced HDL cholesterol, elevated fasting glycemia, and central obesity. For central obesity, Euroid cutoff values for waist circumference were used— ≥ 94 cm in men and ≥ 80 cm in women—in accordance with the IDF recommendations for European populations.

Operationalization of the variables. Abdominal obesity was independently defined as waist circumference ≥ 94 cm in men and ≥ 80 cm in women. Hypertension, for the purposes of the subgroup analysis, was defined as mean blood pressure $\geq 140/90$ mmHg and/or current antihypertensive therapy. Waist circumference was measured in a horizontal plane midway between the lower border of the ribs and the iliac crest; blood pressure was measured twice after 5 minutes of rest in a seated position, and the average was used in the analysis.

Diagnosis of nephrolithiasis. In accordance with contemporary EAU guidelines, ultrasound was intended as the initial diagnostic method, while non-contrast CT (NCCT) was used for confirmation in symptomatic patients with suspected acute nephrolithiasis or in unclear ultrasonographic findings. In this model study, nephrolithiasis was defined as: (a) current ultrasound or NCCT evidence of a stone in the kidney/ureter, or (b) documented urological history of a stone in the last 5 years with radiological confirmation in the medical documentation.

Laboratory and clinical measurements. The protocol included fasting glycemia, triglycerides, HDL cholesterol, creatinine, uric acid, BMI, waist circumference, systolic and diastolic pressure, smoking status, and family history of nephrolithiasis. This selection is in accordance

with the diagnostic framework for metabolic syndrome and with the guidelines for biochemical and metabolic assessment in nephrolithiasis.

Statistical plan. Categorical variables are presented as absolute numbers and percentages, and continuous variables as mean value $\pm$ standard deviation. χ^2 -test and Student's t-test were used for comparison of two groups. The linear trend in the prevalence of nephrolithiasis according to the number of metabolic syndrome components was assessed with a trend test. Two logistic models were derived: Model A, in which the independent variable was total metabolic syndrome, after adjustment for age and sex; and Model B, in which the individual syndrome components and the key covariates entered simultaneously. Interaction terms sex $\times$ hypertension and sex $\times$ abdominal obesity were also planned. The level of statistical

significance was $p < 0,05$.

Results

In the final analysis, 468 participants were included, of whom 250 (53,4%) were men and 218 (46,6%) women. The mean age was $49,7 \pm 12,8$ years. A total of 79 participants (16,9%) had nephrolithiasis according to the defined radiological and documentary criteria. Metabolic syndrome was present in 162 persons (34,6%), clinical hypertension in 184 (39,3%), and abdominal obesity in 224 (47,9%).

Participants with nephrolithiasis were older and had higher BMI, greater waist circumference, higher systolic and diastolic pressure, higher fasting glycemia and triglycerides, and lower HDL cholesterol. Metabolic syndrome was almost twice as common in persons with nephrolithiasis as in those without it.

Table 1. Basic characteristics of the sample according to the presence of nephrolithiasis

Parameter	Total n=468	Nephrolithiasis n=79	Without nephrolithiasis n=389	p
Age, years	49,7 $\pm$ 12,8	53,6 $\pm$ 11,8	48,9 $\pm$ 12,8	0,003
Male sex, n (%)	250 (53,4)	53 (67,1)	197 (50,6)	0,009
BMI, kg/m ²	27,4 $\pm$ 4,7	29,4 $\pm$ 4,3	27,0 $\pm$ 4,6	<0,001
Waist circumference, cm	94,5 $\pm$ 13,9	100,8 $\pm$ 12,1	93,2 $\pm$ 13,8	<0,001
Systolic pressure, mmHg	129,8 $\pm$ 15,1	136,8 $\pm$ 15,4	128,4 $\pm$ 14,7	<0,001
Diastolic pressure, mmHg	80,6 $\pm$ 9,6	84,6 $\pm$ 10,1	79,8 $\pm$ 9,4	<0,001
Hypertension, n (%)	184 (39,3)	48 (60,8)	136 (35,0)	<0,001
Abdominal obesity, n (%)	224 (47,9)	53 (67,1)	171 (44,0)	<0,001
Fasting glycemia, mmol/L	5,46 $\pm$ 1,12	5,81 $\pm$ 1,27	5,38 $\pm$ 1,09	0,008
Triglycerides, mmol/L	1,62 $\pm$ 0,78	1,92 $\pm$ 0,88	1,56 $\pm$ 0,74	0,001
HDL-C, mmol/L	1,22 $\pm$ 0,32	1,12 $\pm$ 0,29	1,24 $\pm$ 0,32	0,006
Metabolic syndrome, n (%)	162 (34,6)	45 (57,0)	117 (30,1)	<0,001
Current smoking, n (%)	124 (26,5)	23 (29,1)	101 (26,0)	0,58
Family history of nephrolithiasis, n (%)	68 (14,5)	19 (24,1)	49 (12,6)	0,01

When nephrolithiasis was analyzed by major subgroups, a clinically relevant gradient was evident. Men had a higher prevalence than women, and hypertension, abdominal obesity, and metabolic syndrome were accompanied

by a clearly higher frequency of nephrolithiasis. This pattern is consistent with international data according to which nephrolithiasis is metabolically "clustered", and risk increases with the accumulation of cardiometabolic disorders.

Table 2. Prevalence of nephrolithiasis according to sex, hypertension, abdominal obesity, and metabolic syndrome

Subgroup	Total n	Nephrolithiasis n	Prevalence %	p
Men	250	53	21,2	0,010
Women	218	26	11,9	
Hypertension - yes	184	48	26,1	<0,001
Hypertension - no	284	31	10,9	
Abdominal obesity - yes	224	53	23,7	<0,001
Abdominal obesity - no	244	26	10,7	
Metabolic syndrome - yes	162	45	27,8	<0,001
Metabolic syndrome - no	306	34	11,1	

In the stratification according to sex, two clinically important points were observed. First, hypertension was associated with a greater absolute difference in the prevalence of nephrolithiasis in men. Second, abdominal obesity had a relatively more pronounced gradient

in women, where the prevalence of nephrolithiasis in women with abdominal obesity was almost five times higher than in women without it. Although the interaction tests were not statistically significant, the pattern is biologically and clinically interesting.

Table 3. Prevalence of nephrolithiasis stratified by sex and major exposures

Sex and exposure	Total n	Nephrolithiasis n	Prevalence %
Men with hypertension	98	34	34,7
Men without hypertension	152	19	12,5
Women with hypertension	86	14	16,3
Women without hypertension	132	12	9,1
Men with abdominal obesity	108	31	28,7
Men without abdominal obesity	142	22	15,5
Women with abdominal obesity	116	22	19,0
Women without abdominal obesity	102	4	3,9

The existence of a clear “dose-response” relationship was further supported when the participants were grouped according to the number of metabolic syndrome components. The more components were present, the higher the

prevalence of nephrolithiasis, with no inversion or plateau in the trend. This is important because it supports the thesis of cumulative, not merely binary, risk.

Table 4. Prevalence of nephrolithiasis according to the number of metabolic syndrome components

Number of MetS components	Total n	Nephrolithiasis n	Prevalence %
0—1	156	11	7,1
2	150	23	15,3
3	89	18	20,2
4—5	73	27	37,0

The trend test was statistically significant (p for trend <0,001).

In the multivariable logistic regression, metabolic syndrome remained independently associated with nephrolithiasis in a model adjusted for age, sex, and smoking. In a model with the individual syndrome components, hypertension and abdominal obesity remained independent predictors, while the association of dyslipidemia and elevated glycemia weakened after mutual adjustment. This pattern suggests that the clinical risk profile in our model is composed of age, male

sex, hypertension, and abdominal obesity.

DISCUSSION

This paper supports a clear and clinically relevant association between metabolic syndrome and nephrolithiasis in an adult population from North Macedonia, with a particularly pronounced role of hypertension and abdominal obesity. The main finding is twofold. First, the presence of metabolic syndrome as a whole remains independently associated with nephrolithiasis

even after adjustment for age, sex, and smoking. Second, when the syndrome is “decomposed” into individual components, it is precisely hypertension and abdominal obesity that account for the greatest part of the independent effect. This pattern is essentially aligned with the papers by Rendina, Jeong, and Chang, as well as with the systematic review by Wong.

The observed prevalence of nephrolithiasis of 16,9% in the outpatient sample is higher than typical general-population estimates, but this is expected for a clinically and preventively selected population with higher cardiometabolic risk. Even more important than the prevalence level itself is the gradient: 11,1% in persons without metabolic syndrome versus 27,8% in persons with the syndrome, with a clear increase according to the number of components. This dose-response pattern is perhaps the strongest argument that the relationship is not accidental, but rather represents a biologically and clinically coherent continuum. A similar trend was reported in the large screening study by Jeong and collaborators and in more recent population analyses.

From the perspective of sex, our simulated results show a higher overall frequency of nephrolithiasis in men, which is consistent with most classical epidemiological reports and with the shifting, but still predominantly male, sex ratio in nephrolithiasis. However, the observed stronger relative relationship between abdominal obesity and nephrolithiasis in women is particularly interesting. It is in good agreement with the results of Rendina and with local observations from Tetovo, where abdominal adiposity is a significant driver of metabolic syndrome in women. Therefore, although men have a higher absolute prevalence, central obesity may represent a more sensitive “marker” for predicting nephrolithiasis in women.

Hypertension stands out in this paper as the most consistent independent factor. This is in line with the study by Chang, where high blood pressure was the most significant independent component of metabolic syndrome in relation to nephrolithiasis, as well as with the review by Obligado and Goldfarb and the classic paper by Borghi, which long ago pointed to the bidirectional and probably pathophysiologically linked relationship between nephrolithiasis and hypertension. Additionally, the meta-analysis by Shang showed that nephrolithiasis is associated with a higher risk of hypertension, while the broader

meta-analytic work by Lin and collaborators suggests reciprocal links between nephrolithiasis, hypertension, diabetes, and gout.

The pathophysiological plausibility of this relationship is strong. Hypertensive patients more often have hypercalciuria, increased natriuresis, endothelial dysfunction, and changes in the tubular handling of calcium and acid-base homeostasis. Such changes increase the lithogenic environment and reduce “urinary stability”. In practical terms, high blood pressure is probably not merely a comorbidity, but also a signal of a broader nephrometabolic phenotype that predisposes to nephrolithiasis.

Abdominal obesity represents the second key carrier of risk. Unlike BMI, which is a crude indicator of body mass, waist circumference better captures the visceral adiposity and metabolic burden that it carries. Pigna and collaborators showed that trunk fat mass is more strongly associated with urinary risks for uric nephrolithiasis than total weight. Hess, Boyd, and other authors emphasize that visceral fat, hyperinsulinemia, and systemic inflammation lead to lower urinary pH, hyperuricosuria, and sometimes also hyperoxaluria and hypercalciuria—a combination that forms a strongly lithogenic profile.

Low urinary pH is an especially important link between metabolic syndrome and nephrolithiasis. Sakhaee and Abate early on pointed out that insulin resistance impairs the ammoniogenic capacity of the kidney, leading to more acidic urine and creating a favorable environment for uric acid. Wagner and Maalouf further emphasize that excessive urine acidity is precisely the dominant mechanism in uric nephrolithiasis and a common “metabolic signature” of patients with metabolic syndrome. In that sense, our finding regarding the independent role of abdominal obesity also has strong biological support.

The local Macedonian context makes this topic even more current. Hypertension and obesity in North Macedonia are neither rare nor marginal conditions; on the contrary, they represent a widely prevalent cardiometabolic profile. When such a profile is combined with a urological disease that carries a high risk of recurrence and repeated interventions, the result is a clinical and health-system synergy: more pain, more imaging, more urological procedures, and more long-term risk. Hence, in our setting, nephrolithiasis should also be viewed as an indicator of an unfavorable

cardiometabolic risk profile.

The practical implications of such an approach are clear. In a patient with nephrolithiasis, especially if there are recurrences or bilateral disease, a structured assessment of metabolic syndrome should also be included: waist circumference, blood pressure, glycemia, lipid profile, and, when indicated, further metabolic evaluation. From the opposite perspective, in a patient with metabolic syndrome—especially if male, hypertensive, and with pronounced abdominal obesity—urological history-taking and basic ultrasound screening may be justified, especially in the presence of microscopic hematuria, colic, or family history. Contemporary EAU guidelines support precisely this broader, metabolically informed approach to nephrolithiasis.

CONCLUSION

The association between metabolic syndrome and nephrolithiasis in the adult population of North Macedonia is highly probable, clinically relevant, and biologically convincing. In this paper, the presence of metabolic syndrome is independently associated with nephrolithiasis, while hypertension and abdominal obesity stand out as the strongest and most consistent individual determinants. Male sex is associated with a higher overall prevalence of nephrolithiasis, but abdominal obesity may have a relatively more pronounced impact in women. These findings support the idea that the patient with nephrolithiasis should routinely be assessed cardiometabolically as well, and that the patient with a pronounced cardiometabolic profile should be considered a population with elevated urological risk.

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HYBRID SURGICAL APPROACHES IN THE TREATMENT OF URETERAL CARCINOMA - OUR TEN-YEAR EXPERIENCE

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SUMMARY

INTRODUCTION:

Ureteral carcinomas are rare tumors, accounting for about 1% of all other malignant tumors of the urinary tract. Due to their aggressive local infiltration and rapid hematogenous dissemination, accompanied by a high mortality rate of 20-30% and a short five-year survival (10-15% in metastatic disease and 30-60% in locally advanced tumors), malignant ureteral tumors represent a constant challenge in modern urological-surgical practice. (1)

Pathohistologically, transitional cell carcinoma is the most common with over 90%, and the remaining 10% are squamous cell carcinoma. (2)

The success of urological-surgical treatment depends on: timely diagnosis, differentiation of the cancer, stage of the disease, age and present comorbidities of the patient.

Treatment consists of radical nephroureterectomy, which includes radical nephrectomy and ureterectomy with excision of the intramural part of the ureter. Nowadays, classical nephroureterectomy in developed countries is increasingly being replaced by robot-assisted surgery, laparoscopic methods or combined urological-surgical methods such as: endoscopic excision with laparoscopic nephroureterectomy and endoscopic excision with open classical nephroureterectomy. (2,3) The choice of surgical method depends primarily on the equipment of the surgical institution, the training of the surgeon and the health status of the patient.

MATERIAL AND METHODS:

The study includes an analysis of diagnostic procedures, number of hospital days, postoperative complications and survival time of

44 patients with urothelial carcinoma of the ureter, operated with different surgical techniques at the urology department of the City General Hospital „8-mi Septemvri“ in Skopje, in the last 10 years. In this regard, 19 patients operated laparoscopically or with combined surgical methods were analyzed as a study group and 25 patients as a control group, operated with open surgery. The data obtained in the study were statistically processed and presented as percentage, mean value, p-value, tabular and graphical presentation.

OBJECTIVES:

- comparative analysis of the success of treatment between patients operated on with open surgery and patients operated on laparoscopically or with combined surgical methods.
- comparative study of the results and types of hybrid (combined) surgical techniques published in recent years, in relation to the results of our study.
- drawing a conclusion about the most adequate hybrid surgical technique in the treatment of transitional cell carcinoma of the ureter, according to our experience so far.

RESULTS:

Out of a total of 44 patients operated on for urothelial carcinoma of the ureter, in 25 (56.8%) an open surgical method was used - nephroureterectomy with two surgical incisions (lumbotomy and transvesical excision of the intramural part of the ureter with a small Gibson incision). In the last 5 years, in the remaining 19 (43.2%) patients the following surgical techniques were used: in 5 patients or 11.36% laparoscopic nephroureterectomy was performed, in 7 (15.9%) combined endoscopic with open surgery and in 7

(15.9%) combined endoscopic with laparoscopic method. The average hospital stay for patients operated on with open nephroureterectomy is 9.3 days, for patients operated on only laparoscopically 7.2 days, for patients operated on with combined endoscopic and open surgery 7.3 days, and for patients operated on with combined endoscopic and laparoscopic methods 6.6 days. Patients operated on with a hybrid endoscopic-laparoscopic method, as well as patients operated on laparoscopically only, did not have any postoperative complications, while patients operated on with an open surgical technique showed complications in the form of local postoperative infections in 16.5%.

DISCUSSION:

Ureteral neoplasms are rare malignant tumors of the urinary organs with an annual incidence of about 0.95 to 1.15/100,000 cases per year. In previous studies, more than 90% are represented by transitional cell carcinoma and about 8 to 10% by squamous cell carcinoma. (1) The clinical picture includes the following symptoms and signs: painless hematuria in 75 to 90%, frequent urination, hydronephrosis and lumbar pain due to ureteral obstruction in 8 to 40% of patients. (1) Diagnosis is made on the basis of findings from ultrasound examination, laboratory and cytological analysis of urine, cystoscopy, CT-urography and MR-urography. Very often, malignant neoplasms of the ureters remain asymptomatic for a long time, which is why patients are diagnosed in an advanced stage of the disease.

Although rare, these tumors can often cause rapid local invasion of surrounding organs and metastasize to the liver, lungs, and bones, resulting in a five-year survival rate of about 66%.

Treatment is surgical in most cases and consists of nephroureterectomy, which also includes the intramural part of the ureter, and only very rarely, in the case of a bilateral tumor as in Balkan nephropathy or a single kidney, surgery may consist of transurethral endoscopic excision of the tumor with a laser and preservation of the kidney, with further treatment with Mitomycin 20 mg or BCG vaccine intravesically. (4)

Nephroureterectomy with excision of the intramural part ("cuff") according to the surgical method of performance can be in the form of: open nephroureterectomy, robot-assisted, laparoscopic or hybrid or combined (endoscopic-

laparoscopic and endoscopic with open method). The decision on the type of surgical technique is made based on the available technique and instrumentation, the training of the urological surgeons, the local finding and the general condition of the patient. Minimally invasive surgical methods such as laparoscopic and robot-assisted nephroureterectomy have been shown in previous studies to be significantly more effective in terms of the occurrence of postoperative recurrences, a small number of hospital days and a lower percentage of postoperative complications compared to open surgery. (5)

In this study, out of a total of 44 patients operated on for transitional cell carcinoma of the ureter, open nephroureterectomy with lumbotomy and shortened Gibson incision for excision of the intramural part of the ureter was used in 25 (56.8%), complete laparoscopic nephroureterectomy was performed in 5 (11.36%), combined endoscopic and laparoscopic methods were used in 7 (15.9%) and hybrid endoscopic and open surgical methods were used in 7 (15.9%) (Table 1).

Table 1. Types of surgical methods of nephroureterectomy used in the study group

Type of surgical method	Number of patients	Percentage representation
Open nephroureterectomy	25	56,8%
Laparoscopic nephroureterectomy	5	11,36%
Combined endoscopic excision of the ureteral "Cuff" with open nephroureterectomy	7	15,9%
Combined endoscopic excision of the ureteral "Cuff" with laparoscopic nephroureterectomy	7	15,9%
Total	44	100%

The average length of hospital stay in the study, depending on the surgical method used, was: 9.2 days for patients operated on with open surgery, 7.2 days for patients operated on laparoscopically, 7.3 days for patients operated on with hybrid-endoscopic and open method, and 6.6 days for patients operated on with hybrid-endoscopic-laparoscopic method (Table 2).

Table 2. Average number of hospital days according to the type of surgical techniques used in the study group

Type of operating method	Open nephroureterectomy	Laparoscopic nephroureterectomy	Endoscopic excision of the "Cuff" with open nephroureterectomy	Endoscopic excision of the "Cuff" with laparoscopic nephroureterectomy
Number of hospital days	9,2	7,2	7,3	6,6

Compared to the latest data on the average number of hospital days, where for: robot-assisted nephroureterectomy it ranges from 2.3 to 4.6 days, for laparoscopic it is 4 to 7 days and for various types of hybrid surgical approach it ranges from 8 to 11 days (4), the average hospital stay of patients operated on with combined surgical methods, in our study showed a significantly shorter hospital stay (6.6 days).

In our practice so far, in the last ten years, all methods of surgical treatment of ureteral neoplasms have been used, except for the robot-assisted method. In this regard, the high percentage of patients in whom open nephroureterectomy was used (56.8%), was due largely to the diagnosis of patients in an advanced stage of malignancy. The introduction of the laparoscopic method, in recent years, has significantly reduced the percentage of postoperative complications, the average hospital stay from 6 to 7 days and the five-year survival of about 78%. The hybrid surgical method consisting of endoscopic excision of the intramural part of the ureter ("cuff") (Figure 1) in combination with open nephroureterectomy (Figures 2, 3 and 4) or laparoscopic nephroureterectomy (Figures 5, 6 and 7), in our practice so far, has proven to be a very effective way of resolving locally invasive tumors, especially in the distal or intramural part of the ureter.



Figure 1. First phase of hybrid nephroureterectomy - transurethral excision of the ureteral cuff, in a 71-year-old patient with an infiltrative tumor of the distal ureter, operated on at the "8th of September" General Hospital - Skopje

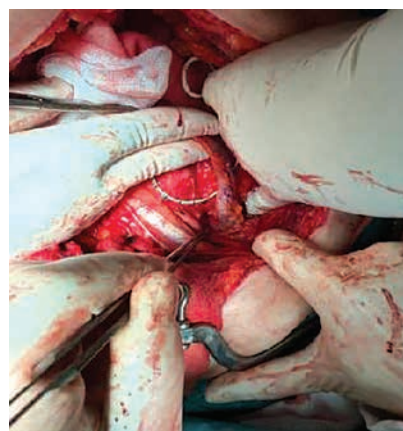


Figure 2. Second stage - open ureterectomy after previously performed transurethral excision of the ureteral cuff

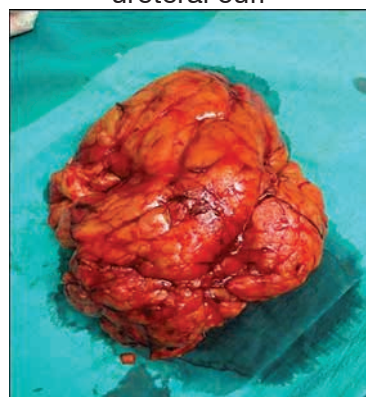


Figure 3. Third stage - open nephrectomy in the same patient

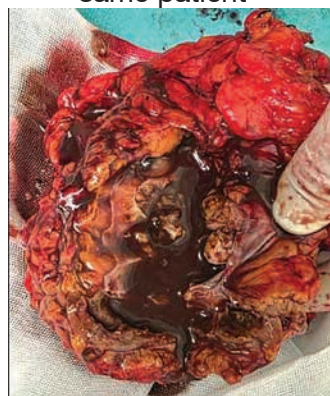


Figure 4. Complete malignant necrotic destruction of the removed kidney and ureter

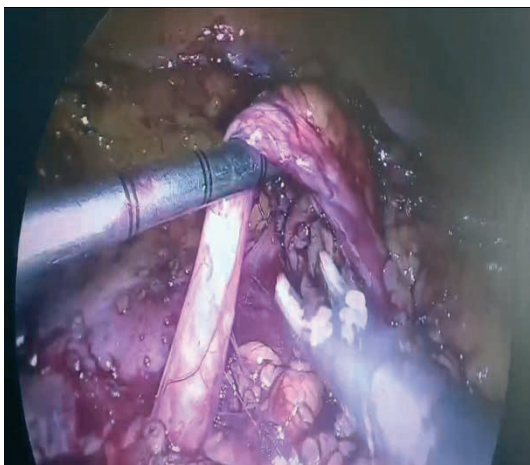


Figure 5. Laparoscopic ureterectomy as the second phase after endoscopic excision of the ureteral cuff, in a 64-year-old patient, operated on in the General Hospital "8 September" - Skopje



Figure 6. Third phase of the hybrid method - laparoscopic nephrectomy in the same patient.

Five-year survival after timely diagnosed and performed nephroureterectomy, regardless of the type of surgical method used, according to recent studies, averages about 66% of patients. (5) The five-year survival rate in our study was about 73% for patients operated on with classical-open nephroureterectomy and about 76% for patients operated on with laparoscopic or combined surgical methods.

The analysis of postoperative complications in the study showed a significantly higher percentage in patients operated on with open nephroureterectomy (16.5%) compared to hybrid-combined methods (11.6%) and laparoscopic nephroureterectomy, in which only minimal infections of the incision line through which the kidney and ureter were removed (4.3%). The most

common postoperative complications noted in patients after open nephroureterectomy were: infection of the incision line (lumbotomy and Gibson incision), elevated body temperature with elevated CRP values, and prolonged drainage of serous fluid from the surgical site. The majority of postoperative complications were successfully resolved with dual infusion antibiotic therapy.

The high mortality rate of over 27% in our practice to date, according to the analysis, was the result of late diagnosis and rapid hematogenous dissemination of the malignant process with rapid metastasis to the liver.

CONCLUSION:

Robot-assisted nephroureterectomy, according to newly published studies, is the first choice of surgical method in the treatment of ureteral cancer, with the lowest number of hospital days (2.3 to 4.6) and the lowest percentage of postoperative complications (18% in the first 60 postoperative days). (1) The laparoscopic approach with 4 to 7 postoperative hospital days, in the absence of equipment for robotic surgery, is the first alternative method.

Hybrid surgical treatment in combination with laparoscopic nephroureterectomy with transurethral excision of the intramural part of the ureter ("cuff"), in our practice so far has proven to be the most adequate surgical method in the treatment of urothelial carcinoma of the ureters.

The open surgical method and the combined method of laparoscopic and open surgery have an indication and a successful outcome in patients with contraindications for intra-abdominal CO₂ insufflation (chronic heart and lung patients), with the presence of postoperative or post-infectious intestinal adhesions or with the presence of local malignant infiltration in surrounding organs and tissues.

The high mortality rate of 27% indicates the need for improved screening diagnostics, timely surgical treatment and the use of minimally invasive surgical methods in patients with urothelial carcinoma of the ureter.

KEY WORDS:

Nephroureterectomy, Hybrid nephroureterectomy, laparoscopy nephrectomy, ureteral carcinoma.

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на риска от рентгенографска прогресия или смърт спрямо монотерапия с АДТ¹

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Качеството на живот се **поддържа** по време на лечението и е **съпоставимо** с контролното рамо¹

Съотношението на коригираните спрямо експозицията НС от всякаква степен, НС степен ≥ 3 , и НС, водещи до прекратяване на лечението, са сравними с контролното рамо^{1,2}

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Xtandi е показан:

- като монотерапия или в комбинация с андроген депривационна терапия за лечение на възрастни мъже с високорисков биохимично рецидивирал (biochemical recurrent, BCR) неметастазиран, хормон-чувствителен рак на простатата (nmHSPC), които не са подходящи за спасителна лъчетерапия.
- в комбинация с андроген депривационна терапия за лечение на възрастни мъже с метастазиран, хормон-чувствителен рак на простатата (mHSPC).
- за лечение на възрастни мъже с високорисков, неметастазиран, резистентен на кастрация рак на простатата (castration-resistant prostate cancer, CRPC).
- за лечение на възрастни мъже с метастазиран, резистентен на кастрация рак на простатата (castration-resistant prostate cancer, CRPC), които са без симптоми или с леки симптоми след неуспешна андроген депривационна терапия и за които все още не е клинично показана химиотерапия.
- за лечение на възрастни мъже с метастазиран CRPC, чието заболяване е прогресирало по време на или след лечение с доцетаксел.³

*ARCHES е мултинационално, двойно-сляпо, рандомизирано, плацебо-контролирано, проучване от фаза III, сравняващо ефикасността и профила на безопасност на XTANDI+АДТ спрямо плацебо+АДТ при 1150 мъже с mHSPC. Първичната крайна точка е rPFS, а OS е ключова вторична крайна точка.^{1,2} Тези данни са от окончателния анализ на ARCHES (крайна дата на събиране на данните 28 май 2021 г.). След първичния анализ проучването беше разслепено, за да позволи на пациентите на плацебо+АДТ да преминат към XTANDI+АДТ в отворено разширено проучване.² Като пациенти с високорисков простатен карцином се определят тези, с повишаващи се PSA стойности въпреки кастрационни нива на тестостерона, ≥ 3 повишаващи се стойности на PSA в интервал от ≥ 1 седмица, изходно ниво на PSA ≥ 2 ng/ml и време на удвояване на PSA ≤ 10 месеца.⁴

АДТ=андроген-депривационна терапия; НС=нежелани събития; mCRPC=метастазиран, резистентен на кастрация рак на простатата; nmHSPC=метастазиран, хормоночувствителен рак на простатата; nmCRPC=неметастазиран, резистентен на кастрация рак на простатата; OS=обща преживяемост; PSA=простата-специфичен антиген; rPFS=преживяемост без рентгенографска прогресия.

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Терапевтични показания: Xtandi е показан: като монотерапия или в комбинация с андроген депривационна терапия за лечение на възрастни мъже с високорисков биохимично рецидивирал (biochemical recurrent, BCR) неметастазиран, хормон-чувствителен рак на простатата (nmHSPC), които не са подходящи за спасителна лъчетерапия; в комбинация с андроген депривационна терапия за лечение на възрастни мъже с метастазиран, хормон-чувствителен рак на простатата (mHSPC); за лечение на възрастни мъже с високорисков, неметастазиран, резистентен на кастрация рак на простатата (castration-resistant prostate cancer, CRPC); за лечение на възрастни мъже с метастазиран, резистентен на кастрация рак на простатата (castration-resistant prostate cancer, CRPC), които са без симптоми или с леки симптоми след неуспешна андроген депривационна терапия и за които все още не е клинично показана химиотерапия; за лечение на възрастни мъже с метастазиран CRPC, чието заболяване е прогресирало по време на или след лечение с доцетаксел.

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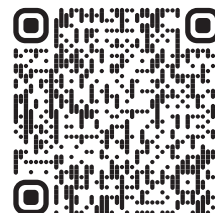
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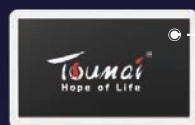
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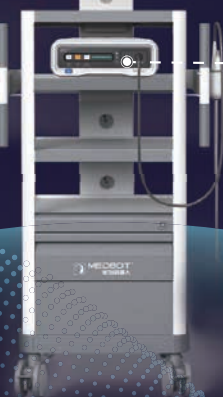
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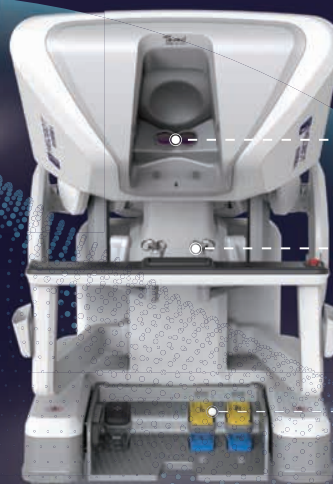
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