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Original article

ЛАПАРОСКОПСКА ТАПП НАСПРОТИ ПОПРАВКА ПО LICHTENSTEIN; РАН КЛИНИЧКИ ИСХОД

LAPAROSCOPIC TAPP VERSUS LICHTENSTEIN REPAIR - ERLY CLINICAL OUTCOME

Aleksandar Mitevski[1], Svetozar Antovikj[2], Petar Markov[3] and Nikola Jankulovski[2]

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Abstract

Introduction. Laparoscopy as a minimally invasive technique has itsplace in inguinal hernia repair. Lower postoperative pain, earlier mobilization and earlier return to usual activities are comparable to an initially high cost of the hospital charge. Also, there is a lower percentage of postoperative complications especially related to the wound.
Methods. The study was designed as a prospective randomized controlled study conductedin a three-year-period. Sixty-five patients were randomly assigned into two groups, *examined*-35 patients treated with TAPP technique and *controlled*-30 patients treated with Lichtenstein technique.
Surgicaltime, preoperative pain, hospital stay, postoperative analgesia, functional status and convalescence were evaluated. The postoperative complications, hematoma, seroma, wound infection and urinary retention were also taken into consideration.
Results. A significant diference was found in the surgicaltime favoring Lichtenstein over TAPP technique; postoperative hospitalization was significanlly longer in case of the Lichtenstein procedure. There wasa significant difference concerning postoperative pain and functional status between the groups, as well as in the same group regarding the postoperative days.
The percentage of early postoperative complications wassignificantly lower in TAPP group (6.3% versus 16.7%); there wasa significant difference in convalescence (TAPP 4.6±1.2 / Lichtenstein 6.6±1.10).
Conclusion. Patients treated with laparoscopic TAPP technique had better early clinical outcome compared to open Lichtenstein technique. It is a result of a lower intensity of the postoperative pain, less postoperative complications which leads to a shorter hospital stay, better functional status and short convalescence.

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Keywords: inguinal hernia, laparoscopic hernia repair, open hernia repair, TAPP, early clinical outcome

Апстракт

Вовед. Лапароскопијата како минимално инвазивна техника има свое место во поправката на ингвинални хернии. Помалата болка, раната мобилизација и враќање на секојдневните активности се компарабилни со иницијалната повисока цена на болничкиот третма. Исто така има низок процент на компликации, особено поврзани со оперативната рана.
Методи. Студијата е дизајнирана како проспективна, рандомизирана и контролирана, спроведена во период од три години.
Шеесет и пет пациенти се поделени во две групи, *испитувана* од 35 испитаници третирани со ТАПП техника и *контролна* од 30 испитаници третирани херниопластика според Lichtenstein.
Се евалуираше времетраењето на оперативен зафат, периоперативната болка, времето на испишување од болница, постоперативна анлгезија, функционален статус и реконвалесценцијата. Исто така со евалуирање и појавата на компликации-хематом, сером, инфекција на рана и уринарна ретенција.
Резултати. Значителни разлики има во времетраењето на оперативниот зафат, постоперативната хоспитализација Во однос на болкатаи функционалниот статус има значителна разлика помеѓу групите, како и во групите по однос на постоперативните денови.
Процентот на постоперативни компликации е значително помал кај лапароскопската ТАПП метода (6,3%, Lichtenstein 16,7%), исто така има значителна разлика и во реконвалесценцијата (ТАПП изнесуваше 4,6±1,2 дена, а на оперираните според Lichtenstein 6,6±1,10 дена).
Заклучок. Пациентите третирани со лапароскопската ТАПП метода, споредено со пациентите третирани со отворената Lichtenstein метода имаат подобар ран клинички исход. Тоа е резултат на помалата периоперативната болка, поретката појава

на рани постоперативни компликации што води до пократка хоспитализација, подобар постоперативен функционален статус и реконвалесценција.

Клучни зборови: ингвинална хернија, лапароскопска хернопластика, отворена хернопластика, ТАПП, ран клинички исход

Introduction

Inguinal hernia is the most common pathology in general surgery; it is estimated that more than 20 million inguinal hernia repairs are performed in the world annually [1]. In USA that number is close to 800000 and in Macedonia according to the data from the Republic Institute for Public Health around 2000 annually. Till 2012 laparoscopic hernia repairin Macedonia was performed only at the University Clinic for Digestive Surgery in Skopje (from 147, only 4 were laparoscopic surgeries in 2012). Laparoscopic hernia repair is present less than 20% from all inguinal hernia repairs in the developed countries, 15% in USA [2] and 16%in Denmark [3].

Contemporary open tension-free inguinal hernia repair was presented by Lichtenstein in 1986 [4]. Today it is considered as a "gold" standard for open tension-free inguinal hernia repair and it is a recommended technique from hernia associations [5].

The first depiction of laparoscopic hernia repair was presented by Ger in 1982, but the current TAPP (Trans AbdominalPrePeritoneal) approach was independently presented by both Arregui and Dion in 1992 [6,7]. TAPP enables repair through peritoneal cavity of inguinal hernia, there for it is a genuine laparoscopic technique. Today totally extraperitoneal technique (TEP)is also used. It was first presented in 1992 by Dulucq and as an endoscopic technique it is comparable and equal in its performance and results toTAPP [5].

When comparing open mesh technique with endoscopic approach, TAPP and TEP, we found that the initial intraoperative cost washigher in endoscopic, but overall costs and socio-economic impact wasequal or lower in endoscopic techniques [8]. Also, the postoperative pain was lower in the minimally invasive approach; postoperative convalescence wasshorter and patients returned to their usual activities earlier [9-11].

Primary unilateral inguinal hernia repair in male patients according to the last guidelines [5] has favored endoscopic techniques, yet in the discussion it is stated "large-scaledatabase studies are urgently needed to compare endoscopicwith Lichtenstein operations for primary unilateralIHs in males".

The aim of the study wasto compare laparoscopic TAPP approach and open Lichtenstain technique for unilateral inguinal hernia in male patients regarding early clinical outcome, pain, convalescence and complications.

Materials and methods

The study was designed as a controlled prospective randomized study, with predetermined protocol and data collection. It was carried out at the Clinical Hospital-Shtip, as a single center study, with collaboration of the Faculty of Medicine in Skopje, University Clinic for Digestive Surgery. The study was approved by the EthicsCommitteeof the hospital in Shtipand Faculty of Medicine in Skopje and a written consent for participation in the study was compiled and approved.

To avoid bias that would occur during surgery, especially in the laparoscopic group (n=35), all patients were operated by the same surgeon. This invalidates the possibility of greater variations in the technique and duration of the surgery that would occur in the operation of different surgeons depending on their training and individual abilities.

In the control group (n=30) patients were also operated by the same surgeon or with active assistance; some patients were operated on by another team but with the same training and technique (working together for 12 years).

Inclusion criteria for the study were: male patients aged 18 to 65, with primary unilateral inguinal hernias, that when standing up did not pass the horizontal line at the lower edge of the symphysis of the pubic bones (endoscopic classification according to Nyhys type 1, 2 and 3), with ASA (American Society of Anesthesiologists) grading 1 and 2 and BMI (Body Mass Index) smallerthan 30.

Patients with previous interventions in the area of the inguinal region, surgery in the infraumbilical region by entering the pre-peritoneal area (not including appendectomy with McBourny incision) were excluded.

Patients with an occult contralateral hernia were excluded from the study. Only the presence of occult contralateral hernia, which had previously been clinically not diagnosed, was shown.

Also, patients in whom adhesions in the inguinal region were intraoperatively verified through transabdominal approach and there was a risk of laparoscopic adhesiolysis were excluded from the study.

Patients were divided into two groups:

1. **Examined group**, treated with laparoscopic technique (TAPP), n=35 patients;
2. **Control group**, treated with standard open hernioplasty method - Lichtenstein, n=30.

Patients included in the study were examined one day preoperatively. Laboratory analysesand clinical physical examination were performed; the responses were recorded in the VRS (verbal rating scale) for pain and functional status. The nextday surgical treatment was performed and patients were assigned to laparoscopic or control group in ratio 1:1 (one to laparoscopic and one to control group); the last five patients were treated with the laparoscopic technique.

In the laparoscopic-examined group, patients were treated with TAPP (Trans Abdominal Pre Peritoneal) technique. Preoperatively, a single dose of an antibiotic from the group 3 generation cephalosporins was given; ampicillin or clindamycin were used in patients with known allergy to cephalosporins. A standard laparoscopic TAPP procedure was performed, with a patient in Trendelenburg 10-15º position, hands along the body and without a urinary catheter. Three ports were used with intra-abdominal pressure up to 12 mm Hg. Direct and indirect hernias were reduced, peritoneum wasincised and a pre-peritoneal space behind the myopectineal orifice wascreated; transversalis fascia of larger direct hernia wasfixed to the Cooper ligament with one or two tackers. A single large polypropylene mesh prosthesis wasused (with a mass of>35 g/m², Paha® polypropylene mesh, Altaylar Medical), 13-15 cm wide, high 10-12 cm on the medial part and 8 cm on the lateral. It wasfixed with titanium spiral „tackers"(ProTack ™ 5 mm fixation device), 1-3 on the Cooper ligament, 1-2 on the back side of the rectus abdominal muscles and one laterally higher and medial to the level of the anterior upper iliac spine. The peritoneum wasalso closed above the mesh with titanium tackers.

Patients in the control group were treated with a standard anterior open approach with a polypropylene prosthesis-Lichtenstein technique. They received the same dose of the antibiotic drug as the examined group. The surgery wasperformed without a urinary catheter, with incision and tissue dissection to the posterior wall of the inguinal canal. Dissection of the nerves and sometimes transaction (most often the ilioinguinal, the iliohipogastric and genital branch of the genitofemoral nerve) was performed as well as cremasterectomy.Hernia sac, direct or indirect, was dissected and pushed in the pre-peritoneal space. The same polypropylene mesh-prosthesis as in the laparoscopic group was used, with dimensions of 13-15x7-8 cm. It wasplaced with a slit for the spermatic cord on the posterior wall of the inguinal canal. The mesh wasthen fixed with a polypropylene stitch 3/0.

The duration of surgery from incision of the skin to the closure of the surgicalwound was recorded.

VRS (verbal rating scale) was used to ratethe pain. We made the recordings preoperatively, POD 1, POD 3 and POD 7 (POD-Postoperative Day).

We used the four-level verbal rating scale: level 1-no pain; level 2-mild pain; level 3-moderate pain; level 4-severe pain.

Pain was measured in a supine position, when resting and provoked pain by coughing.

The number of peroralanalgesic drugs was also required in the first three days. Ibuprofen tablets of 400 mg, 500 mg Metamizole sodium and 500 mg Paracetamol tablets were used. Patients were divided into two groups, patients who took ≤ 2 tablets a day and patients who took >2 tablets a day.

VRS (verbal rating scale) for functional status was used. A four-level scale was developed: level 1-capable; level 2-light fatigue, level 3-fatigued; level 4-tired.

Recordings of functional status were made preoperatively, POD 1, POD 3 and POD 7.

Seroma, hematoma or surgicalwound infection on the day of the discharge and the seventh postoperative day were recorded; we used clinical examination and if needed ultrasound. Also, urinary retention was recorded with the need for catheterization of the bladder.

All patients in the study were given"non-restrictive" recommendations on the day of the discharge (all of the activities they feel they can perform) with a weight lifting limit of 5 kg, and a recommendation for the 2ndday convalescence in terms of carrying out daily usual activities.Convalescence was determined in relation to postoperative days (POD). The discharge from the hospital was based on the subjective ability of the patient to cope with the pain and activity at home, and postoperative complication occurrence.

Results

Duringa period of three years (from March 2013 to March 2016), the study involved 65 patients with primary unilateral uncomplicated inguinal hernia. In the group of examined patients/TAPP group (N1) there were 35 examinees; three were excluded due to occult contralateral inguinal hernia. In the control group/Lichtenstein group (N2) therewere 30 patients. The study analyzed a total of 62 patients treated foringuinal hernia.

Demographic characteristics

The analysis showed that there was no statistically significant difference in age between the two examined groups; the average age was 46.1 years in both groups (44.5 in TAPP and 47.7 in Lichtenstein).

Duration of surgical intervention

The average duration of intervention in patients treated with TAPP was 45.3±11.7 minutes, and with Lichtenstein technique 34.8±5.3 minutes. The performed analysis showed a statistically significant difference in the duration of the intervention between the two examined groups. The intervention was significantly shorter in the control Lichtensteingroup (Mann-Whitney U test: $Z=4.04$ $p=0.00005$).

Days of hospitalization after surgery

There wasa difference in terms of hospital discharge in the postoperative period between the two examined groups. Patients operated with TAPP were hospitalized shorter after surgery, 60% of the TAPP group were discharged POD1.

Perioperative pain

Prior to the intervention, all patients operated with TAPP, as well as all those operated with the Lichtenstein method, stated that they had no pain while resting.

According to the verbal rating scale, while coughing, 27(84.4%) patients from the first group had no pain before the intervention and 25(83.3%) patients from the second examined group. A mild pain was confirmed by 5 patients in both groups.

The first postoperative day, 19(59.4%) patients treated with TAPP said they had no pain, and 13(40.6%) felt a mild pain. Of those operated with the Lichtenstein method, 24(80%) patients confirmed a mild and 6(20%) a moderate pain. The analysis showed a statistically significant difference in the presence and intensity of pain on the first postoperative day between the two investi-gated groups (Mann-Whitney U test: Z=4.56 p=0.000005).

The first postoperative day, while coughing, 31(96.9%) patients treated with TAPP stated that they had a mild pain and 1(3.1%) patient had no pain. Of those operated with the Lichtenstein method, 6(20%) patients confirmed a mild and 24(80%) a moderate pain. The analysis showed a statistically significant difference in the presence and intensity of pain while coughing on the first postoperative day between the two investigated groups (Mann-Whitney U test: Z=5.45 p=0.000001).

The third postoperative day, 31(96.9%) patients treated with TAPP said they had no pain, and 1(3.1%) felt a mild resting pain. Of those operated with the Lichtenstein method, 9(30%) patients said they had no pain, and 21 (70%) confirmed the presence of a mild pain. None of the patients had moderate and severe pain. The analysis showed a statistically significant difference in the presence and intensity of pain on the third postoperative day between patients from both examined groups (Mann-Whitney U test: Z=4.52 p=0.000006).

The third postoperative day, when provoked with coughing, 14(43.8%) patients treated with TAPP stated that they had no pain, and 18(56.2%) patients had a mild pain. Of those operated with the Lichtenstein method, 22(73.3%) patients confirmed a mild and 8 (26.7%) patients amoderate pain while coughing. The analysis showed a statistically significant difference in the presence and intensity of pain on the third postoperative day between patients in the two examined groups (Mann-Whitney U test: Z=3.97 p=0.00007) (Table 1).

Table 1. Distribution of respondents comparing the strength of pain on the third postoperative day while coughing

Examined groups	Without pain	Mild pain	Moderate pain	Severe pain	Total
TAPP(N1)	14 43.8%	18 56.2%	0 0.0%	/ /	32
Lichtenstein (N2)	0 0.0%	22 73.3%	8 26.7%	/ /	30
Total	14	40	8	/	62

On the seventh postoperative day, all 62 respondents said they had no pain while resting. While coughing, all 32(100%) patients treated with TAPP said they did not feel any pain. In the controlled group, 4(13.3%) said they had no pain, and 26(86.7%) confirmed the presence of a mild pain while coughing. The analysis showed a statistically significant difference in the presence and intensity of provoked pain on the seventh postoperative day between patients in the two examined groups (Mann-Whitney U test: Z=5.86 p=0.000001).

Following the intervention, of the total of 32 patients treated with TAPP, 26(81.3%) took up to 2 painkillers and 6(18.7%) more than two daily. Of the patients treated with Lichtenstein technique, 8(26.7%) patients took up to 2 painkillers, the remaining 22(73.3%) needed more pills a day. The analysis showed a statistically significant difference in the need for analgesia after surgery between the two study groups (Mann-Whitney U test: Z=3.69 p=0.00020) (Figure 1).

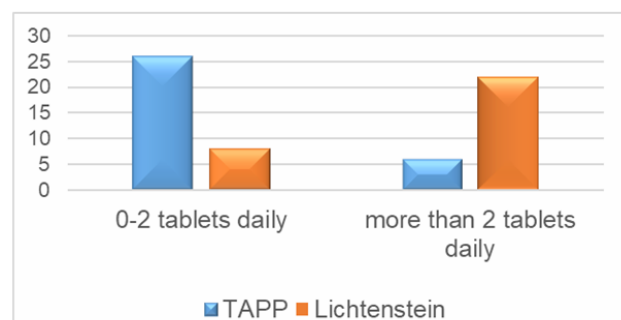

Fig. 1. Distribution of respondents according to the need for analgesics postoperatively

Functional status

Prior to the intervention, all patients stated that they were functionally capable.

According to the verbal rating scale, on the first postoperative day, 12(37.5%) patients operated on with TAPP stated that they felt capable of daily activities and 20(62.5%) felt light fatigue. In the Lichtenstein method group, 15(50.0%) reported light fatigue, and the remaining 15(50.0%) reported feeling fatigue. There was a statistically significant difference in functional status on the first postoperative day between the two groups examined (Mann-Whitney U test: Z=4.65 p=0.000003).

On the third postoperative day, analysis showed that there was a very strong statistically significant difference in the functional status on the third postoperative day

between the two study groups (Mann-Whitney U test: Z=5.98 p=0.000000) (Table 2).
On the seventh postoperative day, all 32 TAPP-treated patients stated that they were functionally capable. In the Lichtenstein group, 17(56.7%) patients reported being functionally capable, 12(40.0%) patients felt light fatigue, and 1(3.3%) fatigued. The analysis showed a statistically significant difference in the functional status of the seventh postoperative day between the two study groups (Mann-Whitney U test: Z=2.93 p=0.0033)

Table 2. Distribution of respondents by functional status on the third postoperative day

Examined groups	Capable	Light fatigue	Fatigue	Tired	Total
TAPP(N1)	29 90.6%	3 9.4%	0 0.0%	/ /	32
Lichtenstein (N2)	1 3.3%	25 83.3%	4 13.4%	/ /	30
Total	30	28	4	/	62

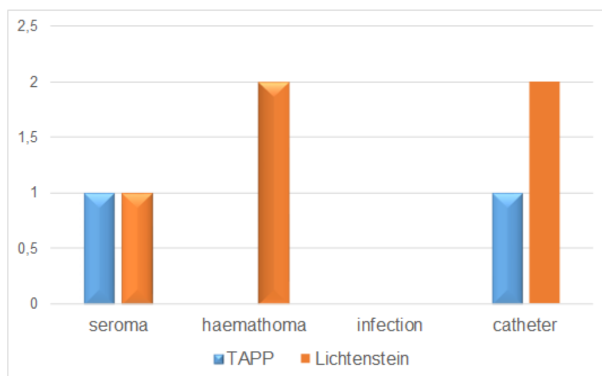

Fig. 2. Distribution of respondents according to the occurrence of a certain complication

Convalescence
The mean time of convalescence expressed in daysgroup was 4.6 ± 1.2 daysin TAPP, and 6.6 ± 1.10 daysin the Lichtenstein group. The analysis showed a statistically significant difference in the convalescence time between the two groups (Mann-Whitney U test: Z=5.14 p=0.000001). Convalescence was significantly longer in patients who underwent surgery with the Lichtenstein method.

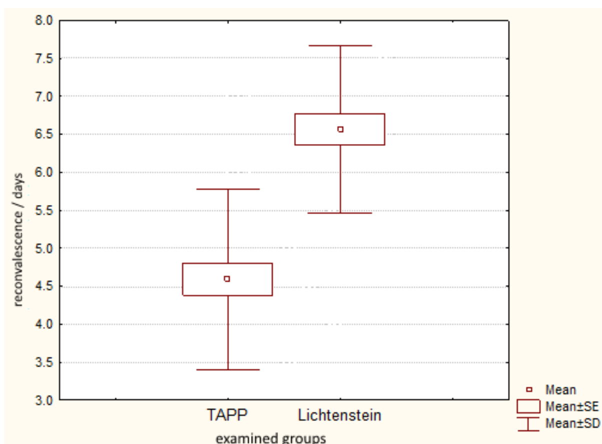

Fig. 3. Mean convalescence per day for respondents in both groups

Postoperative complications
In the TAPP group, from 32 patients one patient developed a seroma and one patient had a catheter. In the Lichtenstein group, a total of 5 patients (16.7%) experienced some postoperative complication-1 person with seroma, 2 with hematoma, and 2 with urinary catheterrization (Figure 2).

Discussion

Repair of inguinal hernias is one of the most commonly performed surgeries in the world. Although it is a historically old problem, nowadays its solution has enormous socio-economic implications. In the United States, the cost of resolving inguinal hernias and their complications is estimated to reach $ 28 billion annually [1].
The last paradigm related to inguinal hernioplasty appeared 27 years ago and concerned the laparoscopic repair of inguinal hernias.
Almost every abdominal surgery that requires incision of different length on the abdominal wall today has its own laparoscopic replacement. As with any new method or technique, a debate about laparoscopic versus open technique has arisen. Controversy has emerged over the repair of primary unilateral inguinal hernia-whether laparoscopic or open hernioplasty should be performed.
Superior results in favor of laparoscopic hernioplasty have demonstrated the studies that include recurrent hernias, and there is also a clear benefit in laparoscopic bilateral inguinal hernia repair [5].
Numerous studies have clearly shown the benefit of laparoscopic repair of primary unilateral hernias in relation to postoperative pain, complications, convalescence, and recurrences. Laparoscopic repair also has proven benefits in some complex hernias [12,13]. However, laparoscopic inguinal hernioplasty depends on advanced medical technology and requires good technical knowledge and appropriate medical expertise. There are also potential complications that rarely occur with conventional open hernioplasty.

Despite the extensive data in favor of laparoscopic repair, many surgeons are still reserved, especially for unilateral primary inguinal hernias.
Most laparoscopic procedures have a longer duration than open methods, due to the association of laparoscopy with a special abdominal approach and the use of specific instruments. Laparoscopy is also associated with the development of specific manual abilities and intraoperative evaluation of physiological and anatomical parameters, which distinguishes it from the open surgery [14].
The most commonly performed laparoscopic surgery is laparoscopic cholecystectomy, following the national consensus of the National Institutes of Health (NIH) in 1992. It has become the procedure of choice for gallbladder removal. Although a laparoscopic procedure is most commonly performed, we find that surgeons have a routine in performing it, when compared to open methods it lasts longer.
McCormack *et al.* made a survey ofrandomized controlled trials and detected 41 studies with 7,161 patients. When analyzing the duration of surgery, it wasconcluded that laparoscopically operated patients had a longer duration of surgery [15].
In several studies Anadol and Abbas [16] point out that no significant differences were observed in the duration of laparoscopic and open inguinal hernioplasty.
In our studythe differencewassignificant; it showed that the intervention was significantly shorter in patients treated with the open Lichtenstein method.
It is interesting to note that in the laparoscopic group 10 patients (out of 32 analyzed) had left inguinal hernias. In all 10 patients, the duration of surgery was longer with an average duration of 56 minutes. The remaining 22 analyzed patients had right inguinal hernia with a median surgicaltime of 36.7 minutes. I find this connected to the surgeon's technical skills, which in our case works with the right hand and due to the heavier dissection of the left-sided hernias where the sigmoid colon is often positioned above the peritoneum in the inguinal region, which requires dissection.
One of the parameters for evaluating surgical techniques is the time of hospital discharge (postoperative hospitalization). Laparoscopy reduces tissue trauma at the site of access (incision in open methods), has less postoperative pain, faster mobilization of patients, and less postoperative morbidity associated with the surgicalapproach that indirectly affects the postoperative requirement for hospitalization.
McCormack in his study found no significant difference in postoperative hospitalization of patients, i.e. the length of postoperative hospital treatment of patients treated laparoscopically and with an open method [15].
Also Abbas stated that there was no significant difference in hospitalization of patients treated with laparoscopic and open method [16].
Salma in their studies founda slightly longer postoperative open hospitalization compared to laparoscopicsurgery [17].
In our study the results showed that patients treated for unilateral uncomplicated inguinal hernia had a shorter hospitalization.
Postoperative pain is of particular importance given that most patients treated for primary uncomplicated hernia do not have pain as a symptom. Pain is one of the parameters for comparison of inguinal hernioplasty and is common to all techniques [18].
The laparoscopic approach reduces the tissue injury at the site of surgery which directly affects the pain, acute postoperative pain. Direct tissue trauma leads to the release of mediators, primarily histamine, leukotrienes, prostaglandins, bradykinin and cytokines that cause hyperalgesia at the site of trauma and local tissue. The degree of trauma is commensurate with their release, and accordingly with the degree of pain that appears. A particular problem is the transition from acute postoperative pain to persistent postoperative pain. It is described as a pain that persists for 7 days after surgery and is one of the main causes of prolonged hospitalization and readmission of patients. One of the factors affecting the transition from acute postoperative pain to persistent postoperative pain is the inadequate early treatment of postoperative pain. Other factors affecting are prolonged duration of surgery, type of surgery (laparoscopy *versus* laparotomy), as well as prosthesis placement and type of theimplant [19].
The type of surgery has affect trough the dissection and nerve injury in the inguinal region. In addition to the direct lesion, exposure of the nerve to the prosthesis is also important; namely through the inflammatory response that causes the prosthesis on the tissue and releaseof active mediators that cause hyperalgesia. One of the causes of pain is the prosthesis fixation. The fixation can lead to nerve injury or reduce the elasticity of the abdominal wall at the place of the prosthesis, causing tension and pain [20].
McCormack [15] and Neumayer [10] in their studies presentedless postoperative pain in laparoscopically treated patients.
The EU Hernia Trialists Collaboration [21] in a systematic review of 34 studies of 6.804 patients found that patients treated with laparoscopic technique had less pain.
The analysis of pain showed a significant difference in pain in the first seven postoperative days, lower incidence and lower intensity of pain in patients treated with TAPP approach after the third postoperative day.
In order to obtain a response to postoperative pain indirectly and to correlate it with the results fromVRS, we also used information about the postoperative use of pills (analgesics) in the first three days after the end of hospitalization.
It can be noticed that the number of patients who used more than two tablets per day in the open technique treated group was larger. The larger number of pills in the open technique group also correlatedwith VRS res-

ponses to pain done on the third postoperative day when nearly two-thirds reported feeling a mild pain at rest.

Functional status is an important parameter in assessing early clinical outcome with a direct impact on convalescence [22]. It is a subjective parameter, but in most studies when comparing certain treatment methods, the determination of functional status hasan important place [23].We measured this by experiencing fatigue as one of the subjective manifestations of functional status in patients postoperatively.

There was an overall better functional status in the TAPP group. The results also correlated with the postoperative pain scale.

The risk of complications after inguinal hernia surgery is low. The introduction of laparoscopy as a method for hernioplasty has led to complications that are specific to laparoscopy and its approach.

The most common complications of inguinal hernioplasty regardless of the approach are: hematoma, seroma, infection at the site of the hernioplasty (or sites of incision), as well as urinary infection. More serious complications include bladder injury, testicular injury, and funiculus elements [18].

Specific and more serious complications that occur more frequently in laparoscopic hernioplasty are visceral injury and injury to the vascular structures, McCormack [15] in his study in the laparoscopic group noted 8 visceral and 7 vascular injuries in 2,315 laparoscopic hernioplasties 49.

The EU Hernia Trialists Collaboration [21] in 2000 conducted a systematic review of randomized controlled trials comparing open methods with laparoscopic one. They foundthat overall complications were rare in the compared methods, but the more severe, predominantly vascular and visceral injuries occurred more frequently in laparoscopic methods (4.7 per 1,000 and open 1.1 per 1,000).

There were no serious complications in our study in terms of injury to vascular structures or visceral organs.

Schmedt in a meta-analysis of randomized controlled trials in 2005, comparing both laparoscopic TAPP and TEP with the Lichtenstein and other open methods found that significant differences arosein the area of hernioplasty infections and hematoma occurrence, which was smaller in laparoscopic methods. In terms of visceral injuries and vascular structures and bladder catheterization there wasno difference between the two methods. The incidence of seroma following the Lichtenstein method was only lower compared to laparoscopic [24].

Ciftci in 2015 conducted a comparative study between laparoscopic and open method. The number of patients screened in the study, open (n=32) and laparoscopic TAPP (n=31) wasclose to the number of our included patients. The results obtained for early postoperative complications in the open group showed 4 patients or 12.5% with urinary retention, one hematoma, one wound infection and one lung atelectasis. In the laparoscopic group complications occurred in 2 patients or 6.4%, one with urinary retention and one with atelectasis [25].

Kargar also found in his comparative study between laparoscopic TAPP and open Lichtenstein method that the incidence of early postoperative complications was lower in laparoscopic TAPP. These included hematoma (TAPP 6.6%/Lichtenstein 13.3%), seroma (TAPP 10%/ Lichtenstein 13.3%) and infection (TAPP 0%/Lichtenstein 1.6%) [26].

The results of our study indicated that the percentage of early postoperative complications that occurred with the TAPP was lower compared to the open Lichtenstein method. The lower incidence of complications in laparoscopy is probably due to the concept of minimal accessless incision and correspondingly less tissue dissection.

Convalescence, the return to usual daily activities, isthe end-point of any treatment method and isparticularly important for evaluating surgicalprocedures and their success. It is directly dependent on the parameters listed above, such as pain and postoperative complications, but also on the recommendations given by the surgeon [27]. Convalescence data provide answers to postoperative recovery of patients.

In a study of McCormack [15], a systematic review of the Cochrane database, the results showed that patients undergoing a laparoscopic procedure had a 7-day shorter reconvalescence compared to the open group. The trial of EU Hernia Trialists Collaboration [21] including 24 studies showed that laparoscopically treated patients had a faster return to their daily activities compared to open methods. Only in one study did the results show that there was equal reconvalescence in both groups.

Gong compared 62 patients treated with an open method, 50 patients treated with the TAPP laparoscopic method, and 52 patients treated with the TEP (total extraperitoneal) method. The time to return to daily activities in laparoscopic groups wassignificantly shorter than in the open group [28].

Treadwell [29] also published in 2012 the results of 15 analyzedstudies in which the return to daily activities was shorter in laparoscopic techniques. Results showed a median difference in days of -3.9; 95% CI, from -5.6 to -2.2 in favor to laparoscopy.

Ciftci [25] in hisstudy determined the mean time necessary to return to work in the open technique group, which was 11.5 and in the laparoscopic TAPP group 5.1.

In our study, convalescence in both groups ranged from 2 to 7 days. According to the results, convalescence was significantly shorter in laparoscopic TAPP group. We believe the result would have shown even greater difference if we followed patients for a longer period.

However, the obtained results indicate that convalescence wasshorter whenthe laparoscopic techniques were used and correlated with the outcomes for postoperative pain and complications.

Conclusion

Patients in the study group treated with the laparoscopic TAPP method had a better early clinical outcome than patients in the control group.
The perioperative pain in the laparoscopic group was less than in the control group, as wasthe postoperative need for analgesics.
Early postoperative complications in patients treated with the laparoscopic TAPP method wereless frequent than in patients treated with the open Lichtenstein method.
Laparoscopically treated patients had better postoperative functional status expressed through a feeling of fatigue than patients in the open group. They also had shorter hospitalizations and convalescence.
The duration of the surgery was shorter in patients treated with the open Lichtenstein method than with the laparoscopic TAPP method.

Conflict of interest statement. None declared.

Reference

1. Rutkow IM. Demographic and socioeconomic aspects of hernia repair in the UnitedStates in 2003. *SurgClin North Am* 2003; 83(5): 1045-1051, v–vi.
2. Laparoscopic versus open repair: A superior approach to inguinal herniorrhaphy?OA Minimally Invasive Surgery [Internet]. Available from: https://www.oapublishinglondon.com/article/618#3.
3. Rosenberg J, Bay-Nielsen M. Current status of laparoscopic inguinal hernia repair in Denmark. *Hernia* 2008; 12(6): 583-587.
4. Lichtenstein IL, Shulman AG. Ambulatory outpatient hernia surgery. Including a new concept, introducing tension-free repair. *Int Surg* 1986; 71(1): 1-4.
5. HerniaSurge Group. International guidelines for groin hernia management. *Hernia* 2018; 22(1): 1-165. doi: 10.1007/s10029-017-1668-x. Epub 2018 Jan 12.
6. Arregui ME, Davis CJ, Yucel O, Nagan RF. Laparoscopic mesh repair of inguinal hernia using a preperitoneal approach: a preliminary report. *SurgLaparoscEndosc* 1992; 2(1): 53-58.
7. Dion YM, Morin J. Laparoscopic inguinal herniorrhaphy. *Can J Surg* 1992; 35(2): 209-212.
8. McCormack K, Wake B, Perez J, *et al*. Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation. *Health Technol Assess* 2005; 9(14): 1-203, iii-iv.
9. Eklund A, Montgomery A, Bergkvist L, Rudberg C. Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. *Br J Surg* 2010; 97(4): 600-608.
10. Neumayer L, Giobbie-Hurder A, Jonasson O, *et al*. Open mesh versus laparoscopic mesh repair of inguinal hernia. *N Engl J Med* 2004; 350(18): 1819-1827.
11. Memon MA, Cooper NJ, Memon B, *et al*. Meta-analysis of randomized clinical trials comparing open and laparoscopic inguinal hernia repair. *Br J Surg* 2003; 90(12): 1479-1492.
12. Kapiris SA, Brough WA, Royston CM, *et al*. Laparoscopic transabdominal preperitoneal (TAPP) hernia repair. A 7-year two-center experience in 3017 patients. *SurgEndosc* 2001; 15(9): 972-975.
13. Peitsch WKJ. A modified laparoscopic hernioplasty (TAPP) is the standard procedure for inguinal and femoral hernias: a retrospective 17-year analysis with 1,123 hernia repairs. SurgEndosc 2014; 28(2): 671-682.
14. Chapter 44. Fundamentals in Laparoscopic Surgery. In: Michael J. Zinner, Stanley W. Ashley (Editors). Maingot's Abdominal Operations. 11th Ed. The McGraw-Hill Companies; 2011.
15. McCormack K, Scott NW, Go PM, *et al*. EU Hernia Trialists Collaboration. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst Rev* 2003; (1): CD001785.
16. Abbas AE, AbdEllatif ME, Noaman N, *et al*. Patient-perspective quality of life after laparoscopic and open hernia repair: a controlled randomized trial. *SurgEndosc* 2012; 26(9): 2465-2470.
17. Salma U, Ahmed I, Ishtiaq S. A comparison of post operative pain and hospital stay between Lichtenstein's repair and Laparoscopic TransabdominalPreperitoneal (TAPP) repair of inguinal hernia: A randomized controlled trial. *Pak J Med Sci* 2015; 31(5): 1062-1066.
18. Chapter 37. Inguinal hernia In: F. Charles Brunicardi (Editor). *Schwartz's Principles of surgery*. Ninth edition. *McGraw-Hill* 2010; 1305-1342.
19. Misiołek H, Cettler M, Woron J, *et al*. The 2014 guidelines for post-operative pain management. *Anaesthesiol Intensive Ther* 2014; 46(4): 221-244.
20. Sajid MS, Craciunas L, Singh KK, *et al*. Open transinguinal preperitoneal mesh repair of inguinal hernia: a targeted systematic review and meta-analysis of published randomized controlled trials. *Gastroenterol Rep (Oxf)* 2013; 1(2): 127-137.
21. EU Hernia Trialists Collaboration. Laparoscopic compared with open methods of groin hernia repair: systematic review of randomized controlled trials. *Br J Surg* 2000; 87(7): 860.
22. Tolver MA, Strandfelt P, Forsberg G, *et al*. Determinants of a short convalescence after laparoscopic transabdominal preperitoneal inguinal hernia repair. *Surgery* 2012; 151(4): 556-563.
23. Rubin GJ, Hardy R, Hotopf M. A systematic review and meta-analysis of the incidence and severity of postoperative fatigue. *J Psychosom Res* 2004; 57(3): 317-326.
24. Schmedt CG, Sauerland S, Bittner R. Comparison of endoscopic procedures vs Lichtenstein and other open mesh techniques for inguinal hernia repair: a meta-analysis of randomized controlled trials. *SurgEndosc* 2005; 19(2): 188-199.
25. Ciftci F, Abdulrahman I, Ibrahimoglu F, Kilic G. Early-Stage Quantitative Analysis of the Effect of Laparoscopic versus Conventional Inguinal Hernia Repair on Physical Activity. *Chirurgia (Bucur)* 2015; 110(5): 451-456.
26. Kargar S, Shiryazdi SM, Zare M, *et al*. Comparison of postoperative short-term complications after laparoscopic transabdominal preperitoneal (TAPP) versus Lichtenstein tension free inguinal hernia repair: a randomized trial study. *Minerva Chir* 2015; 70(2): 83-89.
27. Callesen T, Klarskov B, Bech K, Kehlet H. Short convalescence after inguinal herniorrhaphy with standardised recommendations: duration and reasons for delayed return to work. *Eur J Surg* 1999; 165(3): 236-241.
28. Gong K, Zhang N, Lu Y, *et al*. Comparison of the open tension-free mesh-plug, transabdominalpreperitoneal (TAPP), and totally extraperitoneal (TEP) laparoscopic techniques for primary unilateral inguinal hernia repair: a prospective randomized controlled trial. *SurgEndosc* 2011; 25(1): 234-239.
29. Treadwell J, Tipton K, Oyesanmi O, *et al*. Surgical Options for Inguinal Hernia: Comparative Effectiveness Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 [cited 2016 Mar 25]. (AHRQ Comparative Effectiveness Reviews). Available from: http://www.ncbi.nlm.nih.gov/books/NBK100633/.

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MMP

Original article

THE ROLE OF NT-PROBNP AS A DIAGNOSTIC MARKER IN PATIENTS WITH COPD

УЛОГАТА НА NT-PROBNP ВО ЕВАЛУАЦИЈА НА ПАЦИЕНТИТЕ СО ХОББ

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Abstract

Introduction. BNP and Nt-proBNP are well known biomarkers of heart failure and are primarily used for diagnosis and risk stratification. Increased values of NT-proBNP are found in patients with COPD without any signs of heart failure mostly as a result of right ventricular overload.

Methods. Our study included 38 patients with established COPD with severe/very severe form of the disease. Patients were divided into two subgroups-patients with acute exacerbation and clinically stable patients. All patients were clinically evaluated (anamnesis, status of the patient, ECG) and underwent echocardiography. All patients had NT-proBNP serological examination. Demographic background and correlation of risk factors was done in all 38 patients. Echocardiography analysis included several parameters with emphasis to right chamber echo parameters in correlation to natriuretic peptide.

Results. In our study male gender was predominant, and the average age was 67.

Three risk factors (HTA, HLP, DM) were taken for analysis: HTA was 57.9%, DM 18.4%, dyslipidemia 42.2%. According to BMI, most of the patients were obese (42.2%). In both group of patients NT-proBNP was with increased values, especially in the group of patients with acute exacerbation. In relation to parameters that indicates right ventricular function, we found that TAPSE, S' wave from the tissue doppler of the right ventricle and FAC were with reduced values, especially in the group of patients with acute exacerbation.

Conclusion. Echocardiography is a noninvasive method and successful strategy for evaluation of right chamber parameters and function, especially in patients with COPD. The availability of NT-proBNP as a serological marker and its increasing applicability assist in early diagnosis and monitoring of patients with right heart failure.

Keywords: COPD, right heart failure, NT-proBNP, echocardiography

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Абстракт

Вовед. BNP и Nt-proBNP се добро познати биомаркери за срцева слабост и примарно се користат за дијагноза и ризик стратификаицја. Зголемените вредности на Nt-proBNP се најдени и кај пациенти со ХОББ без знаци за срцева слабост, најчесто заради услови на десно вентрикуларно оптеретување.

Методи. Нашата студија вклучи 38 пациенти кои беа со потврдена хронична белодробна болест (ХОББ) во изразена/многу изразена форма на болеста. Пациентите беа поделени во две подгрупи-пациенти со акутно влошување и клинички стабилни пациенти. Сите пациенти беа клинички евалуирани (анамнеза, статус на пациентот, ЕКГ) и им беше направена ехокардиографска проценка. Кај сите пациенти беше направена анализа на Nt-proBNP серолошки. Демографска анализа и анализа на ризик фактори беше направена кај сите 38 пациенти. Ехокардиографија беше направена кај сите пациенти со посебен осврт на десно срцевите параметри во корелација со натриуретски пептид.

Резултати. Во нашата студија предоминантен беше машкиот пол, а просечна возраст на пациентите беше 67 години. Три ризик фактори беа анализирани (ХТА, ДМ, ХЛП) и тоа: ХТА со 57.9%, ДМ со 18,4%, дислипидемија 42,2%. Во однос на БМИ, најголем дел од пациети беа обезни (42,2%). Во двете групи на пациенти вредностите на Nt-proBNP беа покачени посебно во групата со акутно влошување на болеста. Во однос на параметрите кои укажуваат на десно вентрукуларната функција најдовме дека TAPSE, S' од ткивниот доплер на десната комора и FAC беа со редуцирани вредности особено во групата со акутно влошување.

Заклучок. Ехокардиографијата како неивазивна метода успешно се користи во евалуација на десносрцевите параметри посебно кај пациентите со ХОББ. Достапноста на Nt-proBNP како серолошки маркер и зголемените апликабилни можности помагаат во

рана дијагноза и мониторинг на пациентите со ХОББ и десно срцева слабост.

Клучни зборови: ХОББ, десно срцева слабост, Nt-proBNP, ехокардиографија

Introduction

B-natriuretic peptide is also known as porcine type of natriuretic peptide and it was first described in 1988 and extracted from a porcine brain. Soon it was established that it derived from the heart and was defined as a cardiac hormone.

BNP belongs to the family of natriuretic peptides along with ANT (atrial natriuretic peptide), C type of natriuretic peptide (CNP) and urodilatin. The natriuretic peptides have in common a characteristic biochemical structure which consists of a 17 amino-acid ring and disulfide bridge between two cysteine molecules. Synthesis and secretion of BNP is mainly done from the heart chambers. BNP and Nt-proBNP are well known biomarkers for heart failure and are primarily used for diagnosis and risk stratification. Increased values of NT-proBNP are found in patients with COPD without any signs of heart failure mostly as a result of right ventricular overload. Cor pulmonale, secondary pulmonary hypertension and hypoxemia are important stimuli for natriuretic peptide release and increased BNP expression from the right side of the heart.

B-natriuretic peptide is a product of the prohormone pro-BNP, which is composed of 108 amino acids and divided into two fragment and secreted from the myocytes. The final product is BNP and NT-proBNP composed of 76 amino acids. Its pathophysiological role is in maintaining homeostasis of plasma volume and blood pressure as well as in prevention of salt and fluid retention in the body. There are several mechanisms of action: regulation of the sympathetic nerve system and the system of renin-angiotensin-aldosterone, improvement of diuresis and natriuresis, acting on afferent and efferent blood vessels and distal tubules on kidney level, reduction of peripheral vascular resistance and improvement of muscular relaxation [1].

BNP and Nt-proBNP are substances that are released from the heart muscle as a result of increased stretching and ventricular dilatation.

Recent studies suggest that ventricular “end-diastolic” stress of the myocardial wall as well as its rigidity may be a predominant factor for Nt-proBNP release. These markers are suitable for diagnosis and evaluation of the degree of the heart failure. They play a big role in patients with COPD due to existence of pulmonary hypertension and right ventricular dysfunction which are a result of pulmonary pressure overload. COPD by itself can cause stretching of the myocardial wall and right ventricular dilatation, increased vascular pressure that promotes secretion of NT-proBNP.

BNP is a biomarker used for prognostic purposes in patients with pulmonary hypertension. In patients with COPD who have advanced parenchymal changes, there may be increased values of NT-proBNP and prognostic significance.

NT-proBNP is not a standard test in itself that is conclusive. Its role comes to the fore together with the overall clinical picture and history of the disease.

Aim

The aim of the study was to:

- determine the role of Nt-proBNP as an indicator for the severity of the disease
- the role of Nt-proBNP in patient assessment with severe and very severe stage of the COPD (Gold 3 and 4), in the chronic phase and in conditions of acute exacerbation of the disease.

Material and methods

The study included 38 patients with confirmed lung disease, that is chronic obstructive lung disease (COPD), and classified by Gold classification into two groups: severe and very severe stage of COPD (Gold 3 and 4)

Standard classification according to Gold covers 4 groups of patients, but in our study only patients with stage 3 and 4 were evaluated.

- severe stage of COPD (FEV1 30-50%)-Gold 3
- very severe stage of COPD (FEV1<30%)-Gold 4

Patients were further classified based on whether they were in acute exacerbation of the disease (hospital patients) or outpatient patients with severe form of the disease, Gold 3 or 4.

Patients with coronary artery disease, congenital heart disease, cardiomyopathies (dilatata hypertrophica), idiopathic pulmonary hypertension, asthma and pulmonary fibrosis were excluded from the study.

In collaboration with the University Clinic for Pulmology and Allergology some of the patients were examined and classified by a pulmonologist (according to spirometric parameters and gas analyzes) and were sent to our Clinic for cardiac evaluation. On admission to the University Clinic for Cardiology, anamnesis and status of the patient were taken, present risk factors, ECG and echocardiographic evaluation was done, with special reference to the right ventricular function.

Other patients who were hospitalized, were sent to our Clinic by prior agreement for reevaluation.

After the examination, venous blood was taken in a test tube together with KEDTA (serum blood, 5 ml) for the analysis of natriuretic peptide hormone NT-proBNP. Processing was done with commercially available tests by immunoassay fluorescent method [2]. The results after their processing were issued in a printed form.

Echocardiographically, a couple of parameters were analyzed which gave special reference to right ventricular function in correlation with Nt-proBNP.

- Tricuspid annular systolic excursion (TAPSE) measured by M-mode is an indicator of the longitudinal systolic function of the right ventricle. Cursor in M-mode is placed on the lateral wall of the right ventricle at the level of the tricuspid annulus in 4-chamber view.
- Reduction under 16 mm is one of the markers of an impaired longitudinal function of the right ventricle.
- Estimation of the functional area of changes of the right chamber which gives information on the global function of the right ventricle (FAC %). FAC above 35% means a neat right systolic function.
- S' wave of tissue doppler of the right chamber is for evaluation of the longitudinal function. Values below 0.095 met/sec are a marker of an impaired longitudinal function of the right ventricle.

Results

In our study 38 patients with COPD (chronic obstructive pulmonary disease) were included. All patients were in sinus rhythm. Of all analyzed patients, 71.1% were males, and 28,9% females. The average age of the patients was 67.1±6.3, in range from 55 to 82 years. The following risk factors were noted: smokers 68.4%, hypertension 57.9%, diabetes mellitus 18.4%, dyslipidemia 7.9%. According to BMI, most of the patients were obese (42.2%), followed by overweight (28.9%) and normal weight (28.9%).

Table 1. Demographic features of COPD patients

Variables	Average	Min.	Max.	St.dev
age	67.1	55.0	82.0	6.26518
body weight	82.1	50.0	130.0	20.30017
height	169.6	155.0	186.0	7.85212
gender	**No**		**%**	
female	11		28.9	
male	27		71.1	
	Yes			
diabetes mellitus	7		18.4	
hypertension	22		57.9	
hyperlipidemia	3		7.9	
smoker				
yes	26		68.4	
no	12		31.6	
BMI kg/m^2				
18,5-24.9 normal	11		28.9	
25-29.9 overweight	11		28.9	
>=30 obese	16		42.2	

Of the total number of 38 patients, 31 had elevated values of NT-proBNP above cut-off of 125 pg/ml.

In 81.6% (31) of patients, the reference values of NT-proBNP were above 125 pg/ml, in 18.4% [7] of the patients reference values of NT-proBNP were found; the percentage difference was statistically significant, p<0.05(difference test).

Table 2. Breakdown Table of Descriptive Statistics N=38 (No missing data in dep. var. list)

Acute pts/ chr. ill	NT-probn-average value	NT-probn-N	NT-probn-st deviation	NT-probn minimum	NT-probn max
Acute patients	786.7350	20	986.9921	291.1000	4570.000
Chronically ill	141.1778	18	74.3675	33.1100	279.000
All patients	480.9447	38	780.6968	33.1100	4570.000

The analysis of the average values of NT-proBNP showed very high values of NT-proBNP in patients with acute exacerbation in correlation with clinically stable patients (Table 2).

All 20 patients with acute exacerbation (100%) had elevated values of Nt-proBNP above the reference values.

In the group of chronically ill patients, 11(61%) patients had elevated values of Nt-proBNP. The percentage difference was statistically significant, p<0.05 (difference test, p=0.224) (Table 3).

Table 3. Number of patients with increased values of NT-proBNP in both groups

NT-probBNP	Acute patients	Chronically ill	Total
<125	0	7(39%)	7
>125	20(100%)	11(61%)	31
All Groups	20	18	38

The analysis of the velocity of S' wave and the values of Nt-proBNP showed that values of S' below 0.095 were more common in the group of patients with acute exacerbation as a sign of deterioration of the longitudinal function of the right ventricle *versus* patients with stable form of the disease. In 13 patients with acute exacerbation (65%), S' was below 0.095, and 4(22.3%) patients were with stable form of the disease (Table 4).

Table 4. Speed display of S' wave and NT-probBNP

S wave	Acute patients	Chronically ill	Total
>0.095	7(35%)	14(77,7%)	21
<0.095	13(65%)	4(22,3%)	17
All Groups	20	18	38

A correlation was registered between the velocity of S' in both groups of patients (p<0.05) (Pearson Chi-square: 7.01220, df=1, p=.008096).

The average values of NT-proBNP in patients where TAPSE was below 16 mm were 1045.5±15155.3, in range from 70.8 to 4570; the average value of Nt-proBNP was above the reference one. The average values of Nt-proBNP in patients where TAPSE was above 16 mm were 330.4±334.7, in range 33.11 to 1881.0; the average value of Nt-proBNP was above the reference one. According to Student test, the difference was statistically significant, $p<0.05$.

In 7 (22.6) patients where TAPSE was below 16 mm, values above the reference ones for NT-proBNP were registered. In 24 (77.4%) patients, TAPSE was above 16 mm. There was a statistical significance, $p<0.05$.

Table 5. Correlation between TAPSE and NT-proBNP

TAPSE	NT-probBNP	N	St.deviation	min	max
>16 mm	330.4	30	334.664	33.11	1881.0
<16 mm	1045.5	8	1515.297	70.8	4570.0

The average values of NT-probNP in patients where functional area of shortening of the right chamber was above 35% were 465.6±836.0, in range 10.77 to 4470.0. The average value of Nt-proBNP was above the reference values. FAC below 35% was registered in only one patient (345.4 pg/ml), which was above the reference values for NT-probNP.

Due to the small sample of patients, no further analyses could be performed regarding FAC.

The patient with the reduced right ventricular function, who was assigned in the group of patients with acute exacerbation, had reduced velocity of S' wave from the tissue doppler of the right ventricle, TAPSE 19 mm, and preserved DA area above 18 sm2.

The average value of Nt-proBNP in the group of patients with acute exacerbation and FAC above 35% was 810.0±1008.4; the average value of Nt-proBNP was above the reference values. The average value of Nt-proBNP in the group of chronic patients and FAC above 35% was 141.2±74.4; the average value of NT-proBNP was above the reference one. In the group of patients with acute exacerbation, values of NT-proBNP were very high. According to Student t-test, the difference was statistically significant, $p <0.05$ ($t=2.804457$, $p=0.008170$).

Table 6. Correlation between NT-proBNP and FAC%

FAC	NT-probBN	N	St deviation	min	max
> 35%	484.6	37	791.1343	33.11	4570.0

Table 7. Mean values of NT-proBNP in correlation with acute exacerbated patients and clinically stable patients where FAC was above 35%

average/ acute pts NT-probBN	**average/ chr pts** NT-probBN	**t-value**	**P**	**N-acute pts**	**N-chronic pts**	**St deviation Acute pts**	**St deviation Chr pts**
810.0	141.2	2.804457	0.008170	19	18	1008.406	74.36748

Discussion

Natriuretic peptide is produced and released from the heart as a response to increased pressure and stretching of the wall.

Quantification of NT-proBNP is an increasingly relevant and useful diagnostic tool for heart failure differentiation, especially in patients with COPD and right heart failure. This statement has been confirmed in one study comprising a small series of patients, named: "The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease". It has been published by a group of authors from the Department of pulmonary medicine in Ankara, Turkey [2].

Several large studies have concluded that a more common cause for death in patient with COPD is cardiac rather than pulmonary cause. Secondary pulmonary hypertension and cor pulmonale are important predictors in this group of patients for poor prognosis and death.

Plasma NT-proBNP is a noninvasive biomarker for diagnosis and monitoring of heart failure. Increased values of Nt-proBNP are an independent risk factor for death in patients with COPD, hence some studies confirm the importance of NT-proBNP in determining the progression of COPD as well as the possibility of developing secondary pulmonary hypertension [3].

In our group of patients, male gender was predominant (71.1%), female gender was represented with 28.9 %. In most studies, male gender dominates, as well as in our study, but one retrospective study from Sweden, published in 2019 found that COPD was more common in females than in males (53.,8%). This trend tended to decrease in later years of the observation period. Another paper published in 2019 in China gives information that prevalence of COPD is larger in male gender [4]

In relation to our study, we found that most of the patients had three dominant risk factors: hypertension was found in 59.7%, diabetes mellitus in 18.4% and hyperlipidemia in 7.9% of patients.

In several studies diabetes was found to be not a rare risk factor in patients with COPD, ranging from 1.6 to

16%. Smoking increases the level of LDL cholesterol, triglycerides and lowers HDL cholesterol [5].
In our study, 16 patients or 28.9% were overweight, with BMI above 30 kg/m2. Our results are in agreement with the results presented in one paper where a group of patients with COPD overweight and risk factors was compared with a group of patients with COPD with normal BMI. The prevalence of obesity was 21.8% and 32.4% of patients were overweight. It was noticed that patients with COPD in class Gold (1 and 2) were more prone to obesity than patients in class Gold (3 and 4). This was not the subject of our current analysis [6].
In our study of 38 patients, 31 patients (81.6%) were found to have significantly higher values of Nt-proBNP above the cut-off values of 125 pg/ml [7].
In one recent study published in 2019 by a group of authors from Egypt, an analysis of the increased values of NT-proBNP and acute exacerbation of COPD patients in hospital conditions was performed. Their results largely correspond to ours. Our study group of 20 patients (64.5%) with acute exacerbation of COPD had a significantly elevated value of Nt-proBNP [3,7,8,12]. Patients classified in stage 3 and 4 by Gold without signs of acute exacerbation, had elevated values of Nt-proBNP due to the severity of the disease, progression of chronic respiratory failure and development of secondary pulmonary hypertension. This coincides with the results presented in one study from 2012 by a group of authors from the Egyptian society of chest diseases and tuberculosis [3].
In terms of S' wave from the tissue doppler of the right ventricle, in the group of patients with acute exacerbation there was a positive correlation between Nt-proBNP and the values of S' under 0.095m/sec. In 13 patients (65%), S' was below 0.095 in patients with acute exacerbation.
In a recent study entitled "Acute exacerbation impairs right ventricular function in patients with COPD", published by a group of authors in 2015 in Istanbul, Turkey, was noticed that the filling conditions of the right ventricle might affect S' wave from the tissue doppler of the right ventricle. Their results are comparable with ours. This is of great importance because patients that have acute exacerbation of COPD might develop deterioration of the parameters of the right ventricle (TAPSE, S',TDI) as well as negative concordance with the prognosis in this group of patients. Their study as well as other representative papers have not correlated parameters from the right ventricle with Nt-proBNP. In that sense, our study has significant contribution [9].
In the text from 2015, forementioned in this study, (da se navede referencata i da se izmeni pocetokov na recenicata) was found that their group of patients with acute exacerbation had reduced values for TAPSE, below 16 mm. After recovery, echocardiography was performed and TAPSE values as an indicator of the longitudinal function of the right ventricle was elevated but statistically insignificant [9]. In our study, 8 patients had TAPSE below 16 mm and elevated levels of Nt-proBNP. These patients belong to the group of patients with acute exacerbation.
In our study the average value of Nt-proBNP and FAC showed increased values in both groups, especially in the group with acute exacerbation that was statistically significant. In one paper published in 2013 by a group of authors, entitled **"**NT-proBNP accurately reflects the impact of severe COPD exacerbation on the right ventricle" was found that patients with acute exacerbation of COPD had increased values of Nt-proBNP and a reflection on both morphology and function of the right ventricle.

Conclusion

Increased values of Nt-proBNP are promising serological markers, which may suggest right ventricular dysfunction in patients with COPD. They can also be a marker for acute deterioration of the condition of the patients with COPD.
Transthoracic echocardiography is probably the best noninvasive method for right heart evaluation in patients with COPD. It can give a quick assessment of the size and thickness of the right ventricle, size and area of the right atrium, as well as other parameters that are used for evaluation of the right ventricular systolic function such as: TAPSE, FAC% and S' from the tissue doppler of the lateral wall of the right ventricle as more subtle parameters.
In patients with COPD, TAPSE, FAC and S' wave (from the tissue doppler of the lateral wall) of the right ventricle can be significant prognostic markers for disease monitoring. Right ventricular remodeling process is often seen in patients with COPD, but without any signs of right ventricular failure even in patients with a long history of the disease.
The possibility to use NT-proBNP as a serological marker in daily routine and the availability of the echocardiography as a noninvasive and repetitive method are crucial for monitoring parameters in this group of patients.

Conflict of interest statement. None declared.

References

1. Doust J, Lehman R, and Glasziou P. The Role of BNP Testing in Heart Failure. *Am Fam Physician* 2006; 74(11): 1893-1900.
2. Bozkanat E, Tozkoparan E, Baysan O, *et al*. The Significance of Elevated Brain Natriuretic Peptide Levels in Chronic Obstructive Pulmonary Disease. *The Journal of International Medical Research* 2005; 33: 537-544.
3. El Gazzar AG, Hibah NA, Gouda TM, *et al*. Plasma brain natriuretic peptid levels in COPD without pulmonary hypertension. *The Egyptian Journal of Chest Diseases and Tuberculosis*. 2017; 66(1): 49-54.
4. Zhenqiu Zha, Ruixue Leng, Wei Xu, *et al*. "Prevalence and risk factors of chronic obstructive pulmonary disease

in Anhui Province, China": a population-based survey, Zha *et al*. *BMC Pulmonary Medicine* 2019; 19: 102. doi.org/10.1186/s12890-019-0864-0.
5. Chatila WM, Thomashow BM, Minai OA, *et al*. Comorbidities in Chronic Obstructive Pulmonary Disease, *Proceedings of the American Thoracic Society* 2008 vol 5:549-555.
6. Zewari S, Hadi L, van den Elshout F, *et al*. Obesity in COPD: comorbidities with practical consequences? *COPD* 2018; 15(5): 464-471.
7. Abdelnabya NK, Shabanaa HA, Arafat WR. B-type natriuretic peptide as a predictor of severity in admitted patients with acute exacerbation of COPD. *Egyptian Journal of Bronchology* 2019; 13: 289-297.
8. Inoue Y, Kawayama T, Iwanaga T, and Aizaw H. High Plasma Brain Natriuretic Peptide Levels in Stable COPD without Pulmonary Hypertension or Cor Pulmonale. *Inter Med* 48: 503-512, 2009 (DOI: 10.2169/internalmedicine.48.1701).
9. Ozben B, Eryuksel E, Tanrikulu AM, *et al*. Acute Exacerbation Impairs Right Ventricular Function in COPD Patients. *Hellenic Journal of Cardiology* 2015; 56: 324-331.
10. Kolb TM, and Hassoun PM. Right Ventricular Dysfunction in Chronic Lung Disease. *Published in final edited form as: Cardiol Clin* 2012; 30(2): 243-256. doi: 10.1016/j.ccl.2012.03.005.
11. Inoue Y, Kawayama T, Iwanaga T, and Aizaw H. High Plasma Brain Natriuretic Peptide Levels in Stable COPD without Pulmonary Hypertension or Cor Pulmonale. *Inter Med* 48: 503-512, 2009 (DOI: 10.2169/internalmedicine.48.1701).
12. Hawkins NM, Khosla A, Virani SA, *et al*. *BMC* B-type natriuretic peptides in chronic obstructive pulmonary disease: a systematic review. *Pulmonary Medicine* (2017) 17:11 DOI 10.1186/s12890-016-0345-7.

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Original article

TREATMENT OF PATIENTS WITH CHRONIC WOUNDS DURING THE COVID-19 PANDEMIC IN REPUBLIC OF NORTH MACEDONIA

ТРЕТМАН НА ПАЦИЕНТИТЕ СО ХРОНИЧНИ РАНИ ВО ТЕК НА ПАНДЕМИЈАТА НА КОВИД-19 ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Abstract

Introduction. The COVID-19 pandemic has had an impact on the routine management of the chronic wounds which are defined as wounds that have not proceeded through orderly and timely reparation to produce anatomic and functional integrity after three months.
Aim. The aim of the study was to evaluate the clinical characteristics and outcomes of patients with chronic wounds managed through a modified treatment protocol during the COVID-19 pandemic.
Methods. This retrospective study included a sample of 224 patients with chronic wounds, 152 males (67.9%) and 72 females (32.1%), aged 32 to 94 years (mean age of 64.4±10.5 years), examined during the period of 11 March to 30 November 2020. Demographic data, comorbidities, laboratory and imaging findings, photographs, and clinical outcomes (persistent lesions, healed wounds, amputations and lethal outcome) were analyzed. For statistical data analysis we used Chi-square test with level of significance $p<0.05$.
Results. The most common type of chronic wound was arterial ulcer (44.2%) treated in outpatients settings ($p=0.026$). Diabetic, venous, and pressure ulcers were represented with 32.6%, 14.7%, and 8.5%, respectively. The current ongoing treatment of patients is 53.1%, whereby 37.5% of patients’ wounds have healed, 8.5% resulted in amputations, and three patients (1.3%) have lost their lives.
Conclusion. A specific triage pathway and modified treatment protocol for patients with chronic wounds during the COVID-19 pandemic were beneficial and showed adequate management of chronic wounds. The proposed algorithm reduced the exposure to SARS-CoV-2 of both, medical staff and patients, while providing a good healing rate in all chronic wounds types.

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Keywords: chronic wounds, COVID-19, SARS-CoV-2, patient management

Апстракт

Вовед. Пандемијата на Ковид-19 има влијание врз вообичаениот начин на лекување на хроничните рани, кои се дефинираат како рани кај кои нема уредно и навремено заздравување кое ќе доведе до анатомски и функционален интегритет по три месеци.
Цел. Целта на студијата беше да се евалуираат клиничките карактеристики и резултатите од третманот на пациентите со хронични рани лекувани преку модифицираниот протокол за време на пандемијата на Ковид-19.
Методи. Оваа ретроспективна студија вклучува примерок од 225 пациенти со хронични рани, 152 мажи (67,9%) и 72 жени (32,1%), на возраст од 32 до 94 години (средна возраст 64,4±10,5 години), прегледани во периодот од 11 март до 30 ноември 2020 година. Беа анализирани демографските податоци, коморбидитетите, лабораториски и дијагностички наоди, фотографии и резултатите од третманот (перзистентни лезии, излекувани рани, ампутации и летален исход). За статистичка анализа на податоците го користевме Хи-квадрат тестот со ниво на значајност $p<0,05$.
Резултати. Најчест тип на хронична рана беше артерискиот улкус (44,2%) лекуван во амбулантски услови ($p=0.026$). Дијабетичните, венските улкуси и декубиталните рани беа застапени во 32,6%, 14,7%, и 8,5%, последователно. Кај 53,1% третманот е во тек, кај 37,5% од пациентите раните се излекувани, 8,5% со ампутација на екстремитет и тројца пациенти (1,3%) починаа.
Заклучок. Специфичната тријажна патека и модифицираниот протокол за третман на пациентите со хронични рани за време на пандемијата на Ковид-19 беа корисни и покажаа адекватно лекување на

хроничните рани. Предложениот алгоритам го намали изложувањето на SARS-CoV-2 на медицинскиот персонал и на пациентите, истовремено обезбедувајќи висок процент на заздравување кај сите видови хронични рани.

Клучни зборови: хронични рани, Ковид-19, SARS-CoV-2, третман на пациенти

Introduction

Chronic wounds are defined as wounds that have not proceeded through an orderly and timely reparation to produce anatomic and functional integrity after three months, or barrier defects that have not healed in three months [1,2]. In developed countries, it is estimated that 1 to 2% of the population will experience a chronic wound during the lifetime [3]. Chronic, non-healing wounds can be debilitating for the affected individual and place a massive financial burden on healthcare system [4].
The physiological process of wound healing is divided into four phases. The first phase *hemostasis* is characterized by vasoconstriction and clotting. The subsequent *inflammation* phase is mediated through neutrophil granulocytes which prevent bacterial contamination and cleanse the wound from cell debris. The *proliferation* phase is primarily characterized by tissue granulation and formation of new blood vessels. During the last phase *remodeling*, the provisional wound matrix is replaced by more rigid scar tissue [5]. Wound healing depends on many factors, including adequate tissue perfusion, an intact immune system, appropriate level of wound hydration, removal of necrotic tissue and management of infection, if present [6].
All wounds have potential to become chronic wounds. They are classified by etiology into four categories: arterial, diabetic, pressure, and venous ulcers [7]. Despite differences in etiology at the molecular level, chronic wounds share certain common features, including excessive levels of proinflammatory cytokines, proteases, reactive oxygen species, and senescent cells, as well as the existence of persistent infection, and a deficiency of stem cells that are often also dysfunctional [8]. Comorbid illnesses induce adverse effects on the healing process of wounds and may need different strategies such as modification of drug therapy, diet, or behavior to promote wound healing. Diabetes, obesity, autoimmune diseases, malnutrition, cardiovascular disease, end-stage renal disease and cancer are the most common comorbidities that impact wound healing [9]. The presence of bacteria is most likely to influence the wound healing. The most common bacterial species detected in chronic venous leg ulcers were *Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa,* coagulase-negative staphylococci, anaerobic bacteria, *Enterobacter cloacae,* and *Escherichia coli* [10].
The effective care of chronic wounds requires a multimodal approach, including wound bed optimization, management of chronic medical conditions, and consistent follow-up. Advanced wound therapies, such as negative pressure wound therapy (NPWT), can have benefit in some patients, but evidence to support the use of one specific advanced dressing type over another is limited [11]. A primary aspect in effective wound care is exudates management. The excessive presence of exudate in the wound bed acts to delay healing. An effective dressing must maintain a moist wound bed, but not wet; absorb and retain excess exudate; maintain normal tissue temperatures at and around the wound bed and be impermeable to external pathogens and fluids, but allow gas exchange between the wound bed and the environment [12].
The spread of COVID-19 pandemic and limited hospital access caused significant limitation of patients' access to treatment, affecting in particular chronic wounds patients [13]. The current general strategy is to minimize the number of nonessential hospitalizations for three main reasons: providing intensive care units (ICU) the capacity for COVID-19 patients requiring intensive care, preserving medical staff due to the shortage of medical personnel, and reducing the risk of infection for hospitalized patients and medical staff [14]. Wound care practitioners should take necessary steps to minimize hospital admission of patients with chronic wounds. A specific triage is required to differentiate between critical, severe and stable patients. The first priority should be given to critical patients with ICU care. Alternative services like telemedicine with proper patient education should be adopted and homecare services should be provided as continuity of care [15].
The COVID-19 pandemic had an impact on the routine management of the chronic wounds in North Macedonia. There are several challenges faced by any clinician while managing chronic wounds during this pandemic. Since the beginning of the pandemic, we have modified our triage pathway accordingly, both chronic wound severity and comorbidities in patients to provide an appropriate chronic wound management and reduce the risk of SARS-CoV-2 exposure. The aim of the study was to evaluate the clinical characteristics and outcomes of patients with chronic wounds managed through specific triage pathway and modified treatment protocol during the COVID-19 pandemic.

Materials and methods

This retrospective study included a sample of 224 patients with chronic wounds, 152 males (67.9%) and 72 females (32.1%), aged 32 to 94 years (mean age of 64.4±10.5 years), examined at the University Clinic for Thoracic and Vascular Surgery, Faculty of Medicine-Skopje and University Clinic for Surgical Diseases "St. Naum Ohridski"-Skopje, during the period of 11

March to 30 November 2020. Inclusion criteria were: presence of chronic wound, follow-up of at least one month, both hospital and outpatient treatment settings. Demographic data, comorbidities, laboratory and imaging findings, consultation history, photographs, and clinical outcomes (persistent lesions, healed wounds, amputations, and lethal outcome) were analyzed. For statistical data analysis we used Chi-square test with level of significance $p<0.05$.

Results

The total number of patients with chronic wounds was 224,152 males (67.9%) and 72 females (32.1%). Majority of patients (39.7%) were in 61-70 age range. The most common comorbidities were cardiovascular diseases (57% of all comorbidities). Three patients (1.3%) were infected with SARS-CoV-2. Demographic and clinical characteristics of the patients are displayed in Table 1. Chronic wounds were classified into four categories: arterial, venous, diabetic, and pressure ulcers. Types of chronic wounds in all patients and treatment settings are presented in Table 2. The most common type of chronic wound was arterial ulcer (44.2%), and most of the wounds were treated in outpatient settings (p=0.026). Only patients who needed surgeries were hospitalized.

Table 1. Demographic and clinical characteristics of patients

Characteristics	No (%)
Age (Years)	64.4±10.5 (Mean±SD)
32-40	3(1.3%)
41-50	20(8.9%)
51-60	51(22.8%)
61-70	89(39.7%)
71-80	50(22.3%)
≥ 81	11(4.9%)
Gender	
Male	152(67.9%)
Female	72(32.1%)
Comorbidities*	
Cardiovascular disease	183(57%)
Diabetes	73(22.7%)
Obesity	45(14%)
Chronic kidney disease	9(2.8%)
COPD	8(2.5%)
Cancer	3(0.9%)
COVID-19 positive	3(1.3%)

*There were several comorbidities in some patients (Percentage calculated from the total number of comorbidities: 321)

Table 2. Types of chronic wounds and treatment settings

Type of chronic wound	Outpatient treatment No (%)	Hospital treatment No (%)	Total No (%)	p*
Arterial ulcer	74 (33)	25 (11.2)	99 (44.2)	0.026
Diabetic ulcer	65 (29)	8 (3.6)	73 (32.6)	
Venous ulcer	28 (12.5)	5 (2.2)	33 (14.7)	
Pressure ulcer	12 (5.4)	7 (3.1)	19 (8.5)	
Total	179 (79.9)	45 (20.1)	224 (100)	

*Chi-square test

The statistical analysis showed that there was a statistically significant difference between the type of chronic wound and treatment settings (χ^2=9.258, df=3, p=0.026). The types of chronic wounds and clinical outcomes in all patients were illustrated in Table 3. Persistent lesions, the rate of healing (complete wound closure), amputation, and lethal outcome were evaluated. There was still a need for wound treatment in majority of patients (53.1%) during the period surveyed. In total of 84(37.5%) patients, the wounds healed, 19(8.5%) patients had worsened ulcers and unavoidable amputations. Three patients have died. They had serious comorbidities, and one of them was positive for COVID-19.

Table 3. Types of chronic wounds and clinical outcomes

Type of wound	Ongoing care No (%)	Healed No (%)	Amputation No (%)	Death No (%)	Total No (%)
Arterial ulcer	46 (20.5)	35 (29.4)	16 (7.1)	2 (0.9)	99 (44.2)
Diabetic ulcer	40 (17.9)	29 (12.9)	3 (1.3)	1 (0.4)	73 (32.6)
Venous ulcer	20 (8.9)	13 (5.8)	/ (0)	/ (0)	33 (14.7)
Pressure ulcer	12 (5.4)	7 (3.1)	/ (0)	/ (0)	19 (8.5)
Total	118 (52.7)	84 (37.5)	19 (8.5)	3 (1.3)	224 (100)

The case of healed lower limb arterial ulcers infected with *Pseudomonas aeruginosa* is shown in Figure 2. The patient was treated ambulatory in a period of five months. There was also a good home care in this case. Since the beginning of the COVID-19 pandemic, we modified our triage pathway in accordance with both chronic wound severity and comorbidities in patients. The main goal in this activity was to provide an appropriate chronic wound management and reduce the risk of SARS-CoV-2 exposure. In Figure 3 our algori-

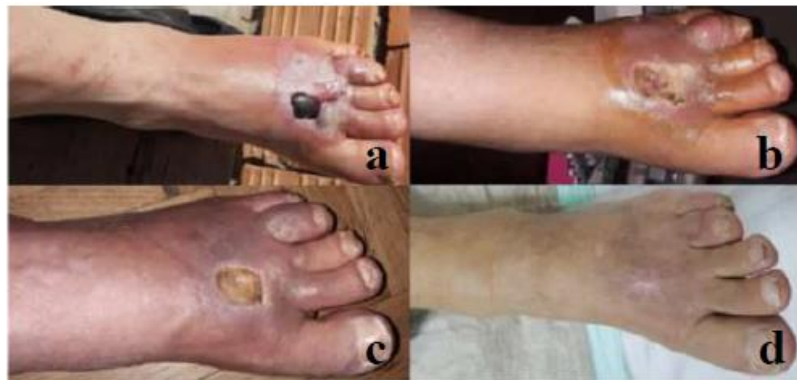

Fig. 1. Diabetic foot ulcer
a) First examination, **b**) after three weeks, **c**) after four weeks, **d**) after three months

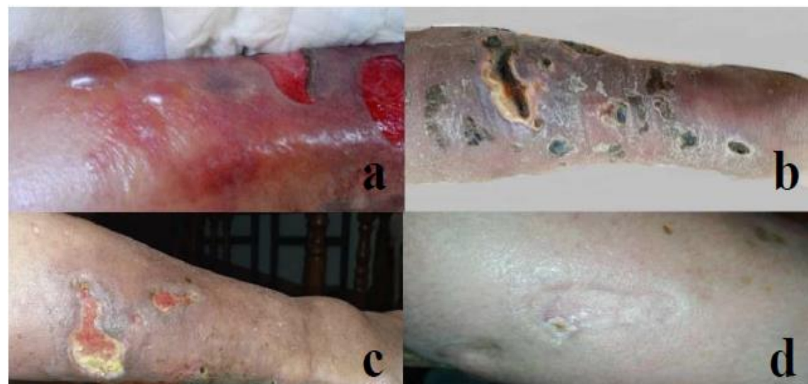

Fig. 2. Lower limb arterial ulcer
a) First examination, **b**) after five weeks, **c**) after three months, **d**) after five months

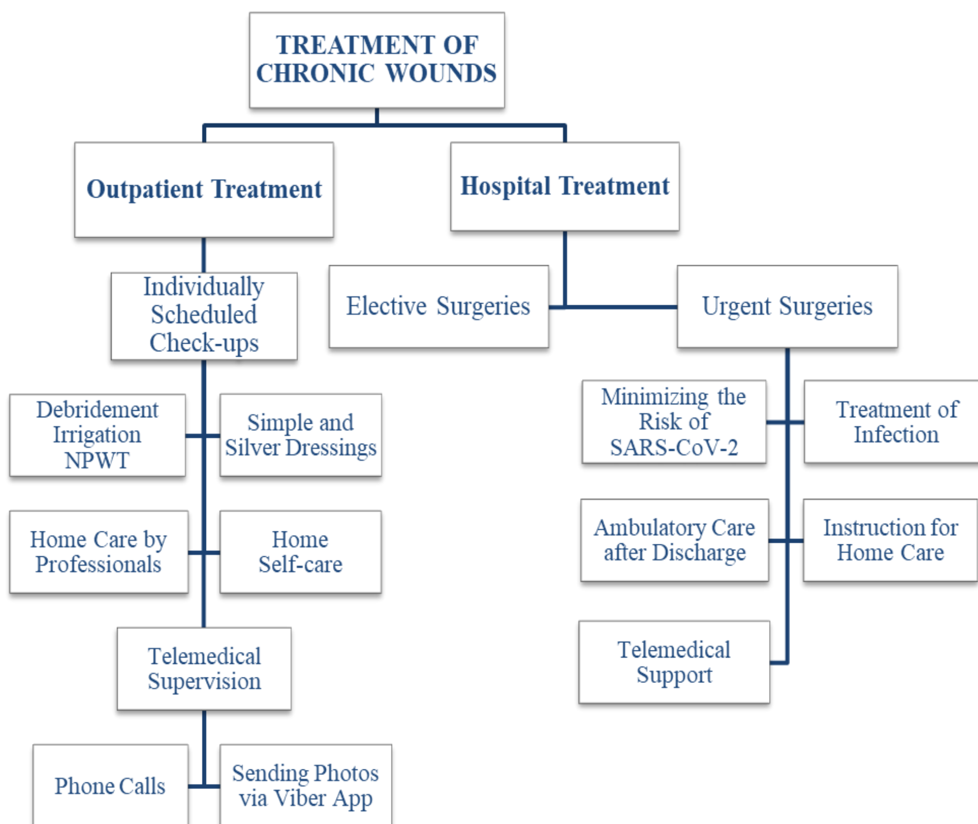

Fig. 3. Algorithm for chronic wounds management during COVID-19 pandemic

thm for chronic wound management during COVID-19 pandemic is presented.

Discussion

Managing patients during COVID-19 pandemic has been modified for all patients with chronic wounds, including patients with peripheral arterial disease, chronic venous insufficiency, diabetic foot, and pressure ulcers in terms of restricted visits to hospital facilities and applying simplified self-care. It is crucial to minimize probability of exposure to SARS-CoV-2, having in mind that the most critical preventive measures are keeping physical distance and avoiding contacts, as well as, wearing a mask. This is beneficial for both patients and healthcare providers. Patients with chronic wounds fit several of the high-risk criteria for COVID-19 infection and mortality. They are often older, immunocompromised, and have multiple comorbidities. The answer is not to avoid clinical evaluation and wait for wound infection, but to mitigate the risk of COVID-19 and ulcer infection [16]. Many patients have always been ambivalent about the need of referral to hospital and would often prefer to be managed in the community if possible, but this ambivalence during COVID-19 pandemic is magnified by a very real fear of being exposed to potential risk of infection in crowded waiting rooms and increased difficulty of transport [17].

From the beginning of COVID-19 crisis in the Republic of North Macedonia we have switched to a modified managing of patients with chronic wounds, to reduce their visits and therefore minimize the risk of transmission of SARS-CoV-2. Patients urgently admitted to the hospital were considered and treated as positive to SARS-CoV-2 until the test results proved to be negative. The approach to treat these patients was time consuming requiring additional medical equipment as well as more staff engagement. These preventive measures were critical to minimize the risk of exposure for both patients and medical staff within the hospital. Three patients in our sample were positive for COVID-19. Patients who have been infected with COVID-19 combined with chronic infective wound should be closely monitored and isolated for treatment, negative pressure wards should be used during the surgery, and standardized preoperative, intraoperative, and postoperative treatment should be carried out to improve their prognosis [18].

During this period, majority of our patients were treated in outpatient settings. First of all, it was crucial to establish rigorous criteria during the process, which means to distinguish patients that require hospital admission and reduce the admission as much as possible only for urgent and critical patients (sepsis, chronic limb-threatening ischemia and gas gangrene). In terms of the wound type, the most common wounds were arterial ulcers, followed by diabetic, venous, and pressure ulcers. In relation to age, majority of patients were older than 60 years. In a study about the incidence of chronic wounds, Goh *et al.* reported an increased trend across all wound types, with the highest increase of incidence rate among the oldest age groups. The burden of wounds is expected to increase as the population ages [19]. During the period surveyed there was an ongoing treatment in majority of patients. In 37.5% of patients the wounds healed, 8.5% had amputations, and three patients (1.3%) have died.

We presented our algorithm for chronic wound management during the COVID-19 pandemic. The treatment was reorganized to treating patients in outpatient conditions, as infrequent as possible, and self-care with instructions from healthcare professionals as well. After the initial examination and decision that the patient can be treated ambulatory, a sharp surgical debridement to the vital margins of the wound was done. Thorough lavage was done mostly with saline, and usually after wards silver hydrocolloid dressings were applied. For signs of infection the patients were treated with antibiotics, non-steroid anti-inflammatory drugs and anti-edematous enzyme-based drugs. Some of the treatment strategies utilized in chronic wounds include offloading, compression, warming, and vacuum-assisted closure devices [20].

After ambulatory treatment, the patients were advised not to open the wound for three days at least if silver hydrocolloid dressing was applied, or if simple dressing with betadine gauze pads were applied. Then, after removing those, simple shower with medical antibacterial soap or betadine baths should be done. In some cases, patients were advised to perform irrigation of wound with hypochlorous acid-based solutions after doing a shower and apply simple sterile dressing as a final step. These patients were also instructed to notice every important change and signs if the wound was getting worse and to inform their surgeon immediately.

Meloni *et al.* proposed a new triage pathway for management of persons with diabetes and foot ulcers (DFUs) according to ulcer features and comorbidities. Critical patients with severely complicated DFUs were urgently referred to a hospital. Patients with complicated DFUs received outpatient evaluation. Patients with uncomplicated ulcers were only managed by telemedicine after the first outpatient evaluation [21]. Shankhdhar presented a case of preventing diabetic foot amputation during COVID-19. The author and his diabetes care team managed the patient using online services and phone calls. The patient's self-care at home was successful and his ulcer healed completely, saving his toe from amputation [22].

In our sample, there was a good healing rate of diabetic ulcers. Patients with diabetes mellitus develop various microvascular and macrovascular complications, of which peripheral neuropathy and diabetic foot ulcers cause a significant negative impact on their quality of life [23]. Shin *et al.* reported a successful management of diabetic foot ulcers during the COVID-19 pandemic. Their approaches included virtual consultations using

physician-to-patient and physician-to-home nurse telemedicine as well as home podiatry visits [24]. Tao *et al.* suggested that in patients with small diabetic foot ulcers and mild infections, conservative treatment and small-scale debridement can be performed. In patients with irreversible injury and necrosis as the infection progresses, toxin absorption leads to a severe liver and kidney dysfunction. To save the lives of patients who cannot be stabilized by a non-surgical treatment, amputation must be performed. Patients with mild to moderate COVID-19 symptoms can tolerate more extensive or longer operations. For patients with severe or critical COVID-19, it is necessary to evaluate the potential risks of surgery [25].

Without an established public telemedicine system provided from wound or podiatric specialists in our country, the treatment of patients with wounds in general, especially vascular patients, is guided by the vascular surgeon in direct communication with the patient. Regular or video call, as well as, photos sent by patients are using for supervision and advice. It is of great importance that patients involved in this way of modified treatment have either previous basic medical knowledge or are educated for this purpose. Wang *et al.* presented their model for managing chronic wounds of outpatients during the COVID-19 pandemic. For stable wounds they recommended consulting through WeChat system online, teaching patients about basic wound managing skills, using foam dressings, and facilitating NPWT. For unstable and aggravated wounds they recommended multidisciplinary discussion online, choosing the nearest wound healing clinic, individual protection before going out, and fever and novel coronavirus screen [26]. COVID-19 has accelerated the adoption of telehealth among clinicians. Telehealth platforms make possible structured follow-up [27].

We provided telemedical support also for patients who underwent surgeries. After discharge they were scheduled for ambulatory check-ups and were advised for home care. Through efficient and effective application of telehealth strategies, health care providers can bypass infection risks while enabling the continuation of care for chronic wounds. Wound specialists, including physicians and registered nurses, can perform wound assessment through questions in text message format or phone calls, as well as photos and videos, to determine whether the lesions are stable, improving, or deteriorating [28]. It is important for the specialist to always keep the contact with the patients, assess by phone the presence of signs and symptoms: pain, redness, heat, swelling, drainage, fever, and increased pain, as well as, educate patients and their families how to perform the wound care [29]. We used Viber application in communication with our patients or their family members for sharing the photos of chronic wounds. Telehealth services can be used to screen patients who may have symptoms of COVID-19 and may provide the following: low-risk urgent care for non-COVID-19 conditions to identify those persons who may need medical consultation or assessment to make appropriate referrals; coaching and support for patients managing chronic health conditions; follow-up of patients after hospitalizations to decrease readmissions; and education of health care providers. Communication between healthcare providers and the population including telemedicine platforms can deliver healthcare and advice safely and quickly [30,31]. Persons with chronic wounds require regular care. As such, regular contact is inevitable not only for assessment but also for treatment (i.e. dressing changes). We can redesign the way in which wound care is delivered to fulfill the new norm of social distancing. Some elements, like self-care or family care, have existed for some time and others have been tested (e.g. telewound options), but none are the routine. That is about to change [32]. COVID-19 has reinforced that wound care is an essential service. Outpatients who do not receive frequent care, including wound monitoring and debridement, are at risk of loss of limb or even loss of life [33].

This model of providing surgical healthcare and treating of patients with chronic wounds in general can be absolutely beneficial even in normal circumstances, mostly because patients who are suffering from chronic wounds are weak and exhausted. Every visit to the hospital for them is an additional effort and psychological stress. Many of them are depended on transport to the hospital from their family members or other caregivers. In existing possibilities and circumstances we make efforts to provide safe and effective treatment of chronic wounds during the COVID-19 pandemic as our contribution to the global efforts to flatten the curve.

Conclusion

A specific triage pathway and modified treatment protocol for patients with chronic wounds during the COVID-19 pandemic were beneficial and showed an adequate management of chronic wounds. The proposed algorithm reduced the exposure to SARS-CoV-2 of both, medical staff and patients, while providing a good healing rate in all chronic wound types.

Conflict of interest statement. None declared.

References

1. Werdin F, Tenenhaus M, Rennekampff HO. Chronic wound care. *Lancet* 2008; 372(9653): 1860-1862.
2. Martin P, Nunan R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. *Br J Dermatol* 2015; 173(2): 370-378.
3. Gottrup F. A specialized wound-healing center concept: importance of a multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. *Am J Surg* 2004; 187(5) Supplement 1: 38S-43S.

4. Nunan R, Harding KG, Martin P. Clinical challenges of chronic wounds: searching for an optimal animal model to recapitulate their complexity. *Dis Model Mech* 2014; 7(11): 1205-1213.
5. Tsourdi E, Barthel A, Rietzsch H, *et al*. Current aspects in the pathophysiology and treatment of chronic wounds in Diabetes Mellitus. *BioMed Res Int* 2013; 2013: 385641.
6. Hoversten KP, Kiemele LJ, Stolp AM, *et al*. Prevention, diagnosis, and management of chronic wounds in older adults. *Mayo Clin Proc* 2020; 95(9): 2021-2034.
7. Bowers S, Franco E. Chronic wounds: evaluation and management. *Am Fam Physician* 2020; 101(3): 159-166.
8. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care* 2015; 4(9): 560-582.
9. Mahmoudi M, Gould LJ. Opportunities and challenges of the management of chronic wounds: a multidisciplinary viewpoint. *Chronic wound care management and research* 2020; 7: 27-36.
10. Gjødsbøl K, Christensen JJ, Karlsmark T, *et al*. Multiple bacterial species reside in chronic wounds: a longitudinal study. *Int Wound J* 2006; 3: 225-231.
11. Jones RE, Foster DS, Longaker MT. Management of chronic wounds-2018. *JAMA* 2018; 320(14): 1481-1482.
12. Gefen A, Ousey K. Safe and effective wound care during the COVID-19 pandemic. *J Wound Care* 2020; 29(11): 622-623.
13. Ligresti C, Facchin F, Armstrong DG, *et al*. Practical management of skin lesions during COVID-19 pandemic-IAWC International Academy of Wound Care. *World Journal of Surgery and Surgical Research* 2020; 3: 1253.
14. Banasiewicz T, Becker R, Bobkiewicz, A, *et al*. Prevention and therapy of acute and chronic wounds using NPWT devices during the COVID-19 pandemic, recommendation from The NPWT Working Group. *Negative Pressure Wound Therapy Journal* 2020; 7(2): 4-9.
15. Milind RG, Savai J. Chronic wound management during COVID-19 pandemic. *EC Endocrinology and metabolic research* 2020; 5(6): 37-46.
16. Rogers LC, Armstrong DG, Capotorto J, *et al*. Wound center without walls: The new model of providing care during the COVID-19 pandemic. *Wounds* 2020; 32(7): 178-85.
17. Kong WM, Harrington A, Michalowski J, *et al*. Implications of the COVID-19 pandemic on the management of foot disease in diabetes. *Diabetic Foot J* 2020; 23(2): 8-9.
18. Zhou H, Jin Q, Lu H. Exposure risk of patients with chronic infectious wounds during the COVID-19 outbreak and its countermeasures. *J Orthop Surg Res* 2020; 15: 452.
19. Goh OQ, Ganesan G, Graves N, *et al*. Incidence of chronic wounds in Singapore, a multiethnic Asian country, between 2000 and 2017: a retrospective cohort study using a nationwide claims database. *BMJ Open* 2020; 10: e039411.
20. Mustoe TA, O' Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plast Reconstr Surg* 2006; 117(7 Suppl.): 35S-41S.
21. Meloni M, Izzo V, Giurato L, *et al*. Management of diabetic persons with foot ulceration during COVID-19 health care emergency: Effectiveness of a new triage pathway. *Diabetes Res Clin Pract* 2020; 165: 108245.
22. Shankhdhar K. Case report: diabetic foot amputation preventing during COVID-19. *The Diabetic Foot Journal,* 2020; 23(3): 57-59.
23. Atri A, Kocherlakota CM, Dasgupta R. Managing diabetic foot in times of COVID-19: time to put the best "foot" forward. *Int J Diabet Developing Countries* 2020; 40(3): 321-328.
24. Shin L, Bowling FL, Armstrong DG, Boulton AJM. Saving the diabetic foot during the COVID-19 pandemic: A tale of two cities. *Diabetes Care* 2020; 43(8): 1704-1709.
25. Tao F, Tang X, Tao H, *et al*. Surgical treatment of diabetic foot ulcers during the COVID-19 pandemic. *J Diabetes Complications* 2020; 34(9): 107622.
26. Wang R, Peng Y, Jiang Y, Gu J. Managing chronic wounds during novel coronavirus pneumonia outbreak. *Burns Trauma,* 2020; 8: tkaa016.
27. Azizzadeh K, Hamdan US, Salehi PP. Effect of coronavirus disease 2019 and pandemics on global surgical outreach. *JAMA Otolaryngol Head Neck Surg* 2020; 146(9): 783-784.
28. Willie Hsieh MC, Lee CC, Ou SF, Kuo YR. Telemedicine algorithm for chronic wound care during COVID-19. *Int Wound J* 2020; 17(5): 1535-1537.
29. Tinelli G, Sica S, Guarnera G, *et al*. Wound care during COVID-19 pandemic. *Ann Vasc Surg* 2020; 68: 93-94.
30. Ratliff CR, Shifflett R, Howell A, Kennedy C. Telehealth for wound management during the covid-19 pandemic. *J Wound Ostomy Continence Nurs* 2020; 47(5): 445-449.
31. DiFazio LT, Curran T, Bilaniuk JW, *et al*. The impact of the COVID-19 pandemic on hospital admissions for trauma and acute care surgery. *Am Surg* 2020; 86(8): 901-903.
32. Queen D, Harding K. COVID-19 a short-term challenge, telewound a lifetime change. *Int Wound J* 2020; 17: 529.
33. Waller HD, McCarthy MW, Goverman J, *et al*. Wound care in the era of COVID-19. *J Wound Care* 2020; 29(8): 432-434.

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Original article

NGAL AND CYSTATİN C: TWO POSSİBLE EARLY MARKERS OF DİABETİC NEPHROPATHY İN PATİENTS WİTH TYPE 2 DİABETES MELLİTUS

NGAL И CYSTATİNC ДВА МОЖНИ РАНИ МАРКЕРИ ЗА ДИЈАБЕТИЧНА НЕФРОПАТИЈА КАЈ ПАЦИЕНТИ СО ДИЈАГНОСТИЦИРАН ДИЈАБЕТЕС МЕЛИТУС ТИП2

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Abstract

Introduction. Diabetic nephropathy (DN) is a progressive renal impairment characterized by impaired renal architecture and function and is one of the leading causes of permanent renal impairment. Patients with DN have a high mortality rate, which is primarily due to cardiovascular complications. In everyday practice in the Republic of North Macedonia, serum creatinine, microalbuminuria and glomerular filtration rate are used to detect DN. However, these standard tests do not always allow for detection of initial DN damage.

Aim. The aim of this study was to investigate the role of NGAL (in urine) and Cystatin C (in serum) values as adjunctive testing of existing markers (microalbuminuria and creatinine) in unmasking early structural and functional renal impairment in asymptomatic patients with type 2 diabetes mellitus (DM type 2).

Methods. This was a prospective, observational (6-month follow-up) study, involving 60 patients aged 35-70 years. The first two groups were patients with diagnosed DM type 2 for a minimum of 5 years, 15 patients diagnosed with DM type 2 with diabetic nephropathy and 15 patients without diabetic nephropathy. The third group consisted of healthy respondents (30). In addition to standard biochemical analyses, the three groups were also examined for body fluid concentrations of NGAL (architect urine NGAL) and Cystatin C (nephelometry), as well as standard biomarkers for renal nephropathy (serum creatinine and microalbumin).

Results. The respondents from the three analyzed groups did not differ significantly in terms of gender structure (p=0.71) and age (p=0.068). The study found that (the core values) baseline creatinine, microalbuminuria, NGAL and Cystatin C serum levels were higher in patients diagnosed with DM type 2 and diabetic nephropathy (DN) compared to those with diabetes and without diabetic nephropathy in healthy trials. Also, after 6 months of follow-up, it was proven that in patients diagnosed with DM type 2 and DN all four parameters were higher with confirmed significance unlike the group of patients with DM type 2 without DN. In the group with diabetes and diabetic nephropathy, during the re-evaluation after 6 months of monitoring we registered a non-significant increase in the biomarker NGAL p=0.16), and a significant increase in the biomarker Cystatin C (p=0.016). There was a statistically significant correlation between baseline creatinine values and baseline control values of Cystatin C (p<0.0001), creatinine and NGAL values after a 6-month re-evaluation (p=0.014), all of which were positive. The correlation between the two biomarkers NGAL and Cystatin C were statistically insignificant in the first measurements (p=0.160), and were significant and direct positive on the second measurements, after 6 months (r=0.536, p=0.039). The two markers changed in direct proportion to the serum, with the increasing of one marker in the serum. Also, the other biomarker increased, and vice versa.

Conclusion. NGAL and Cystatin C, biomarkers of renal impairment, are correlated with decreased renal function in patients with DM type 2, suggesting that NGAL and Cystatin C may be used as adjunctive tests to existing ones (creatinine and microalbuminuria) to unmask early renal dysfunction.

Keywords: diabetic nephropathy, NGAL, Cystatin C, diabetes type 2

Апстракт

Вовед. Дијабетичната нефропатија (ДН) е прогресивно бубрежно оштетување кое се карактеризира со нарушување на бубрежната архитектура и функција и е една од водечките причини за трајно бубрежно оштетување. Пациентите со ДН имаат висок

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морталитет, кој пред се се должи на кардиоваскуларни компликации. Во секојдневната пракса во Р. Северна Македонија за детекција на ДН се користат серумскиот креатинин, микроалбуминурија и гломеруларна филтрациона рата. Меѓутоа овие стандардни тестови не овозможуваат секогаш детекција на почетни оштетувања кај ДН.

Цел. Целта на оваа студија беше да се истражува улогата на вредности на NGAL (во урина) и CysC (во серум), како дополнителни-суплементарни тестирања на постоечките маркери (микроалбуминурија и креатинин) при демаскирање на рано структурно и функционално бубрежно оштетување кај асимптоматски, нормоалбуминурични пациенти со дијабетес мелитус тип 2 (ДМ тип2).

Методи. Студијата е проспективна, обсервациска (6 месечно следење), во која беа вклучени 60 пациенти, на возраст од 35-70 години. Првите две групи беа пациенти со дијагностициран ДМ тип 2 во траење од минимум 5 години (15 пациенти со дијагностициран ДМ тип 2 со дијабетична нефропатија и 15 пациенти без дијабетична нефропатија). Третата група ја сочинуваа здрави испитаници (30). Освен стандрадните биохемиски анализи, кај трите групи беа иследувани концентрации во телесните течности на NGAL (ARCHITECT Urine NGAL) и Cystatin C (нефелометрија), како и стандардните биомаркери за бубрежна нефропатија (серумски креатинин и микроалбуминурија).

Резултати. Испитаниците од трите анализирани групи не се разликуваа сигнификантно во однос на половата структура ($p=0.71$) и возраста ($p=0.068$). Студијата покажа дека базичните вредности на креатинин, микроалбуминурија, NGAL и CystatinC во серум, беа повисоки кај пациентите со дијагностициран ДМ тип 2 и дијабетична нефропатија (ДН), во споредба со тие со дијабетес и без дијабетична нефропатија и здравите испитаници. Исто така после 6 месечно следење се докажа дека кај пациентите со дијагностициран ДМ тип2 и ДН сите четири параметри беа повисоки со потврдена сигнификантност за разлика од групата на пациенти со ДМ тип2 без ДН. Во групата со дијабетес и дијабетична нефропатија, при ре-евалуацијата по 6 месечно следење регистриравме несигнификантно зголемување на биомаркерот NGAL ($p=0.16$), а сигнификантно зголемување на биомаркерот Cystatin C ($p=0.016$). Се покажа статистичка сигнификантна корелација на базичните вредности на креатинин со базичните и контролни вредности на Cystatin C ($p<0.0001$), и на вредностите на креатинин и NGAL по ре-евалуација на 6 месеци ($p=0.014$), и сите овие корелации се позитивни. Корелацијата меѓу двата биомаркери NGAL и Cystatin C беше статистички несигнификантна на првото мерење ($p=0.16$), а сигнификантна и директна, односно позитивна при второто мерње, по 6 месеци ($r=0.536, p=0.039$). Двата маркери се менуваа правопропорционално во серумот, со зголемување на едниот маркер во серумот, се зголемуваше и другиот биомаркер, и обратното.

Заклучок. NGAL и Cystatin C, биомаркери на бубрежно оштетување, се во корелација со пад на бубрежната функција кај пациенти со ДМ тип2, што укажува на тоа дека тие може да се користат како дополнителни тестови на постоечките (креатинин и микроалбуминурија) со цел да се демаскира раната бубрежна дисфункција.

Клучни зборови: дијабетична нефропатија, NGAL, Cystatin C, диајбетес тип 2

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by chronic hyperglycemia due to an inherited and/or acquired deficiency in pancreatic insulin production, or the ineffectiveness of the produced insulin [1,2]. Diabetes occurs due to the interaction of various factors, primarily genetic factors, lifestyle and environmental factors.

Diabetes is on a pandemic scale and is one of the major health problems of the 21st century. According to the IDF (International Diabetes Federation), the total number of people with diabetes in the world as of 2019 is 463 million, and this figure is expected to exceed 700 million by 2045 [3].

The most common types of diabetes are: type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes. Type 2 diabetes is more common and covers about 90-95% of all types of diabetes, both globally and in our country [1,2,4].

DM causes acute and chronic micro- and macrovascular complications [5-7].

Acute complications include hypoglycemia, diabetic ketoacidosis, and hyperosmolarity [5]. Chronic microvascular complications include: diabetic retinopathy, nephropathy, and neuropathy [6,7].

Whether and when chronic microvascular complications occur depends on many factors, including:

- Duration of diabetes
- Diet and physical activity
- Appropriate therapy
- Control of glycemia-HbA1c values, fasting glycemia values and postprandial glycemia

Diabetic nephropathy (DN) is a progressive renal impairment characterized by impaired renal architecture and function, and is one of the leading causes of permanent renal impairment [8-10]. As a result, these patients most often require renal replacement therapy (RRT) and/or hemodialysis (HD). In recent years, the number of patients on RRT has been continuously increasing, both in the world and in the Republic of North Macedonia. Thus, in 2002 the total number of patients on RRT was

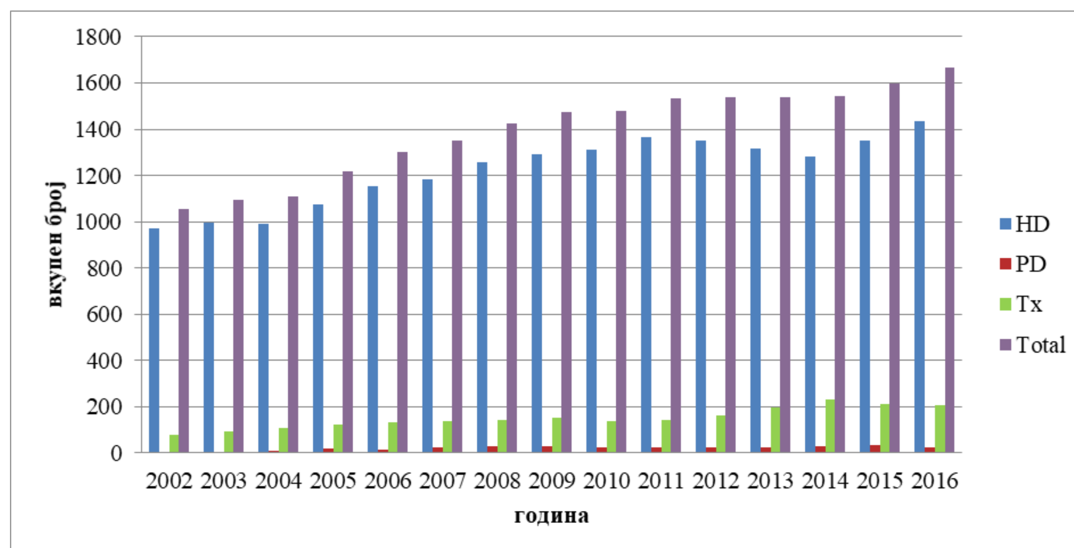

Fig. 1. Number of patients in need of renal replacement therapy - RRT in the Republic of Macedonia for the period from 2002 to 2016; *Data from the annual registers of ERA-EDTA, *Internal data for 2012-2013, *HD-hemodialysis, *PD-peritoneal dialysis, *Tx (transplant), *Total-Total

1056, of which 92% were on HD. In 2016 the number of patients on RRT was 1665, of which 86% were on HD (Figure 1) [11].

The pathophysiological changes in DN that leads to reduction in renal function are associated with cellular and extracellular disorders in the glomerular and tubulo-interstitial structures [10,12,13]. Glomerular and tubular-interstitial kidney injury plays a role in the pathogenesis of DN [13]. Patients with DN have a high mortality rate, which is primarily due to cardiovascular complications.

In everyday practice in R. of North Macedonia, serum creatinine, albuminuria and glomerular filtration rate are used to detect DN.

Microalbuminuria has generally been considered the earliest marker of the development of diabetic nephropathy, and is often associated with a significant glomerular damage. However, recent studies have shown that MA does not always reflect the present renal impairment. In addition, several lines of evidence suggest that early damage to glomerular and tubular structures may be present in subjects with normal albuminuria [13,15,16].

It is necessary to identify markers that will detect early tubular damage independently of the development of albuminuria in patients with early DN and progression, as it may play a significant role in the management of cases of renal failure that are within normal albuminuria [13,15-17].

New biomarkers such as NGAL (neutrophil gelatinase-associated lipocalin) and Cystatin C are thought to be more sensitive to the need of early DN detection.

NGAL, also known as lipocalin 2, is composed of 178 amino acids. It is a 25 kDa protein, first purified and identified in 1993 by Kjeldsen *et al.*, and appears to be a promising biomarker [13,17]. It is mainly produced in the renal tubules in response to structural injury to the kidneys, but also to a lesser extent in the lungs, trachea, stomach, and colon, and excreted in the urine [18,19]. NGAL values may be affected by renal disease, hypertension, inflammatory conditions, hypoxia, and malignancies [18]. NGAL as a renal biomarker was first described in 2003 by causing experimental renal ischemia in mice [20].

Unlike conventional serum markers, such as creatinine, NGAL is considered a marker of renal structural damage, whose plasma and urine values increase as a result of tubular renal damage. Its values rise before renal damage is detected by other methods [18,19,21]. Except in acute and chronic renal failure, this biomarker has significance in the progression of renal damage. In previous studies, NGAL has been shown to be effective in the early diagnosis of acute renal injury (ACI), and in several clinical studies has also been validated for its prognostic role in cardiovascular morbidity [22-24].

Cystatin C is a small protein that is filtered by the body through the glomeruli, which has a high correlation with the degree of glomerular filtration rate (GFR) [25]. It is not affected by inflammatory conditions, muscle mass, sex, body composition and age (after the age of 12 months) [26]. The superiority of Cystatin C (CysC) over the other markers of renal impairment lies in its ability to remain unbound to proteins and to filter freely through the glomeruli. In healthy subjects, CysC is almost freely filtered by the glomeruli and is almost completely reabsorbed in the proximal tubules, as are other low molecular weight proteins with no or only partial tubular secretion.

In renal impairment, with decreasing GFR, the values of this biomarker increase. Several studies have shown that when GFR and creatinine levels are still within normal limits, CysC rises when there is initial renal impairment [27,28].

High CysC values in patients diagnosed with diabetes mellitus increase the risk of cardiovascular morbidity and progression of atherosclerosis [29,30].
Diagnosis of DN (diabetic nephropathy) in the early stages is of particular importance, because therapeutic measures taken in the early stages of DN prevent the progressive course of DN, and thus reduce cardiovascular and overall mortality in the population with diabetes [8,9].
Screening for other microvascular and macrovascular complications is also important to treat and prevent further progression of the damage.

Aims

- The aim of this study was to compare serum values of NGAL and CysC in the three groups of patients, and to determine the possible predictor roles of the serum values of these biomarkers as additional-supplementary testing of urinary albumin excretion in albuminuria, unmasking early structural and functional renal impairment in patients with type 2 diabetes mellitus (DM type 2).
- To see if there was a correlation between the serum values of the marker-NGAL and CysC in relation to serum values of creatinine and microalbuminuria.
- To determine if the values of the new biomarkers (NGAL, Cystatin C) increase with the progression of renal nephropathy.

Material and methods

Study design

This was a prospective, observational study, involving three groups of patients, a total of 60 in number, aged 35-70 years, with a follow-up period of 6 months.
Patients were divided into three groups:

1. In the first group of 15 patients diagnosed with diabetes mellitus (DM) type 2 lasting for more than 5 years, diabetic nephropathy was not detected with standard biomarkers (serum creatinine, albuminuria and glomerular filtration rate).
2. In the second group, 15 patients diagnosed with diabetes mellitus (DM) type 2 with a duration of more than 5 years, in whom with standard biomarkers (serum creatinine, albuminuria and glomerular filtration rate) renal nephropathy was not detected.
3. The third group included 30 healthy individuals (who appeared at the Clinic for screening for diabetes or other endocrine disorder, but had normal findings).

The study was performed at the University Clinic for Endocrinology-Skopje in cooperation with the PHI University Clinic for Clinical Biochemistry- Skopje.
Patient's choice was not influenced by their gender, race, ethnicity or socioeconomic status.
During the study we adhered to the criteria for Basic Good Clinical Practice, the Law on Health Care of the Republic of Macedonia and the Law on Patient's Rights of the Republic of Macedonia.
The selection of patients was performed on the basis of a signed informed consent, as well as the application of criteria for inclusion and exclusion in the study.

Criteria for inclusion and exclusion in the study:
Inclusion criteria: patients with diagnosed DM type 2, age 35-70 years, sex: m/f.
Exclusion criteria: younger than 35 and older than 70 years, patients with DM type 1, gestational diabetes, active urinary tract infection, pregnant patients, if on glucocorticoid therapy, other renal diseases, active malignancy, other chronic diseases, or if the patient requested to be withdrawn from the study.
Venous blood and urine were taken from all three groups of patients to test for standard and new biomarkers for diabetic nephropathy:

- creatinine,
- microalbuminuria,
- NGAL (NGAL- neutrophil gelatinase-associated lipocalin),
- Cystatin C

In patients diagnosed with DM type 2, the diagnosis was confirmed by determination of fasting glycemia, postprandial glycaemia, and HbA1c.
After 12 hours of fasting, morning venous blood was taken to determine creatinine, CysC, HbA1c, and fasting glycemia. Blood was collected in special tubes to determine the specific CysC marker. Part of the blood was centrifuged to separate the serum and kept at -80 until the markers were finally determined.
CysC concentration was measured by immuno-nephelometric technique using a BN Prospec nephelometer (Dade Bering, Siemens Health Diagnostics, Liederbach, Germany). Normal biomarker values are 0.62-1.11 mg/L. The inter-assay coefficient of variation (CV) for the analysis was 5.05% and 4.87% at mean concentrations of 0.97 and 1.90 mg/L, respectively.
Microalbuminuria and NGAL were determined from a urine sample.
NGAL values were measured using the ARCHITECT Urine NGAL assay, which is an immunoassay of chemiluminescent microparticles (CMIA) for quantitative determination of NGAL in urine. Urine can be stored at room temperature for up to 24 hours, or up to 7 days at a temperature of 2-8 degrees Celsius. The calibration range is 0.0 ng/mL-1500 ng/mL, while the measurement interval is 10.0-1500 ng/mL. Normal values are up to 131.7 ng/mL. The ARCHITECT Urine NGAL analysis is designed to have an inaccuracy of <10% of the total CV (coefficient of variation).
Other procedures performed in patients: medical history and status, blood count, lipid status, fasting glycemia and postprandial glycemia.
All of the above examinations and procedures were performed in the three groups of patients. In the first

two groups of patients (patients diagnosed with DM type 2 with and without diabetic nephropathy) the tests were repeated and compared to the control that was performed after 6 months.
In the first two groups (patients diagnosed with DM type 2), Doppler ultrasonography of the kidneys was performed.

Statistical analysis

Statistical processing and data analysis was performed with the statistical program SPSS for Windows, 23.0.
Kolmogorov-Smirnov and Shapiro Wilk's test were used to test the normality in data distribution.
Quantitative parameters are represented by an arithmetic mean with standard deviation and median mean, qualitative parameters are represented by absolute and relative numbers.
Bivariate analysis was performed to compare the analyzed groups (DM with LV, DM without LV and KG). Pearson Chi-square test was used to compare these groups in terms of qualitative characteristics. Analysis of Variance, Kruskal-Wallis and Mann-Whitney test were used to compare these groups in terms of quantitative characteristics. The Wilcoxon Matched pairs test was used to compare the two groups with diabetes. The correlation of the analyzed markers in the group with DM and DN was analyzed with Pearson correlation coefficient. Values of p <0.05 were taken as statistically significant.

Results

The respondents from the three analyzed groups did not differ significantly in terms of gender structure (p =0.71) and age (p=0.068). Patients in the three groups were predominantly male, with a prevalence of 53.3% in the group with diabetes and diabetic nephropathy, 66.7% in the group with diabetes without diabetic nephropathy and 55% in the group of healthy subjects. Patients with diabetes and chronic nephropathy were insignificantly older than patients in the other two groups (61.20±4.9, 55.80±8.2, 55.95±7.8, respectively) (Table 1). Comparison of baseline creatinine, microalbuminuria, NGAL, and cystatin C values in serum showed that patients with diabetes and diabetic nephropathy had higher values than diabetic patients without diabetic nephropathy and healthy subjects.
For p<0.0001, a statistically significant difference in serum creatinine concentrations was confirmed between the three groups. Post-hoc analysis for intergroup comparisons showed that this overall significance was due to significantly higher creatinine in patients with DM and DN compared to patients with DM without DN (median 129.6 *vs.* 67.5; p=0.0009), and in patients with DM and DN in relation to CG patients (median 129.6 *vs.* 64; p=0.0009).
A statistically significant difference was confirmed between the three groups in relation to the initial serum values of microalbuminuria (p<0.0001), which was

Table 1. Socio-demographic characteristics of respondents

Variable	Groups			p value
	DM type 2 with DN	**DM type 2 without DN**	**KG**	
Sex (n%)				
Female	7 (46.67)	5 (33.33)	9 (45)	X^2=0.67 p=0.71 ns
Male	8 (53.33)	10 (66.67)	11 (55)	
Age (mean±SD)	61.20±4.9	55.80±8.2	55.95±7.8	F=2.8 p=0.068 ns

X^2 (Pearson Chi-square) F (Analysis of Variance)

Table 2. Basic values of creatinine, microalbuminuria, NGAL, Cystatin C in respondents of the three groups

Variable (basic)	Groups			p value
	DM type 2 with DN	**DM type 2 without DN**	**KG**	
Creatinine (mean±SD)	133.19±50.7	72.09±13.7	65.77±14.2	H=24.18 p=0.000 sig
median (IQR)	129.6 (112.3-147)	67.5 (63.8-80)	64 (56.1-77.4)	[a]p=0.0009 [b]p=0.000006
Microalbuminuria (mean±SD)	80.11±52.4	18.47±22.9	12.04±5.8	H=23.31 p=0.000 sig
median (IQR)	100 (40.5-100)	10.6 (10.6-15.6)	10.6 (9.9-12)	[a]p=0.0016 [b]p=0.000009
NGAL (mean±SD)	164.79±76.9	49.85±69.6	23.24±22.6	H=19.06 p=0.0001 sig
median (IQR)	166.2 (123.2-224)	20 (11.8-34)	21.85 (10.1-25.5)	[a]p=0.0033 [b]p=0.000082
CystatinC (mean±SD)	1.61±0.9	0.88±0.3	0.69±0.1	H=30.17 p=0.000 sig
median (IQR)	1.29 (1.2-1.6)	0.77 (0.74-0.92)	0.69 (0.58-0.82)	[a]p=0.0025 [b]p=0.000000

p (Kruskal-Wallis test) post-hoc Mann-Whitney test; [a]p (DM type 2 with DN *vs.* CG) [b]p (DM type 2 without DN *vs.* CG)

due to significantly higher values in the group with DM and DN compared to the group with DM without DN (p=0.0016) and in relation to healthy subjects (p= 0.000009). In the three groups were registered main values of 80.1 were, 18.5 and 12 mg/L, consequently (Table 2).
A total statistically significant difference was confirmed in the basal serum values of NGAL (p=0.0001). Post-hoc analysis for intergroup comparisons showed that patients with DM and DN had significantly higher baseline values of NGAL than patients with DM without DN (median 166 *vs.* 20; p=0.0033), and in relation to healthy subjects (median 166.2 *vs.* 21.85; p=0.00008).
The Cystatin C biomarker presented significantly different baseline values between the two groups with diabetes (p=0.0025), and between the group with DM and DN and CG (p<0.0001). The mean values of this marker were 1.29, 0.77 and 0.69 mg/L in the group with DM and DN, the group with DM without DN, and CG, consequently.
We compared patients from both groups with diabetes in terms of analyzed serum parameters after 6 months of follow-up. According to the results in Table 3, all parameters were higher in the group with diagnosed diabetic nephropathy, with confirmed significance of p= 0.0006 for creatinine, p=0.00007 for microalbuminuria, p =0.00036 for NGAL, and p=0.019 for Cystatin C. Serum creatinine concentrations of 132 and 79.8 mmol/L were measured in the group with DM and DN and the group with DM without DN after 6 months, respectively; serum values of microalbuminuria of 60 and 12 mg/L, respectively; serum NGAL values of 178 and 30.2 ng/ml, respectively; and, serum Cystatin C values of 1.48 and 0.88 mg/L, respectively (Table 3).

Table 3. Values of creatinine, microalbuminuria, NGAL and Cystatin C in respondents of the three groups – 6-month follow-up

Variable (after 6 month follow-up)	Groups DM type 2 with DN	DM type 2 with DN	P value	
Creatinine (mean ± SD)	169.42±155.3	81.79±15.9	Z=3.44	p=0.0006 sig
median (IQR)	132 (96-152)	79.8 (73-90)		
Microalbuminuria (mean±SD)	109.97±85.2	23.35±24.2	Z=3.98	p=0.00007 sig
median (IQR)	60 (50-200)	12 (11-20.3)		
NGAL (mean ± SD)	175.87±75.4	57.80±71.9	Z=3.57	p=0.00036 sig
median (IQR)	178 (124-220)	30.2 (15.1-48)		
Cystatin C (mean ± SD)	1.91±1.7	126.25±331.1	Z=2.34	p=0.019 sig
median (IQR)	1.48 (1.22-1.68)	0.88 (0.8-1.39)		

p (Mann-Whitney U Test)

In the group with diabetes and diabetic nephropathy, during the re-evaluation after 6 months of monitoring we registered a non-significant increase in the biomarker NGAL (p=0.16) and a significant increase in the biomarker Cystatin C (p=0.016). Mean serum NGAL concentrations were 166.2 ng/ml on the first measurement and 178 ng/ml on the second measurement.
Mean serum Cystatin C concentrations were 1.29 mg/L on the first measurement and 1.48 mg/L on the second measurement (Table 4) (Figure 2 and 3).

Table 4. Values of NGAL and Cystatin C – group with DM and DN

Group with DM and DN		Descriptive Statistics mean±SD	median (IQR)	p value
NGAL (ng/ml)	basic	164.79±76.9	166.2(123.2-224)	Z=1.42
	re-evaluation	175.87±75.4	178(124-220)	p=0.16 ns
Cystatin C (mg/L)	basic	1.61±0.9	1.29(1.2 -1.6)	Z=2.41
	re-evaluation	1.91±1.7	1.48(1.22 -1.68)	p=0.016 sig

Z (Wilcoxon Matched pairs test)

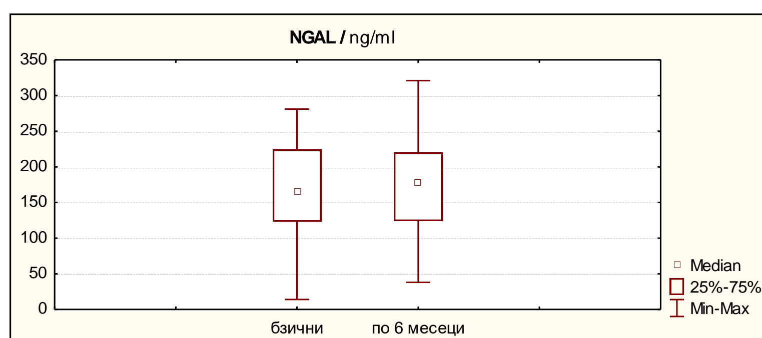

Fig. 2. Mean values of NGAL - group with DM and DN

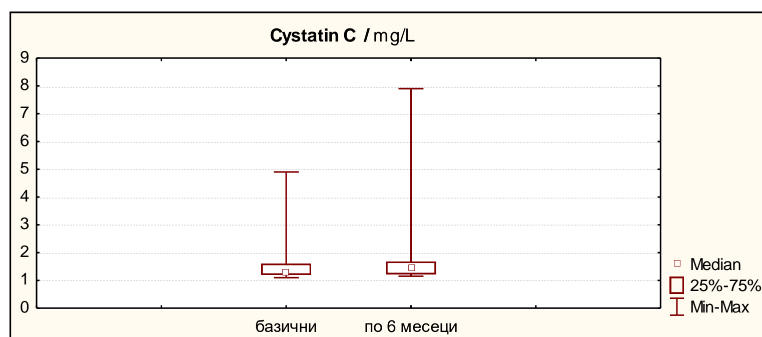

Fig. 3. Mean values of Cystatin C - group with DM and DN

The results of the study on the association of creatinine and microalbuminuria with the biomarkers NGAL and Cystatin C in the group with DM and DN showed a statistically significant correlation of baseline creatinine with baseline and control values of Cystatin C (p <0.0001) and NGAL after 6-month re-evaluation (p= 0.014). According to Pearson correlation coefficient, all these correlations were positive, i.e. direct, with increasing serum creatinine values the biomarkers NGAL and Cystatin C increased, and vice versa (r=0.617, r=0.809, r=0.879, consequently) We did not find a significant correlation of microalbuminuria with NGAL and Cystatin C at baseline and on re-evaluation (Table 5) (Figure 4, 5 and 6).

Table 5. Correlation of microalbuminuria and creatinine with NGAL and Cystatin C

Correlation	r	p-level
basic creatinine & basic NGAL	0.285	0.304 ns
re-evaluation creatinine & re-evaluation NGAL	0.617	0.014 sig
basic creatinine & basic Cystatin C	0.809	0.000 sig
re-evaluation creatinine & re-evaluation Cystatin C	0.879	0.000 sig
basic microalbuminuria & basic NGAL	0.198	0.479 ns
re-evaluation microalbuminuria & re-evaluation NGAL	0.229	0.410 ns
basic microalbuminuria & basic Cystatin C	0.233	0.402 ns
re-evaluation microalbuminuria & re-evaluation Cystatin C	0.452	0.090 ns

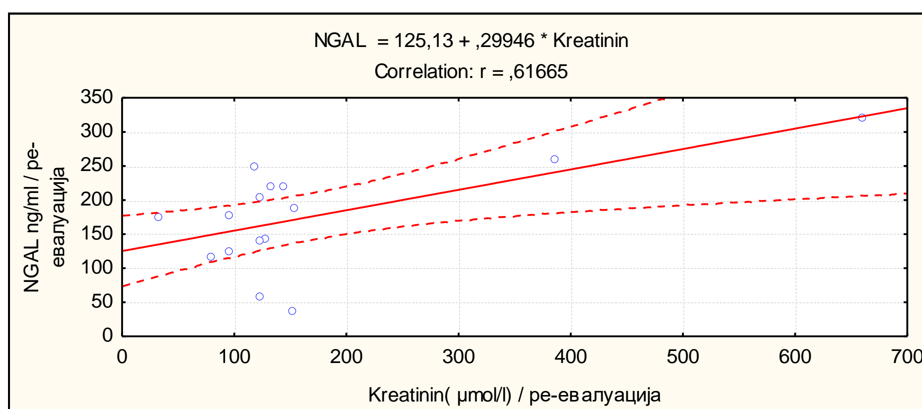

Fig. 4. Correlation of NGAL with creatinine - after 6 months

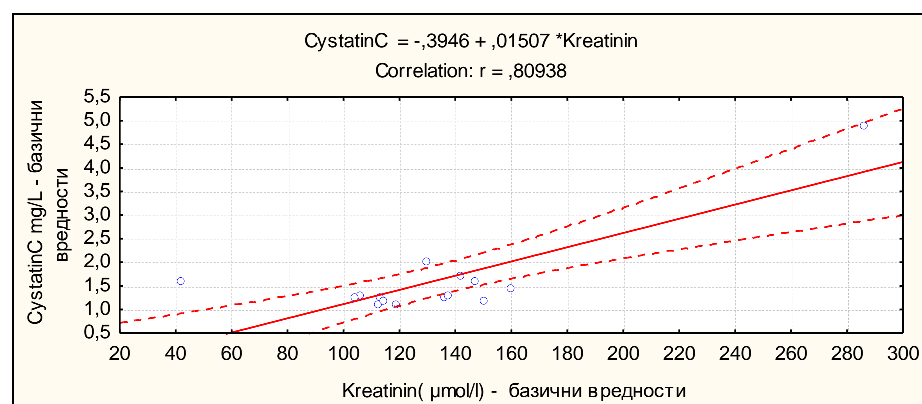

Fig. 5. Correlation of Cystatin C with creatinine - baseline values

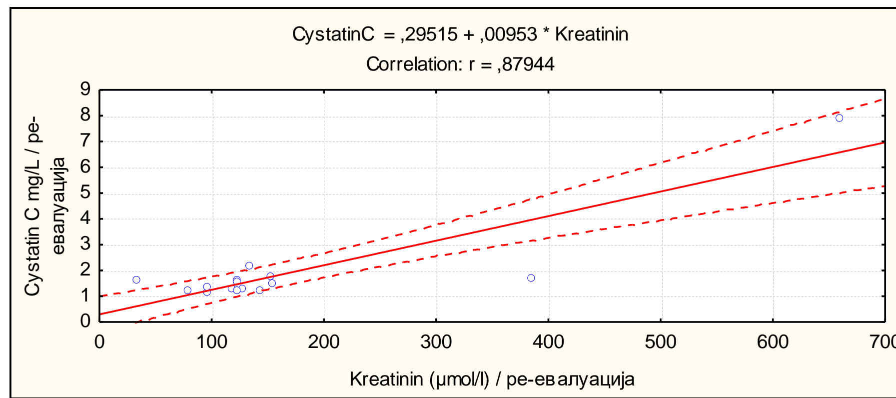

Fig. 6. Correlation of Cystatin C with creatinine - after 6 months

The correlation between the two biomarkers NGAL and Cystatin C was statistically insignificant on the first measurement (p=0.16), and significant and direct, i.e. positive on the second measurement, after 6 months (r =0.536, p=0.039). Both markers changed in direct proportion to serum, by increasing one marker in the serum, the other biomarker increased, and vice versa (Table 6) (Figure 7).

Table 6. Correlation between the two biomarkers NGAL and Cystatin C

Correlation	R	p-level
basic NGAL & basic Cystatin C	0.386	0.156 ns
Re-evaluation NGAL & re-evaluation Cystatin C	0.536	0.039 sig

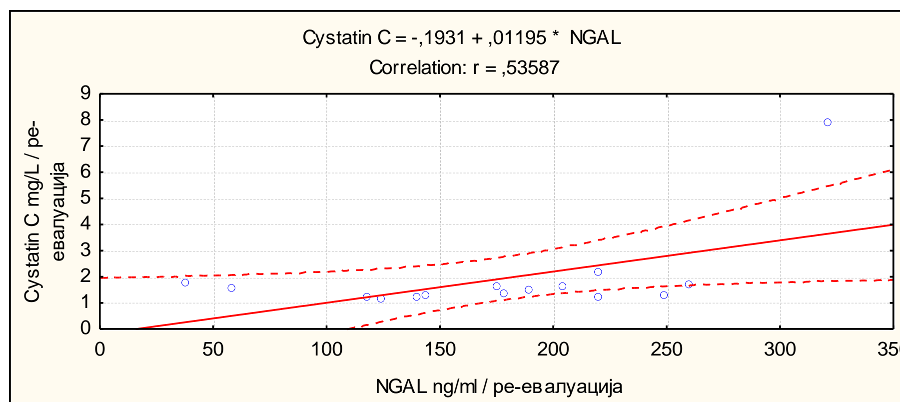

Fig. 7. Correlation of NGAL with Cystatin C - after 6 months

Discussion and conclusion

Microalbuminuria is generally considered to be the earliest marker of the development of diabetic nephropathy and is often associated with significant glomerular damage. However, several studies and lines of evidence suggest that early structural damage to both glomerular and tubular structures may be present in normal albuminuria patients.
The first results of this long-term observational study aimed at assessing the predictability of early markers of renal injury, such as NGAL and CysC, in patients with T2D by detecting renal structural damage long before renal dysfunction occurs.
The study showed that baseline creatinine, microalbuminuria, NGAL, and Cystatin C serum levels were higher in patients diagnosed with DM type 2 and diabetic nephropathy compared to those with and without diabetes and healthy subjects.
Patients in both groups with diabetes (both diabetic nephropathy and non-diabetic nephropathy) were compared in terms of the values of all four markers (creatinine, microalbuminuria, NGAL and Cystatin C) after 6 months of follow-up, and all parameters were higher in the group with diagnosed diabetic nephropathy, with confirmed statistical significance.
In the group with diabetes and diabetic nephropathy, during the re-evaluation after 6 months of monitoring we registered a non-significant increase in the biomarker NGAL (p=0.16), and a significant increase in the biomarker Cystatin C (p=0.016).
The results of the study showed a statistically significant correlation between baseline creatinine values and baseline and control values of Cystatin C (p<0.0001), and creatinine and NGAL values after 6-month re-evaluation (p=0.014), and all these correlations were positive, i.e. with the increase of serum creatinine values the biomarkers NGAL and Cystatin C increased, and vice versa.

The correlation between the two biomarkers NGAL and Cystatin C was statistically insignificant on the first measurement (p=0.16), and significant and direct, i.e. positive on the second measurement, after 6 months (r =0.536, p=0.039). The two markers changed in direct proportion to the serum, with increasing one marker in the serum, the other biomarker increased, and vice versa.
The fact that a certain percentage of normal albuminous patients had elevated values of the biomarkers NGAL and Cystatin C, while a small percentage of microalbuminuria patients had elevated values of NGAL and Cystatin C within normal limits, may reflect different sites of renal impairment during DN.
The use of new biomarkers (NGAL and Cystatin C) as additional tests on existing (creatinine and microalbuminuria) for early diagnosis of DN, speed up effective approaches to management and treatment that are desperately needed to minimize rates of severe cardiorenal morbidity and mortality in patients with T2D. Therefore, these data need to be confirmed by further large-scale longitudinal studies before being integrated into the DN risk assessment in patients with T2D.

Conflict of interest statement. None declared.

References

1. Irfan A, Iskra B, Sasa J, *et al*. Diabetes type 2-from prevention to appropriate treatment. Skopje: 2016.
2. Fauci AS, Kasper DL, Longo DL, *et al*. Harrison's Internal Medicine 17th ed. The McGrawHill Medical: 2008.
3. https://www.prnewswire.com/news-releases/international-diabetes-federation-latest-figures-show-463-million-people-now-living-with-diabetes-worldwide-as-numbers-continue-to-rise-300956922.html
4. Dansinger M. WebMD Medical Reference Reviewed 2019.
5. Marcovecchio ML. Complications of acute and chronic hyperglycemia. *US Endocrinology* 2017; 13: 17-21.
6. Jia W, Xu A, Chen A, *et al*. Chronic Vascular Complications in Diabetes. J Diabetes Res 2013; 2013: 858746.
7. Chawla A, Chawla R and Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab* 2016; 20: 546-551.
8. Remuzzi G, Schieppati A and Ruggenenti P. Nephropathy in patients with type 2 diabetes. *N Engl J Med* 2002; 346: 1145-1151.
9. Jha V, Garcia-Garcia G, Iseki K, *et al*. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; 382: 260-272.
10. Gross JL, Azevedo MJ, Silveiro SP, *et al*. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care* 2005; 28: 164-176.
11. Gjorgjievski N, Stojanoska A, Smokovska A, *et al*. Challenges Facing the Improvement of Kidney Transplantation-Issues in a Developing Country, Republic of Macedonia. *Bantao* 2018; 16: 1-4.
12. Schultz C, Amin R and Dunger D. Markers of microvascular complications in insulin dependent diabetes. *Arch Dis Child* 2002; 87: 10-12.
13. Nauta FL, Boertien WE, Bakker SJL, *et al*. Glomerular and tubular damage markers are elevated in patients with diabetes. *Diabetes Care* 2011; 34: 975-981.
14. Tabaei BP, Al-Kassab AS, Ilag LL, *et al*. Does microalbuminuria predict diabetic nephropathy? *Diabetes Care* 2001; 24: 1560-1566.
15. Colhoun HM, Marcovecchio ML. Biomarkers of diabetic kidney disease. *Diabetologia* 2018; 61: 996-1011.
16. Chen C, Wang C and Hu C. Normoalbuminuric diabetic kidney disease. *Front Med* 2017; 11: 310-318.
17. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL)-A new marker of kidney disease. *Scand J Clin Lab Invest Suppl* 2008; 241: 89-94.
18. Schmidt-Ott KM, Mori K, Li JY, *et al*. Dual action of neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 2007; 18: 407-413.
19. Devarajan P. Neutrophil gelatinase-associated lipocalin: a promising biomarker for human acute kidney injury. *Biomark Med* 2010; 4: 265-280.
20. Bagshaw SM, Bennett M, Haase M, *et al*. Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. *Intensive Care Med* 2010; 36: 452-461.
21. Papadopoulou-Marketou N, Skevaki C, Kosteria I, *et al*. NGAL and Cystatin C: two possible early markers of diabetic nephropathy in young patients with type 1 diabetes mellitus: one year follow up. *Hormones* 2015; 14: 232-240.
22. Haase-Fielitz A, Haase M, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. *Ann Clin Biochem* 2014; 51: 335-351.
23. McKittrick IB, Bogaert Y, Nadeau K, *et al*. Urinary matrix metalloproteinase activities: biomarkers for plaque angiogenesis and nephropathy in diabetes. *Am J Physiol Renal Physiol* 2011; 301: 1326-1333.
24. Hawkins R. New biomarkers of acute kidney injury and the cardio-renal syndrome. *Korean J Lab Med* 2011; 31: 72-80.
25. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002; 40: 221-226.
26. Finney H, Newman DJ, Thakkar H, *et al*. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. *Arch Dis Child* 2000; 82: 71-75.
27. Husain SA, Willey JZ, Moon YP, *et al*. Creatinine- versus cystatin C-based renal function assessment in the Northern Manhattan. *Study* 2018; 13: e0206839.
28. Mussap M, Vestra MD, Fioretto P, *et al*. Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. *Kidney Int* 2002; 61: 1453-1461.
29. Maahs DM, Ogden LG, Kretowski A, *et al*. Serum Cystatin C predicts progression of subclinical coronary atherosclerosis in individuals with type 1 diabetes. *Diabetes* 2007; 56: 2774-2779.
30. Codoner-Franch P, Ballester-Asensio E, Martínez-Pons L, *et al*. Cystatin C, cardiometabolic risk, and body composition in severely obese children. *Pediatr Nephrol* 2011; 26: 301-307.

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Original article

THE INFLUENCE OF MYOPIA ON VISUAL FIELD CHANGES IN PATIENTS WITH AND WITHOUT GLAUCOMA

ВЛИЈАНИЕТО НА МИОПИЈАТА ВО ПРОМЕНИТЕ НА ВИДНОТО ПОЛЕ КАЈ ПАЦИЕНТИ СО И БЕЗ ГЛАУКОМ

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Abstract

Introduction. Glaucoma, one of the leading causes of irreversible blindness in the elderly population worldwide, is a progressive optic neuropathy. Myopia or near sightedness is a refractive anomaly in which parallel rays of light coming from a distance after refraction through the cornea and lens focus in front of the retina in the vitreous and then in a state of divergence create scattered circles on the retina. The visual field is a projection of the functional part of the retina in space, i.e. a projection of all retinal points at which visible sensations can begin. If there is a damage to the nerve fibers of the retina, a decrease or absence of sensitivity to identical stimuli is manifested by defects in the visual field.
Methods. The study included 100 patients, who were divided into two groups: one group with glaucoma and another group without glaucoma. Regarding the degree of myopia, all subjects (with and without glaucoma) were divided into 3 groups: Low from-1Diopt to-3Diopt, Medium from -3 Diopt to -6 Diopt and High>-6 Diopt. A visual field was made in each patient.
Results. The cross tabulation showed in the examined group (glaucoma) and the control group (no glaucoma) for Fisher's Exact Test=28.920 and p<0.001 (p=0.000) /Monte Carlo Exact Sig. (2-sided)/0.000-0.000/. There was a significant difference between the two groups in terms of visual field (finding). For Fisher's Exact Test =31,157 ip <0.001 (p=0.000)/MonteCarloSig. (2-sided) /0.000-0.001 in the performed cross tabulation between the height of myopia and the degree of changes in the visual field, there was a significant difference.
Conclusion. There was a significant difference shown in the performed cross tabulation between the height of myopia and the degree of changes in the visual field.

Keywords: glaucoma, myopia, visual field

Апстракт

Вовед. Глаукомот, една од водечките причини за иреверзибилно слепило кај постарата популација ширум светот, преставува прогресивна оптичка неуропатија. Миопијата или кратковидост е рефрактивна аномалија кај која паралелните светлосни зраци кои доаѓаат од далечина по прекршувањето низ корнеата и леќата се фокусираат пред ретината во стаклестото тело и потоа во состојба на дивергенција, создаваат на ретината расипни кругови. Видното поле претставува проекција на функционалниот дел на ретината во просторот, односно проекција на сите ретинални точки на кои може да започнат видни сензации. Доколку постои оштетување на нервните влакна на ретината, намалување или отсаство на сензитивност при идентични стимулуси се манифестира со испади (дефекти) на видното поле.
Методи. Во студијата беа вклучени 100 пациенти, кои беа поделени во две групи, заболени од глауком, и пациенти без глауком. Во однос на степенот на изразеност на миопијата, сите испитаници (со и без глауком) беа поделени во 3 групи: Ниска од -1Diopt до -3Diopt,Средна од -3Diopt до -6Diopt и Висока >-6 Diopt. Кај секој пациент е направено видно поле.
Резултати. Во прикажаната кростабулација испитуваната група (има глауком) *контролната група (нема глауком) за Fisher's Exact Test=28.920 и p< 0.001(p=**0,000**)/Monte Carlo Exact Sig. (2-sided)/ 0,000-0.000/постои значајна разлика помеѓу двете групи во однос на видно поле (наод). За Fisher's Exact Test=31.157 и p<0.001(p=**0.000**) / Monte Carlo Sig. (2-sided)/0,000-0,001 во извршената кростабулацијата помеѓу висината на миопијата и степенот на промените на видното поле,постои значајна разлика.
Заклучок. Во извршената кростабулацијата помеѓу висината на миопијата и степенот на промените на видното поле,постои значајна разлика.

Клучни зборови: глауком, миопија, видно поле

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Introduction

Glaucoma, one of the leading causes of irreversible blindness in the elderly population worldwide, is a progressive optic neuropathy [1].
According to the European Glaucoma Association, glaucoma is a group of chronic progressive neuropathies most commonly characterized by morphological changes in the papillae of the optic nerve and retinal nerve fibers, without the presence of other eye diseases or congenital anomalies.
According to the American Academy of Ophthalmology, glaucoma is a group of conditions characterized by a damage to the optic nerve and loss of nerve axons, through atrophy of ganglion cells and preservation of the neurofibrillary layer of the retina.
Because glaucoma ranks second on the list of ophthalmic diseases with the highest morbidity, there are many definitions that characterize its importance in the scientific world and in seeking opportunities for its treatment, and thus reducing the percentage of blindness that glaucoma can cause [2].
In the Republic of Macedonia, blindness is defined as a visual acuity equal to or less than 0.1 or equal to or less than 0.25 with a reduced field of view of 20' on the better eye with the best possible correction. A visually impaired person is a person who has visual acuity equal to or less than 0.4 of the better eye, with the best possible correction, or greater than 0.4 if there is a medical prognosis for progressive reduction in visual acuity.
A common term for blindness and low vision is visual impairment. Globally, the latest research on the prevention of blindness shows that the number of blind people in the world is increasing by 1-2 million per year [3]. Glaucoma as an etiological factor for blindness occupies 22%-36% of all causes. This percentage varies depending on the geographical location.
Myopia or nearsightedness is a refractive anomaly in which parallel rays of light coming from a distance after refraction through the cornea and lens focus in front of the retina in the vitreous and then in a state of divergence create scattered circles on the retina. Patients with myopia do not see well in the distance. To improve the image, patients with uncorrected myopia narrow their eyelids, hence this refractive anomaly got its name (myen-closes, ops-eye). Narrowing the lid opening certainly does not move the focus, but minimally reduces the size of the dispersing retinal circles [4].
High myopia is one of the major causes of blindness in many developed countries. The prevalence of myopia varies in different populations and regions of the world. High myopia is more common in Asia than in the European region, and is more common in the younger generation [5,6]. The Handan eye study showed that the prevalence of moderate to high myopia in the Chinese adult population was 26.7% [7], while the Singapore study showed a prevalence of 38.7% [8]. Studies conducted in the European population also show a prevalence of myopia of 24.3%, and nearly half of the people (47%) aged 25-29 years suffer from myopia [9].
In our country there is no accurate data on the total number of patients suffering from this refractive anomaly. But as a result of modern times, with an increased use of computers, tablets and smart phones, the increase in the prevalence of myopia is evident in our country.
Several studies have been conducted on this issue, and it has been found that in urban areas there is a much larger number of patients with myopia, compared to rural areas, and the highest prevalence is observed in preschool and school-age children, due to the declining time spent in nature.
The visual field is one of the basic diagnostic methods used in patients with glaucoma and other ophthalmic diseases.
The visual field is a projection of the functional part of the retina in space, i.e. a projection of all retinal points at which visible sensations can begin. If there is a damage to the nerve fibers of the retina, a decrease or absence of sensitivity to identical stimuli is manifested by defects in the visual field.
The examination of the visual field is performed by perimetry-a diagnostic method that gives us an accurate insight into the functional state of the glaucoma eye. The importance of perimetry stems from the fact that changes in the visual field are a direct indicator of the degree of disability, which directly affects the quality of life of the patient. The most famous devices for computer perimetry are Humphrey and Octopus perimeters. Special programs are designed for the interpretation of computerized perimetry data.
The results of visual field examination can also be influenced by the following factors: the degree of intelligence and cooperation of the patient, the effect of learning, fatigue, poor or inadequate correction of a refractive anomaly, narrow pupil, certain anatomical factors, etc.
Modern diagnostic methods indicate that the progression of glaucomatous visual impairment is usually slow and can rarely be detected by perimetry performed within one year.
According to the European Association of Glaucomatologists, the progression of glaucoma is confirmed if:

- a new glaucoma defect has appeared;
- the existing defect in the field of vision has "deepened";
- the existing defect in the visual field has expanded.

Apart from being one of the most important methods for early detection and diagnosis of glaucoma, perimetry is also a basic method for monitoring its progression, evaluating the effectiveness of the implemented treatment, as well as prognosis of the disease in terms of visual function [10].

The aim of this study was to investigate the effect of myopia on the occurrence and progression of visual field changes in patients with and without glaucoma.

Materıals and methods

A retrospective case-control study was performed, which included patients aged 25 to 70 years.

The study was conducted at the University Clinic for Ophthalmology in Skopje, in the Glaucoma Department, in the period between 2015-2019.

The study included 100 patients, who were divided into two groups:

1. The first group of respondents (group 1-patients with primary open-angle glaucoma) included 60 patients diagnosed with glaucoma. Entry criteria for this group were the following:
- increased intraocular pressure (IOP)-over 24 mmHg without therapy;
- changes of the optic nerve papilla (PNO);
- vision field defect;
- antiglaucoma therapy.
2. The second group of respondents (group 2- control group) included 40 patients without glaucoma. Entry criteria for this group were the following:
- patients without glaucoma;
- normal IOP;
- normal vision field;
- normal finding of PNO (eyeball).

Refractive error was examined in all patients using a TOPCONRM 8900 refractometer. The method is performed in the patient in a sitting position, with four consecutive measurements. The average value of the three measurements is taken as valid. Regarding the degree of myopia, all subjects (with and without glaucoma) were divided into 3 groups: Low from -1 Diopt to -3 Diopt, Medium from -3 Diopt to -6 Diopt and High> -6 Diopt.

A visible field was made in each patient on the OPTOPOLPTS 910 perimeter device, with the glaucoma screening program. During the examination, two visible fields were made, during one year, in order to find, if any, certain changes in the field of vision that had progressed.

For attribute series, structure percentages (%) are specified; association and differences-in attribute series were tested using Pearson Chi-Square test/(p) and Fisher's Exact Test/MonteCarloSig. (2-sided)/(p). The difference in the series with numerical features between the examined and the control group was analyzed using T-tests; Grouping (t/p) and Mann-Whitney U Test (Z/p). Significance of difference was defined if $p < 0.05$. The data are presented in tables and figures.

Results

The results shown in Table 1 and Figure 1 refer to the difference in the visual field between the study group (with glaucoma) and the control group (no glaucoma). Out of 60 patients, 16 (26.70%) patients had normal finding of the visual field; 28(46.70%) patients had paracentral and peripheral relative scotomas; 3(5.00%) patients had peripheral relative and absolute scotomas; 1(1.70%) patient had paracentral relative and absolute scotomas, 9(15.00%) patients had absolute scotomas and in 3(5.00%) patients had only central vision preserved. Out of 40 patients, 32(80.00%) patients had normal finding in the visual field; 7(17.50%) patients had paracentral and peripheral relative scotomas and 1(2.50%) patient had peripheral relative and absolute scotomas.

In the shown cross tabulation the examined group (with glaucoma) and the control group (no glaucoma) for Fisher's Exact Test=28.920 and p<0.001 (p=0.000) /Monte Carlo Exact Sig. (2-sided)/0.000-0.000/. There

Table 1. Visual field (finding)
Difference / Examined group and Control group

			Glaucoma		Total
			yes	no	
Visual Field	normal finding	Count	32	16	48
		%	80.0%	26.7%	48.0%
	Paracentral and peripheral relative scotomas	Count	7	28	35
		%	17.5%	46.7%	35.0%
	Peripheral relative and absolute scotomas	Count	1	3	4
		%	2.5%	5.0%	4.0%
	Paracentral relative and absolute scotomas	Count	0	1	1
		%	0.0%	1.7%	1.0%
	Absolute scotomas	Count	0	9	9
		%	0.0%	15.0%	9.0%
	Only the central vision preserved	Count	0	3	3
		%	0.0%	5.0%	3.0%
	Total	Count	40	60	100
		%	100.0%	100.0%	100.0%

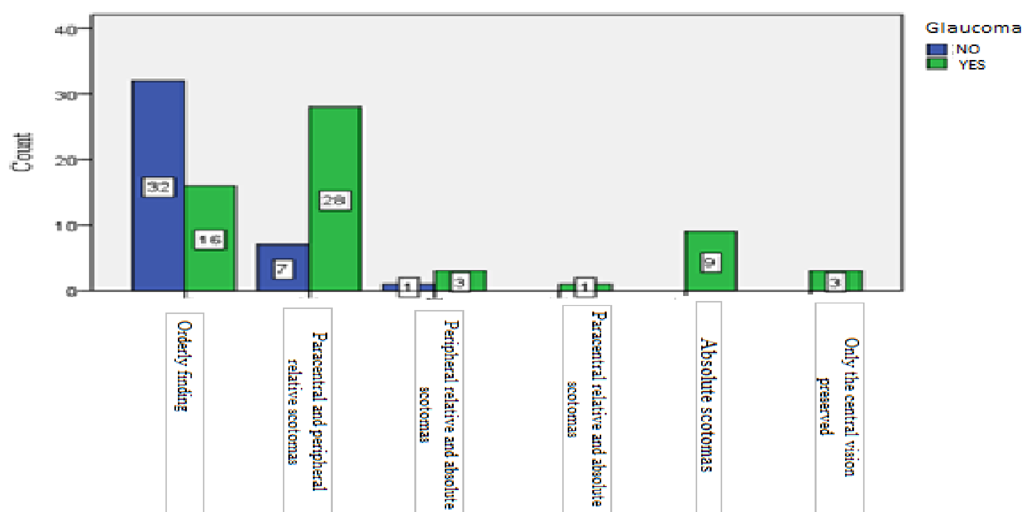

Fig. 1. Visual Field (finding)

was a significant difference between the two groups in terms of visual field (finding).

The results shown in Table 2 and Figure 2 refer to the degree of changes in the visual field in relation to the height of myopia.

Out of a total of 100 patients included in the study, of 4040.00%) patients who did not have myopia, there were 25(25.00%) patients with normal findings in the visual field, 13(13.00%) patients with paracentral and peripheral relative scotomas and 2(2.00%) patients with peripheral relative and absolute scotomas.

Out of 17(17.00%) patients with low myopia, 12(12.00%) patients had normal finding in the visual field and 2 (2.00%) patients had an absolute scotoma.

Out of 21(21.00%) patients with moderate myopia, 7 (7.00%) patients had normal finding in the visual field, 6(6.00%) patients had paracentral and peripheral relative scotomas, 1(1.00%) patient had peripheral relative and absolute scotomas, 5(5.00%) patients had absolute scotoma and in 2(2.00%) patients only central vision was preserved.

Out of 22(22.00%) patients with high myopia, 4(4.00%) patients had normal finding in the visual field, 13(13.00%) patients had paracentral and peripheral relative scotomas, 1(1.00%) patient had peripheral relative and absolute scotomas, 1(1.00%) patient had paracentral relative and absolute scotomas, 2(2.00%) patients had absolute scotoma and in 1(1.00%) patient only central vision was preserved.

For Fisher's Exact Test=31,157 ip <0.001 (p=0.000) / MonteCarloSig. (2-sided)/0.000-0.001 in the performed cross tabulation between the height of myopia and the degree of changes in the visual field, there was a significant difference.

Table 2. Height of myopia and visual field / Crosstabulation

Diopter / right eye		Visual field: Normal finding	Paracentral and peripheral relative scotomas	Peripheral relative and absolute scotomas	Paracentral relative and absolute scotomas	Absolute scotomas	Only central vision preserved	Total
No myopia	Count	25	13	2	0	0	0	40
	%	25.0%	13.0%	2.0%	0.0%	0.0%	0.0%	40.0%
Low myopia	Count	12	3	0	0	2	0	17
	%	12.0%	3.0%	0.0%	0.0%	2.0%	0.0%	17.0%
Medium myopia	Count	7	6	1	0	5	2	21
	%	7.0%	6.0%	1.0%	0.0%	5.0%	2.0%	21.0%
High myopia	Count	4	13	1	1	2	1	22
	%	4.0%	13.0%	1.0%	1.0%	2.0%	1.0%	22.0%
Total	Count	43	35	4	1	14	3	100
	%	43.0%	35.0%	4.0%	1.0%	14.0%	3.0%	100.0%

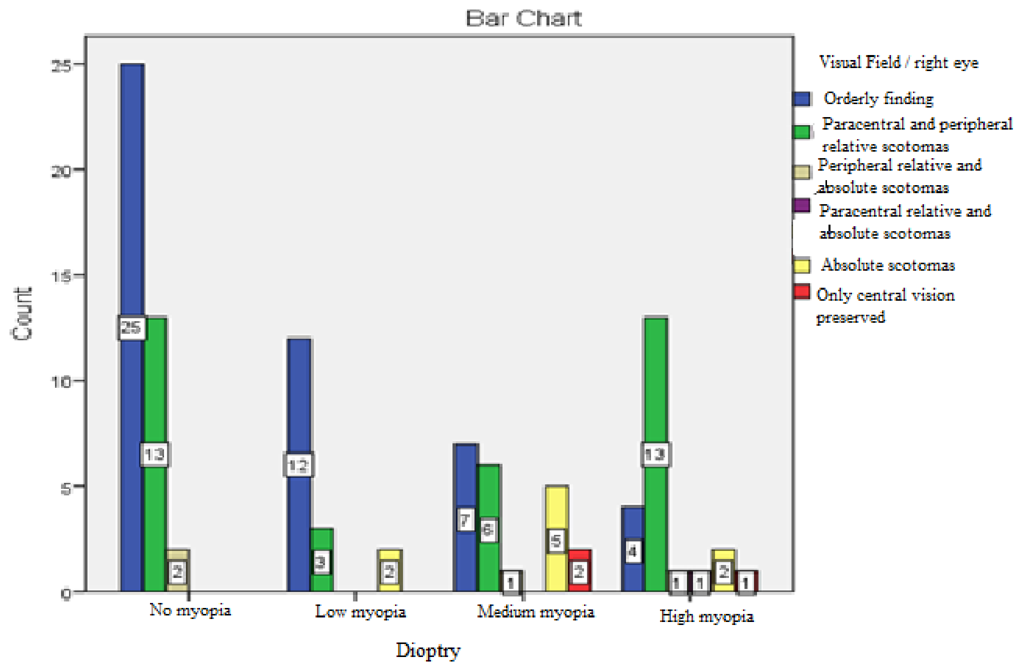

Fig. 2. Height of myopia and visual field / Crosstabulation

Discussion

The results of Sommer A, Tielsch JM, Katz J, *et al.* have shown that primary open-angle glaucoma is more often a bilateral disease, although one eye may be affected more than once [11].
Visual loss begins with a reduction in peripheral vision, but central vision may also be involved [11]. An analysis of the association between myopia and glaucoma in the US population [12] found that the chances of any visual field defects were significantly increased in low-, moderate-, and high-grade myopia compared with emetropia. A significant difference (p=0.001) was found in the distribution of subjects in each category of visual field status, the percentage of subjects with worse visual field defects increased with the worsening of the severity of myopia.
The results of our study were in favor of the previous findings. Namely, in the performed cross-tabulation between the height of myopia and the findings in the field of view, for z=0.000 there is a significant difference, especially in patients performing the method for the first time.
Regarding the comparison of the results of the visual field between the two groups, there was a significant difference in the distribution of visual field (p<0.001). In the group with myopia and glaucoma, the damage was greater. Changes in the visual field can be caused by the myopia itself, especially in high myopia, or if glaucoma occurs in a certain period. Whether changes in vision and visual field defects are due to myopia or glaucoma it is a diagnostic problem and dilemma for many ophthalmologists around the world. Several studies have been done to see the differences in the visual field in both groups.
In a study conducted at the Stanford University in California [13], in 487 patients with myopia and 1434 visual fields, it was found that in 16.1%, the defects in the visual field differed from those in glaucomatous eyes, and in 3%, they were the same as in glaucoma. But, in order to make the diagnosis of glaucoma, only the changes in the field of vision are not enough; other parameters that exist as potential risk factors for the occurrence and progression of the disease need to be taken into account.
In the Beijing Eye Study [14], visual field defects were found to be more common in high myopia with glaucoma. Visual field loss was associated with age (p<0.001), myopic refraction (p<0.001), level of education (p=0.01), and intraocular pressure (p <0.001).
In a larger study conducted in the United States [12], a significant association was found between increased visual field impairment and myopia in all three types: low myopia (OR2.02.95% CI1.28-3,19), moderate myopia (OR3.09.95% CI1.42-6.72), and high myopia (OR1.02.95% CI0.58-1.81).
In a study conducted in Japan [15], a significant association of visual field defects with myopia was found. Namely, out of 492 eyes with high myopia that were examined and monitored for 5 years, new defects in the visual field appeared in 13.2%. The incidence of myopic eye defects was significantly higher in eyes with an elliptical disc than in eyes with a circular papilla. Temporal and nasal defects were identified in these eyes. Among eyes with significant visual field defects, temporal defects were found in 61.5% of eyes with a circular disc, 75% of eyes with an elliptical disc, and 68.2% of eyes with a slanted papilla.

Because visual field defects progress in myopia, myopia has been found to be a high-risk factor for visual field errors, and these eyes should be examined once a year.

Conclusion

1. There was a significant difference between the examined and the control group in terms of changes in the visual field;
2. In the performed cross tabulation between the height of myopia and the degree of changes in the visual field, there was a significant difference.

Conflict of interest statement. None declared.

References

1. Loyo-Berríos NI, Blustein JN Primary-open glaucoma and myopia: a narrative review. *WMJ* 2007; 106(2): 85-89, 95.
2. K. Blazevska. Evaluation of the effects of trabeculectomy, with and without the use of 5Fu-DD Skopje 2009.
3. Daniela Dimitrova Radojcic. Spread and reasons for blindness in the Macedonian adult population. *Jurnal of special education and rehabilitation* 2017;18(1/2): 17-25.
4. Cvetkovic, Correction of refractive anomalies of the eye. Belgrade 1995.
5. He M, Zheng Y, Xiang. Prevalence of myopia in urban and rural children in mainland. *China Optom Vis Sci* 2009; 86(1): 40-44.
6. Lam CS, Lam CH, Cheng SC, Chan LY10. Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *OphthalmicPhysiol Opt* 2012; 32(1): 17-24.
7. Liang YB, Wong TY, Sun LP, *et al*. Refractive errors in a rural Chinese adult population the Handan eye study. *Ophthalmology* 2009; 116(11): 2119-2.
8. Perera SA, Wong TY, Tay WT, *et al*. Refractive error, axial dimensions, and primary open-angle glaucoma: the Singapore Malay Eye Study. *ArchOphthalmol* 2010; 128 (7): 900-905.
9. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology* 1999; 106(10): 2010-2015.
10. Djajkovska E, Dimovska V, Glaukom. Jun 2005.
11. Sommer A, Tielsch JM, Katz J, *et al.* Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*, 1991 Aug 109(8): 1090-1095.
12. Mary Qiu, Sophia Y Wang, Kuldev Singh, Shan C. Lin-Association between Myopia and Glaucoma in the United States Population. *Investigative Ophthalmology & Visual Science* 2013; Vol. 54: 830-835.
13. Robert TC, MD. Is it Glaucoma? Or Just High Myopia? *Review of Ophtalmology* May 2017.
14. Xu L, Wang Y, Wang S, Wang Y Jonas. High myopia and glaucoma susceptibility the Beijing Eye Study. *JB Ophthalmology* 2007; 114(2): 216-217.
15. Kyoko O, Noriaki S, KenjiroY, *et al.* Long term development of significant visual field defects in highly myopic eyes. *Anjophtalmolog* 2011; 152(2): 256-265.

Original article

POSTERIOR APPROACH TO TOTAL HIP ARTHROPLASTY AND COMPLICATION RATE – SINGLE CENTER EXPERIENCE

ПОСТЕРИОРЕН ПРИСТАП НА ТОТАЛНА АРТРОПЛАСТИКА НА КОЛК И КОМПЛИКАЦИИ - ИСКУСТВО НА ЕДЕН ЦЕНТАР

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Abstract

Introduction. Degenerative hip diseases are among the most common musculoskeletal disorders. After decades of progress and development, total arthroplasty of the hip (THA) as surgical intervention has become one of the most frequently performed surgical intervenetions in orthopedics. A number of surgical approaches are used to implant THA, each of them has its own unique advantages and disadvantages, but all can be safely and successfully used to implant a total hip replacement. For this reason, surgeons are advised to choose the approach they are most confident with and have the greatest experience.
Aim. The aim of this study was to determine the complications from the posterior approach to the hip following a total hip arthroplasty and reducing their rate in the next surgeries.
Methods. The study was set up with a retrospective analysis of patients treated surgically during the period from January 2018 to January 2020. A total of 30 patients clinically and radiologically diagnosed with a degenerative hip disease were surgically treated at the University Clinic for TOARILUC (Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre). All patients were aged 50 to 70 years, without any comorbidities and were surgically treated with a conventional posterior approach.
Results. From a total of 30 patients, only one of them who had undergone on a surgery for a total hip replacement due to osteoarthritis, experienced dislocation of the prosthesis two weeks after the surgery. The patient was treated with a conservative method. The serum value of the enzyme creatinine kinase before and after surgery in this patient as well as in all patients treated with posterior approach presented a statistically significant difference ($p<0.0001$), which was an indicator for muscle damage.
Conclusion. Although posterior approach to the hip has many advantages, it has also a high risk of dislocation. Dislocation of the hip is considered to be the second leading cause for arthroplasty failure after loosening. However, further research including a larger series of patients is needed in order to reach a definitive conclusion about the advantages and disadvantages of this surgical approach.

Keywords: total hip arthroplasty, posterior approach, dislocation

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Апстракт

Вовед. Дегенеративните заболувања на колкот се едни од најчестите нарушувања на мускулно-скелетниот систем. По неколку децении напредок и развој, тоталната артропластика на колкот како хируршка интервенција стана една од најчесто изведуваните хируршки интервенции во ортопедијата ширум светот. Голем број хируршки пристапи се користат за имплантирање на тотална ендопротеза на колк, секој од нив има свои уникатни предности и недостатоци, но сите можат безбедно и успешно да се применат. Поради оваа причина, на хирурзите им се препорачува да изберат пристап со кој се најсигурни и имаат најголемо искуство.
Цел на студијата. Да се утврдат компликациите при имплантирање на тотална ендопротеза со заден пристап, со цел да се намали нивната стапка во следните операции.
Методи. Студијата е од ретроспективен карактер и во неа се вклучени пациенти хируршки третирани во периодот од јануари 2018 година до јануари 2020 година. Вкупно 30 пациенти клинички и радиолошки дијагностицирани со дегенеративно заболување на колкот (коксартроза) се хируршки третирани, а потоа следени и евалуирани на Универзитетската клиника за ТОАРИЛУЦ (Клиника за Трауматологија, Ортопедски болести, Анестезија, Реанимација, Интензивно лекување и Ургентен центар). Пациенти-

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те се на возраст од 50 до 70 години без коморбидитети и се хируршки третирани со конвенционален заден пристап.
Резултати. Од вкупно 30 пациенти кои беа хируршки третирани поради коксартроза, кај само еден од нив настана дислокација на протезата две недели по операцијата. Пациентот беше третиран конзервативно, со некрвава односно затворена репозиција. Серумската вредност на ензимот креатин киназа пред и по операцијата кај презентираниот пациент и целата група на пациенти третирани со заден пристап има статистичка сигнификантност со p<0,0001, што е индикатор за оштетување на мускулите. Иако задниот пристап има многу предности, води и кон поголем ризик за дислокација. Потребни ни се дополнителни истражувања од поголеми серии на пациенти за да се донесе дефинитивен заклучок за предностите и недостатоците на овој хируршки пристап.

Клучни зборови: тотална артропластика на колк, заден пристап, дислокација

Introduction

Degenerative hip diseases are among the most common musculoskeletal disorders [1,2]. Approximately 28% of the population over the age of 45 suffers from osteoarthritis of the hip and its prevalence is expected to increase in the coming decades [3-5]. The founder of modern total hip arthroplasty (THA) was Charnley in 1950 [6,7]. After decades of progress and development, this surgical intervention has become one of the most frequently performed surgical interventions in orthopedics. In 2010 in the United States, approximately 2.5 million patients living with artificial hips were registered, and approximately 332,000 interventions were performed annually [8,9]. This number is expected to grow significantly in the coming years [10,11].

A number of surgical approaches are used to implant THA, but the most commonly used are posterior approach, direct lateral approach, and direct anterior approach. Each approach has its own unique advantages and disadvantages, but all can be safely and successfully used to implant a total hip replacement. Convincing, high-quality studies comparing different approaches are currently lacking. For this reason, surgeons are advised to choose the approach they are most confident with and have the greatest experience.

Among the most common early complications following total hip arthroplasty and posterior approach to the hip is dislocation of the prosthesis, which represents number 1 short-term complication that requires revision in the first 2 years [12,13]. The most common type of dislocation is posterior and it occurs when the femoral head moves out from the acetabular component for any reason. Leg shortening with external or internal rotation combined with a pathologic and painful telescoping of the limb are the typical signs of dislocation. More often patients report onset of pain with a kind of snapping feeling, unable to walk or load the affected leg. Our diagnosis is based on a physical exam and radiology findings.

The aim of this study was to determine the complications from the posterior approach to the hip following total hip arthroplasty and reducing their rate in the next surgeries.

Material and methods

Patients and treatment

The study was set up with a retrospective analysis of patients treated surgically during the period from January 2018 to January 2020. A total of 30 patients clinically and radiologically diagnosed with a degenerative hip disease were surgically treated at the University Clinic for TOARILUC (Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre). All patients were aged 50 to 70 years without any comorbidities and they were surgically treated with conventional posterior approach.

Surgical procedure of the posterior approach

Patients are positioned on the unaffected side. The skin incision is made distally and laterally to the spina iliaca posterior superior to the lateral end of the great trochanter and a curve in the direction of the muscle fibers of the m. gluteus maximus and then descends to the femur by about 10 cm. With this incision we expose the gluteal fascia and the tractus iliotibialis. The deep fascia is then cut vertically. The muscles that converge on the great trochanter from top to bottom are: m. gluteus medius, m. piriformis, m. obturator internus, m. gemelli superior et inferior, m. quadratus femoris and the upper end of m. adductor magnus. The posterior border of the m. gluteus medius is then identified, the great trochanter is incised so that the detached part involves the insertion of the following structures: m. quadratus femoris, m. obturator internus together with the inferior and gemelli superior, m. piriformis and posterior third of m. gluteus medius fibers. The osteotomy extends from the junction of the posterior third and anterior two-thirds of the lateral edge of the great trochanter, obliquely and downward, posteriorly to the femur. Arthritic femoral head is cut off with a bone saw, then we prepare the acetabulum for its acetabular cup by using a reamer to grind down and shape the socket in which we place the acetabular cup, made from titanium. After that we put acetabular insert/liner which will facilitate smooth movements within the new joint. We rime the femur and we insert the prosthetic femoral stem in it. The next step is reposition, followed by closure of layers.

Statistical analysis

All results were analyzed with the program Statistics 8 for Windows, and the results are displayed graphically and in a spreadsheet. Methods of descriptive statistics were used, such as non-parametric and parametric statistical analyses. Percentage and structure were determined for attribute series. The relationship between two samples with numerical features were determined by Pearson correlation coefficient (p). Differences between two independent numerical samples were determined by t-test for independent samples. Levels of probability for the realization of the null hypothesis, which were used in accordance with international standards for biomedical sciences, were 0.01 and 0.05.

Results

All 30(100%) patients were treated with a posterior approach. The mean age of patients was 71 year. Figure 1 presents distribution of patients according to gender, female being prevalent. Most of the patients (60%) had normal BMI (18.5-24.9) (Figure 2).

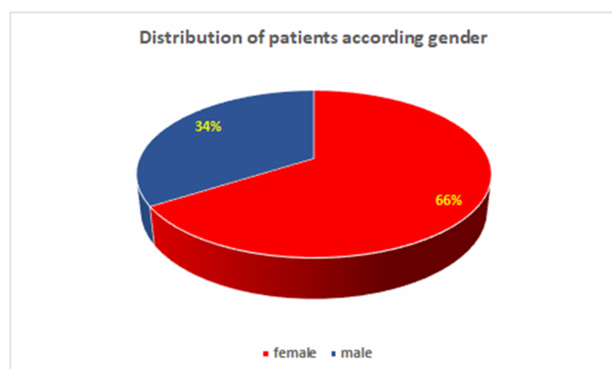

Fig. 1. Distribution of patients according to gender

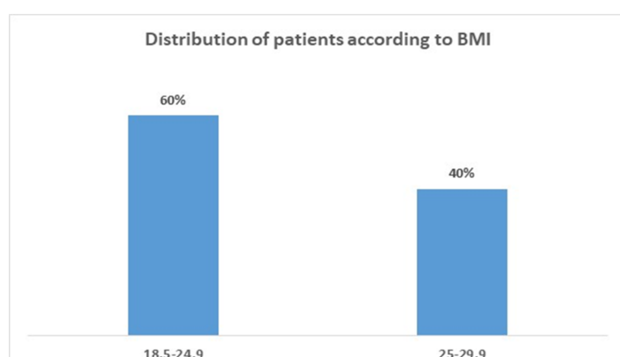

Fig. 2. Distribution of patients according to BMI.

The mean value of preoperative creatinine kinase was 94.3 U/L and postoperative value was 3442 U/L (Figure 3). Then, we used t-test for determining the value of preoperative and postoperative creatinine kinase. We found an extremely statistically significant difference ($p<0.0001$), and 95% confidence interval of this difference was from -3761.98 to -2933.28.

The average operative and postoperative surgical drainage of blood was 461 ml. All of the patients (100%) received one unit of blood after surgery. The

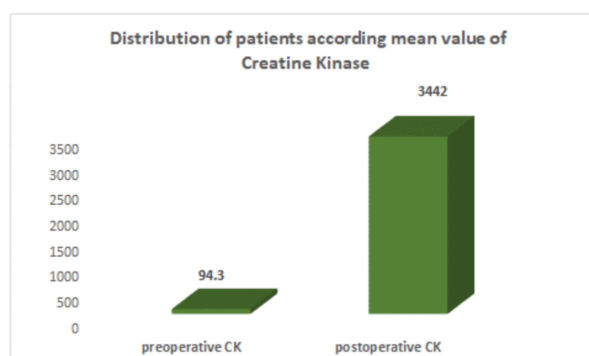

Fig. 3. Distribution of patients according to creatinine kinase

majority of patients (70%) were diagnosed with coxartrosis lat. sinister (Figure 4).
Distribution of patients according to time of hospitallization is presented in Figure 5.

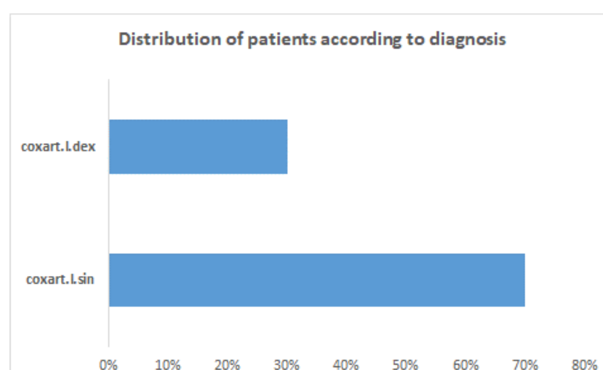

Fig. 4. Distribution of patients according to diagnosis

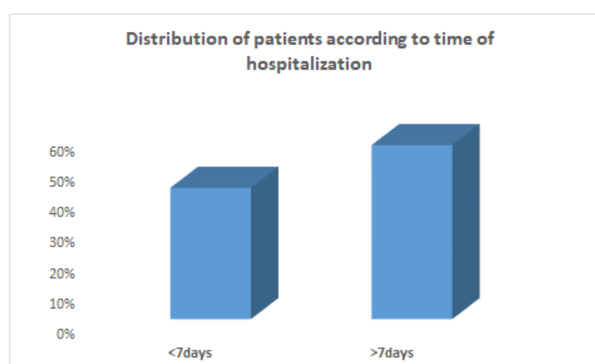

Fig. 5. Distribution of patients according to time of hospitalization

In all of the patients Harris hip score was measured on the first preoperative day, on the 30th postoperative day, 6 and 12 months after the surgery. Visual Analogue Scale (VAS)-pain quantification scale was used before the surgery, 30 days, 6 and 12 months postoperatively.

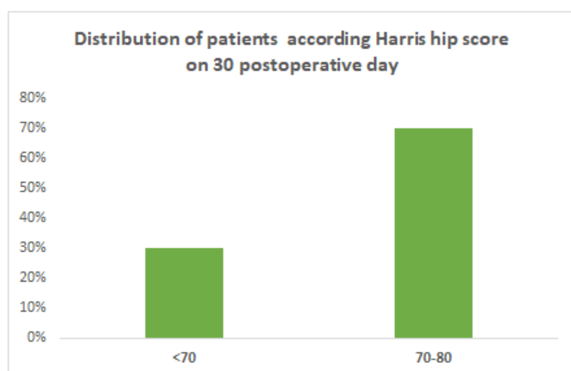

Fig. 6. Distribution of patients according to Harris hip score on 30th postoperative day

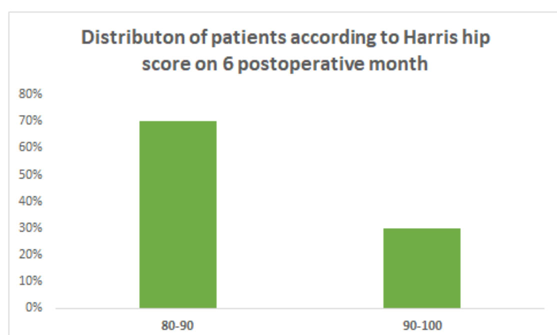

Fig. 7. Distribution of patients according to Harris hip score at 6 month postoperatively

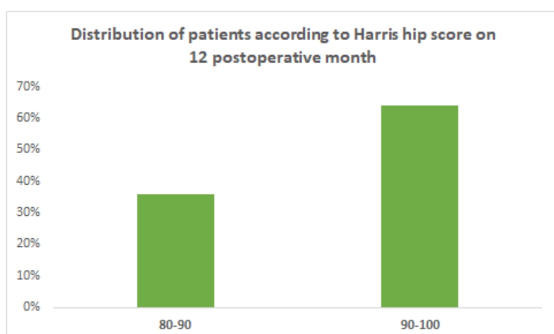

Fig. 8. Distribution of patients according to Harris hip score at 12 month postoperatively

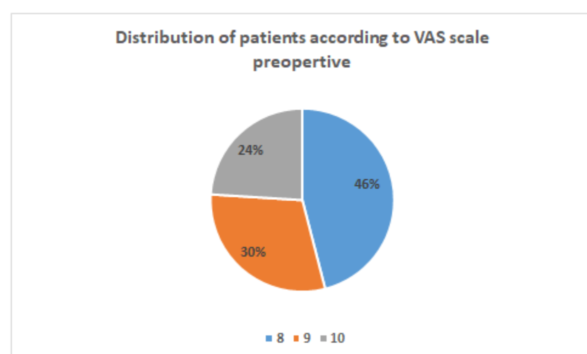

Fig. 9. Distribution of patients according to VAS scale preoperatively

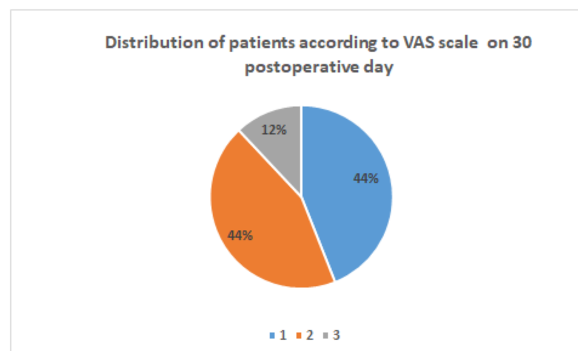

Fig. 10. Distribution of patients according to VAS scale on 30th postoperative day

All patients (100%) had Harris hip score <70 on the first preoperative day. Figure 6 shows distribution of patients according to Harris hip score on the 30th post-operative day.

Distribution of patients according to Harris hip score at 6 and 12 months postoperatively is presented in Figure 7 and Figure 8.

According to VAS scale preoperative patients had score 8 to 10 (Figure 9).

Distribution of patients according to VAS scale on the 30th postoperative day is presented in Figure 10.

Assessment of pain according to VAS scale at 6 and 12 months postoperatively showed 0 score (no pain) in all patients.

The mean value of preoperative D-dimer was 469 and postoperatively 3101. We used t-test to determine the value of preoperative and postoperative D-dimers. We found an extremely statistically significant difference ($p<0.0011$), and 95% confidence interval of this difference was from -4255.17 to -1129.49 (Figure 11).

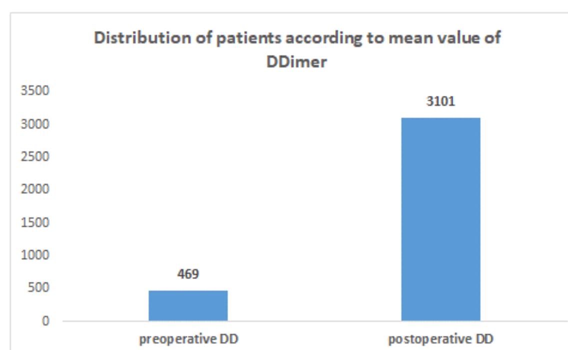

Fig. 11. Distribution of patients according to mean value of D-dimers

From the total of 30 patients, only one who had undergone a surgery for total hip replacement due to osteoarthritis, complained on a severe pain and snapping feeling on the affected hip two weeks after the surgery. Clinical exam and radiology findings revealed dislocation of prosthesis, and the patient was admitted to our Clinic for conservative treatment with a closed reducetion. As we previously mentioned, in all patients we measu-

red serum level of the enzyme creatinine kinase before and the day after surgery. The serum value of the enzyme in this patient before surgery was 89, while after surgery 4893, which was an indicator for muscle damage.

Discussion

Dislocation is an often expected complication from total hip arthroplasty and it is considered to be the second leading cause of arthroplasty failure after loosening [14]. In the literature the rate of dislocation varies between 0.16 and 9.5%, moreover, the frequency tends to increase with the follow-up of patients and some authors report rates of 22% after one year follow-up [15-17]. Main causes for dislocation after THA may be: laxity of the hip joint for any reason, improper choice of the head-neck length ratio which leads to shortening of the neck length, but the most common mechanism of dislocation is impingement [18]. Scar tissue, capsular tissue or osteophytes on both sides can also cause dislocation or displacing the head to anterior or posterior. Also, positional dislocation might occur due to the movements of the patients, when they position their leg into insecure position, especially during the first month after implantation. Technical errors also have their role in dislocation, neuromuscular disorders with pathologically increased muscle tension such as Parkinson's disease, epilepsy and cerebral palsy and surgeons must pay attention while operating patients with such conditions. Traumatic displacement, obesity, developmental dysplasia of the hip, may facilitate this condition [19].

Even though posterior approach to the hip has many advantages, it also increases the risk of dislocation. Some of the researchers suggest that this increase rate might be attributed to the inadequate acetabular exposure and malposition of the acetabular component.

A classification system for THA dislocation was proposed in order to select the proper treatment, and it is based on component position and soft tissue balance, but still it is not in a widespread use [20].

Treatment options for dislocation following THA include non-surgical and surgical treatment. If the dislocation occurs within the first 3 months after the arthroplasty, they are managed by closed reduction, and there is a risk of re-dislocation due to the disruption of the forming soft tissue envelope. If the dislocation occurs 5 weeks after the surgery, the re-dislocation risk is even higher [21]. The majority of patients can be treated successfully in a closed manner such as in our case. On the other hand, surgical treatment is mandatory for those patients with persistent instability following non-surgical treatment and for those having the malposition component. Capsular repair during revision surgery may be effective. Surgical treatment for recurrent dislocations may include: constrained component, revision arthroplasty or trochanteric advancement. Revision surgery is effective in preventing new dislocation and before the surgery; imaging studies should be made to determine the exact position and orientation of the different parts of the replacement, because one or more of them may need to be reoriented or completely exchanged. Also, for the success of the surgery the proper healing of the soft tissue around a revised hip is important.

Patients are instructed to take hip precautions, which means avoiding various maneuvers based on the type of the surgery they had.

Conclusion

Despite all of its advantages like adequate visualization of acetabulum, good cup orientation, proper acetabular preparation and sciatic nerve protection and assessment, the posterior approach has a high risk of dislocation and possible need for a revision surgery. Studies have revealed that if proper soft tissue reconstruction is performed, short rotator reparation with intra-osseous suture to greater trochanter, dislocation rate following the posterior approach could markedly reduce. However, further research including a larger series of patients is needed in order to reach a definitive conclusion about the advantages and disadvantages of this surgical approach.

Conflict of interest statement. None declared.

Reference

1. Felson DT, Lawrence RC, Dieppe PA, *et al*. Osteoarthritis: New insights. Part 1: The disease and its risk factors. *Ann Intern Med* 2000; 133: 635-646.
2. Guccione AA, Felson DT, Anderson JJ, *et al*. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994; 84: 351-358.
3. Jordan JM, Helmick CG, Renner JB, *et al*. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: The Johnston County Osteoarthritis Project. *J Rheumatol* 2009; 36: 809-815.
4. Lawrence RC, Felson DT, Helmick CG, *et al*. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; 58: 26-35.
5. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum* 2006; 54: 226-229.
6. Morrey BF. A historical perspective of hip arthroplasty and reconstructive surgery. In: Cashman J, Goyal N, Parvizi J, editors. The Hip: Preservation, Replacement and Revision. Brooklandville, MD: Data Trace Publishing Company; 2015. pp. 1.1-1.19.
7. Charnley J. Total hip replacement by low-friction arthroplasty. *Clin Orthop Relat Res* 1970; 72:7-21.
8. Maradit Kremers H, Larson DR, Crowson CS, *et al*. Prevalence of total hip and knee replacement in the United States. *J Bone Joint Surg Am* 2015; 97: 1386-1397. [PMC free article] [PubMed] [Google Scholar].
9. "Inpatient Surgery". FastStats. National Center for Health Statistics. Centers for Disease Control and\Prevention. [Last accessed on 2016 Jun 26]. Available from:http://www.cdc.gov/nchs/data/nhds/4procedures/2010pro4_numberprocedureage.pdf .

10. Kurtz S, Mowat F, Ong K, *et al*. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J Bone Joint Surg Am* 2005; 87: 1487-1497.
11. Singh JA. Epidemiology of knee and hip arthroplasty: A systematic review. *Open Orthop J* 2011; 5: 80-85.
12. Biedermann R, Tonin A, Krismer M, *et al*. Reducing the risk of dislocation after total hip arthroplasty: the effect of orientation of the acetabular component. *J Bone Joint Surg Br* 2005; 87: 762-769.
13. Swedish Hip Arthroplasty Register, Annual Report 2011, http://www.shpr.se.
14. Huten D, Langais F. Luxations et subluxations des protheses totales de hanches. J. Duparc (Ed.), Cahiers d'enseignements de la Sofcot n° 90, Elsevier, Paris 2005; 370-417.
15. Letournel E. Lagrange-Letournel hip prosthesis: results of 1355 cases. Proceedings of third Open Scientific Meeting of the Hip Society, CV Mosby, Saint-Louis 1975; 278-299.
16. Vicar AJ, Coleman CR. A comparison of the antero-lateral, transtrochanteric and posterior surgical approaches in primary total hip arthroplasty. *Clin Orthop* 1984; 188: 152-159.
17. Hedlundh U, Ahnfelt L, Fredin H. Incidence of dislocation after total hip arthroplasty. Comparison of different registration methods in 408 cases. *Acta Orthop Scand* 1992; 63: 403-406.
18. Ranawat CS, Rao RR, Rodriguez JA, Bhende HS. Correction of limb-length inequality during total hip arthroplasty. *J Arthroplasty* 2001; 16: 715-720. doi: 10.1054/arth.2001.24442.
19. Queally JM, Abdulkarim A, Mulhall KJ. Total hip replacement in patients with neurological conditions. *J Bone Joint Surg Br* 2009; 91: 1267-1273.
20. Dorr LD, Wolf AW, Chandler R and Conaty JP. Classification and treatment of dislocations of total hip arthroplasty. *Clin Orthop Relat Res* 1983; 173: 151-158.
21. Ali Khan MA, Brakenbury PH and Reynolds IS. Dislocation following total hip replacement. *J Bone Joint Surg Br* 1981; 63-B: 214-218.

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Original article

PREVALENCE OF VERTEBRAL FRACTURES IN POSTMENOPAUSAL PATIENTS WITH RHEUMATOID ARTHRITIS

ПРЕВАЛЕНЦА НА ВЕРТЕБРАЛНИ ФРАКТУРИ КАЈ ПОСТМЕНОПАУЗНИ ПАЦИЕНТКИ СО РЕВМАТОИДЕН АРТРИТИС

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Abstract

Introduction. Rheumatoid arthritis (RA) is an inflammatory arthritis that affects 0.5 to 1% of the general population. The risk of vertebral fractures and hip fractures is much higher in patients with RA than in those with primary osteoporosis (OP). This is due to the severity and activity of the disease in patients with RA, low BMI (body mass index), age, glucocorticoid (GK) use, and the duration of the disease.
Aim. To evaluate the prevalence of vertebral fracture in postmenopausal patients with rheumatoid arthritis on glucocorticoid therapy and their association with risk factors.
Methods. 92 patients were analyzed, all of whom were recorded for osteoporosis evaluation with a dual-energy x-ray absorptiometry -DXA scan, with built-in software for assessment of VF, VFA (Vertebral Fractures Assessments).
Results. The prevalence of vertebral fractures in postmenopausal patients with RA is 63%. In 58 patients, the vertebral fractures are reduced by 2 degrees (height is reduced by 25 to 40%) 58.6%, mild fracture (loss of vertebral height from 20 to 25%) with 31.1% and severe fracture (height reduced by more than 40%) with 10.3%. In patients due to GC therapy, VF are more frequent, smoking is one of the most significant risk factors, while an increased BMI reduces the risk of developing these fractures.
Conclusion. In all patients with RA, especially those on chronic therapy with GC, it is necessary to evaluate osteoporosis and determine the bone density of the vertebral bodies by means of VFA, to enable early, timely detection and prevention of vertebral and non-vertebrale fractures.

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Keywords: Rheumatoid arthritis, prevalence, vertebral fractures

Абстракт

Вовед. Ревматоидниот артритис (RA) претставува воспалителен артритис, кој зафаќа 0,5-1% од општата популација. Ризикот од настанување на вертебрални фракури и фрактури на колкот се многу почести кај пациентите со RA отколку кај оние со примарна остеопороза (OP). Тоа се должи на тежина и активност на болеста кај пациентите со РА, низок BMI (индекс на телесна маса), возраст, употреба на гликокортикоиди (GK) како и времетраење на болеста.
Цел. Да се уочи преваленцата на вертебрални фрактура кај постменопаузални пациентки со ревматоиден артритис на гликокортикоидна терапија и нивната поврзаноста со ризик факторите.
Методи. Беа анализирани 92 пациенти, кај сите беше направено снимање на евалуација на остеопорозата со апарат за двојно-енергетска x зрачна апсорбциометрија-DXA скен, со вграден софтвер за проценка на VF, VFA (Vertebral Frctures Assessments) .
Резултати. Преваленцата на вертебрални фрактури кај постменопаузните пациентки со RA изнесува 63%. Кај 58-те пациентки вертебралните ф-ри се со намалување од 2 степени- (висината е намалена за 25 до 40%) 58.6%, лесна фрактура (губење на висината на пршленот од 20 до 25%) со 31.1% и тешка фрактура (висината е намалена за повеќе од 40%) со 10.3%. Кај пациентките поради терапија со GC регистрирана е зачестена појава на VF, пушењето е еден од позначајните фактори на ризик, додека зголемениот БМИ го намалува ризикот од развој на овие фрактури.

Заклучок. Кај сите пациентки со RA особено оние кои се на хронична терапија со GC, потребно е да се спроведува евалуација на остеопорозата и одредување на коскената густина на пршленските тела со помош на VFA, за да се овозможи рано, навремено детектирање и превенирање на вертебрални и невертебрални фрактури.

Клучни зборови: ревматоиден артритис, преваленца, вертебрални фактури

Introduction

Rheumatoid arthritis (RA) is an inflammatory disease that affects 0.5-1% of the general population [1]. The risk of incidence of vertebral fractures and hip fractures is much higher in patients with RA than in those with primary osteoporosis (OP)[2]. This is due to the severity and activity of the disease in patients with RA, low BMI (body mass index), age, glucocorticoid (GK) use, as well as the duration of the disease [3,4]. Vertebral fractures (VFs), which are one of the most common complications of OP, are associated with chronic back pain, kyphosis, decreased lung function, immobility, and may even lead to lethal outcome in patients [5]. The presence of one vertebral fracture increases the relative risk of future VFs as well as incidence of non-vertebral fractures (non-VFs). These complications of OP may occur regardless of the bone mineral density-BMD [6]. Osteoporosis, including the increased risk of VF and non-VF, has a negative impact on the quality of life in the patients with RA and represents a serious health and socio-economic issue [7-10].

Aim

The aim of this study was to evaluate the prevalence of vertebral fracture in postmenopausal patients with rheumatoid arthritis on glucocorticoid therapy and their association with risk factors.

Material and methods

This was an analytical cross-sectional study, performed in the period of one year-from March 2019 to March 2020, which included 92 patients who met the revised ACR criteria of rheumatoid arthritis [11]. The subjects were treated at the outpatient department and hospitalized at the University Clinic for Rheumatology in Skopje. They were postmenopausal women from 50 to 80 years old, with menopausal status of more than ≥2 years, who had not been previously treated with bisphosphonate therapy. For all subjects with RA, treatment with various NSAID and/or disease-modifying antirheumatic drugs (DMARDS) was allowed, as well as therapy with glucocorticoids. The subjects that were in the functional class 4 according to Steinbrocher were not enrolled in the study.

The demographic data and disease characteristics in all 92 subjects were taken by anamnesis and clinical examination by a rheumatologist. The number of tender and swollen joints was assessed. The anamnesis and status provided valid information about the age, body weight, body height, disease duration, used glucocorticoid therapy at the time of enrollment and in the previous 12 months, current smokers, family anamnesis of hip fracture as well as data on existence of patient's previous fracture.

Exclusion criteria for the study were: acute and chronic infections coinciding with RA, liver, kidney, lung or hematologic diseases, diabetes, diseases of thyroid and parathyroid gland, diseases of adrenal gland, all types of hormone replacement therapy in postmenopausal women, bisphosphonate therapy, psychiatric and neurologic diseases.

Bone mineral density was determined by a device for dual-energy x-ray absorptiometry-DXA scanner, "Lunar iDXA", manufactured at GE, with VF assessment by the method of VFA (Vertebral Fracture Assessment). The bone loss was expressed in T-score defining the deviation of bone density in standard deviations (SD), compared to that in young healthy women. The DXA scanner is located at the University Clinic for Rheumatology, Skopje.

Vertebral fractures were determined by means of VFA with built-in software of the DXA scanner. Vertebral fracture assessment (VFA) is a method of imaging the thoraco-lumbar spine by means of bone densitometer and represents a fast and simple procedure, connected with low exposure to radiation and has good capability of detecting vertebral fractures [12].

The radiation dose for the patient is much lower compared to the standard x-ray (3 μSV of T4-L4 in VFA, and 600 μSV for standard x-ray of the lumbar spine). After the imaging, there is a manual or automatic setting of the VFA image, and the result is expressed in percentages, i.e. a Genant semi-quantitative method is used [13]. When using the semi-quantitative assessment technique, three degrees of bone loss are determined. At degree 1-mild loss of bone mass, meaning loss of vertebral body height from 20 to 25%. Medium loss of bone mass, degree 2, is characterized by a decrease of vertebral body height by 25 to 40%. Severe loss of body mass, degree 3, occurs when the vertebral body height is decreased by more than 40%. Every loss in vertebral body height of more than 20%, i.e. 4 mm of the standard height is considered as vertebral fracture [14].

The C-reactive protein (CRP) with normal values of <5 mg/L was assessed. This biochemical analysis was performed at the Immunological Laboratory of the University Clinic for Rheumatology.

Disease activity assessment was made by using the index DAS 28 score (Disease Activity Score). The value

of DAS 28<3.2 points out to inactive RA, values between 3.2 and 5.1 are characteristic for moderate activity of RA, and values >5.1 point out to active rheumatoid arthritis [15].
For determining the functional capacity of the patients with RA, the following was used: Questionnaire for functional capacity assessment of a patient with RA (Health Assessment Questionnary-HAQ). Patients completed the questionnaire independently within the period of only 5 minutes. This questionnaire contains eight sets of questions of different everyday life domains, with a multiple choice of four possible answers: "without any difficulties, with difficulties, with somebody's help, I cannot". Point count is as follows: without any difficulties=0 points, with difficulties=1 point, with somebody's help=2 points, I cannot=3 points. The total number of points was determined for each patient. Then, the highest scores of each of the mentioned activities were summed up and divided by 8. In that way the functional capacity index was obtained, which was between 0-3 points (3 points means the worst) [16].
The criteria of the basic Good Clinical Practice, Law on Healthcare and Law on the Protection of Patients' Rights of the Republic of North Macedonia were respected during the research. The ethical principles of the Declaration of Helsinki of the World Medical Association, the Belmont Report and UNESCO's Universal Declaration on Bioethics and Human Rights were adhered to.
The statistical analysis was performed in the statistical program STATISTICA 10.0. The attributive statistical series were analyzed by determining the relation coefficient, ratios, rates, and by determining the statistical significance between the differences revealed-Fisher Exact 2 tailed test. The numerical series were analyzed by measures of central tendency and by measures of data dispersion. In the numerical series with no deviation from the normal distribution, the significance of the difference was tested with t-test. For CI (confidence interval 95% CI), statistical significance at the level of error lower than 0.05 (p) was defined. The results are presented in tables.

Results

A total of 92 postmenopausal patients with rheumatoid arthritis were enrolled in the study. Patients were divided in two groups: with and without vertebral fractures. The average age of patients with vertebral fractures was 63.6±8.4 years and was higher compared to the average age of patients without vertebral fractures which was 59.3±6.1; the difference in percentage was statistically significant for $p<0.05$
The prevalence of vertebral fractures in the research group of postmenopausal patients with rheumatoid arthritis was 63%.

Most of the fractures in 58 patients were reduced by 2 degrees (the height was reduced by 25 to 40%)-58.6%, mild fracture (loss of vertebral height from 20 to 25%) -31.1% and severe fracture (height reduced by more than 40%)-10.3% (Table 1).

Table 1. Prevalence of vertebral fractures

VFA /degree	No	%
None	34	37.0
Mild fracture	18	19.5
Medium fracture	34	37.0
Severe fracture	6	6.5

Body mass index (BMI) was 27.5 in patients with vertebral fractures compared to 30.4 in patients without vertebral fractures. The difference was significant (P=0.0156) and suggested that patients with better nutrition and bigger body mass had a smaller risk of developing OP and VF, probably because of the tissue hormones that produce the fatty cells in the organism.
BMD (g/sm^2) in patients with vertebral fractures was insignificantly lower than the values in patients without vertebral fractures (1.01 *versus* 1.04, p=0.3111).
Smoking as a risk factor showed to be one of the most significant risk factors in our study. 79.3% of patients with vertebral fractures were smokers compared to 16.7% of those without vertebral fractures; the difference was highly significant (p=0,000). Rheumatoid arthritis was active in patients without vertebral fractures with average DAS of 4.9 and average HAQ result of 1.4. Rheumatoid arthritis was also active in patients with vertebral fractures with average DAS of 4.6 and average HAQ result of 1.6. In both groups of patients, the average value of DAS was between 3.2 and 5.1, which pointed out to a moderate activity of rheumatoid arthritis. The HAQ-functional capacity in both groups was good.
There was no statistically significant difference in the activity of the disease in both investigated groups, with and without vertebral fractures. This is due to the cross-section made in patients, as it is an older group, postmenopausal, whose duration and severity of the disease in the first years cannot be taken into consideration, which on average starts at a younger age and is most active the onset of the disease. 79.3% of patients with vertebral fractures were RF positive, compared to 70.6% of patients without fractures.
All patients with vertebral fractures were taking corticosteroids-100.0%, but the group with vertebral fractures was bigger than that without vertebral fractures, and the difference was significant (Pearson Chi-square: 10.9494, df=1, p=.000936).
No significant differences between the serologically positive and negative patients (RF status) were registered, and there was no significant difference in the functional capacity in both groups and in CRP values as a nonspecific indicator of the inflammation at the moment of examination (Table 2).

Table 2. Basic characteristics

Characteristics N=92	with vertebral fractures N=58	without vertebral fractures N=34	p-value
age, mean±stand. dev	63.6±8.4	59.3±6.1	0.0110
BMI,mean±stand. dev.	27.5±5.6	30.4±4.2	0.0156
DAS28, mean±stand. dev.	4.6±0.5	4.9±1.7	0.2115
CRP, mean±stand. dev.	21.9±29.0	16.4±12.9	0.2723
HAQ, mean±stand. dev.	1.6±0.5	1.4±0.5	0.0673
BMD (g/sm2)	1.01±0.1	1.04±0.1	0.3811
RF positive No (%)	44(75.9)	24(70.6)	0.5762
smoker yes, No (%)	46(79.3)	6(16.7)	0.0000
cortico. yes, No (%)	58(100.0)	28(82.4)	0.0010

Discussion

Vertebral fractures are the most frequent, but rarely recognized complications which occur in patients with rheumatoid arthritis [6]. Spinal radiography is a gold standard in the diagnostics of vertebral fractures, but the tool for determining the VF incorporated in the DXA scanner represents a possibility for faster diagnostics and prevention of vertebral fractures in patients with rheumatoid arthritis. The lower price and the smaller dose of radiation make this method more accessible and safer for patients. In our study, the prevalence of vertebral fractures was 63%. The large percentage of presence of vertebral fractures was due to the age group of our patients which was 63.6 ±8.4 as well as the use of GK compared to the study of El Maghraoui *et al.* [14], where 36% VF had been detected and lower age of patients was 49.4 years. Also, in the study of Mochamed *et al.*, the presence of VF occurred in a smaller percentage, but the average age in those patients was significantly lower-43.11 years of age [12]. The study of Laan RF *et al.* showed that 9.5% of bone density of the vertebral trabecular bones was lost in the period of only several weeks of therapy at a daily dose of 7.5 mg prednisolone equivalent [25]. Therefore, the relation of patients' age with the presence of VF was clear in our subjects, as well as the administration of glucocorticoids.

In our study, the body mass index (BMI) was 27.5 in patients with vertebral fractures compared to 30.4 in patients without vertebral fractures. The difference was significant, and such difference was also found in the study of El Maghraoui *et al.* [14]. In recent times there have been opposed experiences and opinions that the obesity and the fatty tissue do not reduce the risk of osteoporosis and fractures [24]. In our study, 79.3% of patients with vertebral fractures were smokers compared to 16.7% of those without fractures. The difference was significant, which showed that smoking was a significant risk factor for patients with RA. In the study of Abdellah El Maghraoui *et al.* it was proved that the disturbed physical activity, which was a result of high values of DAS and/or HAQ,, may result in an increased possibility of injuries, which were the main reason for fractures in women with RA [14]. Disease activity in patients with RA is connected with an increased generalized loss of bone mass, most probably because of the increased release of cytokines that lead to bone resorption, such as IL-1, IL-6, TNF-a IFN-g. There are clear associations between the inflammatory cytokines and the bone loss, understanding the role of involvement of the inflammatory cytokines in the bone loss. RANK is a member of the TNF family, pressed by the osteoclasts and their predecessors. By connecting with its receptor-RANK of osteoclast precursors, RANKL controls the differentiation, proliferation and survival of the osteoclasts [17]. Osteoprotegerin (OPG) is a natural inhibitor of RANKL. RANKL through the lymphocytes and the synovial fibroblasts may mediate in the loss of bones which is connected during inflammatory condition as the rheumatoid arthritis. Discovery of the RANK-RANKL-OPG pathway and its implications in the pathogenesis of OP provides possibility for new therapies at molecular level in order to increase the bone strength [18]. In our study, although the disease was with a moderate activity, we had a significant percentage of presence of vertebral fractures which was probably due to the age of our subjects, the GK treatment, and also the fact that they were postmenopausal patients. No significant differences were registered between the disease activity, rheumatoid factor, functional capacity assessment and CRP of patients with and without vertebral fractures.

Spine fractures are the most frequent osteoporotic fractures. They are important for timely detection, because they are related to significant morbidity, mortality and decreased quality of life [6,19,20]. By scanning the thoraco-lumbar spine (T4-L4) by means of a bone densitometer, which has a built-in software for VFA, the detection of vertebral fractures is enabled even when they are not clinically demonstrated [21]. Only one third of VF may be detected and diagnosed by means of radiography. Therefore, imaging with bone densitometer and assessment of VF with VFA is necessary for their discovery. Even when the x-ray fractures are present at radiographies, they are often not recognized by the radiologist and do not lead to diagnosis and appropriate treatment of osteoporosis [22,23].

Conclusion

In postmenopausal patients with RA who were at an older age, and were receiving therapy with GC, more

frequent occurrence of vertebral fractures was registered. It is important to emphasize that subjects who were treated with GC received small doses of glucocorticoids on average, but mostly for a longer period of time, and that had RA, a disease which in itself is a risk factor for osteoporosis. According to our results, smoking was one of the more significant risk factors, while the increased BMI reduced the risk of development of such fractures. The group of patients with fractures was significantly larger than the group without fractures, and no significant difference was shown in the disease activity in both groups at the moment of the examination.

In all patients with RA, the well-controlled disease activity was particularly important, which would contribute to an increased physical activity as well as healthy living habits. It is necessary to perform evaluation of osteoporosis and assessment of bone density of the vertebral bodies by means of VFA at certain time intervals in patients who receive chronic therapy with GC in order to provide early, timely detection and prevention of both vertebral and non-vertebral fractures.

Conflict of interest statement. None declared.

References

1. Kvien TK, Haugeberg G, Uhlig T *et al*. Data driven attempt to create a clinical algorithm for of women with rheumatoid arthritis at high risk of osteoporosis. *Ann Rheum Dis* 2000; 59: 805-811.
2. Coulson KA, Reed G, Gilliam BE, *et al*. Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. *J Clin Rheumatol* 2009; 15: 155-160.
3. El-Wakd M, Omar HO, Abousenna H. Prevalence of silent nontraumatic vertebral fracture in rheumatoid arthritis: relation with disease duration, disease activity, corticosteroid, and hip buckling ratio. *Egyptian Rheumatology and Rehabilitation* 2014; 41: 116-121.
4. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009; 11: 229.
5. Jacobs-Kosmin D, Sandorfi N, Murray H, Abruzzo JL. Vertebral deformities identified by vertebral fracture assessment: associations with clinical characteristics and bone mineral density. *J Clin Densitom* 2005; 8: 267-272.
6. Lindsay R, Silverman SL, Cooper S, *et al*. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; 285: 320-323.
7. Ettinger B, Black DM, Nevitt MC, *et al*. Study of Osteoporotic Fractures Research Group.Contribution of vertebral deformities to chronic back pain and disability. *J Bone Miner Res* 1992; 7: 449-456.
8. Nevitt MC, Ettinger B, Black DM, *et al*. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med* 1998; 128: 793-800.
9. Hall SE, Criddle RA, Comito TL, Prince RL. A case-control study of quality of life and functional impairment in women with long-standing vertebral osteoporotic fracture. *Osteoporosis Int* 1999; 9: 508-515.
10. Matthis C, Weber U, O'Neill TW, Raspe H. Health impact associated with vertebral deformities: results from the European Vertebral Osteoporosis Study (EVOS). *Osteoporosis Int* 1998; 8: 364-372.
11. Arnett FC, Edworthy SM, Bloch DA, *et al*.The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-324.
12. Lewiecki EM, Laster AJ. Clinical review: Clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. *J Clin Endocrinol Metab* 2006; 91: 4215-4222.
13. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993; 8: 1137-1148.
14. El Maghraoui A, Rezqi A, Mounach A, *et al*. Prevalence and risk factors of vertebral fractures in women with rheumatoid arthritis using vertebral fracture assessment. *Rheumatology* 2010; 49: 1303-1310.
15. DAS-SCORE NL. Home of the DAS: Disease activity score in rheumatoid arthritis, http://www.das-score.nl/www.das-score.nl/index.html (accessed 15 February 2007).
16. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980; 23(2): 137-45.
17. McClung M. Role of RANKL inhibition in osteoporosis. *Arthritis Res Ther* 2007; 9(1): S3.
18. Kelman A, Lane NE. The management of secondary osteoporosis. *Best Pract Res Clin Rheumatol* 2005; 19: 1021-1037.
19. Melton LJ 3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs. Vertebral fractures predict subsequent fractures. *Osteoporosis Int* 1999; 10: 214-221.
20. Delmas PD, van de Langerijt L, Watts NB, *et al*. Under diagnosis of vertebral fractures is a worldwide problem: the IMPACT Study. *J Bone Miner Res* 2005; 20: 557-563.
21. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007; 297: 387-394.
22. Fink HA, Milavetz DL, Palermo L, *et al*. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa. *J Bone Miner Res* 2005; 20: 1216-1222.
23. Haugeberg G, Uhlig T, Falch JA, *et al*. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County rheumatoid arthritis register. *Arthritis Rheum* 2000; 43: 522-530.
24. Migliaccio S, Greco's AE, Wannenes F. Adipose, bone and muscle tissues as new endocrine organs: Role of reciprocal regulation for osteoporosis and obesity development. *Hormone Molecular Biology and Clinical Investigation* 2014; 17(1): 39-51.
25. Laan RF, van Riel PL, van de Putte LB, *et al*. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: A randomized, controlled study. *Ann Intern Med* 1993; 119: 963-968.

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Case report

PHTHIRIASIS PALPEBRARUM

PHTHIRIASIS PALPEBRARUM

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Abstract

Phthiriasis palpebrarum is a rare ectoparasitic infestation of the eyelids and eyelashes caused by *Phthirus pubis*. It occurs primarily in people who live in unfavorable, overcrowded places and have poor hygiene habits.
A 45-year-old man came to our Clinic for an ophthalmological examination due to itching in his right eye 4-5 days ago. On the slit lamp examination, we noticed a translucent yellowish-brown louse on the edge of the upper eyelid of the right eye and about 10 eggs attached to the lashes.
The paralyzed parasite and the eggs, after topical application of pilocarpine hydrochloride 2%, proparacaine hydrochloride 0.5% and vaseline (petroleum jelly) on the lashes, were mechanically removed with forceps. One week later, no lice or eggs were seen on the lashes.
Phthiriasis palpebrarum can be easily diagnosed by careful slit-lamp examination of the margins of the eyelids and eyelashes. Mechanical removal with forceps is a simple, cheap and effective way to treat this parasitosis.

Keywords: *Pthirus pubis*, phthiriasis palpebrarum, ectoparasitic infestation

Апстракт

Phthiriasis palpebrarum е ретка ектопаразитарна инфестација на очните капаци и трепките, предизвикана од Phthirus pubis. Се јавува пред се, кај луѓе кои живеат во неповолни, пренаселени места и имаат лоши хигиенски навики.
45-годишен маж се јави на офталмолошки преглед поради чешање на десното око, кое започнало пред 4-5 дена. На биомикроскопот забележавме полупрозирна жолтеникако-кафеава вошка на работ на горниот очен капак на десното око и 10-тина јајца прицврстени на трепките. По локална апликација на pilocarpine hydrochloride 2%, proparacaine hydrochloride 0.5% и нанесување на вазелин на трепките, парализираниот паразит и јајцата беа механички отстранети со форцепс. Една недела подоцна, на трепките не беа забележани вошки и јајца.
Phthiriasis palpebrarum може лесно да се дијагностицира со внимателно биомикроскопско испитување на рабовите на очните капаци и трепките. Механичкото отстранување со форцепс претставува едноставен, евтин и ефективен начин на лекување на ова паразитоза.

Клучни зборови: Pthirus pubis, phthiriasis palpebrarum, ектопаразитарна инфестација

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Introduction

Phthiriasis palpebrarum is a rare ectoparasitic infestation of the eyelids and eyelashes caused by *Phthirus pubis*, also known as pubic lice [1-4]. It appears primarily in people who live in unfavorable, overcrowded places

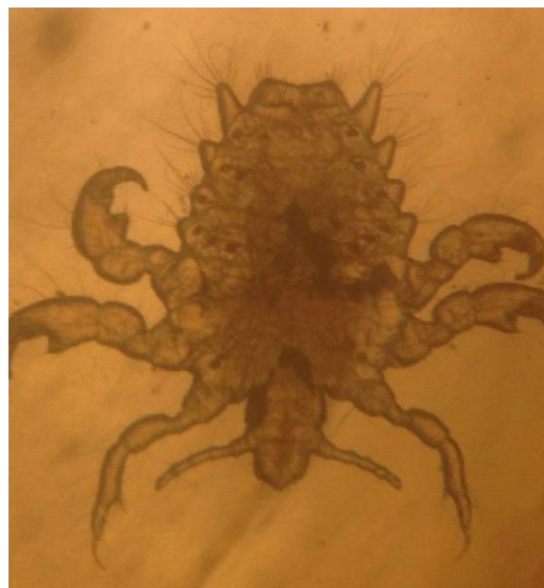

Fig. 1. Microscopic appearance of *Phthirus pubis*
(Source: Ozer AP, Kabataş UE, Gurkan A, Kurtul EB. Treatment of phthiriasis palpebrarum mimicking conjunctivitis in a newborn. Indian J Pediatr. 2016 Jul; 83(7): 730-731.)

and have poor hygiene habits. *Pthirus pubis* is a crab-like parasite with three pairs of legs, of which the second and third pairs end in claws that allow it to attach to the hair (Figure 1) [5].

The exact prevalence of phthiriasis palpebrarum is unknown. Infestation with this parasite is most common in people in the sexually active period, from 15 to 45 years of age [6].

Differentially diagnosed Phthiriasis palpebrarum may resemble seborrheic blepharitis, eyelid eczema, staphylococcal blepharitis, rosacea blepharitis, allergic blepharoconjunctivitis [2,4,7-9].

Preauricular lymphadenopathy is seen in the case of secondary bacterial infection of the eyelids or parasite bites [2].

Case report

A 45-year-old man came to our Clinic for an ophthalmological examination due to itching of the right eye, which had started 4-5 days ago.

In the anamnesis, the patient gave information that 7 days ago he had returned from a trip abroad and stayed in a hotel where the bed linen and towels were not clean.

Slit-lamp examination of the right eye showed the presence of *Pthirus pubis*, translucent yellowish-brown, firmly attached to the upper eyelid margins, and about 10 eggs attached to the lashes (Figure 2). The slit-lamp examination of the left eye showed a normal finding. There was no irritation of the lids and conjunctival hyperemia, nor any other pathology of the anterior and posterior segments of both eyes. Visual acuity was normal in both eyes.

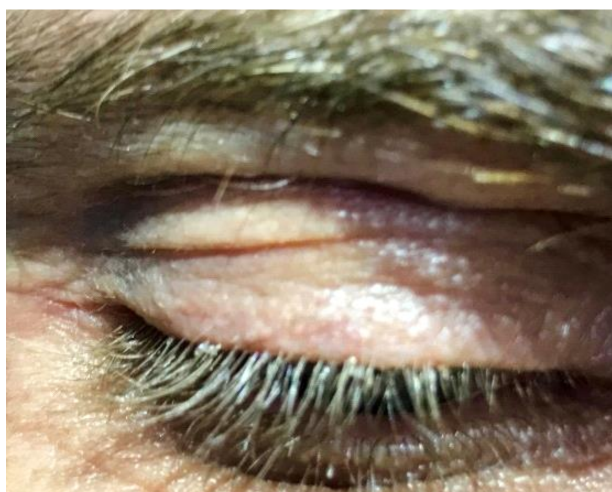

Fig. 2. Phthiriasis palpebrarum. Eggs from the parasite *Phthirus pubis* attached to the lashes of the upper eyelid

We applied a few drops of pilocarpine hydrochloride 2% in the right eye to cause paralysis of *Pthirus pubis*. After five minutes, the parasite's movement was significantly reduced, and it was removed with forceps.

After applying a local anesthetic-proparacaine hydrochloride 0.5% and applying vaseline on the lashes, we carefully removed the eggs from the lashes on the upper eyelid of the right eye with forceps. The patient was advised to apply pilocarpine hydrochloride 2% twice a day in the right eye and vaseline on the lashes. During and after treatment, the patient was also advised to pay special attention to personal hygiene and not to share bedding and/or towels and clothes with other members of his family.

At the follow-up examination 7 days later, no lice or eggs were observed on the eyelids.

Discussion

Pthirus pubis is an arthropod and obligate human parasite belonging to the family *Pthiridae* and the genus *Pthirus* [2]. The other two subspecies found in humans are *Pediculus capitis* (head lice) and *Pediculus corporis* (body lice) [6].

Pthirus pubis is a weakly active parasite [8], adapted to live in the pubic region, but can also be found in other parts of the body that are covered with hair. *Pthirus pubis* feeds on blood, up to five times a day. It cannot live longer than 24 to 48 hours away from his host. The female lays three eggs a day on average, from which young lice hatch on the seventh day. *Pthirus pubis* cannot fly or jump, and therefore transmission is through a direct physical contact between two individuals [10]. Sexual contact and parent-child interaction are the most common forms of infestation [6]. Indirect transmission of this parasite through towels, bedding or clothing is less common. The main symptom is itchy eyelids due to skin hypersensitivity to lice saliva [2]. Most often from pubic hair, this parasitosis can spread to other hairy parts of the body, such as the abdomen, chest, axillary area, chin, as well as eyebrows and eyelashes [9-11]. Accompanying localized or generalized itching of the hairy parts of the body indicates an association with phthiriasis pubis.

The small size (1.3-2 mm) and the transparency of the parasite and its eggs make them barely visible, so it is necessary to make a careful slit-lamp examination in order to be able to diagnose this disease [10]. Phthiriasis palpebrarum usually affects both eyes, very rarely one eye. The upper eyelids are most often involved.

Clinical findings of phthiriasis palpebrarum include blepharitis, accompanied by itching, rash and swelling of the eyelids, follicular conjunctivitis, marginal keratitis, secondary bacterial infection and, less commonly, cellulitis [10].

It is necessary to examine every contact of the patient and if there is an infestation with this parasite to treat it. To avoid reinfestation, disinfection of clothing and bedding in heat ≥50° C for 30 minutes is recommended [1,7]. All sexual contacts and family members of a person with phthiriasis palpebrarum should be evaluated for the possible presence of phthiriasis pubis and phthiriasis palpebrarum and should be treated if necessary.

Although manual infection of the infected hair of the father or mother is the most likely mode of transmission, when diagnosing phthiriasis palpebrarum in a child, the physician should rule out sexual abuse as a possibility [10].
There is no standard treatment. There are several different treatments, depending on the degree of infestation and the age of the patient.
Cutting lashes is a radical technique. The affected lashes can be epilated or the lice and eggs can be removed mechanically [4].
Botulinum toxin A or pilocarpine 2% is used to paralyze the parasite, which facilitates its removal, which can be difficult in children and non-cooperating patients [2,10].
Altinsoy *et al*. presented a case of a 6-year-old boy with phthiriasis palpebrarum, in whom, after topical application of pilocarpine, anesthetic and vaseline, the parasite and its eggs were removed with forceps [10]. This result is in agreement with ours.
Cryotherapy or argon laser photocoagulation can also be used as an effective treatment in this disease [6]. Alternative and/or additional treatment includes lotion or shampoo permethrin 1%, lotion malathion 0.5%, tea tree oil, topically yellow mercuric oxide 1% and fluorescein 20% [7,8,12-14].
Antiparasitic agents such as natural pyrethrins, pyrethroids, and lindane may also be prescribed. Treatment of affected hairy parts of the body with the use of topical antiparasitic agents and/or shaving is mandatory [2].

Conclusion

Phthiriasis palpebrarum can be easily diagnosed by careful slit-lamp examination of the margins of the eyelids and eyelashes. There are several modalities of treatment, depending primarily on the degree of infestation and the age of the patient. Mechanical removal with forceps is a simple, effective and inexpensive way of treating this parasitosis.

Conflict of interest statement. None declared.

References

1. Anane S, Malek I, Kamoun R, Chtourou O. Phthiriasis palpebrarum: diagnosis and treatment. *J Fr Ophtalmol* 2013; 36(10): 815-819. doi: 10.1016/j.jfo.2013.03.018.
2. Badri T, Hafsi W. Phthiriasis palpebrarum. [Updated 2020 Jan 22]. In: StatPearls [Internet]. *Treasure Island (FL): StatPearls Publishing* Jan 2020.
3. Mishra C, Kim U, Dheera MS. Combined treatment modality for phthiriasis palpebrarum. *Indian J Med Microbiol* 2019; 37(2): 296-297.
4. Yi JW, Li L, Luo DW. Phthiriasis palpebrarum misdiagnosed as allergic blepharoconjunctivitis in a 6-year-old girl. *Niger J Clin Pract* 2014; 17(4): 537-539. doi: 10.4103/1119-3077.134063.
5. Ozer AP, Kabataş UE, Gurkan A, Kurtul EB. Treatment of phthiriasis palpebrarum mimicking conjunctivitis in a newborn. *Indian J Pediatr* 2016; 83(7): 730-731.
6. Wu N, Zhang H, Sun YF. Phthiriasis palpebrarum: A case of eyelash infestation with Pthirus pubis. *Exp Ther Med* 2017; 13(5): 2000-2002. doi: 10.3892/etm.2017.4187.
7. Dohvoma VA, Mvogo SRE, Atangana PJA, *et al*. Phthirus pubis infestation of the eyelids presenting as chronic blepharoconjunctivitis in a 6-year-old girl: A Case Report. *Case Rep Ophthalmol* 2018 r; 9(1): 30-34.
8. Karabela Y, Yardimci G, Yildirim I, *et al*. Treatment of phthiriasis palpebrarum and crab Louse: petrolatum Jelly and 1% permethrin shampoo. *Case Rep Med* 2015; 2015: 287906.
9. Khan T. Phthiriasis palpebrarum presenting as anterior blepharitis. *Indian J Public Health* 2018; 62(3): 239-241. doi: 10.4103/ijph.IJPH_296_17.
10. Altınsoy F, Alver O, Doganay S. A rare case of blepharitis: Phthiriasis palpebrarum. *Turkiye Parazitol Derg* 2018; 42: 90-92.
11. Veraldi S, Pontini P, Nazzaro G. Phthirus pubis infestation of the scalp: A case report and review of the literature. *Korean J Parasitol* 2018; 56(5): 487-489. doi: 10.3347/kjp.2018.56.5.487.
12. Askenazi I, Desatnik H, Abraham FA. Yellow mercuric oxide: a tretament of choice for phthiriasis palpebrarum. *BJO* 1991; 75: 356-358.
13. Lin YC, Kao SC, Kau HC, *et al*. Phthiriasis palpebrarum: An unusual blepharoconjunctivitis. *Zhonghua Yi Xue Za Zhi (Taipei)* 2002; 65(10): 498-500.
14. Vandeweghe K, Zeyen P. Phthiriasis palpebrarum: 2 case reports. *Bull Soc Belge Ophtalmol* 2006; (300): 27-33.

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Case report

GANGLIOGLIOMA ASSOCIATED WITH FOCAL EPILEPSY

ГАНГЛИОГЛИОМ ПОВРЗАН СО ФОКАЛНА ЕПИЛЕПСИЈА

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Abstract

Although rare, gangliomas represent the most common tumor entity in young patients suffering from focal epilepsy [1,2].
The current World Health Organization (WHO) classification defines ganglioglioma (GG) as a neoplasm composed of neural (ganglion cells) and glial elements, with both components being neoplastic [3].Ganglioglioma accounts for 0.4% to 9% of primary brain tumors and has been described in all parts of the central nervous system, but most commonly comes to clinical attention when present in the cerebral hemispheres, particularly in the temporal lobe [4,5].
We present a 13-year-old boy with repetitive focal seizures. The implemented EEG revealed right focus ofspike-wave complexes. Contrast-enhancedmagnetic resonance showed findings of TU lesion in the right middle temporal lobe. The patient underwent tumor excision. Patohistological diagnosis of the resected tumor was ganglioglioma. Postoperatively, the patient wasseizure-free, but the control EEG wasthe same asthe first EEG.
In patients with ganglioglioma the appropriate treatment strategy involves not only the complete surgical extirpation of the tumor, but also relatively early surgical intervention, because such an approach provides maximum chance of an epilepsy cure [6].

Keywords: ganglioglioma, focal epilepsy, temporal lobe

Апстракт

Иако се ретки ганглиоглиомите се најчестиот туморски ентитет кај млади пациенти кои страдаат од фокална епилепсија.
Тековната класификација на Светската Здравствена Организација (СЗО), ганглиомот (ГГ) го дефинира како неоплазма составена од нервни (ганглиски клетки) и глијални елементи, при што и двете компоненти се неопластични.
Ганглиоглиомот учествува со 0,4% до 9% од примарните тумори на мозокот и е опишан во сите делови на централниот нервен систем, но најчесто има клиничко значење кога е присутен во церебралните хемисфери, особено во темпоралниот лобус [4,5].
Ние претставуваме случај на 13 годишно момче кое беше упатено на нашата клиника поради повторувачки фокални напади. Реализираното ЕЕГ беше со наод на десностран фокус на шилец-бран комплекси. Ние реализиравме магнетна резонанца со контраст со наод на туморска лезија во десниот, среден темпорален лобус. Пациентот беше подлегнат на туморска ексцизија. Патохистолошката дијагноза на ресекцираниот тумор беше ганглиоглиом. Постоперативно пациентот е без напади, но контролното ЕЕГ е исто како и првото ЕЕГ.
Кај пациентите со ганглиоглиом соодветната стратегија за третман вклучува не само целосна хируршка екстирпација на туморот, туку и релативно рана хируршка интервенција, бидејќи таквиот пристап обезбедува максимална можност за лекување на епилепсијата.

Клучни зборови: ганглиоглиом, фокална епилепсија, темпорален лобус

Introduction

Brain tumors, mostly low-grade ones, are associated with epilepsy in more than half of the cases. Epileptic seizure incidence varies according to tumor location and histotype.
Gangliogliomas (GG) are the most common neoplasms causing chronic focal epileptic disorders. GG can occur in any part of the central nervous system, although the temporal lobe is the most common location, followed by the frontal lobe, the optic pathway, the spinal cord, the brainstem, the cerebellum and the pineal gland.
Gangliogliomas predominantly occur in young patients. The majority of patients present with a history of earlier

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symptoms, such as focal epilepsies. There is a prevalence of male compared to female patients.
Epilepsy associated with ganglioma is generally poorly controlled by antiepileptic drugs while it is extremely responsive to surgical treatment [7].
The aimof this study was to present anearly diagnosis of ganglioblastoma with full recovery from the condition and minimization of the consequences.

Case report

A 13-year-old boy was referred to our Clinic due to repetitive focal seizures during a year and a half. He had seizures with lack of consciousness, nausea and vomiting. The seizures became much more frequent in recent months. The neurological examination revealed normal findings. There was no history of febrile seizures in childhood or family history of seizures.
The implemented EEG revealed findings of basic brain activity with fast alpha wave and right focus of spike-wave complexes. (Figure 1 and 2).

Fig. 1. EEG first page

Fig. 2. EEG second page

Contrast-enhancedMagnetic resonance imaging scans demonstrated a cortical-based solid TU lesion in the right middle temporal lobe. TU lesion wasclearly demarcated and progressed to porencephaly that communicated with the right lateral ventricular trigonum. The lesion had a diameter of about 17 x 10 mm (Figure 3 and 4).

Fig. 3. MR of frontal brain

Fig. 4. MR of sagital brain

In view of clinico-electro-radiological concordance, the patientunderwent tumor excision. Histological diagnosis of the resected tumor was ganglioglioma.There were dysplastic neuronal cells, atypical glial cells, and neovascularization of the tumor lesion.Glial component was positive for glial fibrillary acidic protein (GFAP). The lesion stained positive with synaptophysin and chromogranin. The Ki-67 proliferation index was very low: 1%.
It was reported by the pathologist as a grade I lesion according to the World Health Organization (WHO) classification of tumors of the central nervous system.
In the first postoperative month, the patient wasseizure-free and on oxcarbazepine with a dosage of 600 mg

twice a day. Control EEG wassimilarto the first EEG with findings of basic brain activity offast alpha wave and right focus ofspike-wave complexes (Figure 5 and 6).

Fig. 5. Electroencephalogram after surgical intervention (page 1)

Fig. 6. Electroencephalogram after surgical intervention (page 2)

Discussion

Ganglioglioma is a common epileptogenic tumor, and surgery is currently considered as the treatment of choice. Epilepsy associated with GG is often resistant to pharmacological treatment and the temporal lobe is the most frequent location (in 60% of cases) [8].

Computerized tomography (CT) of brain is important for detection of calcifications and acute hemorrhage, while brain magnetic resonance (MRI) in used for early diagnosing of tumors.

Gangliogliomas (WHO grade I) are rare tumors of the central nervous system (CNS) that account for approximately 0.4% to 9% of primary CNS neoplasms, and they most frequently affect children and young adults, with a slight male predominance; however, it may develop at any age.

Gangliogliomas are benign and well-differentiated neuro-epithelial tumors composed of variable proportions of dysplastic neuronal elements (ganglion cells) and neoplastic glial elements. In 5% of cases, gangliogliomas show aggressive behavior and anaplastic histopathologic features characteristic of WHO grade III tumors [9]. Low-grade gangliogliomas can be cured surgically, and complete tumor resection is the most effective treatment. Radiotherapy is reserved for progressive or malignant tumors after surgical treatment.

Optimal treatment includes gross total resection. Adjuvant chemotherapy or radiation therapy is generally not indicated. Postoperative seizure control is associated with gross total resection of the mass, shorter duration of epilepsy, younger age at surgery, and the absence of generalized seizures. Most of the times, patients with GG have good prognosis [10,11].

Conclusion

Brain MRI is important and useful diagnosing method for early detection of brain tumors and helpful in early surgical treatment.

Gangliogliomas may become aggressive tumors with malignant transformation in either or both neuronal and glial components. In patients with ganglioglioma the appropriate treatment strategy involves not only the complete surgical extirpation of the tumor, but also re-latively early surgical intervention, because such an approach provides the maximum chance of an epilepsy cure [12].

Conflict of interest statement. None declared.

References

1. Lucas JT Jr, Huang AJ, Mott RT, *et al*. Anaplastic ganglioglioma: a report of three cases and review of the literature. *J Neuro-oncol* 2015; 123: 171-177.
2. Thom M, Blumcke I, Aronica E. Long-term epilepsy-associated tumors. *Brain Pathol* 2012; 22: 350-379.
3. Louis DN, Perry A, Reifenberger G, *et al*. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; 131(6): 803-820.
4. Rajneesh KF, Binder DK. Tumor-associated epilepsy. *Neurosurg Focus* 2009; 27: E4.
5. Louis DN, Ohgaki H, Wiestler OD, *et al*. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; 114: 97-109.
6. Giulioni M, Galassi E, Zucchelli M, Volpi L. Seizure outcome of lesionectomy in glioneuronal tumors associated with epilepsy in children. *J Neurosurg* 2005; 102: 288-293.
7. Giulioni M, Rubboli G, Marucci G, *et al*. Seizure outcome of epilepsy surgery in focal epilepsies associated with temporomesial glioneuronal tumors: lesionectomy compared with tailored resection. *J Neurosurg* 2009; 111: 1275-1282.
8. Kwan P, Arzimanoglou A, Berg AT, *et al*. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010; 51: 1069-1077.
9. Zanello M, Pages M, Tauziede-Espariat A, *et al*. "Clinical, Imaging, Histopathological and Molecular Characterization of Anaplastic Ganglioglioma.". *J Neuropathol Exp Neurol* 2016; 75(10): 971-980.
10. Devaux B, Chassoux F, Landre E, *et al*. "Surgery for dysembryoplastic neuroepithelial tumors and gangliogliomas in eloquent areas. Functional results and seizure control". *Neurochirurgie* 2017; 63(3): 227-234.

11. Yang I, Chang EF, Han SJ, *et al*. Early surgical intervention in adult patients with ganglioglioma is associated with improved clinical seizure outcomes. *J Clin Neurosci* 2011; 18: 29-33.

12. Terrier LM, Bauchet L, Rigau V, *et al*. "Natural course and prognosis of anaplastic gangliogliomas: a multicenter retrospective study of 43 cases from the French Brain Tumor Database.". *Neuro Oncol* 2017; 19(5): 678-688.

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Case report

ACUTE APPENDICITIS ASSOCIATED WITH ENTEROBIUS VERMICULARIS – CASE REPORT

АКУТЕН АПЕНДИЦИТИС АСОЦИРАН СО ENTEROBIUS VERMICULARIS – ПРИКАЗ НА СЛУЧАЈ

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Abstract

Enterobius vermicularis, typically found in cecum, appendix or terminal ileum, is the cause of the most common helminthic infestation in humans. A 19-year-old female patient, with normal laboratory results, was admitted for urgent appendectomy via McBurney incision. After ligation and division of the inflamed appendix from the cecal basis, several viable and mobile *enterobius vermiculares* were identified. A short course of albendazole treatment was initiated and was interrupted on the second day as a result of the strong anaphylactic reaction. Contrast enhanced CT of the abdomen identified infundibulum of the gallbladder filled with iregular hyperdense liquid indicative for parasitic infestation. One month later, elective laparoscopic cholecystectomy was performed, and the removed gallbladder was sent for parasitological evaluation confirming non-viable worms. Infestation with *Enterobius vermicularis* obstructs the lumen of the appendix, causing contraction of the wall and results in appendicitis-like symptoms without signs of acute inflammation. In minority of cases, with pure pathological signs of inflammation a finding of *Eneterobius vermicularis* is incidental. There are two possible hypotheses regarding the exact mechanism of gallbladder involvement: hematogenous spread or direct migration through unhealthy intestinal tissue. It is recommended to thoroughly examine all appendiceal specimens for presence of this worm, in order to provide adequate anthelminthic therapy in case of infestation.

Keywords: *Enterobius vermicularis*, appendicitis, laparoscopic cholecystectomy

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Апстракт

Enterobius vermicularis, кој најчесто се наоѓа во цекум, апендикс или терминален илеум, е причина за најчестата инфестација со хелминти кај луѓето. 19-годишна пациентка, со нормални лабораториски наоди, беше хоспитализирана за итна апендектомија низ Мекбурнеова инцизија. По подврзување и разделување на воспалениот апендикс од базата на цекумот, беа идентификувани живи и подвижни ентеробиуси. Се одпочна со краток режим на Албендазол, кој се прекина вториот ден поради јака анафилактичка реакција. Компјутеризираната томографија на абдомен со контраст прикажа инфундибулум на жолно кесе исполнет со неправилна хипердензна течност индикативна за паразитарна инфестација. По еден месец, беше изведена елективна лапароскопска холецистектомија, извадено жолчно кесе беше паразитолошки евалуирано и се потврди присуство на неживи црви. Инфестација со Enterobius vermicularis го обструира луменот на апендиксот, предизвикувајќи контракции на ѕидот и резултира со симптоми слични на апендицит без знаци за акутна инфламација. Во мал број на случаи, со јасни патолошки знаци на инфламација, наодот на Enterobius vermicularis е чисто инциденталeн. Постојат две веројатни хипотези во однос на точниот механизам на зафаќање на жолчното кесе: хематогено ширење и директна миграција низ нездраво интестинално ткиво. Се препорачува темелно иследување на примероци од апендикс за присуство на овој црв, за да се обезбеди адекватна терапија во случај на инфестација.

Клучни зборови: *Enterobius vermicularis*, апендицитис, лапароскопска laparoscopic холецистектомија

Introduction

Enterobius vermicularis is the cause of the most common helminthic infestation in humans [1], mostly in young girls. The worms are typically found in cecum, appendix or terminal ileum adhered to the mucosa, while other locations are rare. Humans get infested via fecal-oral route, ingesting the eggs from contaminated hands, food or water. Ingested eggs hatch onto the stomach and transform into larvae, which then migrate to the cecum, maturing to adult worms. Adult male parasites are smaller than the female ones, which have specific genitals with granular and round-shaped characteristics.

Case report

A 19-year-old female patient, with a two-day history of anorexia, vomiting, fever and right lower quadrant pain, was admitted at our department. Initial laboratory results were within normal parameters, without elevation in the white cell count. An indication for urgent appendectomy was established and open retrograde appendectomy was performed via McBurney incision. Upon laparotomy, careful exploration of the abdominal cavity was performed.

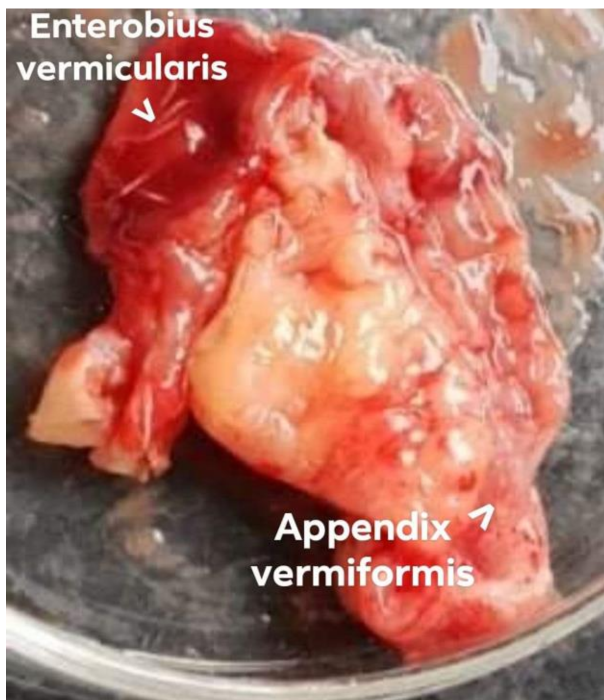

Fig. 1. Appendix with *Enterobius vermicularis*

There was abundant quantity of clear peritoneal fluid and phlegmonous appendicitis was identified. After ligation and division of the inflamed appendix from the cecal basis, several viable and mobile worms were identified. The specimen were sent for parasitological identification. Careful and directed history re-evaluation revealed sporadic episodes of anal pruritus, that were

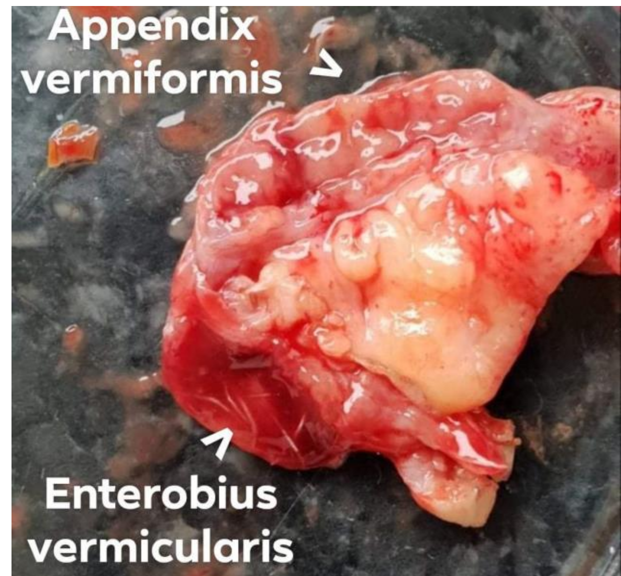

Fig. 2. Appendix with *Enterobius vermicularis*

omitted during the first examination due to sociological and cultural bias.
Scotch tape swab test from the anus in the morning was obtained and parasitological identification confirmed ova of *Enterobius vermicularis*.

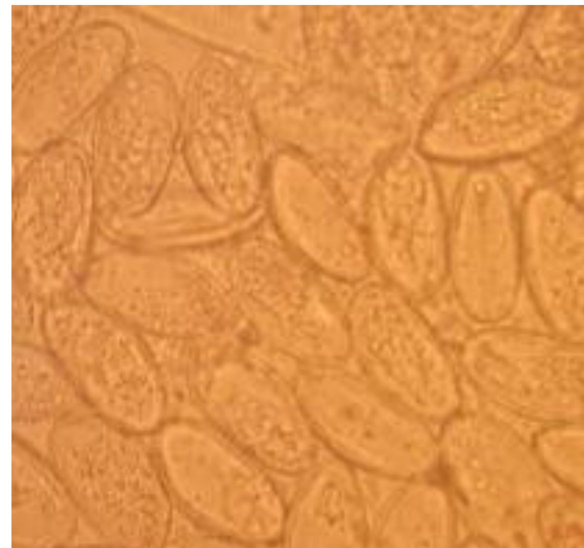

Fig. 3. Ova from scotch tape swab

A short course of albendazole treatment was initiated. On the second day of the albendazole therapy, a strong anaphylactic reaction occurred with tachycardia, tachypnea and serious dyspnea with cyanosis, and hypotension. The therapy was terminated and an antihistaminic was administered. The following day, four short dyspneic episodes with cyanosis were reported and a pulmonologist was consulted. Plain chest X-ray was indicated in order to exclude pulmonary enterobiasis or tuberculosis-like granuloma. The chest X-ray was insignificant and there was normal auscultatory finding. Contrast-enhanced CT of the lungs and abdomen was indicated. The liver had homogenous structure and

normal density. The gallbladder had smooth contours with normal thickness of the gallbladder wall. The infundibulum of the gallbladder was filled with irregular hyperdense liquid indicative for parasitic infestation. One month after the initial appendectomy was performed, elective laparoscopic cholecystectomy was indicated. A short course of albendazole therapy was conducted and laparoscopic cholecystectomy was performed. Considering the fact that there was a strong anaphylactic reaction during the first course of albendazole, prior to dissection of the gallbladder, an antihistaminic was administered. The cholecystectomy was uneventful and the removed gallbladder was sent for parasitological evaluation. The report confirmed absence of viable and mobile worms, while non-viable worms were identified in the bile from the gallbladder. The patient was followed for one year after the initial appendectomy and 6 Scotch tape swab tests from anus were obtained and they all excluded presence of ova of *Enterobius vermicularis*.

Discussion

The true relation between infestation with *Enterobius vermicularis* and appendicitis represents an issue of great debate. The most plausible explanation is obstruction of the lumen of the appendix that causes contraction of the appendix wall, resulting in appendicitis-like symptoms. Histological evaluation of the majority of specimens does not identify signs of acute inflammation [2]. On the other hand, in minority of cases, when there are pure pathological signs of inflammation, as in our case, it is reasonable to contemplate if finding of *Enterobius vermicularis* is purely incidental [3]. Some authors wonder whether the infestation with *Enterobius vermicularis* will cause appendicitis-like symptoms or real inflammation depends on the age of the patient [4]. They suggest that in adult patients it is more probable that the infestation could result in inflammation of the appendix with all the hallmarks, while in children it is more probable that the infestation would cause appendicitis-like symptoms, but without real inflammation of the appendix wall [5].
Infestation with *Enterobius vermicularis* represents the most common helminthic infestation and it usually affects children from 5 to 10 years of age. The typical localization of the worm is the ileum, cecum and colon, from where the female migrates to the anus to deposit the eggs and die. Ectopic localization of the *Enterobius* is very rare and there are only few reported cases of biliary infestation. There are two possible hypotheses regarding the exact mechanism of gallbladder involvement: hematogenous spread or direct migration through unhealthy intestinal tissue [6]. In our case, there was no previous history of abdominal surgery and the presence in the gallbladder was established few days after the initial appendectomy. Taking into consideration the facts that appendectomy is a procedure with minor damage to the intestinal wall, and that there is no history of previous surgeries, the most plausible mechanism is hematogenous spread via the portal system [7].

Conclusion

Acute appendicitis associated with *Enterobius vermicularis* infestation is very rare and, in majority of cases, the infestation causes only appendicitis-like symptoms without real pathological signs of inflammation. It is recommended to thoroughly examine all appendiceal specimens for presence of this worm, in order to provide adequate anthelminthic therapy in case of infestation.

Conflict of interest statement. None declared.

References

1. Shopov ST. Enterobius vermicularis infection associated with appendicitis, Meckel's diverticulitis and peritonitis. *Indian J Case Reports* 2020; 6(8): 423-425.
2. Lala S, Upadhyay V. Enterobius vermicularis and its role in pediatric appendicitis: protection or predisposition? *ANZ J Surg* 2016; 86(9): 717-719.
3. Akkapulu N, Abdullazade S. Is Eneterobius vermicularis infestation associated with acute appendicitis? *Eur J Trauma Emerg Surg* 2016; 42(4): 465-470.
4. Isik B, Yilmaz M, Karadag N, *et al*. Appendiceal Enterobius vermicularis infestation in adults. *Int Surg* 2007; 92: 221-225.
5. Vleeschouwers W, Hofman P, Gillardin JP, *et al*. Appendicitis-like clinical image elicited by Enterobius vermicularis: case report and review of the literature. *Acta Chir Belg* 2013; 113: 139-142.
6. Arkoulis N, Zerbinis H, Simatos G, Nisiotis A. Enterobius vermicularis (pinworm) infection of the liver mimicking malignancy: Presentation of a new case and review of current literature. *International J Surg Case Reports* 2012; 3: 6-9.
7. DickL, Hannay J. Enterobius vermicularis presentation during laparoscopic cholecystectomy. *J Surg Case Reports* 2017; 1: 1-2.

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Case report

ADENOID CYSTİC CARCINOMA TREATED WITH ELECTROCAUTERY–5-YEAR SURVIVAL

ТРЕТМАН НА АДЕНОИДЕН ЦИСТИЧЕН КАРЦИНОМ СО ЕЛЕКТРОКАУТЕР-5 ГОДИШНО ПРЕЖИВУВАЊЕ

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Abstract

Adenoid cystic carcinoma (ACC) is an uncommon neoplasm which arises from the major and minor salivary glands of the head and neck. Rarely, it can develop from secretory glands originating in the trachea, breast, lacrimal glands or other exocrine glands. We present a case of a fifty-years-old female patient with a polypoid adenoid ACC, growing from the middle of the left main bronchus causing obstruction of the bronchial lumen. Complete resection of the polypoid mass was accomplished using an electrocautery snare through the flexible bronchoscope, cauterizing the stalk in one attempt. The tumor was extracted in the manner of foreign body extraction, attaining complete recanalization and providing patency of the visible bronchial tree with no immediate or late complications. The follow-up bronchoscopy after 6 months found no signs of persistent or recurrent disease. The patient was followed at 6 and 12 months and every year for 5 years and no signs for local recidive or metastasis was found. We recommend considering endoscopic electrocautery for selected endobronchial or endotracheal cases of ACC, where surgical or oncologic treatment is not possible, in curative or palliative purposes.

Keywords: adenoid cystic carcinoma, endobronchial electrocautery, resection

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Апстракт

Аденоидниот цистичен карцином (АЦЦ) претставува редок ентитет, малигна неоплазма која вообичаено потекнува од големите и малите плунковни жлезди на главата и вратот. Поретко, АЦЦ може да се се развие и во секреторните жлезди во трахеата, дојките, лакрималните жлезди или други егзокрини жлезди. Презентираме случај на 50 годишна жена со полипоиден АЦЦ на петелка, прикрепен на средниот дел на левиот главен бронх, кој го обструира луменот на бронхот. Со помош на јамка за електрокаутер, низ флексибилен бронхоскоп, направена е ресекција на петелката на туморот во еден акт. Туморот е екстрахиран од бронхот по постапка на екстракција на страно тело. Постигната е комплетна реканализација на бронхот и обезбедена проодност на дисталното бронхално стебло до субсегменти, без рани и доцни компликации. Контролна бронхоскопија е направена по 6 месеци, при што не се видени резидуи ниту знаци за перзистентна или рекурентна болест. Болната е следена на 6, 12 месеци, а потоа еднаш годишно; не се детектирани знаци за рецидив или метастатски промени. Препорачуваме, кај строго селектирани случаи на локализирана форма на АЦЦ, кај кои не е можна хируршка или онколошка терапија да се земе во предвид ендобронхална ресекција со електрокаутер или аргон плазма, како третман или палијативна процедура.

Клучни зборови: аденодиен цистичен карцином, ендобронхална електрокаутеризација, ресекција

Introduction

Adenoid cystic carcinoma (ACC),is an uncommon neoplasm which is historically referred to as a cylindroma. ACC characteristically arises from the major and minor salivary glands of the head and neck. Rarely, it can develop from secretory glands originating in the trachea, breast, lacrimal glands or other exocrine glands. Only 0.04-0.2% of all primary lung tumors are identified as ACC, most are slowly developing central processes [1,2]. Three histologically distinct subtypes, cribriform, tubular, and solid, have been defined, which influence the overall prognosis of the disease [3].

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Tracheobronchial ACC most commonly presents in the fifth decade of life, but it can appear at any age from ten to ninety-six years and does not have a distinct predilection to a certain gender or smoking status [4]. Symptoms derive from the effects of local growth of the tumor, ranging from isolated dyspnea to unspecific complaints such as cough, often productive, hemoptysis, unilateral airway obstruction, wheezing or stridor. The bronchoscopic presentation varies from polypoid tumors with a longer longitudinal axis to broad-based intraluminal masses infiltrating the airway wall. Margins can be lobulated and irregular or smooth. Although ACC generally has a good prognosis, it is often diagnosed in an advanced stage when it is inoperable [5].
We present a case of a fifty years-old female patient with primary adenoid cystic carcinoma of the left mainstem bronchus. This is the first such case treated using endobronchial resection techniques in the Republic of Macedonia.

Case report

A fifty-years-old female patient was admitted to the Univesity Clinic for Pulmonology and Allergy in Skopje, Macedonia on April 20, 2015 with a chief complaint of dyspnea and wheezing. Her symptoms had been progressing since 2013, when she was diagnosed by bronchoscopy with a polypoid adenocarcinoma growing from the middle of the left main bronchus causing a complete obstruction of the bronchial lumen. Surgical treatment was proposed by the bronchoscopist in 2013, but the patient refused. She instead underwent several courses of chemotherapy at the Institute of Oncology. The patient stopped her treatment prematurely and instead chose to be managed using alternative medical treatments.
In April 2015 the patient was referred back to our Clinic because of persistent symptoms. There was no progression of the CT findings (Figure 1) when compared to radiologic imaging from 2013. Bronchoscopy was performed on April 29, 2015. A polypoid tumor with smooth margins attached at the middle part of the left mainstem bronchus with a stalk was identified, the tumor obstructed the bronchial lumen almost completely. Airway intervention was performed under general anesthesia. The patient was intubated with a 8.5 endotracheal tube, which allowed us to perform the procedure and ventilate the patient throughout the procedure without difficulty. Using an electrocautery snare through the flexible bronchoscope (Pentax, FB-18V, Olympus UES-30 Electrosurgical Unit, Olympus Corporation, Tokyo, Japan), the polypoid mass was resected and the stalk cauterized in one attempt (Figure 2). The tumor was grasped with forceps. After several attempts and a slight rotation, the entire tumor was extracted through the endotracheal tube in the manner of foreign body extraction, attaining complete recanalization and providing patency of the visible bronchial tree (Figure 3).

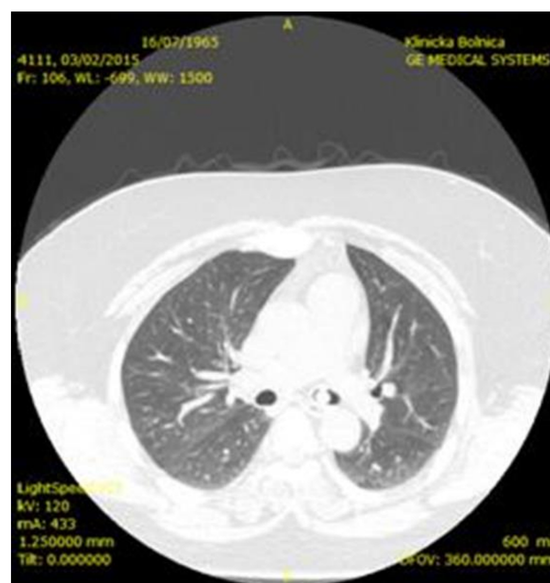
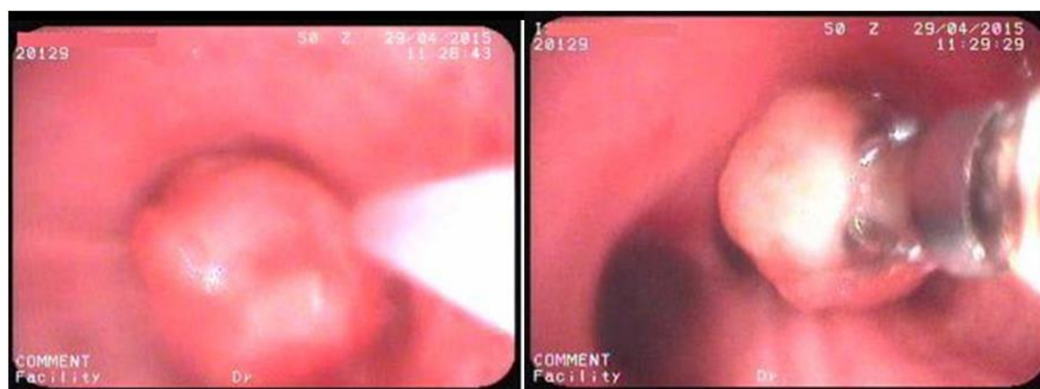


Fig. 1. Chest CT showing a polypoid structure in the main left bronchus



2. a. **2. b.**

Fig. 2. Resection and extraction of the tumor
2a Polypoid tumor of left main bronchus, almost completely obstructing the lumen. Approach to the tumor with electro-snare; 2b. Extraction of the tumor with forceps.

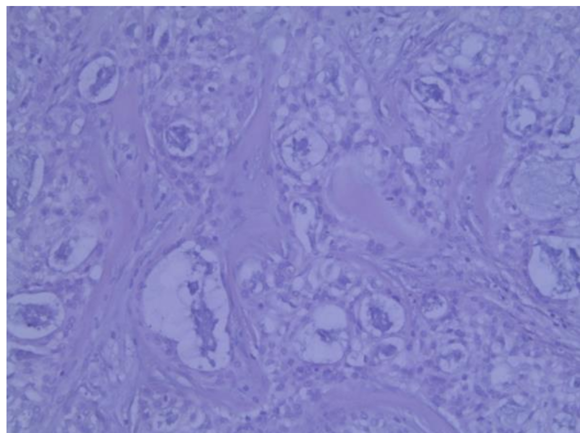


Fig. 3. Histopathology of the extracted mass. Adenoid cystic carcinoma - cribriform type

There was minimal blood loss (<5 ml) during the procedure. The patient tolerated the intervention very well and was extubated immediately postoperatively without complication.

The pathology was consistent with a well-differentiated adenoid cystic carcinoma with a low grade of malignancy. The tumor was reported as superficially covered with regular respiratory epithelium, under which a solid, glanduliform to cribriform tumor was visualized. It was formed of cubical cells with a moderate cytoplasm and monotoneous round to slightly oval nucleus. Mitotic figures were extremely rare; there was a focal presence of myoepithelial cells and no necrosis was detected. Immunochemical analysis revealed low proliferative index Ki67, around 3-4%, as well as a distinguished positivity to CKMNF116 and S100, and smooth muscle ACTIN showed focal accumulations of myoepithelial cells (Figure 4).

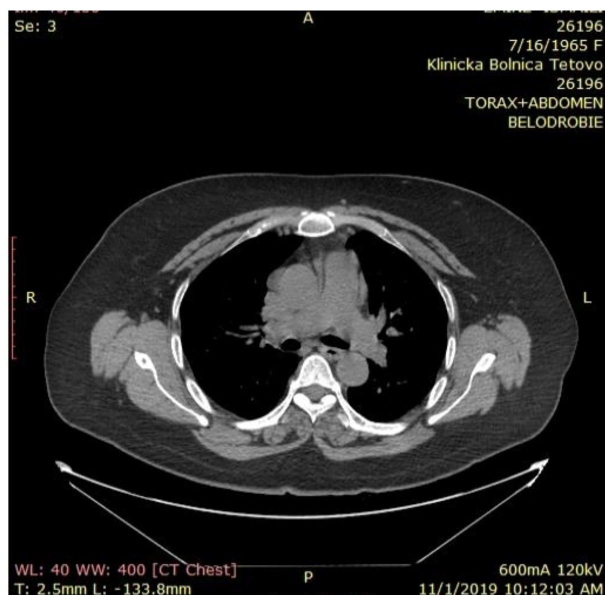


Fig. 4. Control chest CT after 4 years

The patient was presented to the Tumor Board at the Pulmonology and Allergy Clinic. She firmly rejected any further treatment, surgical or oncological. The decision of the Board was that the patient was to be followed-up closely. Postoperatively, the patient had no further respiratory symptoms, and was otherwise in excellent general condition. A follow-up bronchoscopy was performed on October 14, 2015, six months after the intervention. The bronchoscopy found no signs of persistent or recurrent disease. The airways were found to be normal. The patient was followed on every year for the last 5 years. She has had no clinical symptoms and further imaging did not identify any signs of local or distant metastases.

Discussion

Adenoid cystic carcinoma is an infrequent subtype of adenocarcinoma with specific histologic features and clinical characteristics. Rarely, ACC can present as a primary tumor of the lungs with a low grade of malignancy [1]. Sweeny and Thomas described only three cases of ACC out of 1500 lung cancer patients they reported [6].

There has been some correlation of the histological subtype with clinical presentation and prognosis of ACC with the cribriform subtype identified in our patient, suggested to have a more benign natural history [7]. Despite these attempts at clinical prediction based upon histological subtype, similar cribriform ACCs have been reported to have a more aggressive course [5,8]. Molecularly based approaches are being investigated to improve our understanding of the natural history of cancers. Due to its rare nature, our current kowledge remains limited. Lin *et al*. analyzed clinical outcomes data by evaluating DNA flow cytometric analysis and biomarkers of: p53, HER-2/neu, and COX-2. The authors demonstrated that overexpression of HER-2/neu, p53, and COX-2 may impact the prognosis in patients with stage I non-small cell lung cancer, but did not reveal a difference in patients with ACC [9]. In a study of 14 patients, Albers *et al*.. did not find a positive correlation between histologic grade and Ki-67 positivity [10].

Once diagnosed, surgical resection of ACC is the historical treatment of choice where possible. In clinically apparent aggressive subtypes or when metastases are identified, resection is often supplemented with radiotherapy in order to minimize the incidence of recurrence [11]. ACC is known to be resistant to chemotherapy, which is similar to the clinical course our patient experienced.

Management of the endobronchial manifestations of ACC can be accomplished using bronchoscopic techniques, with some examples cited in the literature. Chin *et al*. described a left mainstem bronchus ACC, which was resected using laser techniques, followed by an external beam radiotherapy with the goal of cure [12]. Jordanov *et al.* reported a successful resection of a tracheal ACC using rigid bronchoscopy with an electro-

cautery snare [13]. Endoscopic intervention is a valid option for endobronchial disease. The use of such techniques as the primary management is usually very uncommon other than in repeated interventions as in a palliative procedure. As the number of cases that present are infrequent, the attempt of a true clinical study is very difficult and therefore the choice to attempt the use of endobronchial techniques as the primary therapy must be considered carefully using tumor morphology and the invasion of the airways and other local structures as part of the decision making. Several cases have been published where resection was accomplished endoscopically, with various results. Sato *et al.* reported palliative treatment of locally invasive ACC of the left main bronchus with argon plasma resection which provided stabilization of the patient in 26 months [14]. The combination of local resection with electrocautery, brachytherapy and stent placement can provide a long-term survival in selected patients with tracheal and bronchial ACC, lasting up from five to ten years [15].

The case we have presented was of a patient with primary airway ACC. As the use of rigid bronchoscopy was currently unavailable to us, we modified our approach to use available airway stabilization (intubation) with endobronchial resection techniques (electrocautery snare). We were able to perform what we believed was a complete resection with no local residual disease. Using the facts that the local resection appeared to be complete, there were no detectable metastases or signs for local or distant invasion, the pathology was of a cribriform subtype, and the patient refused further invasive treatment, the decision was not to proceed with radiotherapy. The patient was reassessed clinically and bronchoscopically at six, twelve months after resection, and every year for the following 5 years, with no signs of residual or recurrent disease identified.

The recommended treatment for our patient would have been surgical, with sleeve resection of the left main bronchus, which is a more aggressive procedure. This type of surgery bears the risk of a potential need for a pneumonectomy due to surgical necessity identified at the time of the procedure and the patient did not accept the risk.

Conclusion

We have demonstrated a curative resection of endobronchial ACC, the first such case in the Republic of Macedonia. We recommend considering endobronchial resection techniques in cases of polypoid tracheobronchial ACC. In selected patients, endobronchial resection may be a sufficient therapy. Each case must be discussed with local multi-modality teams for group decisions regarding the potential use of adjuvant radiotherapy or more aggressive surgical interventions as the primary or supplemental treatments.

Conflict of interest statement. None declared.

References

1. Spencer H. Pathology of the lung. *4th ed. Oxford: Pergamon* 1985; 968-969.
2. Reid JD. Adenoid cystic carcinoma (cylindroma) of the bronchial tree. *Cancer* 1952; 5: 685-694.
3. Jaso J, Malhotra R. Adenoid cystic carcinoma. *Arch Pathol Lab Med* 2011; 135(4): 511-515. doi: 10.1043/2009-0527-RS.1.
4. Grenier PA, Kanne JP. Current approaches to chronic and acute airway diseases. In: Hodler J, KubikHuch RA, von Schulthess GK, ZollikoferChL, Diseases of the chest and heart 2015-2018. *Springer-Verlag Italia* 2015; 29-3.
5. Moran CA, Suster S, Koss MN. Primary adenoid cystic carcinoma ofthe lung. A clinicopathologic and immunohistochemical study of 16cases. *Cancer* 1994; 73: 1390-1397.
6. Sweeney WB, Thomas JM. Adenoid cystic carcinoma of the lung. *ContempSurg* 1986;28:97-100
7. Nomori H, Kaseda S, Kobayashi K, *et al*. Adenoid cystic carcinoma of the trachea and main-stem bronchus. Aclinical, histopathologic, and immunohistochemical study. *J Thorac Cardiovasc Surg* 1988; 96(2): 271-277.
8. Hattacharyya TB, Bahl A, Kapoor R, *et al*. Primary adenoid cystic carcinoma of lung:A case report and review of the literature, *Journal of Cancer Research and Therapeutics* 2013; 9 (2): 303.
9. Lin CM, Li AFY, Wu LH, *et al*. Adenoid cystic carcinoma of the trachea and bronchus-a clinicopathologic study with DNA flow cytometric analysis and oncogene expression. *Eur J Cardiothorac Surg* 2002; 22(4): 621-625.
10. Albers E, Lawrie T, Harrell JH, *et al*. Tracheobronchial adenoid cystic carcinoma: a clinicopathologic study of 14 cases. *Chest* 2004; 125(3): 1160-1165.
11. Ming-Ming HU, Ying HU, Jia-Bei HE, *et al*. Primary adenoid cystic carcinoma of the lung: Clinicopathological features, treatment and results. *Oncol Lett* 2015; 9(3): 1475-1481.
12. Chin HW, De-Meester T, Chin RY, *et al*. Endobronchial adenoid cystic carcinoma. *Chest* 1991; 100: 1464-1465.
13. Jordanov H, Andonov, Saltirova, *et al*. Curative resection of endotracheal adenoid cystic carcinoma with flexible bronchoscopy and electrocautery, *Turkish Respiratory Journal,Solunum Dergisi* 2013; Supplement, Vol. 15, p 23.
14. Sato K, Takeyama Y, Kato T, *et al*. Tracheal adenoid cystic carcinoma treated by repeated bronchoscopic argon plasma coagulation as a palliative therapy. *Ann ThoracCardiovasc Surg* 2014; 20 Suppl:602-5. doi: 10.5761/atcs.cr.12.02156. Epub 2013 Apr 11.
15. Ren H. Evaluation of local resection for primary tracheal tumor: a clinical analysis of 23 cases[Article in Chinese]. *ZhonghuaWaiKeZaZhi* 1993; 31(3): 141-142.

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Case report

MANAGEMENT OF HUGE PROSTATE ABSCESS IN A YOUNG PATIENT - A CASE REPORT

МЕНАЏИРАЊЕ НА ОГРОМЕН АПСЦЕС НА ПРОСТАТА КАЈ МЛАД ПАЦИЕНТ - ПРИКАЗ НА СЛУЧАЈ

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Abstract

A prostate abscess is a localized collection of purulent fluid within the prostate, which is often seen as a complication of acute bacterial prostatitis. A 20-year-old patient presented with a 14-day history of increased urinary frequency, dysuria, fever, left gluteal pain and obstipation. The patient claimed that he was not sexually active and did not have any chronic diseases or history of surgical procedures. The digital rectal examination was painful and a firm tumefaction with smooth wall was found. Complete blood count with differential was made and it showed elevated inflammatory markers (WBC-28 x10^9/L, CRP-220 mg/L). An abdominal ultrasound and pelvic MRI scan revealed a cystic lesion 49x67x94 mm found in the prostate. A needle was inserted inside the lesion via transrectal ultrasound (TRUS), and 95 ml of purulent drainage was aspirated. The patient was treated with broad-spectrum intravenous antibiotics – ceftriaxone and ciprofloxacin. The symptoms disappeared immediately after the procedure. Microbiological culture from the purulent specimen was made and it was positive on *Peptococcus*, sensitive on both antibiotics. The patient was discharged 4 days following the intervention.

Keywords: prostate abscess, TRUS aspiration, young patient

Апстракт

Апсцес на простата е локализирана колекција на пурулентна течност во простатата која често се појавува како компликација на акутен бактериски простатит. Дваесетгодишен пациент со 14-дневна анамнеза на зачестено уринирање, дизурија, треска, болка во левата глутеална регија и опстипација. Тврди дека не е сексуално активен, дека нема хронични болести и дека дотогаш не подлегнал на хируршка интервенција. На дигито-ректалниот преглед се почувствува тврда тумефакција со мазни ѕидови која беше болна на палпација. Беше направена комплетна лабораторија со диференцијална крвна слика која покажа покачување на инфламаторните маркери (WBC-28 x10^9/L, CRP-220 mg/L). Ехото на абдомен и магнетната резонанца на мала карлица открија цистична формација во простатата со големина 49x67x94 мм. Со помош на трансректално ехо (TRUS) формацијата се пунктираше и 95 мл пурулентна содржина беше аспирирана. Пациентот беше лекуван со интравенски антибиотици со широк спектар-ceftriaxone и ciprofloxacin. Симптомите исчезнаа веднаш по процедурата. Резултатот од микробиолошката анализа на пурулентниот примерок беше позитивен на *Peptococcus*, сензитивен на двата антибиотика. Пациентот беше отпуштен од болница по четири дена од операцијата.

Клучни зборови: апсцес на простата, ТРУС аспирација, млад пациент

Introduction

A prostate abscess is a localized collection of purulent fluid within the prostate, which is seen as a complication of acute bacterial prostatitis [1,2]. It can result in severe urosepsis and septic shock if appropriate measures are not taken [2]. The judicious use of antibiotics has led to a significant decrease in the number of patients with prostatic abscess.

A case presentation

A 20-year-old patient presented with a 14-day history of increased urinary frequency, dysuria, fever, left gluteal pain and constipation. The patient claimed that he was not sexually active and did not have any chronic diseases or history of surgical procedures. The digital rectal examination was painful and a firm tumefaction with smooth wall was found. Complete blood count with differential was made and it showed eleva-

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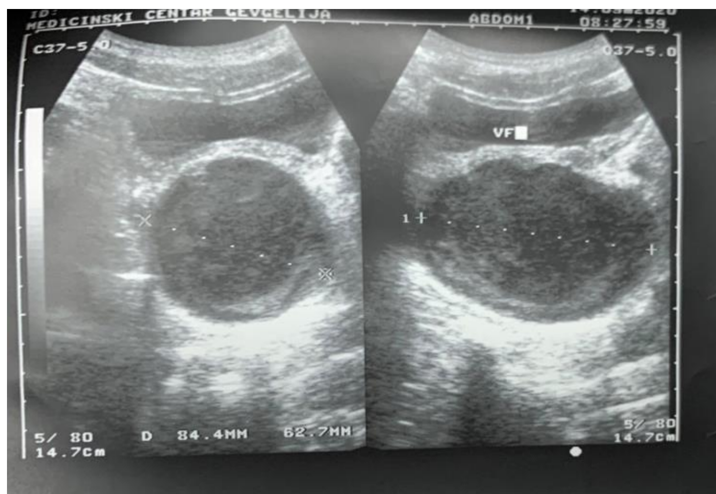

Fig. 1. Abdominal ultrasound

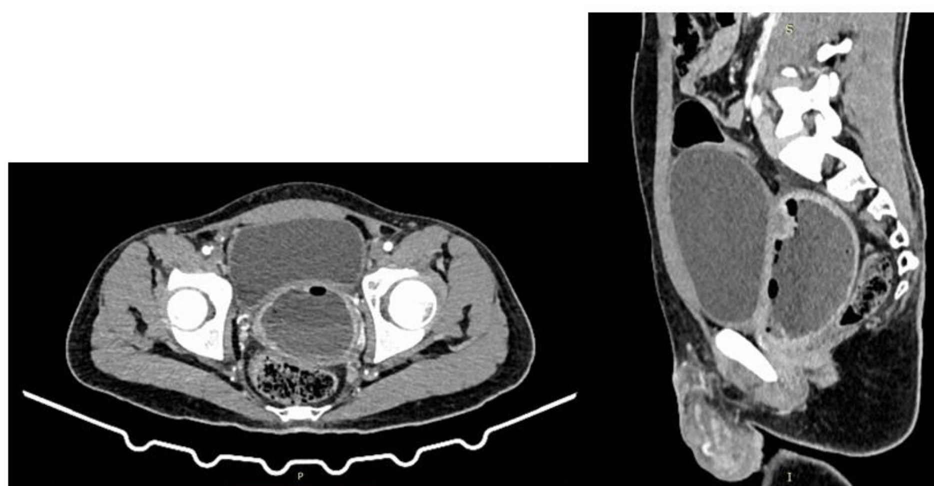

Fig. 2. Abdominal and pelvic CT scan

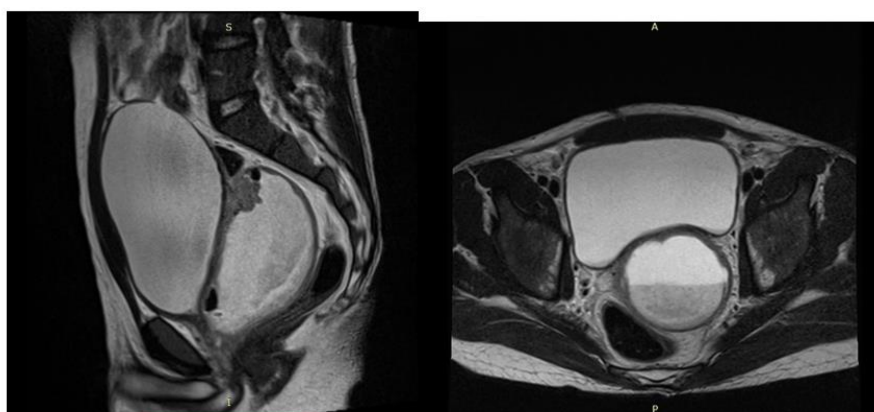

Fig. 3. Pelvic MRI scan

ted inflammatory markers (WBC-28 x10^9/L, CRP-220 mg/L). An abdominal ultrasound (Figure 1), an abdominal and pelvic CT scan (Figure 2), and pelvic MRI scan (Figure 3) revealed a cystic lesion 49x67x94 mm found in the prostate.

A needle was inserted inside the lesion via transrectal ultrasound (TRUS) (Figure 4), and 95 ml of purulent drainage was aspirated (Figure 5) and the symptoms subsided. The patient was treated with broad-spectrum intravenous antibiotics-ceftriaxone and ciprofloxacin. A control blood test showed decreasing inflammatory markers (WBC-10.5 x10^9/L, CRP-27.2 mg/L). Microbiological culture from the purulent specimen revealed *Peptococcus*, sensitive on both antibiotics. The patient

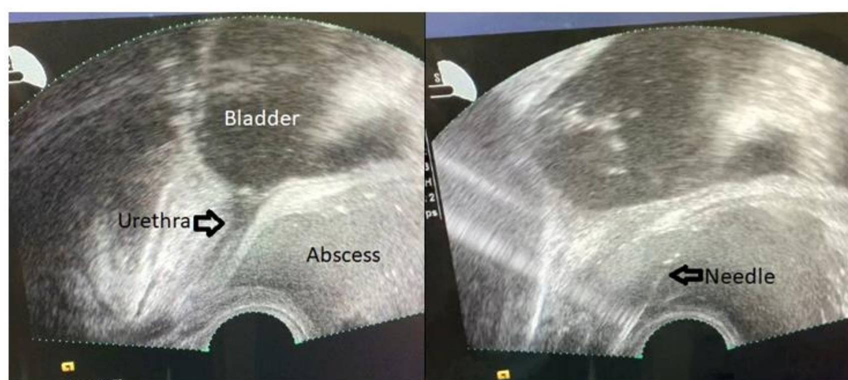

Fig. 4. TRUS insertion of the needle and aspiration of the abscess

Fig. 5. Purulent material aspirated from the abscess

was discharged 4 days following the intervention.

Discussion

A prostate abscess is manifested as a complication of prostatitis. Prostatitis is the most common reason for men under 50 to consult a urologist [3,4]. It may occur in patients who have chronic Foley or suprapubic catheters, diabetes, cirrhosis, end-stage renal disease, immunosuppressed patients including HIV patients who are not treated adequately for acute prostatitis [5], or as a complication following a prostate biopsy [6,7]. In the past, the common infecting organisms were *Neisseria gonorrheae*, *Staphylococcus aureus* and *Mycobacterium tuberculosis* [8]. Nowadays, *Escherichia coli* has been attributed to up to 70 % of the cases [5]. Other bacteria that may be responsible for the disease are *Klebsiella*, *Pseudomonas*, *Proteus*, *Enterobacter*, *Enterococcus* species, *Staphylococcus aureus* [2] and fungal causative organisms like *Blastomyces*, *Cryptococcus*, and *Nocardia* [1]. Prostate abscess occurs in 0.5% of all urologic diseases. Its mortality rate ranges between 1 to 16 percentages. Six percentages of patients with acute bacterial prostatitis develop a prostate abscess [1,5]. Older patients are more affected due to underlying risk factors; however prostate abscess due to sexually transmitted diseases may occur in younger males.

The most common symptoms are increased urinary frequency, dysuria, hematuria, burning sensation while urinating, perineal discomfort, acute urinary retention, fever, chills, myalgia, and low back pain [1,9]. A prostate abscess may present with the following physical examination findings: purulent urethral discharge, painful rectal examination, and possible fluctuant area in the prostate.

Determining whether the patient has prostatic abscess based on history and physical examination findings is difficult because the symptoms are nonspecific and overlap with other lower urinary tract pathology. In order to make the right diagnosis a complete blood count with differential, urine analysis, blood culture, and urine culture must be ordered immediately. Other examinations that can be performed are computed tomography (CT scan) of the abdomen and pelvis [10], magnetic resonance imaging (MRI) [11] and transrectal ultrasound (TRUS) [12,13].

Not all cases of prostate abscesses require a surgical procedure. However, it has been shown that surgical drainage limits antibiotics intake duration. Smaller abscesses which are less than 1 cm big respond well to medical management, whereas larger abscesses, bigger than 1 cm, respond better to either single or continuous drainage [12-14]. Conservative management includes administration of broad-spectrum antibiotics. The most commonly used antibiotics are: levofloxacin, intravenous carbapenem, broad-spectrum beta-lactam penicillin, or cephalosporin. A two-week long treatment with antibiotics is considered to be sufficient for a complete resolution. There are various treatment interventions for prostatic abscess. The most commonly used are trans-

rectal drainage (TRUS) [15,16], transurethral aspiration [9,17], and perineal approach of the abscess [5,9]. Each approach has its advantages and disadvantages, therefore which treatment will be applied depends on the surgeon's informed decision.

Prognosis of prostate abscess mostly depends on the timely diagnosis and treatment. Conservatively treated patients would need a longer duration of antibiotics intake. Underlying medical conditions contributing to abscess development have an influence over the outcome. Delay in diagnosis and treatment can lead to severe complications with significant morbidity and mortality. The infection can spread locally to adjacent tissues. Complications such as bacteremia and sepsis can cause septic shock and multi-organ failure and can increase the mortality.

Conclusion

Although prostate abscess occurs more often in older people and patients with chronic diseases, this case is a proof that it can also occur in young people who have no history of previous diseases or surgery. Early diagnosis and appropriate treatment are keys to a positive outcome.

Conflict of interest statement. None declared.

References

1. Reddivari AKR, Mehta P. Prostate Abscess. [Updated 2020 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing* Jan 2020.
2. Lee DS, Choe HS, Kim HY, *et al*. Acute bacterial prostatitis and abscess formation. *BMC Urol* 2016; 16(1): 38.
3. Vaidyanathan R, Mishra VC. Chronic prostatitis: Current concepts. *Indian J Urol* 2008; 24(1): 22-27. doi:10.4103/0970-1591.38598
4. Collins MM, Stafford RS, O'Leary MP, Barry MJ. How common is prostatitis? A national survey of physician visits. *J Urol* 1998; 159(4): 1224-8. PMID: 9507840.
5. Abdelmoteleb H, Rashed F, Hawary A. Management of prostate abscess in the absence of guidelines. *Int Braz J Urol* 2017; 43(5): 835-840.
6. Brede CM, Shoskes DA. The etiology and management of acute prostatitis. Nat Rev Urol. 2011; 8(4): 207-212.
7. Ackerman AL, Parameshwar PS, Anger JT. Diagnosis and treatment of patients with prostatic abscess in the post-antibiotic era. *Int J Urol* 2018; 25(2): 103-110.
8. Faris G, Metz Y, Friedman B, *et al*. [Prostatic abscess-diagnosis and treatment]. *Harefuah* 2008; 147(7): 594-5966, 663.
9. Jang K, Lee DH, Lee SH, Chung BH. Treatment of prostatic abscess: case collection and comparison of treatment methods. *Korean J Urol* 2012; 53(12): 860-864.
10. Thornhill BA, Morehouse HT, Coleman P, Hoffman-Tretin JC. Prostatic abscess: CT and sonographic findings. *AJR Am J Roentgenol* 1987; 148(5): 899-900.
11. Singh P, Yadav MK, Singh SK, *et al*. Case series: Diffusion weighted MRI appearance in prostatic abscess. *Indian J Radiol Imaging* 2011; 21(1): 46-48.
12. Ludwig M, Schroeder-Printzen I, Schiefer HG, Weidner W. Diagnosis and therapeutic management of 18 patients with prostatic abscess. *Urology* 1999; 53(2): 340-345.
13. Chou YH, Tiu CM, Liu JY, *et al*. Prostatic abscess: transrectal color Doppler ultrasonic diagnosis and minimally invasive therapeutic management. *Ultrasound Med Biol* 2004; 30(6): 719-724.
14. Aravantinos E, Kalogeras N, Zygoulakis N, *et al*. Ultrasound-guided transrectal placement of a drainage tube as therapeutic management of patients with prostatic abscess. *J Endourol* 2008; 22(8): 1751-1754.
15. Granados EA, Riley G, Salvador J, Vincente J. Prostatic abscess: diagnosis and treatment. *J Urol* 1992; 148(1): 80-82.
16. Vyas JB, Ganpule SA, Ganpule AP, *et al*. Transrectal ultrasound-guided aspiration in the management of prostatic abscess: A single-center experience. *Indian J Radiol Imaging* 2013; 23(3): 253-257.
17. Tiwari P, Pal DK, Tripathi A, *et al*. Prostatic abscess: diagnosis and management in the modern antibiotic era. *Saudi J Kidney Dis Transpl* 2011; 22(2): 298-301.

In memoriam

Проф. д-р Момчило Лазаревски
(1934-2020)

“ВИСТИНСКОТО ПАТЕШЕСТВИЕ КОН ОТКРИТИЈА НЕ СЕ СОСТОИ ВО ТРАГАЊЕ ПО НОВИ ПЕЈСАЖИ, ТУКУ ВО ГЛЕДАЊЕ СО НОВИ ОЧИ" (M. Proust)/ "Le véritable voyage de découverte ne consiste pas à chercher de nouveaux paysages, mais à avoir de nouveaux yeux"

Проф. д-р Момчило Лазаревски е роден на 6 февруари 1934 година во Куманово. Дипломира на Медицинскиот факултет во Скопје 1959 година, како најдобар студент на генерацијата и добива специјална нарада од Ректоратот на УКИМ. По едногодишен работен стаж во Општата болница во Гњилане, во 1961 година ја почна својата професионална патека на Клиниката за гинекологија и акушерство во Скопје, каде во 1965 година ја завршува специјализацијата по гинекологија и акушерство. Една година од специјалистичкиот стаж (1963/64), поминува на Втората хируршка клиника, а уште четири месеци на Уролошката Клиника во Белград. Во 1964 година, посетува курс за вагинална хирургија во Болницата „Carregi“ во Фиренца, под раководство на проф. Амрајх од Виена, со што станува дел од познатата Виенска школа за вагинална хирургија и добива можност да ја воведе оваа техника на Клиниката во Скопје. Владее одлично со француски и англиски јазик, а се служи и со руски и италијански јазик.

Во 1967 година добива стипендија од Владата на Франција за шестмесечен престој и усовршување во полето на генитален карцином и урогинекологија во Болницата “Hotel Dieux” во Париз, Франција. Во тек на 1970/71, престојува една година во Болницата „Broca“ во Париз како "Resident etranger des hopitaux de Paris", изучувајќи го проблемот на уринарна стрес инконтиненција, генитален пролапс и радикална хирургија на генитален карцином. Во текот на својата работа во болницата, ги забележува динамичките промени на позицијата на карличните органи на рутинските РТГ иследувања, кои ќе претставуваат основа на неговите понатамошни истражувања на полето на урогинекологијата. На Медицинскиот факултет во Париз во 1971 година ја брани својата докторска дисертација на тема „Etude critique des procedes d'opacification radiologique de l'urethre feminin" (Критичка студија на процедурите за радиолошките сенки на женската уретра) и се здобива со звањето “assistant etrangere” (асистент странец). Во Франција ги објавува и резултатите од радиоанатомското истражување во кое го опишува лизгачкиот пролапс на бешиката како оригинален ентитет во патологијата на пролапсот-откритие за кое се здобива со интернационално признание.

Во 1974 година, ја публицира својата докторска теза „Морфо-топографски, статички и динамички промени во малиот таз при генитален пролапс и уринарна стрес-инконтиненција“ и ја брани во 1976 година на Медицинскиот факултет во Скопје. Во неа ја обработува биомеханиката на карличните органи и ја формулира теоријата на неперманентна субуретрална структурна поддршка во физиологијата и патологијата на уринарната континенција и инконтиненција, како и патогенезата на гениталниот пролапс. Од ова истражување произлегуваат две оригинални хируршки техники за третман на стрес-инконтиненција кај жената, познати како „оригинална модификација на слинговидната колпосуспензија“ и „субуретрална дупликација на вагината“- зафати кои се публикувани во Југословенски и интернационални списанија и рутински се применуваат во многу светски медицински центри. Проф. д-р Лазаревски ја воведе и превентивната субуретрална потпора за превенција на стрес-инконтиненција по вагинална хистеректомија. Неговата неперманентно активна субуретрална потпора е употребена како основа за производство на артефициелните траки за решавање на гениталниот пролапс и уретрална инконтиненција. Неговите откритија резултираат со бројни стипендирани престои во светски центри, каде ја презентира и усовршува својата хируршка дејност (една година како визитинг професор и стипендист на Fulbright во Болницата „Johns Hopkins“ во Балтимор, САД-1976/77; професионална посета на Болницата „St. George“ во Лондон, Велика Британија во соработка со Британскиот Совет-1977;. Програма на Германскиот сервис за академска размена (DAAD), Болницата „ Charite“ во Берлин, Германија-1996 и др.).

Во соработка со дипл. маш. инг. И. Трчковски, во октомври 2000, го презентира и патентира пронајдокот „Дво-балонски латекс катетер за уретрографија“, кој и до денес наоѓа примена во секојдневната пракса и беше презентиран и на саемот „Еурека 2000“ во Брисел, Белгија, каде, во ноември 2000 добива специјална награда од Хрватската асоцијација на иноватори.

Во тек на работата на Клиниката за гинекологија и акушерство во Скопје, проф. д-р Лазаревски минува низ сите нивоа на управување, почнувајќи од шеф на Одделот за функционална гинекологија до директор на Клиниката. Во 1966 година, заедно со проф. д-р Шахпазов го основа Кабинетот за гинеколошка урологија и нарушувања на карличната статика, во 1986, Кабинетот за уродинамика, а во 1987 и Кабинетот за електростимулација на уринарни органи на Клиниката. По своето пензионирање, во септември 1999 година, продолжува да работи како консултант во Специјалната болница за гинекологија и акушерство-„Чаир“ во Скопје, во Општата болница во Куманово и Приватната општа болница „Ремедика“ во Скопје, каде ја продолжува својата едукативна мисија, формирајќи тимови за урогинекологија во секој од овие центри.

Проф. д-р Лазаревски беше извонреден едукатор и наставник. Наставната кариера ја започнува уште во тек на студиите, како демонстратор по анатомија и физиологија. Од 1969 година, активно е вклучен на Медицинскиот факултет, следејќи ги чекорите од асистент, до редовен професор (1988), шеф на Катедрата за гинекологија и акушерство (1987-1991) и продекан за настава (1984-1988). Несебично го пренесува своето знаење на своите ученици и ја формира следната генерација на македонската урогинеколошка школа преку лицето на неговите ученици тројцата наставници од школата по гинекологија и акушерство проф. Илиев, проф. Антовска и доцент Баџаков.

Осознавајќи ја важноста на професионалните релации, проф. д-р Лазаревски активно учествува во организирање на професионални организации и научна размена. Тој е активен член на Асоцијацијата на гинеколозии и акушери на Југославија, нејзин генерален секретар (1976-1980), претседател на Секцијата за гинекологија и акушерство на Македонија (1982-1986) и член на Македонската асоцијација на гинеколозии и акушери (МАГО) од нејзиното основање. Членува и во бројни интернационални здруженија како Интернационалната урогинеколошка асоцијација, Буенос Аирес, Аргентина од 1982, Интернационалното здружение за континенција ,Лондон, од 1989, Светската федерација на гинекологија и акушерство (FIGO), Европското здружение на гинекологија и акушерство, Балканската медицинска унија и станува почесен член на словенската и југословенската урогинеколошка секција. Тој еден од основачите и активен член на Интернационалната урогинеколошка асоцијација (IUGA) и движечка сила која ги внесува источноевропските земји во здружението.

Проф. д-р Лазаревски има публикувано над 150 научни трудови. Неговото откритие за лизгачки пролапс на бешиката како специфичен анатомски и патолошки ентитет е публикувано во 1972 година во Франција, во *J.Gyn.Obst.Biol.Repr* (1333, 1972); оригиналната класификација на радиолошките промени на пелвичните органи, во *Am.J.Obstet.Gynec* (122, 704, 1975). Во 1978 е соработник на Гонзалес Мерло при публикација на "Advances en obstetricia y ginecologia", Salvat editors, Барцелона, Шпанија. Коавтор е на учебникот „Гинекологија“ од Шуловиќ *и сор*, Медицинска книга Белград, на Второто издание на „Гинекологија и перинатологија“, од А. Курјак, Научна Библиотека Вараждинске Топлице 1995, и на второто издание на „Гинеколошка урологија “ од Петар Драча *и сор*., Нови Сад, 1997, кои беа основна литература на студентите по медицина и специјализантите во Југославија. Автор е и на Монографијата „Биомеханика на гениталниот пролапс и уринарна стрес инконтиненција“, Македонска ризница, Куманово, 2001, како и на едно поглавје “Le rôle méconnu des os du bassin: morpho-topographie pelvienne et genèse du prolapses“, во книгата „La Périnéologie...comprendre un équilibre et le preserver“, од J. Beco, J. Mouchel, и G. Nélissen) 1998, Odyssée 1372: Verviers, Belgium. Автор е на публикацијата „Спомените за развојот на Медицинскиот факултет во Скопје“, издадена по повод 40- годишнината од основањето на Медицинскиот факултет во Скопје, главен уредник на Годишниот преглед на Медицинскиот факултет во Скопје, еден од уредниците на „International Journal of Urogynecology and Pelvic Floor Changes“, САД, член на одборот на уредници на „Educatio Medica“ и „Ginecologia et Perinatologia“, од Хрватска.

Добитник е на бројни награди и признанија, од кои најзначајни се Медал од ФИГО за посебни заслуги во гинекологија и акушерство, Орден на трудот со златен венец, "Man of the year 1995" и Доживотен заменик гувернер на Американскиот биографски институт, Орден на заслуги 1996 на Англискиот Интернационален биографски центар во Кембриџ, Плакета на УКИМ како признание за посебен придонес во основањето, развојот и извршувањето на работата на Универзитетот.

Проф. д-р Лазаревски беше голем човек, работник, перфекционист. Неговите широки познавања од медицината, математиката, физиката, странските јазици и социјалните науки, придонесоа за неговиот богат професионален и социјален живот, организациските и едукативните способности. Имаше активен, прагматичен и иновативен ум, секогаш подготвен да ги решава дилемите поставени пред

него, давајќи алтернативен аспект на секој проблем, што често резултира со неочекувани, неконвен-ционални, но успешни решенија. Со истенчено чувство за детали, разбирање на „глобалната слика“ и дефинираниот осет за проблемите и потребите на другите, тој им беше професионален лидер, но и лична поддршка на своите блиски. Имаше татковски однос кон своите ученици, специјализанти и први соработници и силен заштитнички и татковски став кон своите пациенти, кои ги гледаше буквално како свои деца. Нежниот стил на ракување со ткивото и врвните мануелни и артистички капацитети проф. д-р Лазаревски го прават врвен хирург. Неговиот животен предизвик беше да создава нови нешта, да менаџира организации, да открива нови перспективи и хоризонти. Замина сакан од семејството, длабоко почитуван од најблиските соработници, многубројните пациенти и пријатели.

МАКЕДОНСКО ЛЕКАРСКО ДРУШТВО

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Ин мемориам

Проф. д-р Борислав Каранфилски
(1928-2020)

Проф. д-р Борислав Каранфилски е роден 1928 година во Куманово. Основно образование и гимназија завршил во родниот град, а студирал и дипломирал на Медицинскиот факултет во Скопје. За асистент по предметот патолошка физиологија е избран 1956 година, за доцент 1963, за вонреден професор 1968, а за редовен професор 1977 година.

Специјализирал во областа на патофизиологијата и нуклеарната медицина во повеќе центри во земјата и странство: Институт за нуклеарни науки во Винча (1957), Воено медицинска академија во Белград (1957), Carolinska Sjukhuset vo Stokholm (1959), Postgraduate Medical school во London (1959), Институт за постдипломско усовршување на лекарите во Москва (1960), Harvard Medical School во Бостон, САД (1964-1965), University of Edinburgh (1970) и University of Chicago (1974-75) година.

Во 1957 година ја завршил Школата за примена на радиоактивните изотопи во Институтот за нуклеарни науки "Борис Кидрич" во Винча.

Еден е од втемелувачите на Институтот за патофизиологија и нуклеарна медицина во Македонија, уште од неговото формирање и постојано е активен во неговиот развој. Посебен интерес и придонес има за основање на Амбулантата за заболувања на тироидната жлезда, која во континуитет ја развивал и унапредувал.

Од 1997 година е претседател на Националниот комитет за јоден дефицит, кога Комитетот е првпат основан со одлука на Министерството за здравство на Македонија, составен од поединци и претставници на органи и организации кои можат да дадат свој придонес за корекција на јодниот дефицит во Македонија. Благодарение на добро организирана, програмирана и координирана активност на Комитетот, Македонија оствари корекција на јодниот дефицит, што е постигнато во мал број земји, меѓу кои се: САД, Канада, Норвешка, Шведска, Финска, Швајцарија, Австрија, Бутан, Перу, Панама, Македонија и Јапонија (Vitti P.: Iodine deficiency disorders. Up-to-Date, 15: 2018).

Од 1997 година проф. Каранфилски е Национален координатор за Македонија на, порано International Council for Control of Iodine Deficiency Disorders (ICCIDD), а сега Iodine Global network (IGN). По пензионирањето, од 1997 година работел како консултант за заболувања на тироидната жлезда во приватната здравствена организација АТИК-КОР, сé до пред неколку месеци.

Постигнал забележителни резултати во научно-истражувачката работа, а особено во изучувањето на патологијата на тироидната жлезда. Успешно реализирал повеќе научно-истражувачки проекти финансирани од научни фондови во земјата и странство. Реализирал два истражувачки проекти од областа на јодниот дефицит во Босна и Херцеговина како експерт на УНИЦЕФ. Бил ментор на поголем број магистерски трудови и докторати. Бил наставник по предметите патофизиологија и нуклеарна медицина и изведувал настава за студентите по медицина, стоматологија и фармација, постдипломска настава на Медицинскиот факултет во Скопје, на Природно-математичкиот факултет (група биологија) во Скопје, на Медицинскиот факултет во Љубљана и во Школата за примена на радиоактивните изотопи на Институтот за нуклеарни науки во Винча.

Обемна е општествената активност на Проф. Каранфилски: бил продекан на Медицинскиот факултет во Скопје во два мандатни периоди, претседател на Советот на Медицинскиот факул-

тет, Директор на Институтот за патофизиологија и нуклеарна медицина, Претседател на Македонското лекарско друштво, проректор на Универзитетот во Скопје, претседател на Здружението за нукеарна медицина на Југославија, декан на Медицинскиот факултет во Скопје и претседател на Заедницата на медицинските факултети на Југославија.

Бил член на редакцијата на списанијата: Македонски медицински преглед, Годишен зборник на Медицинскиот факултет во Скопје, Radiologia Iugoslavica во Љубљана и на Меѓународниот научен совет на списанието Ендокринологија во Софија.

За научната, здравствената, наставната и општествената активност добил бројни признанија: Државната награда 11 Октомври за животно дело 1986 година, државната награда Гоце Делчев за постигнатите резултати во научно-истражувачката работа во 2006 година и државната награда Свети Климент Охридски како највисоко општествено признание за остварувања во областа на здравството во 2018 година.

Добитник е на Орден заслуги за народ со сребрена звезда 1963 година, Орден на трудот со златен венец 1969 година, Орден заслуги за народ со сребрени зраци 1987 година и Орден на Републиката со сребрен венец 1988 година.

Исто така е добитник на Повелба во знак на признание за вонреден придонес во развојот и унапредувањето на дејноста на Универзитетот "Кирил и Методиј" 1969 година, Диплома за долгогодишна успешна работа и постигнати резултати во лекарските организации од Сојузот на лекарските друштва на Југославија 1971 година, Диплома за посебни заслуги за развој на нуклеарната медицина во Југославија 1975 година, Повелба "Д-р Трифун Пановски" од Сојузот на здруженијата на лекарите на СРМ за исклучителни резултати во унапредувањето на медицинската наука, практика и развој на здравствената заштита во Македонија во1985 година, Повелба на Институтот за патофизиологија и нуклеарна медицина на Медицинскиот факултет во Скопје како признание за воведувањето и развојот на нуклеарната медицина во Македонија 1988 година, Благодарница од Македонско лекарско друштво за посебни заслуги во здравствената заштита во Македонија во 1977 година, Златна плакета од Медицинскиот факултет во Скопје 1997 година, плакета во знак на признание за основањето, развојот и извршувањето на задачите на Универзитетот "Кирил и Методиј" во Скопје 1984 година, Плакета за придонес во развојот на високообразовната и научната дејност и афирмација на Медицинскиот факултет во земјата и странство, по повод 70-годишниот јубилеј на Медицинскиот факултет во Скопје 2017 година и други.

МАКЕДОНСКО ЛЕКАРСКО ДРУШТВО

УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (e-mail) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Изводокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со изводокот, треба да се достават и до 5 клучни, индексни зборови.

Изводокот на англиски јазик мора да е со содржина идентична со содржината на изводокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се доставаат до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):
а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.
б) заеднички автор
GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.
в) ***без автор -*** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).
г) ***поглавје во книга или монографија***
Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

Адресата на Редакцијата
Даме Груев бр. 3
Градски ѕид блок II,
1000 Скопје,
Тел.: ++ 389 02 3162 577

Електронска адреса (Е-маил): mld@unet.com.mk

Известување за членовите на МЛД

Сите што сакаат и натаму да го добиваат списанието треба да ја имаат уплатено членарината за 2021 година во висина од 600 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или на меил.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД - 3162 557.