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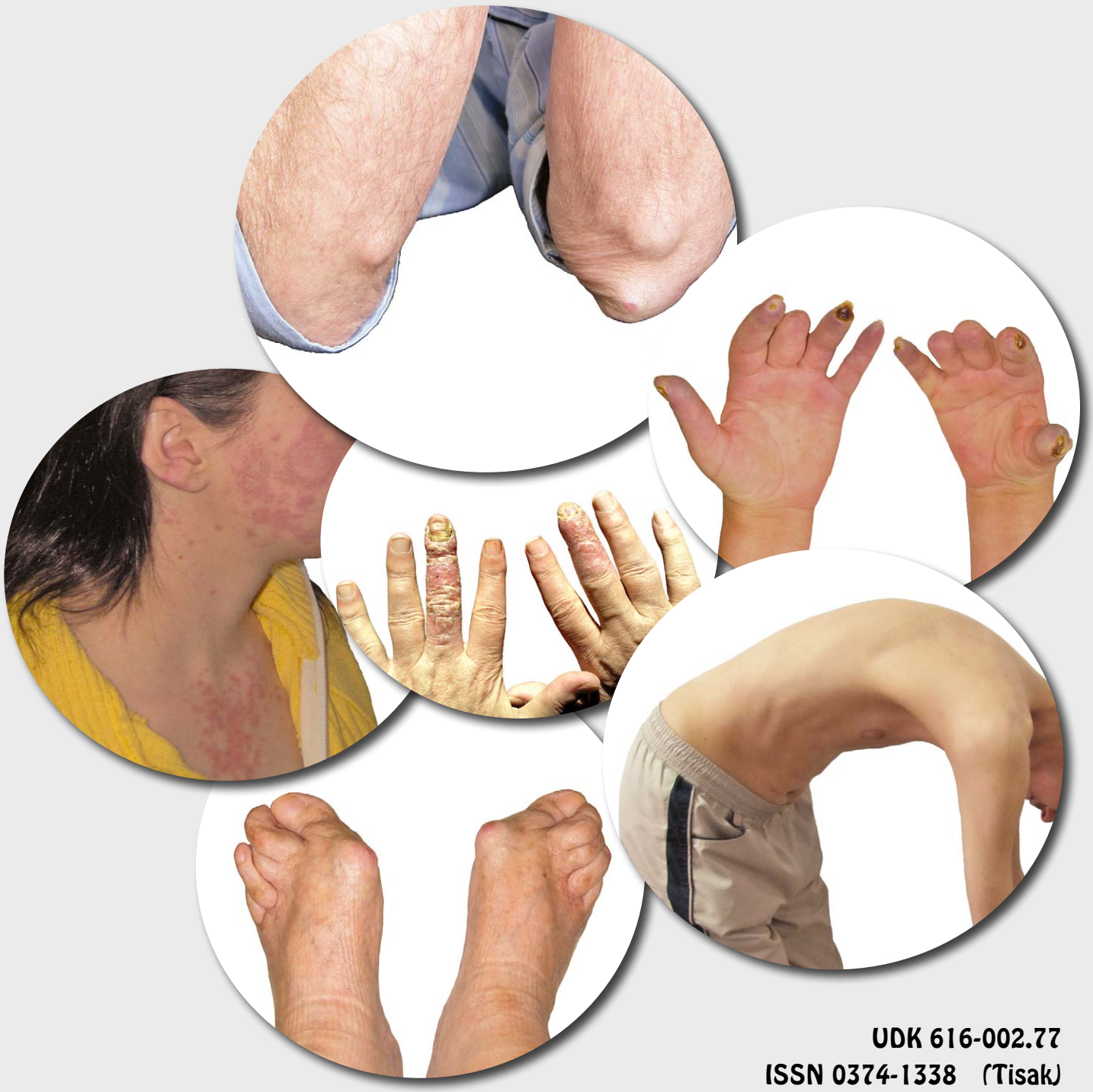

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ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

TREATMENT OF GIANT CELL ARTERITIS USING TOCILIZUMAB*

LIJEČENJE ARTERITISA DIVOVSKIH STANICA TOCILIZUMABOM*

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Abstract

Giant cell arteritis (GCA) or temporal arteritis (TA) is a large-vessel vasculitis of the elderly which, if untreated, can lead to blindness. Glucocorticoids (GCs) remain the main treatment, but high-dose and long-term use can lead to serious side effects. Tocilizumab (TCZ) is increasingly used as an alternative steroid-sparing treatment option with promising results. This case series presents three GCA patients with a refractory form and/or at high risk for side effects treated with TCZ due to diagnoses of glaucoma and osteoporosis. Two of the patients responded to the treatment with good results. All three patients are elderly females who initially presented with classic symptoms of headache and/or vision loss. The first patient also presented with fever, and the second with jaw claudication. Both of them were treated with pulses of GCs, but since the first also had osteoporosis with vertebral fractures, and the second had glaucoma and remained on high doses, TCZ was introduced. Both patients have since been stable. After approximately five years, the third patient developed TA with rheumatic polymyalgia, which was successfully treated with GCs. Later on TCZ was introduced as GCs could not be discontinued in consideration of the presence of osteoporosis and glaucoma. TCZ was discontinued after the patient developed neutropenia. Our case series presents two successful cases of treating GCA patients with TCZ, solidifying the recommendations for TCZ as a viable option for refractory disease and patients at high risk for side effects.

Key Words: Giant cell arteritis – diagnosis, drug therapy; Temporal arteries – pathology; Glucocorticoids – adverse effects, therapeutic use; Antibodies, monoclonal, humanized – adverse effects, therapeutic use; Interleukin-6 – antagonists and inhibitors; Osteoporosis; Glaucoma

Sažetak

Arteritis divovskih stanica (gigantocelularni arteritis – GCA) ili temporalni arteritis (TA) vaskulitis je velikih žila u starijih osoba koji može uzrokovati sljepoću ako se ne liječi. Kao standardna terapija još se upotrebljavaju glukokortikoidi (GK), ali njihove visoke doze i dugotrajna primjena mogu dovesti do teških nuspojava. Tocilizumab (TCZ) se sve više rabi kao alternativna poštedna steroidna terapija s dojmljivim rezultatima. U ovom radu prikazujemo tri pacijentice koje boluju od GCA refraktornog oblika i/ili se smatraju visokorizičnima zbog dijagnoze glaukoma ili osteopo-

* This topic and work was previously presented as both an oral communication and poster during the 21st Congress of the Croatian Society of Rheumatology held in Šibenik, Croatia, on October 17-20, 2018, and published under the title "Single Center Case Series: Management of Giant Cell Arteritis with Tocilizumab" in the accompanying congress journal Reumatizam, 66 (Supp 1): Oct 15. 2019. / Ova tema i znanstveni rad prethodno su predstavljeni u obliku usmene prezentacije i postera tijekom 21. godišnjega kongresa Hrvatskoga reumatološkog društva koji je održan u Šibeniku od 17. do 20. listopada 2018., a rad je pod nazivom „Serija prikaza bolesnika jednog centra: Liječenje gigantocelularnog arteritisa tocilizumabom" objavljen i u kongresnom broju časopisa „Reumatizam", svezak 66. (Supl 1) od 15. listopada 2019.

roze, a liječene su TCZ-om koji je u dvije od njih dao dobre rezultate. Sve tri pacijentice starije su žene koje su primarno navele klasične simptome glavobolje i/ili gubitka vida. Prva pacijentica imala je i febrilitet, a druga je imala i klaudikacije čeljusti. Obje su liječene pulsevima GK. S obzirom na to da je prva pacijentica imala i osteoporozu s prijelomima kralježaka, a druga glaukom uz neuspješno sniženje doze GK, uveden je TCZ te su obje pacijentice otad stabilne. U treće pacijentice razvio se TA nakon pet godina reumatske polimijalgije (PMR) uspješno liječene primjenom GK. Budući da ukidanje GK nije bilo moguće, s obzirom na dijagnoze osteoporoze i glaukoma TCZ je uveden poslije, ali je liječenje njime prekinuto nakon razvoja neutropenije. Naš prikaz dviju pacijentica oboljelih od GCA i uspješno liječenih primjenom TCZ-a podupire trenutačne smjernice koje TCZ navode kao održivu opciju za liječenje refraktornih bolesti i/ili bolesnika u kojih je viši rizik od razvoja nuspojava.

Ključne riječi: Arteritis divovskih stanica – dijagnoza, farmakoterapija; Temporalne arterije – patologija; Glukokortikoidi – nuspojave, terapijska uporaba; Humanizirana monoklonska protutijela – nuspojave, terapijska uporaba; Interleukin-6 – antagonisti i inhibitori; Osteoporoza; Glaukom

INTRODUCTION

Giant cell arteritis (GCA) is a systemic vasculitis of the large vessels affecting patients over the age of 50 years, commonly the elderly (1 – 3). The disease is often associated with rheumatic polymyalgia (RPM) (1 – 3). The cranial form is known as temporal arteritis (TA), which usually presents with headache, although jaw claudication and vision loss are also possible, apart from constitutional symptoms such as fever or malaise (1 – 3). Vision loss can lead to permanent blindness if untreated (1 – 3). The pathophysiology of the disease is unclear, but interleukin 6 (IL-6) is known to play a role (1 – 3). Diagnosis is made using imaging techniques, Doppler ultrasonography, computed tomography (CT), or magnetic resonance (MR) angiography, but temporal artery biopsy is the gold standard (1 – 3). Screening for involvement of other vessels in TA is done in some, but not all centers (1, 2).

Glucocorticoids (GCs) remain the main treatment. Usually prednisone at a dose of 1 mg/1 kg body mass is recommended, or pulses of methylprednisone at a dose of 1 g for more serious ocular symptoms to prevent blindness (1 – 4). Doses are subsequently tapered upon improvement until remission is achieved (1 – 4). However, high-dose or long-term use of GCs can lead to a number of side effects, including cataracts, increased intraocular pressure, hypertension, hyperglycemia, osteoporosis, gastritis, ulcers, immunosuppression, and infection. The majority of patients require one to two years of GC treatment before discontinuation (1 – 3, 5). Due to bone loss which can lead to fracture, additional treatment should be started, especially in those with osteoporosis, including biphosphonates, teriparatide, or denosumab (1). Because of these side effects, alternative steroid-sparing treatment is needed. Methotrexate, azathioprine, leflunomide, mycophenolate, cyclosporin, cyclophosphamide, and biologics like abatacept and tumor necrosis factor (TNF) α inhibitors, have shown moderate to weak, or negative results (1 – 5). These drugs have shown efficacy in the treatment of other rheumatologic diseases, such as rheuma-

UVOD

Arteritis divovskih stanica (gigantocelularni arteritis – GCA) sustavni je vaskulitis velikih krvnih žila koji najčešće pogađa pacijente starije dobi, nakon 50. godine (1 – 3). Ta se bolest često povezuje s reumatskom polimijalgijom (PMR) (1 – 3). Kranijalni oblik ove bolesti poznat je pod nazivom temporalni arteritis (TA) koji obično uključuje simptome poput glavobolje, iako su mogući i simptomi klaudikacije čeljusti i gubitka vida, uz uobičajene simptome vrućice ili slabosti (1 – 3). Ako se ne liječi, gubitak vida može uzrokovati trajnu sljepoću (1 – 3). Patofiziologija ove bolesti nije potpuno jasna, ali poznato je da protein interleukin 6 (IL-6) ima ključnu ulogu (1 – 3). Dijagnoza se postavlja s pomoću različitih tehnika snimanja, Dopplerove ultrasonografije, računalne tomografije (CT) ili magnetske angiografije (MRA), ali kao zlatni standard najčešće se upotrebljava postupak biopsije temporalne arterije (1 – 3). Testovi za probir krvnih žila u TA-u mogu se obaviti u nekim centrima, ali ne u svima (1, 2).

Kao glavna terapija još se rabe glukokortikoidi (GK). Uobičajeno se preporučuju primjena prednizona u dozi od 1 mg/kg tjelesne mase ili pulsna doza metilprednizona od 1 g kad se radi o težim očnim simptomima, a da bi se spriječila moguća sljepoća (1 – 4). Nakon poboljšanja stanja doze se snizuju sve dok se ne postigne remisija (1 – 4). No, previsoke doze ili dugoročna uporaba GK mogu uzrokovati velik broj nuspojava poput katarakta, povišenog intraokularnog tlaka, hipertenzije, hiperglikemije, osteoporoze, gastritisa, čireva, imunosupresije, infekcije, a kod većine pacijenata potrebno je liječenje tijekom jedne do dvije godine prije prekida terapije (1 – 3, 5). Zbog gubitka koštane mase koji može dovesti do lomova kostiju potrebno je uvesti dodatnu terapiju, osobito u pacijenata što boluju od osteoporoze, a najčešći lijekovi koji se pri toj terapiji rabe jesu bisfosfonati, teriparatidi ili denosumab (1). Takve nuspojave nalažu uvođenje alternativne poštedne steroidne terapije. Primjena metotreksata, azatioprina, leflunomida, mikofenolata,

Table 1. GCA patient case series presentation and treatment summary
Tablica 1. Sažeti pregled serije prikaza pacijentica koje boluju od GCA i njihova liječenja

Patient / Pacijentica	Age / Dob	Initial symptoms / Inicijalni simptomi	Comorbidities / Komorbiditet	Diagnosis based on / Dijagnoza postavljena na temelju	Treatment / Liječenje	GC / GK Side effects / Nuspojave	TCZ Side effects / Nuspojave
1	66	fever, headache, vision loss / vrućica, glavobolja, gubitak vida	asthma, hypertension / astma, hipertenzija	clinical, visual field / kliničke slike, vidnog polja	GC (initial pulses), TCZ / GK (inicijalne pulsne doze), TCZ	Yes (osteoporosis, vertebral fractures) / Da (osteoporoza, prijelom kralježaka)	Yes (mild neutropenia) / Da (blaga neutropenija)
2	81	vision loss, headache, jaw pain / gubitak vida, glavobolja, bol u čeljusti	glaucoma, discopathy, hypertension / glaukom, diskopatija, hipertenzija	clinical, ultrasound / kliničke slike, ultrazvuka	GC (initial pulses), TCZ / GK (inicijalna pulsna doza), TCZ	No / Ne	No / Ne
3	83	RPM, headache, jaw pain / PMR, glavobolja, bol u čeljusti	glaucoma, osteoporosis, verterbral fractures, hypertension / glaukom, osteoporoza, prijelom kralježaka, hipertenzija	clinical / kliničke slike	GC (initial 80 mg), TCZ / GK (inicijalna pulsna doza od 80 mg), TCZ	No / Ne	Yes (significant neutropenia) / Da (teška neutropenija)

Legend/Legenda: GC/GK – glucocorticoid/glukokortikoid; TCZ – tocilizumab

toid arthritis, systemic lupus erythematosus, and some vasculitides, but evidently the pathophysiology of GCA is distinct (3, 5).

Recent studies, in particular the GiACTA trial by Stone et al. in 2017 and others, showed that tocilizumab (TCZ), an IL-6 inhibitor, yielded great results in inducing remission and reducing relapse and cumulative steroid dose (1 – 5). However, questions on the long-term efficacy and safety of TCZ in GCA remain, including preventing blindness and increased risk for lower gastrointestinal tract perforation (1). TCZ was approved for GCA treatment by the European Commission (2) in September 2017. Notable follow-up studies have yet to emerge, but recently various case reports have surfaced looking at these questions. One such case report points out hypofibrinogenemia as a possible side effect which can increase bleeding risk; also, it reports neutropenia and thrombocytopenia as, albeit rare, side effects (6). Another case describes fatal tuberculosis reactivation in a GCA patient treated with TCZ, despite an initial negative screening result (7). TCZ was also shown to induce cutaneous sarcoidosis in a GCA patient, although this was also previously found in RA patients on TCZ (8).

ciklosporina, ciklofosfamida i bioloških lijekova poput abatacepta i inhibitora čimbenika tumorske nekroze alfa (TNF-α) pokazala je umjereno dobre, slabe ili negativne rezultate (1 – 5). Ovi su se lijekovi pokazali učinkovitima u liječenju drugih reumatskih bolesti poput reumatoidnog artritisa, sustavnog eritemskog lupusa i nekih slučajeva vaskulitisa, ali očito je da je patofiziologija GCA drugačija (3, 5).

Nedavno provedene studije, a posebice studija GiACTA koju su 2017. godine proveli Stone i suradnici, pokazale su da primjena tocilizumaba (TCZ), inhibitora IL-6, daje odlične rezultate pri induciranju remisije, smanjenju pojave relapsa i sniženju kumulativne doze steroida (1 – 5). Ipak, pojedina pitanja o dugoročnoj učinkovitosti i sigurnosti TCZ-a pri liječenju GCA i dalje su neriješena, uključujući njegovu ulogu u sprječavanju sljepoće i povišenom riziku od perforacije donjega gastrointestinalnog trakta (1). U rujnu 2017. Europska je komisija odobrila TCZ za liječenje GCA (2). Još nisu objavljene bitne popratne studije o učinku ovog lijeka, ali objavljeno je nekoliko prikaza bolesnika u kojima se raspravlja o prije navedenim pitanjima. U jednom od prikaza bolesnika kao moguće nuspojave ističu se hipofibrinogenemija, koja može povisiti rizik

Apart from TCZ as a steroid-sparing agent, other possibilities are being investigated, including ustekinumab, a human IgG1 kappa monoclonal antibody, which has also shown initial good results, but further investigation is required (3, 5). Studies are also already underway or planned for anakinra and gevokizumab (IL-1β inhibitor), rituximab (B cell depletion), and baricitinib (Janus kinase [JAK] inhibitor) (3).

As of March 2018, the Croatian Society for Rheumatology has recommended TCZ for GCA in disease relapse, in refractory disease where GCs could not be successfully tapered, and as an initial treatment in patients with comorbidities or at high risk (9). These recommendations describe refractory disease in patients where the initial GC dose could not be tapered after 4 to 6 weeks of treatment, or in patients who remained on a dose of prednisone over 0.2 mg/kg/day after 6 months, or on a dose over 0.1 mg/kg/day (9) after 12 months. TCZ can be considered as an initial treatment in patients with unregulated hypertension or diabetes, cardiovascular comorbidity, severe osteoporosis, glaucoma, a history of ulcer disease, or at high risk of developing side effects of GC use (9).

In our center, GCA is diagnosed approximately 4–5 times a year, and currently about 20–25 patients with GCA are being managed. TCZ was indicated in the three patients with refractory disease and comorbidities presented below.

CASE SERIES

Clinical characteristics and treatment summary of the patients are shown in Table 1.

The first patient, a 66-year-old female, presented with fever 40° C, and left-sided headache over the previous month, in July 2018. The patient had prior diagnoses of asthma and arterial hypertension. She was referred to a neurologist by her family doctor, having been previously examined by a pulmonologist for a respiratory tract infection and treated with antibiotics. Laboratory workup showed elevated C-reactive protein (CRP) (169 mg/L), and brain computed tomography (CT) showed no notable pathology. Upon excluding neurological disease, the neurologist referred the patient to an infectologist, and subsequently to a rheumatologist who discovered the patient also complained of vision loss. Temporal arteritis was immediately suspected, and the patient was hospitalized for treatment and further workup. The patient received an initial dose of methylprednisone 80 mg. On the following day, the patient was seen by a neuroophthalmologist, and visual field testing showed signs of optic neuropathy. General workup, including routine chest X-ray and abdominal ultrasound, along with more specific tests including color Doppler ultrasound of the temporal arteries and magnetic resonance imaging (MRI) of

od krvarenja, te neutropenija i trombocitopenija, iako su to rijetke nuspojave (6). U drugom se prikazu opisuje reaktivacija tuberkuloze sa smrtnim posljedicama u pacijenta koji je bolovao od GCA i liječio se primjenom TCZ-a, premda je prvotni rezultat njegova testa za probir bio negativan (7). Također, dokazana je uloga TCZ-a u induciranju kožnog oblika sarkoidoze u pacijenta koji boluje od GCA, iako je to prethodno prikazano u oboljelih od reumatoidnog artritisa što su primali TCZ (8).

Osim primjene TCZ-a kao sredstva s poštednim učinkom na primjenu steroida, istražuju se i druge mogućnosti, uključujući i primjenu ustekinumaba, ljudskog IgG1 kapa-monoklonskog protutijela, koje je također pokazalo dobre rezultate pri prvoj primjeni, ali iziskuje daljnja istraživanja (3, 5). Trenutačno se planiraju ili već provode studije o učinku anakinre i gevokizumaba (inhibitor IL-1β), rituksimaba (deplecija B-stanica) te baricitiniba (inhibitor Janusove kinaze – JAK) (3).

Od ožujka 2018. Hrvatsko reumatološko društvo preporučuje primjenu TCZ-a u pacijenata oboljelih od GCA kod kojih je došlo do pojave relapsa, i to pri refraktornim bolestima u kojima se doza GK ne može sniziti, te kao inicijalnu terapiju u pacijenata s komorbiditetima ili visokorizičnih pacijenata (9). U ovim preporukama opisuju se i pacijenti s refraktornim bolestima u kojih se inicijalna doza GK nije mogla sniziti nakon 4 do 6 tjedana liječenja, zatim pacijenti u kojih se i poslije 6 mjeseci primjenjivala doza prednizona viša od 0,2 mg/kg/dan, kao i oni kojima se nakon 12 mjeseci davala doza viša od 0,1 mg/kg/dan (9). TCZ se može razmatrati kao inicijalna terapija u pacijenata s nereguliranom hipertenzijom ili dijabetesom, kardiovaskularnim komorbiditetima, teškim oblikom osteoporoze, glaukomom, kao i u onih s poviješću čireva ili za koje postoji visok rizik od pojave nuspojava zbog primjene GK (9).

U našem KBC-u dijagnoze arteritisa divovskih stanica postavljaju se 4 – 5 puta na godinu, a trenutačno liječimo 20 – 25 pacijenata koji boluju od GCA. U ovom radu prikazujemo tri naše pacijentice kojima je propisan TCZ, a bolovale su od refraktornih bolesti i komorbiditeta.

PRIKAZI BOLESNICA

Sažetak kliničkih obilježja i liječenja pacijentica prikazani su u tablici 1.

U prvom prikazu radilo se o 66-godišnjoj pacijentici koja je na liječenje pristigla u srpnju 2018. sa simptomima vrućice od 40 °C i glavoboljom u lijevom dijelu glave što je trajala otprije mjesec dana. Pacijentici su u prošlosti dijagnosticirane astma i arterijska hipertenzija. Neurologu ju je uputio liječnik obiteljske medicine. Pacijenticu je prethodno pregledao pulmolog zbog in-

the aortic arch and its branches, did not show significant pathology. Densitometry verified the presence of osteoporosis. Due to progression of vision loss, in collaboration with a neuroophthalmologist the patient received pulses of methylprednisone 1,000 mg over three days with tapering, which resulted in significant regression of symptoms and normalization of CRP (2.4 mg/L). The patient was discharged on oral methylprednisone 56 mg with a tapering scheme, and ibandronic acid along with calcium and vitamin D for osteoporosis.

During follow-up the patient was stable until September, when she presented with leg weakness and numbness in the left leg. Due to the earlier diagnosis of osteoporosis and GC treatment, the patient was hospitalized for further assessment of possible vertebral fractures. MRI of the lumbosacral spine showed multiple vertebral compression fractures from L2 to L4, confirming the earlier suspicion. The patient was started on teriparatide and pain medication for osteoporosis with vertebral fractures, and discharged on prednisone 30 mg. Initiation of TCZ was planned as an alternative treatment due to the higher dose of GC and progression of osteoporosis with vertebral fractures. In October the patient was started on TCZ 162 mg subcutaneously (SC) once weekly, with a GC tapering scheme. She was followed up by a rheumatologist and neuroophthalmologist. As of November 2019, she has remained on TCZ, stable, without relapse or any serious side effects except for recent minor neutropenia, due to which the TCZ dosage has been reduced to biweekly application.

The second patient, an 81-year-old female, presented with right-sided vision loss and temporomandibular joint pain in March 2018. The patient had previously been diagnosed with cervical discopathy, arterial hypertension, and glaucoma. She was referred to hospital by her general ophthalmologist. She was examined by a neuroophthalmologist, and visual field testing confirmed optic neuropathy. Laboratory test results showed elevated CRP (102.1 mg/L). Temporal arteritis was diagnosed, and pulses of methylprednisone 1,000 mg were started. The following day, temporary artery ultrasound was performed showing arterial wall thickening of the right temporal artery. Temporal artery biopsy was suggested, but rejected by the patient. On the third day, the patient was hospitalized due to poor general condition. She was treated and observed over six days, then discharged on oral methylprednisone 64 mg with a tapering scheme. During follow-up, the patient was referred to a rheumatologist who hospitalized her for further investigation. As a part of additional workup, a routine abdominal ultrasound was performed, which was insignificant apart from gallstones. MRI cranial angiography was normal. Rheuma factor (RF),

fekcije respiratornog trakta te joj je propisao antibiotike. Laboratorijska obrada pokazala je povišen C-reaktivni protein (CRP) (169 mg/L), a računalna tomografija (CT) mozga nije pokazala znatnu patologiju. Nakon isključenja mogućnosti neurološke bolesti neurolog je pacijenticu uputio na pregled infektologu, a zatim reumatologu koji je otkrio da pacijentica ima i simptom gubitka vida. Odmah se posumnjalo na dijagnozu temporalnog arteritisa, a pacijentica je hospitalizirana radi liječenja i daljnje obrade. Pacijentica je primila inicijalnu dozu metilprednizona od 80 g. Sljedećeg dana pacijenticu je pregledao neurooftalmolog, podvrgnuta je ispitivanju vidnog polja te je otkriveno da pokazuje znakove optičke neuropatije. Opća obrada, koja je uključivala rutinsko rendgensko snimanje prsnog koša i ultrazvuk abdomena zajedno sa specifičnijim testovima poput ultrazvučnog snimanja temporalnih arterija obojenim doplerom i magnetsku rezonanciju (MR) luka aorte i njegovih grana, nije pokazala bitnu patologiju. Također, pacijentici je napravljena denzitometrija koja je pokazala znakove osteoporoze. U dogovoru s neurooftalmologom pacijentica je zbog uznapredovala gubitka vida primila pulsnu dozu metilprednizona od 1000 mg tijekom 3 dana, s postupnim sniženjem doze, što je rezultiralo znatnom regresijom simptoma i normalizacijom CRP-a (2,4 mg/L). Pacijentica je otpuštena s bolničkog liječenja s uputom da oralnim putem uzima metilprednizon u dozi od 56 mg i prati plan postupnog sniženja doze te da uzima ibandronatnu kiselinu, kalcij i vitamin D za osteoporozu.

Na kontrolnom pregledu utvrđeno je da je pacijentica stabilna. No, u rujnu su se pojavili simptomi poput slabosti u nogama i osjećaja utrnuća lijeve noge. Na temelju prije postavljene dijagnoze osteoporoze i liječenja GK-om pacijentica je hospitalizirana radi daljnje obrade, a zbog sumnje na moguće prijelome kralježaka. MR-om lumbalno sakralne kralježnice otkriveni su višestruki kompresivni prijelomi kralježaka L2 do L4, čime je potvrđena prethodna sumnja. Pacijentica je stavljena na terapiju teriparatidom i analgeticima za osteoporozu s prijelomima kralježaka te je otpuštena s bolničkog liječenja s uputom da uzima prednizon u dozi od 30 mg. Inicijalna terapija TCZ-om planirana je kao alternativna terapija zbog visoke doze GK i uznapredovale osteoporoze s prijelomima kralježaka. Pacijentica je u listopadu podvrgnuta terapiji TCZ-om u dozi od 162 mg koju je primala supkutano, jedanput na tjedan, u skladu s praćenjem plana postupnog sniženja doze GK. Pacijenticu su na kontrolnim pregledima pregledali reumatolog i neurooftalmolog, a od studenoga 2019. prima terapiju TCZ-om, stabilna je, bez pojave relapsa ili teških nuspojava, osim nedavne pojave blage neutropenije zbog koje je primjena doze TCZ-a snižena na jedanput svaka dva tjedna.

anti-cyclic citrullinated peptide (CCP), anti-nuclear antibodies (ANA), extractable nuclear antigen (ENA), and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Densitometry confirmed osteoporosis. The patient was discharged on methlyprednisone 40 mg and ibandronic acid, calcium, and vitamin D for osteoporosis.

The patient was further followed by a rheumatologist and neuroophthalmologist, but the GC dose could not be tapered below 32 mg without symptoms worsening, specifically that of left-sided vision loss, and since the patient was basically blind in the right eye, this was unacceptable. In July, the patient was considered for TCZ treatment by her rheumatologist. In October, after essential workup for biologic treatment, she was started on TCZ 162 mg SC once weekly. In the following months, TCZ was administered without any remarkable side effects, with regular check-ups by a rheumatologist and neuroophthalmologist, and GC was successfully tapered. As of November 2019, the patient has been stable on TCZ and methylprednisone 2 mg.

The third patient was an 83-year-old female followed by a rheumatologist since 2013 for RPM on methylprednisone, varying between 2 and 8 mg. The patient had previous diagnoses of arterial hypertension and glaucoma, and later developed osteoporosis, along with vertebral compression fractures, and cervical and lumbar discopathy. In March 2017 the patient was seen by a neurologist for neck pain which radiated to the occipital and parietal regions of the head as well as the mandible. She also complained of difficulty swallowing and left-sided ear pain. She had elevated CRP (120.6 mg/L). The patient was then referred to a rheumatologist who increased the methylprednisone dosage to 12 mg daily with a tapering scheme. During follow-up 2 weeks later she was clinically better, but symptoms worsened when the GC dose was tapered to 4 mg. At this point the patient was hospitalized for treatment and further workup under suspicion of temporal arteritis. An initial dose of methylprednisone 80 mg was administered. Routine chest X-ray and abdominal ultrasound, color Doppler ultrasound of the temporal, carotid, and vertebral arteries, and CT aortography were performed, and did not show any significant pathology. The neuroophthalmogist exam did not reveal optic neuropathy. RF, anti-CCP, ANA, ENA, and ANCA were negative. The patient was discharged on oral methylprednisone 32 mg with a tapering scheme, along with calcium and vitamin D for osteoporosis, as she did not tolerate alendronic acid and tetraparatide, which she had been taking previously. The patient was followed by a rheumatologist and remained stable on methylprednisone 4 mg. She was hospitalized in May 2018 for physical rehabilitation.

Drugi je prikaz 81-godišnje pacijentice koja je na liječenje stigla u ožujku 2018. sa simptomima gubitka vida u desnom oku i bolima u temporomandibularnom zglobu. Pacijentici su prije dijagnosticirani cervikalna diskopatija, arterijska hipertenzija i glaukom. Njezin oftalmolog uputio ju je na bolnički pregled. Ondje ju je pregledao neurooftalmolog, a ispitivanjem vidnog polja potvrđena je dijagnoza optičke neuropatije. Rezultati laboratorijskog ispitivanja otkrili su povišen CRP (102,1 mg/L). Pacijentici je dijagnosticiran temporalni arteritis i stavljena je na terapiju pulsnom dozom metilprednizona od 1000 mg. Sljedećeg dana napravljen je ultrazvuk temporalnih arterija na kojem je otkriveno zadebljanje arterijske stijenke u desnoj temporalnoj arteriji. Predložena je biopsija temporalne arterije, ali pacijentica je odbila podvrgnuti se tom postupku. Trećeg je dana pacijentica hospitalizirana zbog lošeg općeg stanja. Liječenje i praćenje stanja pacijentice trajali su šest dana, a zatim je otpuštena s bolničkog liječenja s uputom da oralnim putem uzima metilprednizon u dozi od 64 mg te da prati plan postupnog sniženja doze. Na kontrolnom pregledu pacijentica je upućena reumatologu koji je donio odluku o njezinoj hospitalizaciji radi obavljanja daljnjih pretraga. Kao dio dodatne obrade napravljen je rutinski ultrazvuk abdomena koji, osim otkrivanja žučnih kamenaca, nije dao nikakve bitne rezultate. MR kranijalna angiografija nije pokazala znatnija odstupanja. Reumatoidni faktor (RF), antitijela na cikličke citrulinirane peptide (anti-CCP), antinuklearna antitijela (ANA), antitijela na ekstrahirani nuklearni antigen (ENA) i antineutrofilna citoplazmatska antitijela (ANCA) bili su negativni. Denzitometrijom potvrđena je osteoporoza. Pacijentica je otpuštena s bolničkog liječenja s uputom da uzima metilprednizon u dozi od 40 mg te ibandronatnu kiselinu, kalcij i vitamin D za osteoporozu.

Pacijenticu su na kontrolnim pregledima pregledali reumatolog i neurooftalmolog, ali dozu GK nije se moglo sniziti ispod 32 mg bez pogoršanja simptoma, osobito gubitka vida u lijevom oku, jer je pacijentica bila gotovo slijepa na desno oko. Reumatolog je u srpnju počeo razmatrati da pacijenticu liječi primjenom TCZ-a. U listopadu je stavljena na terapiju TCZ-om u dozi od 162 mg koju je primala supkutano, jedanput na tjedan, nakon obvezatne obrade za biološko liječenje. Tijekom sljedećih nekoliko mjeseci terapija TCZ-om primjenjivala se bez pojave znatnih nuspojava te uz redovite preglede reumatologa i neurooftalmologa, a doza GK uspješno je snižena. Od studenoga 2019. pacijentica je stabilna i uzima terapiju TCZ-om i metilprednizonom u dozi od 2 mg.

Treći i posljednji u seriji jest prikaz 83-godišnje pacijentice koja je od 2013. godine odlazila na kontrolne preglede reumatologu zbog reumatske polimijalgije (PRM) te joj je propisana terapija metilprednizonom u

In March 2019, taking into consideration the patient's comorbidities and persistent GC use, TCZ was considered as an alternative GCA treatment option. Pre-biologic workup yielded a positive quantiferon test, and the patient was started on prophylactic isoniazid, followed by TCZ at the end of April 2019. The patient quickly developed neutropenia, and her liver enzymes became elevated, which could have been due to TCZ or isoniazid. As such, both drugs were discontinued as early as June 2019, after which the laboratory results normalized. The patient has remained stable on methylprednisone 4 mg, and is being routinely followed by a rheumatologist.

DISCUSSION

The three patients discussed in this case series from our center all presented with similar symptoms highly suggestive of GCA. The first two patients with vision loss along with other symptoms which fall within the domain of GCA (headache, jaw claudication, fever) were highly convincing, and therefore a temporal artery biopsy was not performed, as is common practice in our center, was not performed. Although temporal artery biopsy is still the gold standard for diagnosis, it seems that many centers, including ours, are moving more towards non-invasive imaging techniques, namely ultrasound, as opposed to biopsy. The third patient developed typical symptoms of GCA after an established diagnosis of RPM, and the association between these entities is well-known. It is worthy to emphasize that these patients, due to the nonspecific symptoms, are frequently referred to one or even two other specialists before reaching a rheumatologist. All patients were treated with GCs, the first two with pulses of large doses due to the expressed vision loss, and especially the second patient who had already lost vision in the right eye. As described in the case presentations, the patients were also evaluated for additional large vessel involvement, autoimmune disease, and paraneoplastic syndrome, but only temporal arteritis was found, along with osteoporosis that required treatment. All three cases, taking into consideration the high GC dose or long-term GC use as well as the risk factors including osteoporosis and glaucoma, warranted alternative steroid-sparing treatment. The first two patients have shown favourable clinical results on TCZ, effectively reducing or eliminating GC use, and remaining in remission for over a year, without relapse or serious side effects other than for the recent minor neutropenia in one patient. Unfortunately, the third patient developed neutropenia almost immediately, leading to discontinuation of the drug. Still, two high-risk GCA patients have been successfully treated with TCZ, and likely there will be more candidates in the future.

dozama od 2 do 8 mg. Pacijentici su prije dijagnosticirani arterijska hipertenzija i glaukom, a poslije su se u nje razvile i osteoporoza s kompresivnim prijelomima kralježaka te cervikalne i lumbalne diskopatije. U ožujku 2017. pacijenticu je pregledao neurolog zbog boli u vratu koje su zatim prešle u područje glave, okcipitalnog i tjemenog režnja te mandibule. Pacijentica se žalila i na teškoće pri gutanju i bol u lijevom uhu. Imala je i povišen CRP (120,6 mg/L). Upućena je na pregled reumatologu koji je povisio dozu metilprednizona na 12 mg na dan uz praćenje plana postupnog sniženja doze. Dva tjedna poslije, na kontrolnom pregledu, pacijentica se klinički osjećala bolje, ali došlo je do pogoršanja simptoma nakon sniženja doze GK na 4 mg. Pacijentica je tada hospitalizirana radi liječenja i daljnje obrade, pod sumnjom pojave temporalnog arteritisa. Primila je inicijalnu dozu metilprednizona od 80 mg. Napravljeni su rutinsko rendgensko snimanje prsnog koša i ultrazvuk abdomena, ultrazvučno snimanje obojenim doplerom temporalnih, karotidnih i vertebralnih arterija i CT aortografija. Nijedna od navedenih pretraga nije otkrila znatnu patologiju. Neurooftalmološkim pregledom nije ustanovljena optička neuropatija. RF, anti-CCP, ANA, ENA i ANCA bili su negativni. Pacijentica je otpuštena s bolničkog liječenja s uputom da oralnim putem uzima metilprednizon u dozi od 32 mg uz praćenje plana postupnog sniženja doze te da uzima kalcij i vitamin D za osteoporozu jer je imala intoleranciju na alendronatnu kiselinu i teriparatid koje je prije uzimala. Na kontrolnim pregledima pregledavao ju je reumatolog te joj je stanje bilo stabilno za vrijeme uzimanja terapije metilprednizonom u dozi od 4 mg. Hospitalizirana je u svibnju 2018. radi fizikalne rehabilitacije.

S obzirom na pacijentičine komorbiditete i stalnu primjenu GK, u ožujku 2019. počeo se razmatrati TCZ kao alternativna opcija liječenja GCA. Predbiološkom obradom dobiveni su pozitivni rezultati kvantiferonskog testa, pacijentici je propisano profilaktičko uzimanje izonijazida, a zatim je, krajem lipnja 2019., podvrgnuta terapiji TCZ-om. Ubrzo nakon toga u pacijentice su se pojavile neutropenija i povišene vrijednosti jetrenih enzima, što je moglo biti uzrokovano primjenom TCZ-a ili izonijazida. U lipnju 2019. prekinuto je davanje obaju lijekova, a nakon toga laboratorijski su testovi pokazali rezultate u okviru normale. Pacijentica je trenutačno stabilna, prima terapiju metilprednizonom u dozi od 4 mg te odlazi na kontrolne preglede reumatologu.

RASPRAVA

Tri pacijentice prikazane u ovom radu liječene su u našem KBC-u, a sve su pokazivale slične simptome koji su upozoravali na pojavu GCA. Prve dvije pacijentice imale su simptome gubitka vida i druge simptome

Other centers in Croatia have reported similar positive experiences in treating GCA with TCZ. A recent case series from the University Hospital Center Zagreb reports a total of 7 patients diagnosed with GCA, presenting with similar symptoms like our patients but with a greater emphasis on headache and RPM, having been successfully treated with TCZ with no relapses or side effects (10). A separate, interesting report from the same center describes two cases of rheumatoid arthritis patients on etanercept developing GCA, one of which was successfully treated with TCZ (11). The Clinical Hospital Dubrava reports treating 13% of GCA patients with TCZ, but the report only lists the characteristics of GCA patients over the previous 10 years and does not go into more detail on the topic of TCZ treatment, although one case was described in another report (12, 13). That case report describes a 69-year-old patient who presented with fever and high inflammatory markers, and was diagnosed with GCA after imaging showed inflammation of the carotid arteries and aorta (13). Since the patient was still showing signs of active disease after a year on GCs, TCZ was started and complete remission was achieved after three months (13). The further outcome has not been reported.

CONCLUSION

The positive experiences presented here, albeit on a small case series, of treating GCA patients at high risk for GC treatment with the alternative TCZ, contribute to the current recommendations. Additionally, these data support the evidence of TCZ as an effective steroid-sparing drug for patients with GCA, especially those with refractory disease or at risk, such as patients with glaucoma and osteoporosis with vertebral fractures. Our initial experience with TCZ is good, and likely there will be more cases in the future.

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REFERENCES / LITERATURA

1. Rinden T, Miller E, Nasr R. Giant cell arteritis: An updated review of an old disease. Cleve Clin J Med [Internet]. 2019;86 (7):465–72. Dostupno na: https://www.mdedge.com/ccjm/article/203524/vascular/giant-cell-arteritis-updated-review-old-disease. [Pristupljeno: 23. listopada 2019.].
2. Uppal S, Hadi M, Chhaya S. Updates in the diagnosis and management of giant cell arteritis. Curr Neurol Neurosci Rep [Internet]. 2019;19(9):68. Dostupno na: https://link.springer.com/

koji su karakteristični za GCA (glavobolja, klaudikacija čeljusti, vrućica) te je kod njih sve upućivalo na tu dijagnozu. Stoga nije bilo potrebno da budu podvrgnute biopsiji temporalne arterije, koja se obično ne izvodi u našem KBC-u. Iako se biopsija temporalne arterije još smatra zlatnim standardom za postavljanje dijagnoze, čini se da se mnoge zdravstvene ustanove, uključujući i naš KBC, sve više okreću neinvazivnim tehnikama snimanja, poglavito ultrazvuku. U treće pacijentice s već dijagnosticiranom reumatskom polimijalgijom (RPM) razvili su se tipični simptomi GCA, što je potvrdilo već dobro poznatu povezanost ovih dviju bolesti. Valja naglasiti da se ovi pacijenti, s obzirom na nespecifične simptome, često upućuju na pregled jednom ili čak dvama specijalistima prije nego što budu upućeni na pregled reumatologu. Sve su pacijentice liječene primjenom GK; prve dvije pacijentice primile su visoke pulsne doze zbog izrazita gubitka vida, što je bilo osobito izraženo u druge pacijentice koja je već izgubila vid u desnom oku. Sve su pacijentice pregledane i napravljen je probir drugih velikih krvnih žila, autoimunosnih bolesti i paraneoplastičnog sindroma, ali otkriven je samo temporalni arteritis s osteoporozom koju je trebalo liječiti. S obzirom na visoke doze GK ili njegovu dugoročnu uporabu i faktore rizika, uključujući osteoporozu i glaukom, svim je trima pacijenticama trebalo uvesti alternativnu poštednu steroidnu terapiju. Primjenom terapije TCZ-om u prve su dvije pacijentice dobiveni dobri klinički rezultati, čime se učinkovito snizila doza GK ili se terapija GK-om potpuno prekinula te su pacijentice bile u stanju remisije dulje od godine dana, bez pojave relapsa ili teških nuspojava, osim nedavne pojave blage neutropenije u jedne pacijentice. Nažalost, kod treće se pacijentice neutropenija pojavila gotovo odmah, zbog čega je trebalo prekinuti terapiju ovim lijekom. No, druge dvije visokorizične pacijentice koje su bolovale od GCA imale su uspješne rezultate liječenja TCZ-om, a u budućnosti se očekuje i više potencijalnih kandidata za primjenu ovog lijeka.

I drugi klinički bolnički centri u Hrvatskoj objavili su izvještaje u kojima iznose pozitivna iskustva pri primjeni TCZ-a u liječenju GCA. U nedavno provedenoj seriji prikaza bolesnika koju je objavio Klinički bolnički centar Zagreb navodi se liječenje ukupno 7 pacijenata kojima je dijagnosticiran GCA i koji su pokazivali slične simptome kao i naše pacijentice, s većim naglaskom na glavobolju i PRM, a primjenom TCZ-a u tih pacijenata dobiveni su uspješni rezultati, bez pojave relapsa ili nuspojava (10). Drugi zanimljivi izvještaj također je objavio Klinički bolnički centar Zagreb: u njemu se prikazuju dva pacijenta koji boluju od reumatoidnog artritisa, liječeni su etanerceptom i u kojih je došlo do pojave GCA, a kod jednoga su postignuti uspješni rezultati liječenja nakon primjene TCZ-a (11).

article/10.1007%2Fs11910-019-0982-3. [Pristupljeno: 23. listopada 2019.].

3. Al-Mousawi AZ, Gurney SP, Lorenzi AR, Pohl U, Dayan M, Mollan SP. Reviewing the pathophysiology behind the advances in the management of giant cell arteritis. Ophthalmol Ther [Internet]. 2019;8(2):177–93. Dostupno na: https://link.springer.com/article/10.1007%2Fs40123-019-0171-0. [Pristupljeno: 11. studenoga 2019.].
4. Hellmich B, Agueda A, Monti S i sur. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis [Internet]. 2019. Dostupno na: https://ard.bmj.com/content/early/2019/08/03/annrheumdis-2019-215672.long. [Pristupljeno: 28. listopada 2019.].
5. Low C, Conway R. Current advances in the treatment of giant cell arteritis: the role of biologics. Ther Adv Musculoskelet Dis [Internet]. 2019;11:1759720X19827222. Dostupno na: https://journals.sagepub.com/doi/10.1177/1759720X19827222. [Pristupljeno: 23. listopada 2019.].
6. Uskudar Cansu D, Demirtas E, Andic N, Uskudar Teke H, Korkmaz C. Is it required to routinely check fibrinogen level in patients with rheumatic diseases on tocilizumab? Case-based review. Rheumatol Int [Internet]. 2019;39(4):743–50. Dostupno na: https://link.springer.com/article/10.1007%2Fs00296-019-04268-x. [Pristupljeno: 26. prosinca 2019.].
7. Kherani I, Chin C, Kherani RB, Kherani F. Refractory giant cell arteritis on prednisone and tocilizumab: improvement with subsequent tuberculosis reactivation. Can J Ophthalmol [Internet]. 2019;54(4):e192–4. Dostupno na: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(18)30640-9/fulltext. [Pristupljeno: 26. prosinca 2019.].
8. Del Giorno R, Iodice A, Mangas C, Gabutti L. New-onset cutaneous sarcoidosis under tocilizumab treatment for giant cell arteritis: a quasi-paradoxical adverse drug reaction. Case report and literature review. Ther Adv Musculoskelet Dis [Internet]. 2019;11:1759720X19841796. Dostupno na: https://journals.sagepub.com/doi/10.1177/1759720X19841796. [Pristupljeno: 26. prosinca 2019.].
9. Mišljenje o primjeni tocilizumaba u liječenju bolesnika s arteritisom divovskih stanica radne skupine Hrvatskoga reumatološkog društva HLZ-a [Internet]. Zagreb: Hrvatsko reumatološko društvo; 17. ožujka 2018. Dostupno na: http://reumatologija.org/Preporuke.aspx?link=Misljenje_o_primjeni_tocilizumaba. [Pristupljeno: 28. listopada 2019.].
10. Bosnić D, Sentić M, Mayer M i sur. Tocilizumab u liječenju bolesnika s arteritisom divovskih stanica – Serija bolesnika iz KBC-a Zagreb. Reumatizam [Internet]. 2019;66(1):19. Dostupno na: https://hrcak.srce.hr/227049. [Pristupljeno: 26. prosinca 2019.].
11. Bosnić D, Sentić M, Čubeić D, Padjen I, Anić B. Arteritis divovskih stanica u dva bolesnika liječena inhibitorima TNF-alfa. Reumatizam [Internet]. 2019;66(1):33. Dostupno na: https://hrcak.srce.hr/227050. [Pristupljeno: 26. prosinca 2019.].
12. Sutić A, Čulo M-I, Gudelj Gračanin A i sur. Klinička obilježja, dijagnoza i liječenje bolesnika s arteritisom divovskih stanica u Kliničkoj bolnici Dubrava. Reumatizam [Internet]. 2019;66(1):28–9. Dostupno na: https://hrcak.srce.hr/227049. [Pristupljeno: 26. prosinca 2019.].
13. Golob M, Gudelj Gračanin A, Tičinović N, Morović-Vergles J. Tocilizumab u arteritisu divovskih stanica: Prikaz bolesnika. Reumatizam [Internet]. 2019;66(1):33. Dostupno na: https://hrcak.srce.hr/227050. [Pristupljeno: 26. prosinca 2019.].

Klinička bolnica Dubrava objavila je izvještaj u kojem navodi da se primjenom TCZ-a liječilo 13% pacijenata oboljelih od GCA. No, u tom izvješću spominju samo značajke pacijenata koji su bolovali od GCA i liječili se u toj bolnici tijekom posljednjih 10 godina, a ne iznose detaljan opis liječenja TCZ-om, iako je upravo takav slučaj opisan u drugom izvješću (12, 13). U prikazu bolesnika opisuje se 69-godišnji pacijent sa simptomima vrućice i povišenim upalnim markerima kojemu je GCA dijagnosticiran nakon što je snimanjem otkrivena upala karotidnih arterija i aorte (13). Poslije godine dana terapije GK-om pacijent je i dalje pokazivao znakove aktivne bolesti pa je stavljen na terapiju TCZ-om, čime je nakon tri mjeseca postignuto stanje potpune remisije (13). Daljnji rezultati nisu navedeni.

ZAKLJUČAK

Premda se radi o malenom broju bolesnika, prije navedena pozitivna iskustva u primjeni alternativnog lijeka TCZ-a pri liječenju pacijenata koji boluju od GCA i za koje postoji visok rizik od pojave nuspojava zbog uzimanja GK uvelike pridonose trenutačnim preporukama za primjenu tog lijeka. Isto tako, prethodno navedeni podatci govore u prilog dokazima o TCZ-u kao učinkovitom poštednom steroidnom lijeku za pacijente koji boluju od GCA, a osobito za one s refraktornim bolestima ili visokorizične pacijente poput onih s glaukomom ili osteoporozom s prijelomima kralježaka. Naše prvotno iskustvo s primjenom TCZ-a dobro je, a vjerujemo da će u budućnosti biti i više pozitivnih iskustava s ovim lijekom.

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ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

NEW PARAMETERS OF HAND GRIP IN RHEUMATOID ARTHRITIS PATIENTS BASED ON ELECTRODYNAMIC MEASUREMENTS – A PILOT EVALUATION STUDY

NOVI PARAMETRI STISKA ŠAKE U BOLESNIKA S REUMATOIDNIM ARTRITISOM TEMELJENI NA ELEKTRODINAMIČKIM MJERENJIMA – PILOT EVALUACIJSKA STUDIJA

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Abstract

Introduction: In rheumatoid arthritis, inflammation and damage lead to functional impairment. As the hand is a typical site of involvement, lower grip strength is often found in patients with rheumatoid arthritis. In these patients it is necessary to evaluate the hand grip impairment in a more detailed way. The aim of this study was to analyze a new method for measuring hand grip.

Methods: An expert electronic measuring system for obtaining dynamic time series of hand grip force was developed. We tested it in a sample of 24 participants, 12 patients with rheumatoid arthritis and 12 age- and sex-matched healthy controls. The main dynamometric parameters obtained were: maximum grip force, fatigue, grip velocity, and functional potential. These were measured at the baseline and at 60, 120, and 180 days.

Results: Compared to the control group, at baseline the patients with rheumatoid arthritis had a significantly lower maximum grip force (68.2 vs. 97.3), earlier occurrence of fatigue (22.4 vs. 24.9), as well as lower grip velocity (14.8 vs. 22.2) and functional potential (808.2 vs. 1876.3). A significant improvement in all measured variables was observed during the follow-up period.

Conclusion: In our pilot study we tested a newly developed electrodynamometer measuring system and found that it can provide an objective and detailed description of the hand condition. This system has the potential to be used as a relevant indicator of hand function in patients with rheumatoid arthritis as well as to help tailor their rehabilitation.

Key words: Arthritis, rheumatoid – physiopathology, rehabilitation; Hand – physiopatholoy; Hand strength; Muscle strength dynamometer; Pilot projects

Sažetak

Uvod: U reumatoidnom artritisu upala i oštećenje dovode do funkcionalne nesposobnosti. Uobičajeno mjesto zahvaćenosti jest šaka i zato ovi bolesnici često imaju slabiju snagu stiska. U bolesnika s reumatoidnim artritisom potrebno je provesti detaljniju evaluaciju oštećenja šake. Cilj ove studije bila je analiza nove metode mjerenja snage stiska šake.

Metode: Razvijen je ekspertni elektronički mjerni sustav za dobivanje dinamičkih vremenskih serija sile stiska šake. Testirali smo ga na uzorku od 24 sudionika: 12 bolesnika s reumatoidnim artritisom i 12 zdravih kontrolnih ispitanika koji se podudaraju po dobi i spolu. Glavni dobiveni dinamometrijski parametri bili su: maksimalna sila stiska šake, zamor šake, brzina stiska te funkcionalni potencijal. Navedeni parametri izmjereni su pri početnomu mjerenju i nakon 60, 120 i 180 dana.

Rezultati: U usporedbi s kontrolnom skupinom bolesnici s reumatoidnim artritisom imali su znatno manju maksimalnu silu stiska šake (68,2 prema 97,3), raniju pojavu zamora šake (22,4 prema 24,9), manju brzinu stiska (14,8 prema 22,2) i manji funkcionalni potencijal (808,2 prema 1876,3) pri početnomu mjerenju. Tijekom praćenja primijećeno je znatno poboljšanje svih izmjerenih varijabla.

Zaključak: U našoj pilot studiji testirali smo novorazvijeni elektrodinamometrijski sustav mjerenja te smo utvrdili da se njegovom uporabom može objektivno i detaljno opisati stanje šake. Taj se sustav može upotrijebiti kao relevantan pokazatelj funkcije šake u bolesnika s reumatoidnim artritisom i može pomoći u prilagodbi njihove rehabilitacije.

Ključne riječi: Reumatoidni artritis – patofiziologija, rehabilitacija; Šaka – patofiziologija; Snaga šake; Dinamometar za mišićnu snagu; Pilot istraživanja

INTRODUCTION

Polyarthritis of the hand is a hallmark of rheumatoid arthritis (RA). Standard hand dynamometry registration of one-grip force or the recording of a series of multiple grips are commonly used to evaluate the function of the hand (1, 2). This provides an approximate measurement of handgrip strength, but not a detailed insight (3). A more detailed assessment would be useful for tailored rehabilitation of the hand in patients with RA, but also in patients with other non-rheumatic conditions involving the hand. Therefore, we developed a custom-designed electronic dynamic sensor in order to measure different minutely specified parameters for handgrip evaluation. The aim of this pilot study was to evaluate the hand grip in patients with RA using this new electrodynamic method.

METHOD

This pilot study included 24 subjects, 12 patients with RA (6 women and 6 men, aged 35–55 years) in the early phase of the disease, and 12 healthy sex- and age-matched controls. The patients with RA were enrolled consecutively from the outpatient clinic according to the following inclusion criteria: newly diagnosed RA with disease duration < 6 months, age 35–55 years, and treatment with orally taken methotrexate 15 mg/week. In the evaluation of motor hand function a new expert electronic measuring system for dynamic measurements of the hand grip force, developed at the Ruđer Bošković Institute, was used (Figure 1). The device was calibrated in accordance with hand grip comparison on a mechanical dynamometric device with the same mechanical handrail. The dynamics of the dynamometric hand grip parameters in both groups was measured at the baseline and after 60, 120, and 180 days. All the patients were treated with the anchor disease-modifying anti-rheumatic drug (DMARD) methotrexate, and during the follow-up period its dosage

UVOD

Poliartritis šake jedna je od glavnih značajka reumatoidnog artritisa (RA). Za evaluaciju funkcije šake uobičajeno se upotrebljava standardna dinamometrija šake koja omogućava registraciju sile jednog stiska šake ili bilježenje serije vrijednosti višestrukih stisaka šake (1, 2). Tako se može dobiti okvirna vrijednost snage stiska šake, ali nedostatak ove metode jest detaljan uvid u stanje (3). Detaljnija ocjena je korisna za prilagođenu rehabilitaciju šake u bolesnika s RA, ali i za pacijente s drugim nereumatskim bolestima koje zahvaćaju šake. Stoga smo razvili prilagođen elektronički, dinamički senzor da bismo mogli izmjeriti različite, detaljno određene parametre za evaluaciju stiska šake. Cilj ove pilotne studije bila je evaluacija stiska šake u bolesnika s RA uporabom nove elektrodinamičke metode.

METODA

Pilotnu studiju proveli smo na 24-ero ispitanika: 12-ero bolesnika s RA u ranoj fazi bolesti (6 žena i 6 muškaraca u dobi od 35 do 55 godina) i 12-ero zdravih kontrolnih ispitanika koji su se podudarali po dobi i spolu. Bolesnici s RA uključeni su u studiju uzastopno iz ambulante u skladu sa sljedećim uključnim kriterijima: nedavno postavljena dijagnoza RA s trajanjem bolesti kraćim od 6 mjeseci, dob od 35 do 55 godina, liječenje peroralnim metotreksatom u dozi od 15 mg/tjedan. Evaluacija motoričke funkcije šake provedena je s pomoću novog ekspertnog elektroničkog mjernog sustava za dobivanje dinamičkih mjerenja sile stiska šake koji je razvijen u Institutu „Ruđer Bošković" (slika 1.). Umjeravanje uređaja izvedeno je u skladu s usporedbom stiska šake na mehaničkom dinamometrijskom uređaju s istim mehaničkim rukohvatom. Dinamika dinamometrijskih parametara stiska šake za obje je skupine izmjerena na početnome mjerenju i nakon 60, 120 i 180 dana. Svi su bolesnici liječeni temeljnim antireumatskim lijekom koji modificira tijek

was not changed. The patients had the option of taking NSAIDs and/or acetaminophen as an escape medication, but were required to stop the medication three days before each visit. The main dynamometric parameters of interest obtained were: maximum grip force (highest achieved power of each grip), fatigue (onset of decreasing tendency in maximum grip force in the grip series), grip velocity (ratio of maximum force and time in which the individual grip is achieved), and functional potential (composite measure combining the average grip force, average grip velocity, and fatigue). The evaluation of the hand's functional deficit was performed by registering and extracting previously defined parameters in time and spectral domain over the processed time grip series of the dominant hand. The described pre-processing was conducted over a grip series (15 times) at baseline (moment t = 0) and at visits every two months thereafter. In order to minimize fluctuation and amplitude effects, Fourier analysis was used for each cycle. The best 10 from a total of 15 individual cycles were selected for each study participant, and the most irregular cycles, such as those containing more irregular maximums, uneven grip phase, or delay at the beginning and at the end of each grip, were removed. Statistical analysis included the T-test and the ANOVA test for repeated measures.

RESULTS

The two groups were well matched to age, and no significant difference was found between them (the mean and SD for age in RA patients was 54.7 ± 8.2 years, and in healthy controls 54.2 ± 8.2; P = 0.883). The baseline data on the dynamometric parameters of interest in the patients with RA and healthy controls are shown in Table 1. Compared to the control group, the RA patients had a significantly lower maximum grip force, fatigue (earlier occurrence of fatigue), grip velocity, and functional potential.

During the follow-up period, the measured dynamometric parameters in the patients with RA showed significant improvement at each visit as follows: maximum grip force – P = 0.040, fatigue – P = 0.032, grip velocity – P = 0.026, and functional potential – P = 0.014 (Table 2). Nevertheless, they did not reach the values measured in the healthy controls.

DISCUSSION

This pilot study presents the results of the application of a new measuring system, involving a unique data processing algorithm and proposed parameters of the hand function. It also considers the implications of this system for rheumatology. Previous studies based on single-grip measurement found that hand grip strength and net forces vary by sex, age, and anthropometric characteristics (4, 5). Generally, in conditions affecting the hand the observed dynamometric param-

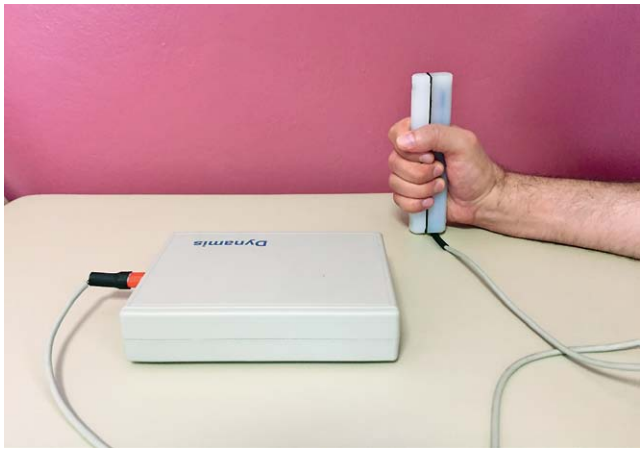

Figure 1. Hand grip acquisition system
Slika 1. Sustav za ocjenu snage stiska šake

bolesti (DMARD), metotreksatom, a tijekom praćenja njegova doza nije promijenjena. Postojala je i mogućnost uzimanja nesteroidnih antireumatika (NSAR) i/ili acetaminofena kao simptomatskog lijeka, ali ne u razdoblju od tri dana prije svake kontrole. Dobiveni glavni dinamometrijski parametri od interesa bili su: maksimalna sila stiska šake (najveća postignuta snaga svakog stiska), zamor šake (trenutak početka tendencije smanjenja maksimalne sile stiska u seriji stisaka), brzina stiska (omjer maksimalne sile i vremena u kojem se postiže pojedinačan stisak) i funkcionalni potencijal (složena mjera koja uključuje prosječnu silu stiska, prosječnu brzinu stiska i prosječan zamor šake). Evaluacija funkcionalnog deficita šake pacijenta provedena je registracijom i izdvajanjem prethodno utvrđenih parametara u vremenskoj i spektralnoj domeni tijekom obrađenih vremenskih serija stiska dominantne šake. Opisana predobrada provedena je na serijama stisaka (15 puta) pri početnomu mjerenju (t = 0) i na kontrolama koje su se provodile svaka dva mjeseca nakon početnog mjerenja. Da bi se utjecaji fluktuacije i amplitude smanjili na minimum, za svaki je ciklus provedena Fourierova analiza. Za svakog je ispitanika odabrano 10 najboljih ciklusa od ukupno 15 pojedinačnih ciklusa, a uklonjeni su najnepravilniji ciklusi poput onih koji su sadržavali više nepravilnijih maksimalnih vrijednosti, neravnomjernu fazu stiska, kašnjenje na početku i na kraju svakog stiska. Statistička analiza uključivala je T-test i analizu varijance (ANOVA) za ponovljena mjerenja.

REZULTATI

Dvije skupine dobro su se podudarale po dobi, jer između njih nije utvrđena znatna razlika (srednja vrijednost i SD za dob u bolesnika s RA iznosila je 54,7 ± 8,2 godine, a za kontrolne ispitanike iznosila je 54,2 ± 8,2; P = 0,883). Podatci s početnog mjerenja u vezi s interesnim dinamometrijskim parametrima u bolesnika s RA i kontrolnih ispitanika prikazani su u tablici 1.

Table 1. Differences between patients and control group at baseline (T-test for independent groups)
Tablica 1. Razlika između bolesnika i kontrolne skupine u odnosu prema početnom stanju (T-test za nezavisne skupine)

	Control group / Kontrolna skupina N = 12			Patients / Bolesnici N = 12			t	*p*
	Mean / Srednja vrijednost	SD	Std. Error Mean / Standardna pogreška srednje vrijednosti	Mean / Srednja vrijednost	SD	Std. Error Mean / Standardna pogreška srednje vrijednosti		
Max grip force at baseline (N) / Maksimalna sila stiska izmjerena na početnome mjerenju (N)	97,3	3,5	1,0	68,2	14,6	4,2	6,7	< 0,001
Fatigue at baseline / Zamor šake na početnome mjerenju	24,9	0,3	0,1	22,4	1,8	0,5	4,8	< 0,001
Grip velocity at baseline (N/s) / Brzina stiska na početnome mjerenju (N/s)	22,2	1,3	0,4	14,8	2,0	0,6	10,7	< 0,001
Functional potential at baseline / Funkcionalni potencijal na početnome mjerenju	1876,3	174,1	50,2	808,2	266,0	76,8	11,6	< 0,001

Table 2. Changes in dynamometric variables during follow-up – patients with RA (n=12) (ANOVA)
Tablica 2. Promjene dinamometrijskih varijabla tijekom praćenja – bolesnici s RA (n = 12) (analiza varijance, ANOVA)

Patients / Bolesnici N = 12	Mean / Srednja vrijednost	SD	Wilks' Lambda value / Wilksova lambda--vrijednost	F	*p*
Max grip force at baseline (N) / Maksimalna sila stiska izmjerena na početku (N)	68,2	14,6	0,41	4,24	0,040
Max grip force after 2 months (N) / Maksimalna sila stiska izmjerena nakon 2 mjeseca (N)	67,4	12,4			
Max grip force after 4 months (N) / Maksimalna sila stiska izmjerena nakon 4 mjeseca (N)	71,1	14,1			
Max grip force after 6 months (N) / Maksimalna sila stiska izmjerena nakon 6 mjeseci (N)	71,8	13,6			
Fatigue at baseline / Zamor šake izmjeren na početku	22,4	1,8	0,39	4,63	0,032
Fatigue after 2 months / Zamor šake izmjeren nakon 2 mjeseca	23,2	1,5			
Fatigue after 4 months / Zamor šake izmjeren nakon 4 mjeseca	23,7	1,4			
Fatigue after 6 months / Zamor šake izmjeren nakon 6 mjeseci	23,8	1,6			
Grip velocity at baseline (N/s) / Brzina stiska izmjerena na početku (N/s)	14,8	2,0	0,38	4,97	0,026
Grip velocity after 2 months (N/s) / Brzina stiska izmjerena nakon 2 mjeseca (N/s)	14,8	2,3			
Grip velocity after 4 months (N/s) / Brzina stiska izmjerena nakon 4 mjeseca (N/s)	15,9	3,1			
Grip velocity after 6 months (N/s) / Brzina stiska izmjerena nakon 6 mjeseci (N/s)	16,7	3,1			
Functional potential at baseline / Funkcionalni potencijal izmjeren na početku	808,2	266,0	0,32	6,25	0,014
Functional potential after 2 months / Funkcionalni potencijal izmjeren nakon 2 mjeseca	831,9	251,6			
Functional potential after 4 months / Funkcionalni potencijal izmjeren nakon 4 mjeseca	964,0	332,1			
Functional potential after 6 months / Funkcionalni potencijal izmjeren nakon 6 mjeseci	1027,4	340,1			

eters increased, as strength, velocity, and grip stability grew (2). Compared to the baseline values, the increase in these parameters during the treatment represented a clear indicator of improvement of the hand function. The meticolous evaluation of the hand function using this new dynamometric system offers the possibility to plan appropriate exercises in order to obtain the best possible result. During a period of 6 months, the method showed good resolution at all stages.

U usporedbi s kontrolnom skupinom, bolesnici s RA imali su znatno slabiju maksimalnu silu stiska šake, manju vrijednost zamora šake (zamor se dogodio puno prije nego u kontrolnih ispitanika), manju brzinu stiska i manji funkcionalni potencijal.

Tijekom praćenja pri svakoj kontroli utvrđene su promjene u izmjerenim dinamometrijskim parametrima u bolesnika s RA: maksimalna sila stiska šake (P = 0,040), zamor šake (P = 0,032), brzina stiska (P = 0,026) i funk-

It is important to note that within the framework of this study, data on grip force and velocity are primarily significant in relative relations. Hence, they should be considered with caution, whereas for accurate absolute values of the abovementioned parameters it would be necessary to perform a study on a larger number of subjects and with a stringently defined protocol of device calibration (6). The development of this expert diagnostic system could allow an objective hand functional status evaluation. For further research, along with net functional force and velocity in hand grip evaluation, and with adequate probe modification, it would also be possible to analyze the grip force of a specific group of digits – mostly that of the thumb plus one finger ("pinch testing").

CONCLUSION

In this pilot evaluation study we present a new electronic dynamometric system for obtaining hand function parameters based on dynamic measurements. By comparing the results of healthy subjects and patients, and by recording the changes occurring during the treatment, we can conclude that this system measures the hand condition objectively. It can be safely used to monitor the status of individual patients during treatment and rehabilitation as a relevant indicator of recovery. Further studies with a larger number of patients are needed to confirm its value.

Conflict of interest statement: Authors declare no conflict of interest.

REFERENCES / LITERATURA

1. Sheehy C, Gaffney K, Mukhtyar C. Standardized grip strength as an outcome measure in early rheumatoid arthritis. Scand J Rheumatol. 2013;42(4):289–93.
2. Dias JJ, Singh HP, Taub N, Thompson J. Grip strength characteristics using force-time curves in rheumatoid hands. J Hand Surg Eur Vol. 2013;38(2):170–7.
3. Björk M, Thyberg I, Haglund L, Skogh T. Hand function in women and men with early rheumatoid arthritis. A prospective study over three years (the Swedish TIRA project). Scand J Rheumatol. 2006;35(1):15–9.
4. Beenakker KGM, Ling CH, Meskers CGM i sur. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Res Rev. 2010;9(4):431–6. doi: 10.1016/j.arr.2010.05.005.
5. Chandrasekaran B, Ghosh A, Prasad C i sur. Age and anthropometric traits predict handgrip strength in healthy normals. J Hand Microsurg. 2010;2(2):58–61. doi: 10.1007/s12593-010-0015-6.
6. Shiratori AP, da Rosa Iop R, Gomes Borges Júnior N i sur. Evaluation protocols of hand grip strength in individuals with rheumatoid arthritis: a systematic review. Rev Bras Reumatol. 2014;54(2):140–7.

cionalni potencijal (P = 0,014) (tablica 2.). No, bez obzira na prije navedeno, bolesnici s RA nisu uspjeli postići jednake rezultate kao kontrolni ispitanici.

RASPRAVA

U ovoj smo pilot studiji, s pomoću jedinstvenog algoritma obrade podataka i predloženih parametara za mjerenje funkcije šake, opisali primjenu novog sustava mjerenja i njegovo značenje u reumatologiji. U prije provedenim studijama, koje su se temeljile na mjerenju pojedinačnog stiska šake, utvrđeno je da se snaga stiska šake i neto sila razlikuju ovisno o spolu, dobi i antropometrijskim značajkama (4, 5). Općenito se, u uvjetima koji utječu na funkciju šake, promatrani dinamometrijski parametri povećavaju s povećanjem snage, brzine i stabilnosti stiska šake (2). U usporedbi s početnim vrijednostima mjerenja, povećanje tih parametara tijekom liječenja jasno upućuje na poboljšanje funkcije šake. Precizna evaluacija funkcije šake koja se provodi s pomoću ovoga novog dinamometrijskog sustava pruža mogućnost planiranja odgovarajućih vježbi s ciljem dobivanja najboljih mogućih rezultata. Ovom metodom dobiveni su dobri rezultati u svim fazama tijekom razdoblja od 6 mjeseci.

Valja napomenuti da u ovoj studiji podatci o sili i brzini stiska imaju primarnu važnost u okviru relativnih odnosa parametara. Stoga ih treba uzimati s oprezom, dok bi za točne apsolutne vrijednosti gore navedenih parametara trebalo provesti istraživanje na većem broju ispitanika i sa strogo utvrđenim protokolom umjeravanja uređaja (6). Razvoj ovog ekspertnog dijagnostičkog sustava omogućio bi provođenje objektivne evaluacije funkcionalnog statusa šake. U daljnjim se istraživanjima, uz odgovarajuću modifikaciju sonde, zajedno s neto funkcionalnom silom i brzinom u evaluaciji stiska šake može analizirati i sila stiska šake određene skupine prstiju – uglavnom sila palca i jednoga dodatnog prsta (ispitivanje snage stiska prstima) (engl. *pinch testing*).

ZAKLJUČAK

U ovoj smo pilot evaluacijskoj studiji predstavili novi elektronički dinamometrijski sustav za dobivanje parametara funkcije šake koji se temelje na dinamičkim mjerenjima. Usporedbom rezultata u zdravih kontrolnih ispitanika i u bolesnika s RA te bilježenjem promjena tijekom liječenja možemo zaključiti da ovaj sustav objektivno mjeri stanje šake. Sustav je siguran za uporabu u praćenju stanja pojedinih bolesnika tijekom liječenja i rehabilitacije, kao bitan pokazatelj njihova oporavka. Potrebno je provesti daljnje studije na većem broju bolesnika da bi se potvrdile vrijednost i učinkovitost ovog uređaja.

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PROFESSIONAL PAPER STRUČNI RAD

KIDNEY INVOLVEMENT IN ADULTS WITH IGA VASCULITIS: EXPERIENCES FROM CLINICAL HOSPITAL DUBRAVA, ZAGREB

IGA-VASKULITIS SA ZAHVAĆANJEM BUBREGA U ODRASLOJ DOBI: ISKUSTVA IZ KLINIČKE BOLNICE DUBRAVA, ZAGREB

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Abstract

Introduction: IgA vasculitis, formerly named Henoch-Schönlein purpura, is a systemic small-vessel vasculitis that occurs commonly in children, while in adults, the disease remains rare. It is characterised by non-thrombocytopenic palpable purpura, arthritis, arthralgia, kidney disease and gastrointestinal pain. This study aimed to determine clinical signs and symptoms, laboratory and pathohistological parameters and therapy of IgA vasculitis in adults with renal involvement, by conducting our research on a sample of patients of a tertiary referral hospital.

Research subjects and methods: In this retrospective cohort study, patients treated at Clinical Hospital Dubrava from 2011 to 2019 were included, who were diagnosed with IgA vasculitis, based on clinical, laboratory and pathohistological criteria. Clinical and laboratory parameters, were determined through the use of methods commonly used in clinical practice. In patients with symptoms and signs of kidney involvement and after patients' consent, kidney biopsy was performed, and analysed by light, immunofluorescence and electron microscopy.

Results: twenty-two adults (12 M, 10 F), whose median age was 57, were included in our study. Palpable purpura and nephritis were present in all patients. Thirteen (59.1%) patients had arthralgia and five of them (22.5%) experienced abdominal pain. Respiratory infection preceded vasculitis in six (27.3%) patients, six patients ((27.3%) were taking medications and got vaccinated prior to the occurrence of vasculitis, and in ten (45.4%) patients the predisposing factor was unknown. Asymptomatic hematuria was present in ten (47.6%), subnephrotic proteinuria in three (14.3%), nephrotic syndrome in nine (42.9%) and nephritic syndrome in three (14.3%) patients. According to the findings of kidney biopsy, which was performed on 18 patients, eleven (61.6%) had mesangial proliferation, fourteen

(77.8%) had endocapillary proliferation, and eleven (61.6%) had extracapillary (crescents) proliferation. After the diagnosis, renin-angiotensin inhibitors were used by eighteen (81.8%) patients, glucocorticoids by twenty-one (95.5%) and cyclophosphamide by five (22.7%) patients. Patient follow-up was performed for 23 to 84 months and, in the said period, all of them had improved or stagnant renal function, except for one patient who died.

Conclusion: Renal manifestations of IgA vasculitis may change the commonly mild course of this disease and lead to an increase in morbidity as well as affect the type and duration of treatment. So, in everyday work, it is important to determine characteristics of renal changes in IgA vasculitis in order for an adequate therapeutic option to be applied.

Key words: Purpura, Schoenlein-Henoch – complications, diagnosis, drug therapy; Kidney diseases – diagnosis, drug therapy, etiology; Kidney – pathology; Biopsy; Glomerulonephritis, IgA – dijagnoza, farmakoterapija, patologija; Immunoglobulin A; Arthralgia – etiology; Abdominal pain – etiology; Glucocorticoids – therapeutic use; Angiotensin – converting enzyme inhibitors – therapeutic use; Angiotensin receptor antagonists – therapeutic use

Sažetak

Uvod: IgA-vaskulitis, prije nazivan Henoch-Schönleinova purpura, vaskulitis je malih krvnih žila posredovan imunoglobulinom A (IgA). Najčešće obolijevaju djeca, dok je u odraslih incidencija manja. Kliničkom slikom dominiraju palpabilna, netrombocitopenična purpura, artralgije, artritis, znakovi bubrežne bolesti i abdominalna bol. Cilj ovog istraživanja bio je utvrđivanje kliničkih i laboratorijskih karakteristika te načina liječenja odraslih oboljelih od IgA-vaskulitisa sa zahvaćanjem bubrega na uzorku bolesnika iz jednoga tercijarnog centra.

Ispitanici i metode: U retrospektivno kohortno istraživanje uključeni su bolesnici liječeni u razdoblju od 2011. do 2019. godine u Kliničkoj bolnici Dubrava u Zagrebu, kojima je na osnovi kliničkih, laboratorijskih i patohistoloških kriterija dijagnosticiran IgA-vaskulitis. Klinički i laboratorijski parametri određivani su metodama uobičajenima u kliničkoj praksi. U bolesnika sa znakovima zahvaćanja bubrega učinjene su biopsija bubrega i analiza svjetlosnom, imunofluorescentnom i elektronskom mikroskopijom.

Rezultati: U istraživanju su sudjelovala ukupno 22 bolesnika (12 muškaraca, 10 žena), medijana dobi 57 godina. Svi su bolesnici imali purpuru i znakove bubrežne bolesti. Artralgije je imalo 13-ero (59,1%) bolesnika, a bol u trbuhu njih 5-ero (22,5%). Infekcija dišnog sustava prethodila je vaskulitisu u 6-ero (27,3%) bolesnika, lijekovi i cjepiva također u njih 6-ero (27,3%), a u 10-ero (45,4%) bolesnika predisponirajući čimbenik bio je nepoznat. Asimptomatsku hematuriju imalo je 10-ero (47,6%) bolesnika, subnefrotsku proteinuriju njih troje (14,3%), nefrotski sindrom 9-ero (42,9%), a nefritički sindrom imalo je također troje (14,3%) bolesnika. Prema nalazu biopsije bubrega, koja je učinjena u 18-ero bolesnika, mezangijsku proliferaciju imalo je njih 11-ero (61,1%), endokapilarnu proliferaciju 14-ero (77,8%), a ekstrakapilarnu proliferaciju (polumjesece) imalo je 11-ero (61,1%) bolesnika. Nakon postavljanja dijagnoze terapiju inhibitorima sustava renin-angiotenzin primalo je 18-ero (81,8%) bolesnika, 21 bolesnik (95,5%) dobivao je glukokortikoide, a njih 5-ero (22,7%) liječeno je ciklofosfamidom. Bolesnici su praćeni tijekom razdoblja od 23 do 84 mjeseca, a u svih se, osim u jedne bolesnice, bubrežna funkcija poboljšala ili je stagnirala.

Zaključak: Bubrežne manifestacije IgA-vaskulitisa mijenjaju inače blagi tijek bolesti, dovode do porasta morbiditeta i utječu na trajanje liječenja. Pri svakodnevnom radu valja utvrditi značajke bubrežnih promjena kod IgA-vaskulitisa da bismo na temelju tih obilježja primijenili prikladnu terapiju.

Ključne riječi: Henoch-Schönleinova purpura – dijagnoza, farmakoterapija, komplikacije; Bubrežne bolesti – dijagnoza, etiologija, farmakoterapija; Bubreg – patologija; IgA nefropatija – dijagnoza, farmakoterapija, patologija; Imunoglobulin A; Biopsija; Artralgija – etiologija; Abdominalna bol – etiologija; Glukokortikoidi – terapijska uporaba; Inhibitori angiotenzin konvertirajućeg enzima – terapijska uporaba; Antagonisti receptora angiotenzina – terapijska uporaba

INTRODUCTION

According to the classification proposed in 1994 at the International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides, immunoglobulin A-mediated vasculitis (IgA vasculitis) is a systemic, nongranulomatous small-vessel (arterioles, venules and capillaries) vasculitis. Systemic vasculitis is most common in children, with an annual incidence of 10 to 30 per 100,000 (1). It occurs significantly less frequently in adults, with an incidence of 0.8 to 1.8 per

UVOD

Prema klasifikaciji iz Chapel Hilla, vaskulitis posredovan imunoglobulinom A (IgA-vaskulitis) sustavni je negranulomatozni vaskulitis malih krvnih žila (arteriola, venula i kapilara). Najčešći je sustavni vaskulitis u djece s godišnjom incidencijom od 10 do 30 na 100.000 (1). Znatno rjeđe pojavljuje se u odraslih uz incidenciju od 0,8 do 1,8 na 100.000 (2). Histopatološki, riječ je o leukocitoklastičkom vaskulitisu s neutrofilnom infiltracijom stijenka zahvaćenih krvnih žila

100,000 (2). From a histopathological standpoint, this is a leukocytoclastic vasculitis with neutrophilic infiltration of the walls of the affected blood vessels and IgA immunocomplex deposits, with possible development of necrosis (3, 4). Disease etiology is not known. It is most likely an interaction of genetic and external factors, which triggers the formation of antigen-antibody immune complexes, with the development of immune-mediated inflammation of the wall of small blood vessels (5). Patients carrying certain HLA antigens are more likely to develop IgA vasculitis: HLA-DRB1:01, HLA-B41:02 and HLA-B35 (6, 7). The most common external factors associated with the occurrence of the disease in children are the causes of upper and lower respiratory tract infections such as streptococci, staphylococci, and parainfluenza viruses (8). IgA vasculitis in children can also occur after acute gastroenteritis, urinary tract infections and vaccinations. In adults, it is most commonly associated with the administration of drugs and vaccines, toxins, food allergens, neoplasms, and insect bites (9). Most patients with IgA vasculitis have high serum IgA levels. IgA vasculitis is manifested by a tetrad of symptoms: non-thrombocytopenic purpura, arthritis or arthralgia, kidney involvement, and abdominal pain. According to the current 2008 EULAR/PRINTO/PRES classification criteria from Ankara, the basic criterion is palpable purpura in patients without thrombocytopenia and coagulopathy with at least one of four other symptoms (10). Skin changes initially manifest as erythema, urticaria, and maculopapular rash, then progress to ecchymoses and petechiae. They are most often distributed on the extensor of the lower and upper extremities (11). According to a study conducted by Kang et al, the incidence of purpura in the upper extremities was higher in adults than in children (9). In about a quarter of patients, IgA vasculitis begins with arthralgia and/or arthritis, and this occurs significantly more often in children than in adults (9, 12). It is most commonly a case of oligoarthritis involving the knee, hip, and ankle (13). Approximately two-thirds of patients, predominantly children, experience abdominal pain caused by submucosal hemorrhage and small bowel wall thickening as part of their clinical features of IgA vasculitis (4, 14). Kidney involvement occurs in more than a third of all patients, usually within the period of one month after the onset of systemic symptoms (15). According to the EULAR/PRINTO/PRES criteria for IgA vasculitis, kidney disease is characterised by proteinuria, hematuria, or histopathological nephritis with IgA deposits in the mesangium (10). Risk factors for the development of nephritis are older age, disease complications, male sex, duration of purpura, relapse of the disease, leukocytosis, thrombocytosis, and low complement 3 (C3) values (16). Kidney disease is sig-

i depozitima imunokompleksa IgA, uz mogući razvoj nekroza (3, 4). Etiologija bolesti nije poznata. Najvjerojatnije se radi o interakciji genskih i vanjskih čimbenika, što pokreće stvaranje imunosnih kompleksa antigen – protutijelo, uz razvoj imunosno posredovane upale stijenke malih krvnih žila (5). Veću vjerojatnost za razvoj IgA-vaskulitisa pokazuju bolesnici nositelji određenih antigena HLA: HLA-DRB1 01, HLA-B41:02 i HLA-B35 (6, 7). Najčešći vanjski čimbenici koji se povezuju s nastankom bolesti u djece jesu uzročnici infekcija gornjeg i donjega dišnog sustava kao što su streptokoki, stafilokoki te virus parainfluence (8). IgA-vaskulitis u djece može nastati i poslije akutnih gastroenteritisa, infekcija mokraćnog sustava i cijepljenja. U odraslih se najčešće povezuje s primjenom lijekova i cjepiva, toksinima, alergenima iz hrane, neoplazmama i ubodima kukaca (9). Većina bolesnika s IgA-vaskulitisom ima povišenu serumsku razinu IgA. IgA-vaskulitis očituje se tetradom simptoma: netrombocitopeničnom purpurom, artritisom ili artralgijama, zahvaćanjem bubrega i bolima u trbuhu. Prema aktualnim klasifikacijskim kriterijima EULAR/PRINTO/PRES-a iz Ankare od 2008. godine, osnovni kriterij jest palpabilna purpura bez trombocitopenije i koagulopatije uz barem još jedan od četiriju simptoma (10). Kožne se promjene u početku očituju kao eritem, urtike i makulopapulozni osip, a zatim prelaze u ekhimoze i petehije. Najčešće su raspoređene po ekstenzornim stranama donjih i gornjih ekstremiteta (11). U istraživanju Kanga i suradnika uočena je veća pojavnost purpure u području gornjih ekstremiteta u odraslih u usporedbi s djecom (9). U oko četvrtine bolesnika IgA-vaskulitis započinje artralgijama i/ili artritisom, i to znatno češće u djece nego u odraslih (9, 12). Najčešće je riječ o oligoartritisu sa zahvaćanjem koljena, kuka i gležnja (13). Približno dvije trećine bolesnika, pretežno djece, u sklopu kliničke slike IgA-vaskulitisa ima bol u trbuhu uzrokovanu submukoznim krvarenjem i edemom stijenke tankog crijeva (4, 14). Zahvaćanje bubrega javlja se u više od trećine bolesnika, obično do mjesec dana poslije nastupa sustavnih simptoma (15). Prema kriterijima EULAR/PRINTO/PRES-a za IgA-vaskulitise, bubrežnu bolest karakteriziraju proteinurija, hematurija ili histopatološki nefritis s depozitima IgA u mezangiju (10). Rizični čimbenici za razvoj nefritisa jesu viša dob, komplikacije bolesti, muški spol, trajanje purpure, relaps bolesti, leukocitoza, trombocitoza i niske vrijednosti komplementa 3 (C3) (16). Bolest bubrega znatno se češće pojavljuje u starije djece i odraslih uz težu kliničku sliku (9). Dijagnoza IgA-nefritisa temelji se na kliničkoj prezentaciji, a potvrđuje dokazom depozita IgA u bioptatu bubrega. Biopsija bubrega s patohistološkom dijagnozom indicirana je kod nejasnog i težega bubrežnog oštećenja. U patohistološkoj dijagnostici bolesnika s IgA-nefritisom upo-

nificantly more common in older children and adults with more severe clinical features (9). The diagnosis of IgA nephropathy is based on clinical presentation and is confirmed by the evidence of IgA deposition in the kidney biopsy. Kidney biopsy with pathohistological diagnosis is indicated for obscure and severe renal impairment. Several classifications are used in the pathohistological diagnosis of patients with IgA nephropathy: the ISKDC classification (*International Study of Kidney Disease in Childr*en), the Haas system of classification and the Oxford classification (17 – 20). Individual morphological features such as mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, and tubular atrophy / interstitial fibrosis are assessed by the Oxford classification. In extremely rare cases, IgA vasculitis can manifest as central nervous system (CNS) vasculitis, encephalopathy, ischemic stroke, and pulmonary affection (21, 22). It is most often a case of self-limiting disease with a good prognosis. Regular monitoring and treatment are required in patients with occurring symptoms of kidney involvement, as well as gastrointestinal tract, respiratory system or CNS involvement. Public recommendations and unanimous views of umbrella organisations are still lacking in the treatment of this disease. Depending on the clinical features, symptomatic treatment, glucocorticoids, and in the most severe cases, immunosuppressants such as mycophenolate mofetil, azathioprine, cyclophosphamide, and rituximab are used.

RESEARCH SUBJECTS AND METHODS

This cohort study was conducted on patients over 18 years of age, who were treated at the Division of Clinical Immunology, Allergology and Rheumatology and at the Division of Nephrology and Dialysis of the Clinical Hospital Dubrava in Zagreb. The study included patients who were treated at the aforementioned divisions in the period from 2011 to 2019. The diagnosis of IgA vasculitis was made on the basis of patient's medical history, clinical status, common laboratory and imaging methods in clinical practice, skin biopsy and kidney biopsy. At the first hospitalisation of patients who had an indication (hematuria and proteinuria and azotemia) and who have signed an informed consent, a kidney biopsy was performed under local anesthesia and ultrasound control, by using an automatic biopsy device Biopty (C. R. Bard, USA). Signs of kidney disease were newly occurring hematuria and/or proteinuria and/or a reduction in the estimated glomerular filtration rate (eGFR). Patients with proteinuria were classified into the group suffering from nephrotic syndrome (24-hour urine protein test > 3.5 g / 1.73 m^2, hypoalbuminemia, hyperlipidemia, oedema) and subtrebljava se nekoliko klasifikacija: ISKDC-ova (engl. *International Study of Kidney Disease in Childr*en), Haasova i Oksfordska klasifikacija (17 – 20). Pojedinačna morfološka obilježja kao što su hipercelularnost mezangija, endokapilarna proliferacija, segmentalna glomeruloskleroza i tubularna atrofija / intersticijska fibroza ocjenjuju se Oksfordskom klasifikacijom. Vrlo se rijetko IgA-vaskulitis može očitovati vaskulitisom središnjega živčanog sustava (SŽS), encefalopatijom, ishemijskim infarktom mozga i afekcijom pluća (21, 22). Najčešće je to samolimitirajuća bolest dobre prognoze. Redovito praćenje i liječenje iziskuju bolesnici s prisutnim simptomima zahvaćenosti bubrega, gastrointestinalnog trakta, respiratornog sustava ili SŽS-a. U liječenju još nedostaju javne preporuke i jednoglasna stajališta krovnih društava. Ovisno o kliničkoj slici, primjenjuju se simptomatsko liječenje, glukokortikoidi, a u najtežim slučajevima i imunosupresivi kao što su mikofenolat-mofetil, azatioprin, ciklofosfamid i rituksimab.

ISPITANICI I METODE

Ovo kohortno istraživanje provedeno je među bolesnicima starijima od 18 godina u Zavodu za kliničku imunologiju, alergologiju i reumatologiju i u Zavodu za nefrologiju i dijalizu Kliničke bolnice Dubrava u Zagrebu. U njega su bili uključeni bolesnici koji su u tim zavodima liječeni od 2011. do 2019. godine. Dijagnoza IgA-vaskulitisa postavljena je na osnovi anamneze, kliničkog statusa, uobičajenih laboratorijskih i slikovnih metoda u kliničkoj praksi, biopsije kože te biopsije bubrega. Pri prvoj hospitalizaciji bolesnicima koji su imali indikaciju (hematurija i proteinurija te azotemija) i potpisali pristanak informiranog pacijenta učinjena je biopsija bubrega u lokalnoj anesteziji pod kontrolom ultrazvuka, i to s pomoću automatskog uređaja za biopsiju *Biopty* (C. R. Bard, SAD). Znakovi bubrežne bolesti bili su novonastala hematurija i/ili proteinurija i/ili smanjenje procijenjene glomerularne filtracije (eGFR). Bolesnici s proteinurijom klasificirani su u nefrotski sindrom (24-satna proteinurija > 3,5 g/1,73 m^2, hipoalbuminemija, hiperlipidemija, edemi) i subnefrotsku proteinuriju (< 3,5 g/1,73 m^2). Nefritički sindrom definiran je nalazom hematurije i novonastalog smanjenja eGFR-a i klasificiran kao akutan (smanjenje eGFR-a nastalo u nekoliko dana) ili brzoprogresivan (smanjenje eGFR-a nastalo tijekom nekoliko tjedana). Nalaz hematurije bez proteinurije i smanjenog eGFR-a klasificiran je kao asimptomatska hematurija. Bubrežno tkivo analizirano je svjetlosnim mikroskopom nakon bojenja hemalaun-eozinom, PAS-om, Massonovim trikromnim bojenjem i Jonesovim bojenjem, imunofluorescentnim mikroskopom nakon bojenja protutijelima za IgG, IgA, IgM, C3, C1q, fibrinogen, albumin, κ i λ-lance imunoglobulina te elektron-

nephrotic proteinuria (<3.5 g / 1.73 m^2). Nephritic syndrome was defined by the finding of hematuria and the newly occurring reduction in the eGFR and was classified as acute (reduction in the eGFR occurring within a few days) or rapidly progressive (reduction in the eGFR occurring over several weeks). The finding of hematuria without proteinuria and reduced eGFR was classified as asymptomatic hematuria. Renal tissue was analysed by light microscopy after staining with hematoxylin and eosin, Periodic acid–Schiff (PAS) staining, Masson's trichrome stain and Jones' stain, immunofluorescence microscope after immunostaining with antibodies for IgG, IgA, IgM, C3, C1q, fibrinogen, albumin, kappa (κ) and lambda (λ) immunoglobulin light chains and electron microscopy. Some parameters of the Oxford classification and other parameters were used in the pathohistological diagnosis. The pathohistological parameters analysed were the following: degree of interstitial fibrosis and tubular atrophy (IF/TA, expressed in %), semiquantitative determination of the degree of hyalinosis of the arterioles and changes in the arteries (fibrointimal thickening of the arterial walls) (0 - absence; 1 - mild; 2 - moderate; 3 - severe), degree of deposition of immunoglobulins IgA, IgM, IgG, complement components C3 and C1q (0 - absence; 1 - mild; 2 - moderate; 3 - severe), percentage of glomeruli with focal segmental glomerulosclerosis and completely connectively altered glomeruli. The occurrences of mesangial proliferation, endocapillary proliferation, extracapillary proliferation and the occurrence of podocyte foot fusion were analysed as well. Patients were monitored once a month for the first 6 months and following that period, every 3 months for the next 6 months and consequently every 6 months. Serum creatinine, eGFR, and 24-hour urine protein tests were monitored at each follow-up. Follow-up outcomes were patient survival, development of end-stage chronic kidney disease (defined by permanently reduced eGFR <15 mL / min / 1.73 m^2 or the need for permanent renal replacement therapy or kidney transplantation) and a permanent 50% reduction in the eGFR.

In statistical data processing, variables were presented as median and interquartile (IQ) range, and categorical variables were presented by number and percentage. The analysis was performed using computer programmes SPSS Statistics 19.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 11.4.2.0.

RESULTS

Demographic and clinical characteristics of patients are shown in Table 1. Parameters of renal function are shown in Table 2. Laboratory parameters of patients with IgA vasculitis are shown in Table 3. Kidney biopsy was performed on 18 patients, and in case of the remaining 4 patients, who exhibited symptoms of asskim mikroskopom. Pri patohistološkoj dijagnostici upotrijebljeni su pojedini parametri Oksfordske klasifikacije i drugi parametri. Analizirani patohistološki parametri bili su: stupanj intersticijske fibroze i tubularne atrofije (IFTA, izražen u %), semikvantitativno određivanje stupnja hijalinoze arteriola i promjene arterija (fibrointimalno zadebljanje stijenka) (0 – izostanak; 1 – blaga; 2 – umjerena; 3 – jaka), stupnja odlaganja imunoglobulina IgA, IgM, IgG, komponenata komplementa C3 i C1q (0 – izostanak; 1 – blago; 2 – umjereno; 3 – jako), postotak glomerula s fokalnom segmentalnom glomerulosklerozom i potpuno vezivno promijenjenih glomerula. Također, analizirano je postojanje mezangijske proliferacije, endokapilarne proliferacije, ekstrakapilarne proliferacije i postojanje fuzije nožica podocita. Bolesnici su praćeni jedanput na mjesec prvih 6 mjeseci pa svaka 3 mjeseca sljedećih 6 mjeseci, a zatim svakih 6 mjeseci. Na svakoj kontroli praćeni su serumska koncentracija kreatinina, eGFR i 24-satna proteinurija. Praćeni ishodi bili su preživljenje bolesnika, razvoj završnog stadija kronične bubrežne bolesti (definiran trajno smanjenim eGFR-om < 15 mL/min/1,73 m^2 ili potrebom za trajnim nadomještanjem bubrežne funkcije ili transplantacijom bubrega) i trajno 50%-tno smanjenje eGFR-a.

U statističkoj obradi podataka varijable su prikazane kao medijan i interkvartilni (engl. *interquartile* – IQ) raspon, a kategorijske varijable prikazane su brojem i postotkom. Analiza je provedena s pomoću računalnih programa SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, SAD) i MedCalc 11.4.2.0.

REZULTATI

Demografske i kliničke karakteristike bolesnika prikazane su na tablici 1. Parametri bubrežne funkcije prikazani su na tablici 2. Na tablici 3. prikazani su laboratorijski parametri oboljelih od IgA-vaskulitisa. Biopsija bubrega učinjena je u 18-ero bolesnika, a u preostala 4 bolesnika, koji su se prezentirali asimptomatskom hematurijom, nije izvedena zbog blagog tijeka bolesti i jer bolesnici na nju nisu pristali. Nalazi bubrežne biopsije prikazani su na tablici 4. Lijekovi koji su primjenjivani u liječenju prikazani su na tablici 5. Bolesnici su praćeni tijekom razdoblja od 23 do 84 mjeseca te im se bubrežna funkcija poboljšala ili je stagnirala, osim u jedne bolesnice liječene hemodijalizom, a koja je zbog brojnih komorbiditeta i visoke dobi preminula.

RASPRAVA

U ovom istraživanju analizirali smo kliničke i laboratorijske karakteristike, način liječenja i ishode u odraslih bolesnika oboljelih od IgA-vaskulitisa sa zahvaćanjem bubrega, koje su dijagnosticirali i liječili imunolog-reumatolog i nefrolog tijekom 8-godišnjeg

Table 1. Demographic and clinical characteristics of patients with IgA vasculitis
Tablica 1. Demografske i kliničke karakteristike oboljelih od IgA-vaskulitisa

		All patients / Svi bolesnici (n = 22)
Age during diagnosis (in years) / Dob pri dijagnozi (godine)		57 (40 – 71)
Sex (F/M) / Spol (Ž/M)		10 (45,5%) / 12 (55,5%)
Organ system involved / zahvaćeni organski sustav	Joints / Zglobovi	13 (59,1%)
	Digestive system / Abdominalni sustav	5 (22,7%)
	Nervous system / Živčani sustav	0 (0%)
	Renal / Bubreg	21 (95,5%)
Predisposing factor / Predisponirajući čimbenik	Unknown / Nepoznat	9 (40,9%)
	Respiratory infection / Respiratorna infekcija	6 (27,3%)
	Medications/ vaccines / Lijekovi/cjepiva	6 (27,3%)
	Neoplasms / Neoplazme	0 (0%)
	Other / Ostalo	1 (4,5%)

F/Ž = females / žene; M = muškarci / males

Table 2. Parameters of renal function in patients with IgA vasculitis
Tablica 2. Parametri bubrežne funkcije oboljelih od IgA-vaskulitisa

		All patients / Svi bolesnici (n = 22)
Serum creatinine / S-kreatinin (μmol/L)		93,0 (78,0 – 139,0)
eGFR (ml/min/1.73 m^2) (according to the CKD-EPI equation) / eGFR (mL/min/1,73 m2) (prema formuli CKD-EPI)		59,36 (41,10 – 93,88)
24-hour urine protein test / 24-satna proteinurija (g/dU)		1,87 (0,44 – 5,58)
Hematuria (sediment) / Hematurija (sediment)		22 (7 – 50)
Asymptomatic hematuria / Asimptomatska hematurija		10 (47,6%)
Subnephrotic proteinuria / Subnefrotska proteinurija		3 (14,3%)
Nephrotic syndrome / Nefrotski sindrom		9 (42,9%)
Nephritic syndrome / Nefritički sindrom	acute / akutan	2 (9,5%)
	rapidly progressive / brzoprogresivan	1 (4,8%)

S = serum; eGFR = estimated glomerular filtration rate / procijenjena glomerularna filtracija

Table 3. Laboratory parameters of patients with IgA vasculitis
Tablica 3. Laboratorijski parametri oboljelih od IgA-vaskulitisa

	All patients / Svi bolesnici (n = 22)
Hemoglobin (g/L)	129 (115 – 135)
RDW (%)	13,7 (13,2 – 14,2)
Serum albumin / S-albumin (g/L)	33 (31 – 40)
Serum complement C3 / S-C3 (g/L)	1,34 (1,13 – 1,59)
Serum complement category C3 (normal/elevated) / Kategorija S-C3 (normalan/povišen)	19 (86,4%) / 3 (13,6%)
Serum complement C4 / S-C4 (g/L)	0,33 (0,23 – 0,40)
Serum complement category C4 (normal/elevated) / Kategorija S-C4 (normalan/povišen)	17 (77,3%) / 5 (22,7%)
Serum IgA / S-IgA (g/L)	4,18 (2,72 – 5,34)

RDW = Red blood cell Distribution Width / širina distribucije eritrocita; S = serum

ymptomatic hematuria, it was not performed due to the mild course of the disease and because the patients did not consent to it. Parameters of kidney biopsy are shown in Table 4. Medications used in the treatment are shown in Table 5. Patient follow-up was performed for 23 to 84 months and, in the said period, all of them had improved or stagnant renal function, except for one patient treated with hemodialysis, who died due to numerous comorbidities and old age.

DISCUSSION

In this study, we analysed the clinical and laboratory characteristics, treatment methods, and outcomes in adult patients with renal involvement with IgA vasculitis, who were diagnosed and treated by an immunologist-rheumatologist and nephrologist over an 8-year period. IgA vasculitis is a disease that primarily occurs in children and is rare in adults (2, 23). In clinical practice, there is a lack of data on the characteristics of the disease and recommendations on diagnostic procedures and treatment of IgA vasculitis with kidney involvement in adulthood. In contrast to IgA vasculitis in children, when the disease is most often preceded by infections of the respiratory system, the use of medications and neoplasms is more often mentioned in adults

razdoblja. IgA-vaskulitis bolest je koja se ponajprije javlja u djece, a u odraslih je rijetka (2, 23). U kliničkoj praksi nedostaju podatci o karakteristikama bolesti i preporuke o dijagnostičkim postupcima i načinu liječenja IgA-vaskulitisa sa zahvaćanjem bubrega u odra-

Table 4. Pathohistological features of renal biopsies (in patients who underwent renal biopsy)
Tablica 4. Patohistološka obilježja bioptata bubrega (u bolesnika kojima je izvedena biopsija bubrega)

	All patients / Svi bolesnici (n = 18)
Glomeruli number in a kidney biopsy / Broj glomerula u bioptatu	20 (15 – 28)
Glomeruli number with FSGS (%) / Broj glomerula s FSGS-om (%)	0 (0 – 0)
Number of completely altered glomeruli in the glomerular capillary network (%) / Broj potpuno vezivno promijenjenih glomerula (%)	8,01 (2,78 – 15,0)
Patients with mesangial proliferation / Pacijenti s mezangijskom proliferacijom	11 (61,1%)
Patients with endocapillary proliferation / Pacijenti s endokapilarnom proliferacijom	14 (77,8%)
Patients with extracapillary proliferation (crescents) < 25% glomeruli / ≥ 5% glomeruli) / Pacijenti s ekstrakapilarnom proliferacijom (polumjesecima) (< 25% glomerula / ≥ 5% glomerula)	8 (44,4%) / 3 (16,7%)
IFTA (%)	2,5 (0 – 10,0)
MEST T-score (0 / 1) / MEST T-zbroj (0 / 1)	16 (88,9%) / 2 (11,1%)
Arteriolar hyalinosis (0 / 1 / 2 / 3) / Arteriolarna hijalinoza (0 / 1 / 2 / 3)	7 (38,9%) / 6 (33,3%) / 1 (5,6%) / 4 (22,2%)
Fibrointimal thickening of the arterial walls (0 / 1 / 2 / 3) / Fibrointimalno zadebljanje arterija (0 / 1 / 2 / 3)	11 (61,1%) / 3 (16,7%) / 4 (22,2%) / 0 (0%)
IgA by IF microscopy (1 / 2 / 3) / IgA na IF mikroskopiji (1 / 2 / 3)	5 (27,8%) / 6 (33,3%) / 7 (38,9%)
IgG by IF microscopy (0 / 1 / 2) / IgG na IF mikroskopiji (0 / 1 / 2)	13 (72,2%) / 4 (22,2%) / 1 (5,6%)
IgM by IF microscopy (0 / 1) / IgM na IF mikroskopiji (0 / 1)	16 (88,9%) / 2 (11,1%)
C3 by IF microscopy (0 / 1 / 2 / 3) / C3 na IF mikroskopiji (0 / 1 / 2 / 3)	7 (38,9%) / 9 (50,0%) / 1 (5,6%) / 1 (5,6%)
C4 and C1q by IF microscopy / C4 i C1q na IF mikroskopiji	Svi negativni
Podocyte foot fusion (non-existent/ focal/diffuse) / Fuzija nožica podocita (ne / fokalna / difuzna)	11 (61,1%) / 6 (33,3%) / 1 (5,6%)

FSGS = fokalna segmentalna glomuloskleroza; IFTA = intersticijska fibroza i tubularna atrofija; MEST T = zbroj intersticijske fibroze i tubularne atrofije u Oksfordskoj klasifikaciji; IF = imunofluorescentna

(9). In our study, respiratory system infections and the administration of medications and vaccines equally preceded the occurrence of IgA vasculitis, and there was no occurrence of neoplasm in this patient study group. The data from the research conducted by Mitsui et al. speak in favour of a clear connection between neoplasms and the occurrence of IgA vasculitis, in contrast to the data found in the research conducted by Alojzija Hočevar et al. The median age of our patients was 57, which is higher compared to the published data from the study conducted by Hung et al., in which the median age of patients was 44 (25), as well as the studies conducted by Kang et al., in which the median age of patients was 48 (9), and lower compared to the data from the study conducted by Alojzija Hočevar et al., in which the median age of the patients was 66 (23). In this study, we have observed a slightly more frequent incidence of the disease in males, which is in accordance with the data published so far. So, for example, in a study conducted by García et al., the ratio of males to females was 2.4: 1, in a study conducted by JI Shin et al. it was 1.2: 1, and in our study, it was 1.2: 1 (26, 27). All of our patients experienced skin changes and exhibited signs of kidney disease, and more than half of the patients experienced joint pain. Data from previ-

Table 5. Treatment of patients with IgA vasculitis
Tablica 5. Liječenje oboljelih od IgA-vaskulitisa

	All / Svi (n = 22)
Treatment with renin-angiotensin system inhibitors prior to the diagnosis (no/yes, < 1 year / yes, > 1 year) / Terapija inhibitorima sustava renin-angiotenzin prije dijagnoze (ne / da, < 1 godina / da, > 1 godina)	15 (68,2%) / 3 (13,6%) / 4 (18,2%)
Treatment with renin-angiotensin system inhibitors after the diagnosis / Terapija inhibitorima sustava renin-angiotenzin poslije dijagnoze	18 (81,8%)
Glucocorticoids / Glukokortikoidi	21 (95,5%)
Cyclophosphamide / Ciklofosfamid	5 (22,7%)
Mycophenolate mofetil / Mikofenolat-mofetil	1 (4,5%)
Acute hemodialysis / Akutna hemodijaliza	1 (4,5%)

RAAS = renin–angiotensin–aldosterone system / renin-angiotenzin-aldosteronski sustav

sloj dobi. Za razliku od IgA-vaskulitisa u djece, kad bolesti najčešće prethode infekcije respiratornog sustava, u odraslih se češće spominju primjena lijekova i

ous studies suggest a higher incidence of joint pain in children than in adults (28). It is most commonly a case of oligoarthritis involving the knee, hip, and ankle (13). It is known that IgA vasculitis is generally a mild disease with a good prognosis, and the complications and deaths that can occur are associated with IgA nephritis and other rare complications of the disease. The results of numerous studies show that IgA nephritis in adults is more severe than in children and tends to lead to the development of nephrotic syndrome, arterial hypertension, increased serum creatinine and chronic renal failure (29 – 31). In a study conducted by Kang et al., renal disease, with the development of nephrotic syndrome and renal failure, was present in 80% of adults, while microhematuria and mild renal impairment occurred in 30% of children with IgA vasculitis (9). In our study, almost 50% of patients had asymptomatic hematuria, 49% had nephrotic syndrome, and 14% had subnephrotic proteinuria, while the smallest number of patients experienced the most severe clinical form – nephritic syndrome. Increased serum IgA values are more common in adults with IgA vasculitis. In the case of our patients, mean IgA values were normal, as were the values of the complement components (C3 and C4) and serum creatinine values. Further research should be conducted on more patients in order to make the results and conclusions more reliable. According to the published results of previous research, low C3 values are among the risk factors for the development of nephritis (16). In order to make a pathohistological diagnosis during this study, the Oxford classification was used, in accordance with which the morphological features of the biopsy were evaluated. In clinical practice, there is a lack of consensus on the use of a single classification for the evaluation of the active and chronic components of the disease, which would be validated for IgA nephritis (32). It is a known fact that the Haas classification and the Oxford classification have been validated only for IgA nephropathy, although we also use them for IgA vasculitis with nephritis, as well as the ISKDC classification (*International Study of Kidney Disease in Children*) which is most commonly used in children. IgA vasculitis is spontaneously resolved in 94% of children and in 89% of adults (33). In our study, all patients, except one, were treated with glucocorticoids. Previous research shows that patients with severe IgA nephritis require treatment with glucocorticoids and immunosuppressants in order to achieve remission more quickly (34, 35). Treatment of IgA nephritis patients with hematuria and proteinuria also includes the use of RAAS inhibitors, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (36). In our study, this therapy was administered to 80% of patients. Cyclophosphamide was administered to five pa-

neoplazme (9). U našem istraživanju infekcije respiratornog sustava i uzimanje lijekova i cjepiva podjednako su prethodili IgA-vaskulitisu, a neoplazma u ispitivanoj skupini bolesnika nije bilo. Podatci Mitsuija i suradnika govore u prilog jasnoj povezanosti neoplazma i pojave IgA-vaskulitisa, a za razliku od podataka Alojzije Hočevar i suradnika (23, 24). Medijan dobi naših bolesnika bio je 57 godina, što je više u usporedbi s objavljenim podatcima Hunga i suradnika, kod kojih je medijan dobi bolesnika bio 44 godine (25), kao i istraživanja Kanga i suradnika s medijanom dobi od 48 godina (9), a manje u usporedbi s podatcima Alojzije Hočevar i suradnika u kojih je medijan dobi bolesnika bio 66 godina (23). Uočili smo nešto češću pojavnost bolesti u muškaraca, što je u skladu s dosad objavljenim podatcima. Tako je, primjerice, u istraživanju Garcíje i suradnika omjer muškaraca prema ženama bio 2,4 : 1, u istraživanju Jae Shin i suradnika iznosio je 1,2 : 1, a u našem je istraživanju taj omjer bio 1,2 : 1 (26, 27). Svi naši bolesnici imali su kožne promjene i znakove bubrežne bolesti, a bol u zglobovima imalo je više od polovine bolesnika. Podatci dosadašnjih istraživanja govore u prilog većoj pojavnosti boli u zglobovima u djece nego u odraslih (28). Najčešće je riječ o oligoartritisu sa zahvaćanjem koljena, kuka i gležnja (13). Poznato je da je IgA-vaskulitis uglavnom blaga bolest s dobrom prognozom, a komplikacije i smrtne ishode do kojih može doći povezujemo s IgA-nefritisom i rijetkim drugim komplikacijama bolesti. Rezultati brojnih istraživanja pokazuju da je IgA-nefritis u odraslih teži nego u djece te ima tendenciju razvoja nefrotskog sindroma, arterijske hipertenzije, porasta serumskih vrijednosti kreatinina i kroničnoga bubrežnog zatajenja (29 – 31). U istraživanju Kanga i suradnika bubrežna bolest, uz razvoj nefrotskog sindroma i bubrežnog zatajenja, bila je prisutna u 80% odraslih, dok su u 30% djece s IgA-vaskulitisom bili izraženi mikrohematurija i blago bubrežno oštećenje (9). U našem istraživanju asimptomatsku hematuriju imalo je gotovo 50% bolesnika, nefrotski sindrom njih 49%, a subnefrotsku proteinuriju 14% bolesnika, dok je najmanji dio bolesnika imao najteži klinički oblik – nefritički sindrom. Povišene serumske vrijednosti IgA češće se javljaju u odraslih s IgA-vaskulitisom. Srednje vrijednosti IgA u naših bolesnika bile su uredne, kao i vrijednosti komponenata komplementa (C3 i C4) i serumske vrijednosti kreatinina. Trebalo bi provesti daljnja istraživanja na većem broju bolesnika da bi rezultati i zaključci bili pouzdaniji. Prema objavljenim rezultatima dosadašnjih istraživanja, u rizične čimbenike za razvoj nefritisa ubrajaju se i niske vrijednosti C3 (16). Za patohistološku dijagnostiku tijekom ovog istraživanja rabili smo Oksfordsku klasifikaciju prema kojoj su se ocjenjivala morfološka obilježja bioptata. U kliničkoj praksi nedostaje konsenzus o uporabi jedinstvene klasifikacije s pomo-

tients, mycophenolate mofetil was administered to one patient, and one patient was treated with hemodialysis. There are currently no randomised controlled trials that clearly define the treatment of children and adults with IgA nephritis. However, in addition to the administration of glucocorticoids, ACE inhibitors, and angiotensin receptor blockers, most studies include the administration of immunosuppressants (11). It is generally accepted that morbidity from IgA vasculitis depends on the degree of renal involvement (1). In this study, patient follow-up was performed for 23 to 84 months and, in the said period, all of them had improved or stagnant renal function, except for one patient treated with hemodialysis, who died due to numerous comorbidities and old age.

CONCLUSION

The results of our study confirmed that most patients with IgA vasculitis have a good prognosis. In adults, in whom IgA vasculitis occurs less frequently than in children, renal complications may develop, which are the leading cause of death and the most important factor for the final outcome of the disease. Kidney biopsy is an important invasive diagnostic method to confirm the diagnosis of nephritis. This study demonstrated the importance of knowing the clinical, laboratory, and pathohistological characteristics of adult patients with IgA vasculitis. In everyday work, it is important to determine characteristics of renal changes in IgA vasculitis in order for an adequate therapeutic option to be applied.

ću koje bi se procjenjivale aktivna i kronična komponenta bolesti, a bila bi validirana za IgA-nefritis (32). Poznato je da su Haasova klasifikacija i Oksfordska klasifikacija validirane samo za IgA-nefropatiju, premda ih rabimo i za IgA-vaskulitis s nefritisom, kao i klasifikaciju ISKDC-a (engl. *International Study of Kidney Disease in Children*) koja se najčešće upotrebljava u djece. IgA-vaskulitis prolazi spontano u 94% djece i u 89% odraslih (33). U našem istraživanju svi su bolesnici, izuzevši jednoga, liječeni glukokortikoidima. Dosadašnja istraživanja pokazuju da bolesnici s teškim IgA-nefritisom iziskuju liječenje glukokortikoidima i imunosupresivima radi bržeg postizanja remisije (34, 35). Liječenje oboljelih od IgA-nefritisa s hematurijom i proteinurijom uključuje i primjenu inhibitora RAAS-a, inhibitora enzima koji konvertira angiotenzin (ACE-inhibitore) ili blokatora angiotenzinskih receptora (36). U našem istraživanju navedenu terapiju uzimalo je 80% bolesnika. Ciklofosfamid primalo je petero bolesnika, jedan je bolesnik primao mikofenolat-mofetil, a jedna je bolesnica liječena hemodijalizom. Zasad nema randomiziranih kontroliranih studija koje bi jasno definirale liječenje djece i odraslih oboljelih od IgA-nefritisa. Ipak, uz glukokortikoide, ACE-inhibitore i blokatore angiotenzinskih receptora, većina istraživanja uključuje i primjenu imunosupresiva (11). Općenito vrijedi da morbiditet od IgA-vaskulitisa ovisi o stupnju zahvaćenosti bubrega (1). U svojem istraživanju pratili smo bolesnike tijekom razdoblja od 23 do 84 mjeseca i svi su imali poboljšanu ili stagnirajuću bubrežnu funkciju, osim jedne bolesnice koja je liječena hemodijalizom te je zbog brojnih komorbiditeta i visoke dobi preminula.

ZAKLJUČAK

Rezultati našeg istraživanja potvrdili su da većina bolesnika s IgA-vaskulitisom ima dobru prognozu. U odraslih, u kojih se IgA-vaskulitis javlja rjeđe nego u djece, može doći do razvoja bubrežnih komplikacija koje su glavni uzrok smrtnih ishoda i najvažniji čimbenik za konačan ishod bolesti. Biopsija bubrega važna je invazivna dijagnostička metoda za potvrdu dijagnoze nefritisa. Ovo istraživanje pokazalo je važnost poznavanja kliničkih, laboratorijskih i patohistoloških karakteristika odraslih bolesnika s IgA-vaskulitisom. Pri svakodnevnom radu valja utvrditi značajke bubrežnih promjena da bismo na temelju tih obilježja primijenili prikladnu terapiju.

REFERENCES / LITERATURA

1. Trnka P. Henoch-Schönlein purpura in children. J Paediatr Child Health. 2013;49:995–1003.
2. Piram M, Mahr A. Epidemiology of immunologlobulin A vasculitis (Henoch-Schönlein): cuurrent state of knowledge. Curr Opin Rheumatol. 2013;25:171–8.
3. Heineke MH, Ballering AV, Jamin A i sur. New insights in the pathogenesis of immunoglobulin A vasculitis (Henoch-Schönlein purpura). Autoimmun Rev. 2017;16:1246–53.
4. Jelušić M, Malčić I i sur. Pedijatrijska reumatologija. Zagreb: Medicinska naklada; 2014.
5. Rigante D, Castellazzi L, Bosco A, Esposito S. Is there a crossroad between infections, genetics, and Henoch-Schönlein purpura? Autoimmun Rev. 2013;12:1016–21.
6. López-Mejías R, Genre F, Pérez BS i sur. Association of HLA-B*41:02 with Henoch-Schönlein Purpura (IgA vasculitis) in Spanish individuals irrespective of the HLA-DRB1 status. Arthritis Res Ther. 2015;17:102.
7. Pellegrin MC, Matarazzo L, Neri E, Pennesi M, Crovella S. HLA-B35, a common genetic trait, in a familial case of Henoch-Schoenlein purpura and Berger's disease. Genet Mol Res. 2014;13:2669–73.
8. Saulsbury FT. Epidemiology of Henoch-Schönlein purpura. Cleve Clin J Med. 2002;69(Suppl. 2):SII87–9.
9. Kang Y, Park JS, Ha YJ i sur. Differences in clinical manifestations and outcomes between adults and child patients with Henoch-Schönlein purpura. J Korean Med Sci. 2014;29:198–203.
10. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R i sur. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;69(5):798–806.
11. González LM, Janniger CK, Schwartz RA. Pediatric Henoch-Schönlein purpura. Int J Dermatol. 2009;48:1157–65.
12. Hadman JM, Barqawi MA. Henoch-Schönlein purpura in children. Saudi Med J. 2008;29:549–52.
13. Wang X, Zhu Y, Gao L, Wei S i sur. Henoch-Schönlein purpura with joint involvement: Analysis of 71 cases. Pediatr Rheumatol Online J. 2016;14:20.
14. Da Dalt L, Zerbinati C, Strafella MS i sur. Henoch-Schönlein purpura and drug and vaccine use in childhood: a case-control study. Ital J Pediatr. 2016;42:60.
15. Dalpiaz A, Schwamb R, Miao Y, Gonka J i sur. Urological Manifestations of Henoch- Schönlein Purpura: A Review. Curr Urol. 2014;8:66–73.
16. Chan H, Tang Y-L, Lv X-H i sur. Risk Factors Associated with Renal Involvement in Childhood Henoch-Schönlein Purpura. A Meta-Analysis. Plos One. 2016;11:e0167346.
17. Haas M. IgA nephropathy and Henoch-Schönlein purpura. U: Jennette JC, Olson JL, Schwartz MM, Silva FG (ur.). Pathology of the Kidney. Philadelphia: Lippincott Williams & Wilkins; 2007, str. 423–86.
18. Haas M. Histologic subclassification of IgA nephropathy: A clinicopathologic study of 244 cases. Am J Kidney Dis. 1997; 29:829–42.
19. Cattran DC, Coppo R, Cook HT i sur.; Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45.
20. Trimarchi H, Barratt J, Cattran DC i sur.; IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int. 2017;91:1014–21.
21. Stefek B, Beck M, Ioffreda M, Gardner L i sur. Henoch-Schönlein Purpura with Posterior Reversible Encephalopathy Syndrome. J Pediatr. 2015;167:1152–4.
22. Rajagopala S, Parameswaran S, Ajmera JS, Ganesh RN, Katrevul A. Diffuse alveolar hemorrhage in IgA nephropathy: case series and systemic review of the literature. Int J Rheum Dis. 2017;20:109–21.
23. Hočevar A, Rotar Z, Ostrovršnik J i sur. Incidence of IgA vasculitis in the adult Slovenian population. Br J Dermatol. 2014; 171:524–7.
24. Mitsui H, Shibagaki N, Kawamura T i sur. A clinical study of Henoch-Schönlein Purpura associated with malignancy. J Eur Acad Dermatol Venereol. 2009;23:394–401.
25. Hung S-P, Yang Y-H, Lin Y-T i sur. Clinical manifestations and outcomes of Henoch-Schönlein purpura: comparison between adults and children. Pediatr Neonatol. 2009;50:162–8.
26. García-Porrúa C, Calviño MC, Llorca J, Couselo JM, González-Gay MA. Henoch-Schönlein purpura in children and adults: clinical differences in a defined population. Semin Arthritis Rheum. 2002;32:149–56.
27. Shin JI, Park JM, Shin YH, Hwang DH, Kim JH, Lee JS. Predictive factors for nephritis, relapse, and significant proteinuria in childhood Henoch-Schönlein purpura. Scand J Rheumatol. 2006;35:56–60.
28. Jennette JC, Falk RJ, Andrassy K i sur. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37:187–92.
29. Uppal SS, Hussain MAS, Al-Raqum HA i sur. Henoch-Schönlein purpura in adults versus children/adolescents: A comparative study. Clin Exp Rheumatol. 2006;24:(2 Suppl 41):S26–30.
30. Pillebout E, Thervet E, Hill G i sur. Henoch-Schönlein Purpura in adults: outcomes and prognostic factors. J Am Soc Nephrol. 2002;13:1271–8.
31. Audemard-Verger A, Terrier B, Dechartres A i sur.; French Vasculitis Study Group. Characteristics and Management of IgA Vasculitis (Henoch-Schönlein) in Adults: Data From 260 Patients Included in a French Multicenter Retrospective Survey. Arthritis Rheumatol. 2017:69:1862–70.
32. Jelusic M, Sestan M, Cimaz R, Ozen S. Different histological classifications for Henoch-Schönlein purpura nephritis: which one should be used? Pediatr Rheumatol Online J. 2019;17:10.
33. Roberts PF, Waller TA, Brinker TM, Riffe IZ, Sayre JW, Bratton RL. Henoch-Schönlein Purpura: A review Article. South Med J. 2007;100:821–4.
34. Eleftheriou D, Brogan PA. Therapeutic advances in the treatment of vasculitis. Pediatr Rheumatol Online J. 2016;14:26.
35. González-Gay MA, Llorca J. Controversies on the use of corticosteroid therapy in children with Henoch-Schönlein purpura. Semin Arthritis Rheum. 2005;35:135–7.
36. Pohl M. Henoch-Schönlein purpura nephritis. Pediatr Nephrol. 2014;30:245–52.

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REVIEW PAPER PREGLEDNI RAD

EVIDENCE-BASED NON-PHARMACOLOGICAL TREATMENT OF OSTEOARTHRITIS

NEFARMAKOLOŠKO LIJEČENJE OSTEOARTRITISA UTEMELJENO NA DOKAZIMA

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Abstract

Osteoarthritis (OA) is the most common rheumatic joint disease, but also a disease that affects the entire joint and all structures surrounding the joint (periarticular structures). Literature dealing with this topic most commonly includes results related to the treatment of knee osteoarthritis (OA), while other localisations of degenerative changes of the joints are not researched in such a detailed way. In addition to that, these degenerative changes exhibit less evidence strength, so the same will be used in this review. According to the latest 2019 ESCEO guidelines for the treatment of OA, non-pharmacological treatment (NPT) has an important role in OA treatment and it is a part of all OA treatment algorithms, and it has to be a part of evidence-based medicine (EBM).

With technological progress in rehabilitation medicine, new solutions have appeared, as well as new forms of NPT aimed at helping patients, relieving pain, increasing the patients' functional ability and improving their quality of life. Due to this, in this literature review, which was accessed through the Cochrane library, PEDro database and PubMed search, we mostly found discussions about new technologies in OA treatment.

During that search, we can easily conclude that results of many systematic reviews and meta-analyses about the use of conventional methods of physical therapy did not change much compared to the methods used 10 years ago. When it comes to all of these methods, medical exercise is considered to be the most effective one, with the highest evidence strength. Nowadays, as opposed to literature sources in the past, in most literature we are able to find a significantly more accurate and precise definition of the term "physical activity". It is defined as an activity performed during an individual's stay at their workplace, during transport, while doing one's chores or housework, and during leisure time. We believe that the newest, modern technologies in rehabilitation medicine, such as the following ones: high-intensity laser therapy (HILT), extracorporeal shock wave therapy (ESWT), radio frequency (RF) and electromagnetic therapy super inductive system (SIS), present the biggest challenge in the NPT of OA today. These treatment methods, according to the available EBM data, have shown outstanding efficiency in the treatment of OA by reducing the patients' pain, improving patients' functional ability as well as their quality of life, with minimal adverse effects. Today, the general opinion is that we should give advantage to modern technologies in combination with already well-known and defined medical exercises with implementing preventive activities.

Key Words: Osteoarthritis, knee – rehabilitation, therapy; Exercise therapy; Physical therapy modalities; Laser therapy; Extracorporeal shockwave therapy; Radiofrequency therapy; Pulsed electromagnetic field therapy; Pain; Treatment outcome; Evidence-based medicine

Sažetak

Osteoartritis (OA) najčešća je reumatska bolest zgloba i svih okolozglobnih struktura. U literaturi su najčešće zastupljeni rezultati vezani uz liječenje OA koljena, a ostale lokalizacije degenerativnih promjena zglobnih struktura manje su istraživane. Pritom su i dokazi manje snage pa će tako biti i u ovome preglednom članku. Prema ažuriranim smjernicama ESCEO-a iz 2019. g., bitnu ulogu u liječenju bolesnika s OA ima i nefarmakološko liječenje (NFL) – dio svih algoritama liječenja OA, uz preporuku da mora biti utemeljeno na dokazima (EBM). Tehnološki napredak u rehabilitacijskoj medicini nudi neka nova rješenja, nove oblike NFL-a radi pomoći bolesnicima, uklanjanja boli i povećanja funkcionalnih mogućnosti, čime se poboljšava i kvaliteta života. Zbog toga se u literaturi koja je dostupna pregledom Cochraneove knjižnice, baze PEDro i tražilice PubMed danas najčešće raspravlja o novim tehnologijama u liječenju OA. Primjećujemo da se rezultati brojnih sustavnih pregleda i metaanaliza o primjeni konvencionalne fizikalne terapije nisu bitno promijenili u odnosu prema onima u sličnim analizama i prije 10-ak godina. Najučinkovitijom metodom, uz najkvalitetniju snagu dokaza, smatra se medicinska vježba. No, za razliku otprije, danas u literaturi nalazimo znatno točniju i precizniju definiciju pojma tjelesne aktivnosti: to je aktivnost tijekom boravka na radnome mjestu, za vrijeme transporta, tijekom obavljanja kućanskih poslova i u slobodno vrijeme. Najveći izazov u NFL-u OA danas jesu moderne tehnologije u rehabilitacijskoj medicini, a to su terapije laserom visokog intenziteta (HILT), udarnim valom (ESWT), radiofrekvencijom (RF) i elektromagnetskim poljem visokog intenziteta (SIS). Te metode liječenja, prema dostupnim podatcima EBM-a, pokazale su izrazitu učinkovitost u liječenju OA: reduciranu bol kod ispitanika, poboljšane funkcionalne sposobnosti i kvalitetu života bolesnika. Sve to uz izrazito malo neželjenih događaja. Danas je uvriježeno mišljenje da treba davati prednost modernim tehnologijama, dobro definiranim medicinskim vježbama i provođenju preventivnih aktivnosti.

Ključne riječi: Osteoartritis koljena – liječenje, rehabilitacija; Terapijske vježbe; Fizioterapijske tehnike; Terapija laserom; Izvantjelesna terapija udarnim valom; Radiofrekvencijska terapija; Terapija elektromagnetskim poljem; Bol; Ishod liječenja; Medicina utemeljena na dokazima

INTRODUCTION

Nowadays, osteoarthritis (OA) has become increasingly perceived as a huge global issue and the most common rheumatic disease (1,2). The socioeconomic and health significance of OA in the overall pathology of the population is continuously increasing, mainly due to a significant increase in two risk factors: an increase in the share of the elderly in the overall population and an increase in the number of obese individuals in the overall population, especially in the younger (working-age) age groups (3, 4). There is a significantly positive correlation between the incidence of OA and both risk factors, which is why this disease will continue to be in the centre of interest of both public health workers as well as rheumatologists and physiatrists for a long time. The disease (OA) is manifested by morphological, biochemical, molecular, and biomechanical changes of cells and intercellular substance in all tissues that make up the diarthrodial joint (2, 4). Therefore, we need to be aware of the fact that OA is a disease which affects the entire joint and periarticular structures, not just the articular cartilage as is most commonly thought.

Due to the aforementioned facts, it was necessary to prepare and create certain algorithms, that is, procedures for the prevention, treatment and rehabilitation of patients suffering from the said conditions. So, with this in mind, the professional societies of the Croatian Medical Association, such as the Croatian Society for Rheumatology in 2010 (5) and the Croatian Society of

UVOD

Osteoartritis (OA) se sve više percipira kao velik globalni problem i najučestalija reumatska bolest današnjice (1, 2). Sve je veće i socioekonomsko i zdravstveno značenje OA u sveukupnoj patologiji pučanstva, a poglavito zbog znatnog povećanja dvaju rizičnih čimbenika: porasta udjela starijih osoba u sveukupnoj populaciji i porasta broja pretilih osoba u sveukupnoj populaciji, poglavito u mlađim (radno aktivnim) dobnim skupinama (3, 4). Pritom postoji znatno pozitivna korelacija između pojavnosti OA i obaju rizičnih čimbenika, zbog čega će ova bolest dugo biti u središtu zanimanja i javnozdravstvenih radnika i reumatologa i fizijatara. Bolest (OA) se manifestira morfološkim, biokemijskim, molekularnim i biomehaničkim promjenama stanica i međustanične tvari u svim tkivima koja čine diartrodijalni zglob (2, 4). Zato trebamo biti svjesni činjenice da je OA bolest cijeloga zgloba i okolozglobnih struktura, a ne samo zglobne hrskavice kao što se najčešće mislilo.

Zbog prije navedenih činjenica nužno je bilo osmisliti i napraviti algoritme – postupnike prevencije, liječenja i rehabilitacije ovih bolesnika pa su tako stručna društva HLZ-a – Hrvatsko reumatološko društvo 2010. g. (5) i Hrvatsko društvo za fizikalnu i rehabilitacijsku medicinu 2015. g. (6) – takve dokumente donijela na nacionalnoj razini. Pritom je bitno naglasiti činjenicu da se u oba dokumenta velika važnost pridaje nefarmakološkom liječenju (NFL) OA.

Physical and Rehabilitation Medicine in 2015 (6), have adopted such documents at the national level. It is important to highlight the fact that, in both of these documents, great importance was given to non-pharmacological treatment (NPT) of OA.

NPT includes a number of procedures: education and training, medical gymnastics, weight loss, passive physical therapy, and the use of orthoses (5, 6). All of this is in accordance with the latest recommendations of one of the EU umbrella organisations dealing with both social as well as clinical and economic aspects of this disease: the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) (7). The aforementioned organisation notes that all recommendations on the importance and effectiveness of the NPT must be made only on the basis of data obtained using evidence-based medicine (EBM). The ESCEO states that there is an abundance of evidence strength regarding recommendations for the implementation of NPT interventions, with an objective presentation of their overall effectiveness and limitations, but also with an emphasis on the safety of their use in everyday practice (8).

All of the above mentioned facts prompted us to search the latest medical literature on the basis of evidence-based medicine (EBM) and try to find the answer to the following question: what is the level of importance and effectiveness of NPT in terms of OA treatment?

METHODS

In order to prepare this review article we have performed a search of the following databases that are relevant to the field of rheumatology and rehabilitation medicine: the PEDro database (Physiotherapy Evidence Database), the MEDLINE Library and the Cochrane Library (Cochrane Database of Systematic Reviews). We have also done a search of the references of the relevant papers included in the review article. We have decided to take into consideration only the articles related to the NPT of OA in individuals over the age of 18, which were published by January 2020 at the latest. The included papers were written in both English and Croatian. With the help of the following keywords: osteoarthritis, non-pharmacological treatment, modalities of physical therapy and rehabilitation, which were harmonised in accordance with MeSH (Medical Subject Headings), and after the exclusion of certain protocols, duplicate articles and articles not related to NPT, we have found a total of 27 relevant articles.

Two researchers have independently selected articles that met the above-mentioned criteria and collected relevant data, and we have noted that most of the data is related to OA of large weight-bearing joints, particularly the knees. There is fewer general data on OA, some data are related to the spine, and the least amount of data collected is the data related to small joints. It is

U NFL se ubrajaju brojni postupci: edukacija, medicinska gimnastika, smanjenje tjelesne težine, pasivna fizikalna terapija, uporaba ortoza (5, 6). Sve je to u skladu i s najnovijim preporukama jednog od krovnih europskih tijela koje se bavi i socijalnim i kliničkim te ekonomskim aspektima ove bolesti: Europskog društva za kliničke i ekonomske aspekte osteoporoze, osteoartritisa i mišićno-koštanih bolesti (engl. *European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases* – ESCEO) (7). Ono pritom napominje da se sve preporuke o važnosti i učinkovitosti NFL-a moraju donositi samo na temelju podataka dobivenih s pomoću medicine utemeljene na dokazima (engl. *Evidence-based medicine* – EBM). ESCEO navodi da postoji velika snaga dokaza u svezi s preporukama za primjenu intervencija NFL-om, uz objektivnost prikaza svih njihovih učinkovitosti i ograničenosti, ali i naglašenu sigurnost njihove uporabe u svakodnevnoj praksi (8).

Sve prije navedeno potaknulo nas je da na osnovi medicine utemeljene na dokazima (EBM) pretražimo najnoviju medicinsku literaturu i pokušamo odgovoriti na pitanje: koliko je važno i učinkovito NFL u OA.

METODE

Za izradu ovoga preglednog članka pretražili smo baze podataka koje su relevantne za područje reumatologije i rehabilitacijske medicine: PEDro (engl. *Physiotherapy Evidence Database*), Medline i Cochraneovu knjižnicu (engl. *Cochrane Database of Systematic Reviews*). Dodatno smo pretražili referencije relevantnih radova uključenih u pregledni članak. U razmatranje smo uzeli samo članke koji su se odnosili na NFL OA kod osoba starijih od 18 godina, a objavljeni su zaključno do siječnja 2020. g. Uključeni su radovi pisani na engleskom i hrvatskom jeziku. S pomoću ključnih riječi: osteoartritis, nefarmakološko liječenje, modaliteti fizikalne terapije i rehabilitacije, usklađenih prema MeSH-u (engl. *Medical Subject Headings*), a nakon isključenja protokola, dvostruko ponovljenih članaka i članaka koji se ne odnose na NFL, pronašli smo ukupno 27 relevantnih članaka.

Dvojica su istraživača neovisno odabrala članke koji odgovaraju gore navedenim kriterijima i prikupili relevantne podatke, pri čemu smo uočili da se najveći broj podataka odnosi na OA velikih zglobova, osobito koljena. Manje ima općenitih podataka o OA, ponešto o kralježnici, a najmanje o malim zglobovima. Pritom su, kao kuriozitet, u jednoj analizi nađeni podatci i o OA temporomandibularnih (TM) zglobova (9).

REZULTATI ISTRAŽIVANJA

Pregled najnovijih preporuka o liječenju OA, objavljenih u medicinskoj literaturi, navodimo s obzirom na

an interesting fact that data on OA of temporomandibular joints (TMJ) were found in one analysis (9).

RESEARCH RESULTS

We have provided an overview of the latest OA treatment recommendations published in medical literature, with respect to the type of NPT studied and the efficacy and tolerability monitored on the basis of EBM criteria.

1. *Medical gymnastics / medical exercises / kinesiotherapy / physical activity*

The results of a 2019 study conducted by Natalie Collins et al. showed that 1994 papers were included in the systematic review, including 13 systematic reviews and 36 randomised controlled trials (RCTs). 73% of these studies have evaluated the effect of NPT of knee OA (36 studies) (10). The other studies have evaluated the effect of NPT of hand OA (6 studies), as well as OA of the hip, hip / knee and generalised OA (2 studies each) and cervical spine OA (1 study). Out of all NPT methods, the method of medical exercises was the most commonly evaluated one in the aforementioned studies (31%). Finally, the authors have concluded that, in accordance with the current clinical guidelines, medical exercises should be the main procedure in OA rehabilitation, and that future studies should provide conditions for medical exercise programmes to be well defined and in order for them to be more comparable to each other. Therefore, there is still a clear need for research of rehabilitation procedures in OA of the hip, hand, foot, ankle, shoulder, and spine, which were not sufficiently represented in the reviewed studies (10).

Research conducted in 2018 by Ferreira et al. included an overview of 2188 studies, with only 41 of those studies meeting strictly and precisely set criteria. The opinion was based on the results of 35 classified studies, included in accordance with the set, very precise and strict criteria (11). Based on systematic reviews of the literature, the authors have concluded that there is **valid evidence** that a standard exercise programme can alleviate pain and improve physical function in patients with knee OA (11).

Furthermore, there is **moderate or medium strong evidence** that acupuncture, hydrotherapy, electroacupuncture, interference currents, kinesiology tape, manual therapy, moxibustion, pulsed electromagnetic field therapy, Tai Chi, ultrasound, yoga and vibration techniques that have been applied to the entire body (more as an adjuvant therapy to the set exercises than as a stand-alone intervention) have proved to be effective with regard to the assessed results (11).

According to the systematic reviews of literature, the **quality of evidence** for all other interventions **was low or it did not exhibit sufficient efficiency** which would speak in favour of their application (11).

vrstu NFL-a koja je proučavana te učinkovitost i podnošljivost praćene na temelju kriterija EBM-a.

1. *Medicinska gimnastika / medicinske vježbe / kinezioterapija / tjelesna aktivnost*

Rezultati istraživanja Natalie Collins i suradnika iz 2019. g. pokazali su da su u sustavni pregled bila uključena 1994 rada, među kojima je bilo 13 sustavnih pregleda i 36 randomiziranih kontroliranih studija (RCT). Njih 73% evaluiralo je učinak NFL-a kod OA koljena (36 studija) (10). Ostale su evaluirale učinak NFL-a kod OA šaka (6 studija), kuka, kuka/koljena i generaliziranog OA (po 2 studije za svaki) i OA vratne kralježnice (1 studija). Od svih metoda NFL-a u navedenim je studijama najčešće bila evaluirana metoda medicinskih vježbi (31%). Na kraju su autori zaključili da bi, u skladu sa sadašnjim kliničkim smjernicama, medicinske vježbe trebale biti glavni postupak pri rehabilitaciji OA, a buduće bi studije trebale osigurati uvjete da programi vježbi budu dobro definirani i međusobno bolje usporedivi. Stoga i dalje postoji jasna potreba za istraživanjima rehabilitacijskih postupaka kod OA kuka, šake, stopala, gležnja, ramena i kralježnice, koji u pregledanim studijama nisu bili dovoljno zastupljeni (10).

Istraživanje Ferreire i suradnika iz 2018. g. uključilo je pregled 2188 studija, pri čemu je samo 41 zadovoljavala strogo i precizno zadane kriterije. Mišljenje je doneseno na temelju rezultata 35 klasificiranih studija, uključenih prema postavljenim, vrlo preciznim i strogim kriterijima (11). Na temelju sustavnih pregleda literature autori su zaključili kako postoji **valjani dokaz** da standardni program vježbi može ublažiti bol i poboljšati fizičku funkciju kod bolesnika s OA koljena (11).

Nadalje, postoji **umjereni ili srednje jaki dokaz** da su akupunktura, hidroterapija, elektroakupunktura, interferentne struje, kineziološka vrpca (engl. *kinesiology tape*), manualna terapija, moksibustija, pulsno elektromagnetsko polje, *Tai Chi*, ultrazvuk, joga i vibracijske tehnike primijenjene na cijelo tijelo (više kao dodatak vježbama nego kao samostalna intervencija) učinkovite s obzirom na procijenjene rezultate (11).

Prema sustavnim pregledima literature, **kvaliteta dokaza** za sve ostale intervencije **bila je slaba ili nije pokazivala dovoljnu učinkovitost** koja bi poduprla njihovu primjenu (11).

Osim toga, uspoređujući pregled svih spomenutih metoda NFL-a, potvrđena je vrijednost zajedničke primjene akupunkture i vježbi. Što se, pak, tiče primjene transkutane električne stimulacije živca (TENS) i lasera niskog intenziteta (LLLT) u procesu smanjenja boli i poboljšanja fizičkih mogućnosti bolesnika, nađeni rezultati bili su različiti (11).

U sustavnom pregledu Ceballos-Laite i suradnika iz 2018. g. ispitivao se učinak, zajednički i pojedinačni,

In addition to that, by comparing the overviews of all of the aforementioned NPT methods, the value of the joint application of acupuncture and medical exercises was confirmed. With regard to the application of transcutaneous electrical nerve stimulation (TENS) and low-level laser therapy (LLLT) in the process of reducing pain and improving the physical abilities of patients, the results found were different (11).

In the 2018 systematic review prepared by Ceballos-Laite et al. the joint and individual effects of manual therapy and medical exercises on pain, range of motion and physical abilities of patients suffering from hip OA were researched (12). Finally, the authors have concluded that medical exercises and manual therapy and their combination with patient education and training ensure a good effect on the reduction of pain and improvement of physical function of patients (12). The effect of combination therapy remains unclear due to the inaccurate determination of the effect of individual components on target parameters, so the authors state that further research is required in order to improve knowledge about the effects of these NPT methods on pain and functional capacity of the hip (12).

The significance of physical activity and medical exercises in the treatment of rheumatic diseases, which became increasingly discussed in both medical literature and everyday practice, prompted the European umbrella organisation for rheumatology, European League Against Rheumatism (EULAR), to form a working group that adopted its opinion and published the EULAR guidelines with recommendations for physical activity in patients with inflammatory rheumatic diseases and OA in 2018 (13). According to these guidelines, physical activity includes all forms of movement, i.e. activity in everyday life, including work, recreation and sports activities, and is categorised according to the level of intensity, from low or weak, through moderate to strong or high intensity, with relatively precise variables in their implementation. The recommendations for four types of physical activity are listed below:

a) *occupational physical activity*,
b) *transportation physical activity*,
c) *housework, home maintenance*,
d) *leisure-time physical activity*.

Nevertheless, the authors conclude that it is necessary to define the type, intensity and frequency of exercise in a better way, and in order to make physical activity and medical exercises as similar as possible to pharmacotherapy for which these parameters are very precisely determined today (13).

In 2019, in an attempt to review Cochrane's cumulative presentation of the benefits of medical exercise in patients with hip OA, Elena Ilieva published the results of an article search from the Cochrane Library that included 21 studies and analysed 12 of them, with a moderate and low quality of evidence (14). The analysed

manualne terapije i medicinskih vježbi na bol, opseg pokreta i fizičke sposobnosti u bolesnika s OA kuka (12). Na kraju autori zaključuju da medicinske vježbe i manualna terapija te njihova kombinacija s edukacijom bolesnika osiguravaju dobar učinak na bol i poboljšanje fizičke funkcije (12). Učinak kombinirane terapije ostaje nejasan zbog nepreciznog određivanja utjecaja pojedinih komponenata na ciljne parametre pa autori navode da su potrebna daljnja istraživanja radi unaprjeđenja znanja o učincima spomenutih metoda NFL-a na bol i funkcionalni kapacitet kuka (12).

Značenje tjelesne aktivnosti i medicinskih vježbi u liječenju reumatskih bolesti, kojemu se i u medicinskoj literaturi i u svakodnevnoj praksi počela pridavati sve veća pozornost, potaknulo je i krovno Europsko udruženje reumatologa (EULAR) da formira radnu skupinu koja je o tome donijela svoje mišljenje i 2018. g. objavila EULAR-ove smjernice s preporukama za tjelesnu aktivnost kod bolesnika s upalnim reumatskim bolestima i OA (13). Prema tim smjernicama, tjelesna aktivnost obuhvaća sve pokrete, tj. kretanje u svakodnevnom životu uključujući posao, rekreaciju i sportske aktivnosti, a kategorizirana je s obzirom na razinu intenziteta od niskog odnosno slaboga, preko umjerenoga do snažnog odnosno visokog intenziteta, uz relativno precizne varijable u njihovu provođenju. Navedene su preporuke za četiri vrste tjelesne aktivnosti:

a) tjelesna aktivnost na radnome mjestu (engl. *Occupational physical activity*)
b) tjelesna aktivnost za vrijeme prijevoza, odnosno putovanja s mjesta na mjesto (engl. *Transportation physical activity*)
c) tjelesna aktivnost u kući i oko kuće (engl. *Housework, home maintenance*)
d) tjelesna aktivnost u slobodno vrijeme (engl. *Leisure-time physical activity*).

Ipak, i ovdje autori u zaključku navode da je potrebno bolje definirati vrstu, intenzitet i učestalost vježbanja, a kako bi tjelesna aktivnost i medicinske vježbe postale što sličnije farmakoterapiji za koju su ti parametri danas vrlo precizno određeni (13).

Želeći se osvrnuti na Cochraneov zbrojni prikaz dobrobiti medicinskih vježbi kod bolesnika s OA kuka, Elena Ilieva objavila je 2019. g. rezultate pretraživanja članaka iz Cochraneove knjižnice koji su uključivali 21 studiju, a analizirano je njih 12, osrednje i slabe kvalitete dokaza (14). Analizirani rezultati dokazali su da bi sudjelovanje u programu vježbi moglo imati važnu ulogu u postupcima NFL-a kod bolesnika s OA, jer ono može znatno poboljšati funkciju zgloba, smanjiti bol i depresiju te povećati samoučinkovitost i društveno funkcioniranje (14). Bolesnike bi pritom trebalo ohrabriti da sudjeluju u programima vježbi osmišljenih prema njihovim osobnim sklonostima, sposobnostima i potrebama, uz savjet i upute zdravstvenih pro-

results showed that participation in an exercise programme could play an important role in NPT procedures in patients with OA, as it can significantly improve joint function, reduce pain and depression, and increase self-efficacy and social functioning (14). Patients should be encouraged to participate in exercise programmes prepared in accordance with their personal preferences, abilities, and needs, with the advice and guidance of health professionals. OA treatment was evaluated as a complex and multimodal procedure (14).

Thus, based on all of the above mentioned facts, as well as according to all analysed guidelines in the aforementioned publications (EULAR, ESCEO, ACR, OARSI, Cochrane database), medical exercises were singled out as a key non-pharmacological method of OA treatment that is highly recommended for pain reduction and improving joint function (8, 13, 14). This is a non-invasive and low-cost treatment method whose primary effect is short-term, while long-term positive effects are only achieved through great patient adherence to treatment.

Patient education and training performed with the purpose of implementing exercises in the activities of daily living (ADL) and lifestyle changes is extremely important in achieving these results. The reason for the suboptimal quality of OA treatment with NPT is the patients' motivation to exercise, which may ultimately create a barrier in the implementation of clinical evidence and guidelines.

After studying the significance and effect of medical exercises as a method of non-pharmacological treatment of osteoarthritis, we were interested in what the available medical literature had to say about the so-called **new technologies in medical rehabilitation**, which most often include the following:

a. **High Intensity Laser Therapy (HILT)**: high output power of the laser beam up to 12 W enables deep penetration into the tissue and quality pain relief,

b. **Extracorporeal Shockwave Therapy (ESWT)**: non-invasive extracorporeal shockwave therapy for musculoskeletal pain,

c. **Radio frequency (RF)**: targeted high-frequency electromagnetic energy directed at the selected tissue as a non-thermal method of cellular biostimulation. Most common indications include: localised muscle twitches, trigger points, myalgia, tendinitis, neck pain and posttraumatic oedema, with an extremely rapid effect,

d. **High-intensity electromagnetic field** (the so-called electromagnetic therapy super inductive system, **SIS**): technology based on a high-intensity electromagnetic field that has a positive effect on human tissue. Therapeutic effects include pain reduction, fracture treatment, myorelaxation, myostimulation, and joint mobilisation.

In all of the found studies, which were relatively well prepared and performed, the most frequently monifesionalaca. Liječenje OA ocijenjeno je kao kompleksno i multimodalno (14).

Dakle, na temelju svega navedenoga, kao i prema svim analiziranim smjernicama u spomenutim publikacijama (EULAR, ESCEO, ACR, OARSI, Cochraneova baza podataka), medicinske su vježbe izdvojene kao ključna nefarmakološka metoda liječenja OA koja ima snažnu preporuku s obzirom na smanjenje boli i poboljšanje funkcije zgloba (8, 13, 14). Riječ je o neinvazivnoj, a jeftinoj metodi liječenja čiji je prvotni učinak kratkoročan, dok je za dugoročan pozitivni učinak potrebna dobra adherencija bolesnika.

Edukacija bolesnika radi implementacije vježbi u aktivnosti dnevnog življenja (ADŽ) i promjenu životnog stila iznimno je važna pri postizanju tih rezultata. Suboptimalnoj kvaliteti liječenja OA NFL-om razlog je upravo motivacija bolesnika za vježbanje, što na kraju može stvoriti barijeru pri implementaciji kliničkih dokaza i smjernica.

Nakon proučavanja značenja i učinka medicinskih vježbi kao metode nefarmakološkog liječenja osteoartritisa zanimalo nas je što dostupna medicinska literatura navodi o tzv. **novim tehnologijama u medicinskoj rehabilitaciji**, među koje se najčešće ubrajaju:

a. **Laser visokog intenziteta** (engl. *High Intensity Laser Therapy* – **HILT**): visoka izlazna snaga laserskog snopa do 12 W omogućava duboko prodiranje u tkivo i kvalitetno ublažavanje boli

b. **Udarni val** (engl. *Extracorporeal Shockwave Therapy* – **ESWT**): neinvazivna izvantjelesna terapija udarnim valom za boli mišićno-koštanog sustava

c. **Radiofrekvencija** (**RF**): usmjerena elektromagnetska energija visoke frekvencije upućena u odabrano tkivo kao netermalna metoda stanične biostimulacije. Najčešće indikacije jesu: lokalizirani grčevi mišića, okidačke (engl. *trigger*) točke, mialgija, tendinitis, bol u vratu i posttraumatski edem, uz vrlo brzi učinak

d. **Elektromagnetsko polje visokog intenziteta** (tzv. superinduktivni sustav – **SIS**): tehnologija zasnovana na elektromagnetskom polju visokog intenziteta koja pozitivno djeluje na ljudsko tkivo. Terapijski učinci uključuju smanjenje boli, liječenje fraktura, miorelaksaciju, miostimulaciju i mobilizaciju zglobova.

U svim nađenim studijama, koje su bile relativno dobro osmišljene i izvedene, najčešće praćeni parametri mjere ishoda liječenja bili su: razina oštećenja (morfologija i funkcija), bol i funkcionalne mogućnosti. Pritom su kao instrumenti ishoda liječenja upotrijebljeni: vizualno-analogna ljestvica boli (VAS), WOMAC-ov indeks i Lequesneov indeks (LI) stupnja nesposobnosti, a kao instrument za klasifikaciju težine OA Kellgren-Lawrenceov radiografski indeks, koji su omogućili objektivne procjene učinka liječenja.

U prvome sustavnom pregledu učinka HILT-a na OA koljena 2018. g. Justyna Wyszyńska i suradnici

tored parameters of the treatment outcome measure were the following: level of impairment (morphology and function), pain, and functional abilities. The following instruments were used as instruments of treatment outcome: the visual analogue scale (VAS) of pain intensity, the Western Ontario and McMaster Universities Arthritis Index (WOMAC), the Lequesne Index (LI) of the level of severity, and the Kellgren-Lawrence radiographic index as an instrument for OA severity classification, all of which have enabled objective evaluations of treatment effect to be performed.

In the first systematic review of the effect of HILT on knee OA performed in 2018, Justyna Wyszyńska et al. included 6 studies in the analysis (15). All of the selected studies have confirmed that HILT was useful in the treatment of knee OA because it has reduced pain and increased functional abilities of patients suffering from the said disease (15).

At the same time, it was necessary to draw attention to the difference between the efficacy of the new HILT therapy and previously used LLLT therapy in the treatment of knee OA. In 2014, Kheshie et al. conducted a randomised control study in which they have compared these two energetically different lasers during their application in NPT of patients suffering from knee OA (16). After the treatment was applied for 6 weeks, the result showed that both HILT and LLLT in combination with exercise have proved to be an effective modality of OA treatment, with the results of pain reduction which were obtained using VAS and according to the WOMAC index. HILT used in combination with exercise was more effective than LLLT used in combination with exercise, and both treatment modalities showed better results than just using exercise alone when it came to patients suffering from knee OA (16).

The emergence of new technologies has brought about common comparisons with the methods of treatment which were used prior to their occurrence, although the name "conventional physical therapies" rarely specified which therapeutic methods were implied under this term. Thus, in 2018, Nazari et al. published the results of a randomised control study in which they have compared the effect of HILT and conventional physical therapy with exercise on the Iranian urban population, which showed that HILT was more effective in the treatment of pain measured through VAS and increasing range of motion (17).

The results of their study have shown that HILT was a safe and well-tolerated method in the treatment of patients suffering from knee OA. In addition to this, high-intensity laser therapy used in combination with exercise has proved to be more effective than conventional physical therapy used in combination with exercise or exercise alone in terms of pain relief and improvement of functional ability of patients suffering from knee OA, and it proved to be effective in other

uključili su u analizu 6 studija (15). Sve odabrane studije potvrdile su da je HILT bio koristan u tretmanu OA koljena, jer je smanjio boli i povećao funkcionalne mogućnosti u bolesnika s tom bolesti (15).

Istodobno, pokazalo se potrebnim upozoriti na razliku između učinkovitosti nove terapije HILT-om i prije rabljene terapije LLLT-om u liječenju OA koljena. Godine 2014. Kheshie i suradnici proveli su randomiziranu kontrolnu studiju u kojoj su usporedili ta dva energetski različita lasera tijekom njihove primjene u NFL-u bolesnika s OA koljena (16). Nakon tretmana tijekom 6 tjedana rezultat je pokazao da su i HILT i LLLT u kombinaciji s vježbama učinkovit modalitet liječenja OA, uz smanjenje boli na VAS-u i prema indeksu WOMAC-a. HILT u kombinaciji s vježbama bio je učinkovitiji od LLLT-a kombiniranoga s vježbama, a oba modaliteta liječenja bila su bolja nego samo vježbe u bolesnika s OA koljena (16).

Pojava novih tehnoloških mogućnosti dovela je do čestih usporedba s dotadašnjim načinima liječenja, premda se pod nazivom „konvencionalne fizikalne terapije" rijetko kad specificiralo o kojim je terapijskim metodama riječ. Tako su 2018. g. Nazari i suradnici objavili rezultate randomizirane kontrolne studije u kojoj su na iranskoj urbanoj populaciji uspoređivali učinak HILT-a i konvencionalne fizikalne terapije uz vježbanje te pokazali da je HILT bio učinkovitiji u liječenju boli mjerene VAS-om i povećanju opsega pokreta (17).

Njihovi su rezultati pokazali da je HILT u bolesnika s OA koljena siguran i dobro podnošljiv način liječenja. Također, terapija laserom visokog intenziteta u kombinaciji s vježbama pokazala se učinkovitijom od konvencionalne fizikalne terapije kombinirane s vježbama ili od vježbi samih u pogledu olakšanja boli i poboljšanja funkcije bolesnika s OA koljena, ali i u drugim stanjima (17). Premda je ova studija bila daleko bolje planirana i kompleksnije provedena, slične rezultate na sličnom broju bolesnika (Nazari – 95 bolesnika) mogli smo vidjeti i u nekim jednostavnijim studijama poput, npr., studije Ilieve (18), koja je 2016. g. provedena na 72 bolesnika, kao i studije naših autora Nives Štiglić-Rogoznice i suradnika (19), koji su ispitivanjem obuhvatili 96 ispitanika. Sve to potvrđuje HILT kao uspješnu, učinkovitu i neštetnu metodu liječenja OA koljena.

Uporaba izvantjelesnog udarnog vala (ESWT) u NFL-u OA evaluirana je u većem broju literaturnih navoda, među kojima se ističu sustavni pregled i meta-analiza Lija i suradnika iz 2019. g. (20) koji su, pregledavajući brojne baze podataka (*PubMed*, *Embase*, *Web of Science*, *ResearchGate*, *Cochrane Library*), zaključili da su učinci ESWT-a pri tretmanu OA koljena bolji od placeba i drugih fizikalnih terapija (nisu specificirali što je time bilo obuhvaćeno). Osim ublažavanja boli,

conditions as well (17). Although this study was planned in a far better way and implemented in a more complex manner, similar results on a similar number of patients (Nazari – 95 patients) could be found in some simpler studies such as, for example, the study conducted by Ilieva (18), which was performed in 2016 on 72 patients, as well as studies conducted by Croatian authors such as Nives Štiglić-Rogoznica et al. (19), which included 96 subjects. All of the aforementioned confirms that HILT is a successful, effective, and harmless method of knee OA treatment.

The use of extracorporeal shockwave therapy (ESWT) in NPT of OA has been evaluated in a number of literature citations, including a systematic review and meta-analysis performed in 2019 by Lee et al. (20) who have concluded, by reviewing numerous databases (PubMed, Embase, Web of Science, ResearchGate, Cochrane Library), that the effects of ESWT in the treatment of knee OA were better than placebo and other physical therapies (they did not specify what was covered by this). In addition to pain relief, ESWT has increased knee joint mobility and decreased the Lequesne Index (LI) and the WOMAC index (20). Evidence has confirmed that ESWT is a quality choice for knee OA treatment. However, due to the lack of relevant high-quality literature evidence, similar previous meta-analyses, and the fact that some studies have not been used to achieve quality evidence, it is recommended to continue proving these results (20).

A similar methodology for studying systematic reviews and meta-regression analysis of randomised criteria studies was applied in a 2019 study conducted by Liao et al., which included 50 studies with 4844 patients and the conclusion was that ESWT was beneficial for patients suffering from knee OA (21). This is also followed by common objections that the dosage of the shockwave, and in particular the energy level used, the duration of individual procedures and the overall treatment may contribute differently to the effectiveness of treatment. The authors conclude that shockwave therapy can be used to relieve pain and improve functional abilities of patients suffering from knee OA. In the use of this treatment method, the radial shockwave, applied in the long duration of treatment, is more effective for recovery of functional abilities than the application of a focused shockwave, especially when it comes to knee OA (21).

The studies that have tried to assess which part of the joint is the most suitable for the application of ESWT with the best therapy results are also quite interesting. Thus, a study conducted by Zhong et al. in 2019, mentioned a case of a four-week long treatment of knee OA with low-dose ESWT that proved to be better than placebo treatment in pain relief and improvement of functional abilities in patients with mild to moderate knee OA, but it also had some adverse effects on the articular cartilage (22). In everyday practice, we are of-

ESWT je povećao pokretljivost zgloba koljena te snizio Lequesneov indeks (LI) i indeks WOMAC-a (20). Dokazi su potvrdili da je ESWT kvalitetan odabir za tretman OA koljena. Međutim, zbog nedostatka relevantnih visokokvalitetnih literaturnih dokaza i sličnih prethodnih metaanaliza te činjenice da neke studije nisu iskorištene za postizanje kvalitetnih dokaza preporučuje se nastavak dokazivanja tih rezultata (20).

Sličnu metodologiju proučavanja sustavnih pregleda i metaregresijske analize randomiziranih kriterijskih studija primijenio je Liao sa suradnicima 2019. g, a uključivala je 50 istraživanja s 4844 bolesnika te je donesen zaključak da je terapija ESWT-om korisna za bolesnika s OA koljena (21). Pritom postoje i uobičajeni prigovori da doziranje udarnog vala, a osobito upotrijebljena razina energije, trajanje pojedinih procedura i ukupni tretman mogu različito pridonositi učinkovitosti liječenja. Autori zaključuju da se terapija udarnim valom može iskoristiti za ublažavanje boli i poboljšanje funkcionalnih mogućnosti u bolesnika s OA koljena. Pritom je radijalni udarni val, primijenjen dugim trajanjem tretmana, učinkovitiji za oporavak funkcionalnih mogućnosti od aplikacije fokusiranog udarnog vala, osobito kod OA koljena (21).

Zanimljiva su i istraživanja koja su pokušala ocijeniti koji je dio zgloba najpogodniji za aplikaciju ESWT-a uz najbolje rezultate terapije. Tako Zhong i suradnici 2019. g. navode podatak o četverotjednom tretmanu OA koljena niskim dozama ESWT-a koji se pokazao kvalitetnijim od tretmana placebom za olakšanje boli i poboljšanje funkcionalnih mogućnosti u bolesnika s blagim do umjerenim tegobama zbog OA koljena, ali je imao i neke negativne učinke na zglobnu hrskavicu (22). U svakodnevnoj se praksi često susrećemo s pitanjem koji dio OA zgloba treba tretirati, a odgovor možda nalazimo u članku Choua i suradnika (23), koji navode da su njihovi rezultati pokazali kako je suphondralna kost odlična meta za tretman ESWT-om u odnosu prema zglobnoj hrskavici kod ranog OA koljena, sa znatno boljim učinkom liječenja ovom metodom NFL-a (23).

Među brojnim literaturnim navodima o ESWT-u ističe se jedan koji je usmjeren na ocjenu podnošljivosti ove terapije, često percipirane kao neugodne za bolesnike. Tako je Ying-Chun Wang sa suradnicima u sustavnom pregledu i metaanalizama iz 2019. g. zaključila da je primjena ESWT-a za tretman OA koljena nedvojbeno učinkovita na smanjenje boli i poboljšanje fizičke funkcije zgloba tijekom 12 mjeseci u svim analiziranim člancima, i to uz pojavu tek manjih komplikacija poslije tretmana udarnim valom (24). Međutim, unatoč pregledu brojnih članaka i ovim je autorima ostalo nejasno koja se frekvencija i koje razine doziranja udarnog vala moraju primijeniti da bi se postignulo maksimalno poboljšanje nalaza (24).

ten faced with the question of which part of the OA joint should be treated, and the answer may be found in the article written by Chou et al. (23), who state that their results have shown that the subchondral bone was an excellent target for ESWT treatment in comparison to articular cartilage in the early stages of knee OA, with a significantly better effect of treatment achieved with this method of NPT (23).

Among the numerous literature citations on ESWT, there is one that particularly stands out and is focused on assessing the tolerability of this therapy, which is often perceived as uncomfortable for patients. Therefore, in the 2019 systematic review and meta-analysis conducted by Ying-Chun Wang et al., it was concluded that the use of ESWT in the treatment of knee OA is undoubtedly effective in reducing pain and improving the physical function of joints during a 12-month period in all analysed articles, with the emergence of minor complications following the period of shockwave treatment (24). However, despite the review of a number of articles, these authors are also unsure of the exact frequency and levels of shockwave dosage which must be applied in order to achieve the maximum improvement of the findings (24).

In literature, there is a small number of quality data on the use of radio frequency (RF) in the treatment of OA, as it is a relatively new and expensive technology, so the availability of this method and the possibilities of OA treatment are currently scarce. Therefore, there are no systematic review papers in the Cochrane Library or in the PEDro database.

However, by conducting a literature search, we have managed to find an article written by Canadian authors who have concluded, by analysing the results of 33 studies, 13 of which were randomised controlled trials with 1512 patients, that current evidence confirms that RF modalities in knee OA treatment can reduce pain and improve joint function as well as the quality of life specific for this disease in the period during 3 to 12 months, with minimal localised complications (25). This suggests that RF modalities may be an effective adjuvant therapy for patients suffering from knee OA who do not respond to conservative therapy treatments.

The authors leave open the possibility for a better response to be provided by a future randomised controlled study of a larger sample and long-term follow-up, which will directly compare the 3 primary RF modalities and guarantee their clinical efficacy and advantage for knee OA (25).

In another paper written by American authors, primarily anaesthesiologists, it was stated that, based on recent studies, the current recommendation for RF treatment of OA is related to the inclusion of candidates which were deemed unsuitable for surgical treatment, patients with severe and persistent knee pain, or patients with existing contraindications for other OA treatment options (26).

O uporabi radiofrekvencije (RF) pri liječenju OA u literaturi postoji malo kvalitetnih podataka, jer je riječ o relativno novoj i skupoj tehnologiji tako da su i dostupnost ove metode i mogućnosti liječenja OA zasad malene. Zbog toga nema ni sustavnih preglednih radova u Cochraneovoj knjižnici ni u bazi PEDro.

Ipak, pretraživanjem literature našli smo jedan članak kanadskih autora koji su, analizirajući rezultate 33 studije od kojih 13 randomiziranih kontrolnih studija s 1512 bolesnika, zaključili da sadašnji dokazi potvrđuju kako modaliteti RF-a u liječenju OA koljena mogu smanjiti bol te poboljšati funkciju zgloba i kvalitetu života specifičnu za bolest tijekom 3 do 12 mjeseci, uz minimalne lokalizirane komplikacije (25). Time upućuju na to da su modaliteti RF-a, možda, učinkovita dodatna terapija za bolesnike s OA koljena koji ne reagiraju na konzervativne tretmane.

Autori ostavljaju otvorenom mogućnost da kvalitetniji odgovor pruži buduća randomizirana kontrolirana studija većeg uzorka i dugoročnog praćenja, koja će izravno uspoređivati 3 primarna modaliteta RF-a te jamčiti njihovu kliničku učinkovitost i prednost za OA koljena (25).

U još jednom radu američkih autora, ponajprije anesteziologa, navodi se da se temeljem recentnih studija sadašnja preporuka za tretman OA primjenom RF-a odnosi na uključivanje kandidata koji nisu prikladni za kirurško liječenje, bolesnika s teškom i tvrdokornom boli u koljenu ili bolesnika s postojećim kontraindikacijama za druge opcije liječenja OA (26).

Za primjenu superinduktivnog sustava (SIS) vrijede slične napomene kao i za RF: zasad nema kvalitetnih podataka u velikim bazama. Dostupni podatci temelje se jedino na istraživanjima koja sponzoriraju proizvođači medicinske opreme pa je istaknuta moguća pristranost u iskazivanju rezultata. Pritom se navode i problemi s trenutačnom dostupnosti ovoga terapijskog modaliteta, kvalitetnim prikupljanjem podataka te budućim publiciranjem dobivenih rezultata. Metaanaliza Chena i suradnika, kao jedini članak koji problematizira uporabu elektromagnetskog polja visokog intenziteta (PEMF), pokazala je da je, usprkos tomu što nije bilo nikakvih prednosti postupka s obzirom na bol i ukočenost, terapija PEMF-om navedena je kao korisna za poboljšanje kliničkih simptoma – fizičke funkcije u bolesnika s OA koljena (27).

To bi moglo značiti da terapija PEMF-om može biti koristan i ekonomičan adjuvantni tretman za nekirurški postupak pri liječenju OA koljena. Autori navode da je potrebno daljnje istraživanje kako bi se odredili optimalna učestalost, intenziteti liječenja, režim tretmana i trajanje terapije PEMF-om (27).

Na kraju ovog pregleda literature kratko se osvrćemo i na neke podatke medicine temeljene na dokazima koji se odnose na tradicionalne metode NFL-a OA, a

For the application of the super inductive system (SIS), similar remarks apply as for the RF: so far there is no quality data in large databases. The available data are based only on research sponsored by medical device manufacturers, so, in this regard, the possible bias in presenting the results was highlighted. Issues with the current availability of this therapeutic modality, quality data collection and future publication of the obtained results are also mentioned. A meta-analysis performed by Chen et al., as the only paper to problematise the use of high-intensity electromagnetic fields (pulsed electromagnetic field, PEMF), showed that, although there were no benefits to the procedure in terms of pain and stiffness, PEMF therapy was cited as useful for improving clinical symptoms – physical functions in patients suffering from knee OA (27).

This could mean that PEMF therapy may be a useful and cost-effective adjuvant treatment for a non-surgical procedure in the treatment of knee OA. The authors state that further research is required in order to determine the optimal frequency, treatment intensities, treatment regimen, and duration of PEMF therapy (27).

At the end of this literature review, we will also briefly touch on some EBM data relating to traditional methods of NPT of OA, which we have formerly regarded as being of great importance in the treatment of our patients suffering from OA.

One of the most commonly used methods of NPT of OA in everyday practice is **therapeutic ultrasound** (US) which is often used with sonophoresis. Wu et al. have published a systematic review and meta-analysis on this topic (28). The results of 15 studies were evaluated, including 3 studies with sonophoresis, which included 1074 patients and monitored outcomes using VAS of pain intensity, the WOMAC index, the Lequesne Index, and range of motion (ROM). Their conclusion is that therapeutic ultrasound is a safe and effective treatment for pain relief and the improvement of functional abilities of patients suffering from knee OA, and that sonophoresis does not provide additional benefits in terms of functional improvement, but can be slightly more successful than conventional ultrasound in terms of pain relief (28).

By researching the effects of **cryotherapy** treatment on patients suffering from knee OA in systematic reviews and randomised controlled trials, Dantas et al. have concluded that there is a lack of quality studies required to draw any conclusions about the effectiveness of cryotherapy on pain and physical function of individuals suffering from knee OA (29). We have also found an interesting article on the use of cold in the treatment of knee OA, which will serve as a mere experimental model. Radnovich et al. have published a randomised, double-blind, placebo-controlled study with a six-month follow-up of patients undergoing cryoneurolysis of the infrapatellar branch of the saphenous nerve (IPBSN) of the painful knee, with outcome monitoring in

za koje smo dosad mislili da imaju veliko značenje u liječenju naših bolesnika s OA.

Jedna od najčešće rabljenih metoda NFL-a OA u svakodnevnoj praksi jest **terapijski ultrazvuk** (UZ) i uz njega često upotrijebljena sonoforeza. Wu i suradnici objavili su sustavni pregled i metaanalizu o toj temi (28). Evaluirani su rezultati 15 studija, uključujući 3 sa sonoforezom, koje su obuhvatile 1074 bolesnika i pratile ishode na VAS-u za bol, indeks WOMAC-a, Lequesneov indeks i opseg pokreta (ROM). Njihov je zaključak da je terapijski UZ siguran i učinkovit tretman za ublažavanje boli i poboljšanje funkcije kod bolesnika s OA koljena te da pritom sonoforeza ne ostvaruje dodatne prednosti u pogledu funkcionalnog poboljšanja, ali može nešto više smanjiti bol od konvencionalnog UZ-a (28).

Istražujući učinke liječenja **krioterapijom** bolesnika s OA koljena u sustavnim pregledima i randomiziranim kontrolnim studijama, Dantas i suradnici zaključili su da nema dovoljno kvalitetnih studija kako bi se donijeli bilo kakvi zaključci o učinkovitosti krioterapije na bol i fizičku funkciju pojedinaca s OA koljena (29). Pritom smo našli i zanimljiv članak o primjeni hladnoće u liječenju OA koljena, koja neće biti više od eksperimentalnog modela. Naime, Radnovich i suradnici objavili su randomizirano, dvostruko slijepo istraživanje kontrolirano placebom sa šestomjesečnim praćenjem bolesnika kojima je napravljena krioneuroliza infrapatelarne grane *nervusa safenusa* (IPBSN) bolnog koljena, uz praćenje ishoda prema indeksu WOMAC-a i na VAS-u boli bolesnika (30). Autori su zaključili da je krioneuroliza IPBSN-a rezultirala statistički značajnim smanjenjem boli u koljenu i poboljšanjem kliničke slike u odnosu prema liječenju placebom, s do 150 dana trajanja učinka, a liječenje se pokazalo sigurnim i dobro podnošljivim za bolesnike s OA koljena (30).

Provođenje tradicionalne terapije ventuzama (engl. *cupping therapy*) istraživala je Yu-Ling Wang sa suradnicima te su našli čak 5 studija koje su ispunjavale kriterije za njihovu evaluaciju dokaza. Zaključili su da postoje tek slabi dokazi koji bi poduprli hipotezu da ventuze (*cupping*-terapija) imaju bilo kakve korisne učinke na smanjenje intenziteta boli i poboljšanje fizičke funkcije pojedinaca s OA koljena (31).

Primjenu balneoterapije (SPA-terapije) kao dijela NFL-a OA problematizirali su talijanski autori jer je upravo u Italiji takav način liječenja OA vrlo popularan. Zaključili su da nema dovoljno snažnih dokaza koji bi u njihovu istraživanju i pretraživanju literature o toj temi naveli SPA-terapiju kao važan način rehabilitacije (32).

I na kraju navodimo podatak o uporabi ortoza koje se uvijek spominju kao dio NFL-a OA. Prema literaturnim podatcima Rodriguez-Merchana i suradnice, idealna je opcija za primjenu ortoza u bolesnika s OA

accordance with the WOMAC index and VAS of pain intensity (30). The authors have concluded that cryoneurolysis of the IPBSN resulted in a statistically significant reduction of knee pain and an improvement in the clinical features in comparison to placebo treatment, with its effectiveness lasting up to 150 days, and the treatment proved to be a safe and well-tolerated method for patients suffering from knee OA (30).

The use of traditional cupping therapy was researched by Yu-Ling Wang et al. and they have found as many as 5 studies which met the criteria for their evaluation of evidence. They have concluded that there is still a lack of strong evidence which would support the hypothesis that cupping therapy has any beneficial effects in reducing pain intensity and improving the physical function of individuals suffering from knee OA (31).

The use of balneotherapy (spa therapy) as part of NPT of OA has been problematised by Italian authors because this method of OA treatment is very popular in Italy. They have concluded that there was a lack of strong evidence required to include spa therapy as an important method of rehabilitation in their research and literature search on the topic (32).

Lastly, we have mentioned the use of orthoses that are always included as part of NPT of OA. According to the data found in the paper written by Rodriguez-Merchan et al., the ideal option for the use of orthoses in patients suffering from knee OA remains undetermined because it lacks long-term concrete conclusions and stronger recommendations (33).

DISCUSSION AND CONCLUSION

Nowadays, OA is recognised as a disease with a significant adverse effect on the function and quality of life, psychological health, work ability, and the ability of active participation in the community. From the viewpoint of an individual suffering from OA, the most important effects of the disease, along with functional impairment and pain, are prolonged fatigue and reduced work ability (2). Due to pain, poor functional ability status, and concomitant depression and fatigue, patients suffering from rheumatic diseases, including those suffering from OA, are more likely to have a sedentary lifestyle (1, 2). The aggravating circumstance in the lives of these patients is also the occurrence of numerous comorbidities, which further increase the risk of morbidity of these patients. Unemployment, sick leave and inability to work rates are extremely high in patients suffering from OA, which consequently affects their economic (in)security and (in)ability to actively participate in social activities. The objectives of OA treatment are clear and, according to available guidelines, include all forms of NPT aimed at reducing pain, morning stiffness, swelling, disease progression, and negative psychological impact, thus maintaining a high level of physical, psychological, and social quality of life when it comes to these patients (1 – 4).

koljena i dalje neodređena, jer joj nedostaju dugoročni konkretni zaključci i snažnije preporuke (33).

RASPRAVA I ZAKLJUČAK

Danas je OA prepoznat kao bolest sa znatnim negativnim učinkom na funkciju i kvalitetu života, psihološko zdravlje, radnu sposobnost te sposobnost aktivnog sudjelovanja u zajednici. Sa stajališta oboljelog od OA najvažniji učinak bolesti, uz funkcionalno oštećenje i bol, jesu dugotrajan umor i smanjena radna sposobnost (2). Zbog boli, lošega funkcionalnog statusa te popratne depresije i umora bolesnici s reumatskim bolestima, pa tako i oni s OA, češće provode sjedalački način života (1, 2). Otegotna im je okolnost i pojava brojnih komorbiditeta, koji dodatno povisuju rizik od morbiditeta tih bolesnika. Stope nezaposlenosti, bolovanja i radne nesposobnosti izrazito su visoke u bolesnika s OA, što onda utječe i na njihovu ekonomsku (ne)sigurnost i na (ne)mogućnost aktivnog sudjelovanja u društvenom životu. Ciljevi liječenja OA jasni su i, prema dostupnim smjernicama, uključuju sve oblike NFL-a koji su usmjereni na smanjenje boli, jutarnje zakočenosti, otekline, progresije bolesti i negativnoga psihičkog utjecaja, čime se onda kod bolesnika održava visoka razina fizičke, psihičke i socijalne kvalitete života (1 – 4).

Nikako ne smijemo zaboraviti na aktivnosti koje djeluju na smanjenje umora, osnažuju bolesnika za prikladno nošenje s posljedicama bolesti te preveniraju komorbiditete. Treba imati na umu da se sve te aktivnosti provode radi osposobljavanja za samostalno i aktivno sudjelovanje u zajednici, a prema Svjetskoj zdravstvenoj organizaciji (SZO), to i jest glavni cilj NFL-a (1).

Imajući na umu bolesnikov doživljaj utjecaja bolesti na kvalitetu fizičkog, psihičkog i socijalnog zdravlja, biopsihosocijalni model bolesti SZO-a, poznatiji kao ICF (engl. *International Classification of Functioning, Disability and Health*), trebao bi se rabiti za evaluaciju bolesnika i planiranje NFL-a reumatskih bolesti, pa tako i OA (34).

A što nam je pretraživanje literature donijelo kao odgovor na pitanje koji su oblici NFL-a najbolji, najučinkovitiji i najčešće preporučeni od stručnjaka u procesu liječenja OA? Postupci koji su dobili najvišu ocjenu i imali najviše kvalitetnih dokaza o učinkovitosti na pojedinca spadaju u kategoriju koju nazivamo medicinskim vježbama / kinezioterapijom / terapijskim vježbama / tjelesnom aktivnošću (10 – 14). Nedvojbeno je dokazano da su ti postupci najkorisniji oblik NFL-a OA, iako još nije definirano u kojem bi se okviru oni primjenjivali s obzirom na precizno određivanje vrsta vježbi, učestalost vježbanja, intenzitet provođenja terapije i trajanje takvog liječenja. Sve smjernice snažno preporučuju i neke, nama manje poznate oblike medicinskog vježbanja kao što je *Tai Chi*. Ipak,

We must not forget the activities that reduce fatigue, empower the patient to cope with the consequences of the disease and prevent comorbidities. One should bear in mind that all of these activities are carried out for the purpose of training the patient for an independent and active participation in the community, which is the main objective of NPT, according to the World Health Organization (WHO) (1).

Given the patient's experience of the impact of disease on the quality of physical, psychological and social health, the biopsychosocial model of the disease developed by WHO, better known as ICF (International Classification of Functioning, Disability and Health), should be used for patient evaluation and planning of NPT of rheumatic diseases, including OA (34).

What have we found by doing a literature search in response to the question of which forms of NPT are the best, most effective, and most commonly recommended by experts in the OA treatment process? The procedures that have received the highest score and had the highest quality evidence of efficacy per individual fall into the category known as medical exercises / kinesiotherapy / therapeutic exercises / physical activity (10 – 14). It has been unequivocally proven that these procedures are the most useful forms of NPT of OA, although the framework in which they would be used is not yet defined given the precise determination of exercise types, exercise frequency, therapy intensity and duration of such treatment. All guidelines strongly recommend certain forms of medical exercise we are not that familiar with, such as Tai Chi. However, according to the 2019 American College of Rheumatology (ACR) guidelines, these exercises, which are not that well-defined, should be done with caution because, for example, yoga exercises can cause decompensation of a preexisting knee OA (35). These guidelines also contain precise general recommendations on exercise dosage: aerobic training of medium intensity – 30 minutes per day, progressive exercises of medium to strong intensity used to strengthen the main muscle groups – 8 to 12 repetitions at least 2 times a week (35).

All of this is related to another factor that is extremely important as a measure of treatment success, and that is adherence to treatment. Its level is still very low for this form of treatment. Although EBM did not precisely define it in the analysed reviewed articles, we are well aware of this due to everyday practice and patient surveys.

Nowadays, the use of numerous forms of modern technologies in NPT of OA is highlighted in all guidelines. The articles that we have reviewed proved that all forms of new technologies (HILT, ESWT, RF, SIS) have an enviable effectiveness in improving the clinical findings and functional abilities of monitored patients, both in monotherapy and in combined methods of treatment (usually used in combination with medical exercises) (15 – 27).

prema smjernicama ACR-a iz 2019. g., treba biti oprezan s tim slabije definiranim vježbama, jer, primjerice, vježbe joge mogu izazvati dekompenzaciju postojećeg OA koljena (35). U smjernicama postoje i precizne opće preporuke o doziranju vježbi: aerobni trening srednjeg intenziteta – 30 minuta na dan, progresivne vježbe snaženja glavnih mišićnih skupina srednjega do jakog intenziteta – 8 do 12 ponavljanja barem 2 puta na tjedan (35).

Uza sve to veže se još jedan čimbenik koji je iznimno važan kao mjera uspješnosti liječenja, a to je adherencija. Njezina je razina i dalje veoma niska za taj oblik liječenja. Premda ju EBM nije precizno definirao u analiziranim pregledanim člancima, to najbolje znamo iz svakodnevne prakse i anketiranja svojih bolesnika.

Primjena brojnih oblika moderne tehnologije u NFL-u OA danas se naglašava u svim smjernicama. Članci koje smo proučavali dokazali su da svi oblici novih tehnologija (HILT, ESWT, RF, SIS) imaju zavidnu učinkovitost u ostvarivanju poboljšanja kliničkog nalaza i funkcionalnih mogućnosti praćenih bolesnika, kako u monoterapiji tako i u kombiniranim načinima liječenja (najčešće uz medicinske vježbe) (15 – 27).

Pregled literature koji smo prije citirali nije ostavio previše dobrih dojmova u svezi s uporabom klasične ili konvencionalne fizikalne terapije (28), kao ni nekih tradicionalnih načina liječenja (krioterapija, *cupping*, ortoze) (29 – 33). Premda nema razine dokaza o njihovu učinku na bolesnike s OA, nije rečeno niti da ne postoje dokazi o njihovoj učinkovitosti. S druge strane, prema smjernicama OARSI-ja iz 2019. g., hidroterapija je imala velik konsenzus stručnjaka (više od 75%) kao preporuka za NFL OA koljena, uz napomenu da se ne preporučuje bolesnicima sa znatnijim kardiovaskularnim komorbiditetom iako se na temelju iskazanih rezultata Bernettija i suradnika to ne bi moglo zaključiti (32).

Dakle, i te se metode može u nekim situacijama iskoristiti za postizanje terapijskog boljitka, kao i konvencionalnu terapiju koja u prezentiranim člancima nije izrijekom specificirana. Također, nije navedeno da je ona neučinkovita, nego je snaga dokaza o toj učinkovitosti bila slaba, što je rezultat malenog broja kvalitetnih studija i publikacija o toj temi. Ondje gdje je bilo ponuđeno dovoljno kvalitetnih studija, i snaga dokaza bila je naglašenija, tako da konvencionalna terapija ima pozitivnu i uvjetnu preporuku u smjernicama ACR-a (35) i ESCEO-a (8), dok su smjernice OARSI-ja (36) u tom pogledu neodređene. Na temelju iskustava stručnjaka sve se te procedure i dalje mogu preporučiti kao priprema za medicinsku vježbu u sklopu multimodalnog pristupa liječenju OA, iako postoji manjak znanstvenih dokaza, a spomenute smjernice ne daju valoriziranu preporuku.

Stoga možemo zaključiti da nam moderne tehnologije u NFL-u OA pružaju veći izbor pasivnih oblika

The literature review that we have cited earlier did not give a lot of good impressions regarding the use of traditional or conventional forms of physical therapy (28), and the same can be said for certain traditional methods of treatment (cryotherapy, cupping, orthoses) (29 – 33). Although there is no level of evidence for their effect on patients suffering from OA, none of the information suggest that there is no evidence of their effectiveness. On the other hand, according to the 2019 Osteoarthritis Research Society International (OARSI) guidelines, hydrotherapy had a strong consensus of experts (more than 75%) as a recommendation for NPT of knee OA, with a note that it is not recommended for patients with significant cardiovascular comorbidity, although, based on the results of Bernetti et al., this could not be concluded (32).

Thus, these methods can also be used in some situations in order to achieve therapeutic improvement, as well as conventional therapy, which is not explicitly specified in the presented articles. Also, it is not stated that this therapy is ineffective, but that the strength of the evidence on this effectiveness was weak, which is the result of a small number of quality studies and publications on the topic. In cases in which sufficient quality studies were provided, the strength of the evidence was more pronounced. Therefore, conventional therapy has a positive and conditional recommendation in the ACR (35) and ESCEO (8) guidelines, while the OARSI guidelines (36) are indefinite in this respect. Based on the experience of experts, all these procedures can still be recommended as preparation for medical exercise as part of a multimodal approach to OA treatment, although there is a lack of scientific evidence and the mentioned guidelines do not provide an evaluated recommendation.

Therefore, we can conclude that modern technologies in NPT of OA provide us with a greater choice of passive forms of physical therapy and contribute to the successful treatment of OA. However, a sufficient level of evidence is still non-existent in the aforementioned guidelines for such forms of OA treatment. The results of the cited studies (15 – 27) are encouraging so far, but until we are provided with a higher level of evidence strength, we cannot simply declare these procedures to be so much better than all other conventional NPT methods.

In conclusion, it is safe to say that all the reviewed methods of NPT have shown a significant level of efficacy in the treatment of OA: they reduced pain and improved the functional abilities and quality of life of the subjects. This confirmed the need to include NPT in all algorithms / procedures / guidelines for OA treatment.

Conflict of interest statement: Authors declare no conflict of interest.

fizikalne terapije i pridonose uspješnom liječenju OA. Ipak, još ne postoji dovoljna razina dokaza u prije navedenim smjernicama za takve oblike liječenja OA. Rezultati citiranih studija (15 – 27) zasad ohrabruju, ali sve dok ne dobijemo više razine snage dokaza, ne možemo te procedure jednostavno proglasiti toliko boljima od svih ostalih konvencionalnih metoda NFL-a.

U zaključku možemo reći da su sve proučavane metode NFL-a pokazale izrazitu učinkovitost u liječenju OA: reducirale su bol i poboljšale funkcionalne sposobnosti i kvalitetu života ispitanika. Time je potvrđena i potreba uvrštavanja NFL-a u sve algoritme/postupnike/smjernice liječenja OA.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Global Burden of Disease Study 2013 Collaboration. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995): 743–800.
2. Buelt A, Narducci DM. Osteoarthritis management: updated guidelines from the American College of Rheumatology and Arthritis Foundation. Am Fam Physician. 2021;103(2):120–1.
3. Chamberlain R. Hip pain in adults: evaluation and differential diagnosis. Am Fam Physician. 2021;103(2):81–9.
4. Collins AT, Hu G, Newman H i sur. Obesity alters the collagen organisation and mechanical properties of murine cartilage. Sci Rep. 2021;11(1):1626.
5. Grazio S, Ćurković B, Babić-Naglić Đ i sur. Smjernice Hrvatskoga reumatološkog društva za liječenje osteoartritisa kuka i koljena. Reumatizam. 2010;57(1):36–47.
6. Grazio S, Schnurrer-Luke Vrbanić T, Grubišić F i sur. Smjernice za liječenje bolesnika s osteoartritisom kuka i/ili koljena. Fiz Rehabil Med. 2015;27(3–4):330–81.
7. Kucharz EJ, Szanto S, Goycheva MI i sur. Endorsement by Central European experts of the revised ESCEO algorithm for the management of knee osteoarthritis. Rheumatol Int. 2019; 39(7):1117–23.
8. Bruyère O, Honvo G, Veronese N i sur. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019;49(3):337–50.
9. Chung P-Y, Lin M-T, Chang H-P. Effectiveness of platelet-rich plasma injection in patients with temporomandibular joint osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(2):106–16.
10. Collins NJ, Hart HF, Mills KAG. Osteoarthritis year in review 2018: rehabilitation and outcomes. Osteoarthritis Cartilage. 2019;27(3):378–91.
11. Ferreira RM, Duarte JA, Gonçalves RS. Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: an umbrella review. Acta Reumatol Port. 2018; 43:182–200.
12. Ceballos-Laita L, Estébanez-de-Miguel E, Martín-Nieto G i sur. Effects of non-pharmacological conservative treatment on pain, range of motion and physical function in patients with mild to moderate hip osteoarthritis. A systematic review. Complement Ther Med. 2019;42:214–22.
13. Rausch Osthoff A-K, Niedermann K, Braun J i sur. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018;77(9):1251–60.
14. Ilieva EM. Are exercise interventions beneficial for people with hip and knee osteoarthritis? – A Cochrane Review summary with commentary. Musculoskelet Sci Pract. 2019;44:102041.
15. Wyszyńska J, Bal-Bocheńska M. Efficacy of high-intensity laser therapy in treating knee osteoarthritis: a first systematic review. Photomed Laser Surg. 2018;36(7):343–53.
16. Kheshie AR, Alayat MSM, Ali MME. High-intensity versus low-laser level therapy in the treatment of patients with knee osteoarthritis: a randomized controlled trial. Lasers Med Sci. 2014;29(4):1371–6.
17. Nazari A, Moezy A, Nejati P, Mazaherinezhad A. Efficacy of high-intensity laser therapy in comparison with conventional physiotherapy and exercise therapy on pain and function patients with knee osteoarthritis: a randomized controlled trial with 12-week follow up. Lasers Med Sci. 2019;34(3):505–16.
18. Angelova A, Iieva EM. Effectiveness of high intensity laser therapy for reduction of pain in knee osteoarthritis. Pain Res Manag. 2016;2016:9163618.
19. Štiglić-Rogoznica N, Stamenković D, Frlan-Vrgoč Lj, Avancini-Dobrović V, Schnurrer-Luke Vrbanić T. Analgesic effect of high intensity laser therapy in knee osteoarthritis. Coll Antropol. 2011;35(Suppl. 2):183–5.
20. Li T, Ma J, Zhao T, Gao F, Sun W. Application and efficacy of extracorporeal shockwave treatment for knee osteoarthritis: A systematic review and meta-analysis. Exp Ther Med. 2019;18 (4):2843–50.
21. Liao C-D, Tsauo J-Y, Liou T-H, Chen H-C, Huang S-W. Clinical efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a systematic review and meta-regression of randomized controlled trials. Clin Rehabil. 2019;33(9):1419–30.
22. Zhong Z, Liu B, Liu G i sur. A randomized controlled trial on the effects of low-dose extracorporeal shockwave therapy in patients with knee osteoarthritis. Arch Phys Med Rehabil. 2019;100(9):1695–1702.
23. Chou W-Y, Cheng J-H, Wang CJ-, Hsu S-L, Chen J-H, Huang C-Y. Shockwave targeting on subchondral bone is more suitable than articular cartilage for knee osteoarthritis. Int J Med Sci. 2019;16(1):156–66.
24. Wang Y-C, Huang H-T, Huang P-J, Liu Z-M, Shih C-L. Efficacy and safety of extracorporeal shockwave therapy for treatment of knee osteoarthritis: a systematic review and meta-analysis. Pain Med. 2020;21(4):822–35.
25. Ajrawat P, Radomski L, Bhatia A, Peng P, Nath N, Gandhi R. Radiofrequency procedures for the treatment of symptomatic knee osteoarthritis: a systematic review. Pain Med. 2020;21(2): 333–48.
26. Urtis I, Jones M, Patel R i sur. Minimally invasive interventional management of osteoarthritic chronic knee pain. J Knee Surg. 2019;32(1):72–9.
27. Chen L, Duan X, Xing F i sur. Effects of pulsed electromagnetic field therapy on pain, stiffness and physical function in patients with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. J Rehabil Med. 2019;51(11): 821–7.
28. Wu Y, Zhu S, Lv Z i sur. Effects of therapeutic ultrasound for knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil. 2019;33(12):1863–75.
29. Dantas LO, Carreira Moreira RF, Norde FM, Silva Serrao PRM, Alburquerque-Sendín F, Salvini TF. The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rehabil. 2019;33(8):1310–9.
30. Radnovich R, Scott D, Patel AT i sur. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. Osteoarthritis Cartilage. 2017;25(8):1247–56.
31. Wang Y-L, An C-M, Song S, Lei F-L, Wang Y. Cupping therapy for knee osteoarthritis: a synthesis of evidence. Complement Med Res. 2018;25(4):249–55.
32. Bernetti A, Mangone M, Alviti F i sur. Spa therapy and rehabilitation of musculoskeletal pathologies: a proposal for best practice in Italy. Int J Biometeorol. 2020;64:905–14.
33. Rodriguez-Merchan EC, De La Corte-Rodriguez H. The role of orthoses in knee osteoarthritis. Hosp Pract. 2019;47(1):1–5.
34. Grazio S. Međunarodna klasifikacija funkcioniranja, nesposobnosti i zdravlja (ICF) u najznačajnijim bolestima i stanjima reumatološke prakse. Reumatizam. 2011;58(1):27–43.
35. Kolasinski SL, Neogi T, Hochberg MC i sur. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip and knee. Arthritis Care Res (Hoboken). 2020;72(2):149–62.
36. Bannuru RR, Osani MC, Vaysbrot EE i sur. OARSI guidelines for non-surgical management of knee, hip and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578–89.

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CASE-BASED REVIEW PREGLED TEMELJEN NA PRIKAZU BOLESNIKA

SACRAL INSUFFICIENCY FRACTURES – A COMMONLY OVERLOOKED CAUSE OF LOW BACK AND PELVIC PAIN; A CASE REPORT AND LITERATURE REVIEW

PRIJELOM SAKRUMA U OSLABLJENOJ KOSTI – ČESTO NEPREPOZNAT UZROK KRIŽOBOLJE I BOLI U ZDJELICI – PRIKAZ BOLESNICE S PREGLEDOM LITERATURE

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Abstract

Sacral stress fractures are divided into fatigue fractures and insufficiency fractures. Fatigue fractures occur in a normal bone exposed to abnormal or repetitive stresses, whereas insufficiency fractures occur in weakened bones under normal stress and with no underlying trauma.

Sacral insufficiency fractures are often overlooked causes of nonspecific lumbosacral back pain, especially in elderly women with underlying osteoporosis. In addition to old age and postmenopausal osteoporosis, other conditions which reduce bone mineral density and present risk factors for the occurrence of insufficiency fractures include: long-term glucocorticoid and bisphosphonates therapy, long-term vitamin D insufficiency and osteomalacia, renal osteodystrophy, primary hyperparathyroidism, Paget's disease, long-term immobilisation and radiotherapy for the treatment of malignant diseases. There are no typical clinical signs to suggest sacral stress fracture. These fractures are often associated with degenerative diseases of the spine and intervertebral disc, and they are often accompanied by pre-existing osteoporotic vertebral compression fractures. Plain radiographs of the spine and pelvis, which are the first step in diagnostic imaging, are usually non-diagnostic when it comes to sacral fractures. Due to radicular pain symptoms, magnetic resonance imaging of the lumbosacral spine is the next step in diagnosis, in which sacral fractures are often revealed as accidental findings. In this paper, we shall present a case of an elderly patient with multiple comorbidities and multiple risk factors, in whose case physical therapy did not prove to be effective. During diagnostic testing, a subsequent MRI showed an accidental finding confirming the sacral fracture. Furthermore, we shall highlight the importance of early detection of sacral stress fracture in high-risk patients, in order to avoid unnecessary, and sometimes invasive, diagnostic procedures and to reduce the possibility of possible complications. The imaging method of choice for the diagnosis of sacral stress fractures is MRI.

Key words: Fractures, stress – complications, diagnostic imaging, etiology; Low back pain – etiology; Pelvic pain – etiology; Sacrum – injuries, surgery; Spinal fractures – complications, diagnostic imaging, etiology; Magnetic resonance imaging; Vertebroplasty – methods

Sažetak

Stresne prijelome (engl. *stress fractures*) možemo podijeliti na prijelome zamora ili stresne prijelome u užem smislu (engl. *fatigue fractures*) i na prijelome u oslabljenoj kosti (engl. *insufficiency fractures*). Prijelomi zamora nastaju

u zdravoj kosti zbog dugotrajnog ponavljanja neprimjerenog opterećenja, dok prijelomi u oslabljenoj kosti nastaju spontano, odnosno bez prethodne traume. Prijelomi sakruma u oslabljenoj kosti često su neprepoznat uzrok križobolje i boli u zdjelici, posebice u žena starije dobi s osteoporozom.

Osim starije dobi i postmenopauzalne osteoporoze, rizični čimbenici za prijelom u oslabljenoj kosti jesu dugotrajna terapija glukokortikoidima i bisfosfonatima, dugotrajan teži nedostatak vitamina D i osteomalacija, renalna osteodistrofija, primarni hiperparatiroidizam, Pagetova bolest, dugotrajna nepokretnost i radioterapija zbog maligne bolesti.

Specifični klinički znakovi stresnog prijeloma sakruma ne postoje. Ovakvi prijelomi često su udruženi s degenerativnim promjenama kralježnice i intervertebralnog diska, a često su prisutni i osteoporotični prijelomi kralježaka. Na standardnim radiogramima kralježnice i zdjelice, koji su prvi korak u slikovnoj dijagnostičkoj obradi, prijelomi sakruma najčešće se ne uočavaju. Zbog često prisutnih radikularnih simptoma sljedeći dijagnostički korak jest magnetska rezonancija lumbosakralne kralježnice na kojoj su prijelomi sakruma najčešće slučajan nalaz. Prikazujemo bolesnicu s multiplim komorbiditetima i višestrukim čimbenicima rizika kod koje je zbog prolongirane križobolje provedena fizikalna terapija s nezadovoljavajućim učinkom. Tijekom obrade učinjena je magnetska rezonancija gdje je kao slučajan nalaz potvrđen prijelom sakruma. Ističemo važnost ranog prepoznavanja rizičnih skupina pacijenata čime se postiže izbjegavanje suvišnih, katkad i invazivnih dijagnostičkih postupaka. Slikovna metoda izbora za dijagnozu stresnog prijeloma sakruma jest magnetska rezonancija.

Ključne riječi: Prijelomi zamora – dijagnostički slikovni prikaz, etiologija, komplikacije; Križobolja – etiologija; Zdjelična bol – etiologija; Sakrum – ozljede, kirurgija; Prijelomi kralješnice – dijagnostički slikovni prikaz, etiologija, komplikacije; Magnetska rezonancija; Vertebroplastika – metode

INTRODUCTION

Sacral stress fractures are divided into fatigue fractures and insufficiency fractures (1 – 3). It is crucial to note the difference between the two, due to the different pathophysiological processes they are based upon and the different approaches to their treatment.

Fatigue fractures occur due to prolonged repetition of abnormal stresses on normal and healthy bone (usually related to sports or one's profession) or normal stresses in abnormal biomechanics (e.g., *coxa vara*). In both of the aforementioned cases, bone damage occurs which exceeds the bone's ability to restore itself. Following that, there is an increased osteoclastic activity and cortical bone resorption and, finally, the occurrence of fracture. Fatigue fractures most often occur in lower extremities (4, 5).

Insufficiency fractures occur under normal stresses, are more common in the elderly, they are usually associated with osteoporosis, and typically occur in and around the pelvic bones (6). In addition to old age and osteoporosis, other risk factors for the occurrence of insufficiency fractures include: long-term glucocorticoid and bisphosphonates therapy, long-term vitamin D insufficiency and osteomalacia, renal osteodystrophy, primary hyperparathyroidism, Paget's disease, long-term immobilisation and radiotherapy for the treatment of malignant diseases (6, 7).

Sacral insufficiency fractures which occur spontaneously, with no underlying trauma, are often overlooked causes of nonspecific lumbosacral back pain in old age, especially in elderly women with underlying osteoporosis (6). There are no typical clinical signs to suggest sacral stress fracture, which is why the diagnosis is

UVOD

Stresne prijelome (engl. *stress fractures*) možemo podijeliti na prijelome zamora ili stresne prijelome u užem smislu (engl. *fatigue fractures*) i na prijelome u oslabljenoj kosti (engl. *insufficiency fractures*) (1 – 3). Njihovo je razlikovanje nužno s obzirom na različit patofiziološki proces u podlozi i različit pristup liječenju.

Prijelomi zamora nastaju u zdravoj kosti zbog dugotrajnog ponavljanja neprimjerenog opterećenja (najčešće sportskog ili profesionalnoga) ili pri primjerenim opterećenjima u poremećenim biomehaničkim odnosima (npr., *coxa vara*). U oba slučaja dolazi do oštećenja kosti koje nadvlada njezine reparacijske sposobnosti. Tada dolazi do pojačane osteoklastične aktivnosti i resorpcije kortikalne kosti te, na kraju, do prijeloma. Prijelomi zamora najčešće nastaju na donjim ekstremitetima (4, 5).

Prijelomi u oslabljenoj kosti nastaju pri uobičajenim opterećenjima, češći su u starijih osoba, obično su povezani s osteoporozom te tipično nastaju na kostima zdjelice i oko nje (6). Osim starije dobi i osteoporoze, rizični su čimbenici dugotrajna terapija glukokortikoidima i bisfosfonatima, dugotrajan teži nedostatak vitamina D i osteomalacija, renalna osteodistrofija, primarni hiperparatiroidizam, Pagetova bolest, dugotrajna nepokretnost i radioterapija zbog maligne bolesti (6, 7).

Prijelomi sakruma u oslabljenoj kosti koji nastaju spontano, bez prethodne traume, često su neprepoznat uzrok lumbosakralne i zdjelične boli u starijoj dobi, posebice u starijih žena s osteoporozom (6). Specifični klinički znakovi ne postoje zbog čega se dijagnoza postavlja kasno, najčešće kao slučajan nalaz (8). Ovakvi

made late, and they are most often revealed as an accidental finding (8). These fractures are often associated with degenerative diseases of the spine and intervertebral disc, and they are often accompanied by pre-existing osteoporotic vertebral compression fractures, which makes the diagnosis even more difficult (9). Plain radiographs of the spine and pelvis, which are the first step in diagnostic imaging, are usually non-diagnostic when it comes to sacral stress fractures (10, 11). Due to radicular pain symptoms caused by degenerative changes, magnetic resonance imaging (MRI) of the lumbosacral (LS) spine is the next step in diagnosis, in which sacral fractures are often revealed as accidental findings. MRI of the pelvis is the most sensitive test in the diagnosis of sacral fractures. Computerised tomography (CT) of the pelvis and bone scintigraphy are additional diagnostic methods.

Treatment is mainly conservative, especially when it comes to fatigue fractures (2). Surgical procedure is indicated if there is severe sacroiliac dysfunction and instability (2).

In recent times, sacroplasty is increasingly being used in the treatment of sacral fractures, as a minimally invasive procedure (12).

CASE REPORT

The patient M. L., a 77-year-old woman, was admitted to Clinical Hospital Centre Rijeka for an examination due to pain in her lower back and hips. The patient's medical history revealed that 5 months prior to this examination, the patient's plain radiographs of the LS spine showed vertebral compression fracture of the second lumbar vertebra (L2) without any previous trauma or fall. Due to end-stage renal disease, the patient was treated with chronic (long-term) haemodialysis for 4 years.

During the clinical examination, osteoporotic posture was evident, in the form of a short torso in relation to the extremities and a hunched posture. Kidney percussion came back positive. The patient was walking, by making small steps on a wide surface, without using any aids. The neurological status of the patient showed normal muscle strength in the patient's legs, with preserved reflexes and superficial sensation. The Oswestry Low Back Pain Disability Questionnaire, used for the measurement of the patient's functional disability, showed that the patient had severe functional disability, at the score of 57.7% (13).

Bone densitometry (DXA) findings showed osteoporosis with a measured T-value of –5.4 at the spine, at the vertebral level L1 – L4, and –3.0 at the left hip in total, which confirmed the diagnosis of severe osteoporosis with vertebral compression fracture of the second lumbar vertebra (L2).

prijelomi često su udruženi s degenerativnim promjenama kralježnice i intervertebralnog diska te s osteoporotičnim prijelomima kralježaka, što dodatno otežava dijagnozu (9). Na standardnim radiogramima kralježnice i zdjelice, koji su prvi korak u slikovnoj dijagnostičkoj obradi, stresne frakture sakruma najčešće se ne uočavaju (10, 11). Zbog često prisutnih radikularnih simptoma uzrokovanih degenerativnim promjenama sljedeći dijagnostički korak jest magnetska rezonancija (MR) lumbosakralne (LS) kralježnice na kojoj su prijelomi sakruma najčešće slučajan nalaz. MR zdjelice najosjetljivija je pretraga u dijagnostici prijeloma sakruma. Kompjutorizirana tomografija (CT) zdjelice i scintigrafija kosti dodatne su dijagnostičke metode.

Liječenje je uglavnom konzervativno, posebice prijeloma zamora (2). Kirurški pristup indiciran je pri teškom instabilitetu sakruma (2).

U novije vrijeme sakroplastika kao minimalno invazivan postupak sve češće nalazi svoje mjesto u liječenju prijeloma sakruma (12).

PRIKAZ BOLESNICE

Bolesnica M. L., u dobi od 77 godina, došla je na pregled u KBC Rijeka zbog boli u križima i kukovima. Iz anamneze se saznalo da je prije 5 mjeseci na standardnim radiogramima LS kralježnice ustanovljen kompresivni prijelom trupa drugoga slabinskog (LII) kralješka bez prethodne traume ili pada. Zbog terminalne bubrežne bolesti bolesnica je otprije 4 godine bila na kroničnoj hemodijalizi.

Kliničkim pregledom bio je vidljiv osteoporotičan stav u obliku skraćenog trupa u odnosu prema ekstremitetima i pogrbljenog držanja. Lumbalna sukusija bila je pozitivna. Bolesnica je hodala sitnim koracima po širokoj osnovi bez pomagala. U neurološkom statusu mišićna je snaga na nogama bila uredna, uz očuvane vlastite reflekse i površinski osjet. Oswestryjski upitnik (engl. *Oswestry Low Back Pain Disability Questionnaire*) za procjenu funkcionalne nesposobnosti u bolesnika s križoboljom pokazao je tešku funkcionalnu onesposobljenost od 57,7% (13).

Nalaz denzitometrije skeleta (DXA) pokazao je osteoporozu uz izmjerenu T-vrijednost od -5,4 na kralježnici LI – LIV i -3,0 na lijevom kuku ukupno, što je uz kompresivni prijelom trupa kralješka LII potvrdilo tešku osteoporozu.

Zbog kronične hemodijalize koju je nalagala terminalna bubrežna bolest liječenje osteoporoze u bolesnice bilo je ograničeno na nadomjesnu terapiju aktivnim oblikom vitamina D (kalcitriol). Bolesnica je uključena u program fizikalne terapije, ali nije došlo do smanjenja intenziteta boli, kao ni do poboljšanja funkcionalne sposobnosti mjerene oswestryjskim upitnikom za pro-

Due to chronic (long-term) haemodialysis, which had to be done for the treatment of end-stage renal disease, the osteoporosis treatment in the case of this patient was limited to a replacement treatment with an active form of vitamin D (calcitriol). The patient was put on a physical therapy programme, but there was no improvement with regard to the reduction of pain intensity, nor was there any improvement in the patient's functional ability, measured by the Oswestry Low Back Pain Disability Questionnaire, so, for the aforementioned reasons, additional radiological tests were performed. Plain radiographs of the thoracic and lumbar spine showed no new vertebral fractures, but they have confirmed the diagnosis of vertebral compression fracture of the second lumbar vertebra (L2) (vertebral body compression corresponding to grade II according to the Genant classification of vertebral fractures) (Figure 1). Plain radiographs of the pelvis have shown degenerative changes in both coxofemoral joints with no other signs of pathological remodelling (Figure 2), and the superposition of bowel loops in the projection of the sacrum made it impossible to give a more precise analysis of the bony structure of the sacrum. Due to persistent pain, during further processing an MRI of the LS spine was performed, which showed advanced degenerative changes with neural foraminal stenosis and, with previously confirmed compression fracture of the lumbar vertebra L2 (grade II according to the Genant classification of vertebral fractures), as well as the fracture of the lumbar vertebra L4 (grade I according to the Genant classification of vertebral fractures) which occurred long before this examination. In addition to that, spondylolisthesis of L5 vertebra (grade I) was observed, caused by hypertrophic osteoarthropathy of the intervertebral joints at the same level. At the L3–L5 level, due to the rotation of the vertebra in the sagittal plane, the results of the plain radiographs gave the impression of spondylolisthesis of the L3 vertebra, but the anterior median line was not disturbed, which was confirmed by the MRI. An unexpected finding during the MRI was an extensive oedema of the spongy bone found in the lateral masses of the sacrum (Figure 3). In addition to the extensive oedema of the surrounding spongy bone (Figure 4), which was shown through the fat suppression technique, bilateral linear zones of low signal intensity were observed on the axial sections of the T1-weighted image. This kind of finding is typical for sacral stress fractures. Due to multiple comorbidities, the patient was treated with conservative methods of treatment, with an emphasis on bed rest. During the following two years, the patient went for regular check-ups. The patient has successfully completed another cycle of physical therapy, which included individual medical exercises, as well as electroanalgesia. The Oswestry Low Back Pain Disability

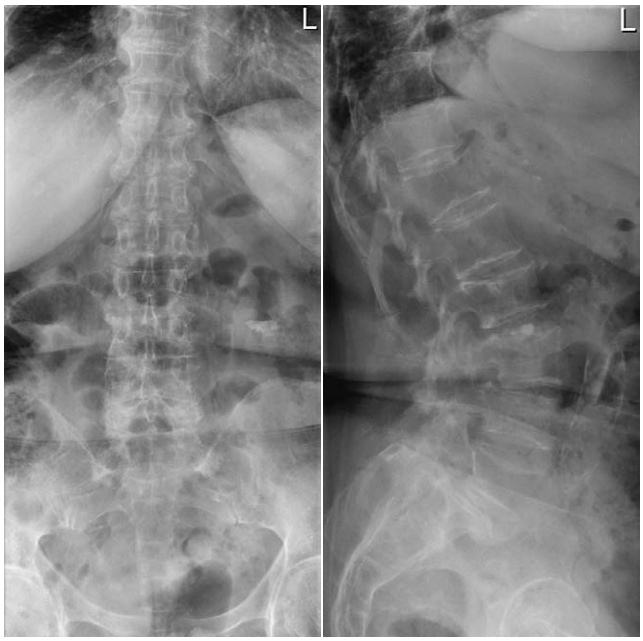

Figure 1. Radiographs of the LS spine showed vertebral compression fracture of the second lumbar vertebra (L2) (grade II according to the Genant classification of vertebral fractures) with diffuse degenerative changes, hypertrophic osteoarthropathy of intervertebral joints at the L3–S1 level, and signs of skeletal osteopenia.

Slika 1. Radiogrami LS kralježnice pokazuju kompresivnu frakturu kralješka L2 (2. stupnja prema Genantovoj klasifikaciji) uz difuzne degenerativne promjene, hipertrofični osteoartritis intervertebralnih zglobova u segmentima L3 – S1 te osteopeničnu strukturu kosti

cjenu funkcionalne nesposobnosti u bolesnika s križoboljom, zbog čega je dodatno učinjena radiološka obrada. Na standardnim radiogramima prsne i slabinske kralježnice nisu uočeni novonastali prijelomi kralježaka, uz potvrdu kompresivnog prijeloma trupa kralješka LII (smanjene visine trupa koji odgovara 2. stupnju prema Genantu) (slika 1.). Standardni radiogrami zdjelice pokazali su degenerativne promjene obaju koksofemoralnih zglobova bez drugih znakova patološke pregradnje (slika 2.), a superpozicija crijevnih vijuga u projekciji sakruma onemogućila je precizniju analizu koštane strukture sakruma. Zbog trajno prisutnih boli u daljnjoj obradi učinjen je MR lumbosakralne kralježnice, koji je pokazao uznapredovale degenerativne promjene sa suženjem neuralnih foramena te, uz prije potvrđen kompresivni prijelom trupa kralješka LII (2. stupanj prema Genantu), i prijelom trupa kralješka LIV (1. stupanj prema Genantu) starijeg datuma. Također, uočena je spondilolisteza kralješka LV 1. stupnja, uvjetovana hipertrofičnim osteoartritisom intervertebralnih zglobova u istom segmentu. U segmentu LIII – LIV, zbog rotacije kralježaka u frontalnoj ravnini, na standardnim se radiogramima stekao dojam listetičkog pomaka kralješka LIII, no prednja interkorporalna linija nije bila narušena, što je

Questionnaire, used for the measurement of the patient's functional disability showed, that the patient's functional disability has improved, and that it was now at the score of 48.88%.

DISCUSSION

Sacral insufficiency fractures can cause low back and pelvic pain which contribute to the debilitation of the patient. These fractures can occur spontaneously or due to small, underlying trauma. The occurrence of pain is usually acute. Pain is mechanical in nature, which means that is subsides when the patient is resting, and it becomes more intense when stress and strain are placed on the muscles (such as standing or walking), so in this case moving is usually significantly more difficult. In rare cases, the pain may be clearly localised in the sacral region. At times, patients may experience radicular symptoms in their legs. Therefore, it is difficult to diagnose a patient based on their medical history and clinical examination and the diagnosis is often made late or delayed (9).

Diagnosis is further complicated by the fact that sacral fractures are not usually shown on a plain radiograph of the lumbar spine and pelvis, and the fact that degenerative changes of the spine, osteoporosis and osteoporotic vertebral fractures are common findings, which can lead to misdiagnosis and complicate the diagnosis of sacral insufficiency fractures (14, 15).

When it comes to risk factors, the patient whose case is described in this case report had the factors of old age and severe osteoporosis with osteoporotic vertebral fractures as well as chronic end-stage renal disease due to which she had to be treated with haemodialysis. Low back pain was additionally caused by degenerative changes and instability of the lumbar spine. Considering the fact that the pain did not subside after the applied physical therapy, the patient was subjected to further diagnostic processing. Standard radiographic testing typically did not indicate a sacral fracture. However, what did indicate this was an accidental finding on the MRI of the LS spine. In the study conducted by Cabarrus et al., out of 108 insufficiency fractures in the pelvic region, which were detected with a pelvic MRI or LS spine MRI, only 16 (14.8%) of those fractures were diagnosed by plain radiographs of the pelvis or LS spine, and only 3.8% (2 out of 53) of them were found to be sacral fractures. This fact clearly confirms that, in most cases, it is not possible to diagnose or rule out pelvic fractures, least of all fractures in the sacral area, through the use of plain radiographs. On a plain radiograph, the presence of a sclerotic line in the bone, a cortical rupture, or a visible fracture gap indicate an insufficiency fracture (15).

Sacral fractures, in addition to insufficiency fractures, are often experienced by athletes, as fatigue frac-

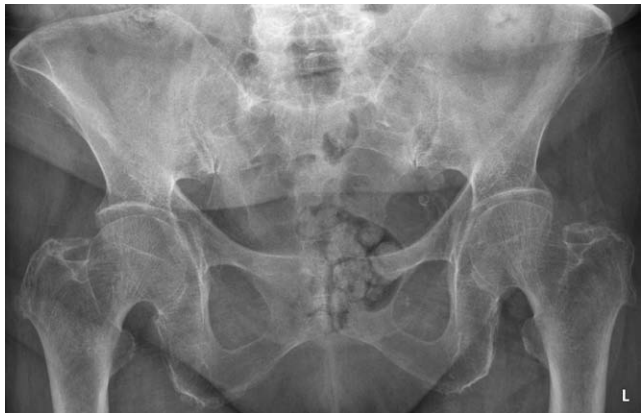

Figure 2. Plain radiograph of the pelvis showed signs of femoroacetabular impingement and bone spurs at the muscle attachments to the pelvic girdle.

Slika 2. Standardni radiogram zdjelice pokazuje znakove femoroacetabularnog sraza i koštana izvučenja na hvatištima tetiva zdjeličnog obruča

potvrdio i MR. Neočekivan nalaz na MR-u bio je opsežan edem spongioze lateralnih masa sakruma (slika 3.). Na aksijalnim presjecima u T1 mjerenoj slici uočene su obostrane linearne zone slabog intenziteta signala uz opsežan okolni edem spongioze kosti prikazan tehnikom supresije masti (slika 4.). Takav je nalaz tipičan za stresne prijelome sakruma. S obzirom na višestruke komorbiditete, bolesnica je konzervativno liječena s naglaskom na mirovanju. Tijekom sljedeće dvije godine odlazila je na redovite kontrole. Proveden je još jedan ciklus fizikalne terapije koji je uključivao individualne medicinske vježbe, uz elektroanalgeziju, sa zadovoljavajućim uspjehom. Oswestryjski upitnik za procjenu funkcionalne nesposobnosti pokazao je sniženje stupnja funkcionalnog onesposobljenja, s vrijednosti od 48,88%.

RASPRAVA

Prijelomi sakruma u oslabljenoj kosti mogu uzrokovati boli u donjem dijelu leđa i zdjelici koje onesposobljuju bolesnika. Mogu nastati spontano ili zbog vrlo male traume. Nastup boli najčešće je akutan. Bol je mehanička karaktera, tj. smanjuje se mirovanjem, a pojačava pri opterećenju (stajanje, hod), tako da je kretanje najčešće znatno otežano. Rjeđe bol može biti jasno lokalizirana u predjelu sakruma. Katkad bolesnici imaju radikularne simptome u nogama. Stoga se dijagnoza teško postavlja na osnovi anamneze i kliničkog pregleda te je često odgođena (9).

Postavljanje dijagnoze dodatno otežava činjenica da se prijelom sakruma najčešće ne prikazuje na standardnoj radiografskoj snimci slabinske kralježnice i zdjelice, a uobičajen su nalaz i degenerativne promjene kralježnice, osteoporoza i osteoporotični prijelomi kralježaka, što sve može voditi prema krivoj dijagnozi i

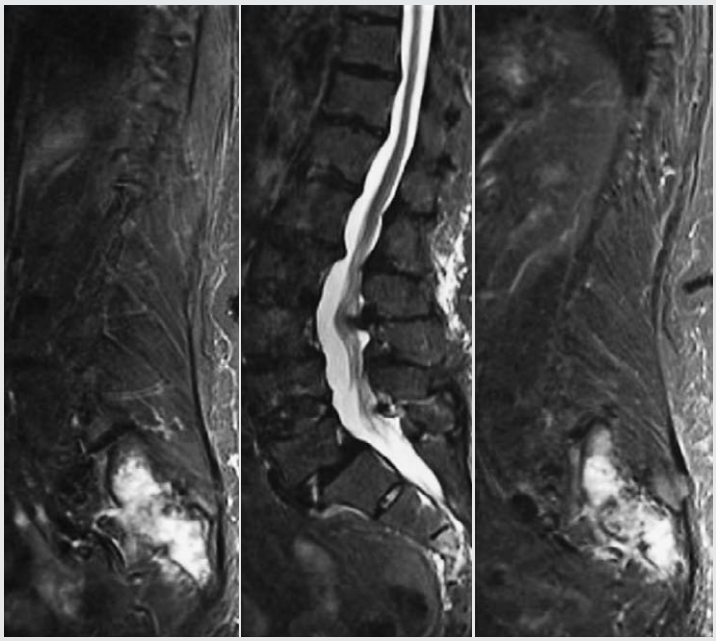

Figure 3. Pathologically increased signal of lateral masses of the sacrum shown on the MRI of the LS spine. Sagittal sections through the LS spine (STIR image) show a pathological increase in the signal of the lateral masses of the sacrum along with signs of discopathy and foraminal stenosis along the lumbar level of the spine.

Slika 3. Patološki povišen signal lateralnih masa sakruma na MR-u LS kralježnice. Sagitalni presjeci kroz LS kralježnicu (slika mjerena STIR-om) pokazuju patološko povišenje signala lateralnih masa sakruma i znakove diskopatije te foraminalne stenoze duž lumbalnog segmenta kralježnice

tures that occur due to stress that is placed on normal bone (4, 5, 16). When it comes to insufficiency fractures in the pelvic area, in 70% of patients two or more fractures are present at the same time (15, 17, 18). In 88% of patients, sacral fractures are associated with pubic rami fractures and / or parasymphyseal fractures (17), and somewhat less frequently, with acetabular fractures and fractures in the area of the wing (ala) of the ilium (18).

According to De Smet et al., there are initial changes in the sacrum with consequent mechanical stress on other pelvic bone structures (17).

Sacral fractures are also one of the possible complications after surgical stabilisation of the lumbar spine (19, 20). A sacral fracture associated with grade II spondylolisthesis at the L5–S1 level, caused by spondylolysis, which, most likely, occurred as a consequence of pathological anterior shear force, has also been described (21). Considering that sacral fracture is one of the possible complications after surgical stabilisation of the spine, and due to the low sensitivity of radiography, in elderly patients with spondylolisthesis for whom surgical treatment is planned, it is recommended to perform an MRI of the spine and the sacrum during preoperative preparation in order to exclude or confirm the underlying sacral insufficiency fracture (19, 21).

In everyday clinical work, and due to the often-present radicular symptoms caused by degenerative changes of the spine, the next diagnostic step, after plain radiographs, is the MRI (9, 22). This was also the case with the patient whose case is described in this case report. MRI of the pelvis shows almost 100% sensitiv-

otežati postavljanje dijagnoze prijeloma sakruma u oslabljenoj kosti (14, 15).

Bolesnica koju smo prikazale u ovom radu od rizičnih je čimbenika imala stariju dob i tešku osteoporozu s osteoporotičnim prijelomom kralješka te kroničnu bubrežnu bolest u terminalnoj fazi zbog čega je provedena hemodijaliza. Boli u donjem dijelu leđa dodatno su uzrokovale i degenerativne promjene te nestabilnost slabinske kralježnice. Budući da se nakon primijenjene fizikalne terapije bol nije smanjila, bolesnica je dodatno dijagnostički obrađena. Standardna radiografska obrada tipično nije upućivala na prijelom sakruma, nego je to bio slučajan nalaz na MR-u lumbosakralne kralježnice. U radu Cabarrusa i suradnika od 108 prijeloma u oslabljenoj kosti u području zdjelice, otkrivenih s pomoću MR-a zdjelice ili MR-a lumbosakralne kralježnice, na standardnim je radiogramima zdjelice ili lumbosakralne kralježnice dijagnosticirano samo njih 16 (14,8%), a od toga tek 3,8% (2/53) prijeloma sakruma. To jasno potvrđuje da standardni radiogrami najčešće ne mogu dijagnosticirati ni isključiti prijelom u području zdjelice, ponajmanje prijelom u području sakruma. Na standardnom radiogramu prisutnost sklerotične linije u kosti, prekid kortikalisa ili vidljiva frakturna pukotina upozoravaju na prijelom u oslabljenoj kosti (15).

Prijelomi sakruma, osim u oslabljenoj kosti, nastaju i u sportaša kao prijelomi zamora u zdravoj kosti zbog preopterećenja (4, 5, 16). Kod prijeloma u oslabljenoj kosti u području zdjelice u 70% bolesnika prisutna su istodobno dva prijeloma ili je prisutno više njih (15, 17, 18). U 88% bolesnika prijelomi sakruma udruženi su s prijelomima grana pubičnih kostiju i/ili parasimfizeal-

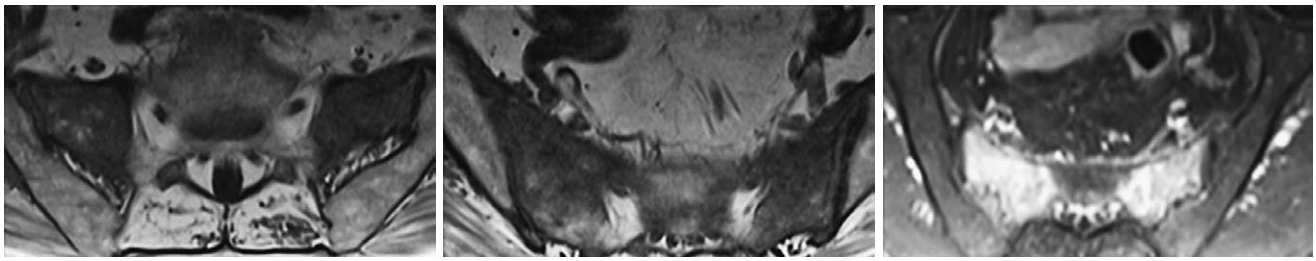

FIGURE 4. On the T1-weighted image, axial sections through the sacrum show linear zones of low signal intensity, which can be seen bilaterally in the areas extending through lateral masses of the sacrum and which correspond to fracture lines. The extensive high signal zones in the STIR image (last image on the right) correspond to the oedema of the surrounding spongy bone. No pathological changes of the SI joints were observed.

SLIKA 4. Transverzalni presjeci kroz sakrum obostrano u području lateralnih masa sakruma pokazuju linearne zone niskog signala u slici mjerenoj T1, koje odgovaraju frakturnim linijama. Opsežne zone visokog signala u slici mjerenoj slici STIR-om (krajnje desna slika) odgovaraju edemu spongioze okolne kosti. SI zglobovi uredna su prikaza

ity during the detection of insufficiency fractures in the pelvic area and it showed better results in fracture detection than the CT scan. Cabarrus et al. state that, through the MRI, they have managed to detect 128 out of 129 (99%) fractures in 63 of 64 (98%) patients, while the CT scan revealed only 89 out of 129 (69%) fractures in 34 of 64 (53%) patients (15).

Typical signs of fracture that were visible on the MRI were bone marrow oedema and fracture gaps. Fracture gaps are most visible in sequences in T1 (spin-lattice) relaxation time. Bone marrow oedema is presented as a region of high intensity in sequences in T2 (spin-spin) relaxation time with fat suppression and in STIR sequences, as well as a region of low intensity in sequences in T1 (spin-lattice) relaxation time in relation to the surrounding normal bone. MRI has an almost 100% sensitivity for detecting spongy bone oedema, but it is a relatively nonspecific sign present in various bone-related pathological conditions, ranging from reactive oedema due to mechanical stress, oedema related to postconcussional syndrome, to processes related to inflammation and tumours (15). During the interpretation of MRI findings, it should be taken into account that a fracture gap is not always visible and that diagnostic errors are possible, especially in patients with malignant diseases. However, in almost 90% of insufficiency fractures, bone marrow oedema and fracture gaps are present at the same time (15).

In the differential diagnosis, primary malignant disease or metastatic lesions in malignant disease and osteomyelitis are most often considered.

Sacral insufficiency fracture most commonly affects both sacral alae and is vertical in shape. The horizontal component, which usually passes through the vertebral body of the second sacral (S2) vertebra (22), is also common. Fractures are most visible on oblique coronal sections through the sacrum. The bone scintigraphy which utilizes technetium, shows a typical pattern of pathological accumulation of radiopharmaceuticals

ne regije (17), a nešto rjeđe s prijelomima u području acetabuluma i krila crijevne kosti (18).

Prema De Smetu i suradnicima, inicijalne su promjene na sakrumu s posljedičnim mehaničkim preopterećenjem na ostalim zdjeličnim koštanim strukturama (17).

Prijelomi sakruma također su jedna od mogućih komplikacija poslije kirurške stabilizacije lumbalne kralježnice (19, 20). Opisan je i prijelom sakruma povezan sa spondilolistezom 2. stupnja segmenta LV – SI, uzrokovanom spondilolizom, a najvjerojatnije kao posljedica patološke anteriorne sile smicanja (21). Budući da je prijelom sakruma moguća komplikacija kirurške stabilizacije kralježnice, a s obzirom na nisku osjetljivost radiografije, u starijih bolesnika sa spondilolistezom kod kojih se planira kirurško liječenje preporučuje se tijekom preoperativne pripreme učiniti MR kralježnice i sakruma te tako isključiti ili eventualno potvrditi podležeći prijelom sakruma u strukturalno oslabljenoj kosti (19, 21).

U svakodnevnom kliničkom radu, a zbog često prisutnih radikularnih simptoma uzrokovanih degenerativnim promjenama kralježnice, nakon standardnih radiograma sljedeći dijagnostički korak jest MR (9, 22). Tako je bilo i u bolesnice koju prikazujemo. MR zdjelice pokazuje gotovo 100%-tnu osjetljivost pri otkrivanju prijeloma u oslabljenoj kosti u području zdjelice te nadmašuje CT. Cabarrus i suradnici navode da su s pomoću MR-a otkrili 128 od 129 (99%) prijeloma u 63 od 64 (98%) bolesnika, dok je primjenom CT-a otkriveno samo 89 od 129 (69%) prijeloma u 34 od 64 (53%) bolesnika (15).

Tipični znakovi prijeloma vidljivi na MR-u jesu edem kosti i frakturna pukotina. Ona se najbolje prikazuje na sekvencijama u mjernom vremenu T1. Edem kosti prikazuje se kao područje visokog intenziteta na sekvencijama u mjernom vremenu T2 sa supresijom masti i na sekvencijama STIR te kao područje smanjenog intenziteta na sekvencijama u mjernom vremenu T1 u odnosu prema okolnoj normalnoj kosti. MR ima gotovo stopo-

(on the posterior scan) in the shape of the letter H (the so-called H sign, the Honda sign or the butterfly sign). In other words, two vertical lines in the area of the sacral alae connected by a horizontal line are shown. It should be noted that, sometimes, the accumulation pattern may be incomplete, e.g., if one vertical component is missing. The sensitivity of scintigraphy in detecting sacral insufficiency fractures is very high (96%), with a positive predictive value of 92% (23).

Although the CT scan has a lower sensitivity than the MRI (between 60 and 75%), this radiological technique can also help to distinguish between insufficiency fractures and malignant bone remodelling, due to a better presentation of cortical destruction, and a clearer picture of possible fracture gap spread, as well as the neural foraminal stenosis affected areas, which is especially important when planning treatment with the sacroplasty procedure (15, 24).

On the other hand, in comparison to the CT scan, the MRI is significantly better in detecting lesions of soft tissue structures. In sacral fractures, oedema of the surrounding soft tissue is less common (in 36% of cases) than in pubic bone fractures (65% of cases) or acetabular fractures (64% of cases), as well as the proximal part of the femur (51% of cases) (15).

Cabarrus et al. showed that soft tissue lesions on the MRI were detected in 99% of patients compared to only 12.6% of these lesions that were visible on the CT scan (15). It should be noted that both methods are significantly better at detecting acetabular and sacral fractures compared to plain radiography (15, 25).

Sacral insufficiency fracture treatment is mostly treated with conservative methods of treatment. The usual approach to treatment includes bed rest during the course of 3 to 6 months, which causes accelerated bone mineral density (BMD) loss. Other unwanted complications for people who are on prolonged bed rest (and immobilised) include thromboembolism and the occurrence of decubitus ulcers with secondary infections (26).

Early mobilisation, on the other hand, stimulates osteoblast activity and new bone formation. Weight-bearing exercises and hydrotherapy are standard methods during rehabilitation (27). Pain management is important in the treatment of sacral insufficiency fractures. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used, but they should be used with caution, as some studies indicate that such drugs may lead to bone mineral density loss and that they can slow down fracture healing by disrupting endochondral ossification (28, 29). Treatment with paravertebral injections with an oxygen-ozone mixture has also shown encouraging results in the treatment of opioid-resistant pain (30).

stotnu osjetljivost za detekciju edema spongiozne kosti, no to je relativno nespecifičan znak koji je prisutan kod različitih patoloških stanja što zahvaćaju kost, počevši od reaktivnog edema zbog mehaničkog preopterećenja, postkontuzijskog edema do upalnih i tumorskih procesa (15). Tijekom interpretacije nalaza MR-a treba uzeti u obzir da frakturna pukotina nije uvijek vidljiva te su moguće dijagnostičke pogreške posebice u bolesnika s malignim bolestima. Ipak, u gotovo 90% prijeloma u oslabljenoj kosti istodobno su prisutni edem kosti i frakturna pukotina (15).

U diferencijalnoj dijagnozi najčešće u obzir dolaze primarna maligna bolest ili metastatske lezije kod maligne bolesti te osteomijelitis.

Prijelom sakruma u oslabljenoj kosti najčešće zahvaća oba krila i vertikalnog je oblika. Česta je i horizontalna komponenta koja obično prolazi trupom drugoga sakralnog (SII) kralješka (22). Prijelomi su najvidljiviji na kosim koronalnim presjecima kroz sakrum. Na scintigrafiji skeleta tehnecijem vidi se tipičan obrazac patološkog nakupljanja radiofarmaka (na posteriornom skenu) u obliku slova H (tzv. znak H ili znak Honda ili znak leptira), tj. prikazuju se dvije vertikalne linije u području krila sakruma spojene horizontalnom linijom. Treba naglasiti da katkad obrazac nakupljanja može biti nepotpun, npr., ako nedostaje jedna vertikalna komponenta. Osjetljivost scintigrafije pri otkrivanju prijeloma sakruma u oslabljenoj kosti veoma je visoka (96%-tna), s pozitivnom prediktivnom vrijednosti od 92% (23).

Iako CT ima manju osjetljivost od MR-a (između 60 i 75%), i ta radiološka tehnika može pomoći pri razlikovanju prijeloma u oslabljenoj kosti i maligne pregradnje kosti, i to zbog boljeg prikaza destrukcije kortikalisa, a jasniji je i prikaz eventualnog širenja frakturne pukotine i zahvaćanja neuralnih foramena, što je osobito važno pri planiranju liječenja metodom sakroplastike (15, 24).

S druge strane, MR je u usporedbi s CT-om znatno bolji pri detekciji lezija mekotkivnih struktura. Kod prijeloma sakruma edem okolnoga mekog tkiva rjeđe je prisutan (u 36%) nego kod prijeloma u području pubičnih kosti (65%) ili acetabuluma (64%), kao i proksimalnog dijela femura (51%) (15).

Cabarrus i suradnici pokazali su da su lezije mekih tkiva na MR-u prepoznate u 99% bolesnika u usporedbi s njih tek 12,6% vidljivih na CT-u (15). Valja naglasiti da su obje metode znatno bolje u detekciji prijeloma acetabuluma i sakruma u usporedbi sa standardnom radiografijom (15, 25).

Liječenje prijeloma sakruma u oslabljenoj kosti uglavnom je konzervativno. Uobičajen pristup jest mirovanje tijekom 3 – 6 mjeseci, što dovodi do ubrzanoga gubitka mineralne gustoće kosti. Neželjene komplikacije dugotrajnog mirovanja jesu i trombo-

In recent times, sacroplasty is increasingly being used in the treatment of sacral stress fractures, as a minimally invasive procedure. It is intended to rapidly relieve the symptoms of clinical conditions, primarily pain, which allows early mobilisation of such patients (12). Vertebroplasty is a technique based on injecting polymethyl methacrylate (PMMA) cement into the fracture gap area. The two biggest challenges of this technique are safe needle insertion and safe cement extrusion. Cement injection into the sacrum was originally used to treat painful skeletal metastases, and twenty years ago it was first performed in the treatment of osteoporotic fractures of the sacrum (31).

There are several ways of performing sacroplasty, which differ primarily in terms of the method of approach and the insertion of the needle. A posterior approach is typically used when, through the use of fluoroscopy or, less commonly, a CT scan, an 11- or 13-gauge bone biopsy needle is inserted percutaneously through the sacral cortex, in a plane parallel to the SI (sacroiliac) joint. When using the approach along the longitudinal axis, the needle is inserted in the caudocranial direction, along the sacral Y-axis (the longitudinal axis of the sacrum). The mediosagittal approach requires a postoperative magnetic resonance imaging, due to the fact that the needle passes through the central canal of the sacrum, so it is necessary to confirm that the tip of the needle is located more to the caudal end than the distal end of the thecal sac. The occurrence of complications in sacroplasty are rare. The highest risk is that of cement leakage outside the fracture gap into the sacral foramina and spinal canal. Neuritis of the sacral spinal nerve 1 (S1) has been described as a consequence of cement migration after sacroplasty (32). Cement leakage into the paraspinal soft tissues holds no major clinical significance. As with vertebroplasty, complications of venous thromboembolism and nerve damage are possible (32, 33). Given the importance of fracture gap localisation and extension for a satisfactory sacroplasty outcome, Gesa Bakker, et al. have proposed a classification of sacral fractures, divided into 3 groups: (i) group A includes fractures that have no mechanical importance and fractures with no cortical disruption, (ii) group B is formed by complete fractures of the sacral alae, starting in the anterior cortical bone or fractures which affect the neural foramina and the sacral canal, and (iii) group C includes fractures in the sacral corpus with fracture lines continuing to the anterior or posterior cortical bone or the sacral foramina (24).

Several other methods for the treatment of sacral fractures have been described, such as balloon-assisted sacroplasty, kyphoplasty, or transiliosacral screw insertion fluoroscopic techniques, but in clinical practice

embolijska bolest te razvoj dekubitusa sa sekundarnim infekcijama (26).

Rana mobilizacija, s druge strane, potiče aktivnost osteoblasta i stvaranje nove kosti. Vježbe opterećenja i hidroterapija standardne su metode tijekom rehabilitacije (27). Kontrola boli važna je u liječenju prijeloma sakruma u oslabljenoj kosti. Nesteroidni protuupalni lijekovi u širokoj su uporabi, no potreban je oprez s obzirom na to da pojedine studije navode kako takvi lijekovi mogu smanjiti mineralnu gustoću kosti te usporavaju cijeljenje prijeloma narušavajući enhondralno okoštavanje (28, 29). Ohrabrujuće rezultate u liječenju boli rezistentne na opioide pokazalo je i liječenje paravertebralnim injekcijama mješavine kisika i ozona (30).

U novije vrijeme sakroplastika kao minimalno invazivan postupak sve češće nalazi svoje mjesto u liječenju stresnih prijeloma sakruma. Namijenjena je brzom olakšavanju kliničkih tegoba, ponajprije boli, što omogućava ranu mobilizaciju takvih bolesnika (12). Vertebroplastika je tehnika koja se temelji na injiciranju polimetilmetakrilatnog (PMMA) cementa u područje frakturne pukotine. Dva najveća izazova ove tehnike jesu sigurno uvođenje igle i sigurna ekstruzija cementa. Injekcija cementa u sakrum prvotno se rabila za liječenje bolnih koštanih rasadnica (metastaza), a prije dvadesetak godina prvi je put izvedena radi liječenja osteoporotičnog prijeloma sakruma (31).

Više je načina izvođenja sakroplastike koji se razlikuju ponajprije s obzirom na način pristupa i uvođenje igle. Tipično se rabi stražnji pristup kada se pod kontrolom fluoroskopije ili rjeđe CT-a perkutano kroz sakralni korteks, u ravnini paralelnoj sa SI zglobom, uvodi igla za biopsije kosti od 11 ili 13 G. Kod pristupa po uzdužnoj osi igla se uvodi u kaudokranijalnom smjeru duž longitudinalne osi sakruma. Mediosagitalni pristup nalaže postproceduralni slikovni prikaz magnetskom rezonancijom budući da igla prolazi centralnim kanalom sakruma pa je potrebno potvrditi da se vrh igle nalazi kaudalnije od distalnog kraja duralne vreće. Komplikacije sakroplastike rijetke su. Najviši je rizik od curenja cementa izvan frakturne pukotine u sakralne foramene i spinalni kanal. Opisan je neuritis živca S1 kao posljedica migracije cementa poslije sakroplastike (32). Curenje cementa u paraspinalna meka tkiva bez većeg je kliničkog značenja. Kao i kod vertebroplastike, moguće su komplikacije venska embolija i neuralna oštećenja (32, 33). S obzirom na važnost lokalizacije i ekstenzije frakturne pukotine za zadovoljavajući ishod sakroplastike, Gesa Bakker sa suradnicima predložila je klasifikaciju prijeloma sakruma u 3 grupe: (i) grupa A obuhvaća prijelome bez mehaničkog značenja koji ne zahvaćaju kortikalis, (ii) grupu B čine potpuni prijelomi krila sakruma s prekidom anteriornog kortikalisa ili koji zahvaćaju neuralne foramene i sakralni kanal, (iii)

these methods have not been increasingly implemented so far (34 – 36).

Surgical methods of treatment are indicated in patients in whom conservative methods of treatment have not yielded any positive results. The challenge of surgical treatment is to achieve satisfactory stability in an already structurally weakened bone. By performing stabilisation using transiliac-transsacral screws, mobility is achieved in a significant number of patients with a satisfactory effect on the absence of pain (37). Better interfragmentary compression is achieved through the placement of a transsacral plate (38). Iliosacral screw fixation ((ISS) is a commonly used treatment method, but some studies have shown that through this method satisfactory mechanical stability is not achieved, which leads to displacement and instability of the screws (39). Lumbosacral fixation technique is indicated in patients with neurological complications due to unstable sacral fractures (40).

CONCLUSION

Sacral insufficiency fractures which occur in the structurally weakened bone are often overlooked causes of nonspecific lumbosacral back pain, especially in elderly women with underlying osteoporosis. Plain radiographs of the pelvis are often non-diagnostic when it comes to this type of fractures, and the diagnostic imaging method of choice is MRI, which is also confirmed in our case report. Inflammation or malignant disease must first be excluded through the process of differential diagnosis. Treatment is mainly performed through conservative methods, and in recent times, sacroplasty is increasingly being used in the treatment of sacral fractures, as a minimally invasive procedure.

Conflict of interest statement: Authors declare no conflict of interest.

grupa C obuhvaća prijelome korpusa sakruma s povišenjem prema anteriornom ili posteriornom korteksu ili sakralnim foramenima (24).

Opisano je još nekoliko metoda za liječenje prijeloma sakruma poput sakroplastike s balonom, kifoplastike ili fluoroskopskog postavljanja transiliosakralnih vijaka, ali u kliničkoj praksi te metode dosad nisu znatnije zaživjele (34 – 36).

Kirurške metode liječenja indicirane su u pacijenata kod kojih konzervativno liječenje nije dalo rezultata. Izazov kirurškog liječenja jest postići zadovoljavajuću stabilnost u već strukturalno oslabljenoj kosti. Stabilizacijom s pomoću transilijakalno-transsakralnih vijaka postiže se mobilnost u znatnog broja bolesnika uz zadovoljavajući učinak na izostanak boli (37). Bolja interfragmentarna kompresija postiže se postavljanjem transsakralne ploče (38). Iliosakralna fiksacija vijcima često je upotrebljavana metoda liječenja, no neka su istraživanja pokazala da se ovom metodom ne postiže zadovoljavajuća mehanička stabilnost, što dovodi do pomicanja i nestabilnosti vijaka (39). Lumbosakralna fiksacija indicirana je u bolesnika s neurološkim komplikacijama zbog nestabilnog prijeloma sakruma (40).

ZAKLJUČAK

Prijelomi sakruma u strukturalno oslabljenoj kosti često su neprepoznat uzrok lumbalne i zdjelične boli bez prethodne traume, osobito u žena starije dobi s osteoporozom. Na standardnim radiogramima zdjelice ovi se prijelomi rijetko uočavaju, a dijagnostička metoda izbora jest MR, što je potvrđeno i u našem prikazu bolesnice. Diferencijalno dijagnostički ponajprije treba isključiti upalni ili maligni proces. Liječenje je uglavnom konzervativno, a u novije vrijeme sakroplastika kao minimalno invazivan postupak sve češće nalazi svoje mjesto pri liječenju prijeloma sakruma u oslabljenoj kosti.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Pentecost RL, Murray RA, Brindley HH. Fatigue, insufficiency, and pathologic fractures. Jama. 1964;187:1001–4.
2. Santolini E, Kanakaris NK, Giannoudis PV. Sacral fractures: issues, challenges, solutions. EFORT Open Rev. 2020;5:299–311.
3. Longhino V, Bonora C, Sansone V. The management of sacral stress fractures: current concepts. Clin Cases Miner Bone Metab. 2011;8(3):19–23.
4. Vajapey S, Matic G, Hartz C, Miller TL. Sacral Stress Fractures: A Rare but Curable Cause of Back Pain in Athletes. Sports Health. 2019;11(5):446–52.
5. Hosey R, Fernandez M, Johnson D. Evaluation and Management of Stress Fractures of the Pelvis and Sacrum. Orthopedics. 2008;31:383–5.
6. Mattila VM, Niva M, Kiuru M, Pihlajamaki H. Risk factors for bone stress injuries: a follow-up study of 102,515 person-years. Med Sci Sports Exerc. 2007;39:1061–6.
7. Ayanaoğlu T, Atik OŞ, Tokgöz N, Uçar M. Sacral and pubic insufficiency fractures due to bisphosphonate treatment. Eklem Hastalik Cerrahisi. 2015;26(2):120–4.
8. Grasland A, Pouchot J, Mathieu A, Paycha F, Vinceneux P. Sacral insufficiency fractures: an easily overlooked cause of back pain in elederly women. Arch Intern Med. 1996;156: 668–74.
9. Sudhir G, Kalra KL, Shankar A, Chahal R. Sacral insufficiency fractures mimicking lumbar spine pathology. Asian Spine J. 2016;10:558–64.
10. Gotis-Graham I, McGuigan L, Diamond T i sur. Sacral insufficiency fractures in the elderly. J Bone Joint Surg Br. 1994;76: 882–6.
11. Finiels H, Finiels PJ, Jacquot JM, Strubel D. Fractures of the sacrum caused by bone insufficiency: meta-analysis of 508 cases. Presse Med. 1997;26:1568–73.
12. Bayley E, Srinivas S, Boszczyk BM. Clinical outcomes of sacroplasty in sacral insufficiency fractures: a review of the literature. Eur Spine J. 2009;18:1266–7.
13. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000;25(22):2940–52.
14. Spiegl UJA, Schnake KJ, Osterhoff G i sur. Imaging of Sacral Stress and Insufficiency Fractures. Z Orthop Unfall. 2019; 157(2):144–53.
15. Cabarrus MC, Ambekar A, Lu Y, Link TM. MRI and CT of insufficiency fractures of the pelvis and the proximal femur. AJR Am J Roentgenol. 2008;191:995–1001.
16. Miletić D, Šestan B, Pusić M, Cicvarić T, Tudor A, Roth S, Šantić V. Unusual consecutive sacral stress fractures in a female distant runner: a case report. Eur J Phys Rehabil Med. 2012; 48(2):283–7.
17. De Smet AA, Neff JR. Pubic and sacral insufficiency fractures: clinical course and radiologic findings. AJR Am J Roentgenol. 1985;145:601–6.
18. Grangier C, Garcia J, Howarth NR, May M, Rossier P. Role of MRI in the diagnosis of insufficiency fractures of the sacrum and acetabular roof. Skeletal Radiol. 1997;26:517–24.
19. Scemama C, D'astorg H, Guigui P. Sacral stress fracture after lumbar and lumbosacral fusion. How to manage it? A proposition based on three cases and literature review. Orthop Traumatol Surg Res. 2016;102:261–8.
20. Asad A, Junaid J, Hashmi I. Sacral insufficiency fracture, a rare complication of posterior spinal instrumentation. J Pak Med Assoc. 2019;69:1380–2.
21. Schizas C, Theumann N. An unusual natural history of a L5-S1 spondylolisthesis presenting with a sacral insufficiency fracture. Eur Spine J. 2006;15(4):506–9.
22. Kim YY, Chung BM, Kim WT. Lumbar spine MRI versus non-lumbar imaging modalities in the diagnosis of sacral insufficiency fracture: a retrospective observational study. BMC Musculoskelet Disord. 2018;19:257.
23. Fujii M, Abe K, Hayashi K i sur. Honda sign and variants in patients suspected of having a sacral insufficiency fracture. Clin Nucl Med. 2005;30:165–9.
24. Bakker G, Hattingen J, Stuetzer H, Isenberg J. Sacral Insufficiency Fractures: How to Classify? J Korean Neurosurg Soc. 2018;61:258–66.
25. Kinoshita H, Miyakoshi N, Kobayashi T, Abe T, Kikuchi K, Shimada Y. Comparison of patients with diagnosed and suspected sacral insufficiency fractures. J Orthop Sci. 2019;24:702–7.
26. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extrem Physiol Med. 2015;4:16.
27. Urits I, Orhurhu V, Callan J i sur. Sacral Insufficiency Fractures: a Review of Risk Factors, Clinical Presentation, and Management. Curr Pain Headache Rep. 2020;24(3):10.
28. Su B, O'Connor JP. NSAID therapy effects on healing of bone, tendon, and the enthesis. J Appl Physiol. 2013;115:892–9.
29. García-Martínez O, De Luna-Bertos E, Ramos-Torrecillas J, Manzano-Moreno FJ, Ruiz C. Repercussions of NSAIDS drugs on bone tissue: the osteoblast. Life Sci. 2015;123:72–7.
30. De Sire A, Baricich A, Minetto MA, Cisari C, Invernizzi M. Low back pain related to a sacral insufficiency fracture: role of paravertebral oxygen-ozone therapy in a paradigmatic case of nociplastic pain. Funct Neurol. 2019;34:119–22.
31. Garant M. Sacroplasty: a new treatment for sacral insufficiency fracture. J Vasc Interv Radiol. 2002;13:1265–7.
32. Frey ME, Depalma MJ, Cifu DX, Bhagia SM, Carne W, Daitch JS. Percutaneous sacroplasty for osteoporotic sacral insufficiency fractures: a prospective, multicenter, observational pilot study. Spine J. 2008;8:367–73.
33. Pommersheim W, Huang-Hellinger F, Baker M, Morris P. Sacroplasty: A Treatment for Sacral Insufficiency Fractures. AJNR Am J Neuroradiol. 2003;24:1003–7.
34. Atalay B, Caner H, Yilmaz C, Altinors N. Sacral kyphoplasty for relieving pain caused by sacral hemangioma. Spinal Cord. 2006;44:196–9.
35. Deen H, Nottmeier EW. Balloon kyphoplasty for treatment of sacral insufficiency fractures. Neruosurg Focus. 2005;18(3):e7.
36. Scuibba DM, Wolinsky JP, Than KD, Gokaslan ZL, Witham TF, Murphy KP. CT fluoroscopically guided percutaneous placement of transiliosacral rod for sacral insufficiency fracture: case report and technique. AJNR Am J Neuroradiol. 2007;28: 1451–4.
37. Walker JB, Mitchell SM, Karr SD, Lowe JA, Jones CB. Percutaneous transiliac-transsacral screw fixation of sacral fragility fractures improves pain, ambulation, and rate of disposition to home. J Orthop Trauma. 2018;32:452–6.
38. Mehling I, Hessmann MH, Rommens PM. Stabilization of fatigue fractures of the dorsal pelvis with a trans-sacral bar. Operative technique and outcome. Injury. 2012;43:446–51.
39. Oberkircher L, Masaeli A, Bliemel C, Debus F, Ruchholtz S, Krüger A. Primary stability of three different iliosacral screw fixation techniques in osteoporotic cadaver specimens – a biomechanical investigation. Spine J. 2016;16:226–32.
40. Maki S, Nakamura K, Yamauchi T i sur. Lumbopelvic fixation for sacral insufficiency fracture presenting with sphincter dysfunction. Case Rep Orthop. 2019;2019:1–4.

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PROFESSOR SYLEJMAN REXHEPI, MD, PHD

(6 November 1953 – 24 July 2020)

Professor Sylejman (Kadrush) Rexhepi, MD, PhD passed away on July 24, 2020 at the age of 66 after contracting coronavirus. He was a distinguished internist-rheumatologist and university professor with a 40-year career at the University Clinical Center in Kosovo (UCCK). He is deeply mourned by his wife Mevlyde, his children Mjellma, Blerta, Lura, and Gresa, grandchildren Heron, Troja, and Diell, as well as other family members and friends.

Professor Sylejman Rexhepi was born on November 6, 1953 in Ferizaj, where he completed his primary and secondary education. He graduated from the Faculty of Medicine at the "Hasan Prishtina" University of Prishtina in 1979, and completed his specialization in Internal Medicine at the University of Nish in 1985. He continued his postgraduate studies in Rheumatology at the University of Zagreb in 1987, where he received a Master of Medical Sciences degree in 1991. Eager for further education and learning, he enrolled in PhD studies at the "Hasan Prishtina" University in Prishtina, earning his Doctor of Medical Sciences degree in 1997.

His work experience was extensive. He started working as a general practitioner at the Primary Health Center in Ferizaj on March 12, 1979. From 1983 to 1990 he was employed in the UCCK Department of Internal Medicine. During the 1990s, Kosovo experienced political challenges when Serbian forces suppressed its autonomy, which caused high unemployment. A large number of Kosovars working in the public sector lost their jobs, and thus Professor Rexhepi established his own private clinic "Rheuma" in Ferizaj and in Prishtina in 1990. After Kosovo attained independence in 1999, he resumed his position at the UCCK, where he worked until his retirement in 2018. He was head of the Rheumatology Department from 1999 to 2012. In 2012 the Rheumatology Clinic was established, and Professor Rexhepi was appointed its Director, a position he held until 2015. His colleagues consider him the main contributor to the development of rheumatology in Kosovo.

Professor Rexhepi was also head of the Department of Internal Medicine for several years. He had an excellent relationship with his patients. A great listener, he was known among his patients as a physician who "could cure with his kind words". They were allowed to express their major concerns and always felt understood. In addition, Professor Rexhepi taught Internal Medicine courses at the "Hasan Prishtina" University of Prishtina Faculty of Medicine from 1987 to 2019, first as a teaching assistant, and later as an Assistant Professor and Associate Professor. He educated new generations of students of General Medicine, Dentistry, Physiotherapy, and Nursing, acting as a facilitator in bringing across information and new concepts in the field of internal medicine. He used a democratic and proactive system of teaching, allowing students to participate in the decision-making process during the semester. He was also a strong advocate of bringing the real world to the classroom by incorporating authentic case studies of patients with various diseases. His door was always open for students to discuss any questions that they might have. His goal was to provide a learning experience that would enable the student to have the opportunity to effectively contribute and excel in the medical environment.

Professor Rexhepi led a scientific project on Rheumatic Fever. One of his main contributions in the early phase of development of rheumatology in Kosovo was the organization of five symposiums on rheumatic fever and one on ankylosing spondylitis in the period 1987–

1989. It is of crucial importance to highlight that he was the organizer of four symposiums: Updates in Rheumatology in 2001, 2002, 2003, and 2006. From 1995 to 2018, he was a mentor and committee member for numerous PhD and master candidates. Also, he was chairman and member of the Specialist Examination Committee during the period 1999–2018. He also served as a mentor or committee member for specialist exams in the fields of Internal Medicine, Rheumatology, Allergology with Immunology, Endocrinology, etc. Besides, he was head of the Nursing and Midwifery Department from March 2016 to 2018.

A big step for Kosovo rheumatology was the establishment of the Association of Rheumatologists of Kosovo, with Professor Rexhepi as president from 2012. Largely owing to his efforts, the association was very active – he was organizing chairman of four National Rheumatology Congresses with international participation. The main topics of the congresses included rheumatoid arthritis, osteoporosis, and other rheumatic diseases. The meetings and exchange of experiences among various health care professionals contributed to the advancement of Kosovo rheumatology. Fortunately, Professor Rexhepi had an extended network established during his participation in numerous conferences around the world, which made it possible to bring many well-known rheumatologists to Kosovo.

Professor Rexhepi authored the university textbook "Rheumatology" (2006) for medical students and rheumatology residents of the "Hasan Prishtina" University of Prishtina. He coordinated and contributed to the Albanian translation of a University of Oxford textbook on Rheumatology. Another contribution was his translation of the textbook Propedeutics in Internal Medicine; he also prepared Chapter 11, Examination of the locomotor system (Prishtina, 2016).

Professor Rexhepi published papers in internationally renowned journals as well as books. He participated in over 50 international and national conferences. His research work was mainly in the field of internal medicine, rheumatoid arthritis, disease-modifying antirheumatic drugs (DMARDs), combined therapy with methotrexate, and osteoporosis. His contributions appeared in international journals such as Arthritis Research and Therapy, Clinical and Experimental Rheumatology, The Journal of Rheumatology, Annals of the Rheumatic Diseases, Arthritis & Rheumatology, Reumatizam, Open Access Macedonian Journal Medical Science, Medical Archive, Materia Socio Medica, Acta Rheumatologica, and many others. Furthermore, he was an active member on a QUEST-RA group project with rheumatoid arthritis patients that involved many European countries.

His awards, memberships, and activities include:

2007–2020: member of the Croatian Society for Rheumatology (HRD), which is part of the European League Against Rheumatism (EULAR)

2009–2020: reviewer in the journal Medicus, Macedonia

2010–2020: member of the Editorial Board of Medicus, Macedonia

2011: award for the presentation of an original scientific work at the Rheumatology International Congress (BRIC) in Tokyo

2011–2012: president of the Kosovo Osteoporosis Association

2012–2020: president of the Association of Rheumatologists of Kosovo

2015–2020: member of the International Osteoporosis Federation (IOF)

2016: reviewer in the journal Reumatizam, Croatia

Professor Rexhepi took part in different professional training programs. More specifically, in 1983 he was an Internal Medicine resident at the University Hospital in Bologna. He also completed a postgraduate course in Internal Medicine-Rheumatology at the University of Hamburg in 2002.

Professor Rexhepi was an exemplary professor as well as a man of broad culture. He was not only a dedicated and hard-working physician, but also a noble, loyal, and charismatic person, a very passionate man who deeply cared about people. The moment you spoke to him about medicine, his eyes would light up. His work on improvements in the treatment of rheumatic diseases, with his two daughters and other professionals in the field, provided ongoing hope and optimism. Every day, for him, was a gift of the opportunity to care for patients in their most vulnerable times. Despite the stress and long hours away from home and family, he never stopped helping people. He really loved his work, and being fit and healthy, he wanted to give his utmost to educate new generations of doctors and cure patients.

He was a beloved husband, father, grandfather, and friend who loved to entertain. To those close to him, he was known as a great basketball player, a man with a beautiful handwriting, good at keeping confidences, and a guardian angel to his friends. As an enthusiastic explorer, he always wanted to learn about new cultures through travelling and keeping memories alive through photography, which he adored. He enjoyed spending time with his family and loved ones. His wife remembers him as her soulmate and a people person with an open heart for everyone. He turned every little daily annoyance or happiness into a story, and he shared all those stories joyfully. Professor Rexhepi touched many lives, including those of the people he

worked with, and especially his two daughters who followed him in his profession.

Professor Rexhepi had good connections with Croatian rheumatology, marked by close collaboration. He actively participated in almost all Croatian national rheumatology congresses, published articles in the journal Reumatizam, and reviewed manuscripts. Also, Croatian rheumatologists were always pleased to accept invitations for lectures at rheumatology congresses and other events in Kosovo. Apart from his professional and scientific achievements, the Croatian rheumatology community will always remember Professor Rexhepi for his exceptional kindness and friendship.

Professor Sylejman Rexhepi passed away prematurely, leaving an irreplaceable gap both for his family and friends, as well as for his patients and the whole medical community.

On behalf of the
Croatian Society for Rheumatology
Branimir Anić
and Simeon Grazio

PROF. DR. SC. SYLEJMAN REXHEPI

(6. 11. 1953. – 24. 7. 2020.)

Prof. dr. sc. Sylejman (Kadrush) Rexhepi preminuo je 24. srpnja 2020. u dobi od 66 godina od posljedica koronavirusne bolesti. Bio je ugledan internist-reumatolog i sveučilišni profesor s 40-godišnjim iskustvom rada u Univerzitetskome kliničkom centru Kosova (UKCK). Za njim tuguju supruga Mevlyde, njegova djeca Mjellma, Blerta, Lura i Gresa, unuci Heron, Troja i Diell, kao i drugi članovi obitelji i prijatelji.

Prof. Sylejman Rexhepi rođen je 6. studenoga 1953. u Uroševcu, gdje je završio osnovnu i srednju školu. Diplomirao je na Medicinskom fakultetu Sveučilišta u Prištini „Hasan Prishtina" 1979., a specijalizirao je internu medicinu na Sveučilištu u Nišu 1985. godine. Poslijediplomski sveučilišni studij Reumatologija nastavio je na Sveučilištu u Zagrebu 1987., a diplomirao je 1991. godine stekavši titulu magistra znanosti. Budući da je imao želju za daljnjim obrazovanjem i usavršavanjem, upisao je i poslijediplomski sveučilišni doktorski studij na Medicinskom fakultetu Sveučilišta u Prištini „Hasan Prishtina", na kojem je diplomirao 1997. stekavši tako titulu doktora znanosti.

Njegovo radno iskustvo bilo je opsežno i dugogodišnje. 12. ožujka 1979. počeo je raditi kao liječnik opće/obiteljske medicine u Domu zdravlja u Uroševcu. Od 1983. do 1990. radio je u Zavodu za internu medicinu UKCK-a. Tijekom 1990-ih Kosovo je bilo suočeno s političkim izazovima i previranjima kada su oružane snage Republike Srbije pokušale ukinuti autonomiju Kosova, što je uzrokovalo visoku stopu nezaposlenosti. Velik broj Kosovljanina zaposlenih u javnom sektoru izgubio je posao, stoga je 1990. prof. Rexhepi odlučio osnovati svoje privatne klinike „Rheuma" u Uroševcu i Prištini. Nakon što je Kosovo proglasilo neovisnost 1999., prof. Rexhepi nastavio je raditi u UKCK-u, gdje je bio zaposlen sve do svojeg umirovljenja 2018. Od 1999. do 2012. bio je kao pročelnik Zavoda za reumatologiju. Godine 2012. osnovana je Klinika za reumatologiju, a prof. Rexhepi imenovan je njezinim predstojnikom i tu je funkciju obavljao sve do 2015. Njegovi suradnici smatraju da je upravo on najviše pridonio razvoju reumatologije na Kosovu.

Prof. Rexhepi nekoliko je godina radio i kao pročelnik Zavoda za internu medicinu. Imao je odličan odnos sa svojim pacijentima. Uvijek je imao vremena da ih sasluša, a među njima je bio poznat kao „liječnik koji liječi lijepim riječima". Njegovi su pacijenti uvijek mogli slobodno reći što ih muči i

uvijek su se u njegovu društvu osjećali shvaćeno. Uz prije navedeno radno iskustvo prof. Rexhepi držao je i predavanja iz predmeta Interna medicina na Medicinskom fakultetu Sveučilišta u Prištini „Hasan Prishtina" od 1987. do 2019., gdje je prvo bio zaposlen kao stručni suradnik u nastavi (asistent), a poslije kao docent i izvanredni profesor. Pomogao je obrazovati nove generacije studenata u području opće medicine, stomatologije, fizioterapije i sestrinstva te je kao posrednik pokušao objasniti i prenijeti podatke i nove koncepte u području interne medicine. Služio se demokratskim i proaktivnim sustavom predavanja, dopuštajući studentima da sudjeluju pri donošenju odluka tijekom semestra. Bio je i velik zagovornik uvođenja primjera iz „stvarnog života" u učionicu, a to je činio uključivanjem stvarnih i autentičnih studija bolesnika u kojima su opisani pacijenti s različitim bolestima. Njegova su vrata uvijek bila otvorena pacijentima koji su htjeli s njim razgovarati o bilo kakvim pitanjima. Njegov je cilj bio da studentima pruži poučno iskustvo koje bi im omogućilo da se djelotvorno istaknu i pridonesu području medicine.

Prof. Rexhepi bio je i voditelj znanstvenog projekta o reumatskoj groznici. Jedan od njegovih glavnih doprinosa u ranoj fazi razvoja reumatologije na Kosovu bila je organizacija pet znanstvenih simpozija o reumatskoj groznici i jednoga znanstvenog simpozija o ankilozantnom spondilitisu u razdoblju od 1987. do 1989. Iznimno je važno navesti činjenicu da je upravo prof. Rexhepi organizirao četiri znanstvena simpozija: Novosti u Reumatologiji 2001., 2002., 2003. i 2006. godine. Od 1995. do 2018. obavljao je funkcije mentora i člana povjerenstva pri obranama radova mnogih kandidata za titulu doktora znanosti i doktora medicine. Bio je predsjednik i član Stručnog ispitnog povjerenstva u razdoblju od 1999. do 2018. godine. Također, obavljao je i funkcije mentora ili člana povjerenstva za specijalističke ispite iz područja interne medicine, reumatologije, alergologije i imunologije te endokrinologije. Osim toga, bio je i pročelnik Zavoda za sestrinstvo i primaljstvo od ožujka 2016. do 2018. godine.

Velik korak za kosovsku reumatologiju bilo je osnivanje Udruge reumatologa Kosova, čiji je predsjednik od 2012. bio upravo prof. Rexhepi. Uvelike zahvaljujući njegovim naporima, ova Udruga bila je iznimno aktivna – prof. Rexhepi organizirao je četiri Nacionalna reumatološka kongresa s međunarodnim sudjelovanjem, kojima je i predsjedao. Neke od glavnih tema tih kongresa bile su reumatoidni artritis, osteoporoza i druge reumatske bolesti. Okupljanje i razmjena iskustava među raznim zdravstvenim stručnjacima pridonijeli su napretku kosovske reumatologije. Srećom, prof. Rexhepi uspio je tijekom godina svojeg sudjelovanja na mnogobrojnim konferencijama diljem svijeta uspostaviti široku mrežu poznanstava, što je omogućilo dolazak mnogih poznatih reumatologa na Kosovo.

Prof. Rexhepi napisao je i sveučilišni udžbenik „Reumatologija" (2006.) za studente medicine i specijalizante reumatologije s Medicinskog fakulteta Sveučilišta u Prištini „Hasan Prishtina". Koordinirao je i pridonio prijevodu udžbenika o reumatologiji sa Sveučilišta u Oxfordu na albanski. Još jedan od njegovih doprinosa bio je njegov prijevod udžbenika „Propedeutika interne medicine", a bio je odgovoran i za pripremu 11. poglavlja „Ispitivanje lokomotornog sustava" (Priština, 2016.).

Radovi prof. Rexhepija objavljeni su u međunarodno priznatim časopisima, a bio je autor i nekoliko knjiga. Sudjelovao je na više od 50 međunarodnih i domaćih konferencija. Njegov istraživački rad uglavnom je bio usredotočen na područje interne medicine, reumatoidnog artritisa, antireumatskih lijekova koji modificiraju tijek bolesti (DMARD), kombinirane terapije metotreksatom i osteoporoze. Njegovi su radovi objavljeni i u međunarodnim časopisima kao što su: *Arthritis Research & Therapy*, *Clinical and Experimental Rheumatology*, *The Journal of Rheumatology*, *Annals of the Rheumatic Diseases*, *Arthritis & Rheumatology*, *Reumatizam*, *Open Access Macedonian Journal of Medical Sciences*, *Medical Archives*, *Materia Socio Medica*, *Acta Rheumatologica* i mnogim drugima. Nadalje, bio je aktivan član grupe QUEST-RA na projektu koji je uključivao pacijente s reumatoidnim artritisom, a u kojem su sudjelovale i mnoge druge europske zemlje.

U nastavku navodimo neka od njegovih članstava te nagrade i aktivnosti:

2007. – 2020.: član Hrvatskoga reumatološkog društva (HRD), koje je dio Europske lige protiv reumatizma (EULAR)
2009. – 2020.: recenzent u časopisu *Medicus*, Makedonija
2010. – 2020.: član uredništva časopisa *Medicus*, Makedonija
2011.: nagrada za predstavljanje izvornoga znanstvenog rada na Međunarodnome reumatološkom kongresu (BRIC) u Tokiju
2011. – 2012.: predsjednik Udruge za osteoporozu Kosova
2012. – 2020.: predsjednik Udruge reumatologa Kosova
2015. – 2020.: član Međunarodne zaklade za osteoporozu (engl. *International Osteoporosis Foundation* – IOF)
2016.: recenzent u časopisu *Reumatizam*, Hrvatska.

Prof. Rexhepi sudjelovao je u različitim programima stručnog osposobljavanja. Konkretno, 1983. g. radio je kao specijalizant interne medicine u Sveučilišnoj kliničkoj bolnici u Bologni. Također, završio je poslijediplomski studij Interne medicine i Reumatologije na Sveučilištu u Hamburgu 2002. godine.

Prof. Rexhepi bio je uzoran profesor, čovjek različitih interesa i široke kulture. Nije bio samo iznimno predan i marljiv liječnik nego i plemenita, odana i karizmatična osoba te vrlo strastven čovjek kojemu je iznimno stalo do ljudi. Kada biste s njim počeli razgovarati o medicini, oči bi mu odmah zasjale. Njegov rad na poboljšanjima u liječenju reumatskih bolesti, tijekom kojeg je surađivao sa svoje dvije kćeri i drugim stručnjacima iz tog područja, mnogima je pružio osjećaje trajne nade i optimizma. Za njega je svaki dan bio dar ostvarivanja mogućnosti da se brine za svoje pacijente u njihovim najranjivijim trenutcima. Unatoč stresu i razdvojenosti od svojeg doma i svoje obitelji nikada nije prestao pomagati ljudima. Doista je volio svoj posao, pazio je na svoje zdravlje i kondiciju, htio je dati sve od sebe u obrazovanju i poučavanju novih generacija doktora te pri liječenju pacijenata.

Bio je voljeni muž, otac, djed i prijatelj koji je volio zabavu. Njegovi najbliži znali su ga i kao odličnog košarkaša, čovjeka koji je imao predivan rukopis, kojemu se uvijek moglo povjeriti, a njegovi prijatelji smatrali su ga anđelom čuvarom. Bio je entuzijast za istraživanje, volio je učiti o novim kulturama na putovanjima i hvatati te trenutke i sjećanja u fotografijama, a fotografiranje je bilo i njegov omiljeni hobi. Volio je provoditi vrijeme sa svojom obitelji i svojim najmilijima. Njegova supruga pamtit će ga kao svoju srodnu dušu i ekstroverta koji je bio omiljen u društvu i uvijek otvoren prema svima. Od svake male neprilike ili vesele situacije znao je napraviti priču koju je s oduševljenjem prepričavao drugima. Prof. Rexhepi imao je ulogu u životima mnogih ljudi, uključujući i svoje suradnike, a posebno u životima svojih dviju kćeri koje su slijedile njegov primjer te su i same odabrale ovu struku.

Prof. Rexhepi imao je brojna poznanstva među hrvatskim reumatolozima, a s mnogima od njih ostvario je i blisku suradnju. Bio je aktivan sudionik na gotovo svim hrvatskim reumatološkim kongresima, njegovi radovi objavljeni su u časopisu *Reumatizam*, a radio je i kao recenzent raznih radova. Hrvatski reumatolozi uvijek su rado prihvaćali pozive za predavanja na reumatološkim kongresima i drugim događanjima na Kosovu. Uz njegova iznimna profesionalna i znanstvena postignuća, hrvatska reumatološka zajednica uvijek će se sjećati prof. Rexhepija zbog njegove iznimne ljubaznosti i prijateljstva.

Prof. Sylejman Rexhepi prerano je preminuo, čime je ostavio golemu i nezamjenjivu prazninu u životima svoje obitelji i prijatelja, ali i svojih pacijenata i cjelokupne zdravstvene zajednice.

Uime
Hrvatskoga reumatološkog društva
Branimir Anić i Simeon Grazio

http://www.reumatologija.org
http://www.reumatizam.hlz.hr

INSTRUCTIONS FOR AUTHORS

ABOUT THIS JOURNAL

Reumatizam (Rheumatism) is the platinum open-access peer-reviewed biannual journal of the Croatian Society for Rheumatology. The journal publishes practice guidelines, editorials, original research, reviews, expert opinion pieces, case reports, letters, interviews, meeting reports, and news items. Priority is given to evidence-based research reports in rheumatology, physical medicine and rehabilitation, orthopedics, and allied health specialties to provide the readership with new scientific information on diagnostic and therapeutic procedures as well as comprehensive care for patients with autoimmune and autoinflammatory rheumatic diseases.

Although the journal primarily serves the interests of rheumatologists and physiatrists from Croatia and other Adriatic-Ionian countries, the editors welcome high-quality submissions from all over the world. The aim of the journal's internationalization is to publicize the best rheumatology research and practice, and monitor the progress in rheumatology and allied health professions in Croatia and neighboring countries.

Reumatizam regularly publishes biannual issues and supplements that include abstracts and full texts of papers presented at national and regional congresses and symposia as part of lifelong medical training. The journal also publishes news from scientific literature (in the form of extended abstracts) and brief information on the professional activities of rheumatology societies and other related associations in Croatia and neighboring countries. Submissions in Croatian and English are welcome, with papers published bilingually to attract the readership in Croatia and other countries. Duplicate items that are processed or published elsewhere in any languages are not considered.

The journal is published in print and electronic versions, employing the platinum open-access model, without processing, publication, and view charges. Publication expenses are covered by the Croatian Society for Rheumatology. The English version of *Reumatizam* is available in electronic format at: http://reumatizam.hlz.hr/ and http://www.reumatologija.org/engCasopis.aspx?link=Reumatizam_pdf_en). All contents of the journal *Reumatizam* are archived in Hrčak, the central portal of Croatian scientific journals, which offers free access to the journals following the Open Access Initiative (https://hrcak.srce.hr/reumatizam).

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UPUTE AUTORIMA

O ČASOPISU

„Reumatizam" je službeni recenzirani časopis Hrvatskoga reumatološkog društva Hrvatskoga liječničkog zbora s platinum slobodnim pristupom koji izlazi dva puta godišnje. Objavljuje kliničke smjernice, uvodnike, originalne znanstvene radove, stručne radove, pregledne radove, dobro dokumentirane prikaze bolesnika, kratka priopćenja i preliminarna priopćenja.. Prioritet časopisa jesu radovi temeljeni na dokazima iz područja reumatologije, ali i srodnih struka (fizikalne medicine i rehabilitacije, ortopedije/kirurgije) čime se čitatelju daju bitne znanstvene informacije o dijagnostičkim i terapijskim procedurama, odnosno pružanju sveobuhvatne skrbi osobama oboljelima od autoimunih i autoinflamatornih reumatskih bolesti.

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U časopisu *Reumatizam* objavljuju se članci na hrvatskom jeziku, s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na engleskom jeziku ili članci na engleskom jeziku (*UK spelling*), s naslovom, sažetkom, ključnim riječima te s naslovom i legendom tablica i slika na hrvatskom jeziku. Stil pisanja treba biti jasan i jezgrovit. Radovi trebaju biti strukturirani sukladno principima EQUATOR Networka (http://www.equator-network.org).

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Pri potrebi izražavanja podataka rabe se SI mjerne jedinice. Kod naziva koji se mogu pisati kraticom pri prvom je pojavljivanju potrebno napisati puni naziv, s kraticom, a u daljnjem tekstu samo kraticu. Latinski nazivi pišu se načinom Italic, i to puni naziv kod prvog pojavljivanja u tekstu, a u daljnjem tekstu navodi se kratica. Lijekovi se navode generičkim imenom, a ako je nužno, može se u zagradi navesti tvorničko ime, s imenom proizvođača. Proizvođače specifičnih instrumenata ili reagensa (naziv i lokacija) treba navesti u zagradi.

Izuzev preglednih radova i pisama uredniku radovi trebaju imati slijedeće elemente: naslovna stranica (posebna stranica), sažetak i ključne riječi (posebna stranica), glavni tekst rada (s dijelovima: uvod, ispitanici i metode, rezultati, rasprava i zaključak), zahvale, financiranje, izjava o sukobu interesa, literatura, popis tablica i slika te tablice i slike.

Naslovna stranica

Na naslovnoj stranici trebaju biti naslov rada (sažet, jasan i informativan) na hrvatskom i engleskom jeziku te puno ime svakog od autora. U sljedećem retku treba navesti puni naziv ustanove, ulicu i broj, grad i državu. Ako su u izradi rada sudjelovali autori iz različitih ustanova, za svakog od njih poslije imena i prezimena te prije navoda ustanove treba napisati odgovarajući broj u superskriptu.

Slijede ime i prezime te puna adresa autora za dopisivanje u vezi s radom, njegov/njezin telefonski broj, broj faksa i e-mail adresa.

The abstract should emphasize new and important aspects of the study, or observations. Below the abstract, three to six keywords or short terms should be listed, both in Croatian and in English, to help index the article. The keywords may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of the National Library of Medicine of US should be used for the keywords. General and plural terms, and multiple concepts (e.g., using "and", "or") should be avoided. The abstract should not include references.

Introduction

The introduction provides a brief outline of the context/background of the topic, as well as the purpose and rationale for conducting the study/research. It is recommended to cite only relevant references, which should be well-balanced and recent (not older than 10 years, if possible). At the end, the objective(s) of the study/research should be stated clearly and precisely. No data from the paper or conclusions should be given in the introduction.

Materials and methods

This section provides details about how the study/research was conducted: the place and time, as well as the eligibility criteria for selecting the experimental or observational participants (or laboratory animals), with all their important characteristics. The author(s) should provide a detailed outline of the study (e.g., a randomized–controlled study, an observational study, a prospective/retrospective study, etc.), the data collection methods applied, the meaning of the descriptors, and explain and identify the methods, devices (including the manufacturer's name in parentheses), and procedures, sufficiently detailed to enable others to reproduce the results. References should be given for established methods, and new or substantially modified methods should be described in detail, stating the reasons for using them, and evaluating their limitations.

Generic names should be used for drugs and chemicals. All measurements should be given in SI units. In Croatian texts a decimal comma should be used, and in texts in English a decimal point.

Ethics / Ethical standards

Studies involving human subjects or animals should have received the approval of the respective ethics committee. The work described should have been carried out in accordance with the ethical standards of an institutional or national committee responsible for experiments involving human subjects, as well as with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964 and its revisions) for experiments involving humans http://www.wma.net/en/30publications/10policies/b3/index.html; EU Directive 2010/63/EU and for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Also, it should be stated explicitly that informed consent was obtained from all participating adult subjects or from parents or legal guardians for minors or incapacitated adults, together with the manner in which informed consent was obtained (i.e., oral or written).

Participants' names and/or surnames should not appear, particularly in figurative/illustrative materials.

Statistics

Statistical methods should be described in detail, to enable a knowledgeable reader with access to the original data to verify the reported results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty. The statistical software used should be specified.

Results

Results should be presented in a logical sequence in the text, tables, and figures. In this section, the results are not interpreted nor are their implications discussed. In addition to absolute numbers

Sažetak i ključne riječi

Druga stranica treba sadržavati sažetak na hrvatskom i engleskom jeziku (do 300 riječi) u kojem su navedeni cilj studije/istraživanja, materijal (ispitanici) i metode, rezultati i zaključci.

U sažetku valja naglasiti nove i važne aspekte studije ili opservacije. Ispod sažetka autori trebaju navesti tri do šest ključnih riječi ili kratkih pojmova na hrvatskom i engleskom jeziku koji će pomoći pri indeksiranju članka. Ključne riječi se mogu objaviti uz sažetak. Za ključne riječi treba se koristiti pojmovima iz popisa *Medical Subject Headings* (MeSH) Indexa Medicusa. Općenite, množine i mnogostruke koncepte (primjerice uz uporabu „i", „ili") treba izbjegavati. Sažetak ne smije sadržavati navode referencija.

Uvod

U uvodu se ukratko navode kontekst/pozadinsko znanje o temi, svrha i razlog provođenja studije/istraživanja. Preporučuje se navesti samo relevantne referencije, koje trebaju biti uravnotežene i recentne (po mogućnosti ne starije od 10 godina). Na kraju treba jasno i točno navesti cilj/-eve studije/istraživanja. U uvodu se ne navode podatci iz rada niti zaključci.

Materijal i metode

Navode se detalji provedbe studije/istraživanja: gdje i kad je provedena, na koji je način učinjen odabir i sve važne karakteristike ispitanika (ili laboratorijskih životinja) koje su studirane ili opservirane. Treba detaljno specificirati nacrt studije (npr., randomizirana-kontrolirana studija, opservacijska studija, prospektivna/retrospektivna itd.), način prikupljanja podataka, značenje deskriptora te objasniti, identificirati metode, aparate (s nazivom proizvođača u zagradi) i postupke, dovoljno detaljno kako bi se rezultati mogli reproducirati. Za poznate metode treba navesti referencije, a nove metode ili metode koje su znatnije modificirane detaljno opisati, navodeći razlog njihove primjene i procjene njihovih ograničenja.

Za lijekove i kemikalije moraju se rabiti generička imena. Sve veličine trebaju biti izražene u SI jedinicama. U tekstovima na hrvatskom jeziku rabi se decimalni zarez, a u tekstovima na engleskome decimalna točka.

Etika / Etički standardi

Radovi koji uključuju ljude ili životinje trebaju imati odobrenje od odgovarajućeg etičkog povjerenstva. Takav rad treba biti proveden sukladno etičkim standardima intitucije ili nacionalnom povjerenstvu odgovornom za eksperimente koji uključuju ljude i s Etičkim kodeksom udruge World Medical Association (Helsinška deklaracija iz 1964. i njezine kasnije inačice) za istraživanja koja uključuju ljude http://www.wma.net/en/30publications/10policies/b3/index.html; EU Direktiva 2010/63/EU I za istraživanja na životnjama http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm. Također, treba jasno navesti da je dobiven informirani pristanak od strane svih odraslih ispitanika ili od strane roditelja ili zakonskih skrbnika za maloljetne ispitanike ili nesposobne odrasle osobe, kao i način na koji je taj pristanak dobiven (npr. usmeno ili pismeno).

Imena i /ili prezimena ispitanika ne smiju biti obznanjena, naročito u grafičkim/slikovnim materijalima.

Statistika

Treba iscrpno opisati statističke metode kako bi se obrazovanom čitatelju koji ima pristup originalnim podatcima omogućilo da potvrdi navedene rezultate. Gdje god je to moguće zaključke treba kvantificirati i prezentirati odgovarajućim indikatorima pogrješke ili odstupanja od mjerenja. Treba navesti upotrijebljeni računalni program.

Rezultati

Rezultati se izlažu logičnim slijedom u tekstu, tablicama i slikama. U ovom se dijelu rezultati ne tumače niti se raspravlja o njiho-

and percentages, it is necessary to include the results of statistical analysis, by stating, for example, P values or other parameters. All the data from the tables or figures should not be repeated in the text, but rather only the most important observations should be emphasized or summarized. Redundant tables and figures (e.g., presenting the same data in different formats) should be avoided, as should the use of figures and tables when it is better to include the data in the textual part (e.g., when there is insufficient data for tables or figures).

Discussion

Most of this section is the interpretation of results. New and important aspects of the study, and its implications, should be emphasized. It is not recommended to repeat in detail data or any other material given in the Introduction or in the Results section. Own findings should be compared with the findings of other studies/research, showing the similarities and differences. It is also important to explain the significance of the results obtained, their limitations, and implications for future research, avoiding, however, making statements and drawing conclusions not completely confirmed by the obtained data. When necessary, new hypotheses may be given, but clearly labelled as such.

Conclusions

The main conclusions are drawn based on the author's or authors' own results (3 – 5 sentences maximum).

Abbreviations

Only standard abbreviations should be used. The spelled-out abbreviation followed by the abbreviation in parentheses should be used at the first mention unless the abbreviation is a standard unit of measurement. Abbreviations should be avoided in the manuscript title.

Symbols

Symbols used in the text should be explained. A detailed list of symbols may be given in an appendix.

Tables

Tables should be presented on a separate page. They should not be submitted as images/photographs. Each table should have a title and be numbered consecutively in the order it appears in the text. Tables should be self-explanatory and as simple as possible. Table legends should be given below the table, and may include a reference to data in the table indicated by a superscript figure or letter. Results presented elsewhere in the article (e.g., in an illustration), should not be repeated in the table. If a table originating from other sources is used, permission for such publication should be obtained from the respective publisher/author.

Figures / Illustrations

All figures should be professionally drawn or photographed. Letters, numbers, and symbols on figures should be clear enough to remain legible when the figure is reduced for publication. Figure titles and descriptions are considered to be a part of the text, and not part of the figure/illustration. Each figure/illustration should be numbered consecutively according to the order in which it appears in the text, and have a clear mark showing which is the upper side. Figures/illustrations should appear in a quality appropriate for print publication. Photocopied images or photographs are not suitable for reproduction. If submitted in electronic format, figures/illustrations should be in a high resolution TIFF or JPEG file format, a minimum of 1,500 pixels wide. Figures/illustrations submitted in other formats may be accepted only with the prior consent of the editorial board. The editorial board reserves the right not to publish any figures/illustrations that fail to meet the above requirevim implikacijama. Uz apsolutne brojeve i postotke potrebno je uključiti rezultate statističke analize, navođenjem obično p-vrijednosti ili drugog parametra. U tekstu se ne ponavljaju svi podatci iz tablica ili slika, već se naglašavaju ili sažimaju samo bitna opažanja. Potrebno je izbjegavati suvišne tablice i slike (npr. prikaz istih podataka u različitim formatima) ili uporabu slika i tablica u slučaju kada je informacije bolje uključiti u tekstualni dio (npr. kada nema dovoljno podataka za tablice ili slike).

Rasprava

Većina ovog dijela odnosi se na interpretaciju rezultata. Potrebno je naglasiti nove i bitne aspekte studije te implikacije koje iz nje proistječu. Ne preporučuje se detaljno ponavljati podatke ni bilo koje druge materijale koji su navedeni u uvodnom dijelu ili u dijelu s rezultatima. U dijelu za raspravu treba usporediti vlastite rezultate s rezultatima iz drugih studija/istraživanja te navesti sličnosti i razlike. Također, važno je objasniti značenje dobivenih rezultata, njihova ograničenja i implikacije vezane uz buduća istraživanja, ali uz izbjegavanje izjava i zaključaka koji nisu potpuno potvrđeni dobivenim podatcima. Kad je potrebno, mogu se navesti nove hipoteze uz jasno naglašavanje da su nove.

Zaključci

Na osnovi vlastitih rezultata izvode se glavni zaključci (maksimalno 3 – 5rečenica).

Kratice

Treba rabiti samo standardne kratice. Puni pojam za koji se rabi kratica mora biti naveden pri prvoj uporabi kratice u tekstu, osim ako je riječ o standardnim kraticama mjernih jedinica. Kratice treba izbjegavati u naslovu rada.

Simboli

U tekstu se simboli moraju objasniti. U dodatku se može navesti iscrpan popis simbola.

Tablice

Tablice se pišu na posebnoj stranici. Ne smiju se slati kao slike/fotografije. Svaka tablica mora imati naslov i redni broj prema redoslijedu pojavljivanja u tekstu. Tablica mora biti pregledna i jednostavna. Legende tablica trebaju biti napisane ispod tablice, uz oznaku u tablici u superskriptu. Tablice ne bi trebale ponavljati rezultate koji su prezentirani bilo gdje drugdje u radu (npr. u slici). Tablice preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihovih izdavača/autora.

Slike / Ilustracije

Sve slike trebaju biti profesionalno nacrtane ili snimljene. Slova, brojevi i simboli moraju biti čitki i u smanjenom obliku u kojem će se objaviti. Svaka slika mora imati broj prema redoslijedu pojavljivanja u tekstu, ime autora i označenu gornju stranu. Svaki crtež mora imati broj prema redoslijedu pojavljivanja u tekstu i označenu gornju stranu. Crteži trebaju biti dovoljno kvalitetno izrađeni za objavu u tisku. Fotokopije slika ili fotografija nisu pogodne za reprodukciju. Ako se dostavljaju u elektroničkom obliku, slike/ilustracije moraju biti u formatu TIFF ili JPEG visoke kvalitete, najmanje širine 1500 piksela. Slike/ilustracije u ostalim formatima mogu biti prihvaćene samo uz prethodni dogovor s uredništvom. Uredništvo pridržava pravo ne objaviti slike/ilustracije koje ne zadovoljavaju ove uvjete. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji (ili skrbnika) ili osoba mora biti neprepoznatljiva (prekrivanje očiju, lica i sl.). Slike preuzete iz drugih izvora treba popratiti dopuštenjem za objavu njihova izdavača/autora.

ments. Photographs of individuals will be published only with the written consent of the person photographed (or his/her guardian), or the individual should be rendered unrecognizable (concealing the eyes, face, etc.). If a figure is taken from other sources, permission for such reproduction obtained from the respective editor/author should be submitted.

Acknowledgments

All contributors who do not meet the ICMJE authorship criteria, such as persons who provide technical help, special equipment or materials, and statistical analyses should be listed in the Acknowledgments section. Funding and material support should also be listed, with details of the institution/organization/company that provided such support (including the grant numbers), and the beneficiary (a project, a program, an individual). The International Committee of Medical Journal Editors – ICMJE provides detailed guidelines as to who to list under this section (https://bit.ly/36oo0UZ).

Conflict of interest statement

The authors must declare whether there is a financial relationship between them and the organization/pharmaceutical company that sponsored the research. Conflicting non-financial relationships that may add bias in the journal submissions should be also transparently declared. All contributors of the journal are advised to consult the recommendations available at https://bit.ly/337vidA. The authors should fill and send the following form (WEB-MJESTO NA NAŠOJ STRANICI ILI http://www.icmje.org/conflicts-of-interest/.

The Statement will be included in a separate section of the paper before the References.

References

Comprehensive and systematic searches through Scopus, Web of Science, PubMed, Directory of Open Access Journals (DOAJ), and specialist bibliographic databases are strongly encouraged to cite highly relevant, updated, and evidence-based items. The following relevant recommendations could be consulted at https://rdcu.be/bVOOt and https://bit.ly/2PxEGDz.

References should be presented using the Vancouver style, a numeric citation style as recommended by the US National Library of Medicine. The most frequent examples can be consulted in the following recommendations: ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detailed instructions can be found in the following book: Citing Medicine (https://www.ncbi.nlm.nih.gov/books/NBK7256).

References in the text, tables, and legends should be numbered in Arabic numerals, in parentheses, consecutively in the order of appearance in the text. When more than one reference is given, these should be separated by a comma.

In the list of references, **authors** and/or **editors** are cited with the surname(s) and followed by the initial(s) of the name(s). Initials do not end with a full stop, unless the initial comes immediately before the title. For several authors/editors, their names are separated by a comma. For more than six authors/editors, the first six should be listed with surnames and initials followed by "et al.", and the others omitted. In **titles**, only the first word is capitalized, and any other words that are usually written with a capital. In pagination, repeated identical initial digits for page numbers are omitted (for example: 123-125 becomes 123-5). Each reference should end with a full stop.

For articles in **English**, it is recommended that titles of references published in other languages are cited in English (if available), or an English translation of the title provided (placed in square brackets), with an indication of the language of the original placed at the end.

Zahvale

U zahvali treba navesti sve suradnike koji nisu zadovoljili ICMJE kriterije za autorstvo poput osoba koje su pružile tehničku pomoć ili osigurale specijalnu opremu i materijale, ili statističku analizu. Financijska i materijalna potpora također trebaju biti navedene, s detaljima institucije/organizacije/tvrtke koja je takvu pomoć pružila (uključivo i identifikacijske brojeve pomoći) te tko je dobio takvu potporu (projekt, program, pojedinac). Međunarodni odbor urednika medicinskih časopisa (*International Committee of Medical Journal Editors* – ICMJE) ima detaljne smjernice koga valja navesti u Zahvalama (https://bit.ly/36oo0UZ).

Izjava o sukobu interesa

Autori moraju izjaviti postoji li financijski odnos između njih i organizacije/tvrtke koja je sponzorirala istraživanje. Ne financijski sukob interesa koji može također utjecati na prihvačanje rada bi također trebao biti jasno naznačen. Molimo pogledati preporuke na stranici http://bit.ly/337vidA. Autori moraju popuniti i poslati sljedeći obrazac (http://www.icmje.org/conflicts-of-interest/)

Izjava će stajati u posebnom dijelu prije navoda literature.

Literatura

Preporuča se sistematično petraživanje u bazama Scopus, Web of Science, PubMed i Directory of Open Access Journals (DOAJ) i specijaliziranim bazama podataka s ciljem citiranja relevantnih, novijih i radova utemeljenih na dokazima. Takve relevantne preporuke mogu se naći na http://rdcu.be/bVOOt i https://bit.ly/2PxEGDz.

Literatura se navodi primjenom Vancouverskih pravila koja propisuju numerički način citiranja, prema preporukama američke *National Library of Medicine*. Najčešći primjeri mogu se naći u preporukama: *ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles* (https://www.nlm.nih.gov/bsd/uniform_requirements.html). Detaljne upute mogu se naći u knjizi *Citing Medicine* (https://www.ncbi.nlm.nih.gov/books/NBK7256).

Literaturu u tekstu, tablicama i legendama treba navoditi arapskim brojevima u zagradi, prema redoslijedu pojavljivanja. Ako brojeva ima više, odvajaju se zarezima.

U popisu literature autori i/ili urednici navode se prezimenom/prezimenima i inicijalima imena. Iza inicijala ne stavlja se točka osim ako je riječ o inicijalu neposredno prije naslova. Ako autora/urednika ima više, odvajaju se zarezima. Ako ih ima više od šest, nakon prva tri t treba napisati „i sur.", a ostale ispustiti. U naslovu se velika slova rabe samo za početno slovo prve riječi u naslovu i u riječima koje se uobičajeno pišu velikim slovima. Kad se navode brojevi stranica, treba ispustiti iste početne znamenke stranica (npr. 123–125 postaje 123–5). Na kraju svake referencije stavlja se točka.

U tekstovima na engleskom jeziku pri navođenju radova objavljenih na drugim jezicima preporučuje se navesti naslov na engleskom (ako postoji) ili ga prevesti na engleski (u tom slučaju treba ga staviti u uglate zagrade), a na kraju se navodi izvorni jezik rada.

Pri navođenju prihvaćenih, ali još neobjavljenih radova na kraju treba dodati: „U tisku." Autori trebaju dobiti pismeno odobrenje za citiranje takvog rada zajedno s potvrdom da je rad prihvaćen za objavu.

Članak u časopisu

Naslovi časopisa trebaju se navoditi uobičajenim kraticama (*NLM Title Abbreviation*) koje se mogu naći u katalogu *National Library of Medicine* (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Za časopise se ne navodi izdavač. Obvezatno se navode godište, volumen i stranice časopisa. Ako časopis ima kontinuiranu paginaciju, mogu se izostaviti mjesec/broj u godištu časopisa i pripadajuća zagrada.

When referencing an accepted, but not yet published, article, "Forthcoming" should be added at the end. Authors should have written consent to cite such an article, with confirmation that the article has been accepted for publication.

Journal article

Journal titles should be cited with the usual abbreviations (NLM Title Abbreviation), to be found in the *National Library of Medicine Catalog* (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journal references omit information about the publisher. It is required to include the year of publication, volume, and page numbers. If the journal uses continuous pagination, the month/volume number of the journal indicated in parentheses may be omitted.

[Example] Journal article, more than six authors:

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J, et al. Proposal for biologic drugs therapy in rheumatoid arthritis. Reumatizam. 2010;57(1):29–35. Croatian.

[Example] Journal article, continuous pagination:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Example] Supplement article:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl 2):ii14–7.

Books

It is required to cite the place of publication, the publisher, and the year of publication. Pagination is provided only if part of a book is cited.

[Example] Book (authors):

4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2nd ed. St. Louis: Saunders; 2004.

[Example] Book (editors):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC, editors. Oxford textbook of rheumatology. 3rd ed. New York: Oxford University Press; 2004.

[Example] Chapter in a book:

6. Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, editor. Spondyloarthropathies. Orlando: Grune and Stratton; 1984. pp. 151–85.

Papers presented at meetings

If a conference paper is published in a journal or a supplement, the instructions for citing a journal or a supplement should be applied. If a conference paper is published in a book, the book title is followed by "Proceedings of", the conference title, date(s), and location (city and country) of the conference.

[Example] Papers presented at meetings, published in a supplement:

7. Matucci Cerinic M, Pignone A. The early diagnosis of rheumatoid arthritis (RA). Reumatizam. 1997;44(Suppl):1.

[Example] Papers presented at meetings, published in a book:

8. Babić-Naglić Đ. Fizička aktivnost i vježbe [Physical activities and exercises]. In: Ivanišević G, editor. Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj [Thalassotherapy, kinesitherapy and aromatherapy in Croatia]. Proceedings of the 14th Lošinj School of Natural Remedies; 2013 Sep 6–7; Veli Lošinj, Croatia. Zagreb: Hrvatski liječnički zbor; 2013, pp. 49–55. Croatian.

[Example] Conference proceedings (book):

9. Gordon DA, editor. Immune reactions and experimental models in rheumatic diseases. Proceedings of the Fourth Ca-

[Primjer] Članak iz časopisa, više od šest autora:

1. Ćurković B, Babić-Naglić Đ, Morović-Vergles J i sur. Prijedlog primjene bioloških lijekova u reumatoidnom artritisu. Reumatizam. 2010;57(1):29–35.

[Primjer] Članak iz časopisa, kontinuirana paginacija:

2. Ritchlin CT. From skin to bone: translational perspectives on psoriatic disease. J Rheumatol. 2008;35:1434–7.

[Primjer] Članak iz suplementa:

3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Supl 2):ii14–7.

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[Primjer] Knjiga (autori):

4. Walker JM, Helewa A. Physical rehabilitation in arthritis. 2. izd. St. Louis: Saunders; 2004.

[Primjer] Knjiga (urednici):

5. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC (ur.). Oxford textbook of rheumatology. 3. izd. New York: Oxford University Press; 2004.

[Primjer] Poglavlje u knjizi:

6. Vasey FB, Espinoza LR. Psoriatic arthritis. U: Calin A (ur.). Spondyloarthropathies. Orlando: Grune and Stratton; 1984., str. 151–85.

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8. Babić-Naglić Đ. Fizička aktivnost i vježbe. U: Ivanišević G (ur.). Talasoterapija, kineziterapija i aromaterapija u Hrvatskoj. Zbornik izlaganja na 14. lošinjskoj školi prirodnih ljekovitih činitelja; 2013 Ruj 6–7; Veli Lošinj, Hrvatska. Zagreb: Hrvatski liječnički zbor; 2013., str. 49–55.

[Primjer] Zbornik izlaganja na znanstvenom skupu (knjiga):

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nadian Conference on Research in Rheumatic Diseases; 1970 Oct 15–17; Toronto, Canada. Toronto: University of Toronto Press; 1972.

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[Example] Journal article on the Internet, with a DOI:

11. Vivar N, Van Vollenhoven RF. Advances in the treatment of rheumatoid arthritis. F1000Prime Rep. 2014 May 6;6:31. doi: 10.12703/P6-31. PubMed PMID: 24860653; PubMed Central PMCID: PMC4017904.

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12. Chen Q, editor. Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Available from: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery. [2013 Oct 8].

[Example] Web page:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Croatian Society for Rheumatology of the CMA; c2014. Available from: http://www.reumatologija.org/Pocetna.aspx. [cited: 2014 Apr 1].

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