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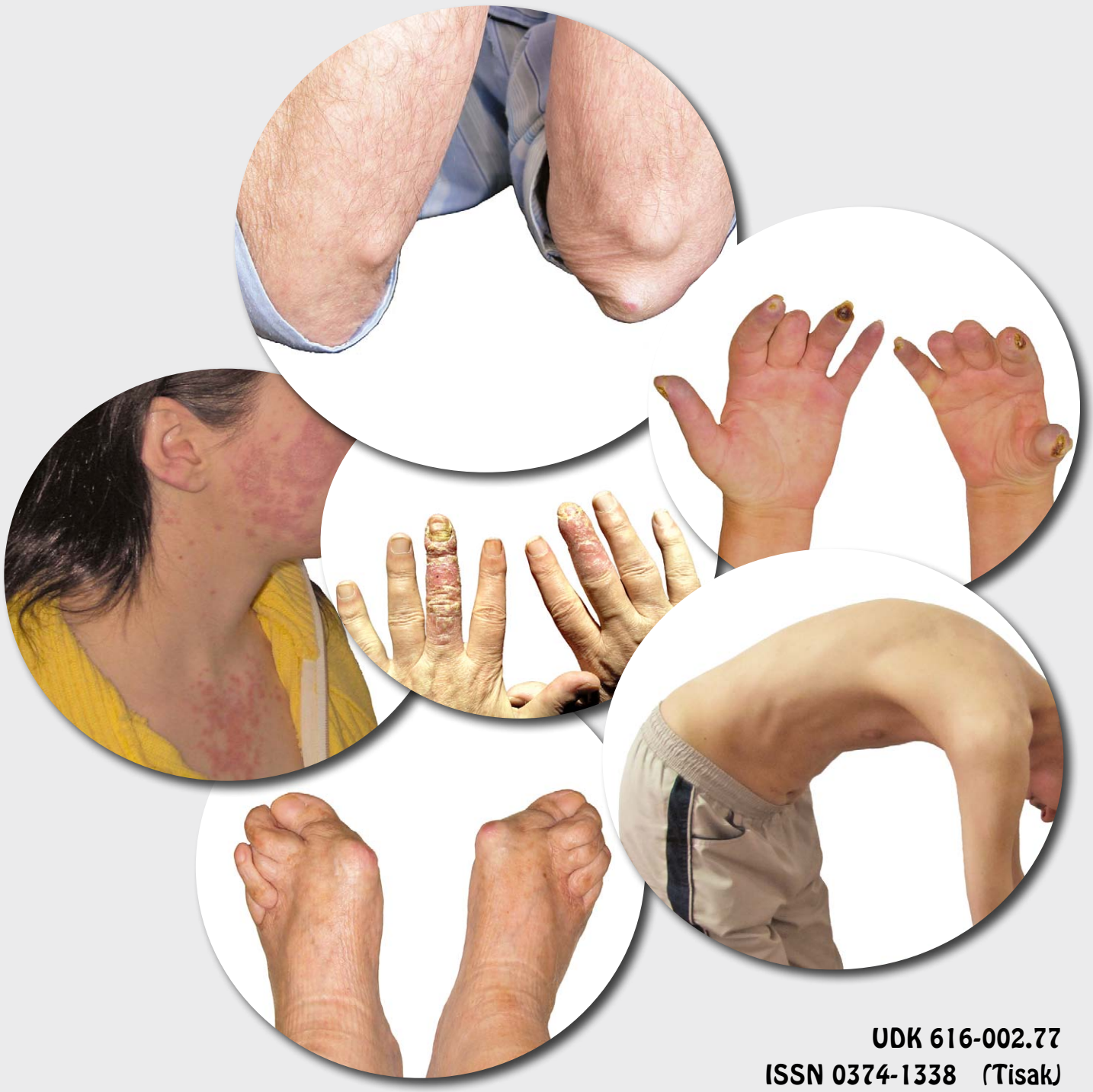

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CONTENT / *SADRŽAJ*

CASE REPORT
PRIKAZ BOLESNIKA

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ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

GENDER DIFFERENCES IN CLINICAL MANIFESTATIONS AND COMORBIDITIES IN PATIENTS WITH SLE: A SINGLE-CENTER EXPERIENCE

RAZLIKE MEĐU SPOLOVIMA U KLINIČKIM MANIFESTACIJAMA I KOMORBIDITETIMA OBOLJELIH OD SUSTAVNOG ERITEMSKOG LUPUSA: ISKUSTVA JEDNOG CENTRA

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Abstract

Aim: The aim of this study was to determine gender differences in the clinical manifestations and comorbidities in SLE patients treated at the University Hospital of Split during a ten-year period.

Methods: The medical records of patients diagnosed with SLE were collected from the Outpatient Clinics, ward, and Day Hospital of the Department of Rheumatology and Clinical Immunology of the University Hospital of Split. All SLE manifestations and comorbidities were recorded. The SPSS 25 (IBM, New York, USA) package was used for statistical analysis. Assessment of the differences between the genders was performed by $\chi 2$ test, univariate logistic regression, and multivariate logistic regression.

Results: The study included 268 SLE patients, 242 (90%) females and 26 (10%) males, aged 22-88 years (median 52; Q1-Q3: 41-62.75 y). In univariate regression analysis significant association was obtained between Sjögren syndrome (SS) and associated neoplasms and the female gender, while antiphospholipid syndrome (APS) and vasculitis were associated with the male gender. In multivariate logistic regression with age and gender as independent variables, a significantly higher frequency of SS ($P = 0.04$) and associated neoplasms ($P = 0.004$) were found in females, while vasculitis ($P = 0.014$) and APS ($P = 0.003$) were more frequent in males. Significant association was found between younger age and skin changes and lupus nephritis in both genders. In older patients, a significant correlation was found for dyslipidemia, hypertension, osteoporosis, gastritis, and heart involvement.

Conclusion: In our study of SLE patients, SS and associated neoplasms were more common in women, whereas in men vasculitis and APS were more frequent. Lupus nephritis and skin changes occured more frequently in patients of younger age in both genders. In elderly patients, dyslipidemia, hypertension, heart involvement, osteoporosis, and gastritis were more likely to occur. For a better understanding of this problem it is necessary to examine a larger population of patients and monitor it over time.

Keywords: Lupus erythematosus, systemic – diagnosis, epidemiology; Comorbidity; Neoplasms – epidemiology, pathology; Sjogren's syndrome – epidemiology; Vasculitis – epidemiology; Antiphospholipid syndrome – epidemiology; Age distribution; Sex distribution; Logistic models

Sažetak

Cilj: Cilj je ovog istraživanja bio ispitati razlike u kliničkim manifestacijama i komorbiditetima između muškaraca i žena oboljelih od SLE-a i liječenih u KBC-u Split.

Ispitanici i metode: Podatci bolesnika koji su imali dijagnozu SLE-a u razdoblju od 1. 1. 2007. godine do 31. 12. 2016. prikupljeni su iz ambulanta, stacionara i dnevne bolnice Zavoda za reumatologiju i kliničku imunologiju Klinike za unutarnje bolesti Kliničkoga bolničkog centra Split. Analizirani su sve zabilježene kliničke manifestacije i pridruženi komorbiditeti. Za statističku je analizu upotrijebljen paket SPSS 25 (IBM, New York, SAD). Služili smo se χ^2-testom te univarijatnom i multivarijatnom logističkom regresijom.

Rezultati: Istraživanje je obuhvatilo 268 bolesnika s dijagnozom SLE-a: 26 muškaraca (10%) i 242 žene (90%). Medijan dobi ispitanika iznosio je 52 godine (min. – maks.: 22 – 88 god.; Q1 – Q3: 41 – 62,75 god.). χ^2-testom utvrdili smo da je ženski spol bio znatno povezan sa Sjögrenovim sindromom (SS) i pridruženim neoplazmama, a antifosfolipidni sindrom (APS) i vaskulitis bili su povezani s muškim spolom. S obzirom na medijan dobi svoje smo ispitanike podijelili u tri skupine. Multivarijatnom logističkom regresijom u kojoj su neovisne varijable bile dob i spol dobili smo statistički značajnu povezanost SS-a (P = 0,04) i pridruženih neoplazma (P = 0,004) sa ženskim spolom, dok su u muškaraca učestaliji bili vaskulitis (P = 0,014) i APS (P = 0,03).

Zaključak: Prema našem istraživanju bolesnika sa SLE-om, u žena su bili učestaliji SS i pridružene neoplazme, a u muškaraca vaskulitis i APS. Lupus nefritis i kožne promjene češće se javljaju u bolesnika mlađe dobi u oba spola. Kod starijih su bolesnika češći dislipidemija, hipertenzija, zahvaćenost srca, osteoporoza i gastritis. Radi jasnijeg objašnjenja ovog problema potrebno je istražiti puno veću populaciju bolesnika te ih pratiti dulje razdoblje.

Ključne riječi: Sistemski eritemski lupus – dijagnoza, epidemiologija; Komorbiditet; Tumori – epidemiologija, patologija; Sjögrenov sindrom – epidemiologija; Vaskulitis – epidemiologija; Antifosfolipidni sindrom – epidemiologija; Dobna distribucija; Spolna distribucija; Logistički modeli

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown etiology that affects numerous organs and organ systems. A feature of the disease is chronic inflammation characterized by the formation of autoantibodies and immune complexes that damage tissues and cells. The clinical picture is characterized by alternating exacerbations and remissions, and the course and prognosis of the disease are unpredictable (1). As many as 90% of patients are women, predominantly of reproductive age, which is attributed to the effect of estrogen on the development of SLE, but the disease can also occur in children and the elderly, when the difference in gender distribution is much smaller (2).

The clinical manifestations of SLE are diverse, often nonspecific, and can be confused with some other diseases. It takes an average of five years to diagnose the disease, which worsens its prognosis. Survival of patients with SLE has improved significantly in the last fifty years, accompanied by an increasing number of comorbidities (3). A large study of 7,732 subjects with SLE showed that the incidence of cardiovascular disease (CVD), stroke, end-stage renal disease, cancer, osteoporosis, and infection was 1.28–7.81 times higher in patients (4).

CVD is the main comorbidity and cause of earlier mortality in SLE, and occurs 3–4 times more often and earlier in these patients than in the general population. The CV risk is higher in younger patients. According to the multinational SLICC cohort, 50/97 vascular

UVOD

Sustavni eritemski lupus (SLE) kronična je upalna autoimunosna bolest nepoznate etiologije koja zahvaća brojne organe i organske sustave. Obilježje bolesti jest kronična upala karakterizirana stvaranjem autoprotutijela i imunokompleksa koji oštećuju tkiva i stanice. Kliničku sliku obilježavaju naizmjenične egzacerbacije i remisije, a tijek i prognoza bolesti nepredvidivi su (1). Čak 90% oboljelih jesu žene, i to dominantno one reproduktivne dobi, što se pripisuje utjecaju estrogena na razvoj SLE-a, no bolest se može pojaviti i kod djece i starijih ljudi kada je razlika u spolnoj distribuciji znatno manja (2).

Klinička očitovanja SLE-a raznolika su, često nespecifična i mogu se zamijeniti s nekim drugim bolestima. Do dijagnosticiranja bolesti u prosjeku prođe pet godina, što pogoršava njezinu prognozu. Posljednjih pedeset godina znatno se poboljšalo preživljenje bolesnika sa SLE-om, što prati sve veći broj komorbiditeta (3). Veliko istraživanje na 7732 ispitanika sa SLE-om pokazalo je da je incidencija kardiovaskularnih bolesti (KVB), moždanog udara, terminalnog stadija bubrežne bolesti, karcinoma, osteoporoze i infekcija 1,28 – 7,81 puta veća u oboljelih (4).

KVB je glavni komorbiditet i uzrok ranije smrtnosti pri SLE-u, a javlja se 3 – 4 puta učestalije i prije u ovih bolesnika nego u općoj populaciji. KV rizik najviši je kod mlađih bolesnika. Prema multinacionalnoj kohorti SLICC, 50/97 vaskularnih događaja bilo je posljedica aktivnog lupusa, 31 ateroskleroze i 16 nekoga drugog uzroka, što upućuje na njihovo multifaktorsko

events were due to active lupus, 31 to atherosclerosis, and 16 to some other cause, suggesting their multifactorial origin in patients with SLE (5). Malignant tumors considered to be more common in people with SLE are: hematological tumors, lung tumors, cervical cancer and dysplasia, and head and neck tumors.

Tumors that have a lower prevalence among SLE patients than among the general population are breast, endometrial, and prostate tumors. Among hematological malignancies there is an increased incidence of and mortality from non-Hodgkin lymphoma and an increased risk of Hodgkin lymphoma, leukemia, and multiple myeloma. Dysplasia and cervical cancer occur as a result of the increased prevalence of HPV infection among patients with SLE. A possible explanation for this infection is inadequate removal of the virus caused by a genetic immune disorder, impaired innate immunity, or the action of immunosuppressants (6).

Other autoimmune diseases such as endocrine autoimmune diseases (Hashimoto thyroiditis, autoimmune hepatitis, type I diabetes) and antiphospholipid syndrome (APS) are often associated with SLE. Systemic infections (most commonly pneumonia and sepsis) are one of the three most common causes of morbidity and mortality in patients with SLE along with active SLE and thrombosis, and are the second most common cause of hospitalization in patients with SLE after an exacerbation of the underlying disease (8).

Numerous studies have shown differences between the genders in the clinical manifestations and comorbidities of SLE. A 2016 meta-analysis (16 studies, 11,934 patients) suggested that alopecia, photosensitivity, butterfly rash, oral ulcers, and arthritis are significantly more common in women, while lupus nephritis, serositis, and thrombocytopenia are more common in men (9).

The aim of this study was to determine differences in the clinical picture and comorbidities between the genders in SLE patients treated in the University Hospital of Split between 2007 and 2017.

MATERIALS AND METHODS

This is a cross-sectional, retrospective study using data collected from the medical history of patients treated at the Department of Rheumatology and Clinical Immunology, as well as the medical history and electronic data of patients treated at the Day Hospital of the Department and electronic data from the two Rheumatology Clinics of the Department of Internal Medicine, Clinical Hospital Center Split in the period from January 1, 2007 to December 31, 2016. Inclusion criteria were: a diagnosis of SLE according to the 1984 American Rheumatological Society (ACR) critera and age over 18 years.

podrijetlo u bolesnika sa SLE-om (5). Maligni tumori za koje se smatra da su češći u oboljelih od SLE-a jesu: hematološki tumori, tumori pluća, rak i displazije vrata maternice te tumori glave i vrata. Tumori koji imaju manju prevalenciju među oboljelima od SLE-a nego među općom populacijom jesu tumori dojke, endometrija i prostate. Od hematoloških maligniteta povećane su incidencija i smrtnost od ne-Hodgkinova limfoma te je povišen rizik od Hodgkinova limfoma, leukemije i multiplog mijeloma. Displazije i rak vrata maternice nastaju kao posljedica povećane prevalencije infekcije HPV-om među bolesnicama sa SLE-om. Moguće objašnjenje ove infekcije jest neadekvatno uklanjanje virusa uzrokovano genskim imunosnim poremećajem, poremećenom prirođenom imunosti ili djelovanjem imunosupresiva (6).

Često su SLE-u pridružene i druge autoimunosne bolesti poput endokrinih autoimunosnih bolesti (Hashimotov tiroiditis, autoimunosni hepatitis, šećerna bolest tipa I) i antifosfolipidni sindrom (APS) (7). Sustavne infekcije (najčešće pneumonije i sepse) jedan su od tri najčešća uzroka morbiditeta i mortaliteta u bolesnika sa SLE-om, uz aktivan SLE i tromboze, te su drugi uzrok hospitalizacija bolesnika sa SLE-om, odmah nakon pogoršanja osnovne bolesti (8).

Brojna istraživanja pokazuju razlike u kliničkim manifestacijama i komorbiditetima između spolova. Metaanaliza iz 2016. godine (16 istraživanja, 11.934 bolesnika) upućuje na to da su alopecija, fotosenzitivnost, leptirasti osip, oralni ulkusi i artritis znatno češći u žena, dok su lupus nefritis, serozitis i trombocitopenija učestaliji u muškaraca (9).

Cilj je ovog istraživanja bio ispitati postoje li razlike u kliničkoj slici i komorbiditetima među spolovima kod oboljelih od SLE-a u populaciji bolesnika liječenih u KBC-u Split od 2007. do 2017. godine.

MATERIJALI I METODE

Ovo je presječno, retrospektivno istraživanje, a kao izvor podataka upotrijebljeni su podatci prikupljeni iz povijesti bolesti bolesnika liječenih u stacionaru Zavoda za reumatologiju i kliničku imunologiju, zatim povijesti bolesti i elektronički podatci bolesnika liječenih u Dnevnoj bolnici Zavoda te elektronički podatci iz dviju reumatoloških ambulanta Zavoda Klinike za unutarnje bolesti KBC-a Split, u razdoblju od 1. siječnja 2007. do 31. prosinca 2016. Kao kriterije uključenja uzeli smo dijagnosticiran SLE i dob višu od 18 godina. Dijagnoza SLE-a nalagala je ispunjenje kriterija Američkoga reumatološkog društva (ACR) iz 1984. godine. Iz povijesti bolesti prikupili smo podatke o dobi, spolu te kliničkim manifestacijama i komorbiditetima. Od kliničkih manifestacija u obzir smo uzeli: kožne promjene, zahvaćenost srca, lupus nefritis, depresiju, za-

Data on age, gender, and clinical manifestations and comorbidities were collected from the disease history. The following clinical manifestations were taken into account: skin changes, heart involvement, lupus nephritis, depression, CNS involvement, joint involvement, APS (revised Sappor criteria from 2006), anemia, thrombocytopenia, pleuritis, psychosis, osteonecrosis, and vasculitis. Recorded comorbidities were: osteoporosis, osteopenia, SS, diabetes, chronic thyroiditis, hypertension, dyslipidemia, systemic infections, rheumatoid arthritis, gastritis, and associated neoplasms. The variable heart involvement included: diseases of the endocardium, myocardium, pericardium, and coronary blood vessels. In systemic infections we analyzed all those that required hospitalization of the patients. Regarding the associated neoplasms, both benign and malignant neoplasms were included. We included all types of vasculitis, except for CNS vasculitis, which was considered as CNS involvement. The diagnosis of vasculitis was based on clinical, histological, or radiological diagnostics. Skin changes included butterfly rash, discoid rash, photosensitivity, oral ulceration, alopecia, and Raynaud phenomenon. The Ethics Committee of the University Hospital of Split approved the implementation of this research.

Statistical analysis

The collected data were entered into a computer database using the SPSS 25 for Windows program (IBM, New York, USA). We used χ2-test, univariate logistic regression, and multivariate logistic regression. A P-value lower than 0.05 was taken as statistically significant. Data are presented as absolute values, percentages, and odds ratio (OR).

RESULTS

The study included 268 patients with SLE, who were ≥ 18 years of age at the time of inclusion. The median age of the respondents was 52 years (22 – 88 years). The respondents were divided into 3 groups according to age: ≤ 50 years, 50 – 70 years, and ≥ 70 years. Of the total number of respondents, 26 (10%) were men and 242 (90%) women. Table 1 shows the number (%) of patients by age groups, type of clinical manifestations, and comorbidities that did not differ according to gender.

Table 2 shows the number (%) of patients by type of clinical manifestations and comorbidities with a significant difference between the genders. Since there were no males older than 70 years, we analyzed the clinical manifestations and comorbidities in relation to two age groups (≤ 50 and 50 – 70), because those two age groups were gender-aligned. Table 3 shows the number (%) of patients according to the type of clinical manifestations and comorbidities that differed be-

hvaćenost SŽS-a, zahvaćenost zglobova, APS (revidirani kriteriji iz Sappora iz 2006. godine), anemiju, trombocitopeniju, pleuritis, psihozu, osteonekrozu, vaskulitis. Od komorbiditeta zabilježili smo: osteoporozu, osteopeniju, SS, šećernu bolest, kronični tiroiditis, hipertenziju, dislipidemiju, sustavne infekcije, reumatoidni artritis, gastritis, pridružene neoplazme. U varijablu zahvaćenost srca uključili smo: bolesti endokarda, miokarda i perikarda te koronarnih krvnih žila. U sustavne smo infekcije uključili sve one koje su iziskivale hospitalizaciju bolesnika. U pridružene neoplazme uključili smo i benigne i maligne neoplazme. U vaskulitis smo uključili sve vrste vaskulitisa, osim vaskulitisa SŽS-a koji smo računali kao zahvaćenost SŽS-a. Dijagnoza vaskulitisa bila je postavljena na temelju kliničke, histološke ili radiološke dijagnostike. U kožne smo promjene uvrstili leptirasti osip, diskoidni osip, fotosenzitivnost, oralne ulceracije, alopeciju i Raynaudov fenomen.

Etičko povjerenstvo KBC-a Split odobrilo je provođenje ovog istraživanja.

Statistička obrada

Prikupljeni podatci uneseni su u računalnu bazu podataka pri čemu smo rabili program *SPSS 25 for Windows* (IBM, New York, SAD). Služili smo se χ^2-testom, univarijatnom logističkom regresijom i multivarijatnom logističkom regresijom. P-vrijednost niža od 0,05 uzeta je kao statistički značajna. Podatci su prikazani kao apsolutne vrijednosti, postotci i OR (engl. *odds ratio*).

REZULTATI

Istraživanjem je obuhvaćeno 268 bolesnika sa SLE-om, koji su u trenutku uključivanja imali ≥ 18 godina. Medijan dobi ispitanika iznosio je 52 godine (min. – maks.: 22 – 88 godina). Ispitanike smo, prema dobi, podijelili u 3 skupine: ≤ 50 godina, 50 – 70 godina, ≥ 70 godina. Od ukupnog broja ispitanika bilo je 26 muškaraca (10%) i 242 žene (90%). Na tablici 1. prikazan je broj (%) bolesnika prema dobnim skupinama, vrsti kliničkih manifestacija i komorbiditetima koji se nisu razlikovali s obzirom na spol. Na tablici 2. prikazan je broj (%) bolesnika prema vrsti kliničkih manifestacija i komorbiditetima sa zabilježenom znatnom razlikom među spolovima. Nijedan muškarac nije bio stariji od 70 godina pa smo analizu kliničkih manifestacija i komorbiditeta napravili u odnosu prema dvjema dobnim skupinama (≤ 50, 50 – 70), jer su te dvije dobne skupine bile usklađene prema spolovima. Na tablici 3. prikazan je broj (%) bolesnika prema vrsti kliničkih manifestacija i komorbiditetima koji su se razlikovali među spolovima ukupno i u odnosu prema dobnim skupinama (≤ 50 i 50 – 70 godina). Sumarni

Table 1. Distribution of patients by age groups, type of clinical manifestations, and comorbidities that did not differ between the genders

Tablica 1. Raspodjela bolesnika prema dobnim skupinama, vrsti kliničkih manifestacija i komorbiditetima koji se nisu razlikovali prema spolovima

		Total / Ukupno (n = 268)	Gender / Spol		*P**
			Men / muškarci (n = 26)	Women / žene (n = 242)	
Age groups (years) / Dobne skupine (god.)	< 50	116 (43)	14 (54)	102 (42)	0,189
	50 – 70	128 (48)	12 (46)	116 (48)	
	> 70	24 (9)	0	24 (10)	
Skin changes / Kožne promjene	da	112 (42)	14 (54)	98 (40)	0,270
Heart disorders / Srčane tegobe	da	38 (14)	3 (11)	35 (14)	0,906
Kidneys / Bubrezi	da	64 (24)	8 (31)	56 (23)	0,532
Osteoporosis / Osteoporoza	da	42 (16)	1 (4)	41 (17)	0,144
Depression / Depresija	da	36 (13)	1 (4)	35 (14)	0,228
CNS / SŽS	da	30 (11)	3 (11)	27 (11)	1
Joints / Zglobovi	da	78 (29)	11 (42)	67 (28)	0,183
Diabetes / Šećerna bolest	da	17 (6,4)	1 (4)	16 (7)	0,895
Chronic thyroiditis / Kronični tiroiditis	da	41 (15)	1 (4)	40 (16)	0,155
Sustavna infekcija / Systemic infection	da	58 (22)	9 (35)	49 (20)	0,153
RA	da	35 (13)	3 (11)	32 (13)	1
Thrombocytopenia / Trombocitopenija	da	43 (16)	4 (15)	39 (16)	1
Anemia / Anemija	da	136 (51)	14 (54)	122 (51)	0,916
Gastritis / Gastritis	da	43 (16)	3 (11)	40 (16)	0,706
Osteopenia / Osteopenija	da	20 (7)	2 (8)	18 (7)	1

P < 0,05; CNS / SŽS = central nervous system / središnji živčani sustav; RA = rheumatoid arthritis / reumatoidni artritis

Table 2. Distribution of patients with SLE according to the type of comorbidity that differed between the genders

Tablica 2. Raspodjela bolesnika sa SLE-om prema vrsti komorbiditeta koji su se razlikovali među spolovima

		Total / Ukupno (n = 268)	Gender / Spol		*P**	OR (95%-tni CI)	*P***
			Men / muškarci (n = 26)	Women / žene (n = 242)			
Sjögren syndrome / Sjögrenov sindrom	da	60 (23)	1 (4)	59 (25)	0,031	8 (1,1 – 61)	0,042
APS	da	45 (17)	10 (38)	35 (15)	0,005	3,7 (1,5 – 8,7)	0,003
Hypertension / Hipertenzija	da	93 (35)	4 (15)	89 (37)	0,05	3,2 (1,1 – 9,5)	0,038
Dyslipidemia / Dislipidemija	da	120 (45)	6 (23)	114 (47)	0,033	2,9 (1,1 – 7,6)	0,024
Neoplasia / Neoplazija	da	66 (25)	1 (4)	65 (27)	0,019	9,2 (1,2 – 69)	0,031
Vasculitis / Vaskulitis	da	17 (6)	5 (19)	12 (5)	0,016	4,5 (1,4 – 14)	0,009

P < 0,05; APS = antiphospholipid syndrome / antifosfolipidni sindrom

tween the genders in total and in relation to the age groups (≤ 50 and 50 – 70 years).

The summary results of univariate logistic regression with gender and age groups as independent variables are shown in Table 4. Multivariate logistic regression, in which the independent variables were gender and age group, found that the following variables were age group-related: skin changes, heart, kidney, hypertension, dyslipidemia, osteoporosis, anemia, and gas-

rezultati univarijatne logističke regresije sa spolom i dobnim skupinama kao neovisnim varijablama prikazani su na tablici 4. Multivarijatnom logističkom regresijom, u kojoj su nezavisne varijable bili spol i dobne skupine, dobili smo da su samo za dobnu skupinu vezane ove varijable: kožne promjene, srce, bubrezi, hipertenzija, dislipidemija, osteoporoza, anemija i gastritis. Multivarijantnom logističkom regresijom, u kojoj smo kao zavisnu varijablu uzeli svaku od kliničkih ma-

Table 3. Distribution of patients according to the type of clinical manifestations and comorbidities that differed between the genders in total and in relation to age groups (< 50 and 50–70 years)

Tablica 3. Raspodjela bolesnika prema vrsti kliničkih manifestacija i komorbiditetima koji su se razlikovali među spolovima ukupno i s obzirom na dobne skupine (< 50 i 50 – 70 godina)

		Total / Ukupno (n = 244)	Age (years) / Dob (godina)		P*	OR (95%-tni CI)	P*
			< 50 (n = 116)	50 – 70 (n = 128)			
Skin changes / Kožne promjene	yes / da	104 (43)	58 (50)	46 (36)	0,037	1,8 (1,1 – 3)	0,027
Heart disorders / Srčane tegobe	yes / da	35 (14)	10 (9)	25 (20)	0,023	2,6 (1,2 – 5,7)	0,017
Kidneys / Bubrezi	yes / da	61 (25)	38 (33)	23 (18)	0,012	2,2 (1,2 – 4)	0,008
Osteoporosis / Osteoporoza	yes / da	33 (13)	5 (4)	28 (22)	< 0,001	6,2 (2,3 – 17)	< 0,001
Hypertension / Hipertenzija	yes / da	80 (32)	24 (21)	56 (44)	< 0,001	3 (1,7 – 5,3)	< 0,001
Dyslipidemia / Dislipidemije	yes / da	102 (42)	35 (30)	67 (52)	0,001	2,5 (1,5 – 4,3)	0,001
Gastritis / Gastritis	yes / da	38 (16)	10 (9)	28 (22)	0,007	3 (1,4 – 6,4)	0,006

**P < 0,05*

Table 4. Summary table of univariable logistic regression (95% CI) of covariables that demonstrated a statistically significant association with gender or age groups (P < 0.05)

Tablica 4. Sumarna tablica univarijatne logističke regresije. OR (95%-tni CI) onih kovarijabla koje su pokazale statistički značajnu povezanost sa spolom ili dobnim skupinama (P < 0,05)

	Gender / Spol	Reference level for gender / Referentna razina za spol	Age groups / Dobne skupine	Reference level for age / Referentna razina za dob
Skin changes / Kožne promjene			1,8 (1,1 – 3)	50 – 70 godina
Heart disorders / Srčane tegobe			2,6 (1,2 – 5,7)	< 50 godina
Lupus nephritis / Lupusni nefritis			2,2 (1,2 – 4)	50 – 70 godina
Osteoporosis / Osteoporoza			6,2 (2,3 – 17)	< 50 godina
Hypertension / Hipertenzija	3,2 (1,1 – 9,5)	men / muškarci	3 (1,7 – 5,3)	< 50 godina
Dyslipidemia / Dislipidemija	2,9 (1,1 – 7,6)	men / muškarci	2,5 (1,5 – 4,3)	< 50 godina
Gastritis			3 (1,4 – 6,4)	< 50 godina
Sjögren syndrome / Sjögrenov sindrom	8 (1,1 – 61)	men / muškarci		
APS	3,7 (1,5 – 8,7)	woman / žene		
Associated neoplasms / Pridružene neoplazme	9,2 (1,2 – 69)	men / muškarci		
Vasculitis / Vaskulitis	4,5 (1,4 – 14)	woman / žene		

χ^2-test; logistic regression / logistička regresija

tritis. Multivariate logistic regression, in which the dependent variables were the clinical manifestations and comorbidities whose gender difference was significant in univariate analysis, and the independent variables were gender and age group, confirmed the association of SS, APS, associated neoplasms, and vasculitis with gender (Table 5, Figures 1 to 4).

DISCUSSION

The main results of our study suggest the existence of significant differences in the incidence of certain clinical manifestations and comorbidities between men and women with SLE in our population. A higher incidence of APS and vasculitis was found in men, and

nifestacija i komorbiditete čija je razlika među spolovima bila znatna u univarijatnoj analizi, a kao nezavisne varijable spol i dobne skupine, potvrdili smo povezanost SS-a, APS-a, pridruženih neoplazma i vaskulitisa sa spolom (tablica 5., slike 1. do 4.).

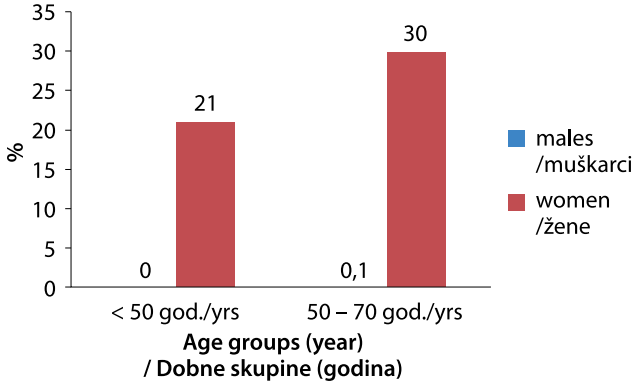
RASPRAVA

Glavni rezultati našeg istraživanja upućuju na postojanje znatnih razlika u pojavnosti pojedinih kliničkih manifestacija i komorbiditeta između muškaraca i žena oboljelih od SLE-a u našoj populaciji. U muškaraca je utvrđena veća pojavnost APS-a i vaskulitisa, a u žena pridruženih neoplazma i SS-a. U muškaraca je 2,5 puta veći udio bolesnika imao APS, dok je izgled za

TABLE 5. Results of multivariate logistic regression for comorbidities that demonstrated a difference between the genders in univariate logistic regression
TABLICA 5. Rezultati multivarijatne logističke regresije za komorbiditete koji su u univarijatnoj logističkoj regresiji pokazivali razliku među spolovima

Dependent variable / Zavisna varijabla	Independent variables / Nezavisne varijable	OR (95%-tni CI)	*P***
Sjögren syndrome / Sjögrenov sindrom	Gender (men*) / Spol (muškarci*)	8,4 (1,1 – 63)	**0,04**
	Age / Dob	1,7 (0,92 – 3)	0,09
APS	Gender (women*) / Spol (žene*)	3,8 (1,6 – 9,2)	**0,003**
	Age / Dob	0,72 (0,36 – 1,5)	0,363
Associated neoplasms / Pridružene neoplazme	Gender (men*) / Spol (muškarci*)	8,5 (1,1 – 64)	**0,039**
	Age / Dob	1,6 (0,5 – 2,9)	0,147
Vasculitis / Vaskulitis	Gender (women*) / Spol (žene*)	4,2 (1,3 – 13)	**0,014**
	Age / Dob	1,4 (0,51 – 3,9)	0,515

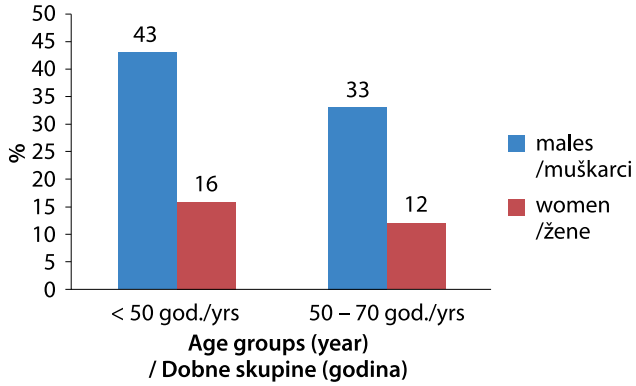
Data are shown as OR (95% CI)
/ Podatci su prikazani kao OR (95%-tni CI)
** reference level / referentna razina;*
*** logistic regression / logistička regresija*



Age < 50 y / Dob < 50 g.: N men / N muškaraca = 14; N women / N žena = 10; Age / Dob 50 –70 y / godina: N men / N muškaraca = 12, N women / N žena = 116

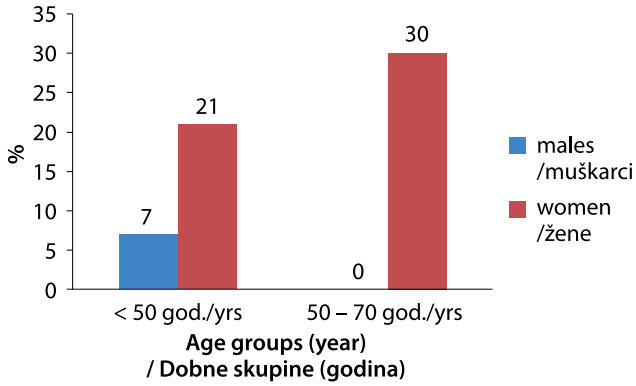
FIGURE 1. Proportion of Sjögren syndrome (%) by gender and age groups
SLIKA 1. Udio Sjögrenova sindroma (%) prema spolu i dobnim skupinama

in women there was higher incidence of associated neoplasms and SS. In men there was a 2.5 times higher proportion of patients with APS, while the incidence of APS was 3.7 times higher than in women. These results coincide with the results of several published studies. In almost all studies which showed a difference in the incidence of APS between men and women with SLE, APS was more common in men (10 – 13).



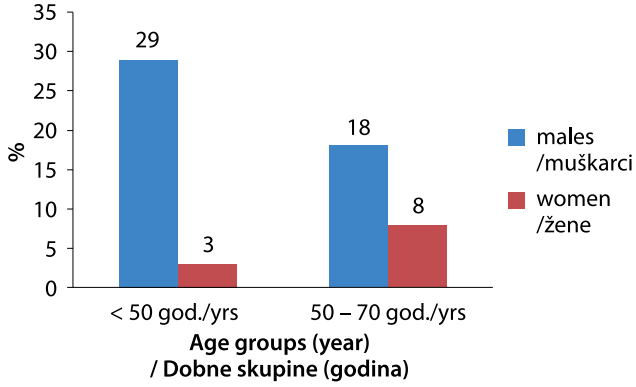
Age < 50 y / Dob < 50 g.: N men / N muškaraca = 14; N women / N žena = 102; Age / Dob 50 – 70 y / godina: N men / N muškaraca = 12, N women / N žena = 116

FIGURE 2. Proportion of APS (%) by gender and age groups
SLIKA 2. Udio APS-a (%) prema spolu i dobnim skupinama



Age < 50 y / Dob < 50 g.: N men / N muškaraca = 14; N women / N žena = 102; Age / Dob 50 – 70 y / godina: N men / N muškaraca = 12, N women / N žena = 116

FIGURE 3. Proportion of neoplasms (%) by gender and age groups
SLIKA 3. Udio pridruženih neoplazma (%) prema spolu i dobnim skupinama



Age < 50 y / Dob < 50 g.: N men / N muškaraca = 14; N women / N žena = 102; Age / Dob 50 – 70 y / godina: N men / N muškaraca = 12, N women / N žena = 116

FIGURE 4. Proportion of vasculitis (%) by gender and age groups
SLIKA 4. Udio vaskulitisa (%) prema spolu i dobnim skupinama

In addition to thrombosis, aCL was elevated in two studies, while elevated aCL without recorded thrombosis was present in a Latin American and another American study (10, 12, 14, 15). In those studies, LAC was elevated, and in one elevated aCL-IgG was found (14). Only one study conducted by British authors found reduced levels of aCL-IgM in men versus women (16). In men with elevated aCL, the triggers for thrombotic events were immobility, smoking, and dyslipidemia (12–16).

Vasculitis as a manifestation of SLE was noted in 17 (6%) subjects, of whom 5 (19%) were men and 12 (5%) were women. Our study proved with statistical significance that gender and vasculitis were related in our patients. The proportion of vasculitis was 3.8 times higher in men than in women, and the likelihood of vasculitis in men was 4.5 times higher than in women. In 1987 Sthoeger observed a higher incidence of vasculitis among men (13). In a Mexican study, vasculitis was more prevalent in male patients with SLE; both the disease and follow-up lasted longer, and patients were younger at the time of disease detection.

Clinical manifestations of SLE associated with vasculitis were myocarditis, psychosis, Raynaud phenomenon, serositis, leukopenia, lymphopenia, pleuritic, and APS (17). A Catalan study on vasculitis in SLE found it in 11% of respondents, but did not provide data on the gender association. One third of the patients in that study had associated autoimmune diseases including APS, SS, autoimmune hepatitis, and SSc, and according to localization, cutaneous vasculitis was the most common. Patients with vasculitis had a higher disease activity and a higher prevalence of lymphopenia and hypocomplementemia. More manifestations associated with APS, such as livedo reticularis and elevated aCL, have been found in patients with SLE and vasculitis versus those without vasculitis (18).

Therefore, the possible role of aCL or APS in the pathogenesis of vasculitis in SLE patients is being onsidered, as some manifestations such as arterial occlusion, venous thrombosis, leg ulcers, livedo reticularis, and thrombocytopenia have been shown to correlate with APS as well as with vasculitis (17: 19–22). Our significant result in favor of men is a possible consequence of the fact that men, according to some studies, have a more severe clinical picture of SLE with higher disease activity than women, and the higher incidence of APS in men certainly contributed to our result (17).

In our study, SS was significantly associated with the female gender. The proportion of SS was 6 times higher and the probability of its occurrence (OR) was 8 times higher in women than in men. According to previous studies in which a difference in the incidence of SS and / or sicca syndrome was observed, there was no significant difference between genders, but in all of them the

pojavnost APS-a 3,7 puta veći nego u žena. Ovakvi se rezultati podudaraju s rezultatima nekoliko objavljenih istraživanja. Gotovo u svim istraživanjima, u kojima je dokazana razlika u pojavnosti APS-a između muškaraca i žena oboljelih od SLE-a, u muškaraca je APS bio češći (10 – 13). Uz trombozu je u dva istraživanja bio povišen i aCL, dok je povišen aCL bez zabilježenih tromboza bio prisutan u latinoameričkom i još jednom američkom istraživanju (10, 12, 14, 15). U tim je istraživanjima najčešće bio povišen LAC, a u jednom aCL-IgG (14). Samo je u jednom istraživanju britanskih autora utvrđena snižena razina aCL-IgM u muškaraca naspram ženama (16). U muškaraca s povišenim aCL-om okidač za nastanak trombotskih događaja bili su nepokretnost, pušenje i dislipidemija (12 – 16).

Vaskulitis kao manifestacija SLE-a zabilježen je kod 17 (6%) ispitanika, od kojih su 5 (19%) bili muškarci, a 12 (5%) žene. Sa statističkom značajnošću dokazali smo da su u naših pacijenata spol i vaskulitis povezani. Udio vaskulitisa bio je 3,8 puta veći u muškaraca nego u žena, a izgledi za vaskulitis bili su kod muškaraca 4,5 puta veći od onih u žena. Sthoeger je još 1987. uočio veću pojavnost vaskulitisa među muškarcima (13). I u meksičkom je istraživanju vaskulitis bio zastupljeniji kod muškog spola, u bolesnika sa SLE-om i vaskulitisom bolest i vrijeme praćenja dulje su trajali, a bolesnici su bili mlađe dobi pri otkrivanju bolesti. Kliničke manifestacije SLE-a povezane s vaskulitisom bile su miokarditis, psihoza, Raynaudov fenomen, serozitis, leukopenija, limfopenija, pleuritis i APS (17). Katalonsko istraživanje o vaskulitisu u SLE-u otkriva ga u 11% ispitanika, ali nije dalo podataka o spolnoj povezanosti. Trećina bolesnika u tom istraživanju imala je pridružene autoimunosne bolesti uključujući APS, SS, autoimunosni hepatitis i SSc, a prema lokalizaciji, najčešći je bio kožni vaskulitis. Bolesnici s vaskulitisom imali su veću aktivnost bolesti te veću prevalenciju limfopenije i hipokomplementemije. Više manifestacija koje su povezane s APS-om poput *livedo reticularis* i povišenog aCL-a nađeno je u bolesnika sa SLE-om i vaskulitisom naspram onima bez vaskulitisa (18). Stoga se i razmatra moguća uloga aCL-a ili APS-a u patogenezi vaskulitisa u oboljelih od SLE-a, budući da su neke manifestacije poput arterijske okluzije, venskih tromboza, ulkusa nogu, livedo reticularis i trombocitopenije pokazale korelaciju s APS-om, kao i s vaskulitisom (17, 19 – 22). Naš znatan rezultat u korist muškaraca moguća je posljedica toga što muškarci, prema nekim istraživanjima, imaju težu kliničku sliku SLE-a, s većom aktivnosti bolesti od žena, a svakako tomu pridonosi i veća pojavnost APS-a u muškaraca (23).

U našem je istraživanju SS znatno povezan sa ženskim spolom. Udio SS-a 6 je puta veći, a izgled za njegovu pojavnost (OR) 8 je puta veći u žena nego kod

incidence of SS was higher in women than in men. Thus in a Greek study 1.7% of men and 3.37% of women had SS, while sicca syndrome was present in 5.1% of men and 11% of women (2).

In a study conducted by Renau and Isenberg, it was also observed that SS is more common in women (9.9%) versus men (6.7%) (16). We explain our result by the fact that SS is generally more common in women, and the ratio of women to men in our study was 10: 1 (25).

According to our research, associated neoplasms showed a significant correlation with the female gender, and they were mostly benign tumors. Gynecological tumors, uterine fibroids, polyps, and ovarian cysts predominated. Dysplasia and cervical cancer are known to be associated with HPV infection, which is more common in individuals with SLE. Other gynecological tumors, such as polyps and uterine fibroids, are associated with female sex hormones, the importance of which has already been mentioned in the introduction. Other benign neoplasms of other sites were cysts (liver, kidney, parotid gland, lung, breast, and spleen), hemangiomas of the liver, brain angiomas, polyps, and adenomas of various sites.

Malignant tumors were present on the thyroid gland in one patient, three had papillary thyroid carcinoma, and one patient had cervical cancer. Other localizations of gynecological malignancies were the vulva, fallopian tube, and uterus. The remaining malignancies were cancer of the lung, kidney, bladder, Bauhinia valve, colon, and skin. The only neoplasm we noted in men was hemangioma of the liver. No significant gender difference in tumors was observed in other studies, but a study by Antonelli et al. showed that there was a higher incidence of papillary thyroid cancer among patients with SLE (26).

Extensive research on comorbidities in SLE suggests an increased overall risk of developing malignancy and an increased incidence among men (27). Bernatsky et al. warned about a slightly increased risk of developing malignancies in SLE, particularly lung cancer, lymphoma, and other hematologic malignancies according to previous studies (28, 29).

Neither a higher risk of vulvar, thyroid, and pancreatic malignancies nor a reduced risk of breast or endometrial tumors were confirmed in SLE (30, 31). In contrast to our results, Crosslin and Wiginton found more malignancies in men than in women (23). It has been hypothesized that the increased risk of malignancy in patients with SLE is due to a damaged immune system, immunosuppressive drugs, and elevated common risk factors such as smoking (31).

A total of 64 (24%) patients in our study had lupus nephritis, of which 8 (31%) were men and 56 (23%) were women. Although we did not get a statistically

muškaraca. Prema dosadašnjim istraživanjima, u kojima je promatrana razlika u pojavnosti SS-a i/ili sindroma *sicca*, nije bilo znatne razlike među spolovima, no u svima je pojavnost SS-a bila veća u žena nego kod muškaraca. Tako je u grčkom istraživanju SS imalo 1,7% muškaraca i 3,37% žena, dok je sindrom *sicca* bio prisutan u 5,1% muškaraca, a 11% žena (24). U istraživanju Renaua i Isenberga također je primijećeno da je SS češći u žena (9,9%) naspram muškarcima (6,7%) (16). Naš rezultat objašnjavamo činjenicom da je SS inače učestaliji kod žena, a omjer žena i muškaraca bio je 10 : 1 (25).

Pridružene neoplazme pokazale su, prema našem istraživanju, znatnu povezanost sa ženskim spolom, a uglavnom se radilo o benignim tumorima. Prednjačili su ginekološki tumori, miomi maternice, polipi i ciste jajnika. Poznato je da su displazije i rak grla maternice povezani s infekcijom HPV-om koja je učestalija kod oboljelih od SLE-a. Ostali ginekološki tumori kao, npr., polip i miom maternice povezani su sa ženskim spolnim hormonima, o čijoj smo važnosti u SLE-u već pisali u uvodu. Od ostalih benignih neoplazma drugih sijela bilo je cista (jetre, bubrega, parotidne žlijezde, pluća, dojke i slezene), hemangioma jetre, angioma mozga, polipa i adenoma raznih sijela. Maligni tumori bili su prisutni kod jednog bolesnika na doštitnoj žlijezdi, troje je imalo papilarni karcinom štitnjače, a jedna bolesnica rak vrata maternice. Ostale lokalizacije ginekoloških malignoma bile su vulva, jajovod i maternica. Preostali malignomi bili su karcinomi pluća, bubrega, mokraćnog mjehura, Bauhinijeve valvule, debelog crijeva i kože. Jedina neoplazma koju smo imali zabilježenu kod muškarca bio je hemangiom jetre. U drugim istraživanjima nije zabilježena znatna spolna razlika u tumorima, ali je istraživanje Antonellija i suradnika dokazalo da je među oboljelima od SLE-a veća incidencija papilarnog karcinoma štitnjače (26). Veliko istraživanje komorbiditeta u SLE-u upućuje na povišen ukupni rizik od razvoja malignoma i povećanu pojavnost među muškarcima (27). Bernatsky i suradnici upozorili su na malo povišen rizik od razvoja malignoma u SLE-u, osobito karcinoma pluća, limfoma i drugih hematoloških malignoma sukladno prijašnjim istraživanjima (28, 29). U SLE-u nije potvrđen viši rizik od malignoma vulve, štitnjače i gušterače ni snižen rizik od tumora dojke ili endometrija (30, 31). Nasuprot našim rezultatima, Crosslin i Wiginton u svojem su istraživanju utvrdile više maligniteta u muškaraca nego u žena (23). Pretpostavka je da je povišen rizik od malignoma u bolesnika sa SLE-om posljedica oštećenog imunosnog sustava, imunosupresivnih lijekova i povišenih uobičajenih rizičnih faktora poput pušenja (31).

Lupus nefritis imalo je ukupno 64 (24%) oboljelih, od čega je bilo 8 (31%) muškaraca, a 56 (23%) žena.

significant result considering the proportion of male and female patients, we found that lupus nephritis is more common in men. Other studies have also confirmed a higher incidence of lupus nephritis in men (16, 23, 24).

The proportion of lupus nephritis was almost twice as high in the group of patients <50 years of age in comparison to the patients aged 50 to 70 years, which is consistent with the results of other studies (16, 24).

Skin changes were found in 112 (42%) of our patients with SLE, of which 14 (54%) were men and 98 (40%) were women. Most studies analyzed individual skin changes taking gender into consideration; thus, in a study by Tan et al., men were less likely to develop butterfly rash, photosensitivity, oral ulceration, alopecia, and Raynaud phenomenon than women (10). According to a large Latin American cohort of patients with SLE, in men there were fewer cases of alopecia, photosensitivity, butterfly rash, and Raynaud phenomenon (14).

An Asian study also found that alopecia and Raynaud phenomenon were more common in women. Also, in a Greek study photosensitivity, Raynaud phenomenon, and oral ulcerations were more common in women (32, 33). We did not get a difference in the incidence of skin changes with respect to gender, as only individual skin changes differed.

Osteoporosis was present in 42 (16%) of our patients, of which only 1 (4%) was a man and 41 (17%) were women. The proportion of osteoporosis was 5.5 times higher in the group of patients aged 50 to 70 years compared to patients aged < 50 years, and the probability of osteoporosis in the group of patients aged 50 – 70 years was 6.2 times higher than in the group of patients aged < 50 years. Although the gender gap did not reach the level of statistical significance, our results show that osteoporosis is more common in women than in men with SLE. A Spanish study in the RELESSER cohort showed that osteoporosis with fractures was more common in women, but the difference did not reach statistical significance, similar to our study (12).

Rees et al. found a higher incidence of osteoporosis in women with SLE compared to the control group, while men had a very high relative risk of developing osteoporosis compared with the control group (27). Other factors that can affect the incidence of osteoporosis in men are glucocorticoid use and SLE activity. Salman-Monte et al. reported an incidence of osteoporosis in 8.9% female patients with SLE and 4.4% of consequent fractures. In each of these women osteopenia was diagnosed by densitometry, but found no association between bone density and glucocorticoids or disease activity (11).

Iako nismo dobili statistički značajan rezultat s obzirom na udio muških i ženskih bolesnika, vidimo da je lupus nefritis češći kod muškaraca. I druga su istraživanja potvrdila veću pojavnost lupusnog nefritisa kod muškaraca (16, 23, 24).

Udio lupusnog nefritisa gotovo je dvostruko veći u skupini bolesnika u dobi < 50 godina od onoga kod bolesnika u dobi od 50 do 70 godina, što je u skladu s rezultatima drugih istraživanja (16, 24).

Kožne promjene imalo je 112 (42%) naših bolesnika sa SLE-om, od kojih je bilo 14 (54%) muškaraca, a 98 (40%) žena. Većina istraživanja analizirala je pojedinačne kožne promjene s obzirom na spol pa su u istraživanju Tana i suradnika muškarci imali manji izgled da se u njih razviju leptirasti osip, fotosenzitivnost, oralne ulceracije, alopecija i Raynaudov fenomen nego žene (10). Prema velikoj latinoameričkoj kohorti bolesnika sa SLE-om, u muškaraca je bilo manje alopecije, fotosenzitivnosti, leptirastog osipa i Raynaudova fenomena (14). Azijsko je istraživanje također pokazalo da su alopecija i Raynaudov fenomen češći u žena, a u grčkom su istraživanju fotosenzitivnost, Raynaudov fenomen i oralne ulceracije bili učestaliji kod žena (32, 33). Nismo dobili razliku u pojavnosti kožnih promjena s obzirom na spol, jer se razlikuju samo pojedinačne kožne promjene.

Osteoporozu su imala 42 (16%) naša bolesnika, od kojih je u skupini muškaraca bio samo 1 (4%), a žena je bila 41 (17%). Udio osteoporoze bio je 5,5 puta veći u skupini bolesnika u dobi od 50 do 70 godina u odnosu prema bolesnicima u dobi < 50 godina, a izgled za pojavnost osteoporoze u skupini bolesnika u dobi od 50 – 70 godina bio je 6,2 puta veći nego u skupini bolesnika u dobi < 50 godina. Premda razlika među spolovima nije dosegla razinu statističke značajnosti, naši rezultati pokazuju da je osteoporoza češća u žena nego u muškaraca oboljelih od SLE-a. Španjolsko istraživanje na kohorti RELESSER pokazalo je da je osteoporoza s frakturama češća kod žena, ali razlika nije dosegla statističku značajnost slično kao i u našem istraživanju (12). Rees i suradnici utvrdili su veću pojavnost osteoporoze u žena oboljelih od SLE-a u odnosu prema kontrolnoj skupini, dok su muškarci imali vrlo visok relativni rizik od razvoja osteoporoze u usporedbi s kontrolnom skupinom (27). Ostali faktori koji mogu utjecati na pojavnost osteoporoze i kod muškaraca jesu upotreba glukokortikoida i aktivnost SLE-a. Salman-Monte i suradnici izvijestili su o učestalosti osteoporoze od 8,9% u bolesnica sa SLE-om i 4,4% posljedičnih prijeloma. Svakoj od tih žena denzitometrijom je dokazana osteopenija, no nisu našli povezanost između gustoće kostiju i glukokortikoida ili aktivnosti bolesti (11).

Prema istraživanju Reesa i suradnika, incidencija kardiovaskularnih bolesti (KVB), malignoma i osteo-

According to the research by Rees et al., the incidence of cardiovascular disease (CVD), malignancy, and osteoporosis in SLE increased with age; the incidence of infections did not show an age association, while the incidence of end-stage renal failure decreased with age. The risk of all comorbidities, except infection, was elevated at a younger age compared to the controls (27).

Our results greatly coincide with the results of Rees et al., although we had a different division of age groups. Since we considered heart disorders as all disorders of the endocardium, myocardium, pericardium, as well as coronary blood vessels, we cannot compare this variable with the CVD variable from that study.

Hypertension and dyslipidemia are traditional risk factors for CVD and, like CVD in our study, are more common in elderly patients. Still, the question remains as to how much of this is a consequence of age and how much of SLE activity, but given the absence of a control group without SLE, we could not examine it.

There were several other limitations to our study. First and foremost is the large difference in the representation of men and women, which is a reflection of the real difference in the incidence of this disease. Another limitation is the retrospective data and part of the comorbidities that were suspected, but without clear evidence. A number of patients did not come for regular follow-up, so it is possible that some clinical manifestations or comorbidities were missed.

In conclusion, differences in clinical manifestations and comorbidities between women and men with SLE were found in a sample of our population. The incidence of SS and associated neoplasms is much higher in women than in men, while in men with SLE, the incidence of APS and vasculitis is higher than in women. Hypertension and dyslipidemia are more common in women than in men in the population of our patients with SLE. Lupus nephritis and skin changes occur in both genders in younger patients. In order to elucidate this problem more clearly, it is necessary to examine a much larger population of patients and monitor them for a longer period of time.

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

poroze u SLE-u rasla je s dobi; incidencija infekcija nije pokazivala dobnu povezanost, dok se incidencija terminalnog stadija zatajenja bubrega s godinama smanjivala. Rizik od svih komorbiditeta, osim infekcije, u mlađoj je dobi bio povišen u usporedbi s kontrolom (27). Naši se rezultati uvelike podudaraju s rezultatima Reesa i suradnika, premda smo imali drugačiju podjelu dobnih skupina. S obzirom na to da smo pod zahvaćenošću srca razumijevali sve poremećaje endokarda, miokarda, perikarda, kao i koronarnih krvnih žila, tu varijablu ne možemo uspoređivati s varijablom KVB-a iz ovog istraživanja.

Hipertenzija i dislipidemija tradicionalni su rizični čimbenici za KVB te su, kao i KVB u ovom istraživanju, češći kod starijih bolesnika. Ipak, ostaje otvoreno pitanje koliko je to posljedica dobi, a u kojoj mjeri aktivnosti SLE-a, ali s obzirom na nepostojanje kontrolne skupine bez SLE-a, nismo to ni mogli istražiti.

U našem je istraživanju bilo još nekoliko ograničenja. Prvo i najvažnije jest velika razlika u zastupljenosti muškaraca i žena koja je odraz stvarne razlike u pojavnosti ove bolesti. Druga su slabost retrospektivno uzimani podatci i dio komorbiditeta na koje se sumnjalo, ali bez jasnog dokaza. Dio bolesnika nije dolazio na redovite kontrole pa je moguće da su neke kliničke manifestacije ili komorbiditeti promakli evidentiranju.

Zaključno, u uzorku naše populacije nađene su razlike u kliničkim manifestacijama i komorbiditetima između žena i muškaraca oboljelih od SLE-a. Izgled za pojavnost SS-a i pridruženih neoplazma višestruko je veći u žena nego u muškaraca, dok je kod muškaraca sa SLE-om veći izgled za pojavnost APS-a i vaskulitisa nego u žena. Hipertenzija i dislipidemija češće su u žena nego u muškaraca u populaciji naših bolesnika sa SLE-om. Lupus nefritis i kožne promjene javljaju se kod oba spola u bolesnika mlađe dobi. Radi jasnijeg objašnjenja ovog problema potrebno je istražiti puno veću populaciju bolesnika te ih pratiti dulje razdoblje.

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Petra Kovačević

REFERENCES / LITERATURA

1. Lahita RG. The Clinical Presentations of Systemic Lupus Eritematosus. U: Lahita RG, Tsokos G, Buyon JP, Koike T (ur.). Systemic Lupus Erythematos. Academic Press; 2010., str. 525–41.
2. Jönsen A, Clarke AE, Joseph L, Belisle P, Bernatsky S, Nived OA i sur. Association of the Charlson Comorbidity Index with Mortality in Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2011;63:1233–7.
3. Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. Expert Rev Clin Immunol. 2017;13:799–814.
4. González LA, Alarcón GS. The evolving concept of SLE comorbidities. Expert Rev Clin Immunol. 2017;13:753–68.
5. Urowitz MB, Gladman D, Ibañez D, Bae SC, Sanchez-Guerrero J, Gordon C i sur. Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010;62:881–7.
6. Choi MY, Flood K, Bernatsky S, Ramsey-Goldman R, Clarke AE. A review on SLE and malignancy. Best Pract Res Clin Rheumatol. 2017;31:373–96.
7. Setoue DN, Pitta AC, Fiorot FJ, Nastri MM, Novak GV, Molinari BC i sur. Symptomatic polyautoimmunity at diagnosis of 1463 childhood-onset lupus. Autoimmun Rev. 2018;17(8): 836–9.
8. Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, Martinez-Berriotxoa A, Egurbide MV, Aguirre C. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther. 2009;11:R109.
9. Boodhoo KD, Liu S, Zuo X. Impact of sex disparities on the clinical manifestations in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95:e4272.
10. Tan TC, Fang H, Magder L, Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. J Rheumatol. 2012;39:759–69.
11. Stefanidou S, Benos A, Galanopoulou V. Clinical expression and morbidity of systemic lupus erythematosus during a post-diagnostic 5-year follow-up: a male:female comparison. Lupus. 2011;20:1090–4.
12. Riveros Frutos A, Casas I, Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J, Galindo M i sur. Systemic lupus erythematosus in Spanish males: a study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. Lupus. 2017;26:698–706.
13. Sthoeger ZM, Geltner D, Rider A, Bentwich Z. Systemic lupus erythematosus in 49 Israeli males: a retrospective study. Clin Exp Rheumatol. 1987;5:233–40.
14. Garcia MA, Marcos JC, Marcos AI, Pons-Estel BA, Wojdyla D, Arturi A. Male systemic lupus erythematosus in a Latin-American inception cohort of 1214 patients. Lupus. 2005;14:938–46.
15. Rivest C, Lew RA, Welsing PM, Sangha O, Wright EA, Roberts WN i sur. Association between clinical factors, socioeconomic status, and organ damage in recent onset systemic lupus erythematosus. J Rheumatol. 2000;27:680–4.
16. Renau AI, Isenberg DA. Male versus female lupus: a comparison of ethnicity, clinical features, serology and outcome over a 30 year period. Lupus. 2012;21:1041–8.
17. Drenkard AR, Villa E, Reyes M, Abello D, A1larcón-Segovia A. Vasculitis in systemic lupus erythematosus. Lupus. 1997:6; 235–42.
18. Ramos-Casals M, Nardi N, Lagrutta M, Brito-Zerón P, Bové A, Delgado G. Vasculitis in systemic lupus erythematosus: Prevalence and Clinical Characteristics in 670 patients. Medicine. 2006;85:95–104.
19. Alarcón-Segovia D, Pérez-Vázquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. Semin Arthritis Rheum. 1992;21:275–86.
20. Danning CL, Illei GG, Boumpas DT. Vasculitis associated with primary rheumatologic diseases. Curr Opin Rheumatol. 1998; 10:58–65.
21. Goldberger E, Elder RC, Schwartz RA, Phillips PE. Vasculitis in the antiphospholipid syndrome. A cause of ischemia responding to corticosteroids. Arthritis Rheum. 1992;35:569–72.
22. Toussirot E, Figarella-Branger D, Disdier P, Harle JR, Weiller PJ. Association of cerebral vasculitis with a lupus anticoagulant. A case with brain pathology. Clin Rheumatol. 1994;13: 624–7.
23. Crosslin KL, Wiginton KL. Sex differences in disease severity among patients with systemic lupus erythematosus. Gend Med. 2011;8:365–71.
24. Voulgari PV, Katsimbri P, Alamanos Y, Drosos AA. Gender and age differences in systemic lupus erythematosus. A study of 489 Greek patients with a review of the literature. Lupus. 2002; 11:722–9.
25. Brito-Zerón P, Baldini C, Bootsma H, Bowman SJ, Jonsson R, Mariette X i sur. Sjögren syndrome. Nat Rev Dis Primers. 2016; 2:16047.
26. Antonelli A, Mosca M, Fallahi P, Neri R, Ferrari SM, D'Ascanio A i sur. Thyroid cancer in systemic lupus erythematosus: a case-control study. J Clin Endocrinol Metab. 2010;95:314–8.
27. Rees F, Doherty M, Grainge M, Lanyon P, Davenport G, Zhang W. Burden of Comorbidity in Systemic Lupus Erythematosus in the UK, 1999–2012. Arthritis Care Res (Hoboken). 2016; 68(6):819–27.
28. Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M i sur. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun. 2013;42:130–5.
29. Sultan SM, Ioannou Y, Isenberg DA. Is there an association of malignancy with systemic lupus erythematosus? An analysis of 276 patients under long-term review. Rheumatology (Oxford). 2000;39:1147–52.
30. Dey D, Kenu E, Isenberg DA. Cancer complicating systemic lupus erythematosus: a dichotomy emerging from a nested case-control study. Lupus. 2013;22:919–27.
31. Gayed M, Bernatsky S, Ramsey-Goldman R, Clarke A, Gordon C. Lupus and cancer. Lupus. 2009;18:479–85.
32. Mongkoltanatus J, Wangkaew S, Kasitanon N. Clinical features of Thai male lupus: an age matched controlled study. Rheumatol Int. 2008;28:339–44.
33. Bono L, Cameron JS, Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. QJM. 1999;92:211–8.

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ORIGINAL SCIENTIFIC PAPER ORIGINALNI ZNANSTVENI RAD

NON-PHARMACOLOGICAL TREATMENT OF PAINFUL SHOULDER SYNDROME – COMPARATIVE RESEARCH

NEFARMAKOLOŠKO LIJEČENJE BOLNOG RAMENA – KOMPARATIVNO ISTRAŽIVANJE

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Abstract

Non-pharmacological treatment is undeniably a significant part of painful shoulder syndrome treatment. Medical exercises are its most important segment, according to the results of evidence-based medicine. Due to the fact that exercises are rarely used as monotherapy, we were particularly interested in the data regarding other non-pharmacological methods of treatment found in the Cochrane library and PEDro database (Physiotherapy Evidence Database). Simultaneously, we conducted a research study of painful shoulder syndrome treatment with conventional methods of physical therapy. The study included 157 patients, which allowed us to compare our preliminary results with data found in the previously mentioned databases.

The majority of quality studies that can be found in the literature database involve the use of modern technology, such as extracorporeal shock wave therapy and high-intensity laser therapy, because they have proven to be very effective in the reduction of pain intensity and the increase of functional capacity of the painful shoulder. These methods of treatment have shown to be effective even in patients with calcific tendinitis, a more severe form of the disease, as well as in patients who had no calcifications. Conventional methods of treatment, often referred to as standard physical therapy (low-level laser therapy, electrotherapy, therapeutic ultrasound) have proven to be effective, but less effective compared to the aforementioned methods. The results of our research also corroborate the previously mentioned fact, thus confirming that the use of conventional methods of physical medicine (therapeutic ultrasound, diclofenac sonophoresis, interferential current therapy, low-level laser therapy, cryotherapy) has been successful in reducing pain intensity and increasing the functional capacity of the painful shoulder. Among the conventional methods of treatment, electrotherapy (interferential current therapy) turned out to be the most efficient one.

Non-pharmacological treatment have to be an integral part of all painful shoulder syndrome treatment protocols, and in the future, the use of modern technology in addition to conventional methods of treatment should be encouraged.

Key words: Shoulder pain – etiology, therapy; Physical therapy modalities; Rotator cuff injuries – therapy; Electric stimulation therapy – methods; Extracorporeal shockwave therapy; Laser therapy – methods; Range of motion, articular; Treatment outcome

Sažetak

Nedvojbeno je da u procesu liječenja sindroma bolnog ramena važnu ulogu ima nefarmakološko liječenje (NFL). Pritom, sukladno rezultatima medicine utemeljene na dokazima (EBM), najveću ulogu imaju medicinske vježbe. One

se, pak, rijetko rabe samostalno, kao monoterapija, pa nas je zbog toga zanimalo kakve ćemo podatke pronaći u Cochraneovoj bazi i Fizioterapijskoj bazi podataka (engl. *Physiotherapy Evidence Database* – PEDro) za ostale oblike NFL-a. Istodobno, proveli smo istraživanje o liječenju sindroma bolnog ramena konvencionalnom terapijom, uključivši u istraživanje 157 bolesnika, kako bismo svoje preliminarne rezultate mogli usporediti s podatcima nađenima u rečenim bazama podataka.

Najveći broj kvalitetnih studija, pronađenih u literaturi, vezan je za primjenu modernih tehnologija, primjerice, udarnog vala i lasera visokog intenziteta, koji su pokazali znatan učinak na smanjenje boli i povećanje funkcionalnog kapaciteta bolnog ramena. Ove metode liječenja pokazale su se uspješnima i u bolesnika s kalcificirajućim tendinitisom, kao težim oblikom bolesti, ali i kod onih bez te otegotne činjenice. Konvencionalne metode liječenja, često nazivane klasičnom fizikalnom terapijom (elektroterapija, laser niskog intenziteta i ultrazvuk) pokazale su svoju učinkovitost, iako su uvijek bile inferiorne prije navedenim metodama. Rezultati našeg istraživanja bili su u skladu sa spomenutom činjenicom, tako da se primjena konvencionalne fizikalne terapije (ultrazvuk, sonoforeza, interferentne struje, laser niskog intenziteta, krioterapija) pokazala učinkovitom u smanjenju boli i povećanju funkcionalnog kapaciteta bolnog ramena, pri čemu je primjena interferentnih struja bila nešto uspješnija od drugih metoda.

NFL mora i nadalje ostati sastavni dio svih protokola liječenja sindroma bolnog ramena, pri čemu modernim tehnologijama treba ustupati sve više mjesta u odnosu prema konvencionalnim metodama liječenja.

Ključne riječi: Bolno rame – etiologija, liječenje; Fizioterapijske metode; Oštećenja rotatorne manšete – liječenje; Elektroterapija – metode; Liječenje udarnim valom; Liječenje laserom – metode, zglobna pokretljivost; Ishod liječenja

INTRODUCTION

Non-pharmacological treatment is extremely important in all protocols/algorithms for the treatment of extra-articular rheumatic diseases (1). By using numerous benefits resulting from advances in medicine, modern technology, as an integral part of standard physical therapy, has become an extremely important segment whose efficiency can be compared with that of the most effective non-pharmacological method – kinesiotherapy (2). Painful shoulder syndrome is one of the most prevalent extra-articular rheumatic disease, as well as one of the most frequent cause of pain when it comes to rheumatic diseases in general, and it significantly affects the quality of daily activities and the life of patients who suffer from it (3).

Therefore, it is important to note the main causes of painful shoulder syndrome as well as to analyze the literature data regarding the treatment effectiveness and compare them to the results from our research on conventional physical therapy effects on the functional capacity and pain intensity in patients treated in a tertiary care center. As the majority of our public health facilities including some clinical hospital centers still do not have access to modern technology for the treatment of painful shoulder syndrome, it would be interesting to explore the possibilities that standard (conventional) physical therapy modalities offer.

The main characteristic of extra-articular rheumatic diseases, as their very name implies, is the fact that the changes occur in the immediate vicinity of the joint (synovial bursa, tendon, tendon sheath), with degenerative and inflammatory changes etiologically overlapping in the affected areas (3, 4).

UVOD

U svim postupnicima/algoritmima liječenja izvanzglobnih reumatskih bolesti nefarmakološko liječenje (NFL) zauzima važno mjesto (1). Koristeći se prednostima napretka u medicini, moderna tehnologija, kao sastavni dio uobičajene fizikalne terapije, iznimno je bitna i stavlja se uz bok najučinkovitijoj metodi NFL-a – kinezioterapiji (2). Od svih izvanzglobnih bolesti u reumatološkoj se praksi najviše spominje sindrom bolnog ramena kao jedan od najčešćih uzroka bolnih stanja u reumatologiji uopće, koji znatno utječe na dnevne aktivnosti i kvalitetu života bolesnika (3).

Zbog toga bi bilo dobro podsjetiti se glavnih uzroka nastanka toga bolnog sindroma, provjeriti podatke iz literature o uspješnosti liječenja bolesnika i usporediti ih s nekim našim rezultatima iz istraživanja o učinku konvencionalne fizikalne terapije na funkcionalne mogućnosti i bol u bolesnika liječenih u jednome tercijarnom centru. Naime, velik dio naših državnih ustanova i dalje ne raspolaže modernim tehnologijama za liječenje ovoga bolnog sindroma, a među takvima su i neki klinički bolnički centri, pa bi bilo zanimljivo vidjeti kakve nam mogućnosti nude klasični (konvencionalni) fizikalnoterapijski modaliteti.

Glavna karakteristika izvanzglobnih reumatskih bolesti jest, kao što ime govori, da se promjene događaju u neposrednoj blizini zgloba (sluzne vreće, tetive, tetivne ovojnice), a da se pritom u zahvaćenim tkivima etiološki isprepleću degenerativne i upalne promjene (3, 4).

Sindrom bolnog ramena bolest je kod koje u kliničkoj slici dominiraju bol i smanjenje funkcionalnog kapaciteta ramenog zgloba. U medicinskoj se literaturi taj klinički entitet, koji se s jednakom učestalošću javlja

Painful shoulder syndrome is a disease whose clinical features include pain and a reduced functional capacity of the shoulder joint. In medical literature, this clinical entity, equally frequent in both males and females and most often unilateral, is referred to as "periarthritis humeroscapularis" (from the Greek word *peri* = about, around), and the cause of the disease is inflammation (Greek suffix -itis = inflammation) (5). As opposed to inflammatory rheumatic diseases, this disorder predominantly includes localized, aseptic inflammation and consequent degenerative changes which most often occur in the supraspinatus muscle tendons and the long head of the biceps brachii muscle, while the inflammatory changes, most cases caused by calcification, are present in the subacromial bursa (3, 5).

Mechanical causes found in the patient history, such as data on physical strain of the shoulder joint, repeated shoulder movements with clenched fist carrying a certain load, or movements with hands above the head, are an important determinant in the etiopathogenesis of painful shoulder syndrome. In performing these movements, the joint itself and the area around it are exposed to repeated daily microtraumas, which can lead to an accelerated occurrence of degenerative scarring on the soft tissue around the shoulder joint (3, 5). Calcifications of various sizes can develop in soft tissue, most often in tendons (3, 6). They are often an accidental finding in the tendon area and the joint capsule during an X-ray (7). Thus, they are often detected in patients without standard typical symptoms of painful shoulder. The pain often progresses and intensifies after exertion or falling on one's arm or shoulder, when calcific deposits move and the body starts perceiving them as foreign bodies, initiating an intense inflammatory response in order to defend itself (3, 5). Like any other inflammatory response, this reaction becomes more intense and pronounced (and therefore more painful) when the joint and nearby joint structures start warming up. This is exactly what happens during night-time: the typical nocturnal pain develops while the patient is resting and his/her shoulder starts warming up from the outside. This is a seemingly paradoxical situation: while the patient is resting, we expect the pain to subside, but instead it becomes most intense; this is a common case in inflammation, but not in degenerative musculoskeletal diseases.

In the case of painful shoulder syndrome we are dealing with localized aseptic inflammation, which has no repercussions on laboratory indicators of inflammation, as opposed to inflammatory rheumatic diseases, in which the painful shoulder syndrome is part of a complex clinical picture such as in ankylosing spondylitis or rheumatoid arthritis. Also, the patient shows no symptoms of general inflammation.

u oba spola i najčešće unilateralno, naziva i humeroskapularni periartritis (grč. *peri* = oko, prema), a uzrok bolnosti jest upalno zbivanje (grč. *itis* = upala) (5). Za razliku od upalnih reumatskih bolesti, ovdje se dominantno radi o lokaliziranoj, aseptičkoj upali te posljedičnim degenerativnim promjenama koje su najčešće locirane u tetivama supraspinatusa i duge glave bicepsa, dok su upalne promjene izazvane najčešće kalcifikatima prisutne u subakromijskoj sluznoj vreći (3, 5).

Mehanički momenti – kad u anamnezi bolesnika nalazimo podatke o fizičkim naprezanjima ramenog zgloba, ponavljanim pokretima u ramenu sa stisnutom šakom uz opterećenje ili rad s rukama iznad glave – čine važnu odrednicu u etiopatogenezi bolnog ramena. Pritom je područje zgloba i okolozglobnih struktura izloženo ponavljanim svakodnevnim mikrotraumama, što može dovesti do ubrzanog nastanka degenerativnih, ožiljnih promjena na mekim tkivima oko ramenog zgloba (3, 5). Katkad u mekim tkivima, a najčešće u tetivama, nastaju i kalcifikati različitih veličina (3, 6). Često se događa da se ti kalcifikati na tetivama i u zglobnoj čahuri nađu kao slučajan nalaz pri rendgenskom snimanju (7). Dakle, nerijetko ih imaju i osobe koje nemaju karakterističnu simptomatologiju, odnosno boli u ramenu. Boli se često razviju i intenziviraju nakon nekoga napornog rada, pada na ruku ili rame, kada dođe do pomaka tih nakupina vapnenca te ih organizam doživljava kao strano tijelo pa se od njih brani burnom upalnom reakcijom (3, 5, 6). Kao i sve druge upalne reakcije, i ova postaje to burnija i izraženija (a time i bolnija) pri zagrijavanju zgloba i okolozglobnih struktura. Upravo se to događa noću, kada se tipična noćna bol javlja pri mirovanju i utopljavanju ramena izvana. Dakle, riječ je o, naoko, paradoksalnoj situaciji: kod potpunog mirovanja, kad očekujemo da se bol smiri, ona postaje najjača, što je uobičajeno za upalu, ali ne i za degenerativne muskuloskeletne bolesti.

U ovom je slučaju riječ o lokalnoj aseptičkoj upali, koja nema reperkusija na laboratorijske pokazatelje upalnih zbivanja, za razliku od upalnih reumatskih bolesti, kad je sindrom bolnog ramena dio kompleksne kliničke slike, npr., ankilozantnog spondilitisa ili reumatoidnog artritisa. Pritom se kod bolesnika ne nalaze znakovi opće upale.

Iako nam klasične radiološke pretrage ne pomažu puno pri dijagnostici, znatan je doprinos uporabe dijagnostičkog ultrazvuka, kao i magnetske rezonancije, koji imaju dobru razlučivost pa se s pomoću njih uočavaju morfološke i strukturne promjene pri zahvaćenosti mekih tkiva (7). Dijagnoza sindroma bolnog ramena postavlja se na osnovi kliničke slike dopunjene rezultatima navedenih dijagnostičkih pretraga.

Liječenje je uglavnom konzervativno, pri čemu bitnu ulogu ima i rano medikamentno liječenje, koje što pri-

Although standard radiological examinations do not significantly contribute to the diagnostic process, diagnostic ultrasound as well as magnetic resonance imaging are able to contribute greatly, due to the fact that they can produce images of great resolution in which morphological and structural changes of soft tissues are clearly visible (7). The diagnosis of painful shoulder syndrome is based on the clinical picture in addition to the results of imaging modalities.

The treatment is mainly conservative and largely dependent on early pharmacological treatment, which must be supplemented as soon as possible with various non-pharmacological treatment methods (1, 6). Surgical treatment is extremely rare and used in the most severe cases of soft tissue disorders, such as a complete tendon rupture (6). These patients, especially the ones who suffer from isolated mechanically conditioned diseases, can often develop various complications, such as relapses, which have an adverse effect on the quality of their daily life. Therefore, patient education is important. Patient education can help in prevention of relapses, making it easier to identify the disease in its early stages and start treating it in a fast and efficient way (2, 6, 8).

AIM OF THE RESEARCH

The aim of this paper is to gain insight into the possibilities of an integrated approach to the non-pharmacological treatment of painful shoulder syndrome by analyzing literature data in accordance with the principles of evidence-based medicine (EBM). The other aim of this paper is to present an overview of research data on the effectiveness of painful shoulder syndrome treatment by the use of conventional methods of physical therapy. Our goal was to come to a conclusion regarding the effectiveness and consistency in the process of rehabilitation of this disease as well as to analyze the use of modern technology in the non-pharmacological treatment of painful shoulder syndrome. This could prove useful for the institutions which still do not have access to modern technology used in physical medicine and the rehabilitation of this disease.

METHODS AND SUBJECTS

Research methods

This prospective comparative study on the effectiveness of certain forms of conventional physical therapy, conducted at the Department of Physical Medicine, Rehabilitation, and Rheumatology of the Clinical Hospital Center Split, included 157 subjects suffering from painful shoulder syndrome whose relevant data were recorded before their introduction to physical therapy and after 10 therapy sessions. Conventional passive methods of physical therapy included: therapeutic ul-

je treba dopuniti primjenom različitih metoda NFL-a (1, 6). Kirurško je liječenje iznimno rijetko, a rabi se kod najtežih posljedica rečenih bolesti mekih tkiva kao što je, npr., potpuna ruptura tetiva (6). Ovi bolesnici, poglavito kod izoliranih mehamički uvjetovanih bolesti, mogu razviti komplikacije koje imaju nepovoljne učinka na kvalitetu života. Stoga je u ovih bolesnika iznimno važna edukacija. Njome se smanjuje broj recidiva, bolest se prepoznaje u ranoj fazi, te se može pristupiti brzom i učinkovitom liječenju (2, 6, 8).

CILJ ISTRAŽIVANJA

Cilj su ovog rada uvid u mogućnosti i sjedinjeni pristup NFL-a sindromu bolnog ramena analizom literaturnih navoda, a prema načelima medicine utemeljene na dokazima (EBM). Također, željeli smo prikazati podatke istraživanja o učinku liječenja sindroma bolnog ramena konvencionalnim metodama fizikalne terapije. Time bi se mogli donijeti zaključci o njihovoj učinkovitosti, usuglasiti postupci pri rehabilitaciji bolesti, analizirati primjene modernih tehnologija u NFL-u bolnog ramena te utvrditi što bi bilo korisno za sve one ustanove koje još ne raspolažu modernim tehnologijama fizikalne medicine i rehabilitacije pri ovoj bolesti.

METODE ISTRAŽIVANJA I ISPITANICI

Metode istraživanja

Komparativno istraživanje učinka pojedinih oblika konvencionalne fizikalne terapije, koje je provedeno u Zavodu za fizikalnu medicinu i rehabilitaciju s reumatologijom Kliničkoga bolničkog centra Split, prospektivna je studija provedena na 157 ispitanika sa sindromom bolnog ramena, kod kojih su relevantni podatci bilježeni prije početka fizikalne terapije te poslije 10 terapijskih procedura. Pasivne konvencionalne metode fizikalne terapije uključivale su: terapijski ultrazvuk, sonoforezu, interferentne struje, laser te krioterapiju. Prije terapije i nakon nje mjereni su ovi parametri: opseg pokreta u bolnom ramenu i u svim ravninama te intenzitet boli. Opseg pokreta u ramenu (abdukcija ramena, antefleksija ramena, retrofleksija ramena, unutarnja i vanjska rotacija, udaljenost *vertebrae prominentis* i stiloida palčane kosti – tzv. udaljenost VP – S) mjerio se goniometrom *Universal Inclinometer UI01B*, prema načelima kliničke kineziometrije, i centimetarskom vrpcom (tablica 1.) (8). Intenzitet boli mjerio se horizontalnom vizualno-analognom skalom (VAS) prema vrijednostima koje su upisivali bolesnici (4).

Svi podatci statistički su analizirani, pri čemu su upotrijebljeni neparametrijski testovi (χ^2-test i Mann-Whitneyjev U-test), uz prag prihvaćanja hipoteze $p < 0,05$.

Nakon toga smo, prema načelima medicine utemeljene na dokazima (EBM), pretražili dostupnu literatu-

Table 1. Range of motion measurement in the shoulder with a description of the patient's position and placement of the goniometer
Tablica 1. Mjerenje opsega pokreta u ramenu s opisom položaja bolesnika i postavljanja goniometra

Motion measured / Pokret koji se mjeri	Patient's position / Položaj bolesnika	Placement of the goniometer / Poostavljanje goniometra
Upper arm anteflexion / Antefleksija nadlaktice	Supine lying position, upper arm in adduction leaning to the thorax / Ležeći supinirani položaj, nadlaktica aducirana uz toraks	Lateral aspect of the upper arm (above the elbow) / Lateralna strana nadlaktice iznad lakta
Upper arm retroflexion / Retrofleksija nadlaktice	Prone lying position, upper arm in adduction leaning to the thorax, shoulder fixed / Ležeći pronirani položaj, nadlaktica aducirana uz toraks, a rame fiksirano	Lateral aspect of the upper arm (above the elbow) / Lateralna strana nadlaktice iznad lakta
Upper arm abduction / Abdukcija nadlaktice	Sitting position with upper arm in adduction / Sjedeći položaj, aducirane nadlaktice	Anterior aspect of the upper arm (above the elbow) / Prednja strana nadlaktice iznad lakta
Horizontal abduction of the upper arm / Horizontalna abdukcija nadlaktice	Prone position, upper arm abduction at 90 degrees, lower arm flexion across the surface, shoulder fixed / Pronirani položaj, nadlaktica u abdukciji od 90°, podlaktica flektirana preko podloge, rame fiksirano	Anterior or posterior aspect of the upper arm (above the elbow) / Prednja ili stražnja strana nadlaktice iznad lakta
Horizontal adduction of the upper arm / Horizontalna adukcija nadlaktice	Supine position, upper arm abduction at 90 degrees, lower arm flexion at 90 degrees / Supinirani položaj, nadlaktica u abdukciji od 90°, podlaktica u fleksiji od 90°	Anterior or posterior aspect of the upper arm (above the elbow) / Prednja ili stražnja strana nadlaktice iznad lakta
Internal upper arm rotation / Unutarnja rotacija nadlaktice	Supine position, upper arm abduction at 90 degrees, lower arm flexion at 90 degrees in the medial position, shoulder fixed / Supinirani položaj, nadlaktica u abdukciji od 90°, podlaktica flektirana pod 90° u srednjem položaju, a rame fiksirano	Dorsal aspect of the lower arm above the radiocarpal joint / Dorzalna strana podlaktice iznad radiokarpalnog zgloba
External upper arm rotation / Vanjska rotacija nadlaktice	Same as with internal rotation / Jednako kao pri unutarnjoj rotaciji	Same as with external rotation / Jednako kao pri unutarnjoj rotaciji

trasound, sonophoresis, interferential current therapy, laser therapy, and cryotherapy. The following parameters were measured before and after the treatment: range of motion in the painful shoulder in all directions and intensity of pain. The range of motion in the shoulder (shoulder abduction, shoulder anteflexion and retroflexion, internal and external rotation, and distance between vertebrae prominens and styloid radius (VP-S distance)) was measured with a universal inclinometer UI01B goniometer, in accordance with the principles of clinical kinesiometrics and with a centimeter scale measuring tape (Table 1) (8). Pain intensity was measured with a horizontal visual analogue scale (VAS), and the value was entered by the patient (4).

All data were statistically analyzed using nonparametric tests, χ^2 test, and Mann–Whitney U test, with an acceptance threshold hypothesis of $p < 0.05$.

Next, we researched the Cochrane Review Database, which is accessible via the Cochrane Collaboration official website, by analyzing the available medical literature and taking into account the standard principles of evidence-based medicine (EBM). We also used data from the PEDro database (Physiotherapy Evidence Database) with the purpose of comparing our research results with the results mentioned in the literature. Thus, we used the available data in order to come to a conclusion on the importance of modern technology

ru. Podatke smo tražili u Cochraneovoj bazi podataka, koja je slobodno dostupna na internetskim stranicama organizacije *The Cochrane Collaboration*, i u Fizioterapijskoj bazi podataka (engl. *Physiotherapy Evidence Database* – PEDro), a radi usporedbe rezultata dobivenih našim istraživanjem s rezultatima u literaturnim navodima. Pritom smo iz dostupnih podataka zaključivali i o važnosti modernih tehnologija u postupnicima liječenja sindroma bolnog ramena, istražili njihove prednosti u odnosu prema konvencionalnoj terapiji, kao i sličnosti u učincima tih dvaju pristupa NFL-a sindromu bolnog ramena.

Ispitanici

Ispitanici su bili konsekutivni bolesnici s klinički potvrđenom dijagnozom sindroma bolnog ramena postavljenom od specijalista fizijatra ili specijalista fizijatra / supspecijalista reumatologa. U istraživanje je uključeno 157 bolesnika, čije su tegobe trajale od 20 do 40 dana i bile karakterizirane znatno ograničenim kretnjama u ramenom zglobu uz vrlo naglašenu bolnu komponentu. Fizikalna se terapija provodila u ambulantnim uvjetima 10 puta (2 tjedna, bez terapije tijekom subote i nedjelje). Na tablici 2. prikazani su demografski podatci (broj, dob i spol) ispitanika. Raspon dobi bio je od 26 do 70 godina, a ujednačen je u svim

in the treatment protocols for painful shoulder syndrome. We also researched the benefits of the use of modern technology in comparison with conventional methods of treatment, as well as the similarities in the effectiveness of these two non-pharmacological approaches to the treatment of painful shoulder syndrome.

Subjects

This was a consecutive case series study which included all eligible patients with a clinical diagnosis of painful shoulder syndrome who were diagnosed by a specialist in physical medicine and rehabilitation or by a specialist in physical medicine with a subspecialization in rheumatology. The research included 157 patients with a disease duration of 20 to 40 days, with severely limited movement in the shoulder joint accompanied by a feeling of intense pain. Physical therapy was conducted in the clinical center in the course of 10 sessions (in a period of 2 weeks, with no therapy during weekends). Table 2 contains the patients' demographic data (number, age, and sex). The study included patients aged 26–70, divided into age-based therapy groups of individuals of similar ages.

The patients who underwent the therapeutic ultrasound procedure (using the Cosmogamma Ultrasonic Therapy M 32 device) were treated with a mobile application technique with an intensity of 1.0 W/cm^2. During this procedure the conductive agent used was an ultrasound gel which does not interfere with the accuracy of the test and causes no reactions on the skin. Each therapeutic procedure lasted approximately 5 minutes.

Voltaren Gel (Diclofenac Sodium Gel) was used as a conductive agent in the procedure of diclofenac sonophoresis and was applied to the painful shoulder of each patient who underwent the therapeutic ultrasound procedure (using the Cosmogamma Ultrasonic Therapy M 32 device). This was done by a mobile application technique with an intensity of 1.0 W/cm2, and each application procedure lasted approximately 5 minutes.

Interferential current therapy (IFC) was administered in ten 15-minute sessions by using a 4-pole application with a static interference generated within the Cosmogamma IFA-3 device, with an interferential frequency corresponding to the difference of both AC sinusoidal waveforms in the 1–100 Hz range.

The patients in the group treated with low-level laser therapy underwent 10 therapeutic procedures (in a period of 10 days) and each therapeutic session, during which they were exposed to a continuous-wave laser beam emitted from the Cosmogamma Sistema 9000 device (Laser twin He+Ne/IR), lasted for 10 minutes.

Table 2. Characteristics of the study groups
Tablica 2. Obilježja ispitivanih skupina

Procedure / Procedura	N	Men / Muškarci	Women / Žene	Age (years) / Dob (godine)
US / UZV	33	17	16	47,10
SONOPHORESIS SONOFOREZA	31	17	14	48,10
ICT / IFS	31	15	16	45,70
LASER	30	16	14	43,60
CRYO / KRIO	32	14	18	49,30
Total / Ukupno	157	79	78	46,76

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini

terapijskim skupinama, odnosno prosječna se dob nije znatno razlikovala.

Bolesnici u kojih je primijenjen terapijski ultrazvuk (uređaj *Cosmogamma Ultrasonic Therapy M 32*) tretirani su mobilnom tehnikom aplikacije, intenzitetom od 1,0 W/cm^2. Pritom se rabilo indiferentno kontaktno sredstvo – komercijalno dostupan gel. Svaka terapijska procedura trajala je po 5 minuta.

Svakom od bolesnika liječenih ultrazvukom (uređaj *Cosmogamma Ultrasonic Therapy M 32*) s diklofenakom kao kontaktnim sredstvom (sonoforeza) na bolno je rame apliciran gel Voltaren (diklofenak) kao kontaktno sredstvo. Bolesnici su tretirani mobilnom tehnikom aplikacije, intenziteta od 1,0 W/cm^2, uz trajanje aplikacije od 5 minuta.

Interferentne struje (IFS) primijenjene su po 15 minuta četveropolnom aplikacijom s njihovom statičkom interferencijom na uređaju *Cosmogamma IFA-3*, interferentnom frekvencijom koja odgovara razlici obiju sinusoidnih izmjeničnih strujnih komponenta od 1 do 100 Hz.

Bolesnici u skupini liječenoj laserom niskog intenziteta (LASER) tretirani su 10 puta (dana) po 10 minuta kontinuiranom laserskom zrakom uređaja *Cosmogamma Sistema 9000* (*Laser Twin He-Ne/IR*), valne duljine 623,8 nm i izlazne snage od 5 mW.

U skupini bolesnika tretiranih kriomasažom masaža se provodila kružnim pokretima ledom nastalim od zaleđenja 0,2 litre vode, a procedura je trajala 6 minuta.

Tijekom navedenih 10 dana primjene fizikalne terapije nitko od ispitanika nije uzimao nikakvu medikamentnu terapiju protiv boli i upale (analgetici, nesteroidni antireumatici), a nitko nije istodobno provodio ni kinezioterapiju. Podatci su prikupljani s pomoću

The wavelength of the laser beam was 623.8 nm, and the rated output was 5mW.

The group of patients treated by cryomassage underwent massage performed by softly rubbing ice (obtained by freezing 0.2 liters of water) onto the painful area using circular motions during a 6-minute session.

Throughout the whole physical therapy period in the duration of 10 days, none of the subjects were taking any pain-relieving and anti-inflammatory medications (analgesics, non-steroidal antirheumatics) and none of them were simultaneously exposed to kinesiotherapy. The data were collected through a series of carefully structured questionnaires. The subjects were given an informed consent form to read prior to the start of the procedure and they agreed to take part in this study by signing it.

RESULTS

Research results

By conducting a prospective study whose aim was to objectivize the effectiveness of conventional methods of physical therapy commonly used for the treatment of painful shoulder syndrome (therapeutic ultrasound, diclofenac sonophoresis, laser therapy, interferential current therapy, cryotherapy), we found a general improvement in the measured parameters of functional capacity and pain intensity.

The research yielded the following results, displayed in Tables 3–9:

- statistically significant improvement of shoulder abduction in all groups, excluding those treated by cryotherapy (Table 3);
- statistically significant improvement of shoulder anteflexion in all groups, with the most notable results in the groups treated by interferential current therapy (Table 4);
- statistically significant improvement of shoulder retroflexion in all groups, with the most notable results in the groups treated by interferential current therapy (Table 5);
- statistically significant improvement of internal shoulder rotation in all groups (Table 6);
- statistically significant improvement of external shoulder rotation in all groups, excluding those that underwent laser therapy, and with the most notable effect in the group treated by interferential current therapy (Table 7);
- statistically significant reduction of the VP-S distance in all groups, excluding the one that underwent laser therapy (Table 8);
- statistically significant reduction of pain intensity (measured with a visual analog scale (VAS)) in all groups, with the most notable results in patients who underwent diclofenac sonophoresis and laser therapy (Table 9).

Table 3. Changes in the shoulder range of motion: shoulder abduction (°)

Tablica 3. Promjene pokretljivosti ramena: abdukcija ramena (°)

Procedure / Procedura	N	0	10	P
US / UZV	33	79,03 (± 14,8)	93,22 (± 10,8)	< 0,05
SONOPHORESIS SONOFOREZA	31	81,40 (± 16,1)	94,20 (± 14,6)	< 0,05
ICT / IFS	31	75,8 (± 17,0)	87,9 (± 8,9)	< 0,05
LASER	30	69,5 (± 14,1)	80,83 (± 12,9)	< 0,05
CRYO / KRIO	32	77,09 (± 16,1)	88,54 (± 18,1)	> 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
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LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
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posebno osmišljenih upitnika, a ispitanici su prethodno pročitali informacije i potpisali suglasnost za sudjelovanje u ispitivanju.

REZULTATI

Rezultati istraživanja

Provodeći prospektivno istraživanje radi objektiviziranja učinaka konvencionalnih oblika fizikalne terapije, koji se u našoj ustanovi najčešće primjenjuju za liječenje bolesnika sa sindromom bolnog ramena (terapijski ultrazvuk, sonoforeza diklofenakom, laser, interferentne struje, krioterapija), općenito smo našli poboljšanje u mjerenim parametrima funkcionalnog kapaciteta i stupnja boli.

Rezultati koje smo zabilježili, kako slijedi, prikazani su na tablicama 3. – 9.:

- statistički značajno povećanje abdukcije ramena u svim skupinama bolesnika, osim u onih koji su liječeni krioterapijom (tablica 3.)
- statistički značajno povećanje antefleksije ramena u svim skupinama bolesnika, a najizraženije u onih što su liječeni interferentnim strujama (tablica 4.)
- statistički značajno povećanje retrofleksije ramena u svim skupinama bolesnika, a najizraženije u onih koji su liječeni interferentnim strujama (tablica 5.)
- statistički značajno povećanje unutarnje rotacije ramena u svim skupinama bolesnika (tablica 6.)

Table 4. Changes in the shoulder range of motion: shoulder anteflexion (°)

Tablica 4. Promjene pokretljivosti ramena: antefleksija ramena (°)

Procedure / Procedura	N	0	10	P
US / UZV	33	129,19 (± 21,4)	145,80 (± 18,2)	< 0,05
SONOPHORESIS SONOFOREZA	31	128,14 (± 19,8)	146,91 (± 20,0)	< 0,05
ICT / IFS	31	127,30 (± 36,8)	165,9 (± 27,3)	< 0,001
LASER	30	130,62 (± 21,2)	143,12 (± 25,8)	< 0,05
CRYO / KRIO	32	134,67 (± 25,0)	153,70 (± 18,2)	< 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
0 = value before the treatment / vrijednost prije liječenja
10 = value after 10 therapeutic procedures / vrijednost nakon 10 terapijskih procedura
P = statistical significance level / statistička razina značajnosti

Table 5. Changes in the shoulder range of motion: shoulder retroflexion (°)

Tablica 5. Promjene pokretljivosti ramena: retrofleksija ramena (°)

Procedure / Procedura	N	0	10	P
US / UZV	33	38,26 (± 13,2)	47,74 (± 10,1)	< 0,05
SONOPHORESIS SONOFOREZA	31	37,91 (± 8,8)	58,32 (± 9,1)	< 0,05
ICT / IFS	31	27,11 (± 12,9)	42,7 (± 8,4)	< 0,01
LASER	30	38,12 (± 11,7)	52,08 (± 12,8)	< 0,05
CRYO / KRIO	32	45,64 (± 14,1)	54,83 (± 13,8)	< 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
0 = value before the treatment / vrijednost prije liječenja
10 = value after 10 therapeutic procedures / vrijednost nakon 10 terapijskih procedura
P = statistical significance level / statistička razina značajnosti

Table 6. Changes in the shoulder range of motion: internal shoulder rotation (°)

Tablica 6. Promjene pokretljivosti ramena: unutarnja rotacija ramena (°)

Procedure / Procedura	N	0	10	P
US / UZV	33	50,03 (± 9,8)	65,32 (± 12,3)	< 0,05
SONOPHORESIS SONOFOREZA	31	51,08 (± 10,9)	66,00 (± 10,0)	< 0,05
ICT / IFS	31	36,20 (± 7,6)	48,80 (± 10,6)	< 0,05
LASER	30	40,45 (± 12,9)	65,83 (± 14,2)	< 0,05
CRYO / KRIO	32	48,54 (± 8,8)	63,04 (± 12,4)	< 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
0 = value before the treatment / vrijednost prije liječenja
10 = value after 10 therapeutic procedures / vrijednost nakon 10 terapijskih procedura
P = statistical significance level / statistička razina značajnosti

Table 7. Changes in the shoulder range of motion: external shoulder rotation (°)

Tablica 7. Promjene pokretljivosti ramena: vanjska rotacija ramena (°)

Procedure / Procedura	N	0	10	P
US / UZV	33	51,67 (± 14,2)	62,83 (± 10,4)	< 0,05
SONOPHORESIS SONOFOREZA	31	49,47 (± 15,8)	61,82 (± 11,9)	< 0,05
ICT / IFS	31	35,00 (± 12,7)	67,92 (± 13,5)	< 0,001
LASER	30	57,61 (± 20,1)	63,04 (± 9,2)	> 0,05
CRYO / KRIO	32	55,67 (± 17,2)	67,74 (± 10,4)	< 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
0 = value before the treatment / vrijednost prije liječenja
10 = value after 10 therapeutic procedures / vrijednost nakon 10 terapijskih procedura
P = statistical significance level / statistička razina značajnosti

No adverse effects of physical therapy occurred during the research; no treatment withdrawals were recorded.

Overview of literature data

The data found in the Cochrane library and PEDro databases were important for enabling a comparison with our research results. The effectiveness of specific

– statistički značajno povećanje vanjske rotacije ramena u svim skupinama bolesnika, osim u onih što su liječeni laserom, a najizraženiji učinak postignut je u skupini liječenih interferentnim strujama (tablica 7.)
– statistički značajno kraća udaljenost VP – S u svim skupinama bolesnika, osim u onih liječenih laserom (tablica 8.)

Table 8. Changes in the shoulder range of motion: VP-S distance (cm)
Tablica 8. Promjene pokretljivosti ramena: udaljenost VP – S (cm)

Procedure / Procedura	N	0	10	P
US / UZV	33	40,27 (± 8,5)	35,38 (± 7,1)	< 0,05
SONOPHORESIS SONOFOREZA	31	41,11 (± 4,9)	37,01 (± 8,2)	< 0,05
ICT / IFS	31	50,70 (± 9,8)	40,2 (± 8,1)	< 0,05
LASER	30	43,04 (± 10,2)	37,87 (± 9,0)	> 0,05
CRYO / KRIO	32	38,03 (± 4,2)	34,96 (± 3,9)	< 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
0 = value before the treatment / vrijednost prije liječenja
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P = statistical significance level / statistička razina značajnosti

Table 9. Change in intensity of pain (VAS)
Tablica 9. Promjena intenziteta bola (VAS)

Procedure / Procedura	N	0	10	P
US / UZV	33	8,7	4,6	< 0,05
SONOPHORESIS SONOFOREZA	31	8,8	3,4	< 0,001
ICT / IFS	31	8,7	4,7	< 0,05
LASER	30	8,9	3,2	< 0,001
CRYO / KRIO	32	8,8	4,5	< 0,05

Legend / Legenda:
US / UZV = therapeutic ultrasound / terapijski ultrazvuk
SONOPHORESIS / SONOFOREZA = diclofenac sonophoresis / sonoforeza diklofenakom
ICT / IFS = interferential current therapy / interferentne struje
LASER = low-level laser therapy / laser niskog intenziteta
CRYO / KRIO = cryotherapy / krioterapija
N = number of patients in the group / broj bolesnika u skupini
0 = value before the treatment / vrijednost prije liječenja
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exercises on the short-term treatment effect and recovery of the rotator cuff with long-term improvement of the shoulder function were determined in 26 controlled studies of mediocre methodological quality (2, 9, 10). Their results were expected and they were mentioned in the introductory part of this paper, but they were not considered in comparison with our research due to the fact that our research was focused on different methods of conventional physical therapy. In the treatment of supraspinatus muscle tendinitis, the results of laser therapy were not significantly better than the placebo treatment results, but they were significantly superior to the placebo results in the treatment of adhesive capsulitis of the shoulder (10). In the treatment of calcific tendinitis, pulsed electromagnetic field therapy (PEMFT) and ultrasound therapy had a far better analgesic effect than placebo. In the treatment of painful shoulder syndrome (different diagnoses) and adhesive capsulitis, therapeutic ultrasound as monotherapy had no significant analgesic effect. Moreover, no significant analgesic effect was obtained by the use of combination therapy consisting of ultrasound therapy and exercises compared to ultrasound monotherapy (10).

Regarding the effect of extracorporeal shock wave therapy (ESWT) on rotator cuff changes in painful shoulder syndrome with or without calcific deposits, in the overview of the Cochrane library database, which included 32 research studies (2281 subjects) conducted on patients with calcific deposits, 5 studies conducted on patients without calcific deposits, and 2 studies conducted on patients with and without calcific deposits,

– statistički značajno smanjenje intenziteta boli (mjereno VAS-om) u svim skupinama, a najviše kod bolesnika liječenih sonoforezom (diklofenak) i laserom (tablica 9.).

Tijekom istraživanja nisu prijavljeni nijedan neželjeni učinak provedene fizikalne terapije niti odustajanje od započetog tretmana.

Rezultati pretraživanja literature

Literaturni podatci iz Cochraneove baze i Fizioterapijske baze podataka (PEDro) bili su važni za usporedbu s našim istraživanjem. Iz 26 kontroliranih studija srednje ocijenjene metodološke kvalitete utvrđena je učinkovitost specifičnih vježba na kratkotrajan učinak liječenja i oporavak rotatorne manšete, uz dugotrajno poboljšanje funkcije ramena (2, 9, 10). Takvi su podatci bili i očekivani te su navedeni u uvodnom dijelu, ali nisu razmatrani u usporedbi s našim istraživanjem, jer se ono odnosilo na različite oblike konvencionalne fizikalne terapije. Terapija laserom nije bila bolja od placeba pri liječenju tendinitisa supraspinatusa, dok je kod adhezivnog kapsulitisa bila znatno bolja od placeba (10). Terapija pulsirajućim elektromagnetskim poljem ili ultrazvukom imala je bitno bolji analgetski učinak od placeba pri liječenju kalcificirajućeg tendinitisa (10). Terapijski ultrazvuk nije pokazao znatniji analgetski učinak ni kod bolnog ramena (različite dijagnoze) ni kod adhezivnog kapsulitisa, ni pri samostalnoj primjeni niti u kombinaciji ultrazvuka i vježba, a u odnosu prema samo ultrazvuku (10).

Sustavnim pregledom literature o utjecaju udarnog vala (engl. *Extracorporeal shockwave therapy* – ESWT)

the effects of ESWT (≥0.2 – 0.4 mJ/mm^2) were researched. ESWT was compared to the placebo, a small dose of the ESWT, a local glucocorticoid infiltration and the application of the transcutaneous electrical nerve stimulation (TENS) method (11). The results showed that the majority of patients experienced a reduction of pain intensity (by 50% and more) and an increase of functional capacity when compared to the control subjects, with adverse effects of the therapy recorded in 3–19% of cases, regarding the dose (11). An improved therapeutic effect was related to the application of larger therapeutic doses of ESWT. Wu et al noted that the application of larger doses of the ESWT had a significantly better long-term effect on the treatment of calcific tendinitis of the shoulder (12). The use of the ESWT was also proven to be very effective in combination therapies, for instance, in addition to electromagnetic transduction therapy (EMTT) (13).

In the following systematic overview of the Cochrane library database, the effect of electrotherapy on rotator cuff diseases was researched by investigating its effect on the reduction of pain and the increase of functional capacity in painful shoulder syndrome as well as by focusing on the effect of therapeutic ultrasound and low-level laser therapy (LLLT). This study included the results of 47 research studies conducted on 2388 subjects. The majority of patients in those research studies had no calcific deposits in the rotator cuff (14). Even though the quality of results in this study was evaluated as low, it was shown that ultrasound has a short-term beneficial effect in the treatment of symptoms which appear in patients who suffer from painful shoulder syndrome, and especially in those who have calcific deposits. LLLT proved to be more effective than placebo, as opposed to pulsed electromagnetic field therapy (PEMFT). TENS proved to be superior to placebo, and it was recommended that future similar research studies should be designed to obtain more reliable results, even though noted positive effect of LLLT and TENS in the reduction of pain intensity and the increase of functional capacities was undeniable. It must be noted that no side-effects were reported and that the issue of more frequent use of combination therapy as opposed to monotherapy with this method of non-pharmacological treatment was presented.

Individual, smaller research studies of high-intensity laser therapy (HILT) conducted on a smaller number of subjects (42 patients) have proven this therapy to be effective – even after a short-term session resulted in undeniable, such as a reduction of pain intensity and functional disability of patients suffering from subacromial impingement syndrome (SAIS) (15). Moreover, in some cases it was proven that HILT used in

kod sindroma bolnog ramena na promjene rotatorne manšete s kalcifikatom u njoj ili bez njega, u Cochraneovoj su bazi nađena 32 istraživanja na 2281 bolesniku s kalcifikatom, njih 5 na bolesnicima bez kalcifikata i 2 istraživanja na miješanoj populaciji bolesnika s kalcifikatom i bez njega. Tim su istraživanjima praćeni učinci ESWT-a (0,2 – 0,4 mJ/mm^2 pa naviše) u odnosu prema placebnoj skupini, prema niskoj dozi jednake terapije, zatim u odnosu prema infiltraciji glukokortikoida te s obzirom na aplikaciju transkutane električne živčane stimulacije (engl. *Transcutaneous Electrical Nerve Stimulation* – TENS) (11). Rezultati su pokazali da je u najvećeg broja ispitanika došlo do znatnog smanjenja boli (50% i više) te povećanja funkcionalnih sposobnosti u odnosu prema kontrolnim skupinama. Pritom je neželjene učinke terapije prijavilo 3 – 19% bolesnika, s tim da je problematizirana doza udarnog vala kao standarda terapije (11). Bolji terapijski učinak veže se uz primjenu viših terapijskih doza ESWT-a. Tako prema istraživanju Wua i suradnika, znatno bolji i dugotrajniji učinak na kalcificirajući tendinitis ramena ima primjena viših terapijskih doza (12), a ESWT se pokazao vrlo učinkovit i u kombiniranim terapijama, npr., uz elektromagnetsku transdukcijsku terapiju (13).

Sljedećim sustavnim pregledom literature iz Cochraneove baze pratio se učinak elektroterapije na bolesti rotatorne manšete s obzirom na smanjenje boli i povećanje funkcionalnih mogućnosti kod sindroma bolnog ramena, a s naglaskom na učinke terapijskog ultrazvuka, lasera male izlazne snage (LLLT), TENS-a i pulsirajućega magnetskog polja. Obuhvaćeni su rezultati 47 istraživanja, provedena na 2388 bolesnika, od kojih najveći broj nije imao kalcifikate u rotatornoj manšeti (14). Iako je kvaliteta dokaza u toj studiji ocijenjena slabom, pokazalo se da ultrazvuk kratkotrajno učinkovito djeluje na simptome u bolesnika s bolnim ramenom, osobito kod onih koji imaju kalcifikate. LLLT je bio učinkovitiji od placeba, za razliku od pulsirajućega magnetskog polja. TENS se pokazao boljim od placeba, pri čemu je preporučeno da buduća slična istraživanja budu koncipirana tako da postignu znatno veću snagu dokaza. Ipak, pozitivan učinak tih dviju metoda na smanjenje boli i povećanje funkcionalnih mogućnosti neprijeporan je. Valja napomenuti da nuspojave nisu prijavljene, a postavljeno je pitanje češće primjene kombinirane terapije ovim načinom NFL-a u odnosu prema monoterapiji.

Pojedinačna istraživanja o utjecaju lasera visokog intenziteta (HILT), provedena na manjem broju ispitanika (42 bolesnika), pokazala su znatnu učinkovitost ove terapije: već je kratkotrajan tretman bitno utjecao na smanjenje boli i onesposobljenosti bolesnika sa sindromom subakromijskog sraza (15), a u nekih se bolesnika pokazalo da dobrim rezultatima liječenja HILT-om pridonosi i kombinacija s drugim terapijskim opcija-

combination with other non-pharmacological treatment methods, such as the kinesio taping method, was even more efficient.

We had a short-term option of working on borrowed devices (manufactured by the **kinesis company BLT**) and in that time we were able to experience the effects of extracorporeal shock wave therapy (ESWT) and high-intensity laser therapy (HILT) at first hand. We came to the conclusion that both of these methods are efficient.

In our department the short-term experimental use of ESWT and HILT resulted in a significant reduction of pain intensity in patients suffering from painful shoulder syndrome. More precisely, a total of 16 patients underwent extracorporeal shock wave therapy (ESWT) (VAS difference after application was $p < 0.01$) (18) and a total of 20 patients underwent high-intensity laser therapy (HILT) (VAS difference after application was $p < 0.0001$) (19). The objective disadvantage of these research studies was the small number of subjects. Nonetheless, the results are in line with the aforementioned studies, which were also conducted on small cohorts of subjects.

DISCUSSION

Due to the fact that our institution, like numerous other institutions in Croatia, does not have access to modern technology in the field of physical medicine and rehabilitation, we have tried to present an overview of our research results in order to objectivize the actual treatment options for patients suffering from painful shoulder syndrome through the use of conventional methods of physical therapy and rehabilitation which yielded positive results. In addition to that, by researching databases and trying to draw conclusions on the basis of EBM, we obtained results which point to the fact that the treatment protocols used in such patients should be based on non-pharmacological treatment. It has been recorded, both in large randomized controlled trials as well as in our research, that these treatment methods have very few reported adverse effects. Through the use of modern technology, it is possible to get more impressive treatment results in comparison with conventional therapy methods, and ESWT and HILT were highlighted as the most efficient treatment methods in that regard (11–13). It should be noted that, according to large research studies (10) and data from the literature, medical exercises generally produce the best treatment results (1, 2, 20). However, it can be said that this may be quite controversial when it comes to drawing conclusions, because the type of exercises, their intensity, frequency of exercise cycles, modification according to various age groups, and other elements are rarely explicitly stated, which makes it more difficult to draw proper conclusions about their

ma NFL-a, npr., s kineziološkim vrpcama (engl. *Kinesio Taping*) (16, 17).

Kratkotrajan rad u našem Zavodu na posuđenim uređajima (proizvođača BTL) omogućio nam je stjecanje osobnih iskustava o učinku monoterapije udarnim valom (ESWT) i laserom visokog intenziteta (HILT) te pokazao da su obje ove metode učinkovite. Naime, kod bolesnika sa sindromom bolnog ramena postignuta je znatna redukcija boli, i to s pomoću ESWT-a kod 16 bolesnika (razlika na VAS-u poslije aplikacije $p < 0,01$) (18) te kod 20 bolesnika liječenih HILT-om (razlika na VAS-u poslije aplikacije $p < 0,0001$) (19). Objektivni nedostatak ovih istraživanja bio je malen broj ispitanika, ali se rezultati uklapaju u prije navedene referencije koje, međutim, također nisu imale velike kohorte ispitanika.

RASPRAVA

U našoj se ustanovi, kao ni u brojnim drugim ustanovama u Hrvatskoj, zasad ne mogu rabiti moderne tehnologije iz područja fizikalne medicine i rehabilitacije. Stoga smo, prikazujući rezultate svojeg istraživanja, pokušali objektivizirati stvarne mogućnosti liječenja bolesnika sa sindromom bolnog ramena primjenom konvencionalnih metoda fizikalne medicine i rehabilitacije te smo našli pozitivne rezultate. Osim toga, pretraživanjem baza podataka i izvođenjem zaključaka na temelju EBM-a našli smo dokaze da kod tih bolesnika u protokolima liječenja treba primjenjivati NFL. Zabilježeno je da ta metoda liječenja ima vrlo malo prijavljenih neželjenih učinaka i u velikim kontroliranim randomiziranim studijama i u našem istraživanju. Moderne tehnologije pokazuju impresivnije rezultate liječenja u odnosu prema konvencionalnoj terapiji pa su ESWT i HILT istaknuti kao najkvalitetnije metode (11 – 13). Potrebno je naglasiti da u velikim studijama (10), a i prema stručnoj literaturi, najbolji učinak pri liječenju imaju medicinske vježbe (1, 2, 20). Međutim, tu se uvijek nađemo na „skliskom terenu“ pri izvođenju zaključaka, jer se rijetko gdje izrijekom navodi vrsta vježba, njihov intenzitet, učestalost vježbovnih ciklusa, prilagodba dobnim skupinama i dr. pa nam to znatno otežava izvođenje pravilnih zaključaka o njihovoj učinkovitosti i međusobnoj usporedivosti. Upravo zbog toga u svojem smo se radu usredotočili na druge oblike NFL-a, pokušavajući iskoristiti bolju klasificiranost rezultata koji su međusobno lakše usporedivi. Činjenica jest da ni takvih studija nema previše pa velik broj nađenih istraživanja, navedenih na početku Cochraneovih sustavnih pregleda, na kraju otpadne zbog neujednačenosti i neusporedivosti podataka, kao što je to i inače slučaj kod radova koji su evaluirali NFL. Svakako treba istaknuti još jedan problem u vezi s modernim tehnologijama: zasad još nema dovoljno podataka za sve tehnološki

effectiveness and comparability. Due to this fact, in this paper we have focused our attention on other methods of non-pharmacological treatment by trying to use a better classification of results to make them more comparable. It is a well-known fact that there is a small number of such studies; thus the majority of research studies referred to at the beginning of the Cochrane systematic reviews were eventually dropped due to inconsistencies and incomparability of data, as was the case with most papers which were focused on the evaluation of non-pharmacological treatment methods. It is also important to note another problem regarding modern technology, namely the fact that there is a serious lack of data related to all technologically advanced treatment modalities (such as radiofrequency (RF) or super inductive systems (SIS)), which are only mentioned in individual studies with a relatively small number of subjects (21).

Conventional methods of physical therapy are still widely used, which is extremely important for us due to the fact that the majority of our public health facilities still lack experience in the use of modern and more expensive technology or do not have access to it. These conventional modalities, whose effects were evaluated by EBM methods, proved to be efficient and harmless (14–16). The results of our research also corroborate this conclusion: the evaluated methods in our research proved to be effective as well as harmless. It should also be stated that the most effective method related to the increase of functional capacity of the painful shoulder proved to be interferential current therapy, because its application had the statistically most significant effect on the increase of anteflexion and retroflexion as well as external rotation of the painful shoulder. This comes as no surprise when we consider the action mechanism of these medium-frequency (Nemec) currents, which are generated by two sinusoidal alternating currents that overlap in intensity, phase, and frequency, and whose interference occurs deep within the tissue; thus they have better depth efficiency than other methods.

In accordance with the common and expected analgesic effects of various physical therapy methods (22), the best analgesic effects were noted in the use of sonophoresis, due to the direct activity of its pharmacologically active substance (diclofenac), which has analgesic as well as anti-inflammatory properties, as well as with the use of low-level laser therapy.

In accordance with the aforementioned, our research has shown that our results are in line with those published in the Cochrane systematic review (14, 22). Therefore, conventional therapy methods can be regarded effective in the treatment of painful shoulder syndrome in environments without access to modern technology such as ESWT and HILT.

napredne modalitete liječenja (npr., radiofrekvencija, superinduktivni sustavi) pa nailazimo tek na pojedinačne studije s relativno malenim brojem ispitanika (21).

Konvencionalne metode fizikalne terapije i nadalje su sveprisutne, a za nas je to osobito važno jer u najvećem broju državnih institucija još nemamo previše iskustava ni mogućnosti uporabe modernih i skupljih tehnologija. Ti konvencionalni modaliteti, čiji su učinci evaluirani metodama EBM-a, pokazali su se učinkovitima i neštetnima (14 – 16). I rezultati našeg istraživanja podupiru takav zaključak, odnosno evaluirane metode bile su na kraju i učinkovite i neštetne. Možda bi trebalo izdvojiti činjenicu da su se kao najučinkovitija metoda, s obzirom na povećanje funkcionalnog kapaciteta bolnog ramena, pokazale interferentne struje, jer je njihova primjena imala statistički najznačajniji učinak na povećanje i antefleksije i retrofleksije, kao i vanjske rotacije bolnog ramena, To ne iznenađuje kada znamo mehanizam djelovanja tih srednje frekventnih struja: one nastaju iz dviju sinusoidnih izmjeničnih struja koje se preklapaju u intenzitetu, fazi i frekvenciji, a interferencija se događa u dubinskim tkivima pa te tzv. Nemecove struje imaju jače dubinsko djelovanje od ostalih upotrijebljenih metoda.

Sukladno uobičajenim i očekivanim analgetskim učincima različitih oblika fizikalne terapije (22) najbolje analgetsko djelovanje postigle su sonoforeza, zbog njezina izravnog djelovanja farmakološki aktivne supstancije koja ima i analgetsko i protuupalno djelovanje (diklofenak), te laser niskog intenziteta.

Dakle, naše istraživanje daje nam pravo da kažemo kako su naši rezultati u skladu s onima objavljenima u Cochraneovu sustavnom pregledu (14, 22). Stoga konvencionalnu terapiju i nadalje možemo pozicionirati kao učinkovitu za liječenje sindroma bolnog ramena u situacijama kada nemamo na raspolaganju moderne tehnologije poput ESWT-a i HILT-a.

ZAKLJUČAK

Svojim istraživanjem na uzorku bolesnika sa sindromom bolnog ramena potvrdili smo pozitivne učinke NFL-a primjenom konvencionalnih metoda fizikalne medicine u tih bolesnika pa ih treba ostaviti u protokolima liječenja ove izvanzglobne reumatske bolesti. Pritom valja znati da moderne tehnologije nude brže i učinkovitije rezultate, a osobito u sinergiji s medicinskim vježbama bolesnicima omogućavaju brzu i znatnu redukciju boli te povećanje funkcionalnog kapaciteta ramena. Međutim, u slučajevima kad još nije dostupna primjena modernih tehnologija pri NFL-u bolnog ramena, učinkovitima su se pokazale i metode konvencionalne fizikalne terapije, a tomu pridonose i rezultati pretraživanja dostupne literature. Dobra

CONCLUSION

Our research, conducted on a sample of patients who suffer from painful shoulder syndrome, has confirmed the positive effects of conventional methods of physical therapy as part of non-pharmacological treatment of this disorder, and which should be incorporated in the protocols for the treatment of this extra-articular rheumatic disease. It was concluded that the use of modern technology offers faster and more efficient results, and that this technology, in addition to medical exercises, enables the patients to experience a fast and a significant reduction of pain intensity and an increase in the functional capacity of the shoulder. However, in the settings of non-pharmacological treatment of painful shoulder syndrome in which access to modern technology is still not widely available, the methods of conventional physical therapy have proven to be effective. The results of our literature data research confirm this conclusion. Non-pharmacological treatment methods and all of their modalities are well-tolerated, which gives them additional value.

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

podnošljivost zajedničko je obilježje svih modaliteta NFL-a, što im daje dodatnu važnost i vrijednost.

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Eva Mandić

REFERENCES / LITERATURA

1. Franz A, Klose M, Beitzel K i sur. Conservative treatment of frozen shoulder. Unfallchirurg. 2019;122(12):934–40.
2. Painful shoulder: Exercise can reduce pain and improve mobility and function. J Orthop Sports Phys Ther. 2020;50(3):142.
3. Creech JA, Silver S. Shoulder impingement syndrome. U: StatPearls (Internet). Treasure Island: StatPearls Publishing 2020. Dostupno na: https://www.ncbi.nlm.nih.gov/books/NBK554518/.
4. Vlak T, Pivalica D, Aljinović J. Načela liječenja izvanzglobnih reumatskih bolesti – terapijske dvojbe i postupnici liječenja. Reumatizam. 2013;60(2):84–9.
5. VanBaak K, Aerni G. Shoulder conditions: rotator cuff injuries and bursitis. FP Essent. 2020;491:11–6.
6. Doiron-Cardin P, Lafrance S, Saulnier M i sur. Shoulder rotator cuff disorders: a systematic review of clinical practice guidelines and semantic analyses of recommendations. Arch Phys Med Rehabil. 2020;101(7):1233–42.
7. Miller TT, Schweitzer ME. Diagnostic Musculoskeletal Imaging. McGraw Hill Professional; 2005.
8. Vlak T, Martinović Kaliterna D. Rano prepoznavanje reumatskih bolesti. Split: Medicinski fakultet Sveučilišta u Splitu, 2011.
9. Ilieva EM, Oral A, Küçüdeveci AA i sur. Osteoarthritis. The role of physical and rehabilitation medicine physicians. The European perspective based on the best evidence. A paper by the UEMS-PRM Section Professional Practice Committee. Eur J Phys Rehabil Med. 2013;49:579–93.
10. Green S, Buchbinder R, Hetrick S. Physiotherapy interventions for shoulder pain. Cochrane Database Syst Rev. 2003; 2:CD004258.
11. Surace SJ, Deitch J, Johnston RV, Buchbinder R. Shock wave therapy for rotator cuff disease with or without calcification. Cochrane Database Syst Rev. 2020;3:CD008962.
12. Wu KT, Chou WY, Wang CJ i sur. Efficacy of extracorporeal shockwave therapy on calcified and non-calcified shoulder tendinosis: a propensity score matched analysis. Biomed Res Int. 2019;2019:2958251.
13. KlüterT, Krath A, Stukenberg M i sur. Electromagnetic transduction therapy in 86 patients with rotator cuff tendinopathy: a prospective randomized controlled trial. Electromagn Biol Med. 2018;37(4):175–83.
14. Page MJ, Green S, Mrocki MA i sur. Electrotherapy modalities for rotator cuff disease. Cochrane Database Syst Rev. 2016; 6:CD012225.
15. Karaca B. Effectiveness of high-intensity laser therapy in subacromial impingement syndrome. Photomed Laser Surg. 2016; 34(6):223–8.
16. Pekyavas NO, Baltaci G. Short-term effects of high-intensity laser therapy, manual therapy and kinesio taping in patients with subacromial impingement syndrome. Lasers Med Sci. 2016;31:1133–41.
17. Ghozy S, Dung NM, Morra ME i sur. Efficacy of kinesio taping in treatment of shoulder pain and disability: a systematic review and meta-analysis of randomised controlled trials. Physiotherapy. 2020;107:176–88.
18. Maretić N, Aljinović J, Bećir B i sur. Istraživanje učinka na bol terapije laserom visokog intenziteta u izvanzglobnim reumatskim bolestima. Fiz Rehabil Med. 2016;28(3–4):327–44.
19. Klisović S, Aljinović J, Poljičanin A i sur. Istraživanje analgetskog učinka terapije udarnim valom na izvanzglobne reumatske bolesti. Fiz Rehabil Med. 2018;32(3–4):169–81.
20. Haik MN, Alburquerque-Sendín F, Moreira RFC, Pires ED, Camargo PR. Effectiveness of physical therapy treatment of clearly defined subacromial pain: a systematic review of randomised controlled trials. Br J Sports Med. 2016;50(18):1124–34.
21. Jang JS, Choi HJ, Kang SH i sur. Effect of pulsed radiofrequency neuromodulation on clinical improvements in the patients of chronic intractable shoulder pain. J Korean Neurosurg Soc. 2013;54:507–10.
22. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Buchbinder R. Electrotherapy modalities for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014;10: CD011324.

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PROFESSIONAL PAPER STRUČNI RAD

EFFECT OF DISEASE ACTIVITY AND FUNCTIONAL IMPAIRMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS ON SATISFACTION WITH PROVIDED RHEUMATOLOGY HEALTH CARE

UTJECAJ AKTIVNOSTI BOLESTI I FUNKCIONALNE ONESPOSOBLJENOSTI BOLESNIKA S REUMATOIDNIM ARTRITISOM NA RAZINU ZADOVOLJSTVA PRUŽENOM REUMATOLOŠKOM USLUGOM

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Abstract

Rheumatoid arthritis (RA) is a disease that requires regular monitoring of therapeutic efficacy and patients' quality of life (QOL). The aim of this study is to determine the influence of disease activity and duration, as well as functional disability, on the patients' perception of satisfaction with the provided care, and to evaluate the satisfaction with respect to the patient-physician relationship and the factors that affect the patients' satisfaction level.

The observational non-interventional study included 53 consecutive RA patients who regularly attend the outpatient clinic. Prior to the scheduled examination the patients completed a standardized Patient Satisfaction Questionnaire and a Health Care Assessment Questionnaire (HAQ). The patients were divided according to their HAQ score, disease activity measured by DAS28 score (Disease Activity Score 28), disease duration, and presence of bDMARDs (biologic disease-modifying antirheumatic drugs) in therapy.

The results showed that the patients were largely satisfied with the service provided. The highest scores were achieved in the categories of the technical quality and competence of the physician and the doctor's attitude towards the patient. The lowest scores were related to the inability of an easy telephone access or emergency consultation and to the time spent in the waiting room. The level of disease activity did not significantly affect the degree of satisfaction with the provided health care. Additionally, patients who were classified as having severe to very severe disability by HAQ score had slightly lower satisfaction rates in all examined categories. Furthermore, patients treated with bDMARDs and those with disease lasting more than five years reported higher satisfaction rates in all categories.

In conclusion, patients with a higher degree of disability experience a slightly lower level of satisfaction with medical care, whereas patients with long-standing disease and those treated with bDMARDs report higher levels of

satisfaction with the specialist care. Satisfaction with the professional service provided in the specialist rheumatology unit can contribute to the improvement of the patients' perception of satisfaction with QOL.

Keywords: Arthritis, rheumatoid – drug therapy, psychology; Biological products – therapeutic use; Severity of illness index; Patient satisfaction; Physician-patient relation; Patient reported outcome measures; Rheumatology; Surveys and questionnaires

Sažetak

Reumatoidni artritis (RA) bolest je koja nalaže kontinuirano praćenje učinkovitosti liječenja i kvalitete života bolesnika. Ciljevi istraživanja bili su utvrđivanje utjecaja aktivnosti bolesti na percepciju zadovoljstva bolesnika, evaluacija zadovoljstva bolesnika odnosom liječnik – pacijent te identifikacija čimbenika koji utječu na razinu zadovoljstva.

Ova presječna opservacijska neintervencijska studija obuhvatila je 53 konsekutivna bolesnika s RA koji su dolazili na redovite ambulantne preglede u Zavod za kliničku imunologiju i reumatologiju. Bolesnici su prije pregleda ispunili standardizirani Upitnik o zadovoljstvu pacijenata te Upitnik o procjeni općega zdravstvenog stanja (HAQ). Ispitanici su podijeljeni u skupine prema vrijednostima rezultata HAQ-a, aktivnosti bolesti i njezinu trajanju te ovisno o tome primaju li biološku terapiju.

Rezultati istraživanja pokazali su da su bolesnici uvelike zadovoljni pruženom uslugom. Najviše ocjene postignute su u kategorijama tehničke kvalitete i kompetentnosti liječnika te odnosa liječnika prema bolesniku. Najniže ocjene zadovoljstva odnosile su se na nemogućnost jednostavnoga telefonskog pristupa ili izvanredne konzultacije te na duljinu čekanja u čekaonici.

Razina aktivnosti bolesti mjerena prema DAS 28-SE (engl. *Disease Activity Score 28*) nije bitno utjecala na stupanj zadovoljstva bolesnika pruženom uslugom. Nadalje, bolesnici koji su prema HAQ-u ubrojeni u skupinu teške do vrlo teške onesposobljenosti javili su diskretno niži stupanj zadovoljstva u svim ispitivanim kategorijama. Također, bolesnici liječeni biološkim lijekovima i oni s trajanjem bolesti duljim od 5 godina pokazali su više razine zadovoljstva u svim kategorijama.

Zaključno, bolesnici s višom razinom funkcionalne onesposobljenosti izrazili su nešto nižu razinu zadovoljstva pruženom skrbi u reumatološkoj poliklinici, dok su bolesnici s dugotrajnom bolesti, kao i oni liječeni biološkom terapijom izrazili veće zadovoljstvo pruženom skrbi. Zadovoljstvo pacijenata specijalističkom uslugom pridonosi njihovu većem zadovoljstvu kvalitetom života.

Ključne riječi: Reumatoidni artritis – farmakoterapija, psihologija; Biološki lijekovi – terapijska uporaba; Ocjena težine bolesti; Zadovoljstvo bolesnika; Odnos liječnika i bolesnika; Procjene bolesnika o kvaliteti skrbi; Reumatologija; Ankete i upitnici

INTRODUCTION

Treatment of patients with rheumatoid arthritis (RA) is inconceivable without monitoring disease activity using composite indices, which are part of the current therapeutic recommendations (1). Physicians base their therapeutic decisions mainly on disease activity or measurements of treatment outcome, without taking into account parameters such as patient satisfaction or patients' attitude to the issue of changes in the therapy (1, 2). Composite indices - DAS28 (Disease Activity Score 28), SDAI (Simple Disease Activity Index), and mHAQ (Modified Health Assessment Questionnaire) may be affected by comorbidities such as infections or fibromyalgia, conditions that commonly occur in patients with rheumatoid arthritis (3, 4). Individual understading of the disease is not always related exclusively to the current disease activity, but may be influenced by various factors that are not directly related to the disease or rational factors. Whether the patient's perspective on disease activity is in line with the

UVOD

Liječenje bolesnika s reumatoidnim artritisom (RA) nezamislivo je bez praćenja aktivnosti bolesti s pomoću kompozitnih indeksa, koji su dio vrijedećih terapijskih preporuka (1). Liječnici temelje terapijske odluke uglavnom na aktivnosti bolesti odnosno mjerama ishoda liječenja, ne uzimajući u obzir parametre kao što su zadovoljstvo bolesnika ili njihovo stajalište o pitanju promjene terapije (1, 2). Kompozitni indeksi – DAS 28 (engl. *Disease Activity Score 28*), SDAI (engl. *Simple Disease Activity Index*) i mHAQ (engl. *Modified Health Assessment Questionnaire*) mogu biti pod utjecajem komorbiditeta kao što su infekcije ili fibromialgija, stanja koja se često javljaju u bolesnika s reumatoidnim artritisom (3, 4). Individualno poimanje bolesti ne mora biti povezano samo s trenutačnom aktivnosti bolesti, već može biti pod utjecajem raznih čimbenika koji nisu u direktnoj vezi s bolešću ili racionalnim faktorima. Pitanje je li bolesnikova perspektiva o aktivnosti bolesti u skladu s indeksima aktivnosti bo-

disease activity indices and therapeutic recommendations is crucial for the implementation of these recommendations in everyday clinical practice (5).

Patient-reported outcome measures (PROM) in rheumatology include a global assessment of disease activity as well as a global assessment of pain, physical function, health-related quality of life (HRQoL) measurements, and the level of fatigue in patients. They are used to assess the effectiveness of RA treatment in randomized clinical trials (6), but their inclusion in clinical practice is also becoming increasingly important (7, 8).

The aim of this study was to determine the impact of disease activity on the perception of patient satisfaction, to evaluate patient satisfaction with the doctor-patient relationship, and to identify factors that affect the level of satisfaction. We asked these questions because we wanted to get an insight into the quality of care and subjective perception of the quality of care in the Division of Clinical Immunology and Rheumatology Clinic, in view of the workload of the clinic.

SUBJECTS AND METHODS

The average observational non-interventional study included 53 patients with RA who come to the Division of Clinical Immunology and Rheumatology for regular follow-up examinations. Patients completed the Patient Satisfaction Questionnaire taken from a previous UK study (Likert scale) (9) and the General Health Assessment Questionnaire (HAQ), which divided the subjects into three groups depending on the outcome (0-1: mild to moderate disability; 1-2: moderate to severe disability; 2-3: severe to very severe disability). The subjects had DAS28 calculated independently of the physician and were divided into two groups (< 2.6: remission and > 2.6: active disease). They were also divided into two groups depending on whether they were receiving biological therapy or not. The statistical analysis, in addition to descriptive statistics, included T-test for dependent samples and ANOVA analysis. Significance was determined at the level of $p<0.05$.

RESULTS

A satisfaction questionnaire was completed by 53 patients with established RA. The average age was 55.1 (24 - 72), there were 9 male (17%) and 44 female respondents (83%). Depending on the duration of the disease, the subjects were divided into two groups - 6 subjects with RA duration of less than 5 years, and 47 subjects with the disease diagnosed more than 5 years before. The mean value of DAS28-erythrocyte sedimentation rate (DAS28-SE) result was 3.37 ± 1.39, while the mean value of the HAQ index was 1.09 ±

lesti i terapijskim preporukama ključno je za implementaciju navedenih preporuka u svakodnevnu kliničku praksu (5).

Mjere ishoda koje navodi pacijent (engl. *Patient reported outcome measures* – PROM) u reumatologiji obuhvaćaju globalnu procjenu aktivnosti bolesti, kao i globalnu procjenu boli, fizičke funkcije, zatim mjere kvalitete života povezane sa zdravljem (engl. *Health-Related Quality of Life* – HRQoL) te razinu umora kod bolesnika. One se rabe za procjenu učinkovitosti liječenja RA u randomiziranim kliničkim studijama (6), ali i njihova inkluzija u kliničku praksu postaje sve važnija (7, 8).

Ciljevi ovog istraživanja bili su utvrđivanje utjecaja aktivnosti bolesti na percepciju zadovoljstva bolesnika, evaluacija zadovoljstva bolesnika odnosom liječnik – pacijent te identifikacija čimbenika koji utječu na razinu zadovoljstva. Navedena pitanja postavili smo jer smo željeli dobiti uvid u kvalitetu skrbi, odnosno subjektivnu percepciju kvalitete skrbi u poliklinici Zavoda za kliničku imunologiju i reumatologiju, a s obzirom na opterećenost polikliničkog pogona.

ISPITANICI I METODE

Presječna opservacijska neintervencijska studija obuhvatila je 53-je bolesnika s RA koji dolaze na redovite ambulantne preglede u Zavod za kliničku imunologiju i reumatologiju. Bolesnici su ispunili Upitnik o zadovoljstvu pacijenata preuzet iz prijašnjeg istraživanja provedenoga u Velikoj Britaniji (Likertova ljestvica) (9) te Upitnik o procjeni općega zdravstvenog stanja (HAQ) koji je podijelio ispitanike u tri skupine ovisno o rezultatu (0 – 1: blage do umjerene onesposobljenosti; 1 – 2: umjerena do teška onesposobljenost; 2 – 3: teška do vrlo teška onesposobljenost). Ispitanicima je izračunana vrijednost DAS 28 neovisno o ordinirajućem liječniku te su podijeljeni u dvije skupine (< 2,6 – remisija i > 2,6 – aktivna bolest). Podijeljeni su također u dvije skupine ovisno o tome primaju li biološku terapiju ili ne. Statistička je analiza, uz deskriptivnu statistiku, uključila T-test za zavisne uzorke i analizu ANOVA. Značajnost je utvrđena na razini $p < 0,05$.

REZULTATI

Upitnik o zadovoljstvu ispunilo je 53-je bolesnika s etabliranim RA. Prosjek godina bio je 55,1 (24 – 72), muških ispitanika bilo je 9 (17%), a ispitanica 44 (83%). Ovisno o trajanju bolesti, ispitanici su podijeljeni u dvije skupine: 6-ero ispitanika s trajanjem RA kraćim od 5 godina te 47-ero ispitanika s bolešću dijagnosticiranom prije više od 5 godina. Srednja vrijednost rezultata DAS 28 – sedimentacija eritrocita (DAS 28-SE) iznosila je 3,37 ± 1,39, dok je srednja vrijednost indeksa HAQ-a bila 1,09 ± 0,63. Ukupno je 29-ero paci-

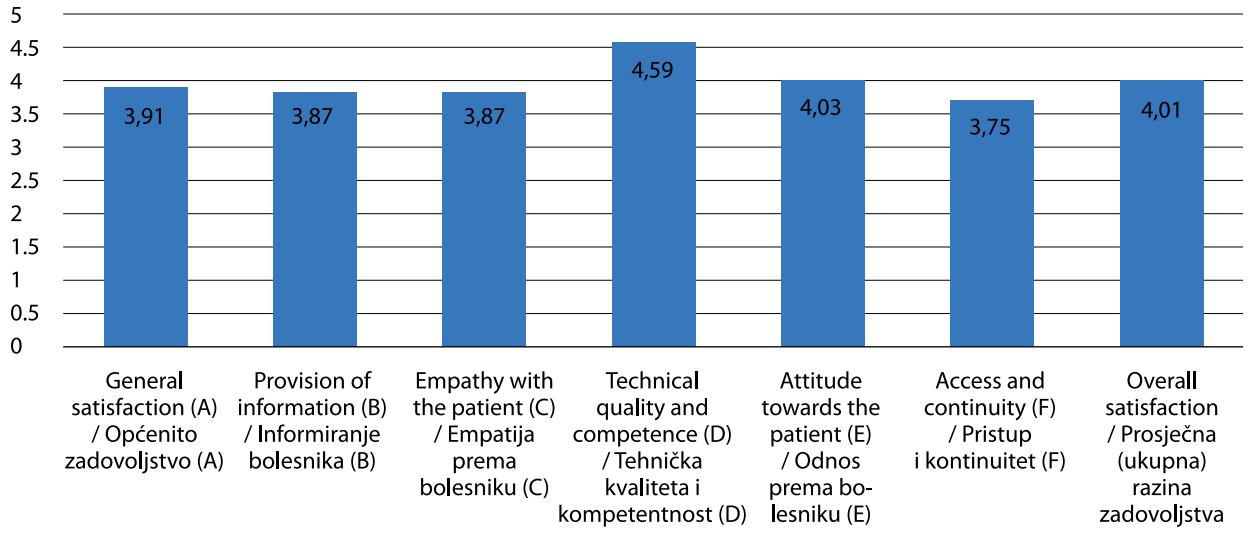

Figure 1. Mean satisfaction scores in the main categories of interest
Slika 1. Srednja vrijednost ocjene zadovoljstva u ispitivanim kategorijama

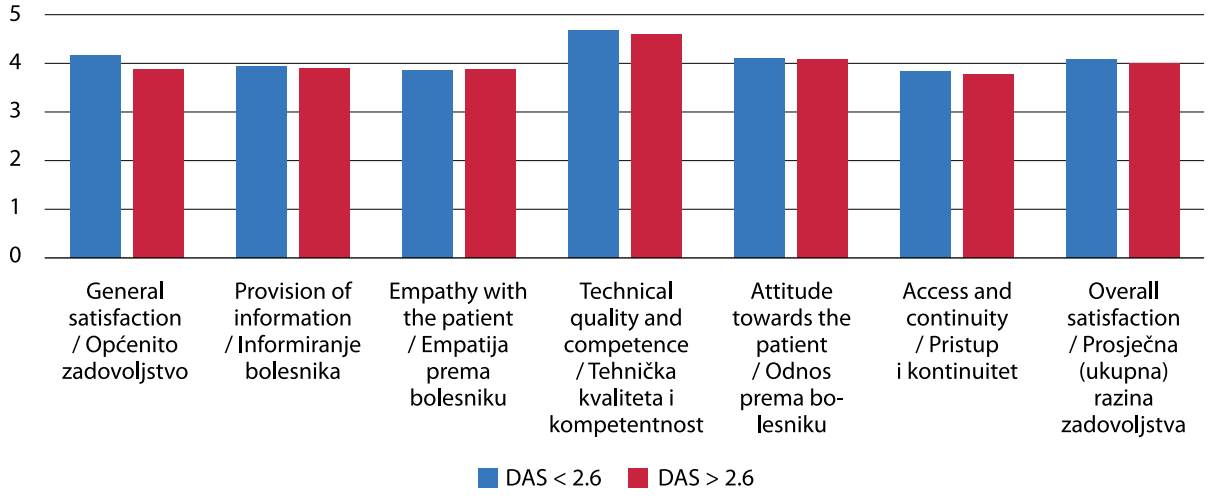

Figure 2. Satisfaction score according to disease activity
Slika 2. Ocjena zadovoljstva s obzirom na aktivnost bolesti

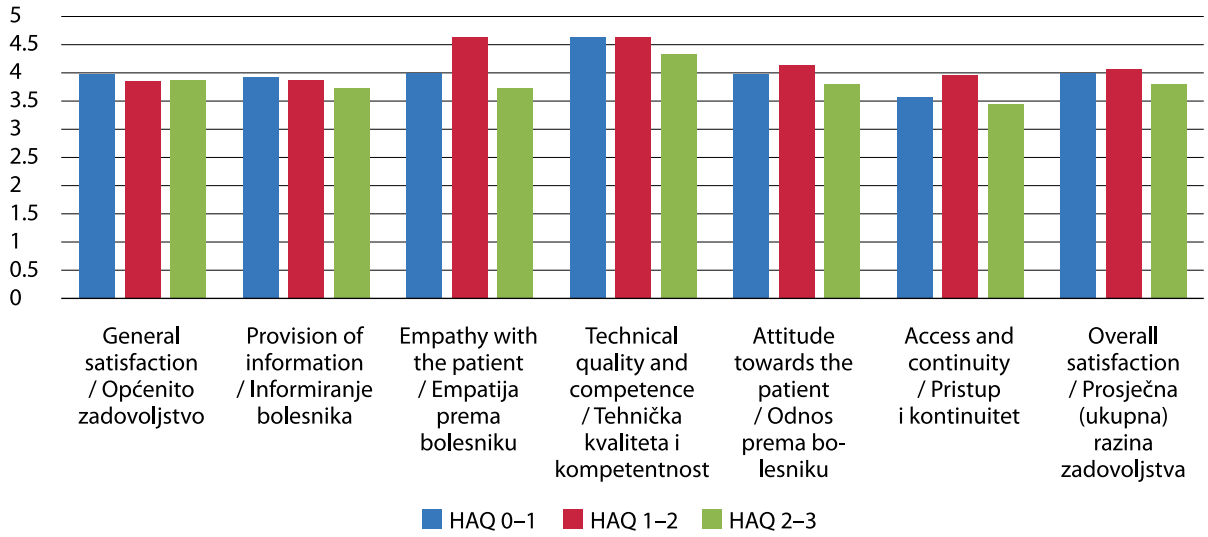

Figure 3. Satisfaction score according to functional disability groups
Slika 3. Ocjena zadovoljstva prema kategorijama funkcionalne onesposobljenosti

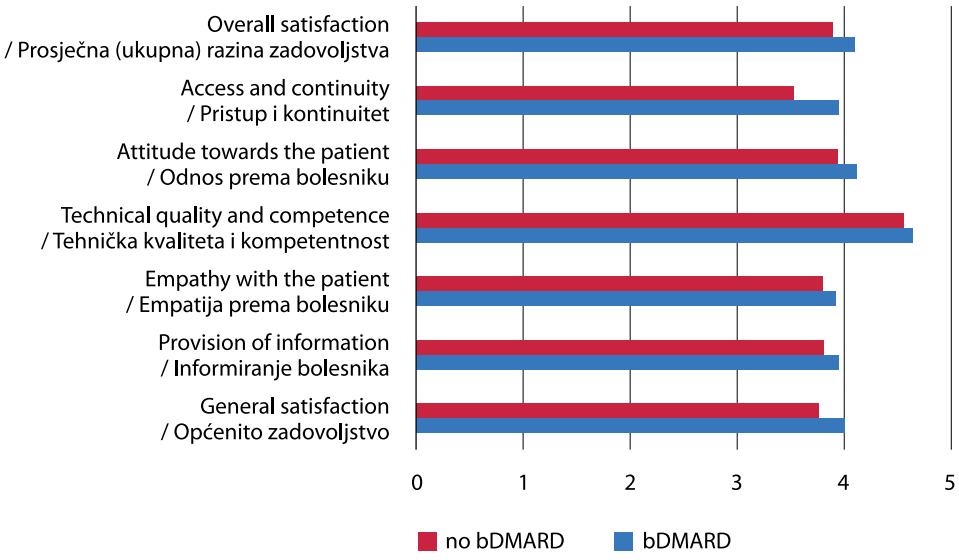

FIGURE 4. Satisfaction scores according to therapy (bDMARD vs. no bDMARD)
SLIKA 4. Ocjene zadovoljstva ovisno o tome primaju li bolesnici biološku terapiju

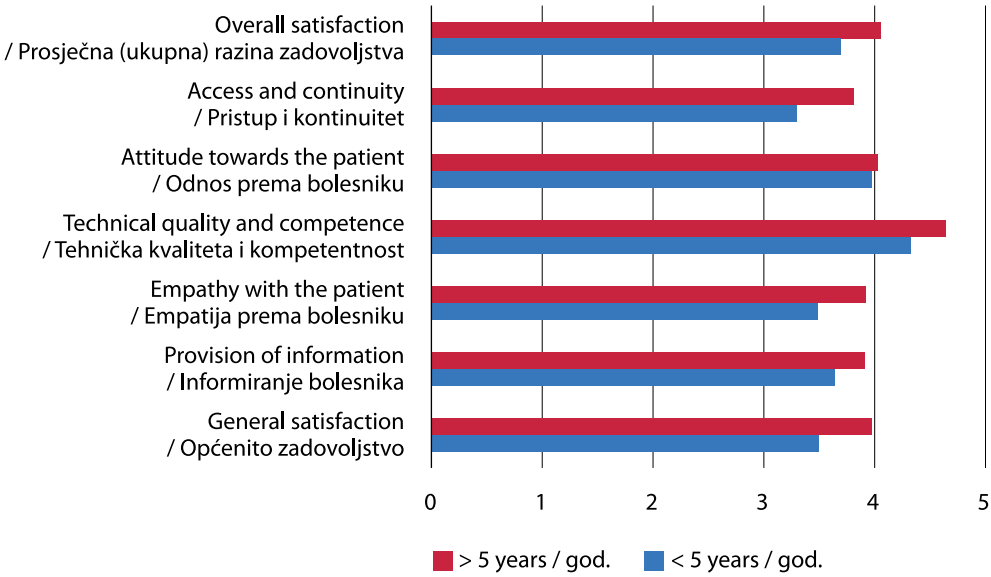

FIGURE 5. Satisfaction scores according to disease duration
FIGURE 5. Satisfaction scores according to disease duration

0.63. A total of 29 patients were treated with biologic therapy (TNF-α inhibitors, tocilizumab, rituximab) at the time of completing the questionnaire.

The questions in the Satisfaction Questionnaire were divided into six categories: General Satisfaction (A), Patient Information (B), Empathy towards the Patient (C), Technical Quality and Competence (D), Attitude towards the Patient (E), Approach and Continuity of Medical Care (F), and a special category of average (total) level of satisfaction that combined all grades. The average satisfaction ratings in the above categories were as follows: A – 3.914; B – 3.875; C – 3.877; D – 4.599; E – 4.034; F - 3.754; and a total score of 4.007.

The obtained results showed that patients are largely satisfied with the service provided. The highest scores were achieved in the categories of technical quality and competence of the doctor (D) and attitude of the doctor towards the patient (E) (Figure 1).

jenata u trenutku ispunjavanja upitnika liječeno biološkom terapijom (inhibitori TNF-α, tocilizumab, rituksimab).

Pri analizi su pitanja iz Upitnika o zadovoljstvu podijeljena u šest kategorija: Općenito zadovoljstvo (A), Informiranost bolesnika (B), Empatija prema bolesniku (C), Tehnička kvaliteta i kompetentnost (D), Odnos prema bolesniku (E), Pristup i kontinuitet skrbi (F) te posebna kategorija Prosječne (ukupne) razine zadovoljstva koja ujedinjuje sve ocjene. Srednje ocjene zadovoljstva u navedenim kategorijama bile su redom: A – 3,914; B – 3,875; C – 3,877; D – 4,599; E – 4,034; F – 3,754; uz ukupnu ocjenu 4,007.

Dobiveni su rezultati pokazali da su bolesnici uvelike zadovoljni pruženom uslugom. Najviše ocjene postignute su u kategorijama tehničke kvalitete i kompetentnosti liječnika (D) te odnosa liječnika prema bolesniku (E) (slika 1.).

The highest ratings of satisfaction were recorded in the patients' feeling that they are in good hands when they come to the clinic, the competence of the doctor, the level of medical care provided in the clinic, thoroughness in the doctor's approach, and the patients' trust in the doctor. The lowest satisfaction ratings were related to the impossibility of easy telephone access, or additional consultation if necessary, and to the length of waiting in the waiting room.

The level of disease activity measured according to the DAS28-SE score did not significantly affect the degree of patient satisfaction with the service provided (Figure 2). In the average satisfaction level, the mean score in the group with DAS28 <2.6 (remission) was 4.06 ± 0.44, and in the group with DAS28 > 2.6 (active disease) it was 3.98 ± 0.39 (T-test of independent samples, t = 0.62, p = 0.534). In contrast, patients enrolled in the severe-to-very severe disability group according to the HAQ questionnaire reported a slightly lower level of satisfaction in all study categories, although the difference between the groups did not reach significance (Figure 3). For example, in the category of average satisfaction level (ANOVA test), in the group with HAQ 0-1 (21 subjects) the mean value was 4.01 ± 0.47, in the group with HAQ 1-2 (26 subjects) it was 4.05 ± 0.35, and in the group with HAQ 2-3 (6 subjects) it amounted to 3.80 ± 0.37 (p = 0.402).

In the group of patients treated with biological therapy (29 subjects), a significantly higher satisfaction score was recorded in the category Approach and Continuity of Care (F) (p = 0.02) (Figure 4).

Patients diagnosed with RA more than 5 years before (n = 47) showed a higher degree of satisfaction in the categories Empathy towards the Patient (C) (p = 0.02) and Average Satisfaction in all Categories (AF) (p = 0.05) (Figure 5).

DISCUSSION

The presented results show relatively high ratings of satisfaction in all observed categories, which indicates that there is a good relationship between patients and the physician (rheumatologist), regardless of the chronic nature of the disease. Satisfaction ratings also signify the benefits of an individual approach to the patient, i.e., the fact that each patient has their own rheumatologist, which was not the case in the original study, in which this was the main source of dissatisfaction (9). The highest scores were recorded in the domain of doctor-patient relationship and patient trust in physician, and the lowest scores were awarded for accessibility and information providing (according to treatment side effects and course of the disease). Although no statistical significance was achieved, there was a tendency towards lower scores in the group of severe-to-very severe disability (HAQ values between

Najviše ocjene zadovoljstva zabilježene su u osjećaju bolesnika da su u dobrim rukama kada dođu u ambulantu, kompetentnosti liječnika, razini skrbi pružene u ambulanti, temeljitosti u pristupu liječnika te povjerenju bolesnika prema liječniku. Najniže ocjene zadovoljstva odnosile su se na nemogućnost jednostavnoga telefonskog pristupa ili izvanredne konzultacije ako je potrebna te na duljinu čekanja u čekaonici.

Razina aktivnosti bolesti mjerena prema DAS 28-SE nije bitno utjecala na stupanj zadovoljstva bolesnika pruženom uslugom (slika 2.). U kategoriji prosječne razine zadovoljstva srednja vrijednost ocjene u skupini bolesnika s DAS 28 < 2,6 (remisija) bila je 4,06 ± 0,44, a u skupini s DAS 28 > 2,6 (aktivna bolest) 3,98 ± 0,39 (T-test nezavisnih uzoraka, t = 0,62, p = 0,534). Nasuprot tomu, bolesnici koji su prema HAQ-u ubrojeni u skupinu teške do vrlo teške onesposobljenosti javili su nešto niži stupanj zadovoljstva u svim ispitivanim kategorijama, premda razlika među grupama nije dosegnula značajnost (slika 3.). Na primjeru kategorije prosječne razine zadovoljstva (test ANOVA), u skupini s HAQ 0 – 1 (21 ispitanik) srednja vrijednost ocjene bila je 4,01 ± 0,47, u skupini s HAQ 1 – 2 (26-ero ispitanika) 4,05 ± 0,35, a u skupini s HAQ 2 – 3 (6-ero ispitanika) 3,80 ± 0,37 (p = 0,402).

U skupini bolesnika liječenih biološkom terapijom (29-ero ispitanika) znatnije viša ocjena zadovoljstva zabilježena je u kategoriji Pristup i kontinuitet skrbi (F) (p = 0,02) (slika 4.).

Bolesnici u kojih je RA dijagnosticiran prije više od 5 godina (n = 47) pokazali su viši stupanj zadovoljstva u kategorijama Empatija prema bolesniku (C) (p = 0,02) i Prosječno zadovoljstvo u svim kategorijama (A – F) (p = 0,05) (slika 5.).

RASPRAVA

Iz iznesenih rezultata mogu se iščitati relativno visoke ocjene zadovoljstva u svim promatranim kategorijama, što upućuje na to da postoji dobar odnos bolesnika s ordinirajućim liječnikom (reumatologom) bez obzira na kroničan karakter bolesti. Ocjene zadovoljstva govore i u prilog dobrobiti individualnog pristupa bolesniku, tj. tomu što svaki bolesnik ima svojeg reumatologa, a toga nije bilo u prvotnoj studiji, što je ujedno bio i glavni izvor nezadovoljstva (9). Najviše ocjene zabilježene su u domeni odnosa liječnik – bolesnik i povjerenja bolesnika u liječnika, a najniže ocjene dodijeljene su za pristupačnost i pružanje informacija (o nuspojavama liječenja i tijeku bolesti). Iako nije dosegnuta statistička značajnost, opaža se tendencija prema nižim ocjenama u skupini teške do vrlo teške onesposobljenosti (vrijednost HAQ-a između 2 i 3). Nadalje, prema rezultatima našeg istraživanja, aktivnost bolesti ne utječe na percepciju kvalitete skrbi. Suprotno tomu, dugotrajna je bolest (> 5 godina) po-

2 and 3). Furthermore, according to the results of our study, disease activity does not affect the perception of care quality. In contrast, long-term illness (> 5 years) is associated with greater satisfaction with the service provided in terms of stronger physician empathy for the patient and greater general patient satisfaction. Also, patients treated with biologic therapy are more satisfied with the possibility of easier health care access in the rheumatology clinic. This probably results from the regular visits to the day hospital during which a routine medical examination is performed before therapy, or the communication with medical staff who provide subcutaneous biologics. Lower grades in individual categories, as well as individual issues, provide insight into the components of care in outpatient work that must be improved (possibility of easy access or additional consultation, length of waiting in the waiting room).

According to a cross-sectional study by Jacobi et al. on the satisfaction of patients with RA who are in the routine care of a rheumatologist, no strong proof has been found that the patient characteristics (e.g., health, social, demographic) are associated with quality assessment (10). In contrast, other studies shown that patients' assessments of health-care quality may be influenced by sociodemographic (age, education, marital status) (11, 12) and health characteristics (11, 13–16). The level of functional disability could affect grades, as shown in some of the studies (11, 13–16). Older patients and women assign slightly better scores than younger patients and men (10). Inadequate quality scores were marked in the domain of drug information, symptom information, and information in understandable language (10), which is in accordance with the lower scores in related categories in our study.

It is known that only a small proportion of patients talk to their physician about pain, physical function, fatigue, and health-related quality of life (HR-QoL) (17).

Other studies also showed that daily pain, despite the new therapeutic options available, continues to be a major ailment for patients, and being free of pain and fatigue is a major indicator of a 'good day'. The responses obtained from the questionnaires clearly emphasize the deeper, hidden effect of the disease, suggesting a loss of self-confidence, feelings of separation and isolation, and stress that negatively affects the patients' emotional well-being and relationships with family, friends, and partners (18, 19). From the patient perspective, a targeted, effective approach to treatment involves setting personal, social, and therapeutic goals as well as monitoring disease progression to achieve those goals.

This is accordant with other studies, in which communication between physician and patient focuses on symptoms or treatment options rather than on health-

vezana s većim zadovoljstvom pruženom uslugom s obzirom na snažnije empatije liječnika prema bolesniku te većim općenitim zadovoljstvom bolesnika. Također, bolesnici liječeni biološkom terapijom zadovoljniji su mogućnošću lakšeg pristupa zdravstvenoj skrbi u reumatološkoj poliklinici koja vjerojatno proizlazi iz redovitih posjeta dnevnoj bolnici tijekom kojih se provodi redoviti liječnički pregled prije aplikacije terapije ili iz komunikacije s osobljem poliklinike pri preuzimanju supkutanog oblika bioloških lijekova. Niže ocjene u pojedinim kategorijama, kao i pojedinačna pitanja daju uvid u komponente skrbi u polikliničkom radu koje je potrebno poboljšati (mogućnost jednostavnijeg pristupa ili izvanredne konzultacije, duljina čekanja u čekaonici).

Prema presječnom istraživanju Catharine Jacobi i suradnika o zadovoljstvu pacijenata s RA koji su u skrbi reumatologa, nije nađen čvrst dokaz da su karakteristike pacijenata (zdravstvene, sociodemografske) povezane s ocjenama kvalitete (10). Suprotno tomu, u drugim provedenim istraživanjima dokazano je da ocjene pacijenata o kvaliteti skrbi mogu biti pod utjecajem sociodemografskih karakteristika (dob, edukacija, bračni status) (11, 12) i zdravstvenih karakteristika (11, 13 – 16). Razina funkcionalne onesposobljenosti mogla bi utjecati na ocjene, što i jest prikazano u nekim od istraživanja (11, 13 – 16). Stariji pacijenti i žene dodjeljuju nešto bolje ocjene nego mlađi bolesnici i muškarci (10). Neadekvatne ocjene kvalitete zabilježene su u područjima informacije o lijekovima, informacije o tijeku simptoma i informacije razumljivim jezikom (10), što je u skladu s nižim ocjenama u srodnim kategorijama u našem istraživanju.

Poznato je da tek manji udio bolesnika razgovara sa svojim liječnikom o boli, fizičkoj funkciji, umoru, kvaliteti života povezanoj sa zdravljem (HRQoL) (17).

Također, iz drugih je istraživanja razvidno da dnevna bol, unatoč dostupnosti novih terapijskih opcija, nastavlja biti glavna tegoba bolesnika, a biti bez boli i umora glavni je indikator 'dobrog dana'. Odgovori dobiveni iz provedenih upitnika jasno naglašavaju dublji, skriveni efekt bolesti upućujući na gubitak samopouzdanja, osjećaje odvojenosti i izoliranosti te stres koji negativno utječe na emocionalno blagostanje pacijenata i odnose s obitelji, prijateljima i partnerima (18, 19). Iz perspektive pacijenata ciljani, učinkovit pristup liječenju sastoji se od postavljanja osobnih, socijalnih i terapijskih ciljeva, kao i nadziranja progresije bolesti kako bi se navedeni ciljevi postigli. To je u skladu s drugim studijama, u kojima se komunikacija između liječnika i bolesnika više usredotočuje na simptome ili opcije liječenja nego na kvalitetu života povezanu sa zdravljem (HRQoL) (20). Zamijećeno je da bolesnici i liječnici uzimaju u obzir različite aspekte RA kada se donose odluke o terapiji (21 – 23). Mnogi bolesnici

related quality of life (HRQL) (20). It has been observed that patients and physicians consider different aspects of RA when making treatment decisions (21–23). Many patients are unable to adequately express the burden of the disease they are feeling or expectations they have of a particular therapeutic approach. Therefore, the physician should initiate a more detailed discussion of expectations with the patient and strive to explain the treat-to-target approach in RA treatment (18, 24). The most important limitation of this study is the small number of respondents.

In conclusion, in this study conducted at a single institution, regardless of the chronic character of RA a satisfactory relationship was found between the patient and the competent rheumatologist, which is partly due to the individual approach to patients. Patients with a higher level of functional disability expressed a slightly lower level of satisfaction with the care provided in the rheumatology clinic, while patients with long-term illness as well as those treated with biologic therapy showed higher satisfaction with the specialist service provided. Inadequate quality assessments in the area of providing information on the course of the disease and prescribed therapy, the availability of physicians, and long waiting times are among the items of care that need to be improved. Finally, research indicates that an important approach in the treatment of RA patients is to set individual goals, which include a psychosocial component, as well as regular monitoring of the course of the disease.

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

nisu u stanju prikladno iskazati teret bolesti koji osjećaju ni očekivanja koja imaju od određenoga terapijskog pristupa. Stoga bi liječnik trebao s bolesnikom inicirati detaljniju raspravu o očekivanjima i truditi se objasniti pristup *treat-to-target* liječenju RA (18, 24). Najvažnije ograničenje ovog ispitivanja bio je malen broj ispitanika.

Zaključno, bez obzira na kroničan karakter RA, u ovom je istraživanju, provedenom u jednoj ustanovi, nađen zadovoljavajući odnos između bolesnika i mjerodavnog reumatologa, što je dijelom zasigurno i zbog individualnog pristupa pacijentima. Pacijenti s višom razinom funkcionalne onesposobljenosti izrazili su nešto nižu razinu zadovoljstva pruženom skrbi u reumatološkoj poliklinici, dok su pacijenti s dugotrajnom bolesti, kao i oni liječeni biološkom terapijom bili zadovoljniji pruženom specijalističkom uslugom. Neadekvatne ocjene kvalitete u područjima pružanja informacija o tijeku bolesti i ordiniranoj terapiji, dostupnosti liječnika i dugog čekanja stavke su skrbi koje je potrebno poboljšati. Konačno, istraživanje upućuje na to da važan pristup pri liječenju bolesnika s RA čine postavljanje individualnih ciljeva, koji uključuju i psihosocijalnu komponentu, kao i redovito praćenje tijeka bolesti.

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REFERENCES / LITERATURA

1. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M i sur. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960–77.
2. Smolen JS, Sokka T, Pincus T, Breedveld FC. A proposed treatment algorithm for rheumatoid arthritis: aggressive therapy, methotrexate, and quantitative measures. Clin Exp Rheumatol. 2003;21(5 Supl 31):S209–10.
3. Wolfe F, Cathey MA, Kleinheksel SM. Fibrositis (Fibromyalgia) in rheumatoid arthritis. J Rheumatol. 1984;11(6):814–8.
4. Leeb BF, Andel I, Sautner J, Nothnagl T, Rintelen B. The DAS28 in rheumatoid arthritis and fibromyalgia patients. Rheumatology (Oxford). 2004;43(12):1504–7.
5. Leeb BF, Andel I, Leder S, Leeb BA, Rintelen B. The patient's perspective and rheumatoid arthritis disease activity indexes. Rheumatology (Oxford). 2005;44(3):360–5.
6. Her M, Kavanaugh A. Patient-reported outcomes in rheumatoid arthritis. Curr Opin Rheumatol. 2012;24(3):327–34.
7. Ward V, Hill J, Hale C, Bird H, Quinn H, Thorpe R. Patient priorities of care in rheumatology outpatient clinics: a qualitative study. Musculoskeletal Care. 2007;5(4):216–28.
8. Taylor P, Manger B, Alvaro-Gracia J, Johnstone R, Gomez-Reino J, Eberhardt E i sur. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. J Int Med Res. 2010;38(4):1213–24.
9. Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic. Ann Rheum Dis. 1992;51(2):195–7.
10. Jacobi CE, Boshuizen HC, Rupp I, Dinant HJ, van den Bos GAM. Quality of rheumatoid arthritis care: the patient's perspective. Int J Qual Health Care. 2004;16(1):73–81.
11. Lewis JR. Patient views on quality care in general practice: literature review. Soc Sci Med. 1994;39(5):655–70.

12. Hall JA, Dornan MC. Patient sociodemographic characteristics as predictors of satisfaction with medical care: a meta-analysis. Soc Sci Med. 1990;30(7):811–8.
13. Bendtsen P, Bjurulf P. Perceived needs and patient satisfaction in relation to care provided in individuals with rheumatoid arthritis. Qual Assur Health Care. 1993;5(3):243–53.
14. Williams B. Patient satisfaction: a valid concept? Soc Sci Med. 1994;38(4):509–16.
15. Donabedian A. The quality of care. How can it be assessed? JAMA. 1988;260(12):1743–8.
16. Hall JA, Dornan MC. Meta-analysis of satisfaction with medical care: description of research domain and analysis of overall satisfaction levels. Soc Sci Med. 1988;27(6):637–44.
17. McInnes IB, Combe B, Burmester G. Understanding the patient perspective - results of the Rheumatoid Arthritis: Insights, Strategies & Expectations (RAISE) patient needs survey. Clin Exp Rheumatol. 2013;31(3):350–7.
18. Strand V, Wright GC, Bergman MJ, Tambiah J, Taylor PC. Patient Expectations and Perceptions of Goal-setting Strategies for Disease Management in Rheumatoid Arthritis. J Rheumatol. 2015;42(11):2046–54.
19. Radawski C, Genovese MC, Hauber B, Nowell WB, Hollis K, Gaich CL i sur. Patient Perceptions of Unmet Medical Need in Rheumatoid Arthritis: A Cross-Sectional Survey in the USA. Rheumatol Ther. 2019;6(3):461–71.
20. Kvrgic Z, Asiedu GB, Crowson CS, Ridgeway JL, Davis JM. "Like No One Is Listening to Me": A Qualitative Study of Patient-Provider Discordance Between Global Assessments of Disease Activity in Rheumatoid Arthritis. Arthritis Care Res. 2018;70(10):1439–47.
21. Robinson SM, Walker DJ. Negotiating targets with patients: choice of target in relation to occupational state. Rheumatology (Oxford). 2012;51(2):293–6.
22. van Hulst LTC, Kievit W, van Bommel R, van Riel PLCM, Fraenkel L. Rheumatoid arthritis patients and rheumatologists approach the decision to escalate care differently: results of a maximum difference scaling experiment. Arthritis Care Res. 2011;63(10):1407–14.
23. Otter SJ, Lucas K, Springett K, Moore A, Davies K, Young A i sur. Identifying patient-reported outcomes in rheumatoid arthritis: the impact of foot symptoms on self-perceived quality of life. Musculoskeletal Care. 2012;10(2):65–75.
24. Gibofsky A, Galloway J, Kekow J, Zerbini C, de la Vega M, Lee G i sur. Comparison of patient and physician perspectives in the management of rheumatoid arthritis: results from global physician- and patient-based surveys. Health Qual Life Outcomes. 2018;16(1):211.

LIST OF REVIEWERS for articles in volume 65 and 66 (2018/2019) / POPIS RECENZENATA za članke u volumenu 65 i 66 (2018./2019.)

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REVIEW PAPER PREGLEDNI RAD

WHEN TO SUSPECT AN AUTOINFLAMMATORY DISEASE?

KADA POSUMNJATI NA AUTOINFLAMATORNU BOLEST?

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Abstract

Autoinflammatory diseases are clinical disorders caused by a deficiency or dysregulation of innate immunity, characterized by recurrent or persistent inflammation (increased levels of acute phase reactants) and the absence of a primary pathogenic role of adaptive immunity (autoreactive T lymphocytes or antibody production). They are clinically manifested by recurrent episodes of systemic inflammation due to the activation of an intense nonspecific inflammatory reaction with no apparent or sufficient cause.

In terms of pathogenesis, autoinflammatory diseases can be divided into monogenic, or those that are caused by a mutation in a well-defined gene, and non-monogenic, also referred to as unclassified. According to the three main pathogenic patterns of emergence in monogenic autoinflammatory diseases described to date, they are divided into inflammasomopathies, interferonopathies, and ubiquitinopathies. Clinically, inflammasomopathies are most commonly manifested by fever (often periodic type), rash, serositis, hepatosplenomegaly, and lymphadenopathy. The therapeutic approach in many of these diseases is based on the use of an interleukin-1 inhibitor. Interferonopathies are most commonly manifested as acral and lung vasculopathy and fibrosis, with an onset of skin changes like chilblains, intracranial calcifications, and myositis. Janus kinase inhibitors are used in the treatment. Ubiquitinopathies are most commonly manifested by granuloma, ulceration, uveitis, and immunodeficiency. The therapeutic approach in these diseases is based on the use of tumor necrosis factor-alpha inhibitors.

Unclassified autoinflammatory diseases include diseases that meet the clinical and biological criteria for autoinflammatory diseases but to date have no detected genetic background (for example, syndrome of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis, Schnitzler syndrome, or systemic-onset juvenile idiopathic arthritis), and some multifactorial diseases that are polygenic or caused by complex interactions of multiple genes and environmental factors and not associated with Mendelian inheritance patterns (eg., gout, Behcet disease).

In the diagnosis of patients with suspected autoinflammatory disease, it is necessary to exclude infections, malignancies, immunodeficiencies, and rheumatic diseases. The main indication for genetic testing is the presence of clinical symptoms that meet the criteria for one or more autoinflammatory diseases. There are a number of unanswered questions in genetic diagnostics, the main problem being the interpretation of the results.

Keywords: Hereditary autoinflammatory diseases – classification, diagnosis, genetics, therapy; Autoimmune diseases – diagnosis, immunology, therapy; Inflammation – immunology; Fever – genetics, immunology; Immunity,

innate – immunology; Inflammasomes – immunology; Interferon type I – immunology; Ubiquitins – immunology; Interleukin-1 – antagonists and inhibitors; Janus kinase inhibitors – therapeutic use; Tumor necrosis factor-alpha – antagonists and inhibitors

Sažetak

Autoinflamatorne bolesti klinički su poremećaji uzrokovani nedostatkom ili poremećajem regulacije prirođene imunosti, a obilježavaju ih ponavljana ili stalna upala (povišeni reaktanti akutne faze) i odsutnost primarne patogenetske uloge stečene imunosti (autoreaktivni T-limfociti ili proizvodnja protutijela). Klinički se manifestiraju ponavljanim epizodama sustavne upale zbog aktivacije intenzivne nespecifične upalne reakcije bez očitog ili dovoljnog uzroka.

U patogenetskom smislu mogu se podijeliti na monogenske, odnosno na one koje su uzrokovane mutacijom u jednom, dobro definiranom genu i na one koje nisu monogenske, a označavaju se i kao neklasificirane. Prema tri glavna patogenetska obrasca nastanka, do danas opisane monogenske autoinflamatorne bolesti dijele se na inflamasomopatije, interferonopatije i ubikvitinopatije. Klinički se inflamasomopatije najčešće manifestiraju vrućicom (nerijetko periodična tipa), osipima, serozitisom, hepatosplenomegalijom i limfadenopatijom. Terapijski pristup u velikom broju ovih bolesti temelji se na primjeni inhibitora interleukina 1. Interferonopatije se najčešće manifestiraju vaskulopatijama ekstremiteta i pluća, nastankom fibroznih promjena, kožnih promjena nalik na ozebline, intrakranijalnim kalcifikacijama i miozitisom. U liječenju se rabe inhibitori Janusove kinaze. Ubikvitinopatije se najčešće očituju nastankom granuloma, ulceracija, uveitisa te imunodeficijencijom. Terapijski pristup u ovim bolestima temelji se na primjeni inhibitora čimbenika tumorske nekroze alfa.

U skupinu neklasificiranih autoinflamatornih bolesti ubrajaju se bolesti koje zadovoljavaju kliničko-biološke kriterije za autoinflamatorne bolesti, ali do danas nemaju otkrivenu gensku podlogu (primjerice, sindrom periodične vrućice, aftoznog stomatitisa, faringitisa i adenitisa, Schnitzlerin sindrom, sustavni oblik juvenilnog idiopatskog artritisa), kao i neke multifaktorske bolesti koje su poligenske, odnosno uvjetovane složenim interakcijama većeg broja gena i okolišnih čimbenika te nisu povezane s mendelovskim obrascem nasljeđivanja (primjerice, giht, Behçetova bolest).

Pri obradi bolesnika sa sumnjom na autoinflamatornu bolest potrebno je isključiti infekcije, zloćudne bolesti, imunodeficijencije i reumatske bolesti. Glavna je indikacija za gensko testiranje prisutnost kliničkih simptoma koji ispunjavaju kriterije za jednu ili više autoinflamatornih bolesti. U genskoj dijagnostici postoji niz neodgovorenih pitanja, među kojima je glavni problem interpretacija nalaza.

Ključne riječi: Autoinflamatorne bolesti – dijagnoza, genetika, klasifikacija, liječenje; Autoimunosne bolesti – dijagnoza, imunologija, liječenje; Upala – imunologija; Vrućica – genetika, imunologija; Prirođena imunost – imunologija; Inflamasomi – imunologija; Interferon tip I – imunologija; Ubikvitini – imunologija; Interleukin-1 – antagonisti i inhibitori; Inhibitori janusove kinaze – terapijska uporaba; Čimbenik tumorske nekroze alfa – antagonisti i inhibitori

DEFINITION OF AUTOINFLAMMATORY DISEASES

Autoinflammatory or self-inflammatory diseases are a relatively new category in the group of immunity disorders, and they differ from autoimmune diseases. They were defined as a specific clinical entity group in 1999 owing to the discovery of the genes involved in the pathogenesis of familial Mediterranean fever (FMF) syndrome and Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) (1). In the same year, Daniel Kastner's research team defined autoinflammatory diseases as a group of clinical syndromes characterized by an inflammatory process of no known cause without detectable autoantibodies (i.e., antibodies directed against self-antigens) or antigen-specific T-lymphocytes / autoreactive T-lymphocyte clones (2). However, as knowledge on the etiopathogenesis of autoinflammatory disease grew, and it

DEFINICIJA AUTOINFLAMATORNIH BOLESTI

Autoinflamatorne ili samoupalne bolesti relativno su nova skupina bolesti izdvojena iz skupine autoimunosnih bolesti. Prvi su put definirane kao zasebna skupina bolesti 1999. godine zahvaljujući otkriću gena koji su u podlozi dvaju sindroma: obiteljske mediteranske vrućice i periodične vrućice vezane uz receptor čimbenika tumorske nekroze (1). Grupa istraživača predvođena Danielom Kastnerom 1999. godine definirala je autoinflamatorne bolesti kao sindrome koje obilježava naizgled ni s čim izazvana upala bez prisutnosti znatnog titra autoprotutijela, odnosno protutijela usmjerenih na vlastite antigene ili T-limfocita specifičnih za antigen, odnosno autoreaktivnih klonova T-limfocita (2). Ipak, s rastućim brojem spoznaja o etiopatogenezi autoinflamatornih bolesti pokazala se potreba za promjenom ove prvotne definicije, budući da je postalo

was realized that there are exacerbating factors such as immunization in mevalonate kinase deficiency and enviromental cold in cryopirin-associated periodic syndrome, it became necessary to change the original definition. Therefore, in 2010 Kastner and his associates defined autoinflammatory diseases as disorders characterized by a hyperinflammatory condition mediated by innate immunity mechanisms in a predisposed host (3). The new definition is broad enough to encompass both monogenic periodic fever syndromes inherited in a Mendelian fashion and complex polygenic inheritance disorders, because, as we know today, autoinflammatory disorders are not only typical monogenic autoinflammatory inheritance disorders formerly known as inherited periodic fever syndromes, but also various polygenic autoinflammatory diseases such as inflammatory bowel disease, gout, autoantibody-negative vasculitis, idiopathic uveitis, etc. (4). Interestingly, several rather prevalent conditions such as type 2 diabetes mellitus and atherosclerosis also have an autoinflammatory component. This latest definition makes it easier to discriminate between innate immunity-associated autoinflammatory diseases and adaptive immunity-associated autoimmune diseases; it also implies that these conditions are a result of an innate immunity system disorder. Hopefully, this knowledge will increase clinical awareness of these rare and often unrecognized disorders, making them easier to diagnose and aiding patients in getting efficient treatment. Since in the past there were no treatment options for these rare conditions, diagnosing them was practically an academic effort. Today, this has changed with novel therapies and growing knowledge.

In the light of new medical knowledge, one can summarize that autoinflammatory diseases are clinical disorders characterized by recurrent or persistent inflammation (increased acute phase reactants) and a deficient primary pathogenic role of adaptive immunity (autoreactive T-lymphocytes or autoantibodies), resulting from a lack of regulation or dysregulation of innate immunity (5). Those diseases manifest with recurrent episodes of systemic inflammation due to intense non-specific inflammatory activation without a known or sufficient cause. Pathogenically speaking, the innate immune system is non-specifically or inadequately activated. Disease flares can occur due to trauma, immunization, infection, stress, etc., or without any apparent triggers.

The key differences between autoinflammatory and autoimmune diseases are shown in Table 1. Although it may seem that these differences are relatively obvious, in clinical practice the features of autoinflammatory and autoimmune disease tend to overlap. Thus, there is a tendency to abandon the classical division into autoinflammatory and autoimmune disorders in favor of

bjelodano kako postoje čimbenici koji mogu potaknuti upalne epizode ovih bolesti poput cijepljenja vezano uz manjak mevalonat kinaze ili hladnoće uz kriopirinske sindrome periodične vrućice. Stoga su 2010. godine Kastner i suradnici predložili novu definiciju autoinflamatornih bolesti kao poremećaja koje obilježava prekomjerno pojačana upala posredovana stanicama i molekulama prirođenog imunosnog sustava, pri čemu postoji znatna predispozicija domaćina (3). Ova je definicija dovoljno široka da obuhvati sindrome periodičnih vrućica s mendelovskim obrascem nasljeđivanja, odnosno monogenske poremećaje, ali i složene poligenske i nasljedne poremećaje. Naime, prema suvremenim spoznajama, autoinflamatornim bolestima ne pripadaju samo klasični monogenski nasljedni autoinflamatorni poremećaji, prije poznati kao nasljedni sindromi periodičnih vrućica, nego i različite poligenske autoinflamatorne bolesti poput upalnih bolesti crijeva, gihta, vaskulitisa koji nisu povezani s protutijelima, idiopatskih uveitisa itd. (4). Ovdje valja pridometnuti da i neke raširene bolesti poput šećerne bolesti tipa 2 i ateroskleroze imaju komponente autoinflamacije. Definicija koju su donijeli Kastner i suradnici, s jedne strane, omogućuje razlikovanje autoinflamatornih bolesti vezanih uz sustav prirođene imunosti od autoimunosnih bolesti koje su vezane uz sustav stečene imunosti. S druge strane, definicija implicira postojanje poremećaja na razini prirođene imunosti u podlozi bolesti. To je važno jer se time povećava vjerojatnost da će s porastom svijesti o postojanju autoinflamatornih bolesti koje su rijetke u kliničkoj praksi kompleksni bolesnici koji su godinama ostali neprepoznati napokon dobiti konačnu dijagnozu, ali i učinkovitu terapiju. Naime, prije su ove bolesti bile relativno nezanimljive budući da se o njima malo znalo i nije postojalo djelotvorno liječenje pa točna dijagnoza nije bila klinički izazov. No, otkad su se naše spoznaje proširile, a učinkovita terapija postala dostupnom, ispravna dijagnoza dobila je novo značenje.

Možemo, dakle, reći da su autoinflamatorne bolesti klinički poremećaji uzrokovani nedostatkom ili poremećajem regulacije prirođene imunosti, a obilježavaju ih ponavljana ili stalna upala (povišeni reaktanti akutne faze) i odsutnost primarne patogenetske uloge stečene imunosti (autoreaktivni T-limfociti ili proizvodnja protutijela) (5). Klinički se manifestiraju ponavljanim epizodama sustavne upale zbog aktivacije intenzivne nespecifične upalne reakcije bez očitog ili dovoljnog uzroka. U patogenetskom smislu riječ je o imunosno nespecifičnoj aktivaciji sustava prirođene imunosti, odnosno o neprimjerenoj aktivaciji prirođenog imunosnog sustava. Napadaji ne moraju imati očite okidače, ali mogu biti i nakon traume, cijepljenja, infekcije, stresa...

Table 1. Differences between autoinflammatory and autoimmune diseases (modified according to reference No. 6)
Tablica 1. Razlike između autoinflamatornih i autoimunosnih bolesti (prilagođeno prema referenciji 6.)

Characteristics / Karakteristika	Autoinflammatory disease / Autoinflamatorna bolest	Autoimmune disease / Autoimunosna bolest
Immune system disorder / Imunosni poremećaj	Native immunity / prirođena imunost	Acquired immunity / stečena imunost
Key cells / Ključne stanice u patogenezi	Neutrophils, macrophages / neutrofili, makrofagi	B and T-lymphocytes / B-limfociti i T-limfociti
Antibodies / Protutijela	Few or none / malo ili nimalo autoprotutijela	Positive / autoprotutijela prisutna
Clinical characteristics / Klinička obilježja	Recurrent episodes, often unprovoked / ponavljane epizode, često naizgled bez provocirajućeg čimbenika	Persistent progression / kontinuirana progresija
Pathogenetic concept / Patogenetski koncept	Tissue-specific danger signals / signali opasnosti specifični za tkiva	Autoantigen intolerance / poremećaj tolerancije na vlastite antigene
Genetic basis / Genska osnova	Cytokines and microbe-recognition pathways / citokini i putovi za prepoznavanje mikroorganizama	Association with MHC II system and acquired immunity genes / udruženost s MHC-om II i genima odgovornima za stečenu imunost
Investigations / Laboratorijska dijagnostika	Gene sequencing / sekvenciranje gena odgovornih za nastanak bolesti	Autoantibody and MHC II gene testing / dokaz autoprotutijela i gena MHC-a
Treatment / Liječenje	Inhibition of native immunity cytokine cascade (anti-TNF, anti-IL-1, anti-IL.6) Inhibition of neutrophil function (inflammasomes), i.e., with colchicine / blokada citokinske kaskade uključene u prirođenu imunost (npr., anti-TNF, anti-IL-1, anti-IL-6); blokada funkcije neutrofila (inflamasoma) (npr., kolhicin)	T-cell blockade (i.e., mycophenolate-mofetil, cyclosporin) B-cell blockade (i.e., rituximab) / blokada T-stanica (npr., mikofenolat-mofetil, ciklosporin); blokada B-limfocita (npr., rituksimab)

Legend / Legenda:
MHC: major histocompatibility complex / geni glavnoga sustava tkivne snošljivosti; TNF: tumor necrotizing factor / čimbenik tumorske nekroze; IL-1: interleukin 1; IL-6: interleukin 6

defining these conditions as immune regulation disorders divided into several categories according to the degree of overlap of innate and adaptive immunity disorders. Immune regulation disorders encompass not only autoimmune and autoinflammatory disease, but also primary immunodeficiency syndromes and several hematologic disorders such as hemophagocytic lymphohistiocytosis, autoimmune lymphoproliferative syndrome, etc. (6, 7).

Since the definition of autoinflammatory diseases is relatively new, incidence data is somewhat sparse. In a paper published in 2013 by Hemminki et al., the presumed incidence of these disorders in Sweden was 2.83 per 1,000,000. However, since autoinflammatory conditions often go unrecognized by clinicians, it is believed that the real numbers are higher, thus making it necessary to increase awareness of these diseases. The prevalence is variable, from 1:1,000 in Sweet syndrome to 1:1,000,000 in PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis) (9).

OVERVIEW OF THE PATHOGENESIS OF AUTOINFLAMMATORY DISEASES

Since new autoinflammation-associated genes are constantly being discovered, and new light is being

Ključne razlike između autoinflamatornih i autoimunosnih bolesti prikazane su na tablici 1. Iako se čini da je distinkcija između autoimunosnih i autoinflamatornih bolesti jasna, u praksi se kod većine poremećaja u različitom stupnju preklapaju fenotipske značajke autoimunosti i autoinflamacije. Stoga se sve više napušta dihotomna podjela autoimunosno/autoinflamatorno te se u svjetlu novih spoznaja govori o poremećajima imunosne regulacije koji obuhvaćaju nekoliko kategorija u kojima se u različitoj mjeri preklapaju poremećaji prirođene i stečene imunosti. U poremećaje imunosne regulacije uključuju se, osim autoimunosnih i autoinflamatornih bolesti, i primarne imunodeficijencije, ali i neki hematološki poremećaji (hemofagocitna limfohistiocitoza, autoimunosni limfoproliferativni sindrom itd.) (6, 7).

Budući da su autoinflamatorne bolesti relativno novodefinirana skupina bolesti, podatci o njihovoj učestalosti slabo su poznati. Hemminki i suradnici u radu iz 2013. godine procijenili su da incidencija autoinflamatornih bolesti u Švedskoj iznosi 2,83 bolesnika na milijun stanovnika (8), no budući da se radi o bolestima koje su relativno nepoznate liječnicima koji se njima uže ne bave i da imaju malenu incidenciju, vjeruje se da znatan broj bolesnika ostaje neprepoznat te

Table 2. Summary of pathogenesis of the most common autoinflammatory diseases
Tablica 2. Sumarni prikaz patogeneze najčešćih autoinflamatornih bolesti

	Inflammasomopathies / Inflamasomopatije	**Interferenopathies / Interferonopatije**	**Ubiquitinopathies (NF-κBpathies/TNFαpathies) / Ubikvitinopatije (NF-κBpatije/TNF-αpatije)**
Pathogenesis / Patogenetski mehanizam	Inflammasome overactivation / prekomjerna aktivacija inflamasoma	Interferon type 1 overactivation / prekomjerna aktivacija interferona tipa I	Disordered ubiquitination / poremećena ubikvitinacija
Genetic basis / Genska osnova	Functional and somatic mutations / mutacije dobitka funkcije i somatske mutacije	Variable; various genes / varijabilna, različiti geni	Function loss mutations, haploinsufficiency / mutacije gubitka funkcije, haploinsuficijencija
Clinical findings / Klinička obilježja	Episodic fever, rash / epizode vrućice, osipi	Lung and extremitiy vasculopathy; fibrosis; CNS calcifications / vaskulopatija okrajina i pluća; fibroza; kalcifikacije u središnjem živčanom sustavu	Granuloma, uveitis, ulcerations; overlap with immunodeficiencies / granulomi, uveitis, ulceracije; preklapanje s imunodeficijencijama
Treatment / Lijekovi	IL-1 inhibitors / inhibitori IL-1	JAK inhibitors / inhibitori JAK-a	TNFα inhibitors / inhibitori TNF-α

Legend / Legenda:
IL-1: interleukin 1; JAK: Janus kinase / Janusove kinaze; TNF-α: tumor necrotizing factor alfa / čimbenik tumorske nekroze alfa; CNS: central nervous system

shed on the mechanisms occurring in these disorders, explaining the pathogenesis of autoinflammation is not a simple task. Autoinflammatory diseases can be divided into monogenic (i.e., resulting from a mutation in one well-defined gene) and non-monogenic or unclassified (10). Conditions falling into the latter group are those with clinical and biological features of autoinflammatory diseases and no known causative gene or genes (for example, PFAPA syndrome, Schnitzler syndrome, systemic juvenile idiopathic arthritis) as well as some multifactorial disorders which are polygenic, i.e., defined by complex interactions of multiple genetic and environmental factors, showing no features of Mendelian inheritance pattern (e.g., gout, Behçet disease).

The majority of known monogenic autoinflammatory diseases are in fact inflammasomopathies since they result from mutations in inflammasome component genes. However, one must be aware that this is not the only autoinflammatory pathogenic mechanism (Table 2). There are several pathogenic patterns which define the known monogenic autoinflammatory diseases as inflammasomopathies, interferonopathies, ubiquitinopathies, complementopathies, and others. (10).

Inflammasomopathies result from mutations of genes associated with components of inflammasomes, intracellular multiprotein complexes that form in granulocyte and macrophage cytoplasm as a response to so-called danger signals. Danger signals are in fact various extracellular molecules derived from microorganisms or damaged cells (11). By binding to respective receptors they trigger an inflammatory cascade

je potrebno povećati svijest o postojanju tih bolesti. Prevalencija može varirati u rasponu od 1 : 1000 ljudi kao pri Sweetovu sindromu do 1 : 1.000.000, što je slučaj sa sindromom PFAPA (engl. *Periodic fever, aphthous stomatitis, pharyngitis, adenitis*) (9).

PREGLED PATOGENEZE AUTOINFLAMATORNIH BOLESTI

S obzirom na to da se kontinuirano otkrivaju novi geni povezani s autoinflamatornim bolestima te dolazi do novih spoznaja o mehanizmima uključenima u njihov nastanak, nije nimalo jednostavan zadatak objasniti njihovu patogenezu. Ugrubo se autoinflamatorne bolesti mogu podijeliti na monogenske, dakle, one koje su uzrokovane mutacijom u jednom, dobro definiranom genu, i na one koje nisu monogenske, a označavaju se i kao neklasificirane (10). U tu skupinu ubrajaju se bolesti koje zadovoljavaju kliničko-biološke kriterije za autoinflamatorne bolesti, ali do danas nemaju otkrivenu gensku podlogu (primjerice, sindrom PFAPA, Schnitzlerin sindrom, sustavni oblik juvenilnog idiopatskog artritisa), kao i neke multifaktorske bolesti koje su poligenske, odnosno uvjetovane složenim interakcijama većeg broja gena i okolišnih čimbenika te nisu povezane s mendelovskim obrascem nasljeđivanja (primjerice, giht, Behçetova bolest).

Glavnina do danas identificiranih monogenskih autoinflamatornih bolesti rezultat je mutacija u genima za komponente inflamasoma pa se ubrajaju u skupinu inflamasomopatija. Odmah treba naglasiti da to nije i jedini patogenetski mehanizam nastanka autoinflamatornih bolesti (tablica 2.). Može se reći da postoji nekoliko patogenetskih obrazaca nastanka do danas opisa-

consisting of two steps: the first step, "signal 1", mediated by nuclear factor kappa B (NF-kB), and the second step, "signal 2", which leads to inflammasome formation. "Signal 1" triggers the transcription of inflammasome components, pro-interleukin 18 and pro-interleukin 1 beta (pro-IL-1B), a precursor of interleukin 1B (IL-1B). "Signal 2", as mentioned, results in inflammasome formation leading to caspase-1 activation that transforms pro-IL-1B into IL-1B and pro-IL-18 into IL-18. Interleukins 1B and 18 are active forms which leave the cell and incite inflammation (9, 12).

Various genes for various inflammasomes are mutated in various inflammasomapathies (10): NLRP1 (arthritis and dyskeratosis syndrome), NRLP3 (cryopirine-associated periodic fever syndromes), NRLC4 (macrophage activation syndrome, syndrome of enterocolitis and self-inflammation), NLRP12 (FCAS2, i.e., familial cold inflammatory syndrome 2). The mentioned mutations lead to an overproduction of proinflammatory cytokines, primarily IL-1 but also IL-6, IL-18, and TNF-α (tumor necrosis factor α). Familial Mediterranean fever and pyrin-associated autoinflammatory disease with neutrophilic dermatosis are a consequence of the pyrin gene mutation. Mevalonate kinase defficiency (formerly known as hyper-IgD syndrome) also results from an overstimulation of pyrin and overproduction of IL-1. Mutations of the TNFRSF1A gene also lead to inflammasome overactivation. PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, acne) is associated with mutations of the PSTPIP1 gene responsible for encoding an adaptor protein that binds to pyrin; due to this mutation IL-1 is overproduced. Under normal conditions, the activity of proinflammatory cytokines IL-1 and IL-36 is controlled by endogenous antagonists IL1RN and IL36RN. Their mutations result in a dysregulation of cytokine signaling and amplification of the inflammatory response. Gene mutations of IL1RN are responsible for DIRA syndrome (deficiency of IL-1 receptor antagonist), and IL36N gene mutations result in DITRA syndrome (deficiency of interleukin thirty-six receptor antagonist). Most common clinical findings in inflammasomopathies are fever (mostly periodic), rash, serositis, hepatosplenomegaly, and lymphadenopathy. The basis of management in the majority of these disorders are IL-1 inhibitors.

Interferonopathies are a group of disorders resulting from an overactivation of interferon type 1 (IFN-α, IFN-β) (13, 14). Interferons can activate Janus kinases (JAK) and signal transducers and activators of transcription (STAT) proteins, leading to the transcription of multiple genes associated with the production of cytokines, chemokines, and apoptosis-controlling proteins, as well as to the liberation of proinflammatory cytokines from innate immunity cells. Inteferonopanih monogenskih autoinflamatornih bolesti, a to su inflamasomopatije, interferonopatije, ubikvitinopatije, komplementopatije i ostale (10).

Inflamasomopatije nastaju zbog mutacija gena vezanih uz komponente inflamasoma, a to su unutarstanični multiproteinski kompleksi koji se okupljaju u citoplazmi granulocita i makrofaga pod utjecajem signala opasnosti. Riječ je o različitim molekulama u izvanstaničnoj tekućini koje potječu iz različitih mikroorganizama odnosno molekulama što potječu od oštećenja vlastitih stanica (11). Nakon njihova vezanja za odgovarajuće receptore otpočinje upalna kaskada koja se sastoji od dva koraka što se označuju kao: signal 1, koji je posredovan nuklearnim čimbenikom kapa B (NF-κB), i signal 2 što završava stvaranjem inflamasoma. Signal 1 rezultira poticanjem transkripcije za komponente inflamasoma i za prointerleukin 1β (pro-IL-1β), koji je prekursor interleukina 1β (IL-1β), te prointerleukin 18. Signal 2 rezultira formiranjem inflamasoma čime se omogućuje aktivacija kaspaze 1 koja cijepa pro-IL-1β u IL-1β odnosno pro-IL-18 u IL-18 koji su aktivne forme, izlaze iz stanice i potiču upalu (9, 12).

U inflamasomopatijama dolazi do mutacija gena za različite inflamasome (10): *NLRP1* (sindrom s artritisom i diskeratozom), *NLRP3* (kriopirinski sindromi periodične vrućice), *NLRC4* (sindrom aktivacije makrofaga i sindrom enterokolitisa i samoupale), *NLRP12* (sindrom periodične vrućice FCAS2 prema engl. *Familial cold autoinflammatory syndrome 2*). Zbog tih mutacija dolazi do prekomjernog stvaranja proupalnih citokina, ponajprije IL-1, ali i IL-6, IL-18 te TNF-α (čimbenik tumorske nekroze alfa). Mutacijom gena za pirin, a to je protein koji je dio kompleksa inflamasoma, dolazi do nastanka obiteljske mediteranske vrućice i autoinflamatorne bolesti povezane s pirinom uz neutrofilnu dermatozu. Zbog manjka mevalonat kinaze (nekoć poznat pod nazivom sindrom hiper-IgD) također dolazi do prekomjerne stimulacije pirina i prekomjerne produkcije IL-1. Kod mutacije u genu *TNFRSF1A* dolazi do prekomjerne aktivacije inflamasoma. U inflasomopatije ubraja se i sindrom PAPA (piogeni sterilni artritis, gangrenozna pioderma, akne) povezan s mutacijom u genu *PSTPIP1* koji kodira adaptorski protein što se može vezati za pirin, pri čemu ponovo dolazi do prekomjerne produkcije IL-1. Aktivnost proupalnih citokina IL-1 i IL-36 u normalnim uvjetima ograničavaju endogeni antagonisti kao što su IL-1RN i IL-36RN. Zbog njihovih mutacija dolazi do poremećaja regulacije citokinske signalizacije i pojačanja upalnog odgovora. Tako zbog mutacije gena *IL1RN* nastaje sindrom DIRA (engl. *Deficiency of IL-1-receptor antagonist*), a mutacijom gena *IL36RN* sindrom DITRA (engl. *Deficiency of interleukin thirty-six-receptor antagonist*). Klinički se inflamasomopatije najčešće manifestiraju vrućicom (nerijetko periodičnog tipa),

thies manifest as extremity and lung vasculopathies, fibrosis, cold-sore-like skin changes, intracranial calcium deposits, and myositis. Examples of interferonopathies are: Aicardi-Goutieres syndrome resulting from DNA repairing TREX1 gene mutations that lead to a hyperproduction of IFN-α type I; STING-associated vasculopathy with onset in infancy (SAVI), a severe vasculitis resulting from STING (stimulator of interferon genes) gene mutations; and chronic atypical neutrophilic dermatosis with lypodystrophy and elevated temperature (CANDLE). JAK inhibitors are the foundation of treatment.

Ubiquitinopathies or NF-kBpathies affect one or more molecules called ubiqutins. These are proteins that mark other proteins for catabolism by binding to them. They are also of importance for the stability, function, and intracelullar position of various proteins. The aforementioned binding process is named ubiquitinization, whose opposite is deubiqutinization. LUBAC (linear ubiquitin chain assembly complex) is a protein complex built from several ubiquitin proteins (HOP, HOIL-1, SHARPIN), and its role is to activate the NF-kB signaling pathway. Mutations in the LUBAC gene result in autoinflammation, immunodeficiency, and myopathy. A20 and OTULIN molecules are deubiquitinases that inhibit the NF-kB signaling pathway; if their respective genes are mutated, autoinflammatory disorders occur: haploinsufficiency A20 and otulipenia (15, 16). Since ubiquitinopathies are associated with NF-kB signaling pathway abnormalities, they are often called NF-kBpathies. Common clinical features are granulomas, ulcerations, uveitis, and immunodeficiency. The basis of treatment are TNF-α inhibitors, thus these disorders are also known as TNF-α-pathies.

Complementopathies result from inappropriate complement activation and some of the disorders in this group are autoinflammatory diseases in nature (17). An example is aHUS, atypical hemolytic-uremic syndrome, caused by mutations in the CFH, THBD, CFI, and CD46 genes, which leads to anemia, thrombocytopenia, and renal failure.

OVERVIEW OF THE MOST COMMON AUTOINFLAMMATORY DISORDERS ACCORDING TO PATHOGENESIS

Inflammasomopathies

Members of this group of disorders are monogenic periodic fever syndromes (i.e., familial Mediterranean fever, mevalonate kinase deficiency, TNF-receptor-associated periodic fever, cyropirine-associated periodic fever syndromes), which were in fact the first described examples of autoinflammatory diseases; DIRA syndrome, Majeed syndrome, as well as a subgroup known as resistent inflammasomopathies which includes

osipima, serozitisom, hepatosplenomegalijom i limfadenopatijom. Terapijski pristup u velikom broju ovih bolesti temelji se na primjeni inhibitora IL-1.

Interferonopatije čine grupu poremećaja s prekomjernom aktivacijom interferona tipa I (IFN-α, IFN-ß) (13, 14). Interferoni mogu aktivirati Janusove kinaze (JAK) i proteine koji posreduju u aktivaciji i prijenosu signala (engl. *Signal transducers and activators of the transcription* – STAT). Na kraju dolazi do transkripcije brojnih gena uz stvaranje citokina, kemokina, proteina koji kontroliraju apoptozu te sekrecije proupalnih citokina iz stanica prirođene imunosti. Klinički se interferonopatije najčešće manifestiraju vaskulopatijama ekstremiteta i pluća, nastankom fibroznih promjena, nastankom kožnih promjena nalik na ozebline, intrakranijalnim kalcifikacijama i miozitisom. Primjeri interferonopatija jesu Aicardi-Goutièresin sindrom zbog mutacije gena *TREX1* koji je uključen u popravak oštećenja DNK, pri čemu zbog mutacije dolazi do hiperprodukcije IFN-a tipa I; zatim teški vaskulitis s početkom u dojenačkoj dobi zbog mutacije u genu *STING* (stimulator interferonskih gena) poznat pod nazivom SAVI (engl. *STING-associated vasculopathy with onset in infancy*); kronična neutrofilna dermatoza s lipodistrofijom i vrućicom poznata pod akronimom CANDLE (engl. *Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature*). U liječenju se rabe inhibitori JAK-a.

Ubikvitinopatije ili NF-κBpatije jesu poremećaji koji zahvaćaju jednu ili više molekula koje se nazivaju ubikvitini. Ubikvitini su bjelančevine koje se vežu na druge proteine i time obilježavaju stanične proteine koji će se razgraditi, a važni su i za stabilnost, funkciju i unutarstanični položaj velikog broja proteina. Ovaj se proces naziva ubikvitinacija. Suprotan proces, kojim se molekule ubikvitina uklanjaju s proteina, naziva se deubikvitinacija. LUBAC (engl. *Linear ubiquitin chain assembly complex*) jest proteinski kompleks što se sastoji od proteina HOP, HOIL-1 i SHARPIN, koji imaju funkciju ubikvitina, i djeluje tako što aktivira signalni put NF-κB. Mutacije u genu za LUBAC dovode do autoinflamacije, imunodeficijencije i miopatije. Molekule A20 i OTULIN imaju funkciju deubikvitinaza i inhibiraju signalni put NF-κB, a mutacije dovode do autoinflamacije: haploinsuficijencija A20 i otulipenija (15, 16). Budući da su, dakle, ubikvitinopatije poremećaji koji su usko vezani uz abnormalnosti signalnog puta NF-κB, često se nazivaju i NF-κBpatijama. Najčešće se manifestiraju nastankom granuloma, ulceracija, uveitisa te imunodeficijencijom. Terapijski pristup u ovim bolestima temelji se na primjeni inhibitora TNF-α pa se katkad označuju i kao TNF-αpatije.

Komplementopatije skupina su poremećaja u kojima dolazi do neprimjerene aktivacije komplementa i neki od tih poremećaja također se ubrajaju u autoinflamatorne bolesti (17). Kao primjer može se navesti atipični

Table 3 a. Eurofever/PRINTO classification criteria for hereditary recurrent fevers (modified according to reference No. 19)
Tablica 3. a. Eurofeverovi/PRINTO-ovi klasifikacijski kriteriji za nasljedne periodične vrućice (prilagođeno prema referenciji 19.)

FMF	MKD	TRAPS	CAPS
Presence of a pathogenic or potentially pathogenic variant in the MEFV gene and at least one of the following criteria: / Prisutnost patogene ili vjerojatno patogene varijante u genu *MEFV* uz zadovoljavanje barem jednog od četiriju kriterija: • febrile episodes lasting up to 3 days / febrilne epizode u trajanju od jednog do tri dana • arthritis / artritis • chest pain / bol u prsima • abdominal pain / bol u trbuhu	Presence of a pathogenic or potentially pathogenic variant in the MVK gene and at least one of the following criteria: / Prisutnost patogene ili vjerojatno patogene varijante u genu *MVK* uz još najmanje jedan kriterij: • gastrointestinal symptoms / gastrointestinalni simptomi • neck lymphadenopathy / limfadenopatija vrata • aphthous stomatitis / aftozni stomatitis	Presence of a pathogenic or potentially pathogenic variant in the TNFRSF1A gene and at least one of the following criteria: / Prisutnost patogene ili vjerojatno patogene varijante u genu *TNFRSF1A* uz još najmanje jedan kriterij: • episodic fever lasting at least for 7 days / febrilne epizode u trajanju od 7 dana ili dulje • myalgia / mialgija • migrating rash / migrirajući osip • periorbital edema / periorbitalni edemi • positive family history / pozitivna obiteljska anamneza	Presence of a pathogenic or potentially pathogenic variant in the NLRP3 gene and at least one of the following criteria: / Prisutnost patogene ili vjerojatno patogene varijante u genu *NLRP3* uz još najmanje jedan kriterij: • urticaria-like rash / osip nalik na urtikarijski • red eye (conjunctivitis, episcleritis, uveitis) / crveno oko (konjunktivitis, episkleritis, uveitis) • sensorineural hearing loss / senzorineuralni gubitak sluha
Presence of a variant not proven to be pathogenic or potentially pathogenic and at least two of the following criteria: / Prisutnost varijante koja nije dokazano patogena ili vjerojatno patogena uz zadovoljavanje barem dvaju od četiriju kriterija: • febrile episode lasting up to 3 days / febrilne epizode u trajanju od jednog do tri dana • arthritis / artritis • chest pain / bol u prsima • abdominal pain / bol u trbuhu		Presence of a variant not proven to be pathogenic or potentially pathogenic and at least two of the following criteria: / Prisutnost varijante koja nije dokazano patogena ili vjerojatno patogena uz zadovoljavanje barem dvaju kriterija: • episodic fever lasting at least for 7 days / febrilne epizode u trajanju od 7 dana ili dulje • myalgia / mialgija • migrating rash / migrirajući osip • periorbital edema / periorbitalni edemi • positive family history / pozitivna obiteljska anamneza	Presence of a variant not proven to be pathogenic or potentially pathogenic and at least two of the following criteria: / Prisutnost varijante koja nije dokazano patogena ili vjerojatno patogena uz zadovoljavanje barem dvaju kriterija: • urticaria-like rash / osip nalik na urtikarijski • red eye (conjunctivitis, episcleritis, uveitis) / crveno oko (konjunktivitis, episkleritis, uveitis) • sensorineural hearing loss / senzorineuralni gubitak sluha

Legend / Legenda: FMF: familial Mediterranean fever / obiteljska mediteranska vrućica; MKD: mevalonate kinase deficiency / manjak mevalonat kinaze; TRAPS: tumor necrosis factor receptor-associated periodic syndrome / periodične vrućice vezane uz receptor čimbenika tumorske nekroze; CAPS: cryopyrin-associated periodic syndromes / kriopirinski sindromi periodične vrućice

PAPA syndrome and NLRC4-associated macrophage activation syndrome (NLRC4-MAS).

Periodic fever syndromes

Periodic or recurrent fever syndromes are autoinflammatory disorders defined by three or more episodes of unexplained/non-infectious fever (i.e., body temperature ≥ 38°C) in a 6-month period with symptom-free intervals between episodes lasting 7 or more days. In most cases the fever is greater than 39°C, and symptom-free intervals can be regular and irregular (18). Between fever episodes, the affected children are usually well, without growth and development impair-

hemolitičko-uremijski sindrom (aHUS) koji je uzrokovan mutacijama u genima *CFH*, *THBD*, *CFI* i *CD46* pri čemu dolazi do hemolitičke anemije, trombocitopenije i zatajenja bubrega.

PRIKAZ NAJČEŠĆIH AUTOINFLAMATORNIH BOLESTI PREMA PATOGENETSKIM MEHANIZMIMA NASTANKA

Inflamasomopatije

U skupinu inflamasomopatija ubrajaju se monogenski sindromi periodičnih vrućica (obiteljska medite-

Table 3 b. Eurofever/PRINTO clinical classification criteria for hereditary recurrent fevers and PFAPA (modified according to reference No. 19)

Tablica 3. b. Eurofeverovi/PRINTO-ovi klinički kriteriji za nasljedne periodične vrućice i sindrom PFAPA (prilagođeno prema referenciji 19.)

FMF	MKD	TRAPS	CAPS	PFAPA
At least 6 out of 9 criteria need to be fulfilled. Presence of: / Ispunjavanje najmanje šest od ukupno devet kriterija. Prisutnost: • Eastern Mediterranean origin / istočnomediteranskog podrijetla • arthritis / artritisa • chest pain / boli u prsima • abdominal pain / boli u trbuhu	At least 3 out of 6 criteria need to be fulfilled. Presence of: / Ispunjavanje najmanje triju od šest kriterija. Prisutnost: • disease onset in the first year of life / početka bolesti prije navršene prve godine života • gastrointestinal symptoms / gastrointestinalnih simptoma • painful lymph nodes / bolnih limfnih čvorova • aphthous stomatitis / aftoznog stomatitisa • maculopapular rash / makulopapuloznog osipa • noticable disease triggers such as infection, immunization, trauma, stress / zamijećenih okidača (trigeri) pojave bolesti kao što su infekcija, cijepljenje, ozljeda ili stres	Five (5) or more points. Presence of: / Ostvarivanje 5 ili više bodova. Prisutnost: • episodes of fever lasting 7 or more days (2 pts) / epizode vrućice u trajanju od 7 ili više dana (2 boda) • febrile episodes lasting 5 or 6 days (1 pt) / epizode vrućice u trajanju od 5 do 6 dana (1 bod) • myalgia (1 pt) / mialgija (1 bod) • migrating rash (1 pt) / migrirajući osip (1 bod) • periorbital edema (1 pt) / periorbitalni edemi (1 bod) • positive family history (1 pt) / pozitivna obiteljska anamneza (1 bod)	At least 2 out of 5 criteria need to be fulfilled. Presence of: / Ispunjavanje najmanje dvaju od pet kriterija. Prisutnost: • urticaria-like rash / osipa nalik na urtikarijski • cold- or stress-induced disease episodes / epizode pojave bolesti potaknute hladnoćom ili stresom • sensorineural hearing loss / senzorineuralnoga gubitka sluha • chronic aseptic meningitis / kroničnog aseptičnog meningitisa • bone anomalies (abnormal epiphyseal growth or prominent forehead) / anomalije skeleta (prekomjerni rast epifiza kostiju ili prominentno čelo)	Seven (7) out of 8 criteria need to be fulfilled. Presence of: / Ispunjavanje najmanje sedam od osam kriterija. Prisutnost: • tonsillo-pharyngitis / tonzilofaringitisa • recurring febrile episodes lasting 3–6 days / ponavljanih febrilnih epizoda koje traju 3 – 6 dana • neck lymphadenitis / limfadenitisa vrata • periodicity / periodičnosti pojavljivanja
Absence of: / Odsutnost: • aphthous stomatitis / aftoznog stomatitisa • urticarial rash / urtikarijskog osipa • maculopapular rash / makulopapuloznog osipa • painful lymph nodes / bolnih limfnih čvorova		Absence of: / Odsutnost: • aphthous stomatitis (1 pt) / aftoznog stomatitisa (1 bod) • tonsillopharyngitis (1 pt) / tonzilofaringitisa (1 bod)		Absence of: / Odsutnost: • diarrhea / proljeva • chest pain / boli u prsima • rash / osipa • arthritis / artritisa

Legend / Legenda: FMF: familial Mediterranean fever / obiteljska mediteranska vrućica; MKD: mevalonate kinase deficiency / manjak mevalonat kinaze; TRAPS: tumor necrosis factor receptor-associated periodic syndrome / periodične vrućice vezane uz receptor čimbenika tumorske nekroze; CAPS: cryopyrin-associated periodic syndromes / kriopirinski sindromi periodične vrućice; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis / sindrom periodične vrućice, aftoznog stomatitisa, faringitisa i adenitisa

ment. Leukocytosis and increased acute phase reactants are characteristic laboratory findings during febrile episodes; these findings, as well as other symptoms, diminish as the fever drops, or within 4 days. Disease onset usually occurs in the first decade, a positive family history is common, and in some cases ethnic origin is also an importan factor (e.g., Eastern

ranska vrućica, manjak mevalonat kinaze, periodična vrućica vezana uz receptor TNF-α, kriopirinski sindromi periodične vrućice), što su prvi opisani primjeri autoinflamatornih bolesti, zatim sindrom DIRA, Majeedov sindrom te skupina bolesti koje su poznate pod zajedničkim nazivom rezistentne inflamasomopatije, kamo pripadaju sindrom PAPA i sindrom aktivaci-

Table 4. Comparative view of disorders within the cryopyrin associated periodic syndromes (made according to reference No. 21)

Tablica 4. Usporedni prikaz kliničkog spektra poremećaja u sklopu kriopirinskih sindroma periodične vrućice (izrađeno prema podatcima iz referencije 21.)

	FCAS	MWS	CINCA/NOMID
Clinical features / Kliničke značajke	• cold-induced rash / osip potaknut hladnoćom • arthralgia / artralgija • myalgia / mialgija • conjunctivits / konjunktivitis • lack of energy / umor • headache / glavobolja • short-lasting episodes of fever (12–24 hours) / kratkotrajne epizode vrućice u trajanju od 12 do 24 sata	• cold-induced rash / osip potaknut hladnoćom • arthralgia or arthritis / artralgija ili artritis • myalgia / mialgija • conjunctivitis / konjunktivitis • lack of energy / umor • headache / glavobolja • fever lasting 2–3 days / epizode vrućice u trajanju od 2 do 3 dana • progressive hearing loss / progresivni gubitak sluha • kidney failure / zatajenje bubrega	• rash / osip • knee-, ankle-, elbow-, and wrist-deforming arthropathy with contracture development / artropatija s deformitetima koljena, gležnjeva, laktova i zapešća uz razvoj kontraktura • short stature, short arms and fingers, macrocranium / nizak rast uz kratke ruke i prste te makrokranij • chronic aseptic meningitis (vomiting, headache, seizures, hydrocephalus, brain and optic nerve atrophy, blindness) / kronični aseptični meningitis (povraćanje, glavobolje, konvulzije, hidrocefalus, atrofija mozga i vidnog živca, sljepoća) • uveitis • intermittent fever / intermitentni febriliteti • progressive hearing loss / progresivni gubitak sluha • kidney failure / zatajenje bubrega
Symptom duration / Trajanje simptoma	Less than 24 hours / najčešće kraće od 24 sata	Daily / svaki dan	Daily / svaki dan
Symptom onset / Početak simptoma	< 20 years / < 20 godina	< 6 months / < 6 mjeseci	infancy / novorođenačka dob
Outcome / Posljedice	• limited daily activites / ograničenje u dnevnim aktivnostima	• limited daily activites / ograničenje u dnevnim aktivnostima • sensorineural hearing loss / senzorineuralni gubitak sluha • amyloidosis and kidney failure / amiloidoza sa zatajenjem bubrega	• development retardation / zaostajanje u razvoju • sensorineural hearing loss / senzorineuralni gubitak sluha • blindness / sljepoća • amyloidosis and kidney failure / amiloidoza sa zatajenjem bubrega

Legend / Legenda: FCAS: familial cold autoinflammatory syndrome / obiteljski autoinflamatorni sindrom uzrokovan hladnoćom; WS: Muckle-Wells syndrome / Muckle-Wellsov sindrom; NOMID/CINSA: neonatal onset multisystem inflammatory disease / chronic infantile neurologic cutaneous articular syndrome / multisustavna inflamatorna bolest s početkom u novorođenačkoj dobi

Mediterranean, Middle East: Turks, Arabs; Southern Europe: Italians, Greeks, Spaniards). Febrile episodes in periodic fever syndromes are classified as short-lasting (24–48 h; familial Mediterranean fever), medium-length (4 to 7 days; mevalonate kinase deficiency), and long-lasting (TNF-receptor-associated periodic fever syndrome) (19).

In March 2017, at a Consensus Conference held in Genoa, an expert group consisting of clinicians and geneticists established a new set of classification and clinical criteria for inherited periodic fever syndromes and PFAPA syndrome (19). The new criteria, known as the Eurofever/PRINTO (Pediatric Rheumatology International Trials Organization) criteria, are used in clinical and epidemiological research and are shown in Tables

je makrofaga povezan s inflamasomom *NLRC4* (engl. *NLRC4-associated macrophage activation syndrome* – NLRC4-MAS).

Sindromi periodičnih vrućica

Sindromi periodičnih ili rekurentnih vrućica jesu autoinflamatorne bolesti obilježene ponavljanim febrilnim epizodama u odsutnosti infekcije, pri čemu je za zadovoljavanje definicije potrebno imati bolesnika s tri ili više epizoda vrućice ≥ 38 °C u razmaku većem od 7 dana u periodu od minimalno 6 mjeseci. Vrućica je nerijetko viša od 39 °C, a intervali između febriliteta mogu biti pravilni ili nepravilni (18). Između epizoda febriliteta dijete je obično dobro i normalno raste. Tijekom epizoda febriliteta prisutni su leukocitoza i povi-

3a and 3b. According to the criteria, each disease needs a confirmed gene mutation. If a gene mutation is pathogenic or its pathogenicity is highly probable, fewer clinical parameters need to be fulfilled for the diagnosis; the opposite is the case if the mutation is not proven to be pathogenic or is unlikely pathogenic. The aforementioned expert group also established clinical criteria that are not based on gene testing and can be used in everyday clinical practice. Since cryopyrin-associated periodic syndromes (CAPS) manifest in a broad clinical spectrum from mild to severe conditions (in order of severity: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease / chronic infantile neurologic cutaneous articular syndrome (NOMID/CINCA)), they are summarized in Table 4 (20, 21).

Colchicine is the basis of FMF management as it reduces leukocyte motility and phagocytosis, in addition to preventing the development of amyloidosis and proteinuria. Anakinra, an IL-1 receptor antagonist, is an alternative treatment option in refractory cases; other options are TNF-α and α-interferon inhibitors (22). Mevalonate kinase deficiency is treated with glucocorticoids, anakinra, TNF-α inhibitors and simvastatin (23). Glucocorticoids and biologics such as TNF-α inhibtors (e.g., etanercept) and anakinra are used in the treatment of TRAPS (24), and IL-1 inhibitors (anakinra, canakinumab) are used for treating CAPS (20, 21).

Although not a monogenic disease like the other mentioned conditions, PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) is traditionally a member of the periodic fever syndrome family, and it is in fact the most common type of periodic fever syndromes. Effective treatment options are glucocorticoids in a solitary dose of 0.1 to 1 mg/kg, tonsillectomy, or anakintra (25). In most cases, the condition spontaneously resolves between the 6th and 8th year of life.

DIRA (IL-1 receptor antagonist deficiency) and Majeed syndrome

DIRA syndrome is an autosomal recessive disease caused by a mutation in the IL1RN gene responsible for coding the IL-1 receptor antagonist that normally controls the inflammatory activity of proinflammatory cytokine IL-1 (26). The result is a dysregulation of cytokine pathways and an amplified inflammatory response. This condition most often presents with skin (usually pustular) and bone (sterile bone inflammation) manifestations that occur within the first several days of life; cerebral vasculitis, pulmonary hemosiderosis with lung fibrosis, hypotonia, and impaired growth and development can also occur. Inflammatory markers are increased and usually there is no fever. IL-1 inhibitors (anakinra) are used for treatment.

šeni reaktanti akutne faze upale uz normalizaciju laboratorijskih nalaza i prestanak simptoma nakon završetka ili u 4 dana od završetka epizode febriliteta. Početak bolesti najčešće je u prvih 10 godina života. Obiteljska anamneza često je pozitivna, a za neke bolesti bitno je i etničko podrijetlo bolesnika (npr., istočni Mediteran, srednji Istok: Turci, Arapi, južna Europa: Talijani, Grci, Španjolci). Prema duljini febrilnih epizoda, mogu se podijeliti na one s kratkim epizodama (od 24 do 48 sati) kao što je obiteljska mediteranska vrućica, na one sa srednje dugim epizodama vrućice (od 4 do 7 dana) kao što je nedostatak mevalonat kinaze te na one s prolongiranim febrilnim epizodama kao što je periodična vrućica vezana uz receptor TNF-α (19).

Skupina od 33 eksperta iz područja autoinflamatornih bolesti (uključujući kliničare i genetičare) na konsenzusnoj je konferenciji, održanoj u Genovi u ožujku 2017., donijela klasifikacijske i kliničke kriterije za nasljedne periodične vrućice i sindrom PFAPA (19). Ti se novi Eurofeverovi/PRINTO-ovi (engl. *Paediatric Rheumatology INternational Trials Organisation*) klasifikacijski kriteriji rabe pri kliničkim i epidemiološkim istraživanjima. Prikazani su na tablicama 3. a i 3. b. Zajedničko im je da za svaku pojedinu bolest iz ove skupine iziskuju potvrđenu mutaciju u genu vezanom uz nastanak bolesti. Ako je dokazana patogena ili vjerojatno patogena varijanta u određenom genu, potrebno je zadovoljiti manji broj ostalih kriterija nego pri mutaciji koja nije dokazano patogena ili vjerojatno patogena. Navedena skupina eksperata donijela je i kliničke kriterije koji se rabe za postavljanje dijagnoze kod pojedinog bolesnika u svakodnevnom radu, a ne temelje se na dokazanoj genskoj mutaciji. Budući da kriopirinski sindromi periodične vrućice (engl. *Cryopyrin-associated periodic syndromes* – CAPS) uključuju spektar bolesti od blagih do teških (prema težini: obiteljski autoinflamatorni sindrom uzrokovan hladnoćom (engl. *Familial cold autoinflammatory syndrome* – FCAS), Muckle-Wellsov sindrom i multisustavna inflamatorna bolest s početkom u novorođenačkoj dobi (engl. *Neonatal onset multisystem inflammatory disease / Chronic infantile neurological cutaneous articular syndrome* – NOMID/CINCA), njihove su značajke sažete na tablici 4. (20, 21).

Temelj liječenja obiteljske mediteranske vrućice (engl. *Familial mediterranean fever* – FMF) jest primjena kolhicina koji djeluje tako što usporava motilitet leukocita i fagocitozu te prevenira razvoj amiloidoze i proteinurije. U rezistentnih oblika bolesti alternativa je antagonist receptora za interleukin 1, odnosno anakinra, a ostali modaliteti liječenja uključuju inhibitore TNF-α i α-interferon (22). Pri liječenju manjka mevalonat kinaze primjenjuju se glukokortikoidi, anakinra, inhibitori TNF-α te simvastatin (23). Liječenje periodične vrućice vezane uz receptor TNF-α (engl. *Tumor ne-*

Majeed syndrome is also an autosomal recessive autoinflammatory disease, monogenic in nature and caused by a mutation in the LPIN2 gene, a coding gene for lipin-2 protein (27). The pathophysiological effects of changes in lipin-2 acitivity are unknown. Majeed syndrome usually occurs in the first 2 years of life with cardinal clinical manifestations such as recurrent fever, skin changes (pustular changes or changes similar to Sweet syndrome), bone inflammation (chronic recurring osteomyelitis), and anemia. Patients can be treated with non-steroidal anti-inflammatory agents, glucocorticoids and IL-1 inhibitors.

PAPA syndrome

PAPA is an acronym for the classical clinical triad of this syndrome: pyogenic sterile arthritis, pyoderma gangrenosum, and acne. The condition is inherited in an autosomal dominant fashion. It results from a mutation in the PSTPIP1 gene which codes a pyrin-binding adaptor protein; this mutation leads to an overproduction of IL-1 (28). This disease usually manifests in the first decade of life. Fever is rarely present, leukocytosis with neutrophilia is a common finding. A recurrent, pyogenic yet sterile, and erosive arthritis is the first manifestation. It begins in early childhood, either spontaneously or after a minor trauma, and it affects the elbows, knees, and ankles. Arthritis continues into adulthood, leading to joint destruction. Skin changes first appear in adolescence as prominent cystic acne or pyoderma gangrenosum. IL-1 inhibitors (anakinra) are efficent in the treatment of pyogenic arthritis, and anti-TNF agents combined with retinoids in the treatment of skin changes.

Interferonopathies

Clinically, the most important interferonopathies are Aicardi-Goutières syndrome, severe neonatal STING-associated vasculopathy with onset in infancy, and a group of diseases known as proteasome-associated autoinflammatory syndrome (PRAAS).

Aicardi-Goutières syndrome

Aicardi-Goutières syndrome is a genetically heterogeonus disorder caused by mutations in one out of seven different genes resulting in an overproduction of type I interferon (29). It most often affects the central nervous system and the skin. There are two types of the disease – early- and late-onset. The early-onset type is more severe; symptoms manifest in the perinatal period and include neurological disorders (involuntary movements, tremor, feeding difficulties), hepatosplenomegaly, increased liver enzymes, and thrombocytopenia. Late-onset disease occurs after several weeks or months of normal development manifesting

crosis factor receptor-associated periodic syndrome – TRAPS) temelji se na primjeni glukokortikoida i bioloških terapije (inhibitori TNF-α kao što je etanercept i anakinra) (24). Liječenje kriopirinskih sindroma periodične vrućice (engl. *Cryopyrin-associated periodic syndromes* – CAPS) provodi se inhibitorima interleukina 1 (anakinra i kanakinumab) (20, 21).

U sindrome periodičnih vrućica tradicionalno se ubraja i sindrom ***PFAPA*** (engl. *Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis*), odnosno sindrom periodične vrućice, aftoznog stomatitisa, faringitisa i adenitisa koji je najčešći sindrom periodičnih vrućica, premda se ne radi o monogenskoj autoinflamatornoj bolesti za razliku od prije nabrojenih. Pri liječenju mogu biti učinkovite jednokratna primjena glukokortikoida u dozi od 0,1 do 1,0 mg/kg, tonzilektomija ili anakinra (25). U većine bolesnika epizode spontano prestanu u dobi od 6 do 8 godina.

Sindrom DIRA (engl. Deficiency of the IL-1-receptor antagonist*) i Majeedov sindrom*

Sindrom DIRA jest autosomno recesivna bolest uzrokovana mutacijom u genu *IL1RN* koji kodira za antagonist receptora za IL-1 i u normalnim uvjetima ograničava aktivnost proupalnog citokina IL-1 (26). Posljedično dolazi do poremećaja regulacije citokinske signalizacije i pojačanja upalnog odgovora. Najčešće su kožne (obično pustularne) i koštane manifestacije bolesti (sterilne upale kostiju) koje se pojavljuju već u prvim danima života, a uz to se mogu pojaviti cerebralni vaskulitis, plućna hemosideroza s razvojem fibroze pluća, hipotonija, nenapredovanje djeteta. Upalni su parametri povišeni, a vrućice obično nema. Pri liječenju se rabi inhibitor IL-1 (anakinra).

Majeedov je sindrom autosomno recesivna monogenska autoinflamatorna bolest uzrokovana mutacijom u genu *LPIN2* koji kodira za protein lipin 2 (27). Nije jasno na koji način promjene u aktivnosti ovog proteina uzrokuju nastanak bolesti. Bolest obično započinje prije navršene 2. godine. Glavna su obilježja bolesti ponavljane epizode vrućice, upala kože (promjene na koži pustularne su ili odgovaraju Sweetovu sindromu) i kostiju (kronični rekurentni osteomijelitis) te anemija. U liječenju se rabe nesteroidni protuupalni lijekovi, glukokortikoidi i inhibitor IL-1.

Sindrom PAPA

Naziv sindroma PAPA akronim je trijasa simptoma koji se u njemu javljaju: piogeni sterilni artritis, gangrenozna pioderma i akne. Bolest se nasljeđuje autosomno dominantno, a rezultat je mutacije u genu *PSTPIP1* koji kodira adaptorski protein što se može vezati za pirin, a to dovodi do prekomjerne produkcije IL-1 (28). Bolest najčešće počinje u prvom desetljeću života. Vrućica je ovdje rijetko prisutna, a u nalazima

with psychomotor retardation, microcephaly, and episodes of encephalopathy marked with irritability, inconsolable crying, and feeding difficulties. Intermittent fever and convulsions can also occur. Ultimately the condition results in permanent neurological damage such as intellectual deficits, hand muscle spasticity, core muscle dystonia, and hypotonia. Leukodystrophy and brain calcifications develop. Vasculitis causes painful, red and swollen frostbite-like skin changes on the fingers, toes, and ears. Some patients have immune system disorders and develop systemic erythematosus lupus. Apart from symptomatic treatment, there were also trials of JAK-inhibitors (with variable results) and antiretroviral agents used for treating HIV infection.

STING-associated vasculopathy with onset in infancy (SAVI)

SAVI is an interferonopathy caused by an autosomal dominant mutation of the STING1 gene, an interferon gene stimulator (14). The skin and lungs are affected in most cases. Vasculopathy-induced skin changes develop in the first few months of life, usually affecting the face, nose, ears, fingers, and toes. These changes begin as skin discolorations which progress to ulcerations and finally to necrotising ulcers leading to scarring, nasal septum perforation, and finger or toe amputation. Interstitial lung disease occurs, leading to pulmonary fibrosis and respiratory insufficiency. Lymphadenopathy and intermittent fever can occur. JAK-inhibitors are the treatment of choice.

Proteasome-associated autoinflammatory syndrome (PRAAS)

An example from this spectrum of disorders is chronic neutrophilic dermatosis with lipodystrophy and fever (30). It is a disease caused by mutations in the proteasome subunit- encoding gene. Proteasomes are protein complexes responsible for eliminating intracellular protein detritus and foreign protein degradation. Proteasome dysfunction leads to accumulation of said detritus within the cell and interferon type I production. The disease manifests in the first few months of life, starting with frostbite-like skin changes, circular plaques, and erythematous edema. Fever is common. The skin changes are followed by lipodystrophy and, ultimately, joint changes. JAK-inhibitor trials are ongoing.

Ubiquitinopathies

These conditions are closely associated with NF-kB signaling pathway abnormalities (15). An example is Blau syndrome, an autosomal dominant disorder caused by a mutation in the NOD2 gene. The syndrome is characterized by a clinical triad – early-onset polyarse često vidi leukocitoza s neutrofilijom. Najprije se pojavljuje artritis. Artritis je rekurentan, piogen, ali sterilan i erozivan, a započinje obično u ranoj dječjoj dobi, spontano ili nakon manje traume te zahvaća laktove, koljena i gležnjeve. Simptomi su prisutni do odrasle dobi, a dovode do destrukcije zglobova. Kožne promjene javljaju se u adolescenciji kao izražene cistične akne ili gangrenozna pioderma. Pri liječenju piogenog artritisa primjenjuje se inhibitor IL-1 (anakinra), a u liječenju kožnih manifestacija pripravci anti-TNF-α u kombinaciji s retinoidima.

Interferonopatije

Najvažnije interferonopatije jesu Aicardi-Goutièresin sindrom, teški vaskulitis s početkom u dojenačkoj dobi zbog mutacije u genu *STING* te skupina bolesti pod nazivom autoinflamatorni sindrom povezan s poremećajem funkcije proteasoma (engl. *Proteasome-associated autoinflammatory syndrome* – PRAAS).

Aicardi-Goutièresin sindrom

Riječ je o genski heterogenoj bolesti uzrokovanoj mutacijama u jednom od sedam različitih gena zbog čega dolazi do prekomjernog stvaranja interferona tipa I (29). Najčešće su zahvaćeni središnji živčani sustav i koža. Postoje dva oblika bolesti – rani i kasni. U ranom obliku bolesti, koji je teži, simptomi se javljaju odmah nakon rođenja i uključuju neurološke poremećaje (nevoljne pokrete, tremor, poremećaje hranjenja), hepatosplenomegaliju, povišene jetrene enzime i trombocitopeniju. U kasnom obliku bolesti nakon nekoliko tjedana ili mjeseci normalnog razvoja dolazi do zaostajanja u psihomotoričkom razvoju, pojave mikrocefalije i epizoda encefalopatije tijekom koje su djeca izrazito razdražljiva uz neutješan plač i poremećaj hranjenja. Mogu se pojaviti intermitentni febriliteti i konvulzije. Naposljetku obično dolazi do trajnih neuroloških oštećenja koja se manifestiraju teškim intelektualnim poremećajima, spasticitetom mišića ruku, distonijom i hipotonijom mišića trupa. Dolazi do razvoja leukodistrofije i kalcifikata u mozgu. Promjene na koži nalikuju na ozebline. Uzrokovane su vaskulitisom, a manifestiraju se kao bolne, crvene i otečene promjene na prstima ekstremiteta i uškama. U nekih bolesnika dolazi i do imunosnih poremećaja i razvoja sustavnog eritemskog lupusa. Osim simptomatskog liječenja, u nekih su bolesnika primjenjivani inhibitori JAK-a s varijabilnim učinkom, kao i antiretrovirusni lijekovi koji se rabe u liječenju infekcije HIV-om.

Teški vaskulitis s početkom u dojenačkoj dobi zbog mutacije u genu STING *(engl.* STING-associated vasculopathy with onset in infancy – *SAVI)*

Ova interferonopatija uzrokovana je autosomno dominantnim mutacijama u genu *STING1* koji je stimu-

Table 5. Comparison of current and proposed new criteria for systemic juvenile idiopathic arthritis (sJIA) (modified according to references No. 31 and 32)

Tablica 5. Usporedba postojećih i predloženih novih kriterija za sustavni oblik juvenilnog idiopatskog artritisa (sJIA) (prilagođeno prema referencijama 31. i 32.)

Current diagnostic criteria for sJIA / Postojeći kriteriji za postavljanje dijagnoze sJIA	**Proposed new diagnostic criteria for sJIA / Predloženi novi kriteriji za postavljanje dijagnoze sJIA**
Arthritis associated with intermittent fever lasting for at least 2 weeks and at least one of the following: / Artritis udružen s intermitentnom vrućicom u trajanju od najmanje 2 tjedna te barem jedan od ovih simptoma: • macular or maculopapular rash / mrljasti ili makulopapulozni osip • splenomegaly or hepatomegaly / splenomegalija ili hepatomegalija • generalized lymphadenopathy / generalizirana limfadenopatija • serositis / serozitis	Fever of uknown origin (39°C or above daily with drops to 37°C or below) ocurring daily for at least 3 consecutive days and recurring for at least 2 weeks / Vrućica nepoznata podrijetla (raste do 39 °C ili više jedanput na dan i pada na 37 °C ili niže tijekom vršaka febriliteta) prisutna svakog dana najmanje 3 dana uzastopno, a ponavlja se tijekom najmanje 2 tjedna + 2 major criteria OR 1 major and 1 minor criterion /2 glavna kriterija ILI 1 glavni i 1 sporedni kriterij
EXCLUSION CRITERIA: / ISKLJUČNI KRITERIJI: • psoriasis (personal history or a first-degree relative) / pozitivna osobna i/ili obiteljska anamneza na psorijazu u prvom koljenu • arthritis in male patients older than 6 and HLA-B27+ / pojava artritisa u dječaka nakon 6. godine s pozitivnim antigenom HLA-B27 • ankylosing spondylitis, enthesitis-associated arthritis, enteropathy-associated sacroiliitis, Reiter syndrome, acute anterior uveitis OR a first-degree relative suffering from any of the mentioned conditions / ankilozantni spondilitis, artritis pridružen entezitisu, sakroileitis s upalnim crijevnim bolestima, Reiterov sindrom, ili akutan prednji uveitis, ili pozitivna obiteljska anamneza na jednu od ovih bolesti u prvom koljenu • positive rheumatoid factor (IgM RF) in at least two measurements at least 3 months apart / pozitivan reumatoidni čimbenik (IgM RF) najmanje u dva mjerenja u razmaku od tri mjeseca	MAJOR CRITERIA: / GLAVNI KRITERIJI: 1. non-fixed and disappearing erythematous rash / eritematozni osip koji nije fiksan i iščezava 2. arthritis / artritis
	MINOR CRITERIA: / SPOREDNI KRITERIJI: 1. generalized lymphadenopathy and/or hepatomegaly and/or splenomegaly / generalizirana limfadenopatija i/ili hepatomegalija i/ili splenomegalija 2. serositis / serozitis 3. artrhralgia lasting for 2 weeks or more (without arthritis) / artralgija u trajanju od 2 tjedna ili dulje (u odsutnosti artritisa) 4. leukocytosis (15,000/mm3 or more) and neutrophilia / leukocitoza (15.000/mm^3 ili veća) uz neutrofiliju

ticular arthirits (tenosynovitis), uveitis (often panuveitis), and rash (in most cases erythematous scaling papules). Skin and eye changes manifest as non-caseous granulomas. Patients with otulipenia have panniculitis, arthritis, and diarrhea; those with A20-haploinsufficiency develop oral ulcerations, uveitis, and pathergy (trauma-induced sterile pustules). Patients with HOP and HOIL-1 defficiencies are immunodeficient and prone to bacterial and viral infections.

Multifactorial inflammatory disease

Systemic juvenile idiopathic arthritis (sJIA) and autoinflammatory bone disease manifesting with sterile inflammatory osteolytic lesions will be reviewed here.

Systemic juvenile idiopathic arthritis (sJIA)

According to the still current 1997 International League Against Rheumatism classification, sJIA is the most severe and most acute form of JIA, resulting from

lator interferonskih gena (14). Bolest najčešće zahvaća kožu i pluća. Kožne promjene počinju se javljati u prvim mjesecima života zbog vaskulopatije. Obično zahvaćaju lice, nos, uške i prste ekstremiteta. Najprije se javlja diskoloracija kože, zatim ulceracije i naposljetku ulkusi zbog nekroze tkiva koji mogu uzrokovati nastanak ožiljaka, perforaciju nosnog septuma i dovesti do amputacije prstiju. Mogu se javiti intersticijska plućna bolest s dispnejom, razvoj plućne fibroze i respiratorne insuficijencije. Nalaze se i limfadenopatija i intermitentni febriliteti. Pri liječenju se primjenjuju inhibitori JAK-a.

Autoinflamatorni sindrom povezan s poremećajem funkcije proteasoma

Kao primjer bolesti iz ovog spektra može se navesti kronična neutrofilna dermatoza s lipodistrofijom i vrućicom (30). Riječ je o bolesti koja je uzrokovana mutacijama u genu koji kodira za podjedinice pro-

genetic and environmental factor interactions. As innate immunity dysregulation plays an important role in the pathogenesis of sJIA, it differs from other forms of JIA which are autoimmune in nature (Table 5). According to the latest criteria by PRINTO established in 2019, in order to be diagnosed with sJIA a patient needs to have a daily fever of 39°C or above that drops to 37°C or below for at least 3 days, recurring for at least 2 weeks (32). Apart from the fever, at least two major or one major and one minor criterion need to be fulfilled. Major criteria are non-fixed, vanishing, erythematous rash and arthritis. Minor criteria are generalized lymphadenopathy and/or hepato/splenomegaly; joint pain without arthritis lasting for at least 2 weeks; leukocytosis (15,000/mm3 or above) with neutrophil predominance. A major difference from earlier criteria is that the presence of arthritis is no longer necessary for a diagnosis of sJIA. The diagnostic process is not simple, as infection and malignancy, as well as systemic autoimmune and other autoinflammatory diseases need to be excluded. During this process patients should be treated with NSAIDs, and once the diagnosis is confirmed the initial choice of treatment can, depending on the disease activity and joint affection, include NSAIDs, glucocorticoids, or IL-1 inhibitors. In refractory disease, other biologics (tocilizumab, abatacept, TNF-inhibitors) or methotrexate are introduced, depending on the joint affection.

Autoinflammatory bone disease

The hallmark of this group of disorders is sterile bone inflammation. Although the typical lesions histologically and radiographically mimic infective osteomyelitis, an infective agent cannot be isolated. Multifactorial autoinflammatory bone diseases are SAPHO syndrome and chronic recurring multifocal osteomyelitis (CRMO). Due to a number of common characteristics, some argue that these are in fact two forms of the same disease with a difference in the age of onset.

SAPHO is an acronym for the five major symptoms occurring in this syndrome: synovitis, acne, pustulosis, hyperostosis, and osteitis (33). It usually affects adolescents and younger adults, more often women. Bone and joint pain and edema are common presenting symptoms of the disease that in most cases affects the anterior thoracic wall (claviculae, sternum, sternoclavicular joints), followed by the spine, primarily its thoracic segment. The arthritis is of axial distribution in most cases. Skin changes occur before, during, or after the musculoskeletal symptoms, or they do not occur at all; they manifest as palmoplantar pustulosis, severe form of acne, suppurative hidradenitis, and pyoderma gangrenosum. CRMO is a spectrum of diseases that have in common sterile bone inflammation, as well as inflammatory skin and inflammatory bowel disease

teasoma. To je proteinski kompleks koji sudjeluje pri uklanjanju otpadnih proteina u stanici i razlaganju stranih bjelančevina. Zbog njegove poremećene funkcije dolazi do nakupljanja otpadnih proteina u stanici i stimulacije proizvodnje interferona tipa I. Bolest započinje u prvim mjesecima života. Manifestira se najprije kožnim promjenama koje mogu biti nalik na ozebline, prstenastim plakovima ili eritematoznim edemima. Često se javljaju febriliteti. Nakon toga javljaju se lipodistrofija, odnosno gubitak masnog tkiva te, naposljetku, promjene na zglobovima. Liječenje se pokušava davanjem inhibitora JAK-a.

Ubikvitinopatije

Riječ je o poremećajima koji su usko vezani uz abnormalnosti signalnog puta NF-κB (15). Kao primjer može se navesti ***Blauov sindrom*** koji je uzrokovan autosomno dominantnom mutacijom u genu *NOD2*. Sindrom čini trijas rano nastaloga poliartikularnog artritisa (tenosinovitis), uveitisa (često panuveitis) i osipa (često male crvenkaste papule koje se ljuskaju), a promjene na koži i očima jesu nekazeozni granulomi. Bolesnici s ***otulipenijom*** imaju panikulitis, artritis i proljeve, a oni s ***haploinsuficijencijom A20*** oralne ulceracije, uveitis i patergiju (stvaranje sterilnih pustula na mjestima traume). U bolesnika s ***manjkom proteina HOP i HOIL-1*** nalazi se imunodeficijencija (učestale bakterijske i virusne infekcije).

Multifaktorske inflamatorne bolesti

Od multifaktorskih inflamatornih bolesti opisat ćemo sustavni oblik juvenilnog idiopatskog artritisa (sJIA) i autoinflamatorne bolesti kostiju koje se manifestiraju sterilnim upalnim osteolitičkim lezijama.

Sustavni oblik juvenilnog idiopatskog artritisa (sJIA)

Prema trenutačno vrijedećoj klasifikaciji Međunarodne lige za borbu protiv reumatizma iz 1997. (31), sJIA je najteži i najakutniji oblik JIA, koji nastaje interakcijom genskih i okolišnih čimbenika. sJIA se od ostalih oblika JIA, koji pripadaju skupini autoimunosnih bolesti, razlikuje po tomu što poremećaj prirođene imunosti ima važnu ulogu u patogenezi ove bolesti (tablica 5.). Prema najnovijim predloženim kriterijima Međunarodne organizacije za provođenje ispitivanja u dječjoj reumatologiji (PRINTO) iz 2019. godine, za postavljanje dijagnoze potrebno je da bolesnici imaju vrućicu nepoznata podrijetla, koja raste do 39 °C ili više jedanput na dan i pada na 37 °C ili niže, a prisutna je svakog dana najmanje 3 dana uzastopno i ponavlja se tijekom najmanje 2 tjedna (32). Uz to moraju biti zadovoljena dva glavna kriterija ili jedan glavni i jedan sporedni kriterij. Glavni kriteriji jesu eritematozni osip koji nije fiksan i iščezava te artritis. Sporedni kriteriji

Table 6. Clinical signs suggestive of autoinflammatory disease
Tablica 6. Klinički znakovi koji upućuju na pojavu autoinflamatorne bolesti

One or more of the following criteria: / Bolesnik koji ispunjava jedan ili više od ovih kriterija:
– periodic/recurring fever / Periodične/rekurentne vrućice
– severe skin inflammation (pustular dermatoses, painful ulcerations, pustular psoriasis, granulomatous inflammation, recurring urticarial changes…) / Teška upalna zahvaćenost kože (pustulozne dermatoze, bolne ulceracije, pustulozna psorijaza, granulomatozne upale, rekurentne urtikarijske promjene...)
– severe bone and joint inflammation / Teška upalna zahvaćenost osteoartikularnog sustava
– vasculopathies / Vaskulopatije
– panniculitis/lipoatrophy / Panikulitis/lipoatrofija
– serous membrane inflammation (peritonitis, pleuritis, pericarditis) / Upale seroznih membrana (peritonitis, pleuritis, perikarditis)
– gastrointestinal tract inflammation / Upale probavne cijevi
– amyloidosis / Amiloidoza
– increased inflammatory markers during disease flares (leukocytosis, increased C-reactive protein, increased erythrocyte sedimentation rate, thrombocytosis) / Za vrijeme epizode bolesti povišeni upalni parametri (leukocitoza, povišen C-reaktivni protein, ubrzana sedimentacija eritrocita, trombocitoza)

(33). Most often they occur during childhood, between the ages of 7 and 12. Typically they present with bone pain with or without fever; the pain can be mild or acute, or intense with edema, warmth, and pathological fracture of the affected bones. The entire skeleton can be involved. Skin changes that occur are palmoplantar pustulosis, psoriasis, and pyoderma gangrenosum.

Whole-body MRI (investigation of choice) and radionuclide bone scan are used in establishing the diagnosis as well as in the follow-up. Sometimes a bone biopsy is needed to confirm the diagnosis. CRMO is managed with NSAIDs, antibiotics (clindamyicin, azithromycin, tetracyclines), glucocortikocids, and, in refractory cases, methotrexate, sulfasalatine, bisphosphonates, and TNF-inhibitors.

An organ system-based summary of the most common symptoms and signs of autoinflammatory diseases

Since there are many autoinflammatory conditions that manifest with a broad spectrum of signs and symptoms that can overlap with those of various autoimmune diseases and immunodeficiencies, and since these are rare disorders, it is far more important to know when to suspect autoinflammatory disease than

jesu generalizirana limfadenopatija i/ili hepatomegalija i/ili splenomegalija; serozitis; artralgija u trajanju od 2 tjedna ili dulje (u odsutnosti artritisa); leukocitoza (15.000/mm^3 ili veća) uz neutrofiliju. Glavna je novost u odnosu prema dosadašnjim kriterijima da artritis više ne mora biti nužno prisutan da bi se postavila dijagnoza sJIA. Postavljanje dijagnoze nije jednostavno i temelji se na isključenju infekcija, malignih bolesti, sustavnih autoimunosnih bolesti i drugih autoinflamatornih bolesti. Do postavljanja dijagnoze primjenjuju se nesteroidni antireumatici (NSAID), a nakon postavljanja dijagnoze inicijalna terapija može, ovisno o stupnju aktivnosti bolesti i zahvaćenosti zglobova, uključivati primjenu NSAID-a, glukokortikoida ili inhibitora IL-1, dok se pri kontinuiranoj aktivnosti bolesti mogu uključiti i drugi biološki lijekovi (tocilizumab, abatacept odnosno inhibitori TNF-α) ili metotreksat, ovisno o stupnju zahvaćenosti zglobova.

Autoinflamatorne bolesti kostiju

Osnovna karakteristika ovih bolesti jest sterilna upala kostiju, pri čemu lezije histološki i radiološki imitiraju infektivni osteomijelitis, ali se ne može izolirati infektivni uzročnik. U multifaktorske autoinflamatorne bolesti kostiju ubrajaju se sindrom SAPHO i kronični rekurentni multifokalni osteomijelitis (CRMO). Zbog mnogih zajedničkih značajka neki smatraju da se radi o dva oblika iste bolesti koje se pojavljuju u različitoj životnoj dobi.

SAPHO je akronim pet glavnih simptoma koji se javljaju u sklopu ovog sindroma: sinovitis, akne, pustuloza, hiperostoza i osteitis (33). Bolest se uglavnom pojavljuje u adolescenata i mlađih odraslih, češće u osoba ženskog spola. Prvi znak bolesti najčešće su bol i oteklina zglobova i kostiju. Najčešće je zahvaćen prednji dio prsnog koša: klavikula, sternum i sternoklavikularni zglobovi, a zatim kralježnica (najčešće torakalni segment). Artritis je najčešće aksijalni (zahvaća male zglobove kralježnice). Kožne promjene mogu se javiti prije, za vrijeme ili nakon koštano-zglobnih simptoma, a mogu i posve izostati. Uključuju palmoplantarnu pustulozu, teške oblike akna, supurativni hidradenitis i gangrenoznu piodermu. CRMO obuhvaća spektar bolesti kojima je zajednička sterilna upalna bolest kostiju uz upalne kožne i crijevne bolesti (33). Najčešće se javlja u djetinjstvu, i to u školskoj dobi (od 7 do 12 godina). Tipično se prezentira bolju u kostima s febrilitetom ili bez njega, koja varira u intenzitetu od blage do akutne intenzivne boli, uz oteklinu, toplinu i patološku frakturu zahvaćenih kostiju. Lezije kostiju mogu zahvatiti cijeli skelet. Kožne promjene uključuju palmoplantarnu pustulozu, psorijazu i gangrenoznu piodermu.

Pri postavljanju dijagnoze ovih bolesti rabe se magnetska rezonancija cijelog tijela kao metoda izbora i za praćenje bolesnika, scintigrafija skeleta, a katkad je po-

to know everything in detail about a single entity. Suspicion should be raised in patients with periodic and recurrent fever when infective, autoimmune, and malignant diseases have been excluded. Some autoinflammatory diseases have elements of immunodeficiencies causing recurrent infections. Also, it is good to know that some autoinflammatory diseases manifest without fever, thus the absence of fever is not an exclusion criterion.

The age of disease onset, ethnic origin, and family history are valuable medical data. Although the majority of these diseases begin in infancy, some can manifest for the first time in adulthood. Most of these conditions are not strictly geographically or ethnically linked; also, since many of them are caused by de novo or somatic mutations, in such cases the family history will be unremarkable. Almost all autoinflammatory diseases can be triggered by stress or infection; other triggering factors may be cold, minor trauma, pregnancy, menstruation, immunization, and exercise.

Skin inflammation should be considered as a "red flag" as almost all of these disorders affect the skin. Since the changes are not pathognomonic, a skin biopsy is necessary. Among the more common skin manifestations are non-pruritic urticaria-like changes, refractory to antihistamines, with neutrophilic infiltrates on histology. They can be found in CAPS and Schnitzler syndrome. Pustular dermatoses are found in Behçet disease and CRMO. Painful ulcerations and pyoderma gangrenosum are a part of PAPA syndrome and of very early inflammatory bowel disease. Granulomatous changes are found in Blau syndrome. Interferonopathies are characterized by vasculopathies, panniculitis, lipoatrophy, and frostbite-like changes, especially on the extremities. Plaques are common in FMF and TRAPS patients.

Musculoskeletal manifestations such as permanent or transient arthritis, synovitis, osteitis, and osteomyelitis, especially in cases of sterile pyogenic inflammation, should prompt suspicion of an autoinflammatory condition. Bone deformities and finger clubbing can be seen in severe forms of CAPS and in DIRA syndrome. Lytic and sclerotic bone lesions are a part of CRMO. Monoarthritis is common in FMF and PAPA syndrome, and polyarthritis in sJIA and mevalonate kinase deficiency. Intense myalgia is characteristic of FMF and TRAPS.

Eye manifestations include conjunctivitis, periorbital edema, and uveitis, which occur in most cases of CAPS and TRAPS. Behçet and NOMID cause the most severe eye pathology, which can result in blindness.

Gastrointestinal manifestations include abdominal pain, diarrhea, aphthae, and mucous ulcerations. Peritonitis is common in FMF and TRAPS. Diarrhea is common in mevalonate kinase deficiency, macrophage

trebno učiniti i biopsiju kostiju. U liječenju se primjenjuju NSAID, antibiotici (klindamicin, azitromicin, tetraciklini), glukokortikoidi, a pri nezadovoljavajućem učinku mogu se primijeniti metotreksat, sulfasalazin, bisfosfonati i inhibitori TNF-α.

Sumarni prikaz najčešćih simptoma i znakova autoinflamatornih bolesti prema organskim sustavima

Budući da je, s jedne strane, autoinflamatornih bolesti mnogo i da se mogu manifestirati čitavim spektrom simptoma i znakova te preklapati s autoimunosnim bolestima i imunodeficijencijama, a da su, s druge strane, te bolesti rijetke, mnogo je važnije od poznavanja pojedinih entiteta posumnjati na postojanje autoinflamatorne bolesti (tablica 6.). Još postoji znatna odgoda u postavljanju dijagnoze autoinflamatornih bolesti. Na njih treba posumnjati u bolesnika s periodičnim i rekurentnim vrućicama kod kojih je obrada na infekcije, autoimunosne i maligne bolesti negativna. U nekim autoinflamatornim bolestima bolesnici imaju znakove imunodeficijencije koji se manifestiraju ponavljanim infekcijama. Nadalje, treba napomenuti da postoje autoinflamatorne bolesti koje se ne manifestiraju febrilitetom, tako da odsutnost vrućice nije isključni kriterij za postojanje neke od ovih bolesti.

Važni anamnestički podatci uključuju dob pojave simptoma i znakova bolesti, etničko podrijetlo i obiteljsku anamnezu. Iako većina tih bolesti započinje u dječjoj dobi, one se mogu prvi put manifestirati tek u odrasloj dobi. Treba napomenuti da većina autoinflamatornih bolesti nije ograničena geografskom lokacijom ni podrijetlom bolesnika. Mnoge od njih uzrokovane su mutacijama *de novo* ili somatskim mutacijama pa će pritom obiteljska anamneza biti negativna. Gotovo sve autoinflamatorne bolesti mogu biti potaknute stresom i infekcijom, a od ostalih okidača treba spomenuti hladnoću, manje traume, trudnoću, mjesečnicu, cijepljenje i vježbanje.

Sumnju treba pobuditi postojanje upalne zahvaćenosti kože. Naime, gotovo sve autoinflamatorne bolesti zahvaćaju i kožu. Budući da promjene nisu patognomonične, često je potrebno učiniti biopsiju kože. Jedna od čestih dermatoloških manifestacija jesu promjene nalik na urtikarijske, ali bez svrbeža, koje se ne povlače primjenom antihistaminika i kod kojih se biopsijom nalaze infiltrati neutrofila koji nisu karakteristični za urtikariju. One se mogu naći kod bolesnika s CAPS-om i Schnitzlerinim sindromom. Pustulozne dermatoze nalaze se kod bolesnika s Behçetovom bolesti i CRMO-om. Bolne ulceracije i *pyoderma gangrenosum* dio su kliničke slike sindroma PAPA, a mogu se naći i kod vrlo rane upalne bolesti crijeva. Granulomatozne promjene nalaze se u Blauovom sindromu. Pri interferonopatijama nalaze se vaskulopatije, paniku-

activation syndrome, and very early-onset inflammatory bowel disease.

The spectrum of neurological disorders is broad - vasculitis (Behçet disease), hearing loss (CAPS), psychomotor retardation (NOMID, interferonopathies). Convulsions are common in most of periodic fever syndromes.

Laboratory abnormalities such as leukocytosis, increased CRP, accelerated ESR, and thrombocytosis are common during disease episodes. However, some patients have only a mild increase in CRP, lymphopenia, and leukopenia during exacerbations. An unexplained increase of inflammatory markers, even when there are no other symptoms, should prompt suspicion of an autoinflammatory disease.

During the work-up of a patient with a suspected autoinflammatory disease it is necessary to exclude infection, malignancy, immunodeficiency, and rheumatic disease (34). A routine laboratory panel consisting of full blood count with differential and peripheral smear, ESR, CRP, electrolytes, urea, creatinine, LFTs, urinalysis, uric acid, and LDH should be ordered. Immunoserological tests (ANA, ANCA) should also be done. Initial microbiology testing consists of a throat swab, blood culture, urine culture, EBV serology, CMV serology, HIV test, and tuberculosis test. Chest X-ray is important in the initial work-up. Depending on the symptoms and differential diagnosis, additional tests can be performed: joint aspiration (to exclude septic arthritis), skin biopsy, audiometry (if CAPS is suspected), whole-body MRI (SAPHO, CRMO), heart ultrasound (FMF, TRAPS), lumbar puncture (CAPS), etc.

Over 30 different systemic autoinflammatory diseases are known today and over 800 genetic variants have been discovered; however, most of the latter are of unknown or undetermined impact or are not pathogenic (35). At the moment, genetic testing for autoinflammatory diseases is still burdened with various issues, and therefore in 50 to 60% of suspect cases a pathogenic mutation cannot be confirmed. The principal indication for genetic testing is the presence of symptoms fulfilling the criteria for one or more autoinflammatory diseases. It is especially difficult to diagnose a patient with signs of overlap between various diseases, or in cases of a partial or atypical clinical course. In such patients, molecular analysis of an individual gene confirms the diagnosis in less than 20% of cases. Although there still are no official recommendations, genetic testing is sometimes a two-step procedure. In the first step, next generation sequencing methods are used for targeted testing through gene panels now available in various European centers. These tests will also be available in Croatia at the Department for Functional Genomics, a part of the University Hospital Center Zagreb Center for Translation-

litis odnosno lipoatrofija te promjene nalik na ozebline, osobito na okrajinama. Plakovi se najčešće vide u bolesnika s FMF-om i TRAPS-om.

Zahvaćenost koštano-zglobnog sustava manifestira se u obliku trajnog ili prolaznog artritisa, sinovitisa, osteitisa i osteomijelitisa, a napose nas sterilne piogene upale trebaju navesti na pomišljanje o autoinflamatornoj bolesti. Deformacije kostiju i batićasti prsti mogu se vidjeti u težim oblicima CAPS-a i pri sindromu DIRA. Litičke i sklerotične koštane lezije mogu se vidjeti u bolesnika s CRMO-om. Monoartritisi se najčešće vide kod FMF-a i sindroma PAPA, a poliartritis kod sJIA i nedostatka mevalonat kinaze. Naglašena mialgija karakteristična je za FMF i TRAPS.

Promjene na očima uključuju konjunktivitis, periorbitalni edem i uveitis, a najčešće se očne manifestacije nalaze u bolesnika s CAPS-om i TRAPS-om. Najteže promjene na očima, koje mogu rezultirati sljepoćom, vide se u bolesnika s Behçetovom bolesti i NOMID-om.

Gastrointestinalne manifestacije uključuju bol u trbuhu i proljev te pojavu afta i ulkusa na sluznicama probavnog sustava. Peritonitis je čest u FMF-u i TRAPS-u. Proljev se može naći kod bolesnika s manjkom mevalonat kinaze, u sindromu aktivacije makrofaga te pri upalnoj bolesti crijeva s vrlo ranim početkom.

Neurološki spektar poremećaja vrlo je širok. U nekim bolestima nalazimo vaskulitis (Behçetova bolest), u drugima gubitak sluha (CAPS), u nekima psihomotoričko zaostajanje (NOMID, interferonopatije). U mnogim sindromima periodičnih vrućica može doći do pojave konvulzija.

Za vrijeme epizode bolesti često se detektiraju povišeni upalni parametri: leukocitoza, povišen C-reaktivni protein (CRP), ubrzana sedimentacija eritrocita i trombocitoza, premda neki bolesnici imaju umjereno povišen CRP, limfopeniju i leukopeniju u pogoršanjima bolesti. Na autoinflamatorne bolesti treba posumnjati i u bolesnika s neobjašnjenim povišenjem upalnih parametara, čak i ako nema simptoma bolesti.

Pri obradi bolesnika sa sumnjom na autoinflamatornu bolest potrebno je isključiti infekcije, zloćudne bolesti, imunodeficijencije i reumatske bolesti (34). Treba učiniti opće laboratorijske pretrage: krvnu sliku s diferencijalnom krvnom slikom i razmazom periferne krvi, brzinu sedimentacije eritrocita, CRP, elektrolite u serumu, ureju, kreatinin, hepatogram, analizu urina, određivanje mokraćne kiseline, laktat dehidrogenaze. Od imunoloških pretraga važni su nalazi antinuklearnih protutijela (ANA) i antineutrofilnih protutijela (ANCA). Od mikrobiološke obrade preporučuje se uzeti obrisak ždrijela, hemokulturu, urinokulturu, serologiju na Epstein-Barrin virus, citomegalovirus i virus humane imunodeficijencije te obaviti testiranje

al and Clinical Research. If the first-step test results are negative, whole exome or whole genome sequencing is performed. The problem with these methods is the interpretation of the findings, especially in the case of de novo genetic variants, as it requires the application of complex software tools by personnel with extensive experience in bioinformatics and biostatistics.

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na tuberkulozu. Od radioloških pretraga savjetuje se učiniti rendgenogram srca i pluća. Ovisno o simptomima i sumnji na pojedine bolesti, dodatno se mogu obaviti punkcija zgloba (radi isključenja infektivnog artritisa), biopsija kože, audiometrija (pri sumnji na CAPS), magnetska rezonancija cijelog tijela (SAPHO, CRMO), ehokardiografija (FMF, TRAPS), lumbalna punkcija (CAPS) i druge pretrage.

Do danas je poznato više od 30 različitih sustavnih autoinflamatornih bolesti te je otkriveno više od 800 genskih varijanta povezanih s autoinflamatornim bolestima od kojih je većina nepotvrđena, odnosno neodređena značenja ili nije patogena (35). Trenutačno je genska dijagnostika autoinflamatornih bolesti bremenita brojnim teškoćama te se u 50 do 60% bolesnika sa sumnjom na autoinflamatornu bolest ne uspije pronaći patogena mutacija. Glavna je indikacija za gensko testiranje prisutnost kliničkih simptoma koji ispunjavaju kriterije za jednu autoinflamatornu bolest ili više njih. Posebno je teško postaviti dijagnozu u bolesnika koji imaju obilježja koja se preklapaju između više bolesti ili imaju nepotpunu ili atipičnu kliničku sliku. Molekularna analiza pojedinačnoga gena u takvih bolesnika dovodi do dijagnoze u njih manje od 20%. Iako još nema usuglašenih preporuka, katkad se gensko testiranje provodi u dva koraka. U prvome se metodama sekvenciranja sljedeće generacije provodi ciljano testiranje primjenom genskih panela koji su dostupni u različitim europskim laboratorijima, a uskoro će biti dostupni i u Hrvatskoj, na Odjelu za funkcionalnu genomiku u Centru za translacijska i klinička istraživanja Kliničkoga bolničkog centra Zagreb. Ako su rezultati takvog testiranja negativni, primjenjuje se sekvenciranje cijelog egzoma ili genoma. Problem s ovim metodama jest interpretacija nalaza, napose genskih varijanta *de novo*, što nalaže primjenu složenih softverskih alata i osoblja s velikim iskustvom u bioinformatici i biostatistici.

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REFERENCES / LITERATURA

1. Pathak S, McDermott MF, Savic S. Autoinflammatory diseases: update on classification diagnosis and management. J Clin Pathol. 2017;70:1–8.
2. McDermott MF, Aksentijevich I, Galon J i sur. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell. 1999;97:133–44.
3. Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded, a clinical perspective. Cell. 2010; 140:784–90.
4. De Jesus AA, Goldbach-Mansky R. Genetically defined autoinflammatory diseases. Oral Dis. 2016;22:591–604.
5. Ben-Chetrit E, Gattorno M, Gul A i sur. Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. Ann Rheum Dis. 2018;77:1558–65.
6. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med. 2006;3:e297.
7. Mujal AM, Krummel MF. Immunity as a continuum of archetypes. Science. 2019;364:28–9.
8. Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Incidence of hereditary amyloidosis and autoinflammatory diseases in Sweden: Endemic and imported diseases. BMC Med Genet. 2013;14:88.
9. Kenealy S, Creagh EM. Autoinflammatory Diseases: Consequences of Uncontrolled Inflammasome Activation. EMJ Allergy Immunol. 2018;3:106–13.
10. Georgin-Lavialle S, Fayand A, Rodrigues F, Bachmeyer C, Savey L, Grateau G. Autoinflammatory diseases: State of the art. Presse Med. 2019;48:e25–48.
11. Malenica B. Imunosni sustav i imunopatogeneza reumatskih bolesti. U: Jelušić M, Malčić I (ur.). Pedijatrijska reumatologija. 1. izd. Zagreb: Medicinska naklada; 2014.
12. Jelušić M, Morović Vergles J, Gagro A (ur.). Autoinflamatorne bolesti u djece i odraslih. Poslijediplomski tečaj stalnoga medicinskog usavršavanja. 1. izd. Zagreb: Medicinska naklada; 2017.
13. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. Nat Rev Immunol. 2015;15:429–40.
14. Liu Y, Jesus AA, Marrero B i sur. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014;371:507–18.
15. Aksentijevich I, Zhou Q. NF-κB Pathway in Autoinflammatory Diseases: Dysregulation of Protein Modifications by Ubiquitin Defines a New Category of Autoinflammatory Diseases. Front Immunol. 2017;8:399.
16. Zhou Q, Yu X, Demirkaya E i sur. Biallelic hypomorphic mutations in a linear deubiquitinase define otulipenia, an early-onset autoinflammatory disease. Proc Natl Acad Sci USA. 2016; 113:10127–32.
17. Manthiram K, Zhou Q, Aksentijevich I, Kastner DL. The monogenic autoinflammatory diseases define new pathways in human innate immunity and inflammation. Nat Immunol. 2017;18:832–42.
18. John CC, Gilsdorf JR. Recurrent fever in children. Pediatr Infect Dis J. 2002;21:1071–7.
19. Gattorno M, Hofer M, Federici S i sur. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis. 2019;78: 1025–32.
20. Tran TA. Muckle-Wells syndrome: clinical perspectives. Open Access Rheumatol. 2017;9:123–9.
21. Booshehri LM, Hoffman HM. CAPS and NLRP3. J Clin Immunol. 2019;39:277–86.
22. Özen S, Batu ED, Demir S. Familial Mediterranean Fever: Recent Developments in Pathogenesis and New Recommendations for Management. Front Immunol. 2017;8:253.
23. Favier LA, Schulert GS. Mevalonate kinase deficiency: current perspectives. Appl Clin Genet. 2016;9:101–10.
24. Quintero J, Saba J, Garcia C. Tumor Necrosis Factor Receptor-1 Associated Periodic Syndrome: Case Report and Review of an Auto-inflammatory Disorder. Cureus. 2019;11:e3916.
25. Rigante D, Corina L. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome: A debate about diagnosis and treatment in children continues. Int J Pediatr Otorhinolaryngol. 2020;130:109830.
26. Cowen EW, Goldbach-Mansky R. DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? Arch Dermatol. 2012;148:381–4.
27. Rao AP, Gopalakrishna DB, Bing X, Ferguson PJ. Phenotypic Variability in Majeed Syndrome. J Rheumatol. 2016;43:1258–9.
28. Holzinger D, Roth J. Alarming consequences – autoinflammatory disease spectrum due to mutations in proline-serine-threonine phosphatase-interacting protein 1. Curr Opin Rheumatol. 2016;28:550–9.
29. Eleftheriou D, Brogan PA. Genetic interferonopathies: An overview. Best Pract Res Clin Rheumatol. 2017;31:441–59.
30. Torrelo A. CANDLE Syndrome As a Paradigm of Proteasome-Related Autoinflammation. Front Immunol. 2017;8:927.
31. Petty RE, Southwood TR, Manners P i sur. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
32. Martini A, Ravelli A, Avcin T i sur. Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol. 2019;46:190–7.
33. Jelušić M, Čekada N, Frković M i sur. Chronic Recurrent Multifocal Osteomyelitis (CRMO) and Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome – Two Presentations of the Same Disease? Acta Dermatovenerol Croat. 2018; 26:212–9.
34. Hashkes PJ, Laxer RM, Simon A (ur.). Textbook of Autoinflammation. 1. izd. Cham: Springer; 2019.
35. Rowczenio DM, Lachmann HJ. How to prescribe a genetic test for the diagnosis of autoinflammatory diseases? Presse Med. 2019;48:e49–59.

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CASE REPORT PRIKAZ BOLESNIKA

PUBIC SYMPHYSIS DIASTASIS IN TWIN PREGNANCY

DIJASTAZA SIMFIZE U BLIZANAČKOJ TRUDNOĆI

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Abstract

Pubic symphysis diastasis is a rare pregnancy complication whose exact incidence is still not known, but it is estimated to be in the range of 1:300 to 1:30,000 pregnancies. It is defined as a distance between the two pubic bones or an interpubic gap greater than 10 mm with typical presentation. Typical symptoms of diastasis symphysis are pain in the symphyseal region that radiates to the lower back and thighs, waddling gait, painful movement, reduced mobility, and, rarely, urinary retention. In this case report we present a case of antepartum pubic symphysis diastasis diagnosed by palpation during a pelvic exam in a multiparous woman with a twin pregnancy. The patient had an uneventful previous antenatal period; at a routine follow-up she reported symphyseal pain over a longer period with exacerbation in the previous three weeks, in addition to difficulty walking and staying in an upright position. On manual palpation a 10-mm interpubic gap was found and the patient was hospitalized. In view of the twin pregnancy and pubic symphysis diastasis it was decided that a cesarean section was the appropriate mode of delivery. A postoperative pelvic X-ray showed an interpubic gap of 14 mm. With regard to the simplicity and reliability of manual palpation in cases of suspected pubic symphysis diastasis, implementing palpation of the pubis in regular obstetrical practice would enable early recognition, immediate treatment, and a better outcome in the long term. Also, as there are no evidence-based guidelines considering antepartum pubic symphysis diastasis and each case is approached individually, a comprehensive investigation of this condition is needed in order to achieve standardization of practice.

Keywords: Pubic symphysis diastasis – diagnosis; Pubic symphysis – diagnostic imaging; Pelvic pain – etiology; Pregnancy complications – diagnosis; Palpation; Twin pregnancy; Radiography

Sažetak

Dijastaza simfize rijetka je komplikacija trudnoće čija točna incidencija još nije poznata, a procijenjena incidencija kreće se u rasponu od 1 : 300 do 1 : 30.000 trudnoća. Definira se kao udaljenost između dvije pubične kosti odnosno kao interpubični razmak veći od 10 mm s tipičnom kliničkom slikom. Tipični simptomi dijastaze simfize jesu bol u području simfize koja se širi u donji dio leđa i bedro, gegavi hod, bolno kretanje, smanjena pokretljivost i, rijetko, urinarna retencija. U ovom radu prikazujemo bolesnicu s antepartalnom dijastazom simfize, koja je dijagnosticirana manualnom palpacijom za vrijeme redovitoga ginekološkog pregleda. Višerotkinja s blizanačkom trudnoćom, koja dotad nije imala kompliciran tijek trudnoće, pri redovitom je pregledu navela da dulje osjeća bol u području simfize, uz pogoršanje tegoba u posljednja 3 tjedna te otežano hodanje i stajanje. Manualnom palpacijom otkriven je interpubični razmak od 10 mm te je trudnica hospitalizirana. S obzirom na blizanačku trudnoću i dijastazu simfize, odlučeno je da trudnoća bude dovršena elektivnim carskim rezom. Postoperativni rendgenogram (RDG) zdjelice pokazao je interpubični razmak od 14 mm. Manualna palpacija jednostavna je i pouzdana metoda pa bi njezino uvođenje u svakodnevnu opstetričku praksu omogućilo rano otkrivanje dijastaze simfize, brži početak terapije i dugoročno bolji

ishod. Također, budući da ne postoje znanstveno dokazane smjernice o zbrinjavanju antepartalne dijastaze simfize, nego se svakoj bolesnici pristupa individualizirano, potrebno je sveobuhvatno istraživanje ove patologije koje bi dovelo do standardiziranja prakse.

Ključne riječi: Dijastaza pubične simfize – dijagnoza; Pubična simfiza – dijagnostički slikovni prikaz; Zdjelična bol – etiologija; Komplikacije u trudnoći – dijagnoza; Palpation; Blizanačka trudnoća; Radiografija

INTRODUCTION

Pubic symphysis diastasis is a rare complication of pregnancy, whose exact incidence is still not known, but it is estimated to be in the range of 1:300 to 1:30,000 pregnancies (1–5). It is defined as a distance between the two pubic bones or an interpubic gap greater than 10 mm (6, 7) with typical presentation. Typical symptoms of diastasis symphysis are pain in the symphyseal region that radiates to the lower back and thighs, waddling gait, painful movement, reduced mobility, and, rarely, urinary retention (3, 7). Mild enlargement of the interpubic gap occurs physiologically during pregnancy (8, 9), just like its subsequent regression to the pregravid state. However, the etiology and pathogenesis of a pathologic distension of the interpubic gap is not known. There is an assumed association between the hormone relaxin and this condition. Relaxin impacts ligaments and cartilaginous joints, which can cause symphyseal widening (6, 10, 11). Also, there are some possible risk factors like multiparity, shoulder dystocia, macrosomic fetus, large fetal head, rapid progression of the second stage of labor and rapid descent of the presenting part, epidural anesthesia, and previous pelvic trauma (2). Treatment is usually conservative (wearing a pelvic belt, physiotherapeutic exercise, and rest) and, in rare instances, surgical (3, 7). In this report we present a case of antepartum pubic symphysis diastasis diagnosed by palpation during a pelvic exam in a multiparous woman with twin pregnancy.

CASE REPORT

A twenty-six-year-old multiparous woman, gravida 3, para 2, with twin pregnancy (2 chorions, 2 amnions), gestational age 31 weeks and 4 days (31 + 4/7), weighing 75 kilograms (+9 in pregnancy) and 154 centimeters tall, had an uneventful previous antenatal period. At a routine follow-up she reported symphyseal pain over a longer period with exacerbation in the previous three weeks, in addition to difficulty walking and staying in an upright position. On manual palpation a 10-mm separation of the interpubic gap was found and the patient was hospitalized. The only comorbidities in her medical history were mild anemia, treated with iron supplements, and thrombocytopenia known since childhood. During the hospital stay she was treated with conservative methods which included wearing a pelvic belt, physiotherapeutic exercise (strengthening of the pelvic floor and

UVOD

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PRIKAZ BOLESNICE

Naša je bolesnica bila 26-godišnja višerotkinja (3 trudnoće, 2 porođaja) s blizanačkom trudnoćom (bikorijat, biamnijat) gestacijske dobi od 31 tjedna i 4 dana (31 + 4/7), visoka 154 cm, tjelesne težine od 75 kg (+9 kg tijekom trudnoće), s dotad urednim tijekom trudnoće. Pri rutinskome ginekološkom pregledu žalila se na bol u području simfize tijekom duljeg vremena, s pogoršanjem u posljednja 3 tjedna, uz teškoće hodanja i stajanja u uspravnom položaju. Manualnom palpacijom dijagnosticiran je interpubični razmak od 10 mm te je bolesnica hospitalizirana. U dotadašnjoj povijesti bolesti kao jedini komorbiditeti spominjale su se blaga anemija, liječena preparatima željeza, i trombocitopenija poznata od djetinjstva. Tijekom hospitalizacije liječena je konzervativnim metodama koje

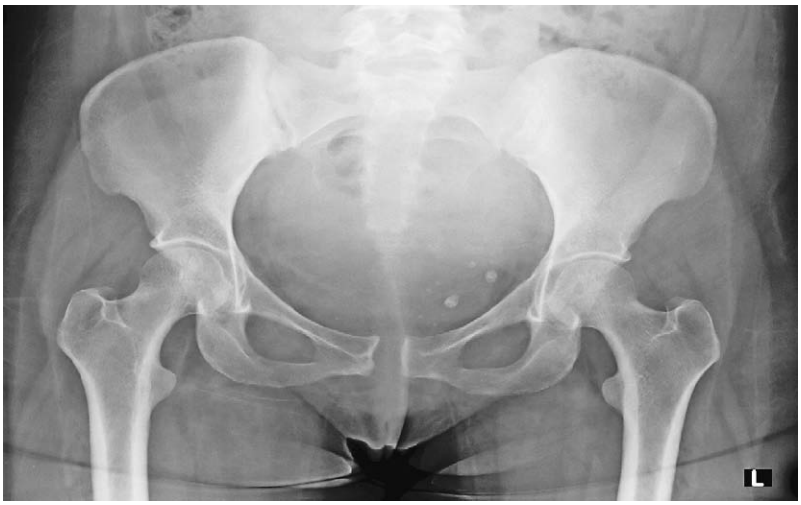

Figure 1. Pelvic X-ray after delivery showing a 14-mm intrapubic gap
Slika 1. Nativni rendgenogram zdjelice nakon porođaja s vidljivim interpubičnim razmakom (14 mm)

abdominal wall muscles), walking with crutches, walking backwards, and resting in the lateral decubitus position. Furthermore, as threatened preterm labor was noted, inhibition of acute preterm delivery was achieved with an intravenous tocolytic agent (fenoterol) administered for two days, along with stimulation of fetal lung maturation with dexamethasone (2 x 6 mg) for two days. In addition to that, intravenous antibiotic therapy (cefazolin) because of elevated blood inflammatory markers was administered for 6 days. Considering the twin pregnancy and pubic symphysis diastasis, it was decided that a cesarean section was the appropriate mode of delivery. Thus, at the gestational age of 36 weeks and 1 day (36 + 1/7), two male eutrophic neonates (each weighing 2,500 grams and 48 centimeters long) were born with Apgar scores 10/10. The postoperative course was uneventful. A pelvic X-ray showed an interpubic gap of 14 mm (Figure 1). The patient's symptoms were reduced and she was discharged from hospital four days afterwards. In the routine follow-up two months after delivery she had no complaints as she was symptomless with normal mobility.

DISCUSSION

Pubic symphysis diastasis is a rare complication of pregnancy considered to be an underdiagnosed pathology without an established incidence. Although authors do not distinguish antepartum from postpartum diastasis when reporting on their incidence (1–5), the difference in the physiological conditions of the aforementioned periods is obvious, and therefore the etiology and risk factors cannot be the same. The suggested risk factors for postpartum symphysis pubis diastasis are multiparity, shoulder dystocia, macrosomic fetus, large fetal head, rapid progression of the second stage of labor and rapid descent of the presenting part, epidural anesthesia, and previous pelvic trauma. For antenatal symphysis pubis diastasis the risk factors are

su uključivale nošenje zdjeličnog remena, fizioterapeutske vježbe (jačanje mišića dna zdjelice i trbušne stijenke), hod sa štakama, hodanje unatrag i odmor u bočnome dekubitalnom položaju. Nadalje, budući da je primijećena prijetnja od prijevremena porođaja, provedene su inhibicija akutnoga prijevremenog porođaja intravenskim tokolitičkim sredstvom (fenoterolom) tijekom 2 dana i stimulacija fetalnog sazrijevanja pluća deksametazonom (2 × 6 mg). Zbog povišenih vrijednosti upalnih markera provedena je parenteralna antimikrobna terapija antibiotikom cefazolinom tijekom 6 dana. S obzirom na blizanačku trudnoću i dijastazu pubične simfize, zaključili smo da je carski rez pravilan način porođaja. Rođena su dva muška novorođenčeta s Apgarinom ocjenom 10/10 u gestacijskoj dobi od 36 tjedana i 1 dana (36 + 1/7), eutrofična, oba tjelesne mase od 2500 grama i dužine od 48 centimetara. Postoperativni tijek protekao je bez teškoća. Obavljen je rendgenogram (RDG) zdjelice koji je pokazao interpubični razmak od 14 mm (slika 1.). Pacijentičini simptomi ublažili su se pa je nakon 4 dana otpuštena iz bolnice. Dva mjeseca poslije, pri rutinskome kontrolnom pregledu pacijentica je negirala sve prijašnje simptome i bila uredne pokretljivosti.

RASPRAVA

Dijastaza pubične simfize rijetka je komplikacija trudnoće i smatra se nedovoljno dijagnosticiranom patologijom bez utvrđene učestalosti. Iako autori, kad prijavljuju incidenciju (1 – 5), ne razlikuju antepartalnu dijastazu od postpartalne, razlika u fiziološkim uvjetima tijekom tih razdoblja očita je pa stoga etiologija i čimbenici rizika ne mogu biti isti. Predloženi rizični čimbenici za postpartalnu dijastazu pubične simfize jesu multiparitet, distocija ramena, makrosomni fetus, velika glava fetusa, brzo napredovanje druge faze porođaja i brzo spuštanje prezentacijskog dijela, epiduralna anestezija te prethodna trauma zdje-

macrosomic fetus, similar difficulties in a previous pregnancy, primiparity, and twin pregnancy. While all other risk factors are speculative, twin pregnancy and primiparity are the only ones proven statistically (2). On the other hand, this distinction can be argued, claiming that is the same continuous pathologic condition with a different timing of manifestation.

Since most of the risk factors of this disorder are speculative, its etiology is unclear and unproven as well. The theory of relaxin-induced laxity of ligaments and joints which could cause pelvic instability and symphyseal separation has not yielded its final conclusion, as published studies report contrary findings (7, 10, 12, 13).

Different terms can be found describing the clinical presentation of pain in the symphyseal region that radiates to the lower back and thighs, waddling gait, painful movement, and reduced mobility in pregnancy or postpartum: symphysis rupture, birth-associated pelvic pain, postpartum pelvic instability, pelvic insufficiency, separated public symphysis, pubic symphysis pain, symphysis pubis dysfunction, symphyseolysis during pregnancy, pubic symphysis diastasis, and symptomatic pelvic girdle relaxation of pregnancy (3, 7). However, only pubic symphysis diastasis is defined by precise imaging findings. The increasing distance between the pubic bones during pregnancy as a preparation for delivery is a physiological process. Reported values of physiological interpubic gap during pregnancy vary among studies (4, 6, 8, 14), but the cut-off value of 10 mm defines pubic symphysis diastasis and differentiates physiological from pathological symphysis separation. The interpubic gap can be measured by ultrasound (5, 14), X ray (6), MRI (8), or CT (4). There is no superiority of one imaging procedure over the others (3, 7). Furthermore, several studies demonstrated no relation between the interpubic gap size and the severity of clinical findings (4, 6, 8, 15). Therefore, clinical findings should be the main focus and imaging workup should be used for confirmation. Pelvic pain, as a nonspecific symptom, cannot be a pathognomonic sign of diastasis symphysis, but with other typical signs and symptoms, and after excluding common causes of pregnancy-related pelvic pain, educated and aware professionals should suspect pubic symphysis diastasis. After an assumption is made, the confirmation should be easy. Manual palpation as the first step in the workup is an easy, fast, and inexpensive method, as we reported in our case. Therefore, we suggest implementing symphysis palpation in regular obstetric practice in cases of suspected pubic symphysis diastasis.

There are no official guidelines regarding the mode of delivery in women with pubic symphysis diastasis. Most authors recommend an individualized approach (3, 7). In this particular case, considering the twin pregnancy which usually involves C-section in our obstetric practice, and the diastasis, we decided that a C-

lice. Za antepartalnu dijastazu pubične simfize čimbenici rizika jesu makrosomni fetus, slične teškoće u prethodnoj trudnoći, primiparitet i blizanačka trudnoća. Iako se o svim ostalim čimbenicima rizika može raspravljati, blizanačka trudnoća i primiparitet jedini su statistički potvrđeni (2). S druge strane, ova se razlika može argumentirati tvrdnjom da je to isto kontinuirano patološko stanje, ali s različitim vremenom manifestacije. Budući da je većina rizičnih čimbenika prijeporna, etiologija stanja također je nejasna i nedovoljno dokazana. Teorija o opuštenosti ligamenata i zglobova izazvanoj relaksinom, koja bi mogla prouzročiti nestabilnost zdjelice i razdvajanje simfize, nije dala konačan zaključak jer provedene studije izvještavaju o proturječnim nalazima (7, 10, 12, 13). Postoje različiti pojmovi koji opisuju kliničku prezentaciju boli u području simfize koja se širi u donji dio leđa i bedra, gegavi hod, bolne pokrete i smanjenu pokretljivost u trudnoći ili nakon porođaja: puknuće simfize, bol u zdjelici povezana s porođajem, postpartalna nestabilnost zdjelice, insuficijencija zdjelice, odvojena pubična simfiza, bol u pubičnoj simfizi, disfunkcija pubične simfize, simfizeoliza tijekom trudnoće, dijastaza pubične simfize, simptomatsko opuštanje zdjeličnog pojasa u trudnoći (3, 7). Međutim, jedino je dijastaza pubične simfize definirana preciznim slikovnim nalazima. Povećavanje udaljenosti između stidnih kosti tijekom trudnoće fiziološki je proces pripreme za porođaj. Izvještavane vrijednosti fiziološkog interpubičnog razmaka tijekom trudnoće razlikuju se ovisno o studiji (4, 6, 8, 14), ali granična vrijednost od 10 mm definira dijastazu pubične simfize i razlikuje fiziološko razdvajanje simfize od patološkoga. Interpubični razmak može se izmjeriti ultrazvukom (5, 14), x-zrakama (6), magnetskom rezonancijom (MR) (8) ili kompjutoriziranom tomografijom (CT) (4). Nijedan slikovni postupak ne nadmašuje ostale (3, 7). Nadalje, nekoliko studija nije pokazalo povezanost između veličine interpubičnog razmaka i težine kliničkog nalaza (4, 6, 8, 15). Stoga bismo se morali usredotočiti ponajprije na kliničke nalaze, a slikovna bi obrada trebala služiti za potvrdu. Bol u zdjelici, kao nespecifičan simptom, ne može biti patognomoničan znak dijastaze simfize, ali uz ostale tipične znakove i simptome, a nakon isključivanja uobičajenih uzroka boli u zdjelici povezanih s trudnoćom, obrazovani i svjesni stručnjaci trebali bi postaviti sumnju na dijastazu pubične simfize. Nakon pretpostavke potvrda bi trebala biti jednostavna. Manualna palpacija, kao prvi korak u obradi, jednostavna je, brza i jeftina metoda, što smo već naveli u svojem prikazu bolesnice. Stoga predlažemo uvođenje palpacije simfize u redovitu opstetričku praksu pri sumnji na dijastazu pubične simfize. Ne postoje službene smjernice o načinu porođaja u žena s dijastazom pubične simfize. Većina autora preporučuje individualizi-

section was a pain free, long-term beneficial mode of delivery. In general, pregnancy-related antepartum pubic symphysis diastasis is an insufficiently investigated condition, with unanswered questions about its exact incidence, risk factors, and prevention, and without evidence-based guidelines for the workup, treatment, and mode of delivery.

CONCLUSION

With regard to the simplicity and reliability of manual palpation in cases of suspected pubic symphysis diastasis, implementing palpation of the pubis in regular obstetrical practice would enable early recognition, immediate treatment, and a better long-term outcome. Also, antepartum pubic symphysis diastasis should be considered with regards to the mode of delivery. As there are no evidence-based guidelines and each case is approached individually, a comprehensive investigation of this condition is needed, with the aim to achieve standardization of practice.

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ran pristup (3, 7). U konkretnom slučaju naše bolesnice, a s obzirom na blizanačku trudnoću, kojoj se u našoj opstetričkoj praksi obično pristupa carskim rezom, i dijastazu, zaključili smo da je carski rez bezbolan način porođaja s dugotrajnom dobrobiti. Općenito, antepartalna dijastaza pubične simfize povezana s trudnoćom nedovoljno je istraženo stanje, bez odgovora na pitanja o točnoj incidenciji, rizičnim čimbenicima i prevenciji te bez smjernica utemeljenih na dokazima za njezinu obradu i liječenje, kao i način porođaja.

ZAKLJUČAK

S obzirom na jednostavnost i pouzdanost manualne palpacije pri sumnji na dijastazu pubične simfize, uvođenje palpacije stidnih kosti u redovitu opstetričku praksu omogućilo bi rano prepoznavanje stanja, neposredno liječenje i dugoročno bolji ishod. Također, valjalo bi donijeti preporuke o načinu porođaja pri antepartalnoj dijastazi pubične simfize. Budući da ne postoje smjernice utemeljene na dokazima, nego se svakoj bolesnici pristupa individualizirano, potrebno je sveobuhvatno istraživanje ovog stanja koje bi dovelo do standardiziranja prakse.

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

REFERENCES / LITERATURA

1. Shnaekel KL, Magann EF, Ahmadi S. Pubic Symphysis Rupture and Separation During Pregnancy. Obstet Gynecol Surv. 2015; 70(11):713–8.
2. Yoo JJ, Ha Y-C, Lee Y-K, Hong JS, Kang B-J, Koo K-H. Incidence and risk factors of symptomatic peripartum diastasis of pubic symphysis. J Korean Med Sci. 2014;29:281–6.
3. Herren C, Sobottke R, Dadgar A i sur. Peripartum pubic symphysis separation - Current strategies in diagnosis and therapy and presentation of two cases. Injury. 2015;46:1074–80. Dostupno na: http://dx.doi.org/10.1016/j.injury.2015.02.030. Pristupljeno: 1. 10. 2019.
4. Scriven MW, Jones DA, McKnight L. The importance of public pain following childbirth: A clinical and ultrasonographic study of diastasis of the pubic symphysis. J R Soc Med. 1995; 88(1):28–30.
5. Chawla JJ, Arora D, Sandhu N, Jain M, Kumari A. Pubic symphysis diastasis: A case series and literature review. Oman Med J. 2017;32:510–4.
6. Hagen R. Pelvic girdle relaxation from an orthopaedic point of view. Acta Orthop Scand. 1974;45:550–63.
7. Owens K, Pearson A, Mason G. Pubic symphysis separation. Fet Matern Med Rev. 2002;13:141–55.
8. Wurdinger S, Humbsch K, Reichenbach JR, Peiker G, Seewald HJ, Kaiser WA. MRI of the pelvic ring joints postpartum: Normal and pathological findings. J Magn Reson Imaging. 2002; 15:324–9.
9. Young J. Relaxation of the Pelvic Joints in Pregnancy: Pelvic Arthropathy of Pregnancy. J Obstet Gynecol Br Emp. 1940;47: 493–524.
10. Kristiansson P, Svärdsudd K, von Schoultz B. Serum relaxin, symphyseal pain, and back pain during pregnancy. Am J Obstet Gynecol. 1996;175:1342–7.
11. MacLennan AH, MacLennan SC. Symptom-giving pelvic girdle relaxation of pregnancy, postnatal pelvic joint syndrome and developmental dysplasia of the hip. Acta Obstet Gynecol Scand. 1997;76:760–4.
12. Hansen A, Jensen DV, Larsen E, Wilken-Jensen C, Petersen LK. Relaxin is not related to symptom-giving pelvic girdle relaxation in pregnant women. Acta Obstet Gynecol Scand. 1996; 75:245–9.
13. MacLennan AH, Nicolson R, Green RC, Bath M. Serum relaxin and pelvic pain of pregnancy. Lancet. 1986;2(8501):243–5.
14. Topuz S, Citil I, Iyibozkurt AC, Dursun M. Pubic symphysis diastasis: imaging and clinical features. Eur J Radiol Extra. 2006;59:127–9.
15. Schwartz Z, Katz Z, Lancet M. Management of puerperal separation of the symphysis pubis. Int J Gynaecol Obstet. 1985; 23:125–8.

INSTRUCTIONS FOR AUTHORS

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UPUTE AUTORIMA

O ČASOPISU

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Editorial: 1200 words maximum; up to 1 figure or table; up to 20 references; 3–6 Medical Subject Heading (MeSH) keywords of the National Library of Medicine of US; unstructured abstract up to 300 words (if applicable).

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The text should be typed in 12-point font, on white A4 paper (210 x 297 mm), double-spaced, with a maximum of 30 lines per page, including the title page, abstract, text, acknowledgments, conflict of interest statement, references, tables, and legends. The left margin should be 35 mm, and the right, top and bottom margins 25 mm each. All the pages, including the title page, should be numbered in the bottom right corner.

Measurements, if needed, should be reported using the International System of Units (SI). Names that can be abbreviated should be spelled out in full followed by the abbreviation in parentheses at the first mention, and referred to only in the abbreviated form further in the text. Latin names should be italicized, with the full name at the first mention, and only the abbreviated form further in the text. Drugs should be referred to by their generic names, and trade names, if necessary, may follow in parentheses, with the manufacturer's name. Manufacturers of specific instruments or reagents (name and location) should be given in parentheses.

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Title page

The title page should include the article title (concise, clear, and informative) both in Croatian and in English, and the full name of each author, followed by the full name of the author's affiliation, with full postal address (street, city, and country) of the institution. If the article was prepared by several authors of various affiliations, all authors should be linked to their corresponding affiliation(s) using superscript numerals after their respective names, and preceding the institution name.

This should be followed by the name, surname, and full contact address of the corresponding author responsible for the correspondence related to the article, with his/her telephone and fax numbers, and e-mail address.

Abstract and keywords

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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.

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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).

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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.

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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.

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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.

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[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

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[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.

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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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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):

9. Gordon DA (ur.). Immune reactions and experimental models in rheumatic diseases. Zbornik izlaganja na Četvrtoj kanadskoj konferenciji o istraživanju reumatskih bolesti; 1970 Lis 15–17; Toronto, Kanada. Toronto: University of Toronto Press; 1972.

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[Primjer] Članak iz časopisa na internetu, sadržava DOI:

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

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:

10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. J Immunol Res [Internet]. 2014;2014:419029. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017881. [cited: 2014 May 25].

[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.

[Example] Book/monograph on the Internet:

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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[Primjer] Knjiga/monografija na internetu:

12. Chen Q (ur.). Osteoarthritis – diagnosis, treatment and surgery [Internet]. Rijeka: InTech; 2012. Dostupno na: http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery. [Pristupljeno: 8. 10. 2013.].

[Primjer] Mrežna stranica:

13. Hrvatsko reumatološko društvo [Internet]. Zagreb: Hrvatsko reumatološko društvo HLZ-a; c2014. Dostupno na: http://www.reumatologija.org/Pocetna.aspx. [Pristupljeno: 1. 4. 2014.].

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