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NEFARMAKOLOŠKO LIJEČENJE UPALNIH REUMATSKIH BOLESTI UTEMELJENO NA DOKAZIMA

EVIDENCE-BASED NON-PHARMACOLOGICAL TREATMENT OF INFLAMMATORY RHEUMATIC DISEASES

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Sažetak

Liječenje upalnih reumatskih bolesti vrlo je kompleksno i zahtjevno. Holistički i individualni pristup takvim bolesnicima obvezuje nas na korištenje svih raspoloživih resursa, kako farmakoloških tako i nefarmakoloških na putu postizanja remisije bolesti, bez obzira o kojoj se upalnoj reumatskoj bolesti radi. U ovom preglednom radu, zasnovanom na proučavanju medicine utemeljene na dokazima, osvrnuo sam se na značaj nefarmakološkog liječenja (NFL) koje je postalo sastavni dio svih algoritama liječenja ovih bolesnika, pri čemu medicinske vježbe imaju najvažniju ulogu među takvim metodama liječenja. Čitav niz dokaza koji su pokazali da je mišić sekretorni organ dokazuju kako se svakim ciklusom vježbanja u mišićima oslobađaju proteini nazvani miokinima, među kojima je najznačajniji u mišiću sintetizirani IL-6, koji onda inhibira proizvodnju TNF-a, stimulira i inducira proizvodnju protuupalnih citokina: IL1-Ra (receptor antagonist) i IL-10 u mononuklearnim krvnim stanicama, čime se ostvaruje značajan protuupalni učinak. Stoga, suprotno ranijim strahovima kako tjelesna aktivnost može pogoršati upalu, sada se smatra kako bi se terapijske vježbe mogle koristiti kao potencijalno potentni lijek za bolesnike s upalnim reumatskim bolestima zbog sinergističkog djelovanja s biološkom terapijom. Pritom ne treba zaboraviti niti ostale metode NFL koje imaju simptomatski učinak, kao što su različiti oblici fizikalne terapije i nutritivna potpora.

Ključne riječi: upalne reumatske bolesti, nefarmakološko liječenje, miokini

Abstract

The treatment of inflammatory rheumatic diseases is a complex and demanding process. In an effort to achieve remission, the holistic and individual approach to patients suffering from inflammatory rheumatic diseases compels us to use all available means, both pharmacological and non-pharmacological, regardless of the particular disease that is being treated. In this review, established on the research of evidence-based medicine literature, I have discussed the importance of non-pharmacological treatment that became a fundamental part of all related treatment algorithms, with medical exercise being the method with the greatest effect amongst all other treatment methods. A whole series of evidence showing that muscle is, in fact, a secretory organ, proved that, with every cycle of exercise, numerous proteins, so-called myokines, are released from the muscle, with IL-6 being the most important one because of its TNF-α inhibition and stimulation of pro-inflammatory cytokines: IL-1-Ra (receptor antagonist) and IL-10 in mononuclear blood cells, which create an anti-inflammatory effect. So, contrary to popular belief that physical activity can increase and

exacerbate the inflammatory process, it is now considered that medical exercise could potentially be used as a potent cure for the treatment of inflammatory rheumatic diseases due to its synergistic effect when used in combination with biological therapy. All things considered, other methods of non-pharmacological treatment, such as various forms of physical therapy and nutritional support, should not be neglected because of their symptomatic and supportive effect.

Keywords: inflammatory rheumatic diseases, non-pharmacological treatment, myokines

UVOD

Upalne reumatske bolesti čine jednu veliku skupinu izrazito devastirajućih bolesti koje se pretežno manifestiraju na lokomotornom sustavu, bez obzira o kojoj vrsti tih bolesti govorimo.

Kao dva antipoda ove velike skupine raznolikih i patofizioloških složenih bolesti među onima koje dominantno zahvaćaju zglobove i okolozglobne strukture najčešće spominjemo reumatoidni artritis (RA) i ankilozantni spondilitis (AS).

Ne zbog toga što druge bolesti nisu važne ni učestale, već radi modela kojim možemo prikazati evoluciju upalnih promjena i njihovu zastupljenost na lokomotornom sustavu: zbog činjenice da ove dvije bolesti imaju svoja pravila pojavnosti promjena na perifernim zglobovima i aksijalnom skeletu, koja su gotovo uvijek ispoštovana. Zato se kod tih bolesti lako mogu pratiti i loše strane učinka bolesti na lokomotorni sustav, ali i dobre strane sveukupnog liječenja (1,2).

Za razliku od nekih drugih bolesti, kao što je npr. psorijatički artritis (PsA), koji u stvarnosti često izgleda kao surogat ovih dviju bolesti, predvidljivost i praćenje učinka i bolesti i liječenja je značajno teže, o čemu sam pisao u časopisu *Reumatizam* 2017., tako da ću se u ovom preglednom radu bazirati na učinke liječenja kod bolesnika oboljelih od RA i AS (3,4). Uostalom, i literaturni podatci koji nam kod sustavnih pregleda i metaanaliza stoje na raspolaganju najčešće su vezani upravo za ove dvije bolesti, dok se podatci o ostalim upalnim bolestima navode usput.

Osim po različitim epidemiološkim karakteristikama, RA i AS se značajno razlikuju i po karakterističnom obrascu upalnih promjena lokomotornog sustava, uz neizbježan sistemski karakter bolesti, čime se razlikuje i njihovo nefarmakološko liječenje:

1. centripetalna afekcija zglobova počevši od malih perifernih zglobova na okrajinama u bolesnika s RA-om pa progresija prema aksijalnom skeletu koji gotovo nikada nije zahvaćen (osim atlanto-aksijalnog zgloba ponekad)
2. centrifugalna afekcija u AS-u, gdje postoji prvotna zahvaćenost sakroilijakalnih zglobova i aksijalnog skeleta, s procesom širenja na velike korijenske zglobove, uz rijetke promjene i na perifernim zglobovima.

Dulje trajanje bolesti doprinosi značajnijim funkcionalnim ograničenjima u svim područjima života kod

INTRODUCTION

Inflammatory rheumatic diseases form one large group of extremely devastating diseases, mainly those of the locomotor system, regardless of the type of these diseases.

When it comes to diseases that predominantly affect the joints and periarticular structures, rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are the two antipodes of this large group of diverse and pathophysiologically complex diseases.

That is not to say that other diseases are not important or frequently occurring, but to present a model with which we can show the evolution of inflammatory changes and their representation on the locomotor system, due to the fact that these two diseases have their own rules that they abide by when it comes to the occurrence of changes on peripheral joints and the axial skeleton. That is why in these diseases it is easy to follow the adverse effects on the locomotor system, as well as the benefits of the overall treatment process (1,2).

Unlike some other diseases, such as psoriatic arthritis (PsA), which in reality often looks like a surrogate of these two diseases, the predictability and follow-up of the effect of both the disease and treatment is significantly more difficult. I have touched upon this issue in some of my articles which were published in the *Rheumatism* journal in 2017, so in this review I will focus on the effects of treatment in patients with RA and AS (3,4). After all, the literature data that are available to us in systematic reviews and meta-analyses are most often related to these two diseases, while data on other inflammatory diseases are mentioned incidentally.

In addition to different epidemiological characteristics, RA and AS also differ significantly in the characteristic pattern of inflammatory changes in the locomotor system, as well as the inevitable systemic nature of the disease, which also contributes to the differentiation of the non-pharmacological treatment of these diseases:

1. centripetal involvement of the joints starting from small peripheral joints of the extremities in patients with RA and progressing towards the axial skeleton which is almost never affected (except the atlanto-axial joint involvement which may occur at times)
2. centrifugal involvement in AS, where there is an initial involvement of the sacroiliac joints and the axial skeleton, with the process of spreading to the

obiju navedenih bolesti. Slično je i kod drugih upalnih reumatskih bolesti, kod kojih devastirajuće promjene zahvaćenih zglobova ne moraju biti manje izražene. Dapače.

Kronična sustavna upala, kao prepoznatljivo obilježje većine upalnih reumatskih bolesti, odgovorna je za široku paletu kliničkih manifestacija u bolesnika s RA-om i AS-om. Teškoj kliničkoj slici često pridonosi i činjenica da većina oboljelih ima i brojne izvanzglobne manifestacije, ali i pridružene bolesti kao što su pretilost, kardiovaskularne bolesti, metabolički sindrom, dijabetes, osteoporoza i depresija, a koje povećavaju rizik morbiditeta i ranog mortaliteta te značajno povećavaju cijenu liječenja bolesti (5,6). Zbog navedenog, fizičke, psihičke i socijalne posljedice bolesti za svakog su pojedinca iznimno složene. Zadirući u sva životna područja te same posljedice i sistemski karakter bolesti, značajno umanjuju kvalitetu života i mogućnost aktivnog sudjelovanja u životu zajednice. Napredak u liječenju RA-a i AS-a uvođenjem bioloških lijekova, pored dotadašnjih lijekova koji su samo modificirali bolest (DMARD-ova), uvelike je promijenio paradigmu liječenja, prebacujući naglasak s dosadašnjeg liječenja simptoma na usporavanje progresije bolesti i postizanje kvalitetne remisije (tzv. liječenje prema zadanom cilju, engl. skr. T2T) (7). Stoga se blokiranje upalne reakcije i kaskade aktiviranja proupalnih citokina biološkim lijekovima danas smatra kamenom temeljcem svih glavnih strategija liječenja najčešćih upalnih reumatskih bolesti (8).

Unatoč tom napretku, a zbog kasnog dijagnosticiranja i kasnog početka liječenja, i dalje velik broj oboljelih ima značajna funkcijska oštećenja, budući da je opterećenost reumatološke službe i čekanje na pregled reumatologa u našem zdravstvenom sustavu i dalje veliki problem.

Prema svim prihvaćenim smjernicama radnih grupa *American College of Rheumatology* (ACR) i *Assessment of SpondyloArthritis* (ASAS) / *European Alliance of Associations for Rheumatology* (EULAR) optimalno liječenje svih upalnih reumatskih bolesti uvijek zahtijeva kombiniranje i farmakološkog i nefarmakološkog liječenja (NFL) (9,10,11). Biološki lijekovi koji danas omogućavaju vrlo rano suzbijanje upalne aktivnosti doprinijeli su promjeni i rehabilitacijske paradigme (12). Rana supresija upale i rano otkrivanje bolesti dovode do sprječavanja pojave teških zglobnih deformacija kojima smo svjedočili prije dvadesetak godina te boljem očuvanju funkcijskih sposobnosti bolesnika (13).

Ipak, oboljeli od upalnih reumatskih bolesti i dalje imaju značajno smanjenu kvalitetu života, a nova saznanja o NFL-u, poglavito o učincima vježbanja na tijek i prognozu bolesti, bude i novu nadu za učinkovitijim liječenjem. Zbog toga se danas naglasak treba sta-

large root joints, with changes that rarely occur in the peripheral joints.

The longer duration of the disease contributes to more significant functional limitations in all areas of life when it comes to both mentioned diseases. Similar process occurs in other inflammatory rheumatic diseases, in which the devastating changes in the involved joints do not have to be less pronounced. On the contrary.

Chronic systemic inflammation, as a recognisable feature of most inflammatory rheumatic diseases, is responsible for a wide range of clinical manifestations in patients with RA and AS. The fact that most patients have numerous extra-articular manifestations, but also comorbidities such as obesity, cardiovascular diseases, metabolic syndrome, diabetes, osteoporosis and depression, (all of which increase the risk of morbidity and early mortality and significantly increase the cost of treatment) contributes to severe clinical features of these diseases (5,6). Due to the aforementioned facts, the physical, psychological and social consequences of the disease are extremely complex for each individual. When it comes to all areas of life, the very consequences and systemic character of the disease have an extremely negative effect on the quality of life and the possibility of active participation in the life of the community. Progress in the treatment of RA and AS was achieved with the introduction of biological drugs, in addition to the previously used drugs that only modified the disease (DMARDs). This has greatly changed the treatment paradigm, shifting the emphasis from the previous treatment of symptoms to slowing down the progression of the disease and achieving a quality remission (so-called treat-to-target approach, T2T) (7). Therefore, in today's terms, blocking the inflammatory reaction and the activation of pro-inflammatory cytokine storm with biological drugs is considered the cornerstone of all the main strategies for the treatment of the most common inflammatory rheumatic diseases (8).

Despite this progress, and due to late diagnosis and late start of treatment, a large number of patients still have significant functional impairments, since the workload of the rheumatology units and the wait-times for a rheumatology consultation are still a big issue when it comes to the healthcare system in Croatia. According to all accepted guidelines of the working groups of the American College of Rheumatology (ACR) and the Assessment of SpondyloArthritis international Society (ASAS) / European Alliance of Associations for Rheumatology (EULAR), optimal treatment of all inflammatory rheumatic diseases always requires a combination of both pharmacological and non-pharmacological treatment (NPT) (9, 10,11). Biological drugs, which today enable a very early suppression of inflammatory activity, have also contributed to a change in the rehabilitation paradigm (12). Early suppression of in-

viti i na rano NFL, a posebice na primjenu dinamičkih i aerobnih vježbi, o čemu će biti riječi u nastavku rada, sukladno analizi podataka medicine utemeljene na dokazima (EBM) (11). Poznato je da se ranije terapijske vježbe nisu preporučivale bolesnicima s upalnim reumatskim bolestima, poglavito ne u akutnoj fazi bolesti, zbog straha od pogoršanja upale i dodatnih oštećenja zglobnih tijela (14). Danas dostupni dokazi ukazuju na činjenicu kako vježbe imaju ne samo funkcijski, nego i značajan protuupalni učinak, kao i neki drugi oblici NFL-a.

Naime, posljednjih godina dostupni su nam i konkretni dokazi koji podupiru tu teoriju i omogućavaju pojavu novog koncepta u području terapijskog vježbanja (15). Pritom su glavni ciljevi NFL-a, pa i rehabilitacije upalnih reumatskih bolesti, kontrola simptoma i progresije bolesti te smanjenje utjecaja bolesti na funkcijske mogućnosti bolesnika, kvalitetu života, psihičko i socijalno zdravlje te radni status oboljelog. Iako posljednjih dvadeset godina interes za područje reumatološke rehabilitacije ubrzano raste, načela rehabilitacije ostalih upalnih reumatskih bolesti zbog nedostatka relevantnih dokaza „posuđena" su i temeljena na spoznajama o NFL-u u AS-u i RA-u (1–4). Možemo li postaviti specifičnije rehabilitacijske ciljeve i učinkovitije koristiti dostupno NFL, a sve s ciljem smanjenja aktivnosti bolesti, poboljšanja kvalitete života i društvene uključenosti oboljelog pojedinca? Odgovor ću pokušati pronaći analizirajući dostupnu nam literaturu, poštujući imperativ ranog i vrlo usmjerenog početka rehabilitacije i potrebe interdisciplinarnog pristupa utemeljenog na bolesnikovim željama i mogućnostima te provedbi kvalitetnih kliničkih istraživanja iz područja NFL-a. Ujedno, treba biti i svjestan činjenice kako pristup biološkim lijekovima u svim zemljama još uvijek nije isti: najčešće zbog administrativnih razloga, a ne zbog nedostatnog znanja i umijeća reumatologa.

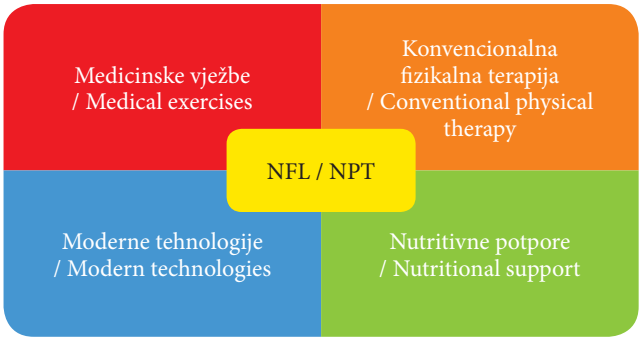
METODE

Za potrebe izrade ovog preglednog članka pretražene su baze podataka relevantne za područje fizikalne i rehabilitacijske medicine: PEDro (*Physiotherapy Evidence Database*), *Medline* i *Cochrane Database of Systematic Reviews*.

Dodatno su pretražene referencije relevantnih radova uključenih u pregledni članak. U razmatranje su uzeti samo članci koji su se odnosili na NFL upalnih reumatskih bolesti kod osoba starijih od 18 godina, a objavljeni su zaključno do svibnja 2022. godine. Uključeni su radovi pisani na engleskom i hrvatskom jeziku, korištenjem MeSH ključnih riječi: reumatoidni artritis, spondiloartropatije, ankilozantni spondilitis, upalne reumatske bolesti, modaliteti fizikalne terapije i rehaflammation and early detection of the disease lead to the prevention of severe joint deformities that we have witnessed twenty years ago and to a better preservation of the patient's functional ability (13).

Nevertheless, patients with inflammatory rheumatic diseases still have a significantly reduced quality of life, and new knowledge about NPT, especially related to the effects of exercise on the course and prognosis of the disease, gives us new hope for a more effective treatment. For this reason, early NPT should be emphasised when it comes to today's treatment methods, especially in relation to dynamic and aerobic exercises, which will be discussed in the following part of the paper, in accordance with the data analysis of evidence based medicine (EBM) (11). It is a well-known fact that previously used therapeutic exercises were not recommended for patients with inflammatory rheumatic diseases, especially in the acute phase of the disease, due to the fear of exacerbating inflammation and causing additional damage to the articular surface (14). Scientific evidence available today points to the fact that, in addition to the functional effect, exercises (as well as some other forms of NPT) also have a significant anti-inflammatory effect.

In recent years, concrete evidence has become available that supports this theory and enables the emergence of a new concept in the field of therapeutic exercise (15). In this respect, the main goals of NPT, and the rehabilitation of inflammatory rheumatic diseases, are the following: the control of symptoms and the progression of the disease, and the reduction of the effect of the disease on the patient's functional ability, quality of life, psychological and social health, and work status. Although the interest in the field of rheumatological rehabilitation has been growing rapidly in the last twenty years, the principles of rehabilitation of other inflammatory rheumatic diseases are still "borrowed" and based on the knowledge of NPT in AS and RA due to the lack of relevant evidence (1–4). Are we able to set more specific rehabilitation goals and use the available NPT methods more effectively, all with the aim of reducing disease activity, improving the quality of life and social inclusion of the affected individual? I will try to find the answer by analysing the literature available to us, respecting the imperative of an early and highly targeted start of rehabilitation and the need for an interdisciplinary approach based on the patient's preferences and possibilities, and the implementation of quality clinical research in the field of NPT. At the same time, one should be aware of the fact that access to biological drugs still may be difficult in some countries. This is most often due to administrative reasons, and not due to insufficient knowledge and skills of rheumatologists.



Legenda / Legend:
NFL /NPT = nefarmakološko liječenje / non-pharmacological treatment

Slika 1. Nefarmakološko liječenje (NFL) upalnih reumatskih bolesti
Figure 1 Non-pharmacological treatment (NPT) of inflammatory rheumatic diseases

bilitacija. Radi uključivanja svih dostupnih radova na hrvatskom jeziku, dodatno su pretražene arhive dvaju hrvatskih časopisa: *Fizikalna i rehabilitacijska medicina* (ranije *Fizikalna medicina i rehabilitacija*) (http://hrcak.srce.hr/frm), period 1984. – 2021., i *Reumatizam* (http://www.reumatologija.org/Casopis.aspx?link=Reumatizam_pdf), period 2004. – 2021., gdje su bili dostupni cjeloviti tekstovi članaka, te Bibliografija časopisa *Reumatizam*, period 1954. – 2003., gdje su pregledani naslovi članaka.

U razmatranje su uzete sve vrste radova za koje smo iz sadržaja ili iz naslova mogli zaključiti da su pisali o rehabilitaciji i NFL-u upalnih reumatskih bolesti. Točnost podataka ograničena je nedostupnošću cjelovitih tekstova određenih članaka iz pojedinog izvora.

Dva istraživača neovisno su odabrala članke koji odgovaraju gore navedenim kriterijima te prikupili relevantne podatke.

REZULTATI

NFL-u pripadaju brojne metode liječenja, koje možemo nazivati i komplementarnim metodama liječenja u odnosu na uobičajenu farmakoterapiju koja je, nedvojbeno, najvažniji oblik i način dostizanja cilja u liječenju ovih sistemskih bolesti – remisije bolesti. Ono što sam ja želio u ovom pregledu istaknuti kod NFL-a usmjerenog k uspješnosti i učinkovitosti postizanja kvalitetnijeg života naših bolesnika, koristeći podatke EBM-a, to je bilo objasniti načine djelovanja takvog načina liječenja te bolje kontrole bolesti, uz što bolju kvalitetu dokaza (11).

NFL obuhvaća mnogo više različitih oblika liječenja, od kojih će neki biti i navedeni, ali fokus ovog članka jest nekoliko najučinkovitijih i najčešće korištenih načina/metoda ostvarivanja remisije i bolje kvalitete života: medicinske vježbe, konvencionalna fizikalna

METHODS

In order to prepare this review article, we have performed a search of the following databases relevant to the field of physical and rehabilitation medicine: PEDro (*Physiotherapy Evidence Database*), *Medline* and *Cochrane Database of Systematic Reviews*.

We have also performed an additional search of the references of the relevant papers included in the review article. In addition to that, we have decided to take into consideration only the articles related to the NPT of inflammatory rheumatic diseases in individuals over the age of 18, which were published by May 2022 at the latest. The included papers are written in English and Croatian, using MeSH keywords: rheumatoid arthritis, spondyloarthropathies, ankylosing spondylitis, inflammatory rheumatic diseases, physical therapy modalities and rehabilitation. In order to include all available papers in the Croatian language, we have performed an additional search of the archives of two Croatian journals: the *Physical and Rehabilitation Medicine* journal (previously known as the *Physical Medicine and Rehabilitation* journal), (http://hrcak.srce.hr/frm), in the period from 1984 to 2021, and the *Rheumatism* journal (http://www.reumatologija.org/Casopis.aspx?link=Reumatizam_pdf), in the period from 2004 to 2021, in which we have found full articles as well as the bibliography of the Rheumatism journal, in the period from 1954 to 2003, which was used for the overview of the article titles.

All types of papers were taken into consideration, and it was obvious from their content or titles that the topics reviewed refer to the rehabilitation and NPT of inflammatory rheumatic diseases. The accuracy of the data is limited by the unavailability of full texts of certain articles from a particular source.

Two researchers independently selected articles that fit the above criteria and collected relevant data.

RESULTS

NPT includes numerous treatment methods, which we can also refer to as complementary treatment methods compared to usual pharmacotherapy, which is undoubtedly the most important form and method of achieving the goal in the treatment of these systemic diseases, which is disease remission. By using EBM data in this review about the NPT aimed at the success and efficiency of achieving a better quality of life for our patients, I wanted to highlight and explain the improved methods of disease control and mechanisms of action of this type of treatment, with the best possible quality of evidence (11).

NPT includes many different forms of treatment, some of which will be listed, but the focus of this article is on several of the most effective and commonly used techniques/methods to achieve remission and a better

terapija, moderne tehnologije u rehabilitaciji i nutritivna potpora (slika 1).

Zašto su nam ove metode liječenja važne?

Za razliku od farmakoterapije, čiji se učinak vrlo brzo ogleda u promjeni vrijednosti brojnih laboratorijskih pokazatelje upalne aktivnosti, učinak NFL-a se evaluira i dokazuje promjenama brojčanih vrijednosti brojnih generičkih upitnika, ali i specifičnih za bolest, koji su postali neizostavni alati u procesu dijagnosticiranja, evaluiranja i dokazivanja kvalitetnog učinka liječenja kako u svakodnevnom radu tako i u svim kliničkim istraživanjima te je njihov učinak na upravo te vrijednosti funkcijskih pokazatelja uspješnosti liječenja postao jako važan. Predmet interesa kod njihovog prikazivanja stvarnog stanja bolesnika jesu pitanja o kvaliteti sna, umoru, boli, (ne)mogućnostima obavljanja svakodnevnih i profesionalnih aktivnosti te brojnim funkcijskim i psihološkim parametrima bolesti.

Stoga te varijable u praćenju bolesnika daju svakom reumatologu za pravo da govori o holističkom i individualiziranom pristupu bolesniku. A upravo to je jedan od glavnih postulata modernog liječenja ovako složenih bolesti.

Naime, nikada ne smijemo zaboraviti da liječeći naše reumatološke bolesnike ne liječimo laboratorijske i radiološke nalaze, već bolesnika kao osobu koja ima svoje probleme u funkcioniranju i djelovanju, a tu nam najveću pomoć pruža upravo NFL.

Sinergijom farmakoterapije i NFL-a ostvarujemo najkvalitetnije rezultate liječenja, ponovno osposobljavamo našeg bolesnika za svakodnevne i profesionalne aktivnosti te umanjujemo njegovu ometenost. Epidemiološki podatci koji govore o tome da od upalnih reumatskih bolesti mahom obolijevaju mlađe, radno aktivne osobe, daju ovoj činjenici veliku važnost (1,2).

Medicinske vježbe

Od svih metoda NFL-a koje koristimo u svakodnevnoj praksi liječenja upalnih reumatskih bolesti, medicinske vježbe (kineziterapija, medicinske vježbe, terapijsko vježbanje) pokazale su se najučinkovitijom metodom. Dugo je to bilo empirijsko propisivanje takvog načina liječenja, mogli bismo ga nazvati i „*ex iuvantibus*“ načinom simptomatskog liječenja te njegovu uporabu vezati uz poznate povijesne detalje koji sežu još od Hipokrata, koji je zapisao „… kako na osnovu simptoma, nije postavljao dijagnozu, nego prognozu bolesti. Uz medikamente, u tretmanu duševnih bolesti (u to vrijeme koristili su se različiti biljni pripravci, opij, kanabis, rauvolfija i druge, empirijski nađene tvari) preporučivao je odmor, dijetu, gimnastiku, a kao najprikladniji lijek – rad…“ (cit. Medicinska enciklopedija).

Od Hipokrata (460. – 377. pr. Kr.) do današnjih dana prošlo je puno vremena, svjedočili smo brojnim pre-

quality of life: medical exercises, conventional physical therapy, modern technologies in rehabilitation and nutritional support (Figure 1).

Why are these treatment methods important?

In contrast to pharmacotherapy, the effect of which is quickly reflected in changes in the values of numerous laboratory markers of inflammatory activity, the effect of NPT is evaluated and proven by changes in the numerical values of numerous generic questionnaires, as well as those specific to the disease. They have become indispensable tools in the process of diagnosis, evaluation and proving the quality effect of treatment both in everyday work and in all clinical research, and their effect on the values of functional indicators of effective treatment has become especially important. When it comes to the presentation of the patient's current condition, these questionnaires are mostly focused on questions about the quality of sleep, fatigue, pain, (in)ability to perform daily and professional activities, and numerous functional and psychological parameters of the disease.

Therefore, these variables in patient follow-up give every rheumatologist the right to talk about a holistic and individual approach to each patient. And this is precisely one of the main postulates of modern treatment of such complex diseases.

We must never forget that, when we are treating patients who suffer from rheumatic diseases, we are not treating laboratory and radiological findings, but the patient who is a real person and who is dealing with their own problems related to their functional ability and activity, and this is precisely where NPT is the most helpful.

Through the synergy of pharmacotherapy and NPT, we are able to achieve the treatment results of the highest quality, conduct the retraining of our patients so they would be able to perform everyday and professional activities, and reduce their level of distraction. Epidemiological data, which show that inflammatory rheumatic diseases mainly affect younger people and working age population, give an even greater importance to this fact (1,2).

Medical exercises

Out of all of the NPT methods that we use in the daily practice of treating inflammatory rheumatic diseases, medical exercises (kinesitherapy, medical exercises, therapeutic exercise) have proven to be the most effective method. For a long time, the prescription of this treatment method was empirical (we could also call it an *ex juvantibus* method of symptomatic treatment) and its use can be linked to well-known historical details dating back to Hippocrates. According to him, the following statements were true: "...he did not make a diagnosis on the basis of symptoms, but the prognosis of the disease. In addi-

porukama i promišljanjima u tom smjeru, pa tako službene ACR preporuke iz 2002. godine preporučuju dinamičke, čak i aerobne vježbe kao program koji će dovesti do poboljšanja mobilnosti, mišićne snage i funkcionalnosti zgloba, bez povećanja umora i pogoršanja zglobnih simptoma (16). U smjernicama EULAR-a iz 2007. nalazimo preporuke za vježbanje u ranom RA, kao „Preporuku br. 11", gdje se kao najvažnija intervencija NFL-a u takvih bolesnika navode dinamičke vježbe, uz radnu terapiju i hidroterapiju (17), a slične smjernice su postojale i za AS od 2006., definirane preporukama ASAS/EULAR-a za liječenje AS-a, naglašavajući da je NFL osnovni alat u globalnoj strategiji liječenja AS-a, kasnije nadopunjen novim spoznajama o biološkoj terapiji te bolesti (18). Vježbanje kod AS-a igra važnu ulogu i u doba biološke terapije, a primjenjuje se za stabilizaciju pacijenata dovodeći time do boljeg i kvalitetnijeg liječenja AS-a, koristeći sinergistički učinak dokaza, koji pokazuju da i vježbe imaju protuupalni učinak (19).

Iako smo ne tako davno imali potpuno drugačiju paradigmu vezanu uz vježbanje kod upalnih reumatskih bolesti, ipak je i tada u jednom opsežnom literaturnom pregledu iz 2007. utvrđeno kako je važno uvjeriti bolesnika s RA-om u efikasnost i sigurnost umjerenog do intenzivnog vježbanja, koristeći dinamičke i aerobne vježbe, budući da one nisu pokazale nikakvih štetnih učinaka na lokalni nalaz njihovih zglobova (20). To su bila empirijska nastojanja da se u liječenju upalnih reumatoloških bolesnika NFL etablira kao nužan dio terapijskog mozaika, poglavito onaj koji se odnosi na medicinske vježbe, tim prije što su u međuvremenu trajala nastojanja brojnih znanstvenika da pokažu kako skeletni mišići koji su pri tome aktivirani nisu tu samo radi boljeg izgleda bolesnika ili funkcije njegovog lokomotornog aparata. Mnogi od njih su se trudili pokazati kako skeletni mišić komunicira sa svim ostalim sustavima u našem tijelu i kako doprinosi brojnim endokrinim zbivanjima. Pojavio se novi koncept da je skeletni mišić zapravo sekretorni organ, a među brojim znanstvenicima koji su radili u tom području mene je osobno najviše impresionirala upornost i složenost onoga što je radio danski znanstvenik B. K. Pedersen, čije smo radove i dostignuća mogli kontinuirano pratiti u tom smislu godinama (21,22,23).

Zbog toga bih se u sljedećem dijelu članka referirao na podatke iz zajedničkog rada F. B. Benattija i B. K. Pedersena objavljenog 2015. godine, iz kojega konačno možemo iščitati analizu koja medicinske vježbe objašnjava na razini citokinske aktivnosti, teorijom koju kolokvijalno možemo nazvati „miokinskim konceptom" (15). To je novi koncept po kojemu su skeletni mišići sekretorni organi koji pri svakoj koncentričnoj kontrakciji oslobađaju proteine nazvane "miokinima", kao što je u mišiću derivirani IL-6 koji inhibira produkciju

tion to medications (at that time various herbal preparations, opium, cannabis, rauwolfia and other empirically found substances were used), he recommended rest, diet, gymnastics, and work, as the most suitable remedy in the treatment of mental illnesses..." (quote adapted from the *Medical Encyclopaedi*a book, translator's comment).

A lot has changed from the age of Hippocrates (460 – 377 BC) to the present day, we have witnessed numerous recommendations and opinions on this matter, so the official 2002 ACR Guidelines recommend dynamic, and even aerobic exercise programmes for achieving improved mobility, muscle strength and joint functionality, without increasing fatigue and exacerbation of joint symptoms (16). The 2007 EULAR guidelines include recommendations for exercise in early RA, listed under "Recommendation 11", in which dynamic exercises, occupational therapy and hydrotherapy (16) are stated as the most important NPT interventions. Similar ASAS/EULAR recommendations for the management of AS were published in 2006, in which NPT was highlighted as the main tool in the global strategy of AS treatment. Later on, new insights related to the biological therapy of this disease were incorporated into the aforementioned recommendations (18). In the age of biological therapy, exercise plays an important role in the treatment of AS, and is used for the stabilisation of patients, thereby leading to an improved and high-quality treatment of AS, using the synergistic effect of evidence, which shows that exercise also has an anti-inflammatory effect (19).

Although not so long ago we had a completely different paradigm related to exercise in inflammatory rheumatic diseases, even then, in an extensive literature review from 2007, it was determined that it is important to convince patients with RA of the effectiveness and safety of moderate to intense exercise, by using dynamic and aerobic exercises, because they had no adverse effects on the patients' joints (20). These were empirical efforts to establish NPT as a necessary part of the therapeutic mosaic in the treatment of patients with inflammatory rheumatic diseases. This is extremely important in relation to medical exercises, especially since, during that time, numerous scientists have tried to show that the skeletal muscles that were activated during this type of exercise had a special role that was not only connected to an improved physical condition of the patient or the function of the patient's locomotor system. Many of them tried to show how the skeletal muscle communicates with all other systems in our body and how it contributes to numerous endocrine events. A new concept emerged, promoting the idea that the skeletal muscle is actually a secretory organ. Due to the fact that I was one of the scientists who worked in this field, I was personally extremely im-

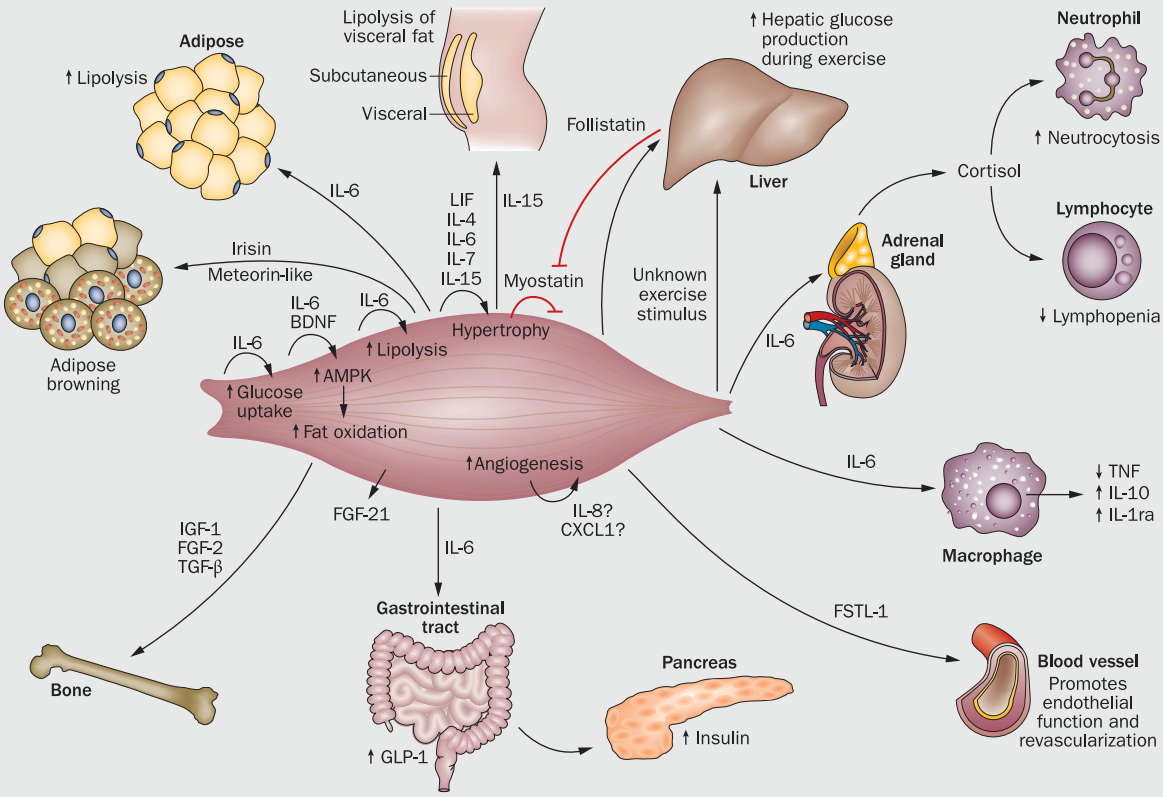
TNFα, stimulira i inducira produkciju protuupalnih citokina IL-1Ra (receptor antagonist) i IL-10, koje luče mononukleari, ostvarujući važan protuupalni efekt. Dokazi su pokazali da cirkulirajuća razina IL-10 i IL-1Ra raste u razdoblju nakon vježbanja i da je njihovo oslobađanje vjerojatno pojačano kao odgovor na spomenuti IL-6 (25). IL-10 i IL-1Ra igraju ulogu u imunološkoj regulaciji i također su uključeni u doprinos protuupalnom odgovoru na tjelovježbu. IL-10 se smatra klasičnim protuupalnim citokinom, jer on potiskuje citokine putem izravne inhibicije djelovanja proupalnih citokina, kao i sprječavanjem sinteze citokina (26). Koristeći posttranslacijske mehanizme, IL-10 je u stanju blokirati nuklearni faktor kappa-β (NF-κβ), transkripcijski faktor koji se naziva „glavnim regulatorom" imunološkog sustava. Pritom IL-10 sprječava stvaranje proupalnih citokina (27) inhibirajući TNF-α i IL-1β, što je važno u kontekstu vježbanja s obzirom na to da su razine ovih citokina niske unatoč povišenom IL-6 (27). Za razliku od djelovanja IL-10, koji utječe na spektar citokina, IL-1Ra posreduje svoje učinke samo na IL-1, inhibirajući transdukciju signala kompetitivnim vezanjem na kompleks IL-1 receptora (28), čime se sprječava vezanje IL-1, i zaustavljajući njegove proupalne učinke. Dakle, taj u mišiću derivirani IL-6 bitno se razlikuje od nama poznatog proupalnog IL-6, koji u patofiziologiji RA ima brojne lokalne učinke na zglob bolesnika (IL-6 je značajno povišen u RA u usporedbi sa zdravom populacijom; IL-6 potiče medijatore upale u sinoviji, uzrokujući pojačano oštećenje zglobova; IL-6 potiče proizvodnju vaskularnog endotelnog faktora rasta (VEGF), koji vodi formiranju panusa; IL-6 potiče osteoklastogenezu te zajedno s ostalim citokinima dovodi do oštećenja hrskavice i kosti u RA) (29). U mišiću derivirani IL-6 iz iste je "obitelji", ali je potpuno drugačije uloge. Njegova funkcija, kao i nekih drugih miokina, jest blokiranje uzvodnih i nizvodnih signalnih putova NF-κβ, unakrsnom reakcijom aktiviranih signalnih puteva nuklearnog faktora aktiviranih T-stanica (NFAT) i mitogenski aktiviranom proteinskom kinazom (MAPK), čime imaju izrazito protuupalno djelovanje (15,24).

To je novi koncept za razumijevanje kako mišići komuniciraju s ostalim organima te objašnjava i dokazuje protuupalni učinak vježbanja (slika 2).

Dakle, kako autori navode, tijekom posljednja dva desetljeća napredak u istraživanju bacio je novo svjetlo na ulogu tjelovježbe kao dijela NFL-a reumatskih bolesti i razjasnio sve one empirijske preporuke od ranije. Jedan od najvažnijih napredaka bilo je konačno otkriće i dokaz da skeletni mišići komuniciraju s drugim organima izlučujući proteine zvane miokini, pri čemu neki miokini induciraju protuupalne odgovore sa svakim aktom vježbanja i posreduju u dugotrajnim poboljšanjima kardiovaskularnih čimbenika rizika uzrokovapressed by the tenacity and complexity of the findings of the Danish scientist B. K. Pedersen, who has published numerous papers and works in relation to this topic over the years (21,22,23).

For this reason, in the following part of this article, I would like to touch upon the data from the paper authored by F. B. Benatti and B. K. Pedersen published in 2015, which presents an analysis that explains medical exercises at the level of cytokine activity through a theory that we can colloquially call the "myokine concept" (15). This is a new concept according to which skeletal muscles are secretory organs that, with each concentric contraction, release proteins called "myokines", such as muscle-derived IL-6, which inhibits the production of TNF-α, stimulates and induces the production of anti-inflammatory cytokines IL-1Ra (receptor antagonist), and IL-10, secreted by mononuclear cells, thus achieving an important anti-inflammatory effect. Evidence has shown that circulating levels of IL-10 and IL-1Ra increase in the post-exercise period and that their release is probably enhanced in response to the aforementioned IL-6 (25). IL-10 and IL-1Ra play an important role in immune regulation and are also involved in contributing to the anti-inflammatory response to exercise. IL-10 is considered a standard anti-inflammatory cytokine, because it suppresses cytokines by directly inhibiting the action of pro-inflammatory cytokines, as well as by preventing cytokine synthesis (26). By using post-translational mechanisms, IL-10 is able to block nuclear factor kappa-β (NF-κβ), a transcription factor called the "master regulator" of the immune system. In doing so, IL-10 prevents the formation of pro-inflammatory cytokines (27) by inhibiting TNF-α and IL-1β, which is important in the context of exercise, given that the levels of these cytokines are low despite the elevated IL-6 (27). In contrast to the action of IL-10, which affects a spectrum of cytokines, IL-1Ra mediates its effects only on IL-1, inhibiting signal transduction by competitively binding to the IL-1 receptor complex (28), thereby preventing IL-1 binding, and inhibiting its pro-inflammatory effects.

Thus, this muscle-derived IL-6 differs significantly from the known pro-inflammatory IL-6, which in the pathophysiology of RA has numerous local effects on the patient's joint (IL-6 is significantly elevated in RA compared to the healthy population; IL-6 stimulates inflammatory mediators in the synovium, causing pronounced joint damage; IL-6 stimulates the production of vascular endothelial growth factor (VEGF), which leads to the formation of pannus; IL-6 stimulates osteoclastogenesis and, together with other cytokines, leads to cartilage and bone damage in RA) (29). Muscle-derived IL-6 is from the same "family", but has a completely different role. Its function, like that of some other myokines, is to block the upstream and down-



Slika 2. – *Figure 2* „Miokinski koncept“ (prema referenciji br. 15) / *“Myokine concept” (according to reference No. 15)*

nih vježbanjem te imaju neizravan protuupalni učinak (15). Osim toga, u svom radu iz 2015. autori su ukazivali na to kako tjelovježba remeti začarani krug kroničnе upale izravno, nakon svake vježbe, i neizravno, poboljšavajući komorbiditete i kardiovaskularne čimbenike rizika. Također, raspravljano je i o mehanizmima kojima neki miokini imaju protuupalne funkcije kod upalnih reumatskih bolesti. Kao što je već naglašeno, došlo je do promjene paradigme pa se sada vjeruje, suprotno ranije izražavanim strahovima da bi tjelesna aktivnost mogla pogoršati upalnom inducirane promjene, da je tjelovježba izuzetno potencijalno važna za liječenje bolesnika s reumatskim bolestima, sinergistički djelujući s brojnim biološkim lijekovima (15,30).

Sve prethodno navedeno dovelo je do brojnih novih istraživanja i dokazivanja navedenog, ali i brojnih novih spoznaja, što je onda dobro sistematizirano i pregledno pokazano u članku Doherty i suradnika, koji je na *webu* postao dostupan u siječnju 2022. godine (30). U njemu se pojedinačno prikazuje učinak medicinskih vježbi na pojedine proupalne citokine, što me je s obzirom na vremenski odmak od sedam godina i znanstveni pregled literature u odnosu na prethodno analizirani članak Benattija i Pedersena navelo da ovaj članak prokomentiram i analiziram kao drugi stožerni rad za moje pretraživanje literature.

stream signalling pathways of NF-κβ, through the cross-reaction of the activated signalling pathways of the nuclear factor of activated T-cells (NFAT) and mitogen-activated protein kinase (MAPK), thus having a pronounced anti-inflammatory effect (15,24).

It is a new concept for understanding how muscles communicate with other organs, which explains and proves the anti-inflammatory effect of exercise (Figure 2).

Thus, as the authors state, over the past two decades, research advances have shed new light on the role of exercise as part of the NPT of rheumatic diseases and clarified all of the previously published empirical recommendations. One of the most important advances was the final discovery and evidence that the skeletal muscle communicates with other organs by secreting proteins called myokines. In this process, some myokines induce anti-inflammatory responses with each bout of exercise and mediate long-term exercise-induced improvements in cardiovascular risk factors, thus producing an indirect anti-inflammatory effect (15). In addition to that, in their 2015 paper, the authors have highlighted the fact that exercise disrupts the vicious cycle of chronic inflammation directly, after each bout of exercise, as well as indirectly, by improving comorbidities and cardiovascular risk factors. The mechanisms by which some myokines have anti-inflammatory functions in inflammatory rheumatic dis-

Sažetak fizioloških promjena u proizvodnji citokina izazvanoj tjelovježbom, s ciljem istraživanja implikacija toga u kontekstu mišićno-koštanog zdravlja i upalnih reumatskih bolesti, prikazan je u tablici 1 koja je kasnije navedena u tekstu. Također, autori podsjećaju da je prva studija koja sugerira protuupalni odgovor citokina izazvan vježbanjem objavljena još 1983. od strane Cannona i Klugera (31) te da su u međuvremenu napravljena brojna istraživanja i pronađeni zaključci u tom smislu, a najočitiji su bili oni publicirani u radu Benattija i Pedersena (15). Poznato je više od 3.000 citokina, nazvanih „miokini", koje proizvode miociti, uključujući među ostalima IL-6, IL-7, IL-5 i miostatin (30). Miokini pritom primarno djeluju na autokrini i parakrini način lokalno na skeletne mišiće, ali mogu djelovati i na endokrini način komunicirajući s raznim drugim tipovima tkiva (21). Otkriće da je skeletni mišić zapravo sekretorni organ stvorilo je novo područje istraživanja unutar područja vježbanja, a znanstvenici su dugo nastojali pronaći „faktor vježbe", koji povezuje kontrakciju skeletnih mišića s metaboličkim promjenama povezanim s tjelovježbom (15,30).

Identifikacija citokina dobivenih iz skeletnih mišića mogla bi predstavljati baš taj „faktor vježbanja" koji su tražili i objasniti imunološke i metaboličke promjene uvjetovane vježbanjem, pri čemu se ovo pozitivno protuupalno djelovanje veže uz kontrolirane koncentrične (dijelom i ekscentrične) kontrakcije, dok pretjerana tjelovježba može povećati rizik infekcije ili čak dovesti do akutnih upalnih događanja kod napornog i nekontroliranog vježbanja (ili trčanja maratona). Oni dovode do promjena u imunološkom sustavu posredovanih nekontroliranim porastom u mišiću sintetiziranim i oslobođenim IL-6 i mogu trajati od 2 do 24 sata, čineći takve osobe vrlo vulnerabilnima. Povećanje koncentracije TNF-α i IL-1β ne vidi se pri umjerenoj tjelovježbi, iako se pokazalo da se povećava tijekom produljenog ili napornog vježbanja (25,26).

Naime, 2000. godine Smith je predstavio „citokinsku hipotezu pretreniranosti", tvrdeći da su skup simptoma i biokemijskih/imunoloških promjena doživljenih sa sindromom pretreniranosti uzrokovani proupalnim citokinima, uglavnom IL-1β, IL-6 i TNF-α, i njihovim porastom (30). Pokazalo se da pretjerana tjelovježba, osobito uz korištenje ekscentričnih kontrakcija (često demonstriranih metodama kao što je trčanje nizbrdo) povećava proupalne citokine u serumu, unutar samog mišićnog tkiva i unutar zglobne hrskavice te da su isti citokini odgovorni za mnoge simptome koji se javljaju kod takvih sportaša, kao što su loše raspoloženje, gubitak apetita, povišene razine kortizola, za razliku od medicinskih koncentričnih kontrakcija (30). Studije su pokazale da su se unutar dva tjedna od pretreniranosti razine tih proupalnih citokina normalizirale tijekom odmora. Također, nakon maratonske utrke pokazalo se eases were also discussed. As it was already emphasised, there has been a paradigm shift, so the current belief, contrary to the previously expressed fears that physical activity could exacerbate inflammation-induced changes, is that exercise is extremely potentially important for the treatment of patients with rheumatic diseases, and that it has a synergistic effect when used with numerous biological drugs (15,30).

All of the mentioned findings have led to numerous new research studies and attempts to prove the aforementioned facts, but also to numerous new insights. This was well systematized at the time and clearly demonstrated in the article authored by Docherty et al., which was published online in January 2022 (30). In this article, the effect of medical exercises on certain pro-inflammatory cytokines is shown individually. Considering the time gap of seven years between this article and the scientific review of literature and the previously analysed article authored by Benatti and Pedersen, this has prompted me to analyse and comment on this article as the second key work for my literature review.

An overview of the physiological changes in exercise induced cytokine production, with the aim of investigating its implications in the context of musculoskeletal health and inflammatory rheumatic diseases, is shown in Table 1, which is listed in the final part of the article. In addition to that, the authors point out the fact that the first study that suggests an exercise-induced anti-inflammatory response of cytokines was published in 1983 by Cannon and Kluger (31) and that, in the meantime, numerous studies were conducted with new findings on this topic, the most obvious being the studies stated in the paper authored by Benatti and Pedersen (15). Over 3,000 cytokines, called "myokines," are known to be produced by myocytes, including, among others, IL-6, IL-7, IL-5, and myostatin (30). Myokines primarily have an autocrine and paracrine effect meaning that they exert functions locally, in the skeletal muscles, but they can also have an endocrine effect by communicating with various other tissue types (21). The discovery that the skeletal muscle is actually a secretory organ created a new area of research within the field of exercise, and scientists have long sought to find the "exercise factor," which links skeletal muscle contraction to exercise-related metabolic changes (15,30).

The identification of skeletal muscle-derived cytokines could represent the very "exercise factor" that they were looking for and explain the immunological and metabolic changes induced by exercise, whereby this positive anti-inflammatory effect is associated with controlled concentric (partially also eccentric) contractions, while excessive exercise can increase risk of infection or even lead to acute inflammatory events during strenuous and uncontrolled exercise (or running a marathon). They lead to changes in the immune

Tablica 1. Uloga ključnih citokina u odnosu na tjelovježbu (prema referenciji br. 30)
Table 1 The role of key cytokines in relation to exercise (according to reference number 30)

Citokin / Cytokine	Učinak / Action	Promjena kod vježbanja / Change with exercise
Pro-upalno djelovanje / Pro-inflammatory action		
TNFα	Aktivacija imunoloških stanica / Immune cell activation Stimulacija sinteze prostaglandina / Stimulation of prostaglandin synthesis	↑
IL-15	Aktivacija adaptivnog imunološkog sustava (B i T stanice) / Activation of adaptive immune system (B cells and T cells)	↔
IL-8	Kemotaksija neutrofila / Neutrophil chemotaxis	↑
1L-1β	Induciranje sinteze NO, prostaglandina i leukotrijena / Induces synthesis of NO, prostaglandins and leukotriens	↑ ↔
Protuupalno djelovanje / Anti-inflammatory action		
IL-4 & IL-13	Inhibicija Th1 stanica / Inhibition of Th1 cells Redukcija IL-1β u plazmi / Reduction of IL-1β levels in plasma Povećanje ekspresije IL-1Ra / Upregulation of IL-1Ra expression	↑ ↔
IL-10	Inhibicija proupalnih citokina, uključujući IL-1β i TNFα / Inhibition of pro-inflammatory cytokines including IL-1β and TNF-α	↑
IL-6	Inducira povećanje IL-10 i IL-1Ra / Induces upregulation of IL-10 and IL-Ra Inhibicija proupalnih citokina / Pro-inflammatory cytokine inhibition	↑
IL-1Ra	Inhibira signalizaciju preko IL-1 receptora / Inhibits signalling through IL-1 receptor	↑

Legenda / Legend:

↑ = *Povećanje nakon vježbe / Upregulated after exercise*

↔ = *Bez promjene tijekom vježbe / No change with exercise*

↑ ↔ = *Više od jedne strelice znači proturječne rezultate studija / More than one arrow indicates conflicting results between studies*

da se koncentracija TNF-α i IL-1β dvostruko povećala. Za usporedbu, koncentracija protuupalnog IL-6 porasla je 50 puta (26,30). Stoga se može zaključiti, iako naporna tjelovježba izaziva povećanje proupalnih citokina, TNF-α i IL-1β, da se to uvelike poništava indukcija sustava mediranog nekontroliranim povećanjem u mišiću zbog sintetiziranog i oslobođenog IL-6, a može trajati od 2 do 24 sata, što je razdoblje u kojem su ti bolesnici vrlo ranjivi. Povećanje koncentracije TNF-α i IL-1β nije evidentno tijekom umjerene vježbe, iako je pokazano da koncentracija raste tijekom produljene ili naporne vježbe (25,26).

In 2000, Smith presented the concept of "cytokine hypothesis of overtraining", arguing that the set of symptoms and biochemical/immunological changes experienced as a consequence of overtraining syndrome are caused by pro-inflammatory cytokines, mainly IL-1β, IL-6 and TNF-α, and their increase (30). Excessive exercise, particularly with the use of eccentric contractions (often demonstrated by methods such as downhill running), has been shown to increase pro-inflammatory cytokines in serum, within the muscle tissue itself, and within the articular cartilage. It has also been shown that these same cytokines are responsible for many of the symptoms that occur in such athletes, such as low mood, loss of appetite, elevated cortisol levels, while the same symptoms were not experienced in medical concentric contractions (30). Studies have shown that within two weeks of overtraining diagnosis, the levels of these pro-inflammatory cytokines were restored to their normal level after a period of rest. Moreover, after a marathon, the concentration of TNF-α and IL-1β was shown to increase twofold. By comparison, the concentration of anti-inflammatory IL-6 has increased 50 times (26,30). Therefore, it is safe to conclude that, even though strenuous exercise induces an increase in the pro-inflammatory cytokines, TNF-α and IL-1β, it is largely counteracted by the induction of anti-inflammatory cytokines, thus causing an overall anti-inflammatory response.

And what is the mechanism of action of other interleukins? This can be seen in the table adapted from the article authored by Docherty et al. (Table 1), where it is evident that there is no change in IL-4 expression immediately after exercise, but its expression within muscles has been shown to increase over time following regular exercise sessions (30). Just like IL-4, IL-13, which is similar in its action, inhibits T helper type 1 (Th1) cells, so it has an anti-inflammatory effect, it increases its concentration during exercise. On the other hand, IL-8 has a minimal systemic response which is only observed during eccentric exercises, while its anti-inflammatory effect is only exerted locally. IL-15 affects the skeletal muscles by acting in an anabolic manner by regulating the production of myosin within the skeletal muscles and adipose tissue mass (Table 1).

With these insights and a scientific approach, and on the basis of EBM data, it finally becomes clear why medical exercises are presented as the most important

cijom protuupalnih citokina, što dovodi do ukupnog protuupalnog odgovora.

A kako se ponašaju ostali interleukini? To je razvidno iz prenesene tablice iz članka Dohertyja i suradnika (tablica 1), gdje je vidljivo da IL-4 ne pokazuje promjenu neposredno nakon vježbanja, ali se njegova ekspresija unutar mišića povećava tijekom vremena nakon ponavljajućih treninga (30). IL-13, koji mu je po djelovanju sličan, poput IL-4 inhibira pomoćne T-stanice tipa 1 tako da ima protuupalni učinak, povećava svoju koncentraciju pri vježbanju, dok IL-8 ima minimalni sistemski učinak kod ekscentričnih vježbi, dok mu je protuupalni učinak tek lokalnog karaktera. IL-15 utječe na skeletne mišiće anaboličkim djelovanjem na regulaciju odnosa miozina u skeletnim mišićima i masti (tablica 1).

Ovakvim promišljanjima i znanstvenim pristupom te temeljem podataka EBM-a postaje konačno jasno zašto se medicinske vježbe pozicioniraju kao najvažniji oblik NFL-a, jer nove spoznaje „spuštanjem" na citokinsku razinu njihovog učinka mogu razjasniti činjenicu zbog čega su iste uvijek bile uvrštavane u algoritme liječenja upalnih reumatskih bolesti (15,30) i onda kada nismo znali objasniti prirodu njihova kvalitetnog učinka na bolest. Sada je znatno jasnije (ono što smo ranije radili tek iskustveno) da njihov protuupalni učinak u fazi postizanja remisije moćnim farmakoterapijskim pristupom JAK inhibitora i pojedinačnih protucitokinskih lijekova vode bolesnika prema očekivanoj remisiji, po načelima T2T pristupa liječenja (7,8).

Moderne tehnologije

Pretraživanje literature u svezi korištenja modernih tehnologija u rehabilitaciji, tj. njihove važnosti u NFL-u upalnih reumatskih bolesti nije dalo očekivane rezultate, za razliku prethodnog očekivanja u korištenju istih rehabilitacijskih modela kod osteoartritisa (32). Ništa relevantno i značajno nije pronađeno u velikim bazama literaturnih podataka, što je donekle i razumljivo, jer se radi o novim načinima liječenja muskuloskeletnih bolesti (izvantjelesni udarni val – engl. skr. ESWT, radiofrekvencija – skr. RF, superinduktivni sustavi – skr. SIS, laser visokog intenziteta – engl. skr. HILT), tako da do sada nije bilo vremena za publiciranje relevantnih kontroliranih kliničkih istraživanja (RKI), metaanaliza i sustavnih pregleda istih u velikim bazama podataka.

Pojedinačni radovi s malim uzorkom, kao i radovi publicirani pod patronatom pojedinih proizvođača medicinske opreme, nisu nudili dokaze značajnije razine važnosti ili su dokazi bili upitnih vrijednosti.

Tako postoje podatci o učinku HILT-a u 30 bolesnika s juvenilnim RA gdje je učinak terapije bio značajno bolji nego u placebo skupini, prateći VAS boli i mogućform of NPT. This is because, by starting from the cytokine level of their effect, new insights can explain the fact why they have always been included in algorithms of inflammatory rheumatic disease treatment (15,30) even when we did not know how to explain the nature of their qualitative effect on the disease. Now the processes that were previously done only in an experimental manner, are much clearer. It is clear that the anti-inflammatory effect of medical exercises in the phase of achieving remission with a powerful pharmacotherapeutical approach of JAK inhibitors and individual anti-cytokine drugs leads the patient towards the expected remission, according to the principles of the T2T treatment approach (7,8).

Modern technologies

A literature search regarding the use of modern technologies in rehabilitation, i.e., their importance in the NPT of inflammatory rheumatic diseases, did not yield the expected results, in contrast to previous expectations in the use of the same rehabilitation models in the treatment of osteoarthritis (32). The search of large databases of literature data did not result in any relevant and significant findings, which is understandable to a certain extent, because we are talking about new methods of treating musculoskeletal disorders (extracorporeal shockwave therapy (ESWT), radio frequency (RF), super inductive systems (SIS), high-intensity laser therapy (HILT)), so there was no time (up until now) to publish relevant controlled clinical trials (RCTs), meta-analyses and systematic reviews of these trials in large databases.

Individual papers with a small sample, as well as papers published under the patronage of certain medical equipment manufacturers, have either failed to provide significant evidence or the evidence was of questionable value.

Thus, there are data on the effect of HILT in 30 patients with juvenile RA, in whose situation the effect of therapy was significantly better than in the placebo group, in accordance with the patients' VAS-pain scores and their ability to walk, in addition to the fact that the research subjects also used medical exercises with or without HILT (33). However, individual papers that have been recently published, which discuss the use of HILT in the treatment of RA pain, offer some insight into the benefit of modern technologies, such as the systematic review and meta-analysis. One of these papers is the one authored by Chia et al., which analysed 10 studies and found data on significant effect of this therapy on reducing pain and increasing the functional ability of patients with RA, but it had no effect on morning stiffness (34). Similar data were published in a paper authored by Liu et al., in which they discuss the use of radial ESWT on patients with RA in the treatment of ar-

nost hoda, uz činjenicu da su ispitanici koristili i medicinske vježbe uz HILT ili bez HILT-a (33). Ipak, pojedinačni radovi koji su nedavno publicirani, a govore o korištenju HILT-a u liječenju boli kod RA, nude nekakav uvid u korist novijih tehnologija, kao što je sistematski pregled i metaanaliza Chia i sur., koji u 10 analiziranih studija nalaze podatke o značajnom učinku ove terapije na smanjenje boli i povećanje funkcijskih sposobnosti bolesnika s RA, ali bez utjecaja na jutarnju zakočenost (34). Slične podatke publicirali su i Liu i sur. korištenjem radijalnog ESWT-a u bolesnika s RA u liječenju artralgije, ali na uzorku od samo 15 bolesnika u jednom od prvih radova te vrste, publiciranom 2017. godine (35).

S druge strane, brojni proizvođači medicinske opreme kao kontraindikaciju za korištenje ovih relativno agresivnih metoda NFL-a upravo ističu bolesnike s upalnim reumatskim bolestima (npr. BTL), tako da je i to bio jedan od razloga zašto je traženih podataka bilo malo i na *PubMed*-ovoj tražilici. Pojedinačni radovi s malim uzorkom praćenih bolesnika te zaključci takvih istraživanja nisu bili relevantni za uvrštavanje u ovaj članak.

Konvencionalna fizikalna terapija

Pod ovom vrstom terapije najčešće mislimo na brojne oblike fizikalne terapije koja je najčešće suportivna terapija medicinskim vježbama, terapija koja ima simptomatski učinak te umanjuje bol kod bolesnika s upalnim reumatskim bolestima. Rijetko se primjenjuje samostalno te je stoga i mali broj kvalitetnih randomiziranih kontroliranih istraživanja. Ona je najčešće usmjerena na poboljšanje kvalitete života bolesnika, neovisnost u djelovanju i socijalnu integraciju, ponekad uključujući u timski rad još neke medicinske djelatnike (fizioterapeuti, psiholozi), čiju važnost u holističkom pristupu liječenja ovih bolesnika ne smijemo zaboraviti.

Stoga je ipak i ona važan dio NFL-a kod ovih bolesnika, iako je snaga dokaza EBM-a relativno niska i nekonzistentna u dostupnim literaturnim bazama podataka. Ovi podatci najčešće uključuju dokaze o učinkovitosti topline/hladnoće, terapijskog ultrazvuka, lasera niskog intenziteta, elektroterapije i magnetoterapije. Pritom nalazimo podatke skromne snage dokaza kako TENS kod bolesnika s AS-om kvalitetno utječe na smanjenje boli u križima, umora i jutarnje zakočenosti te podatak da magnetoterapija aplicirana iznad SI zglobova bolesnika s AS-om ne pokazuje statistički značajni učinak na tegobe tih bolesnika (36). S druge strane, brojni su podatci koji hidroterapiji i balneoterapiji bolesnika s AS-om pripisuju dobar učinak na poboljšanje kvalitete života, značajno više nego kod bolesnika s RA, iako je i tu snaga dokaza vrlo niska (36,37).

thralgia. This therapy method was used on a sample of only 15 patients, and this paper, published in 2017, was one of the first papers of its kind (35).

On the other hand, numerous manufacturers of medical equipment specifically point out patients with inflammatory rheumatic diseases (for example, manufacturers such as BTL) as a contraindication for the use of these relatively aggressive methods of NPT, so this was also one of the reasons why the search resulted in a small number of data, even when it comes to the search performed on the PubMed platform. Individual papers with a small sample of patients included in the follow-up process and the conclusions of such studies were not relevant for this article, so they were not included in it.

Conventional physical therapy

This type of therapy usually implies numerous forms of physical therapy, which is usually support therapy that includes medical exercises, and therapy that has a symptomatic effect and reduces pain in patients with inflammatory rheumatic diseases. It is rarely used independently and therefore there is a small number of high-quality randomised controlled trials. This therapy is most often aimed at improving the patient's quality of life, achieving and promoting patients' independence and social integration, which sometimes calls for the inclusion of other medical staff (such as physiotherapists, psychologists) in this process in order to achieve more efficient teamwork. The important role of these other healthcare professionals in the holistic approach to the treatment of these patients should not be forgotten. Therefore, this therapy is still an important part of NPT in these patients, although the strength of evidence of EBM is relatively low and inconsistent in the available literature databases. These data most often include evidence of the effectiveness of heat/cold treatment, therapeutic ultrasound, low-intensity laser, electrotherapy, and magnetotherapy. In relation to the aforementioned, we have found data with a moderate strength of evidence, which confirm that the application of TENS in patients with AS has a beneficial effect on the reduction of low back pain, fatigue and morning stiffness. We have also found data which prove that magnetotherapy applied over the SI joints of patients with AS does not have a statistically significant effect on the complications of these patients (36). On the other hand, there are numerous data that confirm that, in patients with AS, hydrotherapy and balneotherapy have a beneficial effect on improving their quality of life, and this effect has proven to be significantly better than in patients with RA, although the strength of evidence is also very low (36,37). Natural treatment factors, such as the climatic and physical health benefits of the effect of the Dead Sea on the quality of life, sleep and work ability are mentioned in the literature and in

Prirodni čimbenici liječenja, ali ovaj put klimatske i fizičke blagodati učinka Mrtvog mora na kvalitetu života, spavanje i radnu sposobnost spominju se u literaturi i kod bolesnika s psorijatičnim spondiloartritisom (4). U knjižnici Cochrane može se pronaći i jedan stariji članak iz 2008. koji je zapravo bio obnovljeni prikaz kratkotrajnog učinka lasera niskog intenziteta (LLLT) iz 1998. u bolesnika s RA na bol i jutarnju zakočenost, uz napomenu (kao i kod većine ovakvih ili sličnih analiza) kako bi trebalo standardizirati aplikaciju LLLT kod RA, bolje validirati ishode liječenja, trajanje liječenja, dozu i mjesto aplikacije (38). Možda bi se ovdje moglo uključiti i jedno krovno istraživanje Santosa i sur. iz 2019. koje je istraživalo učinak NFL-a u bolesnika s RA, njih 6.740 kroz 8 sustavnih pregleda, 9 opservacijskih studija i 91 randomizirano kontrolirano istraživanje, gdje opet nije pronađeno dovoljno snažnih dokaza za učinak konvencionalne terapije na bol, funkcionalnost, umor, spavanje, fizičko i emocionalno blagostanje, već je najveći utjecaj opet polučila multikomponentna intervencija, koja je uvijek uključivala tjelesnu aktivnost, psihosocijalne intervencije i ortoze za RA (39).

Nutritivna potpora

I na kraju, nekoliko rečenica o nečemu što danas nije često spominjano u kontekstu NFL-a upalnih reumatskih bolesti, ali sama činjenica da u literaturi nalazimo sve više radova koji se bave problemom sarkopenije i upalnih reumatskih bolesti, poglavito RA, znak je da će o tome ubuduće biti mnogo više kvalitetnih radova (40,41). Počelo je analizom sastava tijela u bolesnika s RA u Južnoafričkoj Republici iz 2014. člankom Lombarda i sur. (42). Uslijedio je velik broj sličnih radova posljednjih godina, koji pronalaze dosta zajedničkog u citokinskim putevima (de)aktivacije kod RA i sarkopenije, u mehanizmima nastanka reumatoidne kaheksije (43,44) te učinku pojedinih aktivnih supstancija u nutritivnoj potpori – β-hidroksi-β-metilbutirat (HMB) u tim mehanizmima (43). Može se naslutiti da će i u ovom segmentu doći do novih spoznaja o međusobnom utjecaju pojedinih citokinskih mehanizama i preklapanja puteva njihove aktivacije i deaktivacije, pa će se o ovom obliku NFL-a, kroz nutritivnu potporu bolesnicima s upalnim reumatskim bolestima, sigurno često govoriti ubuduće, temeljem kvalitetnih uradaka EBM-a.

Ostalo

Kao što sam napisao u jednom ranije spomenutom članku iz 2017., kada sam proučavao literaturu u svezi učinka NFL-a kod PsA, važnu ulogu igraju i edukacija, kognitivna terapija, asistivna tehnologija, vokacijska rehabilitacija i redukcija tjelesne mase, što vrijedi i za

the case of patients with psoriatic spondyloarthritis (4). An older article from 2005 can be found in the Cochrane Library, which was actually an update of the 1998 (original) review on the effect of short-term low intensity laser (LLLT) in RA patients on pain and morning stiffness. In this review, the author stated that LLT application in RA should be standardised and that the treatment outcomes, treatment duration, dosage and site of application should be validated in a better way (as is the case with most of these analyses or similar ones) (38). An umbrella review from 2019 conducted by Santos et al. could also be included here. This study investigated the effect of NPT in 6,470 patients with RA, through 8 systematic reviews, 9 observational studies and 91 randomised controlled trials. This review provided evidence which was not sufficiently strong in relation to the effect of conventional therapy on pain, functionality, fatigue, sleep, and physical and emotional well-being. In this case, multicomponent interventions, which always included physical activity, psychosocial interventions and orthoses for RA, proved to be the most effective once again (39).

Nutritional support

Finally, we must discuss something that is rarely mentioned today in the context of NPT of

inflammatory rheumatic diseases. The very fact that in the literature we find an increasing number of papers dealing with the problem of sarcopenia and inflammatory rheumatic diseases, especially RA, is a sign that there will be many more quality papers on this topic in the future (40,41). It all started with an article authored by Lombardo et al. which was published in 2014, and which analysed the topic of body composition of RA patients in South Africa (42). A large number of similar papers were published in recent years, which have found a great number of similarities in the (de)activation of cytokine-signalling pathways in RA and sarcopenia, in the mechanisms of the occurrence of rheumatoid cachexia (43,44) and the effect of certain active substances in nutritional support with β-hydroxy-β-methylbutyrate (HMB) in these mechanisms (43). It can be inferred that in this aspect new insights will be gained into the mutual influence of certain cytokine mechanisms and the overlapping of the activation and deactivation of cytokine-signalling pathways. Therefore, this form of NPT will surely be often discussed in the future, based on the quality outcomes of EBM, and through the topic of nutritional support for patients with inflammatory rheumatic diseases.

Other methods

As I discussed in the previously mentioned article from 2017, when I studied the literature regarding the effect of NPT in PsA, I have found that education, cog-

sve ostale upalne reumatske bolesti. Ovdje ću samo ponoviti neke od važnih činjenica i pridodati im neke značajke nečega što možemo nazvati „ostalim metodama NFL-a“ (4).

Budući da je edukacija jedna od temeljnih sastavnica rehabilitacijskog procesa, uputno je prije odluke o obliku i načinu edukacije reumatoloških bolesnika odrediti koje su najvažnije potrebe tih bolesnika. Dva presječna istraživanja, na uzorku od ukupno 3.318 osoba oboljelih od reumatskih bolesti (od čega 934 s PsA), proučavala su učinkovitost upitnika za procjenu obrazovnih potreba bolesnika (engl. *The Educational Needs Assessment Tool* – ENAT) (4). Obje studije su potvrdile valjanost i pouzdanost upitnika. Dok Ndosi i sur. nisu ustanovili utjecaj osobnih karakteristika oboljelih na obrazovne potrebe, Dragoi i sur. su ustanovili povezanost obrazovnih potreba pojedinca sa spolom, razinom obrazovanja i duljinom trajanja bolesti kod praćenih bolesnika (4). Trenutno u praksi postoje brojni edukacijski programi za oboljele od upalnih reumatskih bolesti, koji se razlikuju po načinu prijenosa znanja te po stupnju i vrsti obrazovanja članova rehabilitacijskog tima koji prenose znanje (liječnici, fizioterapeuti, medicinske sestre, radni terapeuti, laici). Gronning i sur. preporučuju kombiniranje grupne i individualne edukacije vođene od strane medicinskih sestara, budući da traje kraće od same individualne edukacije te koristi sve prednosti učenja u grupi uz mogućnost individualne prilagodbe programa (4). Njihov program edukacije pokazao je dugotrajan učinak na globalno blagostanje bolesnika, ali ne i na samoučinkovitost.

Program samozbrinjavanja kao dio rehabilitacije u zajednici, vođen od strane educiranih laika, pokazao se kao učinkovita metoda za smanjenje boli, povećanje uključivanja u programe terapijskih vježbi te osposobljavanje za pravilno upravljanje percepcijom bolesti među oboljelima od upalnih reumatskih bolesti, što je pokazano u istraživanju u Hong Kongu (4).

Hammond i sur. preporučuju bihevioralni oblik grupne edukacije vođene od strane fizioterapeuta te ističu njegovu dugoročnu prednost u smanjenju boli te poboljšanju psihološkog stanja i samozbrinjavanja oboljelih od RA i PsA (4).

U Cochraneovom preglednom članku iz 2014. o NFL-u za sprječavanje gubitka posla oboljelih od upalnih reumatskih bolesti na osnovi tri RKI-ja, kod kojih su dva uključivala i oboljele od PsA, a ostali su uključivali bolesnike s RA, AS, SpA i SLE, zaključeno je kako bi intervencije kao što su procjena uvjeta rada, strukovno savjetovanje, edukacija o samozastupanju te uvođenje promjena u radnu okolinu mogle smanjiti opasnost od gubitka posla, smanjiti broj dana bolovanja i poboljšati radnu sposobnost oboljelih od reumatskih bolesti (45). Nešto slično nudi nam i jedan laički

nitive therapy, assistive technology, vocational rehabilitation and weight loss also play an important role in the effectiveness of this method. This also applies to all other inflammatory rheumatic diseases. In this article, I will simply repeat some of the aforementioned important facts and list some characteristics of “other NPT methods” (4).

Given the fact that education is one of the fundamental components of the rehabilitation process, it is advisable to determine the most important needs of these patients before deciding on the form and method of education for patients with rheumatic diseases. Two cross-sectional studies, conducted on a sample of a total of 3,318 research subjects suffering from rheumatic diseases (934 of these patients suffered from PsA), studied the effectiveness of the Educational Needs Assessment Tool (ENAT) questionnaire (4). Both studies confirmed the validity and reliability of the questionnaire. While Ndosi et al. did not establish the effects of needs-based patient education, Drăgoi et al. have established the connection between the educational needs of the individual and gender, educational background and disease duration in relation to the patients who participated in this study (4). Currently in practice there are numerous educational programmes for patients with inflammatory rheumatic diseases, which differ in the method of knowledge transfer and in the degree and type of education of the members of the rehabilitation team who transfer knowledge (physicians, physiotherapists, nurses, occupational therapists, laymen). Grønning et al. recommend combining nurse-led groups and individual patient education programmes, since this type of education takes less time than individual education and uses all the advantages of group learning with the possibility of adaptation of the programme in accordance with the patients’ individual needs (4). It was proved that their education programme has a long-lasting effect on the patients’ global well-being, but not on the self-efficacy.

A study conducted in Hong Kong showed that a community-based lay-led self-management programme is an effective method for reducing pain, increasing participation in therapeutic exercise programmes, and training for the proper management of disease perception among patients with inflammatory rheumatic diseases (4). Hammond et al. recommend a physiotherapist-led behavioral group education programme and emphasise its long-term effect on reducing pain and improving the psychological status and self-management of patients with RA and PsA (4).

In a 2014 Cochrane review article on NPT for preventing job loss in workers with inflammatory arthritis based on three RTCs (two of which included patients with PsA and one which included patients with RA, AS, SpA and SLE), it was concluded that interventions

sažetak iz knjižnice Cochrane iz 2014. o postupcima koji ne uključuju lijekove, a koji mogu spriječiti gubitak radnog mjesta u radnika s upalnim reumatskim bolestima, niske kvalitete dokaza, koji obuhvaćaju postupke radnog savjetovanja kod tri RKI-ja (45).

Abou Raya i sur. u svom RKI-iju na 55 ispitanika oboljelih od PsA dokazali su kako vježbanje uz redukciju tjelesne mase, u trajanju od 12 mjeseci, statistički značajno utječe na poboljšanje funkcionalnog statusa, kvalitete života i globalnog zdravlja, kao i na smanjenje depresije, umora, ali i serumske razine IL-6, TNFα, hsCRP i IL-17 u odnosu na kontrolnu skupinu (4).

Za ostale oblike nefarmakološke terapije koji se koriste u procesu rehabilitacije oboljelih od PsA, kao što su različite procedure fizikalne terapije, ortoze, dijetetske mjere, komplementarna i alternativna medicina, korištenjem protokola pretraživanja navedenog u metodama nismo mogli pronaći nijedan članak.

RASPRAVA

NFL je važna komponenta u liječenju upalnih reumatskih bolesti, o čemu bi se moglo napisati mnogo više od ovdje navedenog. Ovaj pregledni članak trebao je upozoriti na ispravan pristup i nužnost korištenja NFL-a kod holističkog pristupa liječenju bolesnika s upalnim reumatskim bolestima, a u skladu i s postavljenim ciljem u konceptu T2T postizanja remisije, pri čemu je najveći naglasak stavljen na medicinske vježbe, budući da je sada dokazano i EBM-om dokumentirano sinergističko djelovanje tog načina liječenja i biološke terapije. Prava šteta bi bila ne koristiti ove znanstveno potvrđene podatke za koje ranije nismo znali, već smo iskustveno posezali za dobrim učincima NFL-a, ne znajući objasniti konačnu uspješnost i učinkovitost ovog liječenja kod upalnih reumatskih bolesti (15, 30,46).

Zdrav način života ključan je za održavanje sigurnosti i prevenciju upalnih reumatskih bolesti tijekom života. RA je kronična autoimuna i sistemska bolest koja uključuje promjene u zglobovima, upalu, bolove u zglobovima, umor, povećani rizik od razvoja koronarne i srčane bolesti te brzi gubitak mišićne mase. Stoga je tjelovježba u poboljšanju upalnog obrasca izuzetno važna zbog svojih brojnih prednosti, kao što su poboljšanje mišićne mase, snage i učinkovitosti, čemu doprinose i neki drugi oblici NFL-a pa se u budućnosti u tom kontekstu može razmatrati i nutritivna potpora (10,11,17). Za AS ovaj način liječenja je odavno etabliran i uvršten u sve algoritme liječenja ovih bolesnika (18,19).

Danas znamo da tijekom vježbanja skeletni mišići oslobađaju miokine, pokrećući izravan protuupalni učinak sa svakom aktivnošću, a razina upalnih biomarkera kao što su TNF-alfa, C-reaktivni protein i

such as assessment of working conditions, vocational counselling, education on self-advocacy and introduction of changes in the work environment could reduce the risk of job loss, reduce the number of sick days and improve the work ability of patients with rheumatic diseases (45). Something similar can be found in a lay summary from the Cochrane Library from 2014 on non-drug interventions that can prevent job loss in workers with inflammatory rheumatic diseases. The evidence from the three RCTs discussed in this summary was of a very low quality and it was related to vocational counselling interventions (45).

In their RTC conducted on 55 research subjects suffering from PsA, Abou-Raya et al. have proved that exercise and weight loss, which were applied for a duration of 12 months, had a statistically significant effect on the improvement of the functional status, quality of life and global health of these patients, as well as on the improvement of depression, fatigue, but also the reduction in the serum levels of IL-6, TNF-α, hsCRP and IL-17 compared to the control group (4).

By using a search protocol specified in these methods, we were unable to find any articles in relation to other forms of non-pharmacological therapy used in the rehabilitation process of PsA patients, such as various physical therapy procedures, orthoses, dietary measures, complementary and alternative medicine.

DISCUSSION

NPT is an important component in the treatment of inflammatory rheumatic diseases, and it covers a broad range of topics which could be discussed on a much larger scale and more extensively than in this article. This aim of this review article was to raise awareness of the proper approach to NPT, as well as the necessity of using NPT in a holistic approach to the treatment of patients with inflammatory rheumatic diseases, and in accordance with the goal set in the T2T concept of achieving remission. In this respect, the greatest emphasis is placed on the importance of medical exercises, given the fact that the synergistic effect of this treatment method used in combination with biological therapy has been proved to be an effective method documented in EBM. It would be a real pity not to use this scientifically confirmed data, which were previously unknown to us, so we had to rely on the empirical evidence for the beneficial effect of NPT, not knowing how to explain the final success and effectiveness of this treatment in inflammatory rheumatic diseases (15,30,46).

A healthy lifestyle is the key to maintaining safety and preventing inflammatory rheumatic diseases throughout the course of one's life. RA is a chronic autoimmune and systemic disease that includes changes in the joints, inflammation, joint pain, fatigue, increased risk of developing coronary and heart disease, and rapid loss of muscle mass. Therefore, exercise is extremely important

IL-6 te drugi proupalni citokini značajno je niža kod sportaša i bolesnika s RA koji redovito vježbaju. Međutim, razumijevanje točne uloge nekih okolišnih i genetskih čimbenika možda će dodatno pomoći u prevenciji i liječenju upalnih reumatskih bolesti, kao što nam pomaže i simptomatsko korištenje konvencionalne fizikalne terapije i modernih tehnologija, usprkos malom broju potvrda važnosti EBM-a. Više je studija pokazalo da programi vježbanja mogu smanjiti simptome boli i ukočenosti kod bolesnika s RA (30). Nadalje, tjelovježba ima prednosti u smislu poboljšanja funkcionalne sposobnosti i psihološke dobrobiti. Ključno je da nema dokaza koji bi sugerirali da vježbanje pogoršava aktivnost bolesti (15,46). Ovi nalazi pokazuju da bi tjelovježba, i dinamička s otporom i aerobna, trebala biti uključena u liječenje bolesnika s RA. To se odražava u kliničkim smjernicama koje preporučuju da bolesnici s RA trebaju sudjelovati u redovitoj tjelovježbi (9,10).

ZAKLJUČAK

Svrha je ovoga preglednog rada staviti naglasak na utjecaj tjelovježbe i programiranog treninga na upalni moment i sinergistički učinak s biološkom terapijom u bolesnika s najčešćim upalnim reumatskim bolestima te značaj NFL-a u holističkom pristupu bolesniku. Budući da danas postoje značajni dokazi o protuupalnom učinku terapijskih vježbi, nova istraživanja trebala bi definirati specifičan način vježbanja, intenzitet i učestalost vježbanja, što bi onda osiguravalo i optimalan protuupalni učinak, kako bismo NFL-u dali neka od osnovnih, dobro definiranih obilježja farmakoterapije.

Propisivanje terapijskih vježbi kao jednog od značajnih načina za suzbijanje upalne aktivnosti uskoro bi moglo postati rutina kao i propisivanje lijekova kod bolesnika s upalnim reumatskim bolestima.

Izjava o sukobu interesa: Autorica izjavljuje da nije u sukobu interesa.

in improving the inflammatory pattern due to its many benefits, such as improving muscle mass, strength and efficiency. Other forms of NPT also contribute to the achievement of the aforementioned benefits, so in the future, nutritional support can also be considered in this context (10,11,17). For AS, this method of treatment has long been established and included in all treatment algorithms for these patients (18,19).

Today we are well aware that during exercise, the skeletal muscle releases myokines, thus triggering a direct anti-inflammatory effect with each activity or bout. It is also known that the level of inflammatory biomarkers such as TNF-alpha, C-reactive protein and IL-6 and other pro-inflammatory cytokines is significantly lower in athletes and RA patients who exercise regularly. However, understanding the exact role of some environmental and genetic factors may further help in the prevention and treatment of inflammatory rheumatic diseases, as well as the symptomatic use of conventional physical therapy and modern technologies, despite the small number of evidence that confirms the importance of EBM. Several studies have shown that exercise programmes can reduce symptoms of pain and stiffness in patients with RA (30). Furthermore, exercise is beneficial in terms of improved functional ability and psychological well-being. The crucial fact is that there is no evidence to suggest that exercise worsens disease activity (15,46). These findings indicate that exercise, both dynamic with resistance and aerobic, should be included in the treatment of patients with RA. This is also stated in the clinical guidelines that recommend that patients with RA should exercise on a regular basis (9,10).

CONCLUSION

The purpose of this review is to emphasise the effect of exercise and programmed training on inflammation, the synergistic effect used in combination with biological therapy in patients with the most common inflammatory rheumatic diseases, and the importance of NPT in a holistic approach to the patient. Since today there is significant evidence confirming the anti-inflammatory effect of therapeutic exercises, new research should define a specific way of exercising, and the intensity and frequency of exercise, which would ensure an optimal anti-inflammatory effect, in order to attribute some of the basic, well-defined characteristics of pharmacotherapy to NPT.

Prescribing therapeutic exercises as one of the significant methods for the suppression of inflammation could soon become a routine process just like prescribing drugs to patients with inflammatory rheumatic diseases.

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