OSTEOPOROZA U AUTOIMUNSKIM BOLESTIMA

PREGLEDNI RAD

REVIEW ARTICLE

OSTEOPOROSIS IN AUTOIMMUNE DISEASES

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SAŽETAK

Uvod: Osteoporoza je jedna od najčešćih ekstraartikularnih komplikacija u mnogim hroničnim inflamatornim reumatskim bolestima, kao što su: reumatoidni artritis, psorijazni artritis, ankilozirajući spondilitis, sistemski eritemski lupus, i dr.

Metode: Istraživali smo *PubMed, Scopus* i *Web of Science* baze podataka kako bismo pronašli studije objavljene u poslednjih 10 godina. Rad je napisan u vidu preglednog članka.

Rezultati: Većina studija kod postmenopauzalnih žena pronalazi povezanost između visokog nivoa proinflamatornih markera i povećanog gubitka koštanog tkiva. Literaturni podaci ukazuju na povezanost niskog rizika od velikih osteoporotičnih preloma, preloma kuka i nevertebralnih preloma kod pacijenata sa psorijaznim artritisom koji su na terapiji lekovima koji modifikuju tok bolesti. Procena pacijenta sa autoimunskim reumatskim bolestima obuhvata anamnezu, klinički pregled, procenu rizika od preloma, laboratorijske analize, kao i osteodenzitometriju. Neprepoznavanje i netretiranje osteoporoze je uslovljeno sledećim faktorima: nedovoljno znanje o osteoporozi i koristi od terapije, zabrinutost zbog mogućih neželjenih efekata terapije, slaba motivisanost i loša edukacija pacijenata. Razvijeno je nekoliko različitih metoda za smanjenje propusta u prepisivanju terapije, a među njima se *Fracture Liaison Service* pokazao kao najefikasniji. Strategije za upravljanje osteoporozom obuhvataju edukaciju pacijenata, promene životnog stila, prevenciju padova, adekvatnu ishranu, kontrolu aktivnosti bolesti, kao i uvođenje lekova za osteoporozu.

Zaključak: Uprkos značajnim naprecima u prevenciji, dijagnostici i tretmanu, prevalencija osteoporoze je visoka i zahteva pravovremeno prepoznavanje i sveobuhvatniji pristup. Procena faktora rizika od padova i preloma kostiju, kao i potencijala za oporavak, od velikog je značaja kod pacijenata sa autoimunskim reumatskim bolestima.

Ključne reči: osteoporoza, prevalencija, faktori rizika, prelomi, terapija

ABSTRACT

Introduction: Osteoporosis is one of the most common extra-articular complications in many chronic inflammatory rheumatic diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and systemic lupus erythematosus etc..

Methods: We searched the PubMed, Scopus, and Web of Science databases for studies published within the last 10 years. This is a review article.

Results: Most studies on postmenopausal women have found a correlation between high levels of pro-inflammatory markers and increased bone loss. Literature data indicate a link between a low risk of major osteoporotic fractures, hip fractures, and non-vertebral fractures in patients with PsA who are on disease-modifying therapies. Patient assessment in autoimmune rheumatic inflammatory diseases includes medical history, clinical examination, fracture risk assessment, laboratory tests, and bone densitometry. The lack of adequate diagnosis and treatment of osteoporosis is influenced by factors such as insufficient knowledge about osteoporosis and its therapeutic benefits, concerns about potential side effects of treatment, low motivation, and inadequate patient education on the subject. Several methods have been developed to reduce prescribing errors and oversights, with the Fracture Liaison Service proving to be the most effective. Strategies for managing osteoporosis include patient education, lifestyle modifications, fall prevention, proper nutrition, disease activity control, and the introduction of osteoporosis medication.

Conclusion: Despite significant advances in prevention, diagnosis, and treatment, the prevalence of osteoporosis remains high and requires timely recognition and a more comprehensive approach. Assessing risk factors for falls and fractures, as well as recovery potential, is crucial in patients with autoimmune rheumatic inflammatory diseases.

Keywords: osteoporosis, prevalence, risk factors, fractures, therapy

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UVOD

Prema definiciji Svetske zdravstvene organizacije (SZO), osteoporoza je sistemska, progresivna bolest skeleta, koju karakteriše smanjena koštana masa, te mikroarhitektonsko propadanje koštanog tkiva sa posledičnim povećanjem krhkosti kostiju i podložnosti prelomima. Snaga kostiju odražava integraciju dve glavne karakteristike: gustinu i kvalitet kostiju. Osteoporoza je široko rasprostranjeno oboljenje od koje oboleva jedna od tri žene, kao i jedan od pet muškaraca starosti preko 50 godina [1]. Najugroženija populacija su žene u postmenopauzi [2]. Prema rezultatima meta-analize iz 2022. godine, prevalencija osteoporoze i osteopenije se kreće od 19,7%-40,4% [3]. Među najčešćim faktorima rizika od osteoporoze izdvajaju se: godine starosti, ženski pol, genetska predispozicija, pušenje, česta konzumacija alkohola, neadekvatna ishrana i smanjen unos kalcijuma i vitamina D, hronična upotreba sistemskih kortikosteroida, kao i komorbiditeti među kojima su i autoimunska oboljenja, najčešće reumatoidni artritis (RA) [4]. Osteoporoza predstavlja značajnu i često nedovoljno prepoznatu komplikaciju u autoimunskim bolestima. Prevalencija autoimunskih reumatskih bolesti (AIRB) procenjena je na 3.225/100.000 [5]. Rano prepoznavanje ovih bolesti je ključno za sprečavanje njihovih komplikacija i za započinjanje odgovarajućeg lečenja [6].

Prevalencija osteoporoze je značajno veća kod pacijenata obolelih od reumatoidnog artritisa u odnosu na opštu populaciju, i do 27, 6%, što se objašnjava patofiziološkim mehanizmima razvoja ovog oboljenja, kao i terapijskim opcijama kod obolelih od reumatoidnog artritisa, koje vrlo često uključuju hroničnu upotrebu sistemske koritkosteroidne terapije [7]. Rezultati analize 21 objavljene studije pokazuju da se prevalencija osteoporoze kod obolelih od psorijaznog artitisa (PsA) kreće od 1,4% do 68,8% [8]. Prema podacima retrospektivne studije iz 2024. godine, incidencija osteoporoze i osteopenije kod obolelih od psorijaznog artritisa kreće se između 11,7% i 33,1% [9]. Kod osoba muškog pola mlađih od 50 godina, PsA može da doprinese ranijem gubitku koštane mase u odnosu na tradicionalne faktore rizika [9]. Pacijenti sa psorijaznim artritisom imaju i povišeni rizik od preloma kostiju u odnosu na opštu populaciju [10].

Osteoporoza je česta pojava kod obolelih od ankilozirajućeg spondilitisa (AS), ali se nedovoljno prepoznaje u kliničkoj praksi [11]. Kombinovana analiza u vidu dvoenergetske rendgenske apsorptiometrije (engl. *dual-energy X-ray absorptiometry – DXA*) i kvantitativne kompjuterizovane tomografije kod pacijenata sa ranim i dugotrajnim AS pokazala je smanjenu mineralnu koštanu gustinu (engl. *bone mineral density – BMD*) i gubitak koštane mase u kičmi i kukovima [12]. Prevalencija osteoporoze kod obolelih od aksijalnog

INTRODUCTION

According to the World Health Organization (WHO) definition, osteoporosis is a systemic, progressive skeletal disease characterized by reduced bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and susceptibility to fractures. Bone strength reflects the integration of two main characteristics: bone density and bone quality. Osteoporosis is a widespread condition, affecting one in three women and one in five men over the age of 50 years [1]. The population that is at greatest risk comprises postmenopausal women [2]. According to the results of a 2022 meta-analysis, the prevalence of osteoporosis and osteopenia ranges from 19.7% to 40.4% [3]. Among the most common risk factors for osteoporosis are advanced age, female sex, genetic predisposition, smoking, frequent alcohol consumption, inadequate nutrition, reduced intake of calcium and vitamin D, chronic use of systemic corticosteroids, as well as comorbidities, including autoimmune diseases, most commonly rheumatoid arthritis (RA) [4]. Osteoporosis represents a significant and often underrecognized complication in autoimmune diseases. The prevalence of autoimmune rheumatic diseases (ARDs) is estimated at 3,225 per 100,000 population [5]. Early recognition of these diseases is crucial for preventing complications and for initiating appropriate treatment [6].

The prevalence of osteoporosis is significantly higher in patients with rheumatoid arthritis than in the general population, as much as by 27.6%, which can be explained by the pathophysiological mechanisms of the disease as well as by therapeutic approaches in rheumatoid arthritis, which very often include the chronic use of systemic corticosteroid therapy [7]. The results of an analysis of 21 published studies indicate that the prevalence of osteoporosis in patients with psoriatic arthritis (PsA) ranges from 1.4% to 68.8% [8]. According to data from a retrospective study published in 2024, the incidence of osteoporosis and osteopenia in patients with psoriatic arthritis ranges between 11.7% and 33.1% [9]. In males younger than 50 years, PsA may contribute to earlier bone mass loss compared with traditional risk factors [9]. Patients with psoriatic arthritis also have an increased fracture risk, as compared with the general population [10].

Osteoporosis is a common condition in patients with ankylosing spondylitis (AS) but remains underrecognized in clinical practice [11]. A combined assessment using dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography revealed reduced bone mineral density (BMD) and bone loss in the spine and hips of patients with early and long-standing AS [12]. The prevalence of osteoporosis in patients

Tabela 1. Prevalencija osteoporoze u različitim populacijama i autoimunskim reumatskim bolstima (AIRB)

Bolest/Populacija	Prevalencija osteoporoze/osteopenije	Faktori rizika/Napomene	Referenca
Opšta populacija >50 godina	1 od 3 žene, 1 od 5 muškaraca	Starost, ženski pol, genetika, pušenje, alkohol, neadekvatan unos kalcijuma i vitamina D, kortikosteroidi	1-3
Reumatoidni artritis (RA)	Do 27,6%	Patofiziološki mehanizmi + hronična upotreba kortikosteroida	4, 7
Psorijazni artritis (PsA)	1,4%-68,8%	Kod muškaraca <50 godina može uzrokovati raniji gubitak koštane mase; povišeni rizik od preloma	8-10
Ankilozirajući spondilitis (AS)	13%-25%	Nedovoljno prepoznat; smanjena *BMD* u kičmi i kukovima	11, 12
Aksijalni spondiloartritis (*axSpA*)	11,7%-34,4%	Deficit vitamina D, smanjena mobilnost/rizik od preloma 11% – 24,6%	13
Sistemski eritemski lupus (SEL)	Osteoporoza: ~13%; Osteopenija: ~38%	Hronična upotreba glukokortikoida, trajanje bolesti, rana menopauza, hipovitaminoza vitamina D/ 1,8× veći rizik od preloma, 4× veći rizik od preloma kičme	14, 15

Table 1. Prevalence of osteoporosis in different populations and autoimmune rheumatic diseases (AIRDs)

Disease/Population	Prevalence of osteoporosis/osteopenia	Risk factors/Annotations	Reference
General population >50 years	1 in 3 women; 1 in 5 men	Age, female sex, genetics, smoking, alcohol, inadequate calcium and vitamin D intake, corticosteroids	1-3
Rheumatoid arthritis (RA)	Up to 27.6%	Pathophysiological mechanisms + chronic corticosteroid use	4, 7
Psoriatic arthritis (PsA)	1.4%-68.8%	In men <50 years of age, it may cause earlier loss of bone mass; increased risk of fractures	8-10
Ankylosing spondylitis (AS)	13%-25%	Insufficiently recognized; reduced BMD in the spine and hips	11, 12
Axial spondyloarthritis (axSpA)	11.7%-34.4%	Vitamin D deficiency, reduced mobility/fracture risk 11%–24.6%	13
Systemic lupus erythematosus (SLE)	Osteoporosis: ~13%; Osteopenia: ~38%	Chronic glucocorticoid use, disease duration, early menopause, vitamin D hypovitaminosis/1.8 x increased fracture risk, 4 x increased risk of vertebral fractures	14, 15

spondiloartritisa (engl. *axial spondyloarthritis – axSpA*) se kreće između 11,7% i 34,4%, dok je rizik od preloma kostiju između 11% i 24,6%, uz značajne faktore rizika, kao što su deficit vitamina D i smanjena mobilnost pacijenata zbog osnovnog oboljenja [13].

Prevalencija osteoporoze kod pacijenata obolelih od sistemskog eritemskog lupusa (SEL) je oko 13%, a osteopenije oko 38% [14]. Glavni faktori rizika kod ove populacije su hronična upotreba glukokortikoida, dužina trajanja bolesti i rana menopauza sa sniženom koštanom mineralnom gustinom (engl. *bone mineral density – BMD*) i hipovitaminozom vitamina D [15]. Pacijenti sa sistemskim eritemskim lupusom imaju 1,8 puta veći opšti rizik od nastanka preloma i četiri puta veći rizik od nastanka preloma kičmenih pršljenova [14]. Rezultati navedenih studija prikazani su u Tabeli 1. Tabela prikazuje prevalenciju osteoporoze i osteopenije u opštoj populaciji i kod pacijenata sa različitim inflamatornim reumatskim bolestima, uz navođenje glavnih faktora rizika i specifičnih napomena za svaku grupu.

MATERIJALI I METODE

Metodologija ovog rada zasnovana je na pregledu literature iz baza: *PubMed, Scopus* i *Web of Science*, ko-

with axial spondyloarthritis (axSpA) ranges from 11.7% to 34.4%, while the fracture risk ranges from 11% to 24.6%, with significant risk factors including vitamin D deficiency and reduced patient mobility due to the underlying disease [13].

The prevalence of osteoporosis in patients with systemic lupus erythematosus (SLE) is approximately 13%, while the prevalence of osteopenia is approximately 38% [14]. The main risk factors in this population include chronic glucocorticoid use, disease duration, and early menopause associated with reduced bone mineral density (BMD) and vitamin D hypovitaminosis [15]. Patients with SLE are at a 1.8 times higher overall fracture risk and at a four times higher risk of vertebral fractures [14]. The results of the above-described studies are presented in Table 1. The table summarizes the prevalence of osteoporosis and osteopenia in the general population and among patients with various inflammatory rheumatic diseases, highlighting key risk factors and specific annotations for each group.

MATERIALS AND METHODS

The methodology of this study is based on a literature review of the PubMed, Scopus, and Web of Science da-

risteći ključne reči povezane sa reumatskim bolestima i osteoporozom (osteoporoza, prevalencija, faktori rizika, prelomi, terapija). Uključeni su članci objavljeni na engleskom jeziku u poslednjih deset godina, koji se odnose na odrasle pacijente i pružaju podatke o prevalenciji, faktorima rizika i terapijskim pristupima. Isključeni su radovi koji nisu relevantni, studije sa pedijatrijskom populacijom i prikazi slučajeva. Prikupljeni podaci analizirani su deskriptivno i tematski, sa fokusom na kliničke karakteristike, mehanizme gubitka koštane mase i strategije lečenja. Rad je napisan u vidu preglednog članka.

Faktori koji utiču na koštanu mineralnu gustinu kod autoimunskih reumatskih bolesti

Hronični inflamatorni odgovori kod autoimunskih reumatskih bolesti (AIRB), kao što su reumatoidni artritis i sistemski eritemski lupus, aktiviraju osteoklaste, čime ubrzavaju resorpciju kostiju i dovode do smanjenja koštane gustine [16]. Citokini koje oslobađaju imunske ćelije tokom inflamatornog odgovora utiču na metabolizam kostiju, podstičući razvoj osteoporoze. Formiranje sindezmofita i ankiloze dodatno povećavaju opterećenje u kortikalnim zonama i paravertebralnim ligamentima, a gubitak trabekularne kosti u vertebralnim telima može dovesti do smanjenja koštane mineralne gustine [17]. Bol i ograničena pokretljivost uzrokovani ovim bolestima smanjuju fizičku aktivnost pacijenata, što dalje utiče na zdravlje kostiju [18].

Moguća veza između psorijaznog artritisa (PsA) i osteoporoze može se naći u izraženijoj demineralizaciji uočenoj kod pacijenata sa PsA, koja se intenzivira starenjem, nedostatkom estrogena i pogoršanim indeksima kvaliteta života [19]. Istraživanja su pokazala da pacijenti sa PsA imaju veću verovatnoću za razvoj fraktura u poređenju sa zdravom kontrolnom grupom bez psorijaze, ali nije sa sigurnošću potvrđena povezanost visokog rizika od fraktura sa sniženom mineralnom koštanom gustinom. Dalja istraživanja su neophodna radi utvrđivanja PsA kao faktora rizika od osteoporoze [20]. Noviji literaturni podaci su pokazali da kod pacijenata sa PsA, muškarci imaju povećan rizik od osteoporoze, kao i od osteoporotičnih fraktura, čak i ako su mlađi od 50 godina [21]. PsA je opisan kao nezavisni faktor rizika za smanjenu gustinu kostiju i padove, a samim time i za povezane frakture [22].

Pacijenti oboleli od ankilozirajućeg spondilitisa (AS) imaju snižen *BMD* i povećan rizik od preloma. Dodatni rizik od osteoporoze i fraktura imaju mlađi pacijenti i pacijenti u ranim fazama ove bolesti [23]. Vertebralne frakture kod AS su često nestabilne zbog okoštavanja potpornih i elastičnih ligamenata. Inflamatorni citokini, uključujući faktor tumorske nekroze (engl. *tumor necro-*

tabases, using keywords related to rheumatic diseases and osteoporosis (osteoporosis, prevalence, risk factors, fractures, therapy). Articles published in English within the last ten years focusing on adult patients and reporting data on prevalence, risk factors, and therapeutic approaches were included. Studies that were not relevant, those involving pediatric populations, and case reports were excluded. The collected data were analyzed descriptively and thematically, with a focus on clinical characteristics, mechanisms of bone loss, and treatment strategies. This is a review article.

Factors affecting bone mineral density in autoimmune rheumatic diseases

Chronic inflammatory responses in autoimmune rheumatic diseases (ARDs), such as rheumatoid arthritis and systemic lupus erythematosus, activate osteoclasts, thereby accelerating bone resorption and leading to reduced bone density [16]. Cytokines released by immune cells during the inflammatory response affect bone metabolism, promoting the development of osteoporosis. The formation of syndesmophytes and ankylosis further increases mechanical load in cortical bone regions and paravertebral ligaments, while the loss of trabecular bone in vertebral bodies can result in decreased bone mineral density [17]. Pain and reduced mobility caused by these diseases limit patients' physical activity, which further adversely affects bone health [18].

A possible link between psoriatic arthritis (PsA) and osteoporosis may be found in the more pronounced demineralization observed in patients with PsA, which is intensified by aging, estrogen deficiency, and impaired quality-of-life indexes [19]. Studies have shown that patients with PsA are more likely to develop fractures compared with a healthy control group without psoriasis; however, a definite association between a high fracture risk and reduced bone mineral density has not been conclusively established. Further research is needed to confirm PsA as a risk factor for osteoporosis [20]. More recent literature data have shown that in patients with PsA, men have an increased risk of osteoporosis as well as of osteoporotic fractures, even when they are younger than 50 years [21]. PsA has been described as an independent risk factor for reduced bone density and falls, and consequently for associated fractures [22].

Patients with ankylosing spondylitis (AS) have reduced bone mineral density (BMD) and an increased fracture risk. Younger patients and those in the early stages of the disease are at additional risk of osteoporosis and fractures [23]. Vertebral fractures in AS are often unstable due to ossification of supporting and elastic ligaments. Inflammatory cytokines, including

sis factor – TNF)-alfa i interleukini (IL): IL-1, IL-6 I IL-17, povećavaju aktivnost osteoklasta i razgradnju kostiju [24]. Istraživanja pokazuju da su gubitak koštane mase i prelomi povezani sa sistemskim eritemskim lupusom (SEL), što nije u vezi samo sa samom bolešću, već i sa niskim nivoom vitamina D i neželjenim efektima terapije [25].

Uticaj lekova za lečenje autoimunskih reumatskih bolesti na koštanu mineralnu gustinu

Lekovi koji se primenjuju kod autoimunskih reumatskih bolesti su neophodni za lečenje osnovnog oboljenja, ali imaju brojna neželjena dejstva na mišićno-skeletni sistem i gustinu kostiju. Zbog svog antiinflamatornog efekta, glukokortikoidna terapija se često primenjuje kod obolelih od AIRB. Razumevanje mehanizama delovanja glukokortikoida na kost, imunoloških veza i vitamina D, kao i prepoznavanje uticaja hronične inflamacije na koštani metabolizam omogućava bolje razumevanje neželjenih efekata na skelet [26]. Glukokortikoidi umanjuju apsorpciju kalcijuma u digestivnom traktu, povećavaju ekskreciju kalcijuma putem bubrega i suprimiraju funkciju osteoblasta što sve dovodi do smanjene sinteze koštanog tkiva. Takođe doprinose apoptozi osteocita i osteoblasta, što dovodi do povećane resorpcije kostiju. Ovi efekti zajedno doprinose smanjenju *BMD*-a i povećanju rizika od preloma kostiju [27]. Rizik od preloma kostiju, posebno od preloma kičmenih pršljenova, značajno se povećava nakon kontinuirane upotrebe glukokortikoida tokom tri meseca i nastavlja da se povećava sa njihovom sve dužom upotrebom [28]. Doze kortikosteroida koje su na dnevnom nivou veće od 7,5 mg povećavaju rizik od velikih osteoporotičnih fraktura za 15%, a od preloma kuka za 20% [29]. Kako bi se ovi neželjeni efekti ublažili preporučuje se da se koriste najniže delotvorne terapijske doze glukokortikoida i to tokom najkraćeg mogućeg vremenskog perioda. Uz kortikosteroide je neophodna primena vitamina D i kalcijuma, kako bi se smanjili štetni efekti na koštano tkivo [29].

Klasični lekovi koji modifikuju tok bolesti (engl. *disease-modifying therapies/drugs*), uključujući metotreksat i sulfasalazin, koji se rutinski upotrebljavaju kod obolelih od AIRB, imaju manji uticaj na *BMD* u odnosu na glukokortikoide. Metotreksat je u nekim studijama povezan sa redukcijom sinteze koštanog matriksa, međutim razlozi za ovo još uvek nisu u potpunosti razjašnjeni. Pacijenti koji se nalaze na terapiji metotreksatom mogu imati povišen rizik od preloma kostiju, što se ne povezuje sa upotrebom terapije nego sa osnovnom bolešću i drugim faktorima rizika [30].

Biološka terapija (inhibitori *TNF* i inhibitori IL) usmerena je na specifične komponente imunskog

tumor necrosis factor (TNF)-alpha and interleukins (IL) such as IL-1, IL-6, and IL-17, increase osteoclast activity and bone resorption [24]. Studies indicate that bone loss and fractures are associated with systemic lupus erythematosus (SLE), which is associated not only with the disease itself but also with low vitamin D levels and adverse effects of therapy [25].

The effect of medications used in the treatment of autoimmune rheumatic diseases on bone mineral density

Medications used in the treatment of autoimmune rheumatic diseases are essential for managing the underlying condition but have numerous adverse effects on the musculoskeletal system and bone density. Owing to its anti-inflammatory effects, glucocorticoid therapy is frequently used in patients with autoimmune rheumatic diseases (ARDs). Understanding the mechanisms of action of glucocorticoids on bone, the immunological interactions, and the role of vitamin D, as well as recognizing the impact of chronic inflammation on bone metabolism, enables a better understanding of their adverse skeletal effects [26]. Glucocorticoids reduce calcium absorption in the gastrointestinal tract, increase renal calcium excretion, and suppress osteoblast function, all of which lead to decreased bone tissue synthesis. They also promote apoptosis of osteocytes and osteoblasts, resulting in increased bone resorption. Together, these effects contribute to a reduction in BMD and an increased fracture risk [27]. The fracture risk, particularly for vertebral fractures, increases significantly after continuous glucocorticoid use for three months and continues to rise with longer duration of therapy [28]. Daily corticosteroid doses exceeding 7.5 mg increase the risk of major osteoporotic fractures by 15% and the risk of hip fractures by 20% [29]. To mitigate these adverse effects, it is recommended to use the lowest effective therapeutic doses of glucocorticoids for the shortest possible duration. Concomitant administration of vitamin D and calcium is necessary to reduce the harmful effects of glucocorticoids on bone tissue [29].

Conventional disease-modifying drugs (disease-modifying antirheumatic drugs, DMARDs), including methotrexate and sulfasalazine, which are routinely used in patients with ARDs, have a lesser impact on BMD compared with glucocorticoids. In some studies, methotrexate has been associated with reduced bone matrix synthesis; however, the reasons for this association have not yet been fully clarified. Patients receiving methotrexate therapy may have an increased fracture risk, which is attributed not to the medication itself but to the underlying disease and other risk factors [30].

odgovora, kako bi se suzbili inflamatorni procesi u organizmu. Time što umanjuju sistemsku inflamaciju, ovi lekovi imaju pozitivan efekat na *BMD* i umanjuju resorpciju kostiju kod pacijenata sa RA i drugim AIRB [31]. Inhibitori Janus kinaze (JK), kao što su tofacitinib i baricitinib, predstavljaju noviju grupu lekova koji modifikuju tok bolesti primenjivanih u lečenju AIRB. Njihov uticaj na *BMD* je još uvek nepoznat. Prema do sada prikupljenim podacima, smatra se da bi oni mogli da imaju neutralan ili čak pozitivan efekat na koštani metabolizam [32]. Hormonska supstituciona terapija (HST) ima značajnu ulogu u autoimunskim bolestima. Kod hipotireoze indukovane autoimunskim tireoiditisom nadoknada hormona štitaste žlezde održava eutiroidni status, smanjuje simptome hipotireoze i doprinosi očuvanju koštane mase. Time se smanjuje rizik od osteoporoze i preloma, što je čest problem kod pacijenata sa hroničnim autoimunskim poremećajima [33].

DIJAGNOSTIKA

Zlatni standard za postavljanje dijagnoze osteoporoze je *DXA* dijagnostika, koja meri koštanu mineralnu gustinu. Dijagnostički proces započinje kliničkom procenom faktora rizika, koja obuhvata podatke o godinama, polu, prethodnim prelomima, porodičnoj anamnezi osteoporoze, upotrebi glukokortikoida i načinu života [34,35]. Nakon identifikovanja rizičnih pacijenata, sledi izvođenje *DXA* pregleda u predelu lumbalne kičme i vrata femura. Glavni kriterijum neophodan za postavljanje dijagnoze osteoporoze je T-skor < -2,5 [36]. Međutim, dijagnostički kriterijumi se ne zasnivaju samo na T-skoru, već je potrebno uzeti u obzir i rizik od preloma, koji se procenjuje na osnovu prethodnih preloma, komorbiditeta i drugih faktora rizika [37]. Z-skor se koristi kod mlađih osoba i žena u perimenopauzi; vrednosti ≤ -2 ukazuju na *BMD* niži od očekivanog za starosno doba pacijenta [38]. Kliničke smernice preporučuju da se *DXA* uradi kod svih žena starijih od 65 godina, kao i kod mlađih žena u postmenopauzi i muškaraca starijih od 50 godina sa dodatnim faktorima rizika [38].

Dopunska laboratorijska dijagnostika uključuje procenu parametara koštanog metabolizma (parathormon, N - terminalni propeptid prokolagena tipa 1, koštana alkalna fosfataza, beta-kroslaps, fosfor, vitamin D i kalcijum), kao i funkcije tireoidne i paratiroidne žlezde. *Fracture Risk Assessment Tool* (*FRAX*) predstavlja koristan internetski alat koji izračunava desetogodišnju verovatnoću preloma kuka ili drugih značajnih preloma [39]. Unapređena verzija, *FRAX plus*, uključuje dodatne faktore, kao što su: lokalizacija prethodnih preloma, broj padova u prethodnoj

Biological therapy (TNF inhibitors and IL inhibitors) targets specific components of the immune response to suppress inflammatory processes in the body. By reducing systemic inflammation, these agents have a positive effect on BMD and decrease bone resorption in patients with RA and other ARDs [31]. Janus kinase (JAK) inhibitors, such as tofacitinib and baricitinib, represent a newer group of disease-modifying agents used in the treatment of ARDs. Their impact on BMD is not yet fully known. Based on currently available data, they are considered to have a neutral or even potentially positive effect on bone metabolism [32]. Hormone replacement therapy (HRT) plays an important role in autoimmune diseases. In hypothyroidism induced by autoimmune thyroiditis, thyroid hormone replacement maintains a euthyroid state, reduces hypothyroid symptoms, and contributes to the preservation of bone mass. This reduces the risk of osteoporosis and fractures, which are common problems in patients with chronic autoimmune disorders [33].

DIAGNOSTICS

The gold standard for diagnosing osteoporosis is dual-energy X-ray absorptiometry (DXA), which measures bone mineral density (BMD). The diagnostic process begins with a clinical assessment of risk factors, including age, sex, previous fractures, family history of osteoporosis, glucocorticoid use, and lifestyle factors [34,35]. After identifying patients at risk, DXA examination of the lumbar spine and femoral neck is performed. The main criterion required for establishing a diagnosis of osteoporosis is a T-score < −2.5 [36]. However, diagnostic criteria are not based solely on the T-score. The fracture risk must also be taken into account, as assessed on the basis of previous fractures, comorbidities, and other risk factors [37]. The Z-score is used in younger individuals and perimenopausal women; values ≤ −2 indicate BMD lower than expected for the patient's age [38]. Clinical guidelines recommend performing DXA in all women older than 65 years, as well as in younger postmenopausal women and men older than 50 years with additional risk factors [38].

Additional laboratory diagnostics include assessment of bone metabolism parameters (parathyroid hormone, N-terminal propeptide of type I procollagen, bone alkaline phosphatase, beta-CrossLaps, phosphorus, vitamin D, and calcium), as well as evaluation of thyroid and parathyroid gland function. The Fracture Risk Assessment Tool (FRAX) is a useful online tool that calculates the 10-year probability of hip fracture or other major osteoporotic fractures [39]. An enhanced version, FRAX Plus, incorporates additional factors such as

Tabela 2. Tumačenje vrednosti skora trabekularne kosti (engl. *trabecular bone score – TBS*)

Aspekt	Opis	Ref.
Definicija	Indirektni parametar kvaliteta trabekularne mikroarhitekture, izveden iz *DXA* pregleda lumbalne kičme.	41
Način merenja	Računarski algoritam analizira varijacije u sivoj skali *DXA* slike L1–L4 regiona, nezavisno od *BMD*.	41
Vrednosti (granice)	***TBS*** **≥ 1,350** ⟶ normalna mikroarhitektura ***TBS*** **1,200–1,350** ⟶ degradirana mikroarhitektura ***TBS*** **≤ 1,200** ⟶ značajno degradirana mikroarhitektura	49
Klinički značaj	Pruža dodatnu procenu rizika od preloma, nezavisno od *BMD* – Može razlikovati pacijente sa sličnim T-skorom ali različitim rizikom od preloma	41
Prednosti	Jednostavno: koristi postojeće *DXA* preglede – Nema dodatno zračenje – Korisno kod pacijenata sa sekundarnom osteoporozom (RA, SEL, DM tip 2)	43
Ograničenja	Manja pouzdanost kod ekstremnog indeksa telesne mase – *BMI* (< 15 ili >37 kg/m^2) – Samo lumbalni region (L1–L4) – Nije zamena za *BMD*, već dopuna	41
Preporuke za primenu	U kombinaciji sa *BMD* i *FRAX* skorom – za precizniju procenu rizika od preloma, posebno kod pacijenata sa „graničnim" *BMD* vrednostima ili sekundarnim faktorima rizika.	49

Table 2. Interpretation of trabecular bone score values (TBS)

Aspect	Description	Ref.
Definition	An indirect parameter of trabecular microarchitecture quality, derived from DXA assessment of the lumbar spine.	41
Measurement method	A computer algorithm analyzes variations in the grayscale DXA image of the L1–L4 region, independent of BMD.	41
Values (cut-off values)	**TBS ≥ 1.350** ⟶ normal microarchitecture **TBS 1.200–1.350** ⟶ degraded microarchitecture **TBS ≤ 1.200** ⟶ significantly degraded microarchitecture	49
Clinical significance	Provides additional assessment of fracture risk, independent of BMD – Can differentiate between patients with similar T-score but different fracture risk	41
Advantages	Simple: uses existing DXA scans – No additional radiation – Useful in patients with secondary osteoporosis (RA, SLE, Type 2 DM)	43
Limitations	Less reliable in extreme body mass index – BMI (< 15 or >37 kg/m^2) – Lumbar region only (L1–L4) – Not a substitute for BMD, but a supplementary method	41
Recommendations for application	Used in combination with BMD and the FRAX score – for a more accurate assessment of fracture risk, especially in patients with "borderline" BMD values or secondary risk factors.	49

godini, doze kortikosteroida i skor trabekularne kosti (engl. *trabecular bone score – TBS*), čime se poboljšava preciznost procene rizika [40]. Tumačenje vrednosti *TBS*-a prikazano je u Tabeli 2. Tabela prikazuje osnovne informacije o skoru trabekularne kosti – *TBS*: šta meri (mikroarhitektura kosti), kako se meri (analizom *DXA* snimka lumbalne kičme), klinički značaj (dopuna *BMD* u proceni rizika od preloma), prednosti, ograničenja i preporuke za primenu.

Pojedini dijagnostički kriterijumi koji se rutinski koriste kod zdrave populacije mogu biti nepouzdani kod obolelih od autoimunskih reumatskih bolesti. Kod pacijenata sa AIRB (RA, *axSpA*, PsA, SEL) neophodno je prilagoditi dijagnostički pristup jer bolest i terapija mogu da utiču na rezultate *DXA* merenja. Lokalizovana razređenja kostiju kod RA i novoformirana kost kod *axSpA* mogu dovesti do lažno sniženih ili lažno povišenih vrednosti *BMD*, pa je tumačenje nalaza otežano [41].

the location of previous fractures, the number of falls in the preceding year, corticosteroid doses, and the trabecular bone score (TBS), thereby improving the accuracy of risk assessment [40]. Interpretation of TBS values is presented in Table 2. The table summarizes key aspects of TBS: what it measures (bone microarchitecture), how it is measured (analysis of lumbar spine DXA images), clinical significance (complement to BMD in fracture risk assessment), advantages, limitations, and recommended use.

Certain diagnostic criteria routinely used in the general population may be unreliable in patients with autoimmune rheumatic diseases. In patients with ARDs (RA, axSpA, PsA, SLE), it is necessary to adapt the diagnostic approach because both the disease itself and its treatment may affect DXA measurement results. Localized bone loss in RA and new bone formation in axSpA may lead to falsely low or falsely elevated BMD values, making interpretation more challenging [41].

U ovim slučajevima može biti korisno dodatno merenje periferne koštane gustine, kao što je *BMD* distalne podlaktice, kao i upotreba *TBS*-a za precizniju procenu rizika od preloma. Kod pacijenata sa *axSpA* i visokim rizikom od preloma preporučuje se kombinovanje *DXA* i *TBS* metoda radi bolje identifikacije onih kojima je potrebna rana intervencija [42]. Pravovremena procena i kontinuirano praćenje su od ključnog značaja, naročito kod pacijenata na dugotrajnoj terapiji glukokortikoidima, kod kojih se preporučuje češća kontrola *BMD*-a i reevaluacija rizika od preloma [43].

Primena *FRAX* algoritma kod pacijenata sa autoimunskim reumatskim bolestima ima poseban klinički značaj jer omogućava ranu identifikaciju osoba sa povišenim rizikom od preloma i olakšava odluku o započinjanju specifične terapije. Uključivanje podataka o upotrebi glukokortikoida u *FRAX* indeks značajno doprinosi preciznijoj proceni rizika od preloma, imajući u vidu da hronična glukokortikoidna terapija predstavlja jedan od vodećih uzroka sekundarne osteoporoze [41]. Kada se u *FRAX* unese i izmerena vrednost *BMD* na vratu femura, procena rizika postaje još pouzdanija, što je od posebnog značaja kod pacijenata sa RA ili *axSpA*, kod kojih se osteoporoza može javiti u mlađem životnom dobu [44].

Ipak, važno je naglasiti da *FRAX* ne uzima u obzir aktivnost bolesti, stepen inflamacije, funkcionalnu onesposobljenost ili učestalost padova, zbog čega može da potceni rizik kod pacijenata sa visoko aktivnom bolešću ili kod onih sa značajnim strukturnim oštećenjem. Takođe, standardni *FRAX* model ne pravi razliku između niskih i visokih doza glukokortikoida, pa se kod pacijenata na dugotrajnoj terapiji dozama većim od 7,5 mg prednizona preporučuje korekcija izračunatog rizika za dodatnih 15-20% [45].

Zbog ovih ograničenja preporučuje se kombinovanje *FRAX* alata sa dodatnim metodama procene, kao što su *TBS* i vertebralna morfometrija, kako bi se unapredilo identifikovanje pacijenata sa visokim rizikom od preloma i optimizovalo donošenje terapijskih odluka. Vertebromorfometrija (engl. *lateral vertebral assessment – LVA*) predstavlja slikovnu metodu kojom se, korišćenjem *DXA* metode, vrši detekcija i analiza vertebralnih fraktura. Za razliku od klasične radiografije, *LVA* omogućava nižu dozu zračenja i bržu procenu deformiteta kičmenih pršljenova. U kontekstu osteoporoze i autoimuskih bolesti, *LVA* je posebno korisna jer otkrivanjem fraktura omogućava blagovremenu korekciju terapije i precizniju procenu rizika od novih preloma [46]. Table 3 and Figure 1 prikazuje *FRAX* upitnik na srpskom jeziku. Na slici je prikazan algoritam prevencije i lečenja pacijenata sa osteoporozom, prema literaturnim podacima.

In such cases, additional assessment of peripheral bone density, such as BMD of the distal forearm, as well as the use of TBS, may be useful for a more accurate evaluation of fracture risk. In patients with axSpA and a high fracture risk, combining DXA and TBS methods is recommended to better identify those who require early intervention [42]. Timely assessment and continuous monitoring are of crucial importance, particularly in patients receiving long-term glucocorticoid therapy, in whom more frequent BMD monitoring and reassessment of fracture risk are recommended [43].

The application of the FRAX algorithm in patients with autoimmune rheumatic diseases has particular clinical significance, as it enables early identification of individuals at increased fracture risk and facilitates decisions regarding the initiation of specific therapy. Inclusion of data on glucocorticoid use in the FRAX index significantly contributes to a more accurate fracture risk assessment, given that chronic glucocorticoid therapy is one of the leading causes of secondary osteoporosis [41]. When the measured BMD value at the femoral neck is also entered into FRAX, risk estimation becomes even more reliable, which is particularly important in patients with RA or axSpA, in whom osteoporosis may occur at a younger age [44].

However, it is important to emphasize that FRAX does not take into account disease activity, the degree of inflammation, functional disability, or the frequency of falls, and therefore may underestimate risk in patients with highly active disease or those with significant structural damage. In addition, the standard FRAX model does not differentiate between low and high doses of glucocorticoids. Thus, in patients receiving long-term therapy with doses exceeding 7.5 mg of prednisone, adjustment of the calculated risk by an additional 15-20% is recommended [45].

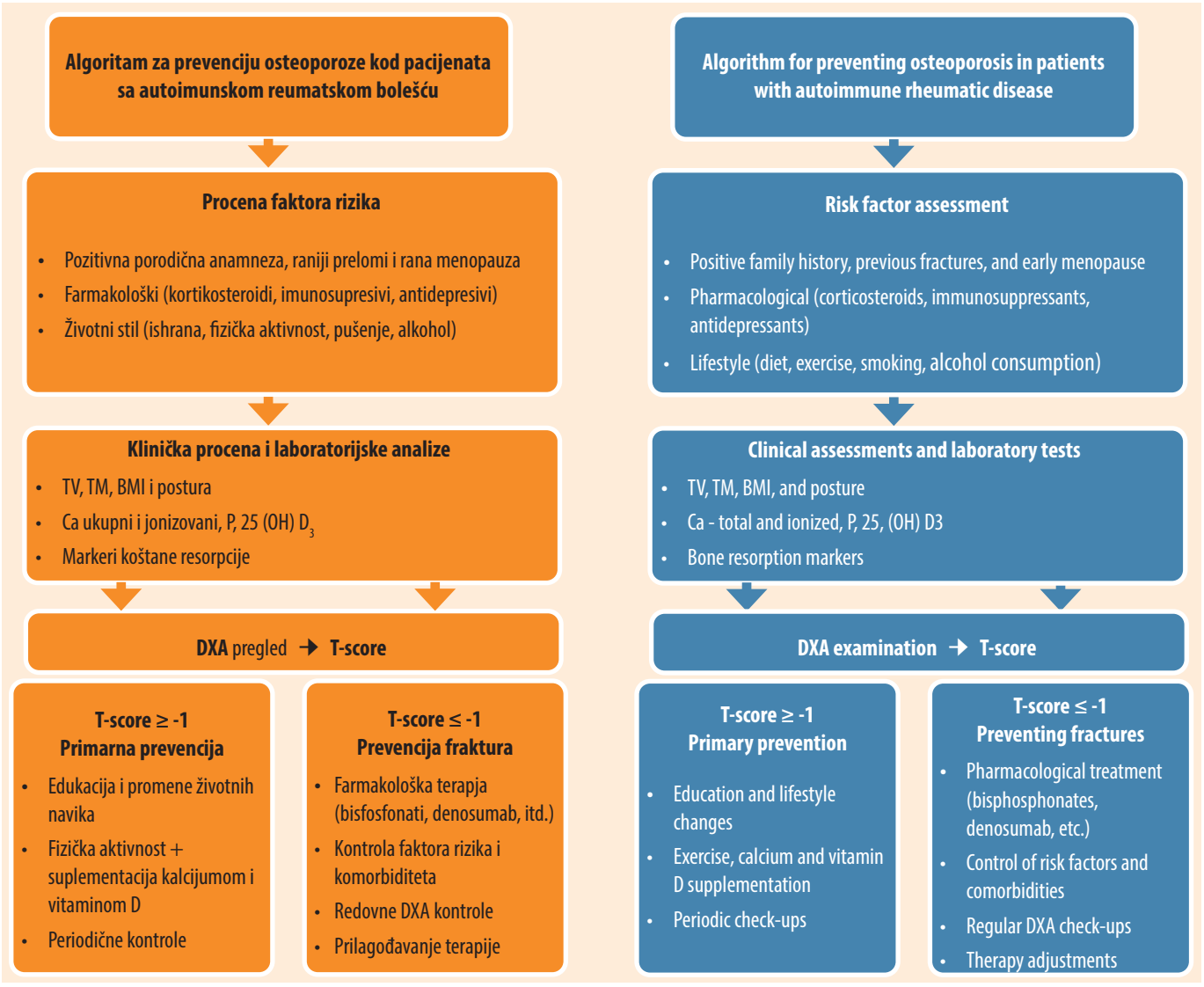
Because of these limitations, combining the FRAX tool with additional assessment methods, such as TBS and vertebral morphometry, is recommended in order to improve identification of patients at high fracture risk and optimize therapeutic decision-making. Vertebral morphometry (lateral vertebral assessment – LVA) is an imaging method that uses DXA to detect and analyze vertebral fractures. Unlike conventional radiography, LVA allows for lower radiation exposure and faster assessment of vertebral deformities. In the context of osteoporosis and autoimmune diseases, LVA is particularly useful because detecting fractures enables timely adjustment of therapy and a more accurate assessment of the risk of subsequent fractures [46]. Table 3 and Figure 1 presents the FRAX questionnaire. Figure 1 presents the algorithm designed to assist in the prevention and treatment of osteoporosis, according to the literature.

Tabela 3. TFRAX upitnik

Pitanje	Odgovor
1. Životno doba (između 40 i 90 godina)	_____
2. Pol	□ Ženski □ Muški
3. Težina (kg)	
4. Visina (cm)	
5. Prethodni prelom	□ Da □ Ne
6. Roditelj sa prelomom kuka	□ Da □ Ne
7. Trenutno pušim	□ Da □ Ne
8. Glukokortikoidi	□ Da □ Ne
9. Reumatoidni artritis	□ Da □ Ne
10. Sekundarna osteoporoza	□ Da □ Ne
11. Alkohol ≥3 jedinice/dan	□ Da □ Ne
12. BMD vrata bedrene kosti	

Table 3. The FRAX questionnaire

Question	Answer
1. Age (between 40 and 90 years)	_____
2. Sex	□ Female □ Male
3. Wight (kg)	
4. Height (cm)	
5. Previous fracture	□ Yes □ No
6. Parent with a hip fracture	□ Yes □ No
7. I currently smoke	□ Yes □ No
8. Glucocorticoids	□ Yes □ No
9. Rheumatoid arthritis	□ Yes □ No
10. Secondary osteoporosis	□ Yes □ No
11. Alcohol ≥3 units/day	□ Yes □ No
12. Femoral neck BMD	



Slika 1. Algoritam za pristup pacijentu sa povišenim rizikom od nastanka osteoporoze [33,34,36]

Figure 1. Algorithm for the management of patients at increased risk of developing osteoporosis [33,34,36]

SMERNICE ZA KLINIČKU PRAKSU

Pravovremeno prepoznavanje faktora rizika, edukacija pacijenata, i započinjanje odgovarajuće terapije mogu značajno da smanje rizik od preloma i poboljšaju kvalitet života. Prevencija obuhvata modifikaciju faktora rizika, suplementaciju kalcijuma i vitamina D, prilagođenu fizičku aktivnost, redovno praćenje gustine kostiju i prevenciju padova [33].

Terapija prvog izbora za lečenje osteoporoze kod većine pacijenata zasniva se na primeni lekova sa antiresorptivnim efektom, pre svega oralnih bisfosfonata, u skladu sa preporukama Američkog udruženja endokrinologa (engl. *American Association of Endocrinologists – AACE*) [47]. Kod pacijenata koji imaju intoleranciju ili kontraindikacije za oralne bisfosfonate, primena intravenskih bisfosfonata ili denosumaba predstavlja alternativu. Obe kategorije medikamenata spadaju u grupu antiresorptivnih lekova. Bisfosfonati, bez obzira na način primene (oralni ili intravenski), direktno inhibiraju osteoklastnu aktivnost, dok denosumab, koji predstavlja monoklonalno antitelo koje se vezuje za ligand aktivatora receptora nuklearnog faktora Kappa-B (engl. *Receptor Activator of Nuclear factor Kappa-B Ligand-RANKL*), svoje antiresorptivno delovanje ostvaruje indirektno [48]. Selektivni modulatori estrogenskih receptora (engl. selective estrogen receptor modulators – *SERMs*) mogu se razmotriti kao dodatna opcija, naročito kod žena u postmenopauzi sa umerenim rizikom. Za pacijente sa visokim rizikom od preloma koji ne mogu da koriste oralnu terapiju, preporučuje se primena denosumaba ili teriparatida (rekombinantnog oblika parathormona), koji se primenjuju subkutano. Kod pacijenata sa veoma visokim rizikom od fraktura ili onih koje su već imali višestruke prelome, preporučuje se uvođenje anaboličkih lekova (teriparatid) ili lekova sa dvostrukim mehanizmom dejstva, kao što je romosozumab. Lek romosozumab je monoklonalno antitelo koje inhibira sklerostin i time utiče na formiranje nove kosti i umanjuje aktivnost osteoklasta. Aplikuje se jednom godišnje subkutanim putem. Važno je naglasiti da se rizik od preloma procenjuje nakon svake nove frakture, bez obzira na vreme njenog nastanka, i da se rizik povećava nakon prekida terapije [49].

Kod pacijenata sa RA dodatnu ulogu u zaštiti kostiju ima adekvatno lečenje osnovne bolesti. Konvencionalni lekovi koji modifikuju tok bolesti (npr. metotreksat) i biološki lekovi (TNF inhibitori, IL-6 inhibitori, rituksimab, abatacept) smanjuju aktivnost bolesti i time redukuju inflamaciju, što može pozitivno da utiče na metabolizam kostiju, iako je njihov efekat na *BMD* ograničen [50].

Kod odraslih osoba, koje započinju ili nastavljaju glukokortikoidnu terapiju duže od tri meseca, pre-

CLINICAL PRACTICE GUIDELINES

Timely identification of risk factors, patient education, and initiation of appropriate therapy can significantly reduce fracture risk and improve quality of life. Prevention includes modification of risk factors, calcium and vitamin D supplementation, appropriately tailored physical activity, regular monitoring of bone density, and fall prevention strategies [33].

First-line therapy for the treatment of osteoporosis in most patients is based on the use of antiresorptive agents, primarily oral bisphosphonates, in accordance with the recommendations of the American Association of Clinical Endocrinology (AACE) [47]. In patients who are intolerant of or have contraindications to oral bisphosphonates, intravenous bisphosphonates or denosumab are alternative options. Both categories of medications belong to the group of antiresorptive drugs. Bisphosphonates, regardless of the route of administration (oral or intravenous), directly inhibit osteoclast activity, whereas denosumab, a monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand (RANKL), exerts its antiresorptive effect indirectly [48]. Selective estrogen receptor modulators (SERMs) may be considered as an additional option, particularly in postmenopausal women who are at moderate risk. For patients at high risk of fracture who are unable to use oral therapy, treatment with denosumab or teriparatide (a recombinant form of parathyroid hormone), administered subcutaneously, is recommended. In patients at very high risk of fracture or those who have already sustained multiple fractures, initiation of anabolic agents (teriparatide) or agents with a dual mechanism of action, such as romosozumab, is recommended. Romosozumab is a monoclonal antibody that inhibits sclerostin, thereby promoting new bone formation and reducing osteoclast activity. It is administered subcutaneously once a year. It is important to emphasize that fracture risk should be reassessed after each new fracture, regardless of the time of occurrence, and that fracture risk increases after discontinuation of therapy [49].

In patients with rheumatoid arthritis (RA), adequate treatment of the underlying disease plays an additional role in bone protection. Conventional disease-modifying antirheumatic drugs (e.g., methotrexate) and biological agents (TNF inhibitors, IL-6 inhibitors, rituximab, abatacept) reduce disease activity and thereby decrease inflammation, which may have a beneficial effect on bone metabolism, although their direct impact on BMD is limited [50].

In adults who are beginning or continuing glucocorticoid therapy for longer than three months, the recommendations of the American College of Rheu-

ma preporukama Američkog reumatološkog koledža (engl. *American College of Rheumatology – ACR*) neophodno je sprovesti inicijalnu procenu rizika od fraktura odmah nakon početka terapije. Kod osoba starijih od 40 godina procena obuhvata kliničku evaluaciju prethodnih fraktura, *DXA* merenje sa vertebralnom procenom fraktura (*LVA*) ili rendgenski pregled kičmenog stuba, kao i izračunavanje *FRAX* rizika kod osoba starijih od 40 godina. Kod pacijenata sa umerenim, visokim ili veoma visokim rizikom od fraktura, snažno se preporučuje započinjanje farmakološke terapije – oralnim ili intravenskim bisfosfonatima, denosumabom ili teriparatidom. Kod pacijenata sa deficitom hormona, supstituciona terapija takođe može da doprinese modulaciji imunskog odgovora i smanjenju rizika od komplikacija povezanim sa autoimunskim bolestima. [50]. Navedene preporuke predstavljene su u Tabeli 4. sa odgovarajućim referencama. Tabela prikazuje različite vrste terapije za osteoporozu, uključujući primere lekova, njihov mehanizam delovanja i indikacije. Obu-

matology (ACR) emphasize the need for an initial fracture risk assessment immediately after beginning treatment. In individuals older than 40 years, this assessment includes clinical evaluation of prior fractures, DXA measurement with lateral vertebral assessment (LVA) or spinal radiography, as well as calculation of the FRAX risk. In patients with moderate, high, or very high fracture risk, initiation of pharmacological therapy – oral or intravenous bisphosphonates, denosumab, or teriparatide – is strongly recommended. In patients with hormone deficiencies, substitution therapy may also contribute to the modulation of the immune response and the reduction of the risk of complications associated with autoimmune diseases [50]. These recommendations are presented in Table 4 with the corresponding references. This table presents different treatments for osteoporosis, including examples of drugs, their mechanisms of action, and indications. It covers oral and intravenous bisphosphonates, RANKL monoclonal antibodies, selective estrogen receptor

Tabela 4. Pregled terapije osteoporoze: mehanizmi i indikacije

Vrsta terapije	Primeri lekova/metoda	Mehanizam delovanja	Indikacije/napomene	Reference
Oralni bisfosfonati	Alendronat, Ibandronat	Direktna inhibicija osteoklasta ⟶ smanjenje resorpcije kostiju	Terapija prvog izbora kod većine pacijenata	49
Intravenozni bisfosfonati	Zoledronat	Direktna inhibicija osteoklasta ⟶ smanjenje resorpcije kostiju	Alternativa kod intolerancije ili kontraindikacija na oralne bisfosfonate	49, 52
Monoklonalno antitelo protiv RANKL	Denosumab	Indirektno antiresorptivno dejstvo: inhibicija aktivacije osteoklasta	Pacijenti sa visokim rizikom od preloma, intolerancija na bisfosfonate	52
Selektivni modulatori estrogenih receptora (SERM)	Raloksifen	Modulacija estrogenih receptora u kostima ⟶ smanjenje resorpcije	Žene u postmenopauzi sa umerenim rizikom od preloma	49
Anabolički lekovi	Teriparatid (PTH 1–34)	Stimulacija osteoblasta ⟶ povećanje stvaranja nove koštane mase	Visok rizik od preloma, višestruke frakture, neefikasna antiresorptivna terapija	49
Lekovi sa dvostrukim mehanizmom	Romosozumab	Anaboličko dejstvo + smanjenje resorpcije	Veoma visok rizik od preloma	49

Table 4. Overview of osteoporosis therapy: mechanisms and indications

Type of therapy	Examples of drugs/methods	Mechanism of action	Indications/annotations	Reference
Oral bisphosphonates	Alendronate, Ibandronate	Direct inhibition of osteoclasts ⟶ reduction of bone resorption	First-line therapy in most patients	49
Intravenous bisphosphonates	Zoledronate	Direct inhibition of osteoclasts ⟶ reduction of bone resorption	Alternative in case of intolerance or contraindication to oral bisphosphonates	49, 52
Anti-RANKL monoclonal antibody	Denosumab	Indirect antiresorptive effect: inhibition of osteoclast activation	Patients with a high fracture risk, intolerance to bisphosphonates	52
Selective estrogen receptor modulators (SERMs)	Raloxifene	Modulation of estrogen receptors in bones ⟶ reduction of resorption	Postmenopausal women with a moderate risk of fracture	49
Anabolic drugs	Teriparatide (PTH 1–34)	Stimulation of osteoblasts ⟶ increased formation of new bone mass	High fracture risk, multiple fractures, ineffective antiresorptive therapy	49
Drugs action drugs	Romosozumab	Anabolic effect + reduction of resorption	Very high fracture risk	49

hvata oralne i intravenske bisfosfonate, monoklonalna antitela protiv RANKL, selektivne modulatore estrogenih receptora (SERM) i anaboličke lekove poput teriparatida i romosozumaba, uz napomenu kada se koja terapija primenjuje.

Fracture Liaison Services (*FLS*) predstavlja organizovani model čiji je glavni cilj smanjenje rizika od preloma kod osoba starijih od 50 godina, kroz pravovremeno postavljanje dijagnoze i započinjanje adekvatnog lečenja osteoporoze. Najnovija istraživanja pokazuju da je implementacija *FLS* protokola dovela do značajnog smanjenja rizika od preloma kod oba pola (za 13% kod žena i za 10% kod muškaraca), kao i do smanjenja stope mortaliteta za 18% kod žena i za 15% kod muškaraca [51]. Uvođenje *FLS* pristupa kod pacijenata sa AIRB ima poseban značaj jer omogućava pravovremenu dijagnostiku, rano započinjanje terapije i multidisciplinarni pristup koji uključuje reumatologa, endokrinologa i fizijatra [52].

ZAKLJUČAK

Osteoporoza je česta i ozbiljna komplikacija autoimunskih reumatskih bolesti koja značajno utiče na kvalitet života i funkcionalni status obolelih. Njeno nastajanje je multifaktorijalno: hronična inflamacija i imunološka disregulacija pospešuju aktivaciju osteoklasta i ubrzano resorptivno propadanje kosti, dok farmakološki tretmani, posebno dugotrajna terapija glukokortikoidima, dodatno inhibiraju osteoblastnu funkciju i smanjuju mineralnu gustinu kostiju. Osim toga, ograničena pokretljivost i smanjena fizička aktivnost kod pacijenata sa bolom i deformitetima doprinose progresiji osteoporoze.

Prevencija osteoporoze predstavlja osnovu očuvanja koštane mase i smanjenja rizika od preloma kod pacijenata sa autoimunskim reumatskim bolestima. Ključni preventivni pristupi uključuju prilagođenu fizičku aktivnost, obezbeđivanje adekvatnog unosa kalcijuma i vitamina D, kao i smanjenje faktora rizika povezanih sa medikamentoznom terapijom i životnim stilom. Pravovremeno identifikovanje pacijenata sa povećanim rizikom putem kliničke procene faktora rizika, *DXA* pregleda, *FRAX* indeksa i dodatnih metoda, kao što je *TBS*, omogućava rano uvođenje preventivnih mera i personalizovanog praćenja. Ukoliko prevencija nije dovoljna i dolazi do progresije osteoporoze, ciljano farmakološko lečenje, uzimajući u obzir tip i aktivnost osnovne bolesti, može značajno da smanji rizik od preloma i očuva funkcionalni kapacitet pacijenata. Farmakološke strategije, uključujući antiresorptivne i anaboličke lekove, trebalo bi da budu individualizovane, uzimajući u obzir tip i aktivnost osnovne bolesti, starost pacijenta i prisustvo komorbiditeta. Integraci-

modulators (SERMs), and anabolic drugs such as teriparatide and romosozumab, along with guidelines on when each treatment is used.

Fracture Liaison Services (FLS) represent an organized care model whose primary goal is to reduce fracture risk in individuals older than 50 years through timely diagnosis and initiation of appropriate osteoporosis treatment. Recent studies show that implementation of FLS protocols has led to a significant reduction in fracture risk in both sexes (by 13% in women and by 10% in men), as well as a reduction in mortality rates by 18% in women and by 15% in men [51]. The introduction of the FLS approach in patients with autoimmune rheumatic diseases is of particular importance, as it enables timely diagnosis, early initiation of therapy, and a multidisciplinary approach involving a rheumatologist, endocrinologist, and physiatrist [52].

CONCLUSION

Osteoporosis is a common and serious complication of autoimmune rheumatic diseases that significantly affects patients' quality of life and functional status. Its development is multifactorial: chronic inflammation and immune dysregulation promote osteoclast activation and accelerated bone resorption, while pharmacological treatments, particularly long-term glucocorticoid therapy, further inhibit osteoblast function and reduce bone mineral density. In addition, limited mobility and reduced physical activity in patients with pain and deformities contribute to the progression of osteoporosis.

Prevention of osteoporosis represents the cornerstone of preserving bone mass and reducing fracture risk in patients with autoimmune rheumatic diseases. Key preventive approaches include appropriately tailored physical activity, ensuring adequate intake of calcium and vitamin D, and reducing risk factors related to pharmacological therapy and lifestyle. Timely identification of patients at increased risk through clinical assessment of risk factors, DXA scanning, the FRAX index, and additional methods, such as TBS, enables early implementation of preventive measures and personalized follow-up. When prevention is insufficient, and osteoporosis progresses, targeted pharmacological treatment – taking into account the type and activity of the underlying disease – can significantly reduce the fracture risk and preserve patients' functional capacity. Pharmacological strategies, including antiresorptive and anabolic agents, should be individualized, taking into account the type and activity of the underlying disease, patient age, and the presence of comorbidities. Integration of therapy for the underlying disease with specific osteoporosis treatment significantly re-

ja terapije osnovne bolesti sa specifičnim tretmanom osteoporoze značajno smanjuje rizik od preloma i doprinosi očuvanju funkcionalnog kapaciteta pacijenata.

Multidisciplinarni pristup je ključan za optimizaciju strategija prevencije, praćenja i lečenja. Buduća istraživanja trebalo bi da se usmere ka ciljanim terapijama koje umanjuju gubitak koštane mase bez ugrožavanja imunske kontrole, kao i na unapređenje alata za procenu rizika kako bi se identifikovali pacijenti sa visokim rizikom od razvoja osteoporoze. Tretirajući osteoporozu kao sastavni deo lečenja autoimunskih bolesti, kliničari mogu da smanje rizik od preloma i da poboljšaju dugoročni kvalitet života obolelih.

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duces fracture risk and contributes to the preservation of functional capacity.

A multidisciplinary approach is essential for optimizing strategies of prevention, monitoring, and treatment. Future research should focus on targeted therapies that reduce bone loss without compromising immune control, as well as on improving risk assessment tools to better identify patients at high risk of developing osteoporosis. By treating osteoporosis as an integral component of the management of autoimmune diseases, clinicians can reduce the fracture risk and improve the long-term quality of life for affected patients.

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