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CONTEMPORARY ASPECTS OF DIAGNOSIS AND TREATMENT OF OSTEOPOROSIS AND OSTEOARTHRITIS

SAVREMENI ASPEKTI DIJAGNOSTIKE I LEČENJA OSTEOPOROZE I OSTEOARTRITISA

Novi Sad, 2022.

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INDICATIONS FOR INITIATION OF DRUG THERAPY AND MODERN THERAPY PROTOCOLS IN PATIENTS WITH OSTEOPOROSIS

INDIKACIJE ZA UVOĐENJE MEDIKAMENTNE TERAPIJE I SAVREMENI TERAPIJSKI PROTOKOLI KOD PACIJENATA SA OSTEOPOROZOM

Ksenija BOŠKOVIĆ

Summary

Introduction. Pharmacotherapy and physical therapy in patients with osteoporosis are aimed at increasing bone density and reducing the risk of fall in order to prevent fractures. Medications approved for the treatment of osteoporosis reduce the risk of fracture, either by reducing bone resorption or by stimulating bone formation. Bisphosphonates are most widely used antiresorptive agents that lower bone turnover markers to premenopausal levels and reduce fracture rates. Bisphosphonates bind to bone minerals and have a long-lasting effect. Long-term, continuous use of oral bisphosphonates is usually interspersed with drug breaks of 1-2 years to reduce the risk of atypical femoral fractures. Denosumab is a monoclonal antibody that also acts as an antiresorptive and it targets receptor activators of nuclear factor-κB ligand thus inhibiting the formation and function of osteoclasts. Denosumab is administered as a subcutaneous injection every 6 months. Anti-fracture effects of denosumab are similar to those of bisphosphonates, but there is a marked loss of antiresorptive effect 7 months after the last dose, which may lead to recurrent vertebral fractures. Anabolic drugs work by stimulating bone formation. Teriparatide and abaloparatide bind to the parathyroid hormone-1 receptor and are given as daily subcutaneous injection for up to 2 years. Romosozumab is a monoclonal antibody that targets sclerostin, stimulates bone formation and inhibits resorption. The effects of anabolics are transient, so it is necessary to switch to antiresorptive medications. **Conclusion.** It is a matter of great importance to determine the optimal strategy for cycles of anabolics, antiresorptive drugs and therapy-free periods.

Key words: Osteoporosis; Drug Therapy; Diphosphonates; Denosumab; Anabolic Agents; Bone Density; Bone Density Conservation Agents; Clinical Protocols

Sažetak

Uvod. Medikamentno i fizikalno lečenje osteoporoze je usmereno na povećanje koštane gustine i smanjenje rizika za pad kako bi se sprečio nastanak preloma. Medikamentna terapija koja se primenjuje za lečenje osteoporoze smanjuje rizik od preloma, bilo smanjenjem resorpcije kostiju ili stimulisanjem formiranja kostiju. Bisfosfonati su najšire korišćeni antiresorptivni lekovi, smanjujući markere koštanog metabolizma na niske koncentracije u premenopauzi i smanjujući stopu preloma. Bisfosfonati se vezuju za koštane minerale i imaju dugotrajni efekat. Dugoročna, kontinuirana upotreba oralnih bisfosfonata obično je isprekidana odmorima od lekova 1-2 godine, kako bi se smanjio rizik od atipičnih preloma butne kosti. Denosumab je monoklonsko antitelo koje takođe deluje antiresorptivno, a usmereno je na aktivator receptora nuklearnog faktora-κB liganda, i na taj način inhibira formiranje i funkciju osteoklasta. Denosumab se primenjuje supkutanom injekcijom svakih šest meseci. Antifrakturni efekti denosumaba su slični onima bisfosfonata, ali postoji izražen gubitak antiresorptivnog efekta sedam meseci nakon poslednje doze, što može dovesti do ponovnih preloma pršljenova. Anabolički lekovi deluju tako što stimulišu formiranje kostiju. Teriparatid i abaloparatid su usmereni na receptor paratiroidnog hormona-1 i daju se svakodnevnom potkožnom injekcijom do dve godine. Romosozumab je monoklonsko antitelo koje je usmereno na sklerostin, stimuliše formiranje kostiju i inhibira resorpciju. Efekti anaboličkih agenasa su prolazni, pa je potreban prelazak na antiresorptivne lekove. **Zaključak.** Potrebno je da se odredi optimalna strategija za cikluse anabolika, antiresorptivnih lekova i perioda bez terapije.

Ključne reči: osteoporoza; farmakoterapija; bisfosfonati; denosumab; anabolički agensi; gustina kostiju; antiresorptivni lekovi; klinički protokoli

Introduction

Osteoporosis (OP) is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, which consequently leads to an increased risk of fracture [1]. According to the World Health Organization (WHO), it is a major socio-economic and health issue considering that it affects about 10% of the population [2]. OP prevalence is at epidemic proportions, and since being asymptomatic until the fracture occurs, it represents a "silent epidemic". OP is associated with disability and mortality, and only a small proportion of the affected population undergoes treatment (10% to 20%). The

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Abbreviations

OP – Osteoporosis
BMD – Bone Mineral Density
WHO – World Health Organization
SERMs – Selective Estrogen Receptor Modulators
IL – Interleukin
TNF-α – Tumor necrosis factor α
TGF-β – Transforming growth factor β
GTPaze – Hydrolase enzymes
RANKL – Receptor activator of nuclear factor-κB ligand
OPG – Osteoprotegerin
PTH – Parathyroid hormone
FRAX – Fracture Risk Assessment Tool

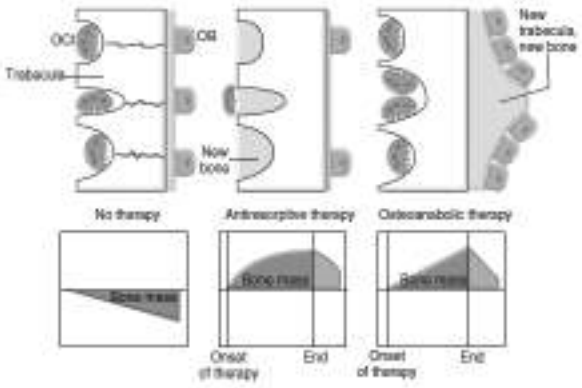

Figure 1. Changes in bone remodeling and bone mineral density under treatment with antiresorptive and osteoanabolic drugs
Slika 1. *Promene u remodeliranju kostiju i gustini kostiju pod antiresorptivnim i osteoanaboličkim lekovima*

increase in overall population, as well as the percentage of elderly, progress in the field of medicine and improvement in health quality resulting in a prolongation of life, could, altogether, explain the higher prevalence of OP in the last 10 years. Advances in technology enable early detection of osteoporosis before symptoms or complications appear. One could anticipate that the increase in the percentage of the elderly and their lifestyle will double the number of patients in the next 50 years. According to evidence-based protocols for diagnosis, prevention, and treatment of OP, the goals of OP treatment are: 1) prevention of fractures, 2) stabilization and increase of bone mass, 3) fracture symptom relief and correction of bone deformities, and 4) maintenance of functional capacity [3, 4]. Additionally, it is necessary to change unhealthy habits (smoking, sedentary lifestyle, poor nutrition), be physically active and exercise, as well as start vitamin D and calcium supplementation [5]. Medications indicated for the treatment of OP work by reducing bone resorption (antiresorptives) [6] or promoting the formation of bone tissue (osteoanabolics) **(Figure 1)**.

Antiresorptive drugs

Antiresorptive drugs reduce the frequency of fractures by 50% to 60%. Inhibitors of resorption used in the treatment of OP are: estrogens, selective estrogen receptor modulators (SERMs), bisphosphonates and calcitonin [7]. They prevent further bone loss, but cannot significantly increase bone mass.

Estrogens

Hormones play an important role in modulating osteoblast function. In both sexes, estrogens are the primary determinants important in maintaining bone health [8]. Estrogens most effectively stop the phase of accelerated bone loss in the early postmenopausal period. The mechanism of action of estrogen regarding the inhibition of bone resorption is not fully elucidated. Estrogen regulates the production of cytokines, such as interleukin (IL-6, IL-1) and tumor necrosis factor α (TNF-α). Functional estrogen receptors are placed on osteoclasts. They are indicated for all conditions with a risk of OP during the reproductive period of a woman. Bone loss is most pronounced in early postmenopause, thereby this therapy is given to 80% of women in perimenopause, respectively in the first three years of postmenopause. A low effective dose of estrogen significantly reduces the risk of falls, which is an important risk factor for fractures, and greatly increases BMD in all skeletal locations and reduces the risk of fractures by 25% to 40%.

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) have the same effect on the skeletal and cardiovascular system as estrogen including also a reduction of lipid serum concentration, but they do not share the accompanying side effects on the uterus and breast that occur with estrogen therapy [8]. The main representative of this class of drugs is raloxifene, a non-steroidal benzothiophene, that binds to estrogen receptors and inhibits bone resorption without stimulating the endometrium and breast glandular tissue in postmenopausal women. Furthermore, it increases the production of transforming growth factor β (TGF-β) in bones. Research results showed that raloxifene reduces the incidence of breast cancer and vertebral fractures, but due to the risk of venous thromboembolism and stroke, it should be used carefully.

Bisphosphonates

Bisphosphonates are analogues of pyrophosphate with different physical and chemical properties [9]. Bisphosphonates are the first-line therapy for OP and other metabolic bone diseases due to their highly marked antiresorptive effect and ability to affect areas of increased bone resorption [10]. They are absorbed in the initial part of the small intestine, but the absorption of the orally taken drug is poor and decreases if taken simultaneously with calcium supplements, as well as after a meal. Bisphophonates should be taken on an empty stomach with plenty of water and food is not allowed for the next 30 minutes after ingestion. Bisphosphonates show no evidence of metabolism. 20% to 50% of the administered dose accumulate in the bones, while a part is excreted by the kidneys. Bisphosphonates affect osteoclast function. Alendronate, risendronate, ibandronate and zoledron-

ic acid are the most commonly prescribed drugs [11, 12]. They reduce GTPase (hydrolase enzymes) activity required for cytoskeletal organization and vesicular trafficking in osteoclasts, which, consequently inactivate osteoclasts and reduce bone resorption. Indirectly, but more slowly, they suppress osteoblast function, in other words bone formation. The safety profile of bisphosphonates in the long-term treatment and prevention of OP in postmenopausal women shows no adverse effects on skeletal health [13]. A few years ago, osteonecrosis of the bone, especially the jaw bone, was reported as an adverse event of bisphosphonate therapy [14]. Excessive inhibition of bone resorption is probably the primary mechanism of pathogenesis of this condition, although other factors also contribute to its development. It has also been shown that alendronate is more effective in preventing bone loss than alfacalcidol in the treatment of glucocorticoid induced OP [15]. Risedronate, a third-generation bisphosphonate, increases bone mass and reduces the risk of fractures and is indicated for the prevention and treatment of OP. It suppresses bone resorption less, which results in lower incidence of osteonecrosis. Ibandronate is a third-generation bisphosphonate and is administered for the prevention and treatment of OP. It is the first registered bisphosphonate given once a month orally or every three months intravenously. Additionally, it reduces the risk of vertebral fractures [16]. Zoledronic acid is a bisphosphonate that is given by intravenous infusion once a year and is characterized by strong suppression of bone resorption. Bisphosphonates are indicated for the prevention and treatment of OP in men and women with low BMD at the spine and hip, when it is necessary to increase BMD bone density as soon as possible and to suppress bone resorption more strongly. They are initiated for the treatment in patients with severe OP with fractures and an increased risk of hip fracture, as well as in patients with secondary OP.

Calcitonin

Calcitonin is a polypeptide produced by the C-cells of the thyroid gland which reduces serum calcium concentrations and suppresses osteoclast activity. Calcitonin binds to receptors on osteoclasts leading to a flattening of the ruffled border and further bone resorption inhibition. Calcitonin is administered in the form of intramuscular injections or a nasal spray for the treatment of OP. It maintains or increases the BMD of the axial skeleton and reduces the risk of vertebral fractures. It is recommended for women with OP and menopause lasting for more than 5 years. It also has an analgesic effect, probably mediated by binding to specific places in the brain and modifying the descending serotonin pathway in the genesis of pain.

Denosumab

Denosumab is a monoclonal antibody which acts as a receptor activator of nuclear factor-κB ligand (RANKL) inhibitor [10, 16]. Preosteoclast, the precursor of osteoclasts, expresses a receptor on its surface, receptor activator of nuclear factor-κB (RANK), a protein member of the TNF receptor superfamily. RANK is activated via osteoblast-produced RANKL thereby inducing differentiation of preosteoclast into an active osteoclast. Denosumab inhibits osteoclast maturation by binding to and inhibiting RANKL. This reaction mimics the natural action of osteoprotegerin (OPG) and protects the bone from resorption. The primary effect is inhibition of osteoclast recruitment, but if discontinued, bone mass will rapidly decrease unless another antiresorptive agent is used. The advantage of this antiresorptive agent is the convenient dosing regime with subcutaneous application twice a year.

Table 1. Drugs used and approved for the treatment of osteoporosis
Tabela 1. *Lekovi koji se koriste i odobreni su za lečenje osteoporoze*

	Oral daily *Oralno dnevno*	Oral weekly *Oralno nedeljno*	Oral montly *Oralno mesečno*	Subcutaneus daily/*Supkutano dnevno*	Subcutaneus every 6 months/*Supkutano svakih 6 meseci*	Injection quarterly/*Injekcija kvartalno*	Infusion annually *Infuzija godišnje*
Alendronate *Alendronat*	10 mg	70 mg					
Risedronate *Rizedronat*	5 mg	35 mg	150 mg				
Ibandronate *Ibandronat*			150 mg			3 mg	
Zoledronate *Zoledronat*							5 mg
Strontium ranelate/*Stroncijum renalat*	2 g						
Teriparatide *Teriparatid*				20 µg			
Abaloparatide *Abaloparatid*				80 µg			
Denosumab *Denosumab*					60 mg		

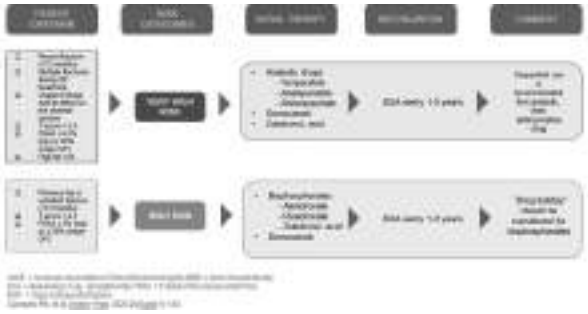

Figure 2. Fracture risk assessment as reported by AACE (taken from Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis 2020 update. Endocr Pract. 2020;26(1):1-46.)

Slika 2. *Određivanje rizika za prelom prema AACE (preuzeto iz Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis 2020 update. Endocr Pract. 2020;26(1):1-46.)*

Bone formation stimulators or osteoanabolic drugs

In elderly people with OP, the function of osteoblasts is impaired therefore their capacity for producing new bone tissue in order to fill defects caused by osteoclast activity is insufficient [17]. Osteoanabolic drugs directly or indirectly affect osteoblast cells to form bone tissue.

Parathyroid hormone

Parathyroid hormone (PTH) administered intermittently in small doses has an anabolic effect on bone. On the other hand, when it is administered continuously in large doses, it induces bone resorption, primarily trabecular bone loss in the axial skeleton. Increased bone resorption during PTH treatment leads to cortical bone porosity with thickening of the endosteum and periosteum, but substantially increases bone density [18]. The anabolic effect of PTH is somewhat weaker in case of previous bisphosphonates usage, and is accompanied by a smaller increase of biochemical bone metabolism markers**.** It is essential to optimize the treatment plan with PTH, because bisphosphonates have proven to be effective for the treatment of OP and will reduce the anabolic effect of PTH. This treatment option is recommended for severe OP in older people who are facing reduced osteoblastogenesis. Teriperatide (1-34 PTH) is given subcutaneously over a period of two years.

Strontium ranelate

Considering its mechanism of action, this drug promotes bone formation via stimulation of immature osteoblasts division and reduces bone resorption through inhibition of osteoclast differentiation and activity. In various animal models, strontium ranelate increases trabecular bone mass, the number and thickness of bone tissue trabeculae. Strontium binds to the surface of the apatite crystal, and to a small extent replaces the calcium atom in the mineral crystals of the newly created bone. This medication prevents postmenopausal osteoporotic fractures, both vertebral and non-vertebral [2, 3]. Strontium activates calcium receptors of the parathyroid gland, which results in a decrease of the calcium and PTH blood concentration followed by an increase of the phosphorus concentration. Calcium

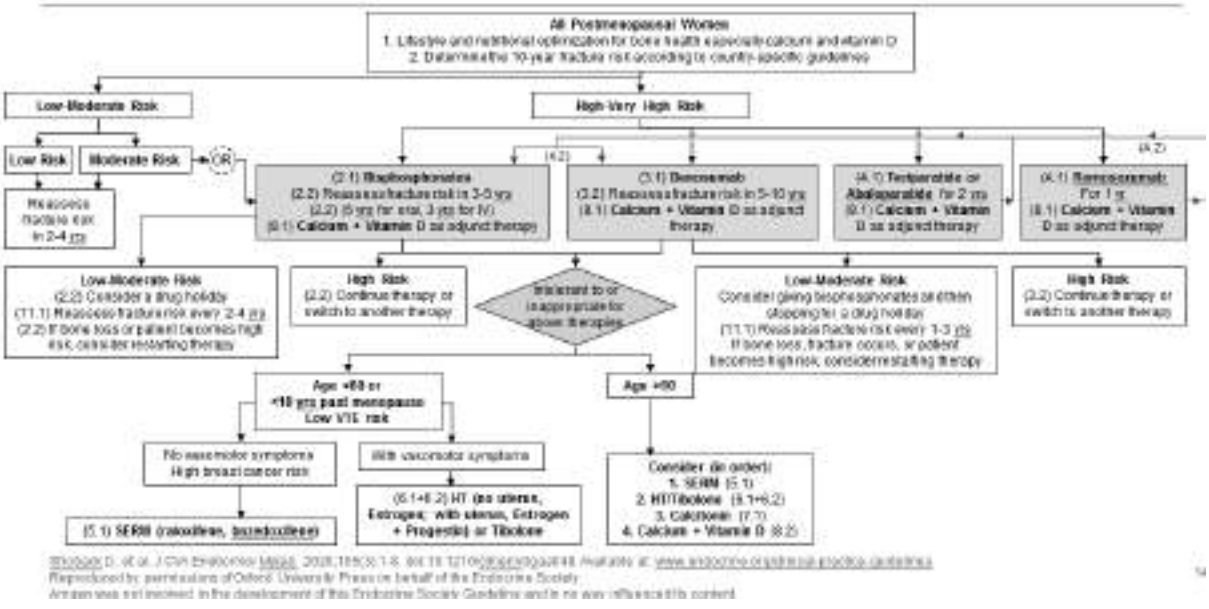

Figure 3. Postmenopausal OP treatment protocol (Taken from Shoback D, et al. J Clin Endocrinol Metab 2020;105(3):1-8)

Slika 3. *Protokol lečenja osteoporoze u postmenopauzi (Preuzeto iz Shoback D, et al. J Clin Endocrinol Metab 2020;105(3):1-8)*

released during osteoclast processes in the cell acts through a feedback mechanism by inhibiting osteoclasts and at the same time stimulating the proliferation of preosteoblasts. Given that strontium is a metal that can incorporate into the bone, it consequently increases BMD by 50% **(Table 1)**.

Recommendations and protocols for osteoporosis treatment

– Antiresorptive drugs (alendronate, risedronate, zoledronic acid, denosumab) should be recommended for women with OP to reduce the risk of hip and vertebral fractures [2, 3].

– Men who have clinically recognized OP should also be recommended anti-osteoporosis therapy in order to reduce the risk of fractures [4].

– Fracture risk should be assessed prior to the initiation of pharmacotherapy. It is determined by factors such as age, previous fractures, T-score at the lumbosacral spine, FRAX index [19, 20]. Treatment should be administered for a sufficiently long time (10 years or more) [21] **(Figure 2)**.

– Measurement of bone density by osteodensitometry should be performed after 1 or 2 years of drug administration in order to assess the progression of OP (T-score). Concentration of bone turnover markers should be obtained from the blood to monitor the effectiveness of therapy [22].

– Menopausal estrogen therapy is not recommended as first line treatment for women with OP [23]. It is indicated in patients with a high risk of fractures and intolerance to previously applied bisphosphonate or biological therapy [24].

– Consider treating women over 65 with osteopenia who have a high risk for fractures considering family history, risk factors, risks of fractures (FRAX index), the benefits [25] **(Figure 3)**.

Conclusion

Long-term follow-up and treatment of patients with OP is necessary. Assessment of fracture risk should precede initiation of adequate pharmacological treatment. The use of antiresorptive or anabolic agents can reduce the risk of fractures in patients even without a measurable increase in bone mineral density. Although novel drugs enhanced osteoporosis treatment, a lot of room remains for improvement.

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DIAGNOSIS OF OSTEOPOROSIS AND PREVENTION OF OSTEOPOROTIC FRACTURES

DIJAGNOSTIKA OSTEOPOROZE I PREVENCIJA NASTANKA OSTEOPOROTIČNOG PRELOMA

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Summary

Introduction. Osteoporosis is a metabolic bone disease characterized by reduced bone mineral density and damage to the bone microarchitecture, which leads to bone fragility, thus increasing the risk of osteoporotic fractures. While different diagnostic methods can be employed for detecting bone mineral density decrement in a timely manner, dual energy X-ray absorptiometry remains the gold standard in research and clinical practice. **Bone mineral density estimation methods.** Osteoporosis can be diagnosed through conventional radiography, quantitative ultrasonography, quantitative computed tomography, and magnetic resonance. Nonetheless, dual energy X-ray absorptiometry is the gold standard in the diagnosis of osteoporosis on which further treatment and monitoring are based. The dual energy X-ray absorptiometry apparatus is equipped with the Fracture Risk Assessment Tool, which estimates the 10-year probability of a major fracture and hip fracture due to osteoporosis. The use and interpretation of osteoporosis diagnostic evaluation modalities is based on the International Society for Clinical Densitometry guidelines for diagnosing osteoporosis in adults and children. According to the International Society for Clinical Densitometry recommendations, the aforementioned quantitative visualization modalities should be used alongside laboratory analyses of bone metabolism markers to supplement diagnostics and monitor treatment efficacy in patients suffering from osteoporosis. **Conclusion.** Assessment of risk factors and early diagnosis are prerequisites for timely treatment and effective monitoring, which is necessary for arresting the progression of bone mineral density loss and preventing the occurrence of osteoporotic fractures.

Key words: Osteoporosis; Diagnosis; Osteoporotic Fractures; Absorptiometry, Photon; Risk Assessment; Densitometry; Risk Factors

Sažetak

Uvod. Osteoporoza je metabolička bolest kostiju koju karakteriše smanjena mineralna koštana gustina i oštećenje mikroarhitekture kostiju što dovodi do krhkosti kostiju i nastanka osteoporotičnog preloma. Radi pravovremene dijagnoze smanjenja mineralne koštane gustine koriste se modaliteti dijagnostičkih procedura od kojih je zlatni standrad dvostruka X-zračna apsorpciometrija (engl. *Dual energy X–ray absorptiometry*). **Metode procene mineralne koštane gustine.** U metode za dijagnozu osteoporoze mogu se uvrstiti: konvencionalna radiografija, kvantitativna ultrasonografija, kvantitativna kompjuterizovana tomografija, magnetna rezonancija i dvostruka X-zračna apsorpciometrija kao zlatni standard u postavljanju dijagnoze osteoporoze na čemu se zasniva dalje lečenje i praćenje. U sklopu dvostruke X-zračne apsorpciometrije je inkorporirana alatka (engl. *The Fracture Risk Assessment Tool*) koja procenjuje 10-godišnju verovatnoću velikog (ozbiljnog) preloma i preloma kuka uzrokovanog osteoporozom. Međunarodno društvo za kliničku denzitometriju (engl. *The International Society for Clinical Densitometry*) dalo je preporuke za dijagnostikovanje osteoporoze kod adultne populacije i dečjeg uzrasta u smislu korišćenja i tumačenja modaliteta dijagnostičke evaluacije osteoporoze. Uz modalitete kvantitativne vizualizacije koriste se i laboratorijske analize markera koštanog metabolizma radi dopune dijagnostike i praćenja lečenja pacijenata koji boluju od osteoporoze. **Zaključak.** Sagledavanje faktora rizika, rana dijagnoza, a samim i tim pravovremeno lečenje, uz monitoring, ključni su faktori kako bi se zaustavila progresija gubitka mineralne koštane gustine i prevencije nastanka osteoporotičnih preloma.

Ključne reči: osteoporoza; dijagnoza; osteoporotični prelomi; apsorpciometrija; procena rizika; denzitometrija; faktori rizika

Introduction

Bone is a dynamic tissue that continuously undergoes a process of modeling and remodeling in order to maintain its strength and rigidity. Bone remodeling capacity is determined by the functioning of osteoblast and osteoclast cells, whereby any imbalance in this process leads to osteoporosis, which can be of primary or secondary type [1]. Osteoporosis is a metabolic bone disease characterized by reduced bone mineral density (BMD) and compromised bone microarchitecture, leading to bone fragility and increased fracture risk. Bone fractures, especially those of the spine and hip, result in increased morbidity and mortality. Until recently, every third woman and one in five men suffered a fracture due to osteoporosis after the age of 50 [2]. As osteoporosis is a metabolic disease, owing to overall population aging, its frequency exhibits an upward trend, whereby currently 50% of women and 25% of men are expected to break a bone during their lifetime as a result of metabolic bone disease

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Abbreviations

BMD – Bone mineral density
ROI – region of interest
QUS – Quantitative ultrasound
DXA – Dual energy X –ray absorptiometry
QCT – Quantitative computed tomography
pQCTP – peripheral Quantitative computed tomography
PL-QCT – phantom-less quantitative computed tomography
LDCT – low-dose computed tomography
MRI – Magnetic resonance imaging
ISCD – The International Society for Clinical Densitometry
WHO – World Health Organization
TBS – Trabecular bone score
SD – standard deviation
VFA – vertebral fracture assessment
GSQ – semi-quantitative
OVD – osteoporotic vertebral deformity
BMC – bone mineral content
FRAX – Fracture Risk Assessment

[3]. The result of metabolic bone disease is weakened bone, leading to an increased risk of fragility fractures. An estimated 9 million osteoporotic fractures occur every year worldwide, which is equivalent to one such incident every 3 seconds [4]. However, the actual figures are likely to be much higher because many osteoporotic fractures go undetected.

As bone homeostasis depends on bone resorption by osteoclasts and bone formation by osteoblasts, imbalance in this process will result in osteoporosis. It has been shown that osteoblasts and osteoclasts can communicate with each other through direct cell−cell contact, cytokines, and extracellular matrix interaction [5]. Risk factors for BMD reduction or loss include lower body mass index, presence of kyphosis, use of glucocorticoids, early menopause onset, and presence of comorbidities. While these factors contribute the most to vertebral osteoporotic fracture occurrence [6], rheumatic inflammatory diseases are an independent risk factor for the development of osteoporosis. As established by Wang Y et al., individuals suffering from psoriatic arthritis are at an increased risk of osteoporosis and fractures compared to age- and sex-matched controls. These authors also found a link between higher psoriatic arthritis activity and lower BMD, and thus greater osteoporotic fracture risk [7]. Psoriatic arthritis can lead to local periarticular and generalized bone loss. Many risk factors contribute to this association, such as chronic joint inflammation, glucocorticoid use, genetics, and the effects of the hormone estrogen. However, it is presently unclear whether this is a consequence of treatment, immobility, or disease activity [8]. Older age, BMI < 18.5 kg/m^2, female sex, and glucocorticoid use are also associated with lower BMD in rheumatic patients [9]. The main clinical consequence of the disease is a fracture, which typically occurs due to minor trauma [10]. Poorer quality of life is also reported by individuals with reduced BMD, as well as those with a history of vertebral fractures, especially if several such fractures had been sustained [11]. Consequently, attention must be focused on the identification of high fracture risk and timely osteoporosis diagnosis. To reduce the osteoporotic fracture incidence, it is also necessary to increase public awareness of this issue through national campaigns [12].

Bone mineral density estimation methods

Osteoporosis is a silent disease, as no symptoms are evident until a fracture occurs [12]. Bone composition includes mineral - mainly calcium hydroxyapatite - embedded in type I collagen, and specialized proteins forming the bone matrix. As calcium is much more effective in absorbing radiation compared to protein or soft tissue, this characteristic facilitates imaging. For example, when X-ray tomography is used, the X-ray energy that is absorbed by calcium in a particular section reflects bone mineral content (BMC), which is divided by the area or volume of the scanned bone to estimate bone densitometry [13]. The ideal locations for BMD measurements are sites with high trabecular/cortical ratio, denoted as regions of interest (ROIs). As extant evidence indicates that the axial skeleton is best suited for detecting changes in trabecular architecture and density, it is the preferred screening site. Nevertheless, other sites characterized by high trabecular/cortical ratio–such as the forearm, tibia, and calcaneus–can also be considered in BMD analysis [14].

1. Conventional radiography: X-ray scans are useful for visualizing gross morphology, but do not allow for a quantitative assessment of the extent of bone loss. X-ray absorption is proportional to the amount of calcium present in the bones, and a BMD decline by 20−40% results in a decrease in bone mass [13]. Thus, when conventional radiography is used in the radiologic evaluation of osteoporosis, cortical thinning, increased radiolucency, and altered trabecular patterns can be identified, and vertebral fractures can be evaluated [15].

2. Quantitative ultrasound: Quantitative ultrasound (QUS) is a noninvasive procedure for investigating skeletal disorders and is typically applied to the calcaneus and phalanx. Still, other long-bone sites can also be assessed, such as the tibial and radial mid-shaft. As the QUS devices are portable, it is essential to consider environmental conditions that can affect measurement results [14]. QUS is particularly useful for detecting changes related to age, menopause, lifestyle factors, and clinical factors that are known to increase the risk of osteoporosis. However, its capability is limited and its accuracy is inferior to that of DXA analysis, which remains the gold standard for the diagnosis of osteoporosis. Still, in the absence of DXA, QUS may be useful for identifying patients at risk of fracture [16], while noting that the heel is presently the only validated skeletal site for the clinical use of QUS in osteoporosis. When validated heel QUS devices are available, these can also be used to predict the fragility fracture risk in postmenopausal women (hip, vertebral, and global fracture risk) as well as men over the age of 65 (hip and non-vertebral fractures).

However, as findings yielded by heel QUS often diverge from those obtained through central DXA, QUS should be used with caution and its findings cannot be considered to evaluate the osteoporosis treatment efficacy [17, 18].

3. Quantitative computed tomography: When DXA is not available, Quantitative computed tomography (QCT) can be adopted for BMD assessment as a suitable alternative due to its high accuracy. Measurements are taken between T12 and L4 and are subsequently converted to physical density (vBMD, g/cm^3) based on a reference sample. Although no official guidelines presently exist, osteoporosis is typically diagnosed when BMD < 80 mg/cm^3 is measured. The main drawback of this approach is greater radiation exposure (60 μSv for single-energy CT) compared to DXA analysis (1 μSv). On the other hand, the main advantages of CT-based methods compared to DXA include the possibility of identifying artifacts induced by degenerative joint disease or arterial calcification (which are common in elderly individuals) and the capacity to restrict measurements to the trabecular bone. Peripheral QCT (pQCT) is also useful in this context, as it requires a much lower radiation dose, but can only be used for areas in which bone-to-soft tissue ratio is relatively high, such as distal radius and ulna. At present, however, this technique is mainly used for treatment control [14]. Still, several authors advocate using pQCT of the forearm at the ultra-distal radius to predict hip, but not spine, fragility fractures in postmenopausal women, but do not recommend such risk assessments for men [17]. Similarly, owing to limited evidence, spine QCT for hip fracture prediction is rarely utilized in clinical practice irrespective of the patient's sex. Therefore, for predicting hip fractures in postmenopausal women and older men, it is necessary to measure total femur trabecular BMD via QCT or hip BMD through DXA. Recently, phantom-less quantitative computed tomography (PL-QCT) system was developed to measure BMD and diagnose osteoporosis, and the preliminary evidence indicates that this novel approach can predict osteoporosis with relatively high accuracy and precision comparable to that achieved by DXA [19].

4. Magnetic resonance imaging: As Magnetic resonance imaging (MRI) does not rely on ionizing radiation, bone is visualized as low-intensity spaces in the high-intensity soft tissue. When used for BMD measurements, focus is given to the parts of the peripheral skeleton where the trabecular area is larger, as that results in greater contrast with fat in the bone marrow. The main advantage of this technique is its noninvasive nature, as patients are not exposed to harmful radiation [14]. However, even the most advanced MRI techniques are inferior to bone densitometry which is more cost-effective and lacks contraindications, such as patient weight and abdominal circumference, and presence of any metals (including pacemakers) [20]. As the patient has to be placed in a confined area during the MRI scan, claustrophobia can also be an issue, while even slight movements can result in blurred images.

5. Dual-energy X-ray absorptiometry: Dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring BMD and thus for the diagnosis of osteoporosis. It is also recommended for monitoring changes in BMD over time and for the determination of fracture risk [21]. However, according to the International Society for Clinical Densitometry (ISCD) guidelines, DXA should only be performed by clinicians with specialized training [22], and the findings should be interpreted in line with the reliable reference ranges. The World Health Organization (WHO) definition of osteoporosis, and published BMD references ranges, can be helpful for this purpose, but do not consider differences in bone size. Because DXA is a two-dimensional technique, bone depth cannot be measured, and the output (denoted as areal BMD or aBMD) is affected by bone size variability. Consequently, mathematical models need to be adopted to correct aBMD for bone size, but none of the presently available tools adequately account for the variations in soft tissue surrounding bone [23]. Therefore, although BMD (as a quantitative parameter) is a major determinant of bone strength and fracture risk, in practice, trabecular bone score (TBS) is typically used as an indicator of bone quality [7]. As both BMD and TBS are independent predictors of fragility fractures, they are the main factors in the WHO clinical definition of osteoporosis [24, 25].

According to the ISCD guidelines, BMD in hip and spine should be measured using DXA apparatus, whereby women older than 65 and men older than 70 should be assessed regardless of risk factors. Moreover, when risk factors are present, DXA should be available to postmenopausal women and men aged 50–70 years. This includes adults with a medical condition or history of pharmacological therapy known to reduce bone mass, as well as perimenopausal women with an increased fracture risk, such as those with low body weight, history of low-trauma fractures and high-risk medications, and postmenopausal women discontinuing estrogen replacement therapy. DXA should also be performed regularly to monitor treatment effectiveness as well as when pharmacological therapy for osteoporosis is indicated. When interpreting DXA findings, it should be noted that BMD in children, as well as females prior to menopause and in males below the age of 50 are reported separately, and are based on Z-scores, not T-scores. A Z-score ≤ -2.0 is defined as "below the expected range for age" while that exceeding -2.0 is "within the expected range for age." While in men aged below 50 osteoporosis cannot be diagnosed on the basis of BMD alone [26], the WHO diagnostic criteria may be applied to perimenopausal women. The 33% forearm (one-third radius) site is recommended if hip and/or spine measurements cannot be taken or interpreted, as well as for individuals diagnosed with hyperparathyroidism and/or severe obesity (i.e., those over the weight limit of the DXA table) [17, 26].

T-score was introduced to simplify the interpretation of BMD findings and facilitate comparisons across

different devices, as an individual's BMD is compared with the mean value pertaining to a young healthy reference population, and the difference is expressed in terms of standard deviation (SD). Alternatively, Z-score can be calculated, reflecting the number of SDs by which BMD in an individual differs from the mean value expected for age and sex. Although Z-score is not used for osteoporosis diagnosis in adults, it can provide insight into the individual's fracture risk compared to age- and sex-matched cohort [17, 27]. The Z-score is the most clinically relevant when secondary osteoporosis in younger patients is being considered, whereby a value below -1.5 warrants further comprehensive investigations [28].

According to the WHO, a BMD measurement that is within 1.0 SD of the mean for young healthy adults is considered normal, while T-scores in the -1.0 to -2.5 range are osteopenic, and those below -2.5 are interpreted as osteoporotic.

Which skeletal sites (regions of interest) should be measured? When measuring ROI L1–L4, it is necessary to exclude the vertebrae affected by local structural changes or artifacts. Thus, while ideally all four vertebrae should be included, even two may suffice, but the diagnosis cannot be established based on only one vertebra, and would require further assessment according to another ROI. A vertebra is excluded if there is more than a 1.0 SD difference between that particular vertebra and the adjacent vertebrae. A lateral scan should not be used for diagnosis, but may have a role in follow-up. When the ROI is located in the hip and forearm, the neck of the femur and the total proximal part of the femur are measured and analyzed. However, currently available data is insufficient to determine whether the mean T-score for bilateral hip BMD can be used for diagnosis. When the ROI is located in the forearm, 33% radius in the non-dominant hand is actually recorded [17].

Indications for vertebral fracture assessment: Lateral imaging of the spine with standard radiography is indicated when T-score is below -1.0 and one or more of the following factors are present: age ≥ 70 years (women) or ≥ 80 years (men), height loss > 4 cm, self-reported vertebral fracture, and glucocorticoid therapy equivalent to ≥ 5 mg/day for ≥ 3 months [17]. When Indications for vertebral fracture assessment (VFA) is combined with BMD, previously unidentified vertebral fractures can be detected, thereby facilitating clinical diagnosis of osteoporosis. Therefore, this method is particularly beneficial for the first BMD assessment in postmenopausal women [29]. In this context, the Genant's semi-quantitative (GSQ) criteria may also be valuable for detecting osteoporotic vertebral deformities (OVDs), also known as osteoporotic vertebral fractures, as the findings yielded by epidemiological studies and clinical trials are highly promising [30]. According to available guidelines, OVDs resulting from osteoporotic fractures are classified as (1) wedge fractures − causing anterior height loss, (2) biconcave fractures − causing central compression of the end-plate regions and maintenance of anterior and posterior height, and (3) crush fractures − causing compression of the entire vertebral body. Likewise, based on the degree of height reduction, each vertebra is scored as follows: Mild (or Grade 1) − 20–25% loss of vertebral height; Moderate (or Grade 2) − 25–40% loss of vertebral height; and Severe (or Grade 3) − >40% loss of vertebral height [30, 31].

Trabecular bone score: Trabecular bone score (TBS) is a recently developed analytical tool for conducting gray-level texture measurements on DXA images of lumbar spine, allowing trabecular microarchitecture to be examined in more detail. However, as this is a novel technique, it must be subjected to further independent evaluations to ascertain the association of the obtained findings with fracture risk before it can be employed in clinical practice [33]. Therefore, at present, TBS analysis should be considered solely as a supplement to other bone fracture risk assessment modalities and in the differential diagnosis of structural bone disorders in secondary osteoporosis [32].

Total Body Composition: Total body composition should be considered in patients with muscle weakness or poor physical functioning to assess fat and lean mass, as well as in all individuals that are expected to experience body weight gain or loss that exceeds 10%, as this will affect the bone-to-soft tissue ratio. This is particularly important for patients living with HIV, as well as those using antiretroviral agents associated with a risk of lipoatrophy, and for obese patients undergoing bariatric surgery or those placed on a weight loss regimen with anticipated large weight loss [17].

Dual-energy X-ray absorptiometry contraindications: While DXA cannot be performed during pregnancy, it is also unfeasible in individuals that exceed the table weight limit, and those that have been recently administered contrast material and/or artifact, as radiopharmaceutical agents may interfere with the accuracy of DXA results [17].

Peripatetic and orthopedic DXA use: When evaluating hip and knee arthroplasty, the ROI should include the periprosthetic metaphyseal and diaphyseal bone around and away from the implant (Gruen zone) [17]. While intervals between measurements will depend on the patient's clinical status, 12 months is recommended after starting or changing therapy, followed by longer intervals once a stable therapeutic response has been achieved. In patients suffering from conditions associated with rapid bone loss, such as those that require glucocorticoid treatment, testing is performed more frequently [17].

Densitometry in infants and young children: According to the currently available guidelines, densitometric criteria should never be used in isolation when diagnosing osteoporosis in children and adolescents [33]. In the absence of vertebral compression (crush) fractures, in this cohort, a clinically significant fracture history and a BMD Z-score ≤ -2.0 are required. In this context, (1) at least two long bone fractures by the age of 10 and/or (2) at least three long bone fractures up to the age of 19 would be deemed a clinically significant fracture history. However, it must be noted methodology and reproducibility is scarce, rendering any ob-

tained data unreliable. The impact of growth delay on the interpretation of DXA results should also be considered in this population, that a Z-score above -2.0 does not rule out skeletal fragility or increased fracture risk. DXA lumbar spine measurements can be performed even in infants and children under the age of five, as BMC and aBMD measurements are reliable and reproducible. However, whole body BMC measurements obtained through DXA are of limited clinical utility for children below the age of three due to the lack of normative data. In addition, difficulty in appropriate positioning may make this method unfeasible in very young patients [33].

Fracture Risk Assessment Tool (FRAX®): The tool is based on an individual model for each patient that combines clinical risk factors with the femoral neck BMD to derive the 10-year probability of a hip fracture (≥ 3%) and a major osteoporotic fracture (≥ 20%; clinical spine, forearm, hip or shoulder fracture). FRAX has been incorporated into more than 80 guidelines worldwide [34–36] and its limitations have been extensively reviewed [34, 35]. The FRAX tool for the Serbian population is available online [35, 37] and is also incorporated into the DXA apparatus as an improved technological feature [36]. The health assessment depends on the quality and validity of the DXA report on which further treatment decisions will be based. Therefore, clinicians working in DXA centers must be adequately trained to work with the DXA machines, and need to undergo regular training to maintain and advance their skills [38].

Bone biomarkers: As bone turnover marker levels are higher during growth and skeleton development than in adulthood, they are considered reliable markers of bone formation and resorption. Their levels increase again in the postmenopausal period, indicating accelerated bone remodeling. Given that BMD is an important predictor of osteoporotic fractures, bone markers should be assessed alongside other osteoporosis risk factors to identify individuals that require treatment [39].

Conclusion

In daily clinical practice, a detailed anamnesis is essential, as is insight into all available medical documentation as is allowing health practitioners to identify potential risk factors for the occurrence of reduced bone mineral density, which would be further assessed through dual energy X-ray absorptiometry imaging as the gold standard in the diagnosis of osteoporosis. The Fracture Risk Assessment Tool findings are invaluable in this process as, when combined with the evaluation of bone metabolism markers, this data assists with a comprehensive diagnostic evaluation and the timely introduction of adequate therapy in order to alleviate or arrest further progression of bone mineral density reduction and there by prevent osteoporotic fractures.

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OSTEOPOROSIS – TREATMENT GAP

OSTEOPOROZA – TREATMENT GAP

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Summary
Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The definition of osteoporosis is based on the T-score for bone mineral density in women and is defined as a value for bone mineral density of 2.5 standard deviation or more below the young female adult mean (T-score less than or equal to −2.5). The clinical significance of osteoporosis lies in the fractures, which are usually the first clinical sign. Approximately one in two adult women and one in five men will sustain one or more fragility fractures (defined as a low trauma fracture sustained from a fall from standing height or less) in their lifetime. More than 9 million osteoporotic or fragility fractures occur annually across the globe, more than a third of which happen in Europe. It was estimated that 10.6 out of the 18.4 million women in Europe who exceeded the threshold risk for osteoporotic fractures were not treated, representing a treatment gap of 57%. The treatment gap is considered such a major concern that multiple global health organizations have issued global calls to tackle this crisis. The increase in the treatment gap could be accredited to several factors such as misbelief about osteoporosis, absence of perceived benefits of therapy, concern about side effects and medication costs, low motivation, and shortfall of patient education. Several methods have been explored to enable fracture risk assessment and initiation of appropriate therapy. The multi-disciplinary Fracture Liaison Service is one of the most successful of these systems.
Key words: Osteoporosis; Osteoporotic Fractures; Bone Density; Therapeutics; Treatment Outcome; Risk Factors

Sažetak
Osteoporoza je oboljenje skeletnog sistema koje se karakteriše niskom koštanom masom i oštećenjem mikroarhitekture koštanog tkiva sa sledstvenim povećanjem koštane fragilnosti i povećanoj sklonosti za nastanak preloma. Definicija osteoporoze se zasniva na odstupanju od vrednosti koštane gustine mlade odrasle žene i izražava se kao *T-score* gde je granica za osteoporozu jednaka ili manja od -2,5 standardne devijacije. Klinički značaj osteoporoze se sagledava kroz pojavu preloma koji su često i prvi znag osteoporoze. Aproksimativno, jedna od dve žene i jedan od pet muškaraca može zadobiti osteoporotski prelom (koji se definiše kao prelom na malu traumu, nastao padom sa sopstvene visine ili manje). Na globalnom nivou, godišnje se dogodi više od 9 miliona osteoporotskih preloma, od čeka jedna trećina na teritoriji Evrope. Procenjuje se da u Evropi od ukupno 18,4 miliona žena koje ispunjavaju kriterijume za lečenje, njih 10,6 miliona ne dobija neophodnu medikamentnu terapiju, što predstavlja *treatment gap* od 57%. Ovoliki propust u prepisivanju terapije je doveo do toga da nekoliko globalnih zdravstvenih organizacija izda saopšenja i pozive na akciju. Postojanje *treatment gap*-a uslovljava nekoliko faktora: neznanje o osteoporozi, manjak informacija o korisnosti terapije, zabrinutost zbog mogućih neželjenih efekata terapije, cena lečenja, slaba motivisanost i loša edukacija pacijenata. Razvijeno je nekoliko različitih metoda za smanjenje propusta u prepisivanju terapije i među njima se *Fracture Liaison Service* se pokazao kao najefikasniji.
Ključne reči: osteoporoza; osteoporotske frakture; koštana gustina; terapija; ishod lečenja; faktori rizika

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. The clinical significance of osteoporosis lies in the fractures, which are usually the first clinical sign. Approximately one in two adult women and one in five men will sustain one or more fragility fractures (defined as a low trauma fracture sustained from a fall from standing height or less) in their lifetime [2]. Bone mineral density (BMD) is the measurement used to diagnose whether an individual has osteoporosis. The definition of osteoporosis is based on the T-score for BMD in women and is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to −2.5) [3]. Diagnosis of the disease relies on the quantitative assessment of bone mineral density, which is a significant determinant of bone strength However, the clinical significance of osteoporosis is the fractures that impact a patient's quality of life. Because a variety of non-skeletal factors contribute to fracture risk, the diagnosis of osteoporosis by using BMD measurements is, at the same time, an assessment of a risk factor for the clinical outcome of fracture [4]. Most people who sustain a fragility fracture will have a femoral neck BMD T-Score above −2.5, reflecting the contribution of many other factors, besides BMD, to fracture risk. Fall-related risk factors add significantly to fracture risk and of-

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Abbreviations

BMD – bone mineral density
SD – standard deviations
EU – European Union
FRAX – Fracture Risk Assessment Tool
HR – hazard ratio
RCT – randomized control trials
FLS – Fracture Liaison Service

ten overlap with risk factors for osteoporosis [5]. Fractures at the hip and vertebrae are among the most common and serious sites of osteoporotic fracture. Fragility fractures of the humerus, forearm, ribs, tibia (in women, but not including ankle fractures), pelvis, and other femoral fractures after the age of 50 years are fractures associated with low BMD [6].

More than 9 million osteoporotic or fragility fractures occur annually across the globe, more than a third of which happen in Europe [7]. In 2010, 3.5 million new osteoporotic fractures in 22 million women over 50 were estimated to have occurred across the EU; incidence is predicted to increase due to changing demographics [8]. It has been suggested that approximately 51% of hip fractures that occur globally could be potentially preventable. Disease awareness, early diagnosis, prevention, and appropriate treatment of fractures are critical in osteoporosis management, but the diagnosis of osteoporosis habitually occurs only after a fracture [9].

Diagnostic methods and fracture risk assessment have improved in recent years, but despite new interventions to reduce fracture risk and new clinical practice guidelines, only a small fraction of eligible women receive osteoporosis medications, implying a high treatment gap. It was estimated that 10.6 out of the 18.4 million women in the EU who exceeded the threshold risk for osteoporotic fractures were not treated, representing a treatment gap of 57%. Recent advances in drug development for the treatment of osteoporosis over the last three decades have led to effective therapies for treating osteoporosis. Despite this, osteoporosis is vastly undertreated, and not enough medications are prescribed. Concerns about rare side effects, current comorbidities, and inadequate long-term efficacy of anti-resorptive drugs have led to an increase in untreated patients, widening the osteoporosis treatment gap. The treatment gap is considered such a significant concern that multiple global health organizations, such as the ASBMR, The Gerontological Society of America, and the Fragility Fracture Network, have issued global calls to tackle this crisis [10].

The increase in the treatment gap could be accredited to several factors such as misbelief about osteoporosis, absence of perceived benefits of therapy, concern about side effects and medication costs, low motivation, and shortfall of patient education [11]. In particular, inadequate or incorrect information in the mass media related to the disease and its treatment is also correlated with inadequate awareness and, subsequently, low treatment rates [12]. Novel strategies will likely be needed to narrow the treatment gap, particularly in older women. Greater awareness and ease of access to fracture risk assessment and treatment are likely to play a part; for example, establishing fracture liaison services in primary or secondary care settings increases osteodensitometry exam uptake and treatment initiation and is associated with reductions in fracture risk [13]. The application of fracture risk assessment in primary care and community settings was the focus of three recent randomized controlled trials of screening using the FRAX tool [14–16]. A meta-analysis of the three studies showed a statistically significant reduction of major osteoporotic fractures (hazard ratio [HR] = 0.91; 95% CI = 0.84–0.98) and hip fractures (HR = 0.80; 95% CI = 0.71–0.91) [17].

When considering long-term therapy, it is necessary to balance benefits and risks. Except for denosumab, the number of patients in randomized control trials (RCT) carried through to 10 years or longer is very small. A particular concern for patients and physicians alike is the apparent association of osteoporosis treatment with atypical femoral fractures and jaw osteonecrosis. However, this risk remains less than 1 in 1000 subjects treated even for ten years, according to most long-term extensions of RCTs and observational studies. Observational data suggest that patients treated with oral bisphosphonates in excess of 10 dose years maintain a low incidence of both hip fractures and fractures of the subtrochanteric femur and femoral shaft. The risk of new clinical fracture was about 20–40% higher in patients who stopped treatment and vertebral fracture risk was approximately doubled. These findings suggest that the concept of a 'drug holiday' as routine must be challenged. This is an urgent public health message that should be conveyed to health professionals, policymakers, and patients [18].

Challenges facing healthcare professionals and policymakers responsible for providing care for populations concerning bone health broadly fall into five distinct themes: (a) Perceived benefits and risks of therapy; (b) Case finding and management of individuals at high risk of fracture; (c) Public awareness of osteoporosis and fragility fractures; (d) Reimbursement and health system policy; and (e) Epidemiology of fractures in the developing world.

Several methods have been explored to enable fracture risk assessment and initiation of appropriate treatment. The multi-disciplinary Fracture Liaison Service (FLS) is one of the most successful systems, including rheumatologists, ortho-geriatricians, other physicians, clinical nurse specialists, and allied health professionals. Members of the FLS multi-disciplinary team, coordinated by a lead clinician, work together to optimize the medical management of patients admitted with fractures, both in the hospital and for long-term fracture prevention [19, 20].

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BIOLOGICAL THERAPY FOR OSTEOPOROSIS – SOLVING CLINICAL PROBLEMS – A CASE REPORT

BIOLOŠKA TERAPIJA OSTEOPOROZE – REŠAVANJE KLINIČKIH PROBLEMA – PRIKAZ SLUČAJA

Tanja JANKOVIĆ, Aleksandra SAVIĆ, Jelena ZVEKIĆ SVORCAN, Marina MAKSIMOVIĆ SIMOVIĆ and Ksenija BOŠKOVIĆ

Summary

Introduction. Elucidation of the pathogenetic mechanisms of osteoporosis has led to the development of new and effective drugs from the group of biological agents. **Case report.** In April 2018, a 64-year-old female patient was presented to the hospital due to low back pain. She was diagnosed with postmenopausal osteoporosis based on bone density scan score and a compression fracture of the L1 vertebral body revealed by X-ray. She was treated with a weekly bisphosphonate and supplementation with vitamin D and calcium. After one year, monthly bisphosphonate was introduced in therapy because of an inadequate response. In April 2020, the patient was treated for COVID-19 according to protocol, and during the treatment, bisphosphonate therapy was discontinued. After five months, she suffered a fracture of her left forearm. Due to the persistence of low mineral bone density, which was complicated by a new fracture, denosumab 60 mg subcutaneously once every six months was initiated with additional vitamin D and calcium supplementation. At six months follow-up, an increase in mineral bone density was verified, and after 12 months, the dual-energy x-ray absorptiometry score was within the osteopenia range. Laboratory findings showed a decrease in bone turnover markers. **Conclusion.** One-year administration of denosumab led to a significant increase in bone mineral density measured at the lumbar spine and neck of the femur, as well as changes in the levels of biochemical markers of bone synthesis and resorption, and reduced the risk of new fractures.

Key words: Biological Therapy; Denosumab; Osteoporosis; Bone Remodeling; Bone Density; Treatment Outcome

Sažetak

Uvod. Razjašnjenje patogenetskih mehanizama osteoporoze dovelo je do razvoja novih i efikasnih lekova iz grupe bioloških agenasa. **Prikaz slučaja.** Pacijentkinja stara 64 godine zbog bolova u donjem delu leđa, aprila 2018. godine javlja se u bolnicu gde je dijagnostikovana postmenopauzalna osteoporoza na osnovu osteodenzitometrijskog i radiografskog nalaza na kome je verifikovana kompresivna fraktura tela L1 pršljena. Lečena je nedeljnim bisfosfonatom uz suplementaciju vitaminom D i kalcijumom. Zbog neadekvatnog odgovora nakon godinu dana, uveden je mesečni bisfosfonat. Aprila 2020. godine pacijentkinja je lečena od COVID-19 infekcije po protokolu tokom kojeg je prekinula bisfosfonatnu terapiju. Nakon pet meseci je zadobila prelom leve podlaktice. Zbog perzistiranja niske mineralne koštane gustine koja je komplikovana novim prelomom, u terapiju je uveden denosumab od 60 mg supkutano na šest meseci uz suplementaciju vitaminom D i kalcijumom. Nakon šest meseci verifikovano je povećanje mineralne koštane gustine, a nakon 12 meseci pacijentkinja ulazi u zonu osteopenije. U laboratorijskim nalazima beleži se pad vrednosti markera koštane sinteze i resorpcije. **Zaključak.** Jednogodišnja primena denosumaba dovela je do značajnog povećanja mineralne koštane gustine, merene na lumbalnom delu kičme i vratu butne kosti, i do promene u nivoima biohemijskih markera koštane sinteze i resorpcije kao i do smanjenja rizika za nastanak novih preloma.

Ključne reči: biološka terapija; denosumab; osteoporoza; koštano remodelovanje; koštana gustina; ishod lečenja

Introduction

Osteoporosis is the most common chronic metabolic bone disease that affects biomechanical properties, leading to changes in bone components and consequently increasing the risk of fractures that often cause disability and in some patients, could be lethal [1]. Bone represents a high metabolic activity tissue, characterized by continuous modeling. This is a complex process depending on the interaction of highly specialized cells: osteoclasts, osteoblasts, and osteocytes. Three proteins from the tumor necrosis factor alpha (TNF-α) cytokine family are essential for the process of bone remodeling and those are receptor activator of nuclear factor kappa B ligand (RANKL), receptor activator of nuclear factor kappa B (RANK) and osteoprotegerin (OPG). RANKL plays an important role in stimulating osteoclast formation, activation, and consequently bone resorption. Its expression is regulated by parathyroid hormone (PTH), 1,25(OH)2D3, and pro-inflammatory cytokines interleukin-1(IL-1), IL-6, IL-17, and TNF-α. On the surface of osteoclasts, RANKL binds to RANK, This interaction leads to the activation of osteoclast and by inhibiting apoptosis it prolongs their survival, thus initiating the process of bone resorption. OPG is a soluble decoy receptor for RANKL, and due to its structure is homologous to RANK, it acts like an

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Abbreviations

TNF-α	– tumor necrosis factor-alpha
RANKL	– receptor activator of nuclear factor kappa B ligand
RANK	– receptor activator of nuclear factor kappa B
OPG	– osteoprotegerin
PTH	– parathyroid hormone
IL	– interleukin
BMD	– bone mineral density
SD	– standard deviation
P1NP	– procollagen type 1 N-terminal propeptide
b-CTX/ Beta- CrossLaps	– C-terminal telopeptide of type 1 collagen
ULV	– upper limit value
LLV	– lower limit value
COVID-19	– Coronavirus disease 2019
DEXA	– dual-energy x-ray absorptiometry
GIOP	– glucocorticoid induced osteoporosis

endogenous antagonist of RANKL. OPG binds to RANKL, which prevents its interaction with RANK. As a result, bone resorption is suppressed via inhibition of differentiation and activation of osteoclasts. Increased RANKL/OPG ratio indicates accelerated bone loss [2, 3]. Various signals and molecules affect the activity of bone cells. Some of them are insulin-like growth factor-1, transforming growth factor β, and the Wnt signaling pathway involved in the process of bone synthesis. The endogenous antagonist of the Wnt signaling pathway is sclerostin, a protein produced by osteocytes, which, by binding to the low density lipoprotein receptor-related protein 5 and 6 on osteoblasts, inhibits osteoblastic activity and thus leads to the activation of osteoclastogenesis and acceleration of bone resorption [4]. Restoration of bone mass in patients who have osteoporosis is of great medical importance. Most of the medications used for the treatment of osteoporosis prevent bone loss by suppressing bone resorption. Bisphosphonates are the first line therapy in this group, although calcitonin, selective estrogen receptor modulators and others have similar beneficial effects on bone tissue [5]. Discoveries in osteoimmunology not only clarified the pathogenetic mechanisms of osteoporosis, but also identified immunological targets and enabled the development of new therapeutic modalities with human monoclonal antibodies as biological therapy. One of the first biological drugs is a human monoclonal IgG2 antibody against RANKL, denosumab, which prevents the binding of RANKL to RANK and thus inhibits osteoclast activity and bone resorption. The mechanism of action of other biological drugs is based on the inhibition of sclerostin, which as a result have activation on the Wnt signaling pathway and bone formation. This group of biological drugs includes romosozumab, blosozumab, setrusumab [6].

Case report

In April 2018, a 64-year-old female patient scheduled a medical appointment with the family doctor due to intense low back pain provoked by high physical activity. Considering earlier episodes of lumbar pain, the patient was prescribed non-steroidal antirheumatic drugs, analgesics, and physical therapy. In June 2018, she was referred to the Special hospital for rheumatic diseases in Novi Sad for further evaluation and treatment because symptom relief was not accomplished. Lower back pain was the main clinical presentation. The physical examination revealed a postural imbalance, including forwarding head posture and thoracic kyphoscoliosis, limitation of the lumbar spine range of motion in all directions with intact sensitivity, and no motor deficits of the lower extremities. Assessment of bone density was performed on the LUNAR Densitometer Machine and obtained values of T-score and bone mineral density (BMD) at the lumbar spine (L1-L4) were -2.8 standard deviation (SD) and 0.798 g/cm², respectively. T-score was -2.5 SD and BMD was 0.814 g/cm² at the left femoral neck. The patient was 156 cm tall and weighed 68 kg; therefore her calculated body mass index was 27.9, indicative of being overweight. Compered to the patient's previously measured height, which was 164 cm, a reduction of 8 cm in total was noted. A compression fracture of the L1 vertebral body was seen on the radiogram of the lumbosacral spine **(Figure 1)**. The results of the laboratory analysis of the serum concentrations of bone formation marker, procollagen type 1 N-terminal propeptide (P1NP) and bone resorption marker, C-terminal telopeptide of type 1 collagen (b-CTX/ Beta-CrossLaps), total and ionized calcium as well as phosphorus were within the reference range. The concentration level of PTH was elevated, 42.6 pg/ml (upper limit value (ULV) 36.8 pg/ml) followed by vitamin D deficiency, 28 nmol/l (lower limit value (LLV) 35 nmol /l). Based on anamnestic data and medical reports, the patient had arterial hypertension, diabetes mellitus, and Hashimoto's disease. She had three vaginal deliveries and her medical history was positive for menopause starting at the age of 45 and a left lower leg fracture sustained from low energy trauma when she was 62. The patient was a smoker for over 40 years, and she smoked about 20 cigarettes a day on average. She worked as a cook and got a state pension. Furthermore, her mother suffered from a hip fracture at the age of 81. Following the diagnosis of postmenopausal osteoporosis complicated by compression fracture, weekly bisphosphonate therapy was started in combination with vitamin D and calcium. After one year, a bone density scan on the same device showed a deterioration of the T-score by 1 SD at the L1-L4 level (T-score -2.9 SD) and 2 SD at the left femoral neck (T-score -2.7 SD). Lower values were also recorded for BMD (g/cm²) for L1-L4 (BMD 0.689 g/cm^2) and neck of the left femur (BMD 0.721 g/cm^2). Repeated laboratory analysis findings revealed an increased concentration of PTH (38.6 pg/ml; ULV 36.8 pg/ml), while the serum concentration of vitamin D was still below the lower limit value (30 mmol/l; LLV 35 nmol/l). The patient was not regularly taking the prescribed bisphosphonates due to gastrointestinal intolerance as well as accompanying back pain that occurred while administering medication. She was

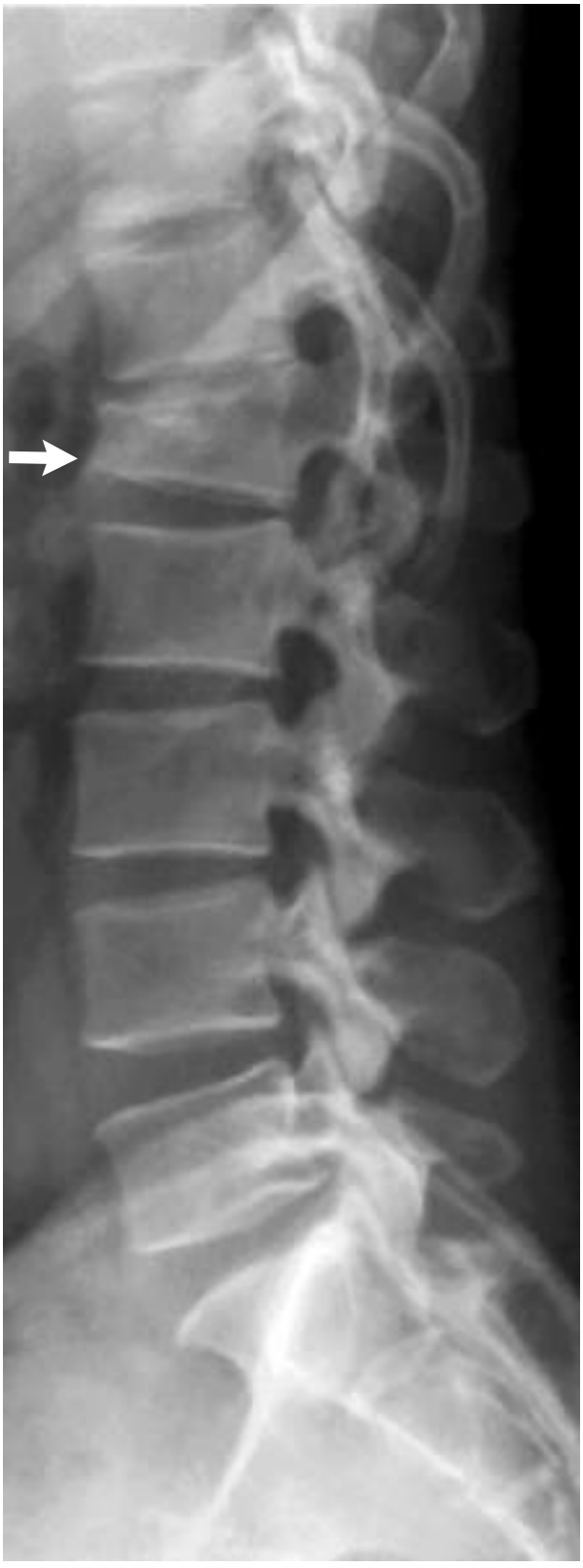

Figure 1. Lateral view of the lumbosacral spine: arrow – compression fracture of the body of the L1 vertebra
Slika 1. *Profilni snimak lumbosakralne kičme: strelica – kompresivna fraktura tela L1 pršljena*

advised to switch to a monthly regime or intravenous bisphosphonate given every three months. In August 2019, oral bisphosphonate therapy was initiated monthly in combination with vitamin D and calcium supplementation. In April 2020, she developed a fever as well as a dry cough; hence a nasopharyngeal swab sample was collected, which came back positive for COVID-19. The chest radiograph displayed features of bilateral pneumonia. Treatment was carried out at home and in accordance with protocol. She was prescribed antibiotics, corticosteroid therapy, low molecular weight heparin, and vitamin supplementation, especially vitamin C and D. In the following period, she stopped taking her monthly antiresorptive therapy. The patient went on regular check-ups with a pulmonologist and a complete regression of pneumonic changes was verified in June 2020. After five months, she broke her left forearm due to low energy trauma. In May 2021, dual-energy x-ray absorptiometry (DEXA) scores were -2,8 SD for T-score and 0,721 g/cm² for BMD at the L1-L4. T-score at the neck of the femur was -2,7 SD and BMD was 0,769 g/cm². PTH was elevated (38.6 pg/ml; ULV 36.8 pg/ml), and low levels of vitamin D were maintained (30 mmol/l; LLV 35 nmol/l); on the other hand, serum concentration of bone turnover markers was normal. Considering the lack of response to previous bisphosphonate therapy, fracture of the left forearm and increase in risk for a new fracture, a biological drug, denosumab, was started in combination with vitamin D and calcium supplementation for the treatment of osteoporosis. Denosumab was applied via a pre-filled syringe at a dose of 60 mg subcutaneously every six months. Before administering the medication, the calcium and creatinine clearance concentration was measured, and the results were within the reference range. The drug was applied subcutaneously in the upper part of the left thigh by a nurse on May 2021, and no injection site reaction was observed. Six months afterward, a bone mineral density measurement was performed, before giving the planned second dose. The DEXA scan showed increased bone mineral density at the lumbar spine (L1-L4) and femoral neck. One year after initiating denosumab in therapy and after applying the third dose, the osteodensitometry score reached the level of osteopenia **(Table 1).** Six months after starting the denosumab, a decrease in the concentration of the biochemical markers P1NP and b-CTX was observed; this downward trend was maintained even after 12 months of drug administration. Regarding other monitored laboratory parameters, an increase in serum concentration of vitamin D was noted, while the others were within the normal range **(Table 2)**.

Discussion

Osteoporosis is a highly prevalent disease, especially in the elderly. It is estimated that more than 200 million people worldwide have osteoporosis. Given that the aging population is increasing rapidly in many countries, osteoporosis could become a global health issue with an impact on the quality of life of affected individuals [7]. Osteoporotic fractures also impact the

Table 1. Change in bone mineral density after 6 and 12 months of Denosumab administration
Tabela 1. *Promena vrednosti mineralne koštane gustine nakon 6 i 12 meseci primene denosumaba*

	L1-L4		Neck of femur/*Vrat butne kosti*	
	T-score (SD) *T-skor (standardna devijacija)*	BMD (g/cm²) *mineralna koštana gustina*	T-score (SD) *T-skor (standardna devijacija)*	BMD (g/cm²) *mineralna koštana gustina*
May 2021/*Maj 2021*	-2.8	0.721	-2.7	0.769
After 6 months/*Nakon 6 meseci*	-2.5	0.912	-2.4	0.858
After 12 months/*Nakon 12 meseci*	-2.1	0.987	-2.3	0.924

Legend: BMD – bone mineral density; SD – standard deviation
Legenda: BMD – mineralna koštana gustina

Table 2. Changes in the values of monitored laboratory parameters after 6 and 12 months of Denosumab administration
Tabela 2. *Promena vrednosti praćenih laboratorijskih parametara nakon 6 i 12 meseci primene denosumaba*

	May 2021 *Maj 2021*	After 6 months *Nakon 6 meseci*	After 12 months *Nakon 12 meseci*
	Value/*Vrednost*	Value/*Vrednost*	Value/*Vrednost*
P1NP/*Prokolagen tip 1 N terminalni propeptid**	68.9 ng/ml	65.8 ng/ml	23.9 ng/ml
b-CTX/*Beta-CrossLaps**	856 ng/ml	552 ng/ml	389 ng/ml
Total Ca in blood*/*Ukupni Ca u krvi*	2.20 mmol/l	2.30 mmol/l	2.20 mmol/l
Ionized Ca in blood*/*Jonizovan Ca u krvi*	1.10 mmol/l	1.15 mmol/l	1.10 mmol/l
Phosphorus*/*Fosfor*	1.10 mmol/l	1.10 mmol/l	1.10 mmol/l
PTH/*Paratireoidni hormon*	35.9 pg/ml	21.4 pg/ml	23.4 pg/ml
Vitamin D in serum/*Vitamin D u serumu**	41 nmol/l	40 nmol/l	45 nmol/l

Legend: P1NP - Procollagen type 1 N propeptide (n:16.3-73.9 ng/ml); b-CTX(Beta-CrossLaps) - C- terminal telopeptide of type 1 collagen (n: 556-1008 ng/ml); Total calcium in blood (n: 2.20-2.70 mmol/l); Ionized calcium in blood (n: 0.95-1.30 mmol/l); Phosphorus (n: 0.80-1.45 mmol/l); PTH - parathyroid hormone (n: 6.5-36.8 pg/l); Vitamin D in serum (n: 35-120 nmol/l).
Legenda: P1NP – prokolagen tip 1 N terminalni propeptid (n:16.3–73.9 ng/ml); b-CTX (Beta-CrossLaps) – C-terminalni telopeptid tip 1 kolagen (n: 556–1008 ng/ml); ukupni kalcijum u krvi (n: 2.20–2.70 mmol/l); jonizovani kalcijum u krvi (n: 0.95–1.30 mmol/l); fosfor (n: 0.80–1.45 mmol/l); PTH – paratireoidni hormon (n: 6.5–36.8 pg/l); vitamin D u serumu (n: 35–120 nmol/l).

patient's quality of life and represent a large financial burden for society, making this disease growing health and economic problem across the globe. Prolongation of life expectancy correlates with fracture risk; thus the healthcare cost of osteoporosis and its consequences will progressively increase as the population ages [8]. The clinical significance of osteoporosis lies in fractures. Approximately one in two adult women and one in five men will sustain one or more osteoporotic fractures during their lifetime. Fracture risk increases progressively with a decrease in bone mineral density [9]. Meta-analyses of population-based observational studies have shown that fracture risk increases approximately twofold for each standard deviation decrease in BMD measured by absorptiometric techniques [10]. The main therapeutic target for patients with osteoporosis treated with medication is preventing fractures and complications. It is essential to provide an individual long-term treatment strategy for each patient. Drugs used in the treatment of osteoporosis can be categorized into a group with an antiresorptive and anabolic effects. Antiresorptive drugs primarily inhibit the activity of osteoclasts and bone resorption, but their secondary effect, which comes afterward, is based on bone formation. Medicines with an anabolic effect primarily promote bone synthesis through the stimulation of osteoblastic activity, while their effect on bone resorption is variable [11]. Physicians nowadays have numerous drugs for the prevention and treatment of osteoporosis, but many patients still have a high risk of fracture and are not being treated. This can be explained by poor adherence, owing to the fact that adherence is affected by concerns about long-term efficacy and safety [12, 13]. Denosumab is the first approved biological drug for the treatment of osteoporosis, which belongs to the group of antiresorptive agents. It is a human monoclonal antibody against RANKL [14]. The results of the FREEDOM trial and its extension showed that patients treated with denosumab had a continuous increase in BMD, a rapid decrease in bone turnover marker, and a reduced risk of recurrent fractures, especially the vertebral [15, 16]. Silva-Fernández et al. included in their review article 25 studies conducted in order to evaluate the efficacy and safety of denosumab in the treatment of osteoporosis. They demonstrated that denosumab reduces the risk of new vertebral fractures in 68% compared to placebo. Additionally, denosumab was superior to alendronate and placebo in increasing BMD at the lumbar spine and femoral neck [17]. Similarly, Zaheer et al., analyzed literature data regarding eight-year experience of continuous use of denosumab. They concluded that this type of antire-

sorptive therapy provided improvement of BMD while reducing the risk of fractures. Moreover, there have not been any safety concerns and its adverse event profile is similar to a placebo [18]. In a 12-month prospective study comparing denosumab and alendronate in 32 participants with glucocorticoid-induced osteoporosis (GIOP), Iserio et al. showed that patients treated with denosumab had greater gains in BMD at the lumbar spine than those treated with alendronate. This change in BMD was seen already six months after the baseline. Although the reduction in serum concentration of bone metabolism markers was noted in both groups, the difference in decreasing the level of bone turnover markers was not statistically significant. Bearing in mind previously mentioned study results, it can be concluded that patients with GIOP could benefit from using this therapeutic option [19]. Brown et al. assessed BMD and bone turnover markers in women with postmenopausal osteoporosis. They pointed out that participants receiving denosumab compared with those receiving alendronate had a greater increase in BMD as well as a decrease in biochemical markers of bone metabolism after 12 months of treatment [20]. Miller et al. conducted an analysis of four randomized studies that investigated the efficacy and safety of switching from bisphosphate to denosumab versus continuing bisphosphonate therapy in women with postmenopausal osteoporosis who were previously treated with oral bisphosphonates. After 1, 6, and 12 months of treatment, serum concentration of b-CTX and P1NP significantly dropped in the denosumab group compared to the group of patients continuing with a bisphosphonate. A significant correlation in the denosumab study group was found between the percentage change in serum b-CTX at month one and the percentage change in the lumbar spine and total hip BMD at month 12. These two groups did not differ in terms of side effect incidence. The authors concluded that the transition from bisphosphonate to denosumab is safe and provides more effective treatment outcomes, more importantly, an increase of BMD than continuing therapy with bisphosphonate [21]. A novel therapeutic approach in osteoporosis treatment focuses on other biological agents with different mechanisms of action dependent on sclerostin inhibition. Sclerostin is a protein produced by osteocytes that suppresses bone formation via blocking the Wnt signaling pathway and therefore inhibiting the activity of osteoblasts. Romosozumab is a humanized monoclonal antibody that inhibits sclerostin and thus increases BMD at the lumbar spine and femoral neck. It also affects the serum concentration of bone turnover markers leading to a transient increase in bone formation and a persistent decrease in bone resorption markers. The recommended dose of romosozumab is 210 mg once monthly for twelve months in the form of subcutaneous injections. After discontinuation of therapy, the effect on BMD decreases [22].

Conclusion

Numerous drugs and therapeutic options are used in the treatment of osteoporosis in order to reduce fracture risk and increase BMD. Achievements in osteoimmunology gave a better insight into many pathogenetic mechanisms of osteoporosis. They identified new immunological targets for treatment, thus opening the way for human monoclonal antibodies as biological drugs. Denosumab is the first human monoclonal antibody used in the management of osteoporosis, which impacts cortical and trabecular bone as well. Due to the rapid onset of action, it continuously increases bone mineral density and affects biochemical bone markers. After the bisphosphonates, denosumab is a second-line therapeutic option for osteoporosis because of its efficacy in preventing new fractures and pharmacological safety profile. On the other hand, it is a first-line treatment in patients with a significant deterioration of renal function.

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THE IMPORTANCE OF SUPPLEMENTATION WITH VITAMIN D AND MINERALS FOR ACHIEVING MAXIMUM EFFECTS IN THE TREATMENT OF OSTEOPOROSIS

ZNAČAJ SUPLEMENTACIJE D VITAMINOM I MINERALIMA ZA POSTIZANJE MAKSIMALNIH EFEKATA LEČENJA OSTEOPOROZE

Nataša MILENOVIĆ

Summary

Introduction. Vitamin D is known to regulate calcium and phosphate metabolism. It plays an essential role in maintaining a healthy mineralized skeleton and it is also an immunomodulatory hormone. Experimental studies have shown that vitamin D has significant biologic activities on the innate and adaptive immune systems. Animal studies have demonstrated that administration of vitamin D or its metabolites leads to changes in the occurrence and progression of various immune-related diseases. This supports the clinical and epidemiological data that link vitamin D with the incidence and severity of many disorders, such as psoriasis, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and infectious diseases. In recent decades, interest in vitamin D has increased exponentially, particularly as a vitamin D deficit has been associated with multiple diseases, and globally, there appears to be a high vitamin D deficiency. **Osteoporosis prevention.** Recent literature states that for the prevention of hypovitaminosis D in children, a daily recommended dose of 400-800 international units (IU) from 0 months to 3 years is required. For ages up to 18, the dose increases to 1000 IU, and from 19 to 70+ the dose is up to 1500 IU. In treating hypovitaminosis D, higher doses than preventive doses are recommended. For ages 0 to 12 months, they vary from 1000 to 1500 IU, while after the age of 9, therapeutic doses increase to 4000 IU. **Osteoporosis therapy.** In osteoporosis therapy, two groups of drugs are most often used – antiresorptive and anabolic. Of the antiresorptive preparations, bisphosphonates are the most important – the gold standard in treating osteoporosis, the first drug of choice. **Conclusion.** Circulating vitamin D has an important physiological role. It is necessary to provide enough vitamin D daily to ensure stable concentrations in the circulation and ensure optimal benefits of vitamin D. Recommendations for vitamin D supplementation differ in terms of preventive versus therapeutic doses. If a person is diagnosed with osteoporosis, before the introduction of antiresorptive or anabolic therapy, it is necessary to determine the method of administration of the appropriate dose of vitamin D. In the treatment of osteoporosis bisphosphonates are the gold standard; in addition to vitamin D.

Key words: Osteoporosis; Vitamin D; Dietary Supplements; Treatment Outcome; Recommended Dietary Allowances; Diphosphonates; Exercise

Sažetak

Uvod. Poznato je da vitamin D reguliše metabolizam kalcijuma i fosfata. On igra suštinsku ulogu u održavanju zdravog mineralizovanog skeleta i takođe je imunomodulatorni hormon. Eksperimentalne studije su pokazale da vitamin D ima značajne biološke aktivnosti na urođeni i adaptivni imunosistem. Studije na životinjama su pokazale da primena vitamina D ili njegovih metabolita dovodi do promena u pojavi i progresiji različitih bolesti povezanih sa imunitetom. Ovo podržava kliničke i epidemiološke podatke koji povezuju vitamin D sa učestalošću i ozbiljnošću mnogih poremećaja kao što su psorijaza, multipla skleroza, reumatoidni artritis, dijabetes tipa 1 i zarazne bolesti. Poslednjih decenija, interesovanje za vitamin D je eksponencijalno poraslo, posebno zato što je deficit vitamina D povezan sa više bolesti, a globalno se čini da postoji visok nedostatak vitamina D. **Prevencija osteoporoze**. U novijoj literaturi se navodi da je za prevenciju hipovitaminoze D kod dece od 0 meseci do 3 godine, dnevna preporučena doza od 400 do 800 internacionalnih jedinica (IJ) dnevno. Za uzrast do 18 godina doza se povećava sa 1.000 IU, a od 19 do 70+ doza je do 1.500 IJ. U lečenju hipovitaminoze D preporučuju se veće doze od preventivnih. Za uzrast od 0 do 12 meseci variraju od 1.000 do 1.500 IJ, dok se posle devet godina terapijske doze povećavaju na 4.000 IJ. **Terapija osteoporoze.** U terapiji osteoporoze najčešće se koriste dve grupe lekova – antiresorptivni i anabolički. Od antiresorptivnih preparata najvažniji su bisfosfonati – zlatni standard u lečenju osteoporoze, prvi lek izbora. **Zaključak.** Cirkulišući vitamin D ima važnu fiziološku ulogu i neophodno je obezbediti dovoljno vitamina D dnevno kako bi se obezbedile stabilne koncentracije u cirkulaciji i obezbedila optimalna korist od vitamina D. Preporuke za suplementaciju vitamina D razlikuju se u pogledu preventivnih i terapijskih doza. Ukoliko se kod osobe dijagnostikuje osteoporoza, pre uvođenja antiresorptivne ili anaboličke terapije potrebno je odrediti način primene odgovarajuće doze vitamina D. U lečenju osteoporoze bisfosfonati su zlatni standard pored vitamina D.

Ključne reči. osteoporoza; vitamin D; suplementi; ishod lečenja; preporučene dnevne doze; bisfosfonati; fizička aktivnost

Introduction

Since the identification of the chemical structure of vitamin D in 1930 by the Nobel Prize laureate Adolf Otto Reinhold Windaus, based on the knowledge acquired by several scientists who preceded him, there have been extraordinary advances in vitamin D research [1]. Vitamin D is classically known to regulate calcium and phosphate metabolism. It not only plays an essential role in maintaining a healthy

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mineralized skeleton, but it is also an immunomodulatory hormone [2]. Experimental studies have shown that vitamin D has significant biologic activities on the innate and adaptive immune systems. Animal studies have demonstrated that administration of vitamin D or its metabolites leads to changes in the occurrence and progression of various immune-related diseases. This supports the clinical and epidemiological data that link vitamin D with the incidence and severity of many disorders, such as psoriasis, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and infectious diseases [3].

In recent decades, interest in vitamin D has increased exponentially, particularly as a vitamin D deficit has been associated with multiple diseases, and globally, there appears to be a high vitamin D deficiency [4].

Osteoporosis is characterized by low BMD and microarchitectural deterioration of the bone tissues, leading to an increased risk of fracture. Vitamin D affects bone turnover rate and overall bone mineralization.. Thus, vitamin D deficiency is associated with a higher bone turnover and fracture incidence [5].

Sources, Synthesis, and Metabolism of Vitamin D

Humans get vitamin D from sunlight, diet, and supplements. There are two major forms of vitamin D: vitamin D2 and vitamin D3. Vitamin D2 is synthesized from ergosterol and found in yeast, sun-dried and ultraviolet-irradiated mushrooms, and plants. Vitamin D3 is synthesized endogenously from 7-dehydrocholesterol in the skin and is found naturally in cod liver oil and oily fish. After entering the circulation, vitamin D is metabolized by the vitamin D-25-hydroxylase (CYP2R1) in the liver to 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is further metabolized by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to the active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2$D exerts its physiologic functions in the target tissue by binding to the vitamin D receptor (VDR) in the nucleus, leading to up- or down-regulation of many genes. It should be noted that the main site of conversion of 25(OH)D into the systemically bioavailable 1,25$(OH)_2$D is the kidneys [3, 6].

The concentration of vitamin D in the body is achieved in two ways: synthesis of vitamin D3 in the skin under the influence of UV rays and diet - D2 ergocalciferol - of plant origin and vitamin D3 cholecalciferol - of animal origin - fatty fish.

Average values of vitamin D are 75 nmol/l or 30 ng/ml, while vitamin D3 deficiency is below 50 nmol/l (20 to 30 ng/ml). Healthy bones require a concentration of 25 hydroxy vitamin D of at least 50 nmol/l.

Osteoporosis prevention

Recommendations for vitamin D supplementation differ in terms of preventive versus therapeutic doses. According to modern understandings, these doses have become variable over time, so recent literature states that for the prevention of hypovitaminosis D in children, a daily recommended dose of 400-800 international units (IU) from 0 months to 3 years is required. For ages up to 18, the dose increases to 1000 IU, and from 19 to 70+, the dose is up to 1500 IU. In the treatment of hypovitaminosis D, higher doses than preventive doses are recommended. For ages 0 to 12 months, they vary from 1000 to 1500 IU, while after the age of 9, therapeutic doses increase to 4000 IU [7].

Circulating vitamin D has an important physiological role. It is necessary to provide enough vitamin D daily to ensure stable concentrations in the circulation and optimal benefits of vitamin D [8].

If a person is diagnosed with osteoporosis, before the introduction of antiresorptive or anabolic therapy, it is necessary to determine the method of administration of the appropriate dose of vitamin D. This can be achieved through a bolus dose, which means once a week for the next eight weeks at 50,000 IU D3, or 6000 IU once a day for eight weeks until reaching a level of 25(OH)D above 30 ng/ml. For the maintenance dose, an intake of 1500 to 2000 IU is recommended daily [7, 9]. It takes min. eight weeks to reach the desired 25(OH)D values, according to some studies, even ≥ 12 weeks (depending on the initial value, obesity...). In obese persons, patients with malabsorption syndromes and patients on certain drugs (anticonvulsant th, glucocorticosteroids, antifungals, th for AIDS) 2-3 x ↑doses (min. 6,000-10,000 IJ/24h) are needed to compensate for vitamin D, and 2-3↑maintenance doses (min. 3000-6000 IJ/24h) (EFSA NDA Panel [10]. The recommendation is regular monitoring of calcium in the serum; if there is renal insufficiency, only the form of Alfa calcidol [11] is recommended.

Risk groups for vitamin D deficiency include: elderly people, people who are rarely exposed to the sun, wear protective clothing and shoes, use sun protection products, obese people, patients with osteoporosis, people with darker skin (melanin in the skin blocks the synthesis of active UVB of vitamin D3), hospitalized patients, autoimmune diseases (endocrinological and neurological), people in nursing homes, people with chronic liver disorders (hepatitis, cirrhosis), people with reduced degradation of 25-OH D, patients with malabsorption syndrome (celiac disease, biliary obstruction, pancreatic insufficiency, cystic fibrosis), people taking drugs that affect the metabolism of vitamin D (corticosteroids, rifamycins, anticonvulants, phenobarbitone, carbamezepine, isoniazid) [12].

Bearing in mind that vitamin D is the main transcriptional regulator of the two most abundant bone matrix proteins: it inhibits the synthesis of type 1 collagen and induces the synthesis of osteocalcin, it stimulates the differentiation of osteoclasts from monocyte-macrophage stem-cell precursors in vitro, it increases osteoclast bone resorption in large doses by stimulating the production of Rank-ligand by osteoblasts.

The main role of vitamin D is to provide an adequate milieu, i.e., microenvironment in the bones so that mineralization can take place smoothly, thereby reducing the risk of osteoporosis [13].

In order to prevent the risk of osteoporosis, timely and non-pharmacological treatment can be carried out, which includes engaging in physical activity - exercise during childhood and adolescence - an important role in increasing bone mass, which is maintained in middle age. In the elderly it slows down the loss of bone mass and reduces the risk of fracture, prevents falls, improves balance. It should be borne in mind that the number of vitamin D receptors in muscles decreases with age and that the risk for "weak" muscles and "weak" bones is increased in people with reduced muscle mass. There are no clear views on the type of activity, intensity, duration, or frequency of exercise. A combination of aerobic dynamic antigravity exercises, coordination exercises, balance exercises, strengthening of the hip and pelvis muscles, muscle strength flexibility exercises and posture correction is recommended. Exercises involving large muscle groups are preferred, as they have a more significant effect than swimming. The simplest form of activity is - daily walking, minimum 30 minutes, so-called fast walk. It is recommended to exercise for life, because the effect on the bones is lost when ceasing excersise. Educational programs are an important part of non-pharmacological treatment - schools on fall prevention, vision regulation, use of orthopedic aids, adequate footwear, removal of architectural barriers, good lighting and dry floors [14].

It is found in food of plant origin as ergocalciferol, vitamin D2, and in food of animal origin as cholecalciferol, vitamin D3.

In order to achieve the daily dose of vitamin D3, it is necessary to consume 40 eggs, or 1.92 - 2.3 kilograms of chicken liver, or 2.44 - 2.93 liters of milk, 6.25 - 7.5 kilograms of feta cheese, or 250-300 grams of salmon; and it is quite clear that due to the impossibility of such an intake, vitamin D3 supplementation is necessary.

Osteoporosis therapy

In osteoporosis therapy, two groups of drugs are most often used - antiresorptive and anabolic. Of the antiresorptive preparations, bisphosphonates are the most important - the gold standard in the treatment of osteoporosis, the first drug of choice. Pyrophosphate analogs have been synthesized according to their chemical composition, which bind to hydroxyapatite in bones. Its role is to strongly inhibit bone resorption by slowing down the maturation and activity of osteoclasts and their apoptosis. Clinically proven effectiveness is the application for 5 years, after which there is "numbing" of the bone. Studies have proven that this type of medicine preserves bone architecture and strength. Osteonecrosis of the jaw is mentioned as a rare but significant side effect. Before taking medicine, it is necessary to get information about possible diseases of the patient's gastrointestinal tract. If there is gastritis or an ulcer, this will not be the medicine of choice. Also, studies have proven that increased bone mineral density and reduced risk of vertebral and non-vertebral fractures are extremely important in the prevention of osteoporosis. This type of medicine is approved for the prevention of fractures and the treatment of postmenopausal osteoporosis in women, osteoporosis in men, osteoporosis induced by glucocorticoids, the treatment of Paget's disease, in the treatment of osteogenesis imperfecta in childhood [15, 16]. The most famous bisphosphonate preparations are: Alendronate - daily regimen 10 mg; Risendronate - weekly regimen 35 mg; Ibandronate - monthly regimen 150 mg (per os, i.v.); Zolendronate - for the treatment of multiple myeloma, malignant hypercalcemia of bone metastases of a solid tumor, since 2007 for the treatment of osteoporosis and prevention of fractures; hormones and selective modulators of estrogen receptors (Raloxifene) - application restrictions due to side effects - thromboembolism, breast CA, only short-term TH.

The group of anabolic drugs - osteoanabolics includes: Teriparatide - an active agent of human parathyroid hormone, approved for use for 24 months; Denosumab – a human monoclonal antibody – inhibits the formation, action, and survival of osteclasts, and consequently reduces resorption in cortical and trabecular bone. Approved for the treatment of osteoporosis in women and men at high risk for fractures, as well as for the treatment of men with prostate cancer. Dose 60 mg for 6 months s.c. Caution with impairment of renal function; Stronciranelate - a dual mechanism promotes the formation of bone tissue by multiplying osteoblasts and increasing collagen synthesis, on the other hand, it reduces the resorptive capacity of osteoclasts. Contraindicated in ischemic heart disease, peripheral arterial disease, CV disease, and unregulated HTA [15].

Before the introduction of any of the mentioned therapies, an individual assessment of the patient in the direction of diagnosing osteoporosis is necessary, which includes looking at risk factors, age, the existence of fractures, the existence of diseases that can directly affect osteoporosis, DXA imaging, as well as the determination of laboratory findings of bone markers. All this is a guideline for the leading doctor that will indicate the correct choice of medication for the treatment of osteoporosis.

Conclusion

Circulating vitamin D has an important physiological role and it is necessary to provide enough vitamin D daily in order to ensure stable concentrations in the circulation and ensure optimal its benefits. Recommendations for vitamin D supplementation differ in terms of preventive versus therapeutic doses. If a person is diagnosed with osteoporosis, before the introduction of antiresorptive or anabolic therapy, it is necessary to determine the method of administration of the appropriate dose of vitamin D. In the treatment of osteoporosis bisphosphonates are the gold standard in the treatment.

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PHYSICAL ACTIVITY AND FALL PREVENTION – SOLVING CLINICAL PROBLEMS

FIZIČKA AKTIVNOST I PREVENCIJA PADA – REŠAVANJE KLINIČKIH PROBLEMA

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Summary

Introduction. A multidisciplinary and therapeutic approach is used for patients with osteoporotic bone fractures. Falls, leading to injuries, including bone fractures, are a common occurrence in the elderly suffering from osteoporosis. Multifactorial risk assessment is of great importance in identifying risk factors for the occurrence of falls, their removal and implementing preventive measures. The issue of risk assessment is very current and treated by related professional recommendations and national and international guidelines. The latter point out the following fall risks: previous falls, use of psychotropic substances, vision impairment, mobility, gait, muscle strength and balance and impairment of cognitive functions. Fear of falling, psychological passivity, urinary incontinence, inadequate footwear and certain neurologic and cardiovascular conditions are also considered additional risks. Fall risks may also be environmental (within the dwelling and outside), such as low lighting, inadequate furniture and its disposition, difficulty in accessing the bed, chair, toilet, bathroom, stairs and other. For a realistic fall risk estimate, besides using adequate questionnaires, several static and dynamic tests may be used to assess balance and mobility. Depending on the type of risk factors present, actions for their removal through information, education and participation of the elderly in preventive measures are also recommended. **Conclusion.** Multifactorial risk assessment of fall occurrence and bone fracture, as of recovery, are of great importance within certain population groups, especially the elderly.

Key words: Osteoporosis; Risk Factors; Accidental Falls; Accident Prevention; Exercise

Sažetak

Uvod. Kod osoba sa osteoporotskim prelomom kosti koriste se multidisciplinarni dijagnostički i terapijski postupci. Padovi koji dovode do povreda, među kojima su i koštani prelomi, dosta su česta pojava kod osoba starije životne dobi sa osteoporozom. Za otkrivanje faktora rizika za nastanak pada, njihovo otklanjanje i preventivno delovanje, veliki značaj ima multifaktorska procena rizika od pada. Ova tematika je veoma aktuelna u današnje vreme i njome se bave odgovarajuće stručne preporuke i nacionalni i internacionalni vodiči. Oni posebno skreću pažnju na sledeće faktore rizika od pada: raniji padovi, uzimanje psihotropnih supstancija, poremećaji vida, pokretljivosti, hoda, mišićne snage i ravnoteže i poremećaji kognitivnih funkcija. Takođe se navode kao dodatni rizici još i strah od pada, psihološka pasivizacija, prisustvo urinarne inkontinencije, korišćenje nepodobne obuće, određene neurološke i kardiovaskularne bolesti. Rizici za pad mogu biti i faktori okoline (u stanu i van njega) kao što su slaba osvetljenost, neadekvatan nameštaj i njegov raspored, poteškoće u vezi sa korišćenjem postelje, stolice, toaleta, kupatila, stepenica i drugi. Pored korišćenja odgovarajućih upitnika, za konkretnu kliničku procenu rizika od pada, mogu da posluže još i razni statički i dinamički testovi za procenu balansa i pokretljivosti. U zavisnosti od toga koji faktori rizika su prisutni, preporučeni su i odgovarajući postupci za njihovo uklanjanje, uz informisanje, edukaciju i podsticanje učešća starijih osoba u merama prevencije padova. **Zaključak.** Multifaktorska procena rizika za nastanak pada i preloma kosti, kao i za oporavak od velikog je značaja kod određene populacije, pre svega kod osoba starije životne dobi.

Ključne reči: osteoporoza; faktori rizika; slučajni padovi; prevencija nesreća; fizička aktivnost

Introduction

The elderly are generally more prone to falls and physical injury [1, 2]. More frequent and easier occurrence of bone fractures [3, 4], beside other injuries, is particularly significant in this population group, which is related to thinning bone tissue, i.e. osteoporosis. This is the reason why, among the elderly, the assessment of fall and injury risk factors is significant, in order to identify and eliminate them, and to introduce preventive measures aimed at hindering these negative events. The problem of falls, injuries and bone fractures is added by the fact that the human population is becoming increasingly older and that in this population these events are increasingly more frequent, while the occurrence of bone fractures is increased by the presence of osteoporosis [5]. Approximately one third of the population aged 65 and over and one half of the population aged 80 and over, fall once per year, and, among those who have already experienced a fall, one third will fall again within the following six months [5, 6]. Consequently, some elderly people are prone to avoiding movement, i.e. becoming passive, which may be related to several psychophysical disorders. Osteoporosis is a bone condition, characterized by weakened bones and diminishing bone mass, with increased fragility. This condition occurs when osteoclasts degrade bone faster then osteoblasts synthetize it [7–11]. Oste-

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Abbreviations

DEXA – dual-energy X-ray absorptiometry
TUG – Timed Up and Go
FABQ-PA– Fear-Avoidance Beliefs Questionnaire – Physical Activity
FABQ-W– Fear-Avoidance Beliefs Questionnaire–Work

oporosis can also be defined as a "condition characterized by diminished bone mass and microdamages, i.e. degradation of bone tissue, leading to increased bone fragility and consequent increased incidence of fractures". Bone densitometry, or the measurement of bone density, is one of the main diagnostic procedures for establishing the presence of osteoporosis, called dual-energy X-ray absorptiometry (DEXA or DEX-Dual-energy X-ray absorptiometry). Hip and/or spine bone density is usually measured [12, 13]. Standard x-ray imaging is not reliable enough, since it shows the presence of osteoporosis only in advanced stages. Bone fractures among the elderly, osteporotic hip fractures especially, are a large burden on public health, increasing social costs and worsening individual health status. Moreover, these fractures among the elderly lead to increased morbidity, reduced quality of life and increased mortality. Statistical analyses show that among the population that suffered a hip fracture, less than one half returned from the hospital in the same functional state as before the fracture, while one fifth requires long-term care and recovery. Slow recovery from a fracture may initiate a vicious cycle, where physical disability, combined with decreased physical activity, may lead to additional bone weakening, increasing the risk of suffering a new fracture. Kinesiophobia, i.e. irrational fear of bodily movements, and fear and avoidance of regular daily activities and work, may consequently arise, which favors passivity and negatively influences functionality and quality of life [14, 15].

The most frequent risk factors, among several others, associated with the occurrence of osteoporosis are: older age, female sex, malnutrition, primary hypogonadism with low sex hormone values (estrogen in women and testosterone in men) or early menopause. Among pre-existing conditions the ones at risk are: Cushing syndrome, hyperthyroidism, hyperparathyroidism, diabetes mellitus, multiple myeloma, renal insufficiency, celiac disease, stroke, autoimmune disorders and other. Social risk factors include smoking, alcohol and coffee abuse and physical inactivity. Moreover, nutrition low in Calcium and vitamin D, high salt intake and malnutrition, are also included among risk factors for developing osteoporosis. Certain medication, when used over a long period of time, may reduce bone density, including: corticosteroids, anticonvulsants, antacids, non-steroid anti-inflammatory drugs, diuretics, lithium, tamoxifen, cyclosporine, immunosuppressants, heparin, etc. Early diagnosis, therapy and preventive measures are fundamental for reducing the negative consequences of osteoporosis. The most frequent risk factors of osteoporotic bone fractures among the elderly are: older age, bone osteoporosis and fragility, previous fractures, fall risks in the immediate and general environment, reduced psychophysical abilities and others. The increasing trend in the occurrence of osteoporosis is combined with insufficient use of preventive and therapeutic measures. Treatment of osteoporosis and the adoption of adequate preventive strategies may reduce negative consequences significantly, including osteoporotic bone fractures [16–21]. Removing fall and bone fracture risks in everyday life is also significant. One of the first steps in the prevention of falls and reduction in the incidence of fractures in osteoporosis is the assessment of fall and bone fracture risks. The following information and assessments are particularly significant:

1. fall anamnesis (current fall and falls over the previous 12 months, falls in closed environments, inability to stand up after falling).
2. use of phychotropic substances (benzodiazepine, antidepressants, sedatives, hypnotics etc.)
3. vision impairment
4. cognitive function impairment
5. mobility and gait, muscle strength and balance impairments
6. balance impairment and inability to pass from seated to standing position

In case fall risk factors are present, their removal is recommended in order to prevent falls and their consequences.

New falls risks and their removal for patients with osteoporosis

Some simple and efficient actions are recommended for removing risk factors of new falls and bone fractures:

1. exercise program improving physical activity (ex. standing, walking and adequate movement, training aimed at strengthening muscles and improving balance) [14, 18].
2. home visits by the doctor and identification of fall risk factors present in the home environment, their modification and removal, including: removing clutter from the dwelling, removing carpets in order to avoid tripping, securing electrical cables, installing handrails on walls and stairs, improving lighting etc.)
3. cessation/reduction of psychotropic drugs
4. if heart arrhythmia and anamnestic information on syncope are present, including a cardiologist is necessary, who will establish an adequate therapy and assess the need for a pacemaker.

Multiple falls risk assessment

It has been proven empirically that a multifactorial fall risk assessment is of great significance for the elderly with osteoporotic bone fractures.

The results of these assessments may be used for the implementation of preventive measures, in order to avoid new falls, injury and their consequences, and complications and problems for individuals and wider community that arise.

The following are used in risk assessment of future falls:

• Focused history and anamnesis_

– history of falls: detailed description of the fall/falls, frequency, symptoms at the time when the fall occurred, injuries and other consequences
– drugs in use: types and dosage (especially psychoactive drugs)
– history of relevant risk factors: acute and chronic conditions (ex. osteoporosis, urinary incontinence, neurological and cardiovascular conditions …)
• *Physical exam*
– assessment of gait, balance, mobility, joint functionality in the lower extremities …
– neurological functions: condition of peripheral nerves in the lower extremities, reflexes, proprioception, cortical, extrapyramidal and cerebellar function, vestibular dysfunction as cause of dizziness, fainting, balance dysfunction, assessment of cognitive status…
– muscle strength in the lower extremities
– cardiovascular status: pulse and rhythm, postural pulse and postural blood pressure
– assessment of visual focus
– assessment of feet and footwear
• Functional assessment
– assessment of everyday activities and skills, including the use of adaptive equipment and mobility devices
– patient's self-perception of functional abilities and fear of falling
• Environmental assessment
– presence of fall risk factors in the environment (mainly within the dwelling and immediate surroundings)

Repeated falls risk assessment in hospitals and nursing homes

This assessment includes the following actions:
• including a physiotherapist who will educate and treat patients adequately during their stay in the hospital, and train them in performing tasks in specific nursing home conditions and at home.
• assessment of the need for personal supervision and assistance in hospital and later at home
• in case of behavioral issues (agitation, delirium, aimless walking and wondering and others) causes should be examined and acted upon understandingly and appropriately
• using appropriate tests and exams aimed at assessing fall risk (balance and gait issues, cognitive issues, incontinence, feet, footwear, drugs, vision, environment, other psychophysical limitations, need for personal supervision and observation etc.)
• assessing the ability to perform everyday activities (moving, carrying, bending, bathing, dressing, walking, need for assistance etc.)

Fall risks and prevention in persons over 65 years of age

For persons over 65 years of age, it is advisable to identify fall and injury risk factors, and possibly remove or decrease some of them. Among these are: muscle weakness, impaired vision, cerebrovascular insult, arthritis, previous falls, anxiety, depression, gait and balance issues, dementia, Alzheimer's, Parkinson's, presence of more than one chronic issue hindering everyday activities, use of several medications simultaneously and age over 80.

Basic functionality and fall risk assessment

The assessment of physical functionality is necessary in identifying the existence of fall risk for patients. Among the most important aspects to consider are previous falls, muscle weakness, gait, balance and stability issues and impaired vision. The test Timed Up and Go (TUG) can be used to assess balance and stability when changing the position of the body and walking. It is a simple and valid instrument, which can be used to assess balance, mobility, walking ability and fall risk in the elderly.

Test performance: the patient stands up from a chair, walks 3 meters straights, turns around, returns to the chair and sits. Ability, quality and time required to perform the test are assessed.

Interpretation of results:
≤ 10 seconds = normal condition
≤ 20 seconds = good mobility, can walk independently, without assistance and walking aids
≤ 30 seconds = significant issues, cannot move independently outdoors, requires assistance walking
* A result of ≥ 14 seconds is already indicative of fall risk and it depends on the individual psychophysical condition.

Additional assessments in case of falls in the elderly

Additional assessments are:
– how the person perceives decreased functionality and fear of falling
– presence of urinary incontinence
– use of inadequate footwear
– neurological condition assessment
– psychological condition assessment
– cardiovascular status of the patient

In case some risk factors are present, adequate actions are recommended for removing or diminishing them, with education and promotion of preventive measures.

Diabetes mellitus as a fall and bone fracture risk factor

Recent studies have shown that diabetes mellitus and its complications can represent a fall and bone fracture risk factor in the elderly. Fracture risk is represented not only by unrecognized hypoglycemia, which may lead to a fall, but also by structural disorders of the cortical part of the bone, which increases the risk of fracture in case of fall. This disorder is caused by prolonged hyperglycemia, usually as consequence of inadequate therapy.

Biopsychosocial disease model

The biopsychosocial disease model in chronic conditions has been shown for the first time by George Engel, in 1977. His leading idea is described as the dynamic interaction between psychological, social and biological variables. It hypothesized that the mind, i.e. thoughts, and the immediate environment, may affect the body, i.e. the organism, and that the condition of the body, and its environment,

may inversely affect mind and thoughts. This model can be applied in the geriatric population with bone fractures.

Fear of injury

Fear is an emotional reaction to a specific, recognizable and immediate threat or danger (ex. of a new injury). This fear can protect the individual from danger through a defensive reaction (offensive or defensive behavior).

For individuals suffering from bone fracture, other injuries, as from lumbar syndrome, existing pain may cause a fear of movement, physical activity and work, and, consequently, they can start to avoid those movements that may increase the sensation of pain or cause new trauma.

However, this avoidance of movement and the forceful and unnatural position of the body, coupled with passivity, worsen the condition and postpone recovery after fractures and other injuries.

Fear of pain

The fear of feeling pain has negative prognostic value and effect on the development of chronic musculoskeletal pain in existing injuries.

The model of exaggerated pain perception and fear, along with avoidance of movement, combined with sensory and emotional aspects, may contribute to developing chronic musculoskeletal pain syndrome, causing fear and avoidance of movement, expressed as kinesiophobia.

Negative impact of the fear of movement, walking, physical activity and their avoidance

Fear and avoidance of movement (kinesiophobia) are often present in the elderly. This refers primarily to walking speed and quality, contributed significantly by comorbidities that can affect mobility and worsen morbidity. In this population, fear of physical movement may be closely related with the fear of balance disorders and falls, which commonly frequently present in the elderly population.

Fear and avoidance of movement (kinesiophobia) influence passivity and slower psychophysical recovery in cases of osteoporotic fractures, which may cause anxiety and depression.

Thus, kinesiophobia, fear, anxiety and depression may be reciprocally related and their combined effect further worsens the overall psychophysical condition of patients with bone fractures.

Fear and anxiety in case of injuries and their differences

Fear primarily motivates the person to react offensively or defensively in an existing situation.

Anxiety is combined with preventive behavior, engaging in avoidance of risky situations and actions.

Thus, anxiety, contrary to fear, represents an affective state oriented towards the future, without a clearly defined source of threat.

In any case, both anxiety, and fear and avoidance of physical activity, influence development, recovery and result after injury negatively and they should be identified and removed through an adequate psychological approach and cognitive-behavioral therapy, introducing gradual and moderate physical activity and physical therapy.

Application of these measures will contribute to a better therapeutic effect and faster patient recovery after injury.

Catastrophisation and kinesiophobia in patients with bone fractures

Catastrophisation of existing pain and development of kinesiophobia may also negatively affect recovery in patients with bone fractures.

Pain catastrophisation, which may be present along with anxiety, is a negative conviction and belief that the existing pain will lead to long-term, or even permanent, negative consequences. Catastrophisation is multidimensional, including negative thoughts, feelings of hopelessness and pessimism, which all contribute to the maintenance of pain, or its chronicity, with a negative impact on recovery after a bone fracture.

Catastrophisation of pain can often be associated with kinesiophobia.

Negative impact of anxiety and fear of movement, i.e. kinesiophobia

Numerous studies have shown that anxiety and fear and avoidance of movement (kinesiophobia) affect negatively overall health condition, everyday life and work activities and quality of life. Identifying and removing psychosocial factors has a positive impact on success and costs related to recovery in the elderly with bone fractures.

Negative consequences of anxiety and avoidance of physical activity after injury

Different studies prove the negative effects of anxiety and fear and avoidance of movement (kinesiophobia), physical activity and work, combined with the belief that they can cause pain or new injuries. These factors may be considered predictors, indicating the possibility of a worse therapeutic outcome and recovery. Numerous negative physiological and cognitive, behavioral and social consequences may arise, hindering everyday activities and diminishing quality of life. Identifying the presence of these factors and their removal are used in forming the therapeutic approach and improving therapy and recovery success in patients with osteoporotic fractures.

Questionnaires for identifying anxiety, kinesiophobia, fear and passivity in patients with injuries

In order to identify the presence of psychological states having negative effects on recovery among the elderly with bone fractures, psychometric assessments can be applied though appropriate questionnaires.

The following questionnaires are mostly used in practice:

– Spielberger Anxiety Inventory - State and Trait
– Tampa Scale of kinesiophobia
– Assessment questionnaire for fear and avoidance of physical activity and work, consisting in two parts:

a) avoidance of physical activity (Fear-Avoidance Beliefs Questionnaire – Physical Activity – FABQ-PA),

b) avoidance of work, or activity in the workplace (Fear-Avoidance Beliefs Questionnaire – Work – FABQ-W).

– other questionnaires and procedures in assessing fear, passivity and negative isolation.

The above mentioned questionnaires may be useful in assessing prognosis and efficiency of therapeutic procedures, but also as indicators of the tendency to chronicity and they may point out the need to include additional psychological, cognitive and behavioral actions aimed at improving therapeutic results.

Conclusion

Multidisciplinary approaches are used in prevention and treatment of osteoporotic fractures and psychophysical disorders, if present, along with physical therapy and rehabilitation. Modern physical therapy is focused on increasing bone and muscle strength, improving physical stability and mobility, but also on improving the overall psychophysical status of the patient. Balance, physical mobility and psychophysical disorders should be emphasized in the elderly, having a higher risk of falls and osteoporotic fractures. These disorders are further worsened by: avoidance of physical activity and movement, leading to passivity, and negative psychological factors, such as fears, anxiety, kinesiophobia and others. Therapeutic and rehabilitative procedures in osteoporotic fractures are multidisciplinary, engaging various specialists, with the aim to adequately educate and motivate the patient through therapeutic and preventive measures. These procedures affect the physical and psychological condition of the patient positively, with the reduction or removal of negative psychological beliefs.

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OSTEOARTHRITIS – ETIOPATHOGENESIS AND REVIEW OF NEW KNOWLEDGE, IMPORTANCE OF EARLY DIAGNOSIS

OSTEOARTROZA – ETIOPATOGENEZA I OSVRT NA NOVA SAZNANJA, ZNAČAJ RANE DIJAGNOSTIKE

Ksenija BOŠKOVIĆ

Summary

Introduction. Osteoarthritis is a chronic joint disease characterized by the degeneration of joint cartilage, surrounding bone and other extra-articular structures, which can cause pain and stiffness. Pathophysiologically, it is considered a multifactorial disease, caused by biochemical, endocrine, metabolic and other factors. An imbalance between pro-inflammatory and anti-inflammatory cytokines, inflammation of the synovial sheath, activation of matrix metalloproteinases and aggrecanases, lack of bone morphogenic proteins in cartilage tissue, increased secretion of nitrogen monoxide, apoptosis of chondrocytes, crystal deposition and the development of inflammation due to the action of adipokinaileptin play a significant role in the pathogenesis of osteoarthritis. Monoclonal antibodies inhibit angiogenesis factors and the action of pro-inflammatory cytokines, so they represent a signpost towards the development of etiological therapy. Research into the action of protease inhibitors indicates encouraging results in the therapeutic sense, as well as intra-articular application of mesenchymal stem cells. **Conclusions.** Establishing a diagnosis as early as possible is necessary in order to eliminate the symptoms of the disease and, more importantly, to prevent its progression and the resulting disability.

Key words: Osteoarthritis; Early Diagnosis; Biomarkers; Pathology; Cartilage, Articular; Cytokines; Antibodies, Monoclonal; Protease Inhibitors

Sažetak

Uvod. Osteoartroza je hronična bolest zglobova koja se karakteriše degeneracijom zglobne hrskavice, okolne kosti i drugih vanzglobnih struktura, što može uzrokovati bol i ukočenost. Patofiziološki se smatra da je multifaktorsko oboljenje, uzrokovano biohemijskim, endokrinim, metaboličkim i drugim faktorima. Značajnu ulogu u patogenezi osteoartroze ima neravnoteža između proinflamatornih i antiinflamatornih citokina, upala sinovijalne ovojnice, aktivacija matriks metaloproteinaza i agrekanaza, nedostatak koštanih morfogenih proteina u tkivu hrskavice, pojačano lučenje azot-monoksida, apoptoza hondrocita, taloženje kristala i razvoj inflamacije usled delovanja adipokina i leptina. Monoklonalna antitela koja inhibišu faktore angiogeneze i dejstvo proinflamatornih citokina tako da predstavljaju putokaz ka razvoju etiološke terapije. Istraživanja u pravcu delovanja inhibitora proteaza ukazuju na ohrabrujuće rezultate u terapijskom smislu, isto kao i intraartikularno aplikovanje mezenhimalnih matičnih ćelija. **Zaključak.** Neophodno je postaviti dijagnozu što ranije kako bi uklonili simptome bolesti ali čini se još značajnije suštinski sprečiti progresiju oboljenja i invaliditet kao posledicu.

Ključne reči: osteoartritis; rana dijagnoza; biomarkeri; patologija; zglobna hrskavica; citokini; monoklonalna antitela; inhibitori proteaze

Introduction

Osteoarthritis (OA) is a chronic joint disease characterized by the degeneration of joint cartilage, surrounding bone and other extra-articular structures, which can cause pain and stiffness [1, 2]. With the increase in life expectancy, especially in developed countries, the prevalence of degenerative rheumatic diseases is rapidly increasing (20% of the population, every tenth inhabitant, and after 65, 2-3 times more often) [3]. The prevalence of OA increases with age, but it is not an integral part of the physiological aging process. It is believed that there is a hereditary predisposition to the development of OA, along with numerous risk factors such as aging, obesity, postural imbalances, metabolic diseases and trauma. The relationship between symptoms (pain, joint thickening, crepitations during movement, transient signs of inflammation, restriction of movement) and radiological findings is not always proportional, so diagnosis and prognosis of disease progression are difficult, especially when it comes to middle-aged and young people [4, 5]. In the last 30 years significant progress has been made in the field of biochemical, immunological and cytohistological research in order to explain the pathogenesis [6].

Degenerative changes in OA affect the joints and interarticular structures, articular cartilage, synovial membrane, subchondral bone tissue, joint capsule, ligaments and muscles. In the earliest phase of OA, long before structural changes within the joint, biomarkers are identified in the synovial fluid that indicate the existence of an inflammatory process as well as changes in cartilage and bone metabolism [7]. Thus, the biomarkers bone sialoprotein (BSP), cartilage oligomeric matrix protein (COMP) and C-reac-

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Abbreviations

OA	– osteoarthritis
BSP	– bone sialoprotein
COMP	– cartilage oligomeric matrix protein
CRP	– C-reactive protein
PDGF	– platelet-derived growth factor
IGF	– 1insulin-like growth factor - 1
TGF	– transforming growth factor
IL-1β	– interleukin-1 β
TNF-α	– tumor necrosis factor - α
IL	– interleukin
IL-1Ra	– interleukin-1 receptor antagonist
MMP	– matrix metalloproteinases
TIMP	– tissue inhibitors of metalloproteinases
LIF	– leukemia inhibitory factor
CCL5	– CC - chemokine ligand 5
NO	– nitric oxide
NOS	– nitric oxyde synthase
eNOS	– endothelial nitric oxyde synthase
nNOS	– neuronal nitric oxyde synthase
iNOS	– inducible nitric oxyde synthase
COX-2	– cyclooxygenase-2
PGE2	– prostaglandin E2
VEGFA	– vascular endothelial growth factor
NGF	– nuclear growth factor
BMP-2	– bone morphogenetic protein - 2
BCP	– basic calcium phosphate
CPPD	– calcium pyrophosphate dihydrate
GRP	– galactosidase alpha-rich protein
JAK/STAT	– janus kinase/signal transducer and activator of transcription
WOMAC	– Western Ontario and McMaster Universities Arthritis Index
ACR	– American College of Rheumatology

tive protein (CRP) are registered in people who complain of pain, but have no radiologically visible changes in the joint [8, 9]. Early changes in OA are histologically shown as an accumulation of chondrocytes into clusters, chondrocyte mitosis, cartilage fibrillation, chondrocyte apoptosis and proteoglycan loss [10].

Cartilage consists mainly of collagen fibers of type II, XI and IX, so mutations affecting the genes for these types of collagen cause chondrodysplasia and faster development of OA [11]. Another important component of cartilage is proteoglycans, mainly aggrecan. They consist of a protein core and polysaccharide chains, chondroitin sulfate and keratan sulfate. Physiological degradation and synthesis of collagen fibers and proteoglycans in the extracellular matrix in equilibrium does not result in significant changes in the cartilage structure [12]. In OA, the balance is disturbed due to the activation of proteases, which cause the breakdown of collagen and proteoglycans. Liquid is released due to the breakdown of hydrophilic proteoglycan molecules, the formation of edema in the cartilage and the increase of pressure inside the cartilage, which causes the breaking of the bonds between the collagen fibers. As the disease progresses, the degenerative process becomes more dominant than the proliferation of chondrocytes and their increased ability to synthesize the extracellular matrix [6]. The surface of the cartilage becomes rough and flat, focal erosions occur, chondrocyte apoptosis occurs and the cartilage collapses.

In OA, the percentage of water in the extracellular matrix is higher, chondrocyte proliferation and cartilage metabolism are accelerated, while in the physiological aging process the number of chondrocytes remains the same or decreases, their response to growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1) and transforming growth factor β (TGF-β) decreases [13]. Aging leads to a decrease in the protective effect of TGF-β on cartilage and a change in the Smad 2/3 signaling pathway through which TGF-β affects chondrocytes, which can explain the link between aging and osteoarthritis. Telomere length and the ability to synthesize extracellular matrix in chondrocytes are also reduced.

The progressive loss of cartilage in OA is most affected by synovitis with mononuclear infiltration of the synovial membrane (macrophages, T-lymphocytes) with the production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines (IL-8). to the synovial fluid, they are presented to the synoviocytes as a foreign body, and therefore they produce mediators of inflammation (cytokines), which stimulate synovial angiogenesis via vascular endothelial growth factor (VEGF), further production of pro-inflammatory cytokines and enzymes, matrix metalloproteinases (MMP), and activate chondrocytes in the superficial layer of cartilage to produce degradation enzymes, but also pro-inflammatory cytokines and angiogenesis factor (VEGF), which closes the vicious circle of inflammation and cartilage degradation [14, 15].

A direct connection between mechanical injury and inflammation was also established. Any abnormal mechanical stress on the joint can lead to the activation of signaling in the cells of the joint, primarily in chondrocytes and bone cells in the subchondral bone, which function as mechanoreceptors [16]. Chondrocytes behave like activated macrophages in OA, and being significantly larger than macrophages, they release numerous pro-inflammatory cytokines (IL-1β and TNF-α, tumor necrosis factor α) that stimulate the production of other cytokines such as IL-6, IL-8 as and own production [17]. Other pro-inflammatory cytokines such as IL-15, IL-17, IL-18, leukemia inhibitory factor (LIF) and chemokines such as CC-chemokine ligand (CCL5) are elevated in OA and are associated with increased synthesis and release of MMP, i.e. reduction of proteoglycan synthesis. Increased serum levels of IL-6, IL-17 and TNF-α are associated with disease progression and pain intensity in OA [18]. Th17 lymphocytes secrete IL-17, which stimulates the infiltration of cartilage by neutrophils, stimulates the enzymes inducible nitric oxide synthase (iNOS) and collagenase with the release of IL-1, TNF-α and IL-6 from inflammatory, connective and epithelial cells. In addition to cytokines, vascular endothelial growth factor (VEGF) is also important, which stimulates angiogenesis, but also affects cartilage and chondrocytes. Recently, its role in the early stage of OA has been proven by inhibiting the regeneration of cartilage, that

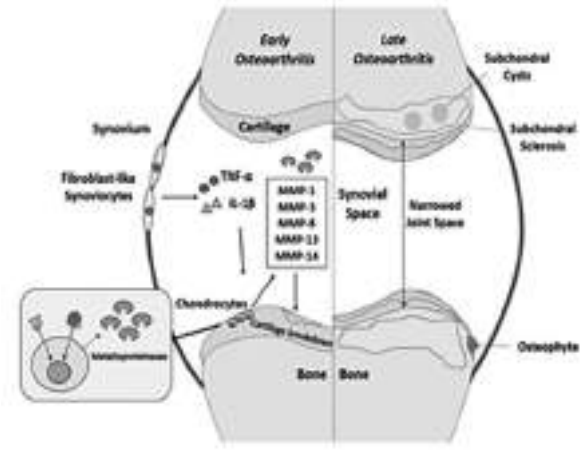

Figure 1. Pro-inflammatory mediators interleukin-1 β and tumor necrosis factor-α, secreted by fibroblast-like synoviocytes bind to receptors on chondrocytes to promote synthesis of matrix metalloproteinases which then break down cartilage leading to progression of osteoarthritis, which is characterized by the cardinal features of narrowed joint space, osteophytosis, subchondral sclerosis and cyst formation.
Slika 1. *Proinflamatorni medijatori interleukina-1β i faktor nekroze tumora-α, koje luče sinoviociti slični fibroblastima, vezuju se za receptore na hondrocitima kako bi stimulisali sintezu matriksnih metaloproteinaza koje zatim razgrađuju hrskavicu što dovodi do progresije osteoartritisa, koji se karakteriše kardinalnim karakteristikama suženog zglobnog prostora, osteofitoza, suphondralna skleroza i formiranje cista.*

is, the synthesis of aggrecan and collagen type II [19]. In addition to pro-inflammatory, anti-inflammatory cytokines are secreted in OA (IL-4, IL-10 and IL-13) that antagonize the effects of IL-1β, TNF-α and proteases. IL-4 inhibits the breakdown of proteoglycans by reducing the secretion of MMP, reduces chondrocyte apoptosis, and reduces the synthesis of IL-1β, TNF-α and IL-6. The anti-inflammatory effect of IL-13 is achieved through synovial fibroblasts, macrophages, B lymphocytes, NK cells and endothelial cells. It inhibits the synthesis of IL-1β, TNF-α and MMP-3 and increases the synthesis of IL-1Ra (interleukin-1 receptor antagonist) **(Figure 1).**

Cartilage destruction is caused by different MMPs, and the cells that produce MMPs produce products and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs) [20]. An imbalance in the production of MMP and TIMP leads to accelerated breakdown of cartilage. A significant role in the pathophysiology of osteoarthritis is played by bone morphogenetic protein (BMP-2) from the transforming growth factor-β (TGF-β) group, which stimulates the synthesis of proteoglycans and enchondral ossification; and BMP-7 from the same group which enhances the synthesis of type II collagen, aggrecan and hyaluronic acid as the main components of the extracellular matrix [21]. Cartilage oligomeric matrix protein (COMP) is an essential structural and functional part of the cartilage extracellular matrix. The use of biomarkers for the assessment of degenerative and inflammatory changes in the joint because it indicates cartilage remodeling and loss of the extracellular matrix. With the beginning of cartilage destruction, the imbalance of COMP, first in the synovial fluid and then in the serum, is observed significantly before the radiological signs of osteoarthritis [22]. Nitric oxide (NO) is important for adequate circulation and is produced by synthase (NOS), endothelial (eNOS) and neuronal (nNOS). In the pathogenesis of osteoarthritis, NO inhibits cell adhesion, reduces extracellular matrix synthesis and promotes chondrocyte apoptosis. It is thought that osteoarthritic chondrocytes exposed to NO produce cyclooxygenase-2 (COX-2) and produce prostaglandin E2 (PGE2) which enhances the inflammatory response [23]. The reduced number of cells and the inability to heal cartilaginous lesions lead to the conclusion that cell death plays an important role in the pathogenesis of osteoarthritis. It is known that NO in micromolar concentrations and the presence of oxygen free radicals lead to chondrocyte apoptosis.

As cartilage is a vascular tissue, mesenchymal stem cells do not reach it, so chondrocytes in healthy cartilage must be resistant to apoptosis [24]. The lack or degradation of the extracellular matrix can cause apoptosis of chondrocytes. Because in the cartilagecinema of phagocytes, the remains of chondrocytes remain in the tissue, coating it with calcium and inflam-

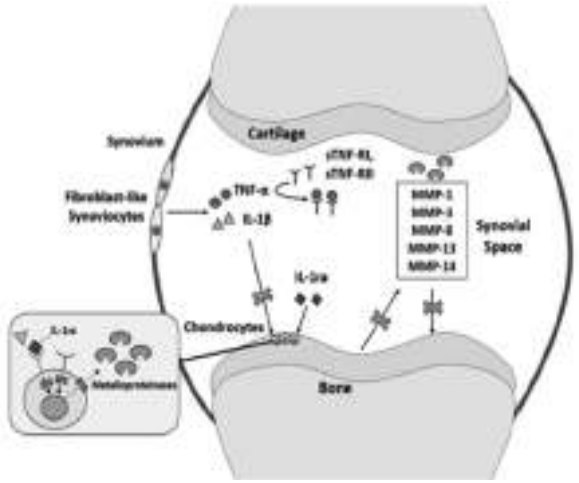

Figure 2. Autologous protein solution (APS) contains a number of anti-inflammatory cytokines including IL-1 receptor antagonist (IL-1ra) and soluble receptors I and II against TNF-α (sTNF-RI, and sTNF-RII), IL-1ra blocks the action of IL-1β by preferentially binding to the receptor on chondrocytes while sTNF-R1 and sTNF-RII bind directly to TNF-α. Via these mechanisms, APS inhibits production of matrix metalloproteinases and thus prevents progression of osteoarthritis.
Slika 2. *Rastvor autolognog proteina sadrži brojne antiinflamatorne citokine uključujući antagonist IL-1 receptora (IL-1ra) i rastvorljive receptore I i II za TNF-α (sTNF-RI i sTNF-RII), IL-1ra blokira dejstvo IL-1β prvenstveno vezivanjem za receptor na hondrocitima, dok se sTNF-R1 i sTNF-RII vezuju direktno za TNF-α. Preko ovih mehanizama, APS inhibira proizvodnju matriksnih metaloproteinaza i na taj način sprečava napredovanje osteoartritisa*

mation occurs. Crystal deposition in cartilage is a common finding in OA, but it is unknown whether this is a consequence or a cause of the disease. Basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) are often found in advanced OA [25]. Delayed CPPD is known to cause chondrocalcinosis, which increases the risk of developing OA of the knee or hand. BCP crystals have been proven to act as a factor-stimulator on fibroblasts, synovial cells and chondrocytes in vitro. They stimulate the synthesis and secretion of prostaglandins, c-fos and c-myc protooncogenes, MMP-1, MMP-3, MMP-8 and MMP-13. Inside chondrocytes, BCP increases the secretion of IL-6, and exogenous IL-6 enhances the formation of BCP crystals. The fact that the inhibitor of mineralization of the extracellular matrix galactosidase alpha-rich protein (GRP) also acts anti-inflammatory could be used in the future development of therapy for the treatment of OA [26] **(Figure 2)**.

The influence of obesity on the occurrence of OA is explained by self-biomechanical and metabolic theory [27]. According to the biomechanical theory, increased joint loading causes OA and a link between obesity and knee OA has been demonstrated, however, no link has been found between obesity and hip OA. On the other hand, the association between obesity and OA has been proven, which supports the metabolic theory [28]. Obesity is associated with insulin resistance, type 2 diabetes and cardiovascular disease, all of which cause a chronic inflammatory response where there is abnormal production of cytokines, increased acute phase proteins and activation of inflammatory signaling pathways. Chronic systemic inflammation is known to be associated with the development of OA. It is assumed that leptin produced by visceral adipocytes also affects chondrocyte metabolism via leptin receptors and janus *kinase/signal* transducer and activator of transcription (JAK/STAT) pathways [29]. Weight reduction reduces the biomechanical and metabolic impact of obesity on OA.

Osteoarthritis diagnosis

The diagnosis of osteoarthritis is based on history, clinical examination and radiological findings. Anamnesis is necessary to determine the character of the pain, its duration and localization, when the stiffness occurs and how long it lasts [30]. The presence of other symptoms should also be examined in order to exclude other types of diseases. On clinical examination, we find pain when manipulating the joint, crepitation and reduced range of motion. As the disease progresses, joint deformations are visible. The joints may be swollen due to the effusion of fluid, the muscles around the affected joint are often atrophied, and sometimes osteophytes or Heberden's nodules can be palpated. Radiological signs characteristic of osteoarthritis are joint fissure narrowing, subchondral bone sclerosis, subchondral cysts, and osteophyte formation. The scale devised by Kellgren and Lawrence in 1957 is used to assess the severity of the disease. The scale has 5 degrees, and the degree of the disease is determined by comparing X-ray images of the affected joint and images of a healthy joint. **Table 1** shows the scale for assessing the progress of knee osteoarthritis.

Table 1. Kellgren - Lawrence degree of knee osteoarthritis (according to Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis)
Tabela 1. *Kelgren-Lorensova klasifikacija osteoartritisa kolena (prema Kellgren JH, Lavrence JS. Radiološka procena osteoartroze)*

Degree *Stepen*	Description of changes *Opis promena*
0	There are no radiological signs of osteoarthritis/*Nema radioloških znakova osteoartritisa*
1	Possible narrowing of the joint space, a sign of osteophytes *Moguće suženje zglobnog prostora, prisustvo naznaka osteofita*
2	Certain presence of osteophytes and possible narrowing of the joint space *Prisutni manji osteofiti i moguće suženje zglobnog prostora*
3	Multiple osteophytes, certain narrowing of the joint space, bone sclerosis and possible deformities of the bone ends *Prisutni veći osteofiti, blago suženje zglobnog prostora, skleroza kostiju i mogući deformiteti koštanih krajeva*
4	Large osteophytes, significant narrowing of the joint space, significant sclerosis and certain deformities of bone ends *Veliki osteofiti, značajno suženje zglobnog prostora, značajna skleroza i određeni deformiteti krajeva kostiju*

Table 2. ACR diagnostic criteria for osteoarthritis of the knee (according to Altman R, Asch E, Bloch D and colleagues. Development of criteria for the classification and reporting of osteoarthritis)
Tabela 2. *Dijagnostički kriterijumi Američkog koledža za reumatologiju za osteoartritis kolena (prema Altman R, Asch E, Bloch D i kolegama. Razvoj kriterijuma za klasifikaciju i prijavljivanje osteoartritisa)*

Criteria/*Kriterijumi*	Knee pain + ≥ 1 sign/*Bol u kolenu + ≥ 1 znak*
Age/*Starost*	> 50 years/> *50 godina*
Stiffness/*Ukočenost*	< 30 minutes/< *30 minuta*
Crepitations/*Krepitacije*	+ osteophytes/+ *osteofiti*

Table 3. ACR diagnostic criteria for osteoarthritis of the hand (according to Altman R, Alarcón G, Appelrouth D and colleagues. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand)
Tabela 3. *Dijagnostički kriterijumi Američkog koledža za reumatologiju za osteoartritis šake (prema Altman R, Alarcon G, Appelrouth D i kolegama. Kriterijumi američkog koledža za reumatologiju za klasifikaciju i prijavljivanje osteoartritisa šake)*

Criteria/*Kriterijumi*	Hand pain or stiffness + ≥ 3 signs/*Bol ili ukočenost ruke + ≥ 3 znaka*
Hard tissue enlargement *Uvećanje tvrdog tkiva*	in ≥ 2 of 10 selected joints *u ≥ 2 od 10 odabranih zglobova*
Hard tissue enlargement *Uvećanje tvrdog tkiva*	in ≥ 2 distal interphalangeal joints *u ≥ 2 distalna interfalangealna zgloba*
&lt/&*lt*	3 swollen metacarpophalangeal joints/*3 otečena metakarpofalangealna zgloba*
Deformities/*Deformiteti*	≥ 1 of 10 selected joints/≥ *1 od 10 odabranih zglobova*

*10 selected joints are the proximal and distal interphalangeal joints of the second and third fingers and the first carpometacarpal joint on both hands/*10 odabranih zglobova su proksimalni i distalni interfalangealni zglobovi drugog i trećeg prsta i prvi karpometakarpalni zglob obe ruke*

Table 4. American College of Rheumatology diagnostic criteria for osteoarthritis (according to Altman R, Alarcón G, Appelrouth D and colleagues. The American College of Rheumatology criteria for classification and reporting of osteoarthritis of the hip)
Tabela 4. *Dijagnostički kriterijumi za osteoartritis Američkog koledža za reumatologiju (prema Altman R, Alarcon G, Appelrouth D i kolegama. Kriterijumi američkog koledža za reumatologiju za klasifikaciju i prijavljivanje osteoartritisa kuka)*

Criteria/*Kriterijumi*	Hip pain + ≥ 2 signs/*Bol u kuku + ≥ 2 znaka*
Sedimentation of erythrocytes *Sedimentacija eritrocita*	< 20 mm/h/< *20 mm/h*
Radiologically/*Radiološki*	Visible osteophytes of the femur or acetabulum/*Vidljivi osteofiti butne kosti ili acetabuluma*
Radiologically/*Radiološki*	Visible narrowing of the joint space/*Vidljivo suženje zglobnog prostora*

The Western Ontario and McMaster Universities Arthritis Index (WOMAC scale) can be used to assess the progress of osteoarthritis of the lower extremities. It is a standardized questionnaire aimed for the evaluation of hip osteoarthritis. It consists of 24 questions divided into three parts, which examine the level of pain, stiffness and functional limitations of the joints. We often find discrepancies between radiological findings on one hand and symptoms and clinical findings on the other. Hence the need to introduce more reliable criteria for the classification of diseases. The classification introduced by the American College of Rheumatology (ACR) is based on a combination of radiological findings, symptoms and clinical findings. In 1986, the ACR introduced a classification for osteoarthritis of the knee, in 1990 for osteoarthritis of the hand, and in 1991 for osteoarthritis of the hip [31, 32]. Joint pain is a mandatory finding for the diagnosis of osteoarthritis **(Tables 2, 3 and 4)**.

Conclusion

Osteoarthritis is a chronic joint disease characterized by degeneration of joint cartilage, surrounding bone and other extra-articular structures, which can cause pain and stiffness. Pathophysiologically, it is considered to be a multifactorial disease, caused by biochemical, endocrine, metabolic and other factors. An imbalance between pro-inflammatory and anti-inflammatory cytokines, inflammation of the synovial sheath, activation of matrix metalloproteinases and aggrecanase, lack of bone morphogenic protein in the cartilage tissue, increased secretion of nitrogen monoxide, apoptosis of chondrocytes, deposition of crystals and the development of inflammation due to the action of the adipokine ileptin play a significant role in the pathogenesis of osteoarthritis. Monoclonal antibodies that inhibit angiogenesis factors (vascular endothelial growth factor, nuclear growth factor) and the action of pro-inflammatory cytokines so that they represent a path towards the development of etiological therapy. Research into the action of protease inhibitors and inducible nitric oxyde synthase shows encouraging results in the therapeutic sense, as well as the intra-articular application of mesenchymal stem cells. Establishing a diagnosis as early as possible is necessary in order to eliminate the symptoms of the disease, but it seems even more important to fundamentally prevent the progression of the disease and the resulting disability.

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PAIN IN FOCUS IN PATIENTS WITH OSTEOARTHRITIS

BOL U FOKUSU KOD PACIJENATA SA OSTEOARTRITISOM

Snežana TOMAŠEVIĆ TODOROVIĆ and Tijana SPASOJEVIĆ

Summary

Introduction. Peripheral joint osteoarthritis is the leading cause of musculoskeletal pain and functional limitation. Osteoarthritis has a high prevalence and incidence and, therefore great socioeconomic importance. **Clinical presentation.** Pain in osteoarthritis results from a complex interaction of sensory, affective, and cognitive processes that include numerous abnormal cellular mechanisms at the affected joints and different levels of the nervous system involved in the pathophysiological mechanisms of chronic pain (spinal and supraspinal). In chronic pain states, central nervous system factors are particularly prominent. Although there are several ways to determine pain sensitivity, data suggest that assessing pressure pain threshold (i.e., tenderness to palpation) is the most reliable and reproducible method for identifying individuals with a centralized pain state. **Conclusion.** Significant advances in our understanding of pain pathophysiology and pain biomarkers are finally making the vision of "personalized analgesia". Clinicians can identify the sub-sets of individuals with what were once considered purely "peripheral" pain syndromes and treat these patients with approaches directed more centrally than peripherally.

Key words: Pain; Osteoarthritis; Pain Threshold; Pain Measurement; Central Nervous System Sensitization; Nociception; Diagnosis; Therapeutics

Sažetak

Uvod. Osteoartritis perifernih zglobova je vodeći uzrok mišićno-skeletnog bola i funkcionalnog ograničenja. Osteoartritis ima visoku prevalenciju i incidenciju, a samim tim i veliki socioekonomski značaj. **Klinička slika**. Bol kod osteoartritisa je rezultat složene interakcije senzornih, afektivnih i kognitivnih procesa koji uključuju brojne abnormalne ćelijske mehanizme na zahvaćenim zglobovima i različitim nivoima nervnog sistema uključenih u patofiziološke mehanizme hroničnog bola (spinalni i supraspinalni). U stanjima hroničnog bola, faktori centralnog nervnog sistema često igraju istaknutu ulogu. Iako postoji više načina da se odredi osetljivost na bol, podaci ukazuju na to da je procena praga bola na pritisak (tj. osetljivost na palpaciju) najpouzdaniji i najreproducibilniji metod za identifikaciju osoba sa centralizovanim stanjem bola. **Zaključak.** Značajan napredak u razumevanju patofiziologije bola su biomarkeri bola koji konačno stvaraju viziju „personalizovane analgezije". Kliničari mogu da počnu da identifikuju podgrupe pojedinaca sa onim što se nekada smatralo čisto „perifernim" sindromima bola i leče ove pacijente više centralno nego periferno usmerenim pristupima.

Ključne reči: bol; osteoartritis; prag bola; merenje bola; centralna senzitizacija; nocicepcija; dijagnoza; terapija

Introduction

Peripheral joint osteoarthritis is the leading cause of musculoskeletal pain and functional limitation. Osteoarthritis (OA) has a high prevalence and incidence and, therefore, great socioeconomic importance. Degenerative diseases most often affect the joints of the hips, knees, hands, and spine but can also affect any joint. Degenerative diseases are generally equally represented in both sexes, except for the hip joint, where they occur more often in women than in men. Data on the prevalence of osteoarthritis vary depending on whether the diagnosis is made clinically or radiologically. In developed countries, 27-44% of the population has radiographic changes in the sense of osteoarthritis, while 7-11% have symptomatic arthrosis [1], indicating a large discrepancy between radiological and clinical findings. In some patients with pronounced problems in the knee joint, minimal changes can be found on X-rays, while in other patients, significant degenerative changes can be found on X-rays, and that person has almost no problems [2, 3].

Risk factors for symptomatic radiologically confirmed OA are, in addition to genetic factors, obesity (body mass index ≥ 30), older age and male gender [4].

The frequency and intensity of chronic pain in conservatively and operatively treated knee OA patients significantly correlate with obesity, helplessness, comorbidities, anxiety, and depression [5, 6].

Clinical presentation

Osteoarthritis major symptoms include joint pain which is described as dull and mild intensity by patients. It occurs during movement and after more prolonged activities such as long walks or standing still [2]. Pain occurs during usage of joints with circadian variations, and intensifies during the night in the early stage of illness (mechanical hyperalgesia). Reflex pain can also occur in other healthy joints, such as knee pain during coxarthrosis or ankle joint during knee osteoarthritis. Major symptom is morning stiffness (up to 15 minutes) or temporary stiffness during the day after a joint has stood still. Feeling of insecurity while using

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Abbreviations

OA	– osteoarthritis
BMLs	– connection between marrow lesions
TNF-α	– tumor necrosis factor - α
CNS	– central nervous system
JNK	– Jun N-terminal kinases
CS	– central sensitization
NF-κB	– nuclear factor κB
ATP	– adenosine triphosphate
TKA	– total knee arthroplasty
QST	– quantitative sensory testing
PNE	– pain neuroscience education

the joint or feeling of the joint being disabled for certain maneuvers can occur in patients diagnosed with osteoarthritis.

Major clinical signs of osteoarthritis include local sensitivity of certain points on a joint or tendon attachment in the vicinity of a joint; hard thickened joint bone ends, and sometimes even mass enlargement of soft tissues of a joint or around the joint: crepitation during movement, outburst in a joint hollow cavity without higher joint temperature; limited and painful movements due to effect of more serious joint injury.

The fact that central factors may be important in osteoarthritis helps explain the fact that co-morbid somatic symptoms known to be associated with centralized pain states (e.g., fatigue, sleep disturbance) are very commonly present in osteoarthritis, and are not explained by a purely "peripheral" model of this condition [5].

Pathophysiology of pain in arthritis

The pathophysiology of osteoarthritis is still not completely clear, but it is believed that the disease is caused by a combination of biochemical, biomechanical, inflammatory and immunological factors.

There is increasing evidence that osteoarthritis is a systemic musculoskeletal disease rather than a local change in the synovial joints. Inflammation of the synovium is considered to be a key factor in the progression of cartilage and subchondral bone damage. Research conducted over the past several decades indicates the importance of subchondral bone remodeling in the initiation and progression of osteoarthritis. It indicates the connection between marrow lesions (BMLs) and synovitis/effusion and pain [7, 8].

Pain in osteoarthritis results from a complex interaction of sensory, affective, and cognitive processes that include numerous abnormal cellular mechanisms at the affected joints and different levels of the nervous system involved in the pathophysiological mechanisms of chronic pain (spinal and supraspinal).

The degree of changes at the level of the subchondral bone and the synovial sheath are predictive factors for the appearance of pain in the affected joints [9]. Richly vascularized and innervated osteochondral junctions, along with periosteal irritation due to increased intraosseous pressure, contribute to worsening pain in patients with OA. The subchondral bone, periosteum, ligaments, periarticular muscle, outer third of the meniscus, synovium, and joint capsule are richly innervated and the likely sources of nociception in OA, particularly early in the course of disease. In an arthroscopy study, an awake, unanesthetized evaluation of the knee joint identified the synovium, joint capsule, infrapatellar fat pad, and outer layers of the meniscus as being painful, while cartilage, which is neural in healthy joints, was not painful (the bone was not probed as it is known to be painful) [10].

The role of peripheral nociceptive neurons in the pathophysiology of joint pain

Sensory and sympathetic peripheral nerve fibers innervate peripheral joints. Unmyelinated C fibers make up ¾ of peripheral nerve fibers, especially in joint structures. In joint structures, 50% of unmyelinated C fibers are responsible for sympathetic efferent signals. Articular nociceptors, i.e., specialized nerve endings, are found in joint capsules and ligaments (not in cartilage) and are classified into the group of "high threshold" mechanoreceptors with a high threshold, polymodal nociceptors, and "silent" nociceptors. "High threshold" mechanoreceptors are activated by very intense mechanical stimuli and movements outside the physiological range. Polymodal receptors respond to stimuli of high intensity (mechanical, chemical, thermal). "silent" nociceptors or "sleep" nociceptors are activated when stimulated by inflammatory conditions or injured tissues. One of the possible explanations for their activation is the lowering of the stimulus threshold and the stimulation of their response by continuous stimulation from the damaged tissue. The activation of "silent" nociceptors could play a major role in the induction of hyperalgesia, central sensitization, and allodynia.

Sensitized afferent fibers respond to pressure in adjacent areas, distant areas, and even in the contralateral limb.

The resulting action potentials are further sent to the dorsal horn of the spinal cord by peripheral afferent fibers, which are divided into two main groups: Aδ-fibers and C fibers.

Type I Aδ-myelinated fibers respond to mechanical and chemical stimuli but have a relatively high excitability threshold for thermal stimuli (> 50ºC). For this type of Aδ-fiber, the occurrence of sensitization at the site of the lesion is important, which means that the mechanical or thermal threshold of excitability will be reduced. Type II Aδ-nociceptors have a much lower threshold for excitability to thermal stimuli and a significantly higher threshold to mechanical stimuli. Therefore, the activity of type II fibers is responsible for the first reaction to harmful heat, while type I Aδ-fibers mediate the appearance of mechanically caused pain. C fibers are thin demyelinated fibers of a polymodal character, which transmit slow, dull, diffuse pain, and are sensitive to several types of stimuli, such as mechanical, thermal, and chemical.

Neurons for processing nociceptive inputs from the musculoskeletal system

Aδ and C fibers enter the spinal cord via the spinal root, after which pain signals are transmitted to the brain via the neospinothalamic or paleospinothalamic tract.

After a peripheral lesion or inflammation, the painful impulse is transmitted by neurons to the spinal cord, where microglia and then astrocytes are activated, which contributes to central sensitization [11]. There are changes in their number, size, then the expression of molecules on their surface and quantity, the type of mediators they release. Activation of microglia secretes signaling molecules, the most important of which are tumor necrosis factor - α (TNF-α) and interleukin 18 (IL-18). TNF-α causes the phosphorylation of c-Jun N-terminal kinases (JNK) enzymes in astrocytes, and affects the biosynthesis of pro-inflammatory cytokines at the transcriptional and translational level. Interleukin 18, released from microglia, activates a specific receptor in astrocytes, further activating the transcription factor nuclear factor κB (NF-κB). Astrocytes release numerous molecules after their activation, and some of them in turn influence the activity of microglial cells, such as adenosine triphosphate (ATP) and interferon-γ.

Aδ Nociceptive stimuli from muscles and joints activate the cortical pain matrix (anterior cingulate cortex, insula and thalamus). Imaging studies show signs of atrophy in the thalamus and gray matter in patients with chronic osteoarthritis, which are reversible in imaging studies after arthroplasty.

Descending inhibitory influences from brain structures (periaqueductal gray mass, nc. raphe magnus and reticular formation, tegmentum pons) through the production of mediators such as serotonin, endogenous opioids, norepinephrine - modulate nociceptive input from the periphery, and knowledge of these mechanisms enables the development of pharmacotherapeutic options for treatment of chronic pain conditions.

The role of the central nervous system in osteoarthritis

Central nervous system (CNS) factors in chronic pain states often play a particularly prominent role. In many individuals with chronic pain, pain can occur with minimal or no evidence of ongoing nociceptive input. The hallmark of these "centrally driven" pain conditions is a diffuse hyperalgesia state identifiable through the use of experimental sensory testing and by functional neuroimaging. Characteristic symptoms of these central pain conditions include multifocal pain, fatigue, poor sleep, memory complaints, and frequent co-morbid mood and anxiety disorders. Central sensitization (CS) is closely associated with more severe and persistent pain after total knee arthroplasty (TKA). Based on reviews, when performing TKA in CS patients, it is important to develop realistic patient expectations through appropriate education on general postoperative pain patterns in CS [12].

Evaluation and diagnostic methods in osteoarthritis patients

Although there are several ways to determine pain sensitivity, data suggests that assessing pressure pain threshold (i.e., tenderness to palpation) is the most reliable and reproducible method for identifying individuals with a centralized pain state [13]. Quantitative sensory testing (QST) is not yet widely available in clinical practice. Many studies have shown that some individuals with osteoarthritis have lower overall pain thresholds than controls and have less efficient descending analgesic activity [14, 15].

Although there is no specific clinical test for CS, signs and symptoms, like ongoing, spontaneous, and widespread pain, or severe and prolonged pain following a seemingly innocuous stimulus, raise clinical suspicion. To identify secondary hyperalgesia (increased pain sensitivity in undamaged tissue away from the site of a painful lesion), nociceptive stimuli are applied in an area innervated by a different segmental level. Tertiary hyperalgesia (increased pain sensitivity on the contralateral side of a painful lesion) has been reported in several conditions (e.g., unilateral neuropathic pain and knee osteoarthritis) [16]. The contralateral side may, therefore, not be a true control in a patient [17], so QST values should be compared to published normative reference values where available.

Central sensitization screening questionnaires (e.g., the Central Sensitization Inventory and Pain Sensitivity Questionnaire) have good clinical measurement properties (e.g., validity and reliability) [18].

Imaging methods (magnetic resonance, ultrasound) are very useful methods for the diagnosis and evaluation of patients with knee osteoarthritis because they can visualize changes in all structures including synovitis, BMLs varying from edema, fibrosis, osteonecrosis, trabecular abnormalities to bone remodeling [19].

Pain therapy in osteoarthritis

The therapeutic approach depends on the stage of the disease, the characteristics of pain, the present risk factors, and the level of biomarkers of poor prognosis. Non-pharmacological (non-surgical) interventions with broad support include patient education and self-management strategies, low-impact aerobic exercise, weight loss if the patient is overweight, use of walking aids and other assistive devices, and thermal modalities [20]. Education of patients with chronic knee OA through pain neuroscience education (PNE) [21] contributes to patient desensitization, reduction of pain and dysfunctionality, fear through a reconceptualization of pain, change of beliefs about pain - application of various cognitive techniques, and serves as a good introduction to manual therapy and other types of treatment [22]. Literature data indicates that patients with osteoarthritis of the knee benefit from kinesitherapy and hydrokinesis therapy (range of motion exercises, strength, aerobic activity), as well as after the application of Taichi [23]. Osteoarthritis is the main cause of disease in elderly patients with frequent comorbidities, who often take multiple medications, and the choice of analgesic must be carefully considered [24, 25].

The emphasis is on the application of kinesitherapy and various forms of physical therapy along with changing lifestyle habits and the application of advice to facilitate the performance of daily activities. There is also some evidence that cognitive-behavioral therapy could be effective in addressing insomnia and other sleep problems frequently observed in osteoarthritis

[26, 27]. Patients with chronic pain accompanied by central sensitization are responsive to CNS neuromodulating agents, such as serotonin-norepinephrine reuptake inhibitors and anticonvulsants.

Conclusion

Significant advances in our understanding of pain pathophysiology and pain biomarkers are finally making the vision of "personalized analgesia". By carefully assembling clues from a history and physical examination, clinicians can now begin to identify the sub-sets of individuals with what were once considered purely "peripheral" pain syndromes, and treat these patients with more centrally - than peripherally-directed approaches. Patient education with the application of non-pharmacological methods and combined therapy with drugs with different mechanisms of action will enable better control of symptoms and improvement of function in patients with chronic degenerative diseases of peripheral joints.

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PHARMACOLOGICAL OSTEOARTHRITIS THERAPY AND MODERN THERAPEUTIC PRINCIPLES

MEDIKAMENTNA TERAPIJA OSTEOARTROZE I SAVREMENI TERAPIJSKI PRINCIPI

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Summary

Introduction. The purpose of treating osteoarthritis is to relieve pain, improve the function of the osteoarthritic joint, and arrest further development of osteoarthritis through non-pharmacological and pharmacological treatment modalities. **Pharmacological osteoarthritis therapy.** In the treatment of osteoarthritis, guidelines and recommendations are often consulted, but they do not dictate the treatment mode, which is tailored to the individual needs of the patient. These guidelines promote desired and positive treatment outcomes, but cannot predict a specific outcome. They are also valuable when analyzing the use of topical and oral non-steroidal anti-inflammatory drugs, keeping dosage as low as possible for the shortest time. For example, monitoring hepatotoxicity is advised when administering paracetamol, while caution is needed when prescribing drugs with a central effect due to the possible development of addiction and appearance of toxic effects. A significant body of research on the use of chondroprotectors exists, but there is a large discrepancy across studies. Nonetheless, their findings indicate benefits of intra-articular administration of glucocorticoids. However, their more frequent administration can lead to accelerated cartilage loss, while guidelines differ concerning intra-articular administration of hyaluronic acid, the administration of plasma enriched with platelets, and the administration of stem cells due to the heterogeneity of the preparations and the lack of standardization in their administration. **Conclusion**. Non-surgical therapy is a growing field of research, especially from a pharmacological point of view, intending to find the best treatment to slow down or completely stop further development of osteoarthritis.

Key words: Osteoarthritis; Pain Management; Drug Therapy; Practice Guidelines as Topic

Sažetak

Uvod. Svrha lečenja osteoartroza je da se ublaži bol, poboljša funkcija osteoartrotičnog zgloba i zaustavi dalji razvoj osteoartroze nefarmakološkim i farmakološkim modalitetima. **Medikamentna terapija osteoartroze.** Za lečenje osteoartroze konsultuju se važeće smernice i preporuke, ali one ne diktiraju način lečenja, i njihova primena se prilagođava individualnim potrebama pacijenata. Vodiči promovišu željene i pozitivne ishode lečenja, ali ne mogu da osiguraju (ili obezbede) specifičan ishod. Takođe je korisno analizirati primenu topikalnih i oralnih nesteroidnih antiinflamatornih lekova, vodeći računa da doza bude što niža uz najkraći vremenski period. Na primer, za primenu paracetamola se savetuje praćenje hepatotoksičnosti, dok je obazriv pristup potreban za lekove sa centralnim efektom zbog mogućeg razvoja zavisnosti i pojave toksičnih efekata. Postoji i mnogo istraživanja u kojim se analizira primena hondroprotektora, uz veliku diskrepancu među studijama. Rezultati ipak ukazuju na benefite intraartikularne primene glikokortikoida. S druge strane, njihova češća primena može dovesti do ubrzanog gubitka hrskavice, dok su smernice neusaglašene kad je u pitanju intraartikularna primena hijaluronske kiseline, primena plazme obogaćene trombocitima i primena stem-ćelija zbog heterogenosti preparata i nedostatka standardizacije primene. **Zaključak.** Neoperativni tretman je rastuće polje istraživanja, posebno sa farmakološkog gledišta sa ciljem pronalaženja najboljeg tretmana koji bi usporio ili potpuno zaustavio dalji razvoj osteoartroze.

Ključne reči: osteoartritis; terapija bola; farmakoterapija; vodiči kliničke prakse

Introduction

Osteoarthritis (OA) is the most prevalent degenerative joint disease, affecting more than one quarter of adults worldwide [1]. This chronic condition is characterized by clinical symptoms and distortion of joint tissues resulting from damage to joint cartilage, which causes pain, swelling, and stiffness around the affected joint, leading to disability in most severe cases [2]. OA causes can be non-genetic (age, gender, obesity, mechanical stress, sedentary lifestyle, occupational activities, joint trauma) or genetic (altered gene expression patterns in the cells comprising cartilage and subchondral bone). Irrespective of its origin, OA can affect any joint, but it is most prevalent in hands and weight-bearing joints in legs [3]. For example, hip osteoarthritis is a major global public health burden and, although age-standardized incidence rate (ASIR) and age-standardized incidence and disability-adjusted life years (DALY) rates vary among countries, they have exhibited an upward trend in almost all countries over the past three decades. The total age-standard-

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Abbreviations

OA – osteoarthritis
ASIR – age-standardized incidence rate
DALY – disability-adjusted life years
BMI – body mass index
HA – hyaluronic acid
ACR – American College of Rheumatology
K-L – Kellgren-Lawrence
CPGs – clinical practice guidelines
EULAR – European League Against Rheumatism
NSAIDs – non steroidal anti-inflammatory drugs
IA – intra-articular
IAHA – intra-articular hyaluronic acid
CMC – carpometacarpal
MTX – Methotrexate
TNF – tumor necrosis factor
IL-1 – Interleukin-1
ESCEO – The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
SYSADOAs – symptomatic slow-acting drugs in osteoarthritis
ASU – avocado soybean unsaponifiables
pCGS – prescription crystalline glucosamine sulfate
CS – chondroitin sulfate
GI – gastrointestinal
CV – cardiovascular
IACSs – intra articular corticosteroids
OARSI – Osteoarthritis Research Society International
COX-2 – cyclooxygenase 2
PPIs – proton pump inhibitors
APAP – acetaminophen/paracetamol
CBT – cognitive behavioral therapy
NICE – National Institute for Health and Care Excellence
MW – molecular weight
FDA – Food and Drug Administration
TKA – total knee arthroplasty
PRP – platelet rich plasma
RBCs – red blood cells
WB – whole blood
WBCs – white blood cells
P-PRP – pure PRP
L-PRP – leukocyte rich PRP
PPP – platelet-poor plasma
RCTs – randomized controlled trials
MSCs – Mesenchymal stem cells

ized prevalence of knee osteoarthritis is also on the increase, especially among older adults, given that 3.1% was reported for the 45–54 age group in 2015, and this percentage increased to 15% in people aged 85 years and older [4]. This upward trajectory is expected to continue due to the rapid aging of the world's population [5]. Existent evidence also indicates variations concerning sex and age, whereby the elderly are most affected by knee and hip OA, while hand OA tends to emerge in perimenopause [6]. Ample evidence also suggests that individuals with lower limb and hand OA are at higher risk of incident knee and hip disease [7]. Similarly, there is a positive correlation between body mass index (BMI) and the risk of OA in weight-bearing joints, but not hand OA. Causality of all OA, knee OA, and hip OA was also established for high femoral neck bone mineral density and low systolic blood pressure [8]. Existent research further suggests that physical workload, participation in high-intensity sports, and being overweight are risk factors for hip and knee OA, hip OA, and clinical hip OA, respectively. In terms of the prognostic factors, high hyaluronic acid (HA) serum levels are presently considered the most reliable marker for knee OA, while a superolateral type of migration of the femoral head and atrophic bone response are prognostic factors for hip OA [9]. It is also widely recognized that metabolic syndrome - a group of cardiovascular conditions, including diabetes and hyperglycemia, abdominal obesity, hypercholesterolemia, and hypertension - and its individual components increase the risk of knee OA [10].

In clinical practice, these findings, along with the American College of Rheumatology (ACR) OA criteria, are often used when planning treatment. The ACR OA criteria were developed to standardize the definition of hip, knee, and hand OA, as well as to delineate the most common joint symptoms and help with the exclusion of inflammatory conditions. In this context, the Kellgren-Lawrence (K-L) system is employed for radiographic grading based upon the presence and severity of certain defined radiographic features, including osteophytosis, joint space narrowing, joint line sclerosis, and subchondral cysts, leading to five grades, anchored at 0 (normal joint) and 4 (complete joint space loss) [11]. These analyses are interpreted for the purpose of OA treatment to alleviate pain and improve joint function through either pharmacological or non-pharmacological means.

Pharmacological Osteoarthritis therapy and modern therapeutic principles

While considerable beneficial advances have been made in the medical, biomedical, and healthcare fields, they have also increased the level of uncertainty in clinical practice. To mitigate this issue, clinicians rely on clinical practice guidelines (CPGs) aimed at establishing standards of care grounded in strong scientific evidence with the goal of improving patient outcomes. These recommendations are based on the assessment of the benefits and costs of specific treatment modalities and available alternatives, as well as areas that require improvement [12]. However, due to the wide range of CPGs [13], it can be challenging to translate best evidence into best practice, as the methodology used when establishing guidelines is often poorly defined and varies greatly within and among organizations [14].

For example, the European League Against Rheumatism (EULAR) has provided one of the most highly respected recommendations for the management of hand OA, but new evidence has emerged since their publication in 2007, indicating that an update is warranted. Still, EULAR recommendations 1–3 which cover different non-pharmacological treatment options (education, assistive devices, exercises, and orthoses) remain highly applicable, while recommendations 4–8 should be more thoroughly revised, as they describe

the role of different pharmacological treatments, and may not necessarily reflect the current experience with all available treatment modalities. At present, OA therapy typically involves the use of topical treatments such as topical non-steroidal anti-inflammatory drugs (NSAIDs), oral analgesics (particularly short-term use of NSAIDs for symptom relief), and chondroitin sulfate (for symptom relief). On the other hand, intra-articular (IA) glucocorticoids are generally not recommended unless the patient presents with interphalangeal OA, and the use of conventional/biological disease-modifying antirheumatic drugs is also discouraged [15].

When treating patients with knee or hand OA, consulting the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee Guideline: Topical NSAIDs is strongly recommended. These guidelines stipulate that topical capsaicin should not be prescribed for hand OA treatment due to the lack of direct evidence to support its use, as well as a potentially increased risk of eye contamination. Similarly, topical capsaicin is not recommended for hip OA owing to the large distance between the skin and the affected joint. Consequently, oral NSAIDs should be prescribed to patients with knee, hip, and/or hand OA, making sure that the treatment duration and dose are kept at the minimum. These guidelines further indicate the beneficial role of IA glucocorticoid injections for patients with knee and/or hip OA as well as for patients with hand OA, which are deemed superior to other forms of IA injections such as HA preparations. Acetaminophen is also conditionally recommended, but should not exceed the maximum daily dosage of 3 gm, while duloxetine is believed to help patients with knee, hip, and/or hand OA, especially when combined with NSAIDs. When NSAIDs and/or surgery are contraindicated, tramadol can be a viable option, while non-tramadol opioids should be considered when all applicable alternatives have been exhausted. On the other hand, glucosamine is strongly discouraged in the treatment of knee, hip, and/or hand OA, deviating from prior guidelines in which its use was conditionally recommended. Likewise, the use of chondroitin sulfate in isolation or in combination with glucosamine is not advised when treating patients with knee and/or hip OA, but can be prescribed with caution to patients with hand OA. Conditional recommendation against intra-articular hyaluronic acid (IAHA) is also given when treating patients with knee and/or first carpometacarpal (CMC) joint OA, while IAHA should not be used when treating hip OA. Similarly, platelet-rich plasma and stem cell injections are strongly discouraged in patients with knee and/or hip OA owing to the concern regarding the lack of standardization in available preparations as well as techniques used. The same conclusions apply to Methotrexate (MTX), hydroxychloroquine, Tumor necrosis factor (TNF) and Interleukin-1 (IL-1) as well as bisphosphonates, while colchicine, vitamin D, and fish oil are seen as potentially beneficial despite limited evidence supporting their efficacy [16].

In this context, The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) step-wise algorithm of recommendations should also be considered, as it has a positive international reputation in the management of knee OA, given that its development was guided by the findings yielded by existent studies on the efficacy and safety of all treatment modalities. The algorithm is a result of collaboration among 18 international working group members comprising rheumatologists, specialists in physical medicine and rehabilitation, clinical epidemiologists, endocrinologists, pharmacologists, orthopedic surgeons, geriatricians, specialists in public health and health economics, research scientists, and patient representatives with extensive knowledge on the performance, analysis, and interpretation of clinical trial evidence related to knee OA. For a treatment to be given a strong recommendation, a positive vote by at least 75% of the members is required. Accordingly, paracetamol (acetaminophen) is recommended as initial analgesia treatment, despite ample clinical evidence of its minimal impact on symptoms as well as its considerable degree of liver and gastrointestinal toxicity, especially in higher doses (4 g/day).

ESCEO also offers guidelines for the use of symptomatic slow-acting drugs in osteoarthritis (SYSADOAs), including glucosamine, chondroitin, diacerein, and avocado soybean unsaponifiables (ASU). As the initial pharmacological treatment, the ESCEO working group specifically advocates the use of pharmaceutical-grade prescription crystalline glucosamine sulfate (pCGS) and chondroitin sulfate (CS) as a long-term background therapy for the management of knee OA, which can also include topical NSAIDs, particularly in elderly OA patients (aged ≥ 75 years) and those with comorbidities or at an increased risk of systemic adverse events. The working group, however, cautions that oral NSAID selection should be guided by the patient risk profile and the level of gastrointestinal (GI) or cardiovascular (CV) risk associated with each NSAID. For example, celecoxib (200 mg/day) is recommended due to its better overall safety profile, while a weak recommendation is given for IAHA injections in patients suffering from knee OA. Specifically, it is advised that IAHA be administered once the acute inflammatory flare has settled, at which point IA corticosteroids (IACSs) may be appropriate for treating knee effusion or for managing severe pain. Among the pharmacological options given weak recommendation by the ESCEO working group are short-term weak opioids (such as tramadol) and duloxetine (which can be used as an alternative to weak opioids, especially in patients with pain from central sensitization). Still, when all treatment modalities have been exhausted, if the patient is severely symptomatic and their quality of life is severely compromised, total knee replacement surgery is the only remaining option [17].

Osteoarthritis Research Society International (OARSI) guidelines should also be consulted, as they offer patient-focused treatment recommendations for

individuals with knee, hip, and polyarticular OA, classified under five levels, depending on the treatment stage in which they should be introduced. According to these guidelines, topical NSAIDs are strongly recommended as Level 1A treatment for individuals with knee OA, while cyclooxygenase (COX-2) inhibitors are considered Level 1B treatment for individuals with gastrointestinal comorbidities, and NSAIDs with proton pump inhibitors (PPIs) are added at Level 2. However, no use of oral NSAIDs is recommended for individuals with CV comorbidities. Depending on the comorbidity status, IACSs, IAHA, and aquatic exercise can be used as Level 1B/Level 2 treatments for knee OA, unless patients present with hip or polyarticular OA. The use of IACSs for short-term pain relief and IAHA for long-term use (due to a better safety profile) is conditionally recommended for treating knee OA in all comorbidity subgroups. On the other hand, Level 4A and 4B treatment with acetaminophen/paracetamol (APAP) is conditionally not recommended, and the use of oral and transdermal opioids as Level 5 treatment is strongly not recommended. These guidelines are incorporated into a treatment algorithm, allowing health practitioners to determine the best modality for patients with diverse profiles [18].

Guided by the success of the aforementioned algorithm, several alternatives have been proposed, including the simplified OARSI and ESCEO treatment algorithms for the non-surgical management of knee OA in patients without comorbidities published in 2019. For example, the OARSI algorithm indicates topical NSAIDs as the first line of treatment, whereas ESCEO recommends referral to health professionals, along with the use of physical therapy and SYSADOAs. In ESCEO Step 2, low-dose, short-term paracetamol and topical NSAIDs are prescribed for persistent symptoms, along with PPI, COX-2-selective drugs and non-selective NSAIDs, intra-articular corticosteroids, and/or IAHA, while OARSI proposes non-selective NSAIDs, non-selective NSAIDs with PPI, COX-2 inhibitors, and IACSs, combined with aquatic exercise, gait aids, and self-management programs. Step 3 according to OARSI includes IAHA and cognitive behavioral therapy (CBT) with exercises, while ESCEO recommends short-term, weak opioids, such as duloxetin. As these OARSI and ESCEO treatment algorithms overlap considerably, they should provide confidence and clarity for practicing clinicians regarding knee OA treatment. Still, the differences between the two sets of recommendations should not be neglected, as they highlight the importance of refining and harmonizing the methodology, allowing more widespread adoption of uniform guidelines by multiple societies and non-governmental organizations [19].

Another set of guidelines was produced by the National Institute for Health and Care Excellence (NICE), which cover topical, oral, and transdermal drugs as well as non-pharmacological treatments, with the aim of prescribing the lowest effective dose for the shortest possible time. These guidelines stipulate that NSAIDs should be administered to all patients with knee OA to prevent compromising other joints. If topical medicines are ineffective or unsuitable, oral NSAIDs combined with gastroprotective treatment (such as PPI) should be offered. In particular, paracetamol or weak opioids should not be routinely prescribed unless they are used infrequently for short-term pain relief in the absence of other more suitable alternatives. Likewise, glucosamine or strong opioids should not be prescribed as a means of managing osteoarthritis, as IACS injections might be more suitable for patients in whom other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise, even though these injections would provide short-term relief (2 to 10 weeks) only [20].

As IAHA does not produce these adverse side-effects, it is a viable alternative to analgesics and NSAIDs in patients with comorbidities, as well as in those that do not respond well to first-line pharmacological OA treatments [21, 22]. However, as there are more than 80 marketed IAHA preparations worldwide, clinicians may find it challenging to select the most suitable one for each patient. They differ in many characteristics, including mean molecular weight (MW; 500–6,000 kDa), MW distribution, molecular structure (linear, cross-linked, or a combination of both), crosslinking method, concentration (0.8–30 mg/ml), injection volume (0.5–6.0 ml), and posology. Moreover, some preparations include additives (such as mannitol, sorbitol, or chondroitin sulfate) in varying concentrations, which may influence the IAHA treatment efficacy. Due to the limited research on this topic, clinicians are advised to consider all available alternatives, noting that the exogenous HA available for IA injections are divided into 3 MW categories: low (500–730 kDa), intermediate (800–2,000 kDa), and high (2,000–6,000 kDa), including cross-linked HA formulations [22, 23]. They should also note that the United States Food and Drug Administration (FDA) has only approved IAHA for pain relief in patients with mild to moderate OA of the knees who have not responded to conservative non-pharmacological measures and/or analgesics [24]. Although IAHA are presently not approved by the FDA for other joints, available evidence suggests that their application may reduce the use of pain medications, such as NSAIDs and opioids, as well as extend the time before total knee arthroplasty (TKA) is required, thus potentially decreasing the overall treatment cost. Furthermore, IAHA treatment was determined to be more cost-effective than NSAIDs, corticosteroids, analgesics, and conservative OA therapy, while being safe for the patient [25].

Platelets are also increasingly considered in the OA treatment as these cytoplasmic fragments of megakaryocytes formed in the bone marrow contain more than 30 bioactive proteins, many of which play a crucial role in hemostasis or tissue healing. Platelet rich plasma (PRP) also includes three blood proteins-fibrin, fibronectin, and vitronectin-known to act as cell adhesion molecules [26, 27]. PRP is prepared by differential centrifugation, whereby red blood cells (RBCs) are separated from the whole blood (WB) before concentrating platelets, which are suspended in the smallest final plasma volume. After the first spin step, the WB separates into an upper layer that contains mostly platelets

and white blood cells (WBCs), an intermediate thin layer rich in WBCs, and a bottom layer that consists mostly of RBCs. For the production of pure PRP (P-PRP), the upper and the intermediate layer are transferred to an empty sterile tube. For the production of leucocyte rich PRP (L-PRP), the entire intermediate layer and a few RBCs are transferred. When the second spin is performed, the centrifugal force should be sufficiently high to aid the formation of soft pellets (erythrocyte-platelet) at the bottom of the tube, separating it from the upper portion of the volume that is composed mostly of platelet-poor plasma (PPP), which can thus be easily removed. Pellets are homogenized in the lower third (5 ml of plasma) to create the PRP. Several commercial PRP systems can be used for this purpose [27].

In 2020, Filardo et al. evaluated the PRP injection effectiveness in terms of knee OA patient-reported outcome measures compared to placebo and other IA treatments. For this purpose, the authors sourced all pertinent literature published in any language from PubMed, Cochrane Library, Scopus, Embase, and Web of Science, as well as gray literature, focusing on articles reporting on randomized controlled trials (RCTs) comparing PRP injections with placebo or other injectable treatments in humans. Based on their findings, the authors concluded that platelet concentrates and PRP injections provide better results than other injectable options. This benefit extends well beyond the placebo effect and increases over time. Nonetheless, the improvement remains partial and is presently supported by insufficient evidence [28].

Mesenchymal stem cells (MSCs) are another promising candidate for OA treatment due to their capacity for differentiation into chondrocytes and their ability to modulate the immune system [29]. While MSCs were first isolated from bone marrow, they can be presently obtained from adipose tissue, placenta, umbilical cord, cord blood, dental pulp, and amniotic fluid among other tissues. Nonetheless, bone marrow and adipose tissue remain the major sources of therapeutic MSCs [29, 30]. Although research in this domain is not extensive, preliminary findings indicate that the use of all MSC types leads to improvement in the clinical and structural condition of OA patients. However, as treatment effectiveness is usually limited to under two years, further research is needed to advance this highly promising therapeutic modality [31]. Health practitioners should also appreciate that, in such regenerative therapy, administered cells are expected to engraft to a lesion site and differentiate into chondrocytes. However, recent studies show that cells, particularly those injected in suspension, rapidly undergo apoptosis and would thus not contribute to structural improvements in the diseased joint, making it difficult to justify the high cost of cell therapy for OA when compared with other injection therapeutics such as corticosteroids and hyaluronic acid [32]. In sum, there is currently little evidence in support of the efficacy of this treatment modality in clinical practice [33].

Conclusion

As osteoarthritis patients are usually older and have other comorbidities, they require bespoke, highly-individualized treatment, making it challenging to develop and adopt universally applicable guidelines. As shown in this review, a wide range of treatment options is presently available, and is expected to include many more non-surgical modalities, as the goal is to find the most effective and unobtrusive treatment with as few side effects as possible while slowing or ideally completely arresting the further development of osteoarthritis.

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THE EFFICACY OF A MODALITY OF PHYSICAL THERAPY IN THE TREATMENT OF OSTEOARTHRITIS OF THE SPINE – A CASE REPORT OF A PATIENT TREATED WITH HORIZONTAL THERAPY

EFIKASNOST MODALITETA FIZIKALNE TERAPIJE U LEČENJU OSTEOARTROZE KIČME – PRIKAZ BOLESNICE LEČENE HORIZONTALNOM TERAPIJOM

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Summary

Introduction. Horizontal therapy is the only electrotherapy modality for the treatment of osteoarthritis that has a simultaneous bioelectrical and biochemical, effect on deep and superficial joint tissues. The objective of this report was to provide evidence of efficacy of horizontal therapy in a patient suffering from lumbar spine osteoarthritis. **Case report.** A 70-year-old female patient was admitted to the hospital due to severe low back pain with radiating pain in both legs followed by tingling in left leg. The patient has had this painful condition since 2010. Physical examination revealed a reduction of the range of motion of the lumbar spine followed by spasm of the paraspinal musculature. Deep tendon reflexes of the lower limbs were 2+ bilaterally, except right patellar reflex which was absent. She had hypoesthesia in L4, L5 and S1 dermatome of the left leg and no motor deficits were noted. Radiographic evaluation showed multilevel degenerative changes of the lumbar spine. The patient was prescribed medication, physical and exercise therapy. She underwent horizontal therapy for lumbar spine with a frequency oscillating between 4357 and 12127 hertz. The patient had a total of 15 treatments, 5 per week and each lasted 30 minutes. **Conclusion.** In a patient with osteoarthritis of the spine, horizontal therapy has proved to be an effective modality of physical therapy leading to pain relief and functional improvement. Additional clinical research is needed for confirming its effectiveness on a larger sample, to define optimal parameters of the application and indication areas.

Key words: Osteoarthritis; Spine; Physical Therapy Modalities; Osteoarthritis, Spine; Electric Stimulation Therapy; Low Back Pain; Treatment Outcome

Sažetak

Uvod. Horizontalna terapija je jedini modalitet elektroterapije za lečenje osteoartroze koja istovremeno ima bioelektrično i biohemijsko dejstvo na duboka i površinska tkiva zgloba. Cilj ovog rada je bio da ukaže na efikasnost primene horizontalne terapije kod pacijentkinje sa hroničnim tegobama u vezi sa osteoartrozom lumbalnog dela kičmenog stuba. **Prikaz slučaja.** Pacijentkinja stara 70 godina primljena je u bolnicu zbog jakog bola u donjem delu leđa sa propagacijom bola u obe noge koji je praćenjen trnjenjem u levoj nozi. Pacijentkinja ima ove tegobe od 2010. godine. Fizikalnim pregledom utvrđeno je smanjenje obima pokreta lumbalne kičme koji je praćen spazmom paravertebralne muskulature. Duboki tetivni refleksi donjih ekstremiteta su bili uredni, osim desnog patelarnog refleksa koji je bio ugašen. Imala je hipersteziju u predelu dermatoma L4, L5 i S1 leve noge, dok motorni deficit nije registrovan. Radiološkom dijagnostikom uočene su degenerativne promene na više nivoa lumbalnog dela kičmenog stuba. Pacijentkinji je propisana medikamentna, fizikalna i kineziterapija. Uključena joj je horizontalna terapija za lumbalni deo kičme sa frekvencijom koja osciluje između 4.357 i 12.127 herca. Pacijentkinja je imala ukupno 15 tretmana, pet puta nedeljno i svaki je trajao po 30 minuta. **Zaključak.** Kod bolesnika sa dugotrajnim tegobama po tipu osteoartroze kičmenog stuba, horizontalna terapija se pokazala kao efikasan modalitet fizikalne terapije koji dovodi do ublažavanja bola i funkcionalnog poboljšanja. Potrebna su dodatna klinička istraživanja na većem uzorku kako bi se potvrdila njena efikasnost da bi se definisali optimalni parametri za njenu primenu kao i indikaciona područja.

Ključne reči: osteoartritis; kičma; modaliteti fizikalne terapije; osteoartritis kičme; elektroterapija; lumbalni bol; ishod lečenja

Introduction

The rise in the prevalence of degenerative musculoskeletal diseases could be explained by the trend of increasing life expectancy, which changed the disease burden globally [1]. Osteoarthritis (OA) represent the most common form of arthritis and it can affect any joint, although pathological changes are usually located at the hips, knees, hands, feet and spine. The main feature is loss of cartilage, but OA is nowadays recognized as a disease of the whole joint, with degenerative processes affecting also the bone and the soft tissues including synovium, menisci and ligaments [2]. This chronic joint disorder is initiated by micro and macro injuries that in turn trigger maladaptive repair responses, including pro-inflammatory pathways of innate immunity, which lead to cellular stress and degradation of the extracellular matrix [3]. Several risk factors that are significant for the development of OA have been identified and those are older

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Abbreviations

OA	– osteoarthritis
HT	– horizontal therapy
VAS	– visual analogue scale
PD	– PainDETECT
DN4	– Douleur Neuropathique 4 Questions
IVD	– inter-vertebral disc
WOMAC	– Western Ontario and McMaster Universities Osteoarthritis Index

age, obesity, genetics as well as occupational activities with repetitive work or joint overload [4]. Symptomatic OA of the spine is usually manifested by pain, stiffness and reduction in range of motion. Pain is the hallmark of OA and its distribution is determined by the involvement of a certain segment of the spine [5]. The treatment of OA is focused on symptom relief and maintenance of joint function. Therapeutic guidelines advise on using a combination of physical and analgesic drug therapy, whereas in case of necessity surgical intervention is recommended [6]. On the other hand, weight loss, exercise, information access and patient education represent an essential component in the treatment algorithm [7]. Horizontal therapy (HT) is a type of electrotherapy for the treatment of OA which has a dual, bioelectrical and biochemical, effect on deep and superficial joint tissues. Compared to other physiotherapy modalities using electric current for therapeutic purposes, its main feature is the ability to "horizontally" exceed the stimulation threshold in low-frequency rhythms to create an action potential in order to achieve bioelectrical effects. On the other hand, it simultaneously has biochemical effects since it maintains the intensity constant [8].

The objective of this report was to provide evidence of efficacy of horizontal therapy in a patient suffering from lumbar spine OA.

Case Report

A 70-year-old patient was admitted to the Special Hospital for Rheumatic Diseases due to severe low back pain with radiating pain in both legs followed by tingling in the left leg. The patient has had this painful condition for the past 12 years, but the flare occurred one month prior to the medical appointment. Acute pain in the lumbar spine could not be explained by either trauma or mechanical provocation. Tolerance to verticalization was decreased, walking for more than 30 minutes and sitting for more than 15 minutes usually provoked worsening of the symptoms. Her medical history was positive for arterial hypertension, angina pectoris and hyperlipidemia. She had an appendectomy in childhood and a ventral hernia repair in 2007. The patient was a smoker and her body mass index was 24,5 kg/m^2.

Physical examination

The spine posture and motion were evaluated while the patient was standing in the upright position with her arms by her sides. Sagittal plane deformities of the spinal column were thoracic kyphosis and a slight decrease in the lumbar depth. The patient was asked to perform flexion, extension, rotation to the right and left side as well as lateral flexion to the right and the left for examination of the lumbar spine range of motion. The observed value of flexion was 25 degrees, extension 10 degrees and 15 degrees in the right and 20 degrees in the left inclination. Rotation was limited to 15 degrees to the right side and 20 degrees to the left side. Reduction of the range of movement was followed by spasm of the paraspinal musculature and every movement was painful. Deep tendon reflexes of the lower limbs were 2+ bilaterally, except right patellar reflex, which was absent. She had hypoesthesia in L4, L5 and S1 dermatome of the left leg and no motor deficits were noted. Lasegue test was performed while the patient was lying on the examination in the supine position. Straight leg raising test was positive at 70 degrees on the left leg. The intensity of pain was assessed using a visual analogue scale (VAS) and she rated the severity of pain in the lumbar spine with a score of 9. The presence of the neuropathic component of pain was determined using the PainDETECT (PD) and the Douleur Neuropathique 4 Questions (DN4) questionnaire. The value of the first score was 21 and the value of the second was 4.

Laboratory evaluation

The results of the laboratory analysis of the complete blood count, biochemistry, acute phase reactants and urine were within the reference range.

Radiographic evaluation

Magnetic resonance imaging of the lumbosacral spine revealed annular swelling of the inter-vertebral disc (IVD) at the L3-L4 and L4-L5 level, absolute spinal canal stenosis with 7 mm and 6mm in diameter, respectively, and a discoradicular contact with both L4 and L5 nerve roots. On these two levels, intervertebral foramens were stenosed followed by the impingement of the left L3 and right L4 nerve roots. Wide dorsal protrusion of the IVD and 8 mm wide spinal canal indicative of absolute stenosis were seen by this imaging technique at the L5-S1 level. Furthermore, a compression of the left S1 nerve root was observed. On this level, both L5 roots were compressed due to a bilateral foraminal stenosis.

Therapeutic intervention

Considering clinical presentation, physical examination, laboratory and radiological findings suggestive of osteoarthritis related degenerative changes; diagnosis of spinal osteoarthritis was confirmed. In accordance with clinical guidelines for managing osteoarthritis, the patient was prescribed a non-steroidal anti-inflammatory drug due to its analgesic and anti-inflammatory effects. The patient had been previously taking pregabalin in a daily dose of 300 mg, which was prescribed by an anesthesiologist specialized in pain management. She continued using this drug throughout the whole period of hospitalization. Aside from pharmaceutical therapy, she was included in a 3-week program of a physical and standard exer-

Table 1. Evaluation of pain intensity, pain features and range of motion of the lumbar spine
Tabela 1. *Procena intenziteta bola, karakteristika bola i pokretljivosti lumbalnog dela kičme*

	Baseline/*Početak*	Week 3/*Treća nedelja*
VAS/*VAS*	9	3
PainDETECT	21	8
DN4	4	1
Flexion/*Fleksija* (degrees/*stepeni*)	25	45
Extension/*Ekstenzija* (degrees/*stepeni*)	10	20
Lateral flexion (R/L)/*Laterofleksija* (*D/L*) (degrees/*stepeni*)	15/20	20/25
Rotation (R/L)/*Rotacija* (*D/L*) (degrees/*stepeni*)	15/20	20/25
Schober test	3 cm	4 cm

Legend/*Legenda*: VAS - visual analogue scale/*VAS – vizuelno analgona skala*; DN4 - Douleur Neuropathique 4 Questions/*DN4-Neuropatski bol 4, Pitanja;* R - right/*D – desno;* L - left/*L – levo*

cise therapy. Regarding modalities of the physical medicine the patient underwent horizontal therapy for the lumbar spine. The device**,** Jena Medical Multi terapico 2 ch, was used for horizontal therapy with a frequency oscillating between 4357 and 12127 hertz. Application of HT consisted of placing 3 cutaneous electrode pads. One of the pads was located on the lumbar spine and the remaining 2 were placed on the abdominal wall just above the anterior superior iliac spine. The patient had a total of 15 treatments, 5 per week and each lasted 30 minutes. The intensity of the pain using VAS was assessed before initiating treatment as well as 3 weeks after the baseline. Additionally, Schober test was performed and the patient was required to fulfill PD and DN4 questionnaires at the same timeline points. The difference between VAS, PD, DN4, range of motion and Schober test are shown in a **Table 1**.

Discussion

Musculoskeletal health is essential for healthy aging, in the first place for maintaining physical and mental health as well as quality of life [9]. The prevalence of the lumbar spine osteoarthritis ranges from 40% to 85% [10]. Older age is recognized as a risk factor for OA with a peak in the prevalence in patients aged from 60 to 75 years, although a slight decrease has been observed in ones older than 75 [11]. Numerous studies have been conducted with the aim of identifying the characteristics of patients with back pain, which are associated with poor recovery. The results showed that prognostic factors for pain chronicity were age, female sex, race, longer duration and previous history of back pain and pain in the leg. General health condition, the number of comorbidities, exposure to stress and the patient's expectations contribute to the recovery process as well. Berg et al. investigated the radiographic features of spinal OA that represent prognostic factors for long-term back pain. The results of their research demonstrated that multilevel osteophytes can predict longstanding persistence and severity of back pain in older adults [12]. Having in mind the previously mentioned prognostic factors, our patient had a predisposition for chronic complaints due to age, sex, number of comorbidities, the clinical features of low back pain and radiating pain in the leg. Treatment with electrical currents provides 2 groups of therapeutic effects in the treated tissue. First one is a stimulatory effect (bioelectric) and the second one is non-stimulatory effects (biochemical) [13]. Zambito et al. conducted a study to examine the effectiveness of horizontal therapy in treating patients with low back pain. In their randomized, double-blind and placebo-controlled study, they showed that horizontal therapy was superior to placebo and interferential currents in reducing pain and improving functional capacity [14]. Similar results were obtained by the same group of authors in a study with 115 female participants suffering from chronic back pain due to multiple vertebral fractures. This study showed that interferential and horizontal therapy were significantly more effective in alleviating pain and disability versus placebo. Another beneficial effect of HT therapy is against osteoporosis, by increasing bone density [15]. Sante el al. conducted a clinical trial in order to assess effectiveness of HT in treatment of knee OA complicated by Backer cyst. 60 patients were randomized into 3 study groups. The first group underwent ultrasound guided aspiration of the cyst and corticosteroid injection, the second group was treated with horizontal therapy and the third group had combination therapy including corticosteroid injection and HT. Treatment outcomes were evaluated using VAS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and ultrasound examination at one and four week follow-up. The results demonstrated that the application of HT and corticosteroid therapy reduce pain and improve functionality. The authors concluded that patients with knee OA and Backer cyst would benefit from this combination therapy [16].

Our patient has had long-term symptoms of spinal OA and has been treated several times with various modalities of physical therapy. None of the physical agents in rehabilitation used so far have led to significant improvements and the duration of the improvements has always been limited in time. For the first time during the last hospitalization, the patient had treatment with HT, which reduced the pain and increased mobility of the spine.

Conclusion

In a patient with long-term osteoarthritis of the spine horizontal therapy was proved to be an effective modality of physical therapy leading to a pain relief and functional improvement. Additional clinical research is needed for confirming its effectiveness on a larger sample as well as to define the optimal parameters of application and indication areas.

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KNEE OSTEOARTHRITIS TREATMENT

TRETMAN OSTEOARTRITISA KOLENA

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Summary

Introduction. Osteoarthritis is the most common form of arthritis which affects millions of people worldwide and represents the leading cause of disability among the elderly. There is a substantial number of guidelines available for the treatment of knee osteoarthritis. The primary aim of this paper is to explore the distinctions and similarities between knee osteoarthritis treatment guidelines. The treatment is divided into core treatment and additional steps**. Core treatment of knee osteoarthritis** involves education of the patient, weight loss in the case of overweight patients and establishing an exercise program. **First step of additional treatment of knee osteoarthritis** consists of non-pharmacological (application of orthoses, lateral wedge insoles, assistive walking devices, therapeutic modalities, manual therapy, aquatic exercise, Tai chi) and pharmacological therapy (topical nonsteroidal anti-inflammatory drugs, topical capsaicin, paracetamol). **Second step of additional treatment of knee osteoarthritis - pharmacological therapy** should be considered if the first step didn't show any significant results. It involves the use of oral nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injections and viscosupplementation. **Third step of additional treatment of knee osteoarthritis - last resort pharmacological therapy** Pain occurring in knee osteoarthritis. can be partially caused by central sensitization. Because of that, use of duloxetine and tramadol may be considered. **Fourth step of additional treatment of knee osteoarthritis-end stage treatment of knee osteoarthritis** is reserved for the most severe patients. It includes total knee replacement surgery, and if it is not possible, treatment with strong opioids could be considered. **Conclusion** There are many possibilities in treatment of knee osteoarthritis. Unfortunately, there is often a lack of concordance between different guidelines. In these circumstances, treatment plans should be personalized, while comprehending potential risks and benefits.

Key words: Osteoarthritis, Knee; Pain; Therapeutics; Practice Guidelines as Topic; Treatment Outcome

Sažetak

Uvod. Osteoartritis je najčešća forma artritisa koja pogađa milione ljudi širom sveta i vodeći je uzrok invaliditeta među starom populacijom. Postoji veliki broj dostupnih vodiča za lečenje osteoartritisa kolena. Cilj ovog rada bio je da se istraže razlike i sličnosti među njima. **Osnovni tretman osteoartritisa kolena** uključuje edukaciju pacijenta, regulisanje telesne težine gojaznih pacijenata i program vežbi. **Prvi korak dodatne terapije osteoartritisa kolena** sastoji se od nefarmakološke (upotreba ortoza, bočnih klinastih uložaka, pomoćnih uređaja za hodanje, terapeutskih modaliteta, manuelne terapije, hidroterapije, *Tai Chi*) i farmakološke terapije (upotreba topikalnih nesteroidnih antiinflamatornih lekova, topikalnog kapsaicina, paracetamola, glukozamin-sulfata i hondroitin-sulfata). **Drugi korak dodatne terapije – farmakološka terapija** treba da se razmotri kada prvi korak ne dovede do značajnih rezultata i uključuje upotrebu oralnih nesteroidnih antiinflamatornih lekova, intaartikularne injekcije kortikosteroida i viskosuplementaciju. **Treći korak dodatne terapije – poslednja mogućnost farmakološke terapije**. Bol u sklopu osteoartritisa kolena delimično može biti uzrokovan centralnom senzitizacijom. Zbog toga treba razmotriti upotrebu duloksetina i slabih opioida. **Četvrti korak dodatne terapije − krajnja faza tretmana osteoartritisa kolena** je rezervisana za najteže pacijente. Uključuje artroplastiku kolena i tretman jakim opioidima. **Zaključak.** Postoji mnogo mogućnosti za lečenje osteoartritisa kolena. Nažalost, često postoje nesuglasice između različitih vodiča. U ovim slučajevima, plan lečenja treba da bude individualizovan sa posebnim osvrtom na potencijalne rizike i benefite terapije.

Ključne reči: osteoartritis kolena; bol; terapija; vodiči dobre prakse; ishod lečenja

Introduction

Osteoarthritis is the most common form of arthritis that affects millions of people worldwide and is the leading cause of disability among the elderly [1–4]. Osteoarthritis is responsible for significant social expenses and public health expenditures [5–9].

The primary cause of osteoarthritis remains unknown. It is, however, well known that it is associated with obesity, inflammation, trauma and hereditary factors. The pathological findings consistent with the disease are damage of the joint cartilage, sclerosis or cystic degeneration of the subchondral bone, bone margin hypertrophy, synovial hyperplasia, joint capsule contracture, ligament laxity or ligament contracture, muscle atrophy and muscle weakness. The disease mainly affects weight bearing joints, which are the most active, the knee joint being the most frequently impacted [10, 11]. Leading symptoms are pain, joint stiffness and activity limitations [12]. It is important to evaluate and follow-up for both pain and disability of patients with this chronic condition [13].

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Abbreviations

KOA	– knee osteoarthritis
ACR	– American College of Rheumatology
NICE	– National Institute for Health and Care Excellence
OARSI	– Osteoarthritis Research Society International
ESCEO	– European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
AAOS	– American Academy of Orthopedic Surgeons
EULAR	– Evidence-Based Clinical Practice Guideline and European League Against Rheumatism
TENS	– transcutaneous electrical nerve stimulation
CS	– central sensitization
TKA	– total knee arthroplasty
NSAIDs	– nonsteroidal anti-inflammatory drugs

There is a substantial number of guidelines regarding the treatment of knee osteoarthritis (KOA). The most prominent ones are: The American College of Rheumatology (ACR) Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee; National Institute for Health and Care Excellence (NICE) Osteoarthritis: care and management; Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis; European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO); American Academy of Orthopedic Surgeons (AAOS) Management of Osteoarthritis of the knee (Non-Arthroplasty): Evidence-Based Clinical Practice Guideline and European League Against Rheumatism (EULAR) recommendations for the non-pharmacological core management of hip and knee osteoarthritis.

The primary goal of KOA treatment is to reduce symptoms, slow down the progression of the disease and to improve the quality of life. The treatment is divided into core treatment and additional steps.

Core treatment of knee osteoarthritis

The core treatment of KOA is safe for all patients regardless of their comorbidity, and it involves educating the patient, weight loss in the case of overweight patients and an exercise program that includes mind-body exercises such as Thai chi and Yoga [14–19]. Evidence shows that 10% loss of body mass can significantly reduce pain intensity and improve function in older and obese patients [20].

First step of additional knee osteoarthritis treatment

The first step of additional treatment of KOA consists of non-pharmacological and pharmacological therapy. As one of the non-pharmacological treatments, knee orthoses are inexpensive and relatively easy to use. They provide realignment of the knee joint and are considered an appropriate treatment for non-surgical handling of knee osteoarthritis. Studies show that knee orthoses in the treatment of knee osteoarthritis, in patients with mild to moderate symptoms, can offer pain relief and improvement of joint function [21]. Like other non-operative approaches a wedge insole also aims at realignment of the knee joint and consequential reduction in pain, thus inhibiting the progression of knee osteoarthritis. Toda and Tsukimura reported that use of the subtalar strapped insole in the treatment of KOA can improve realignment of the femorotibial angle and thus slow down the progression of degenerative articular cartilage damage caused by varus and valgus malalignments [22]. A study by Penny et al. suggests further investigations to determine whether certain subgroups of patients with KOA, such as obese patients or those with accompanying hip osteoarthritis, would benefit from wearing wedge insoles more than others [23]. Weight bearing activity is a common cause of pain in just about all patients with KOA. Canes, walkers and other assistive walking devices can improve the reduction in pain in these patients by reducing the ground force acting on the affected limb, therefore minimizing the compressive load on the surrounding tissues. Assistive walking devices are highly recommended in the treatment of KOA [14–18]. It is very important to fit the cane individually to every patient and to maintain the correct walking pattern by teaching the patient how to use the cane correctly in the contralateral hand [24].

Therapeutic modalities such as applying heat and cold can be effective in reducing pain sensation in patients with KOA. They are conditionally recommended for these patients[14–16].

It is not clear whether transcutaneous electrical nerve stimulation (TENS) is useful in treating KOA. Some studies found no effect, while certain guidelines recommend the use of TENS [14–16]. There is not enough evidence to recommend manual therapy as an efficient tool for reducing symptoms of knee osteoarthritis [25]. Due to decrease of the load on the joints aquatic exercise may be beneficial for these patients and is conditionally recommended by ESCEO and OARSI [15, 17] and strongly recommended by AAOS and ACR [14, 19].

Potential pharmacological therapy in the first additional step of the KOA treatment includes topical nonsteroidal anti-inflammatory drugs (NSAIDs), topical capsaicin, paracetamol, glucosamine sulfate and chondroitin sulfate. The main reason for introducing these therapeutics is their low potential to cause adverse effects. Topical NSAIDs are strongly recommended as they have a lower risk of side effects, especially in elderly with a large number of comorbidities and polypharmacy. They are known to accumulate in the synovial tissue and to have a similar effect in reducing pain and enhancing function, and therefore quality of life, in the same manner as oral NSAIDs [26]. Topical capsaicin is strongly recommended by NICE [16] but contraindicated by OARSI due to the lack of good quality evidence [17]. According to Perrson et al. topical capsaicin should be considered as a treatment option for KOA. In case that topical capsaicin is not providing pain relief, patients should be encouraged to try other topical treatments [27]. Paracetamol is commonly prescribed as the first line treatment medication for pain

accompanying KOA. In comparison to placebo there is little evidence that shows its efficacy in reducing pain intensity at 12 weeks of use [28]. Glucosamine sulfate and chondroitin sulfate preparations have been promoted as safe options in the treatment of KOA. However, the majority of guidelines do not recommend these substances for the treatment of KOA as the majority of unsponsored studies did not find them to decrease pain and functional impairment [29–32].

Second step of additional knee osteoarthritis treatment – pharmacological therapy

If the first step treatment shows no significant results clinicians should consider the second step of treatment. Therapy of KOA with NSAIDs is strongly recommended, albeit with caution, depending on the patient's profile and risk of developing side effects. There is a significant risk of developing stomach ulcers, cardiovascular complications and acute kidney injury especially in the first month of treatment. Non-selective NSAIDs in combination with a proton pump inhibitors can be considered for those patients that have no risk of developing gastrointestinal complications. Treatment with NSAIDs at the lowest effective dose should always be for the shortest possible period, considering their potential for developing complications. In those patients that have a higher risk of developing complications, selective COX2 inhibitors in combination with proton pump inhibitors are a preferable choice. They have good potential for analgesic effect in patients with knee osteoarthritis and relatively low potential for causing gastrointestinal complications [15].

If the treatment with oral NSAIDs proves to be ineffective or if there are contraindications for use of oral NSAIDs, the next treatment option is intra-articular application of corticosteroids or hyaluronic acid. Intra-articular glucocorticoid injections are strongly recommended by ACR and NICE in therapy because of how efficacious they are in reducing pain symptoms in the short-term [14, 16]. Nevertheless, there is not enough evidence to prove the benefits of intra-articular corticosteroid in the long-term [33]. Another study shows that there are significant positive clinical results correlating repetitive intra-articular application of corticosteroid with no crucial change in the anatomy of the joint [34].

Viscosupplementation with intra-articular application of hyaluronate is conditionally contraindicated in patients with knee osteoarthritis by AAOS and ACR [14, 19] and strongly contraindicated by NICE [16]. It should be considered only when previous treatment options fail to succeed in controlling symptoms related to this disease [14]. The main obstacle of viscosupplementation therapy is its low potential for the reduction of pain intensity [35, 36].

Third step in additional knee osteoarthritis treatment – last resort pharmacological therapy

Interestingly, several studies indicate a significant improvement in pain reduction during the course of treatment with duloxetine [37–39]. Therefore, duloxetine is recommended for the treatment of KOA [14, 15, 17]. This poses a question as to the possible mechanism involved in pain reduction during treatment with antidepressants. Recent studies suggest that chronic pain could lead to the development of central sensitization (CS). CS represents a dysfunction in the central pain modulating mechanisms resulting in "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" [40]. The imbalance of serotonin and norepinephrine could play a significant role in these processes [38]. Via its effect on serotonin and norepinephrine reuptake inhibition, duloxetine has the potential to balance these two neurotransmitters and be effective in certain patients with chronic pain due to KOA [39]. Having this in mind it would be a good idea to identify the subgroup of patients with central sensitization. While there were many attempts at indirectly measuring central sensitization, from questionnaires to quantitative sensory testing, the gold standard is still missing [41–47]. As tramadol also poses the ability to modulate the perception of and response to pain through inhibition of serotonin and norepinephrine reuptake [48] it should be considered in the third step. Additionally tramadol is a selective agonist of mu opioid receptors and its dual action distinguishes tramadol from other "classic" opioids [49]. The majority of guidelines conditionally recommended this weak opioid as a treatment option [14–16]. It is effective in reducing pain but has significant adverse effects [50].

Fourth step – end stage knee osteoarthritis treatment

If all of the above options do not provide desired pain relief and improvement in quality of life of the patient, total knee arthroplasty (TKA) should be considered [15]. TKA offers significant reduction in pain, improvement in the quality of life in these patients, however, potentially serious complications should be considered [51].

If TKA is not possible, introduction of strong opioids could be considered [15, 16]. They should be administered with caution and patient response to therapy should be evaluated regularly, due to the severity of their side effects [50]. The opinions on the use of strong opioids in patients with KOA are divided. While certain guidelines recommend their use [15, 16], others are strongly against it [17, 19].

Conclusion

In conclusion, there are many possibilities in the knee osteoarthritis treatment. Unfortunately, there is often a lack of concordance between different guidelines (use of wedge insoles, therapeutic modalities, manual therapy, topical capsaicin, oral nonsteroidal anti-inflammatory drugs, glucosamine sulfate, chondroitin sulfate, viscosupplementation and strong opioids). In these circumstances, treatment plans should be personalized while comprehending potential risks and benefits.

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HIP OSTEOARTHRITIS – UPDATE ON ETIOPATHOGENESIS, CLINICAL PRESENTATION AND MANAGEMENT

OSTEOARTRITIS KUKA – NOVA SAZNANJA O ETIOPATOGENEZI, KLINIČKOJ PREZENTACIJI I AKTUELNE PREPORUKE U LEČENJU

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Summary
Osteoarthritis is the most frequent form of arthritis, and the hip is the second most frequently affected joint. The effects of osteoarthritis on the hip joint often lead to marked physical impairment that can contribute to increased disability and dependency in everyday activities. Hip osteoarthritis is a degenerative process with progressive loss of articular cartilage, followed by a reparative process such as reactive bone hypertrophy, which causes osteophyte formation and remodelling. The joint responds with subchondral and synovial inflammation. Patients with hip osteoarthritis report pain in the groin area which can develop slowly and worsen over time. With the progression of the disease, the range of motion of the affected hip is reduced, which affects the walking pattern and may cause a limp. Therapeutic options for hip osteoarthritis should be based on the etiopathogenesis of the disease. The approach to treatment for every patient should be multidisciplinary, multimodal and individualised taking into account personal beliefs and preferences, social and psychological factors and prior medical history. It is important to avoid unnecessary delays in referring patients with advanced hip osteoarthritis for surgical treatment, in order to prevent worse outcomes after total hip arthroplasty. The aim of this article is to offer a concise update on etiopathogenesis, clinical presentation, and management options for hip osteoarthritis.
Key words: Osteoarthritis, Hip; Pain; Therapeutics; Treatment Outcome; Risk Factors; Diagnosis; Signs and Symptoms

Sažetak
Osteoartritis je najčešći oblik artritisa, a zglob kuka je drugi najučestalije zahvaćeni zglob. Efekti osteoartritisa na zglob kuka često dovode do izražene funkcionalne limitiranosti što može doprineti povećanju invaliditeta i zavisnosti u aktivnostima svakodnevnog života. Osteoartritis kuka je degenerativni proces sa progresivnim gubitkom zglobne hrskavice, praćen reparativnim procesima kao što je reaktivna hipertrofija kostiju, koja izaziva formiranje osteofita i remodeliranje kosti. Zglob odgovara suphondralnom i sinovijalnom upalom. Pacijenti sa osteoartritisom kuka opisuju bol u predelu prepona koji se može sporo razvijati i pogoršavati tokom vremena. Sa progresijom bolesti, opseg pokreta u zahvaćenom kuku se smanjuje, što utiče na poremećenu biomehaniku hoda i može izazvati razvoj patološke šeme hoda. Terapijske opcije za osteoartritis kuka treba da budu zasnovane na etiopatogenezi bolesti. Pristup lečenju svakog pacijenta treba da bude individualan, multidisciplinaran i multimodalan i da uzima u obzir lična uverenja i sklonosti pacijenta, socijalne i psihološke faktore i prethodnu medicinsku istoriju. Važno je izbeći nepotrebno odlaganje upućivanja pacijenata sa uznapredovalim osteoartritisom kuka na hirurško lečenje, kako bi se sprečili nezadovoljavajući ishodi nakon totalne artroplastike kuka. Cilj ovog članka je da ponudi sažet osvrt i prikaže najnovija saznanja o etiopatogenezi, kliničkoj prezentaciji i opcijama lečenja osteoartritisa kuka.
Ključne reči: osteoartritis kuka; bol; terapija; ishod lečenja; faktori rizika; dijagnoza; znaci i simptomi

Introduction

Osteoarthritis (OA) is the most frequent form of arthritis, which affects up to 302 million people worldwide [1, 2]. As a degenerative disorder, it causes progressive damage to both articular cartilage and the surrounding joint structures. The hip joint is one of the largest weight-bearing joints, and is the second most affected joint, after the knee joint [3]. Lifetime risk for symptomatic hip OA ranges from 18.5% in men to 28.6% in women [4]. The effects of OA on the hip joint, often lead to marked physical impairment that can contribute to increased disability and dependency in everyday activities [5]. The aim of this article is to offer a concise update on ethiopatogenesis, clinical presentation and management options for hip OA.

Material and Methods

For this review article, Medline was searched using the terms „hip osteoarthritis“, „pathogenesis“, „risk factors“, „epidemiology“ and „management“. Through this process, as well as from the authors' prior knowledge of the literature, key articles were selected. We used National Institute for Health and Care Excellence (NICE), Osteoarthritis Research Society International (OARSI), American College of Rheumatology (ACR) and American Academy of

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Abbreviations

OA – osteoarthritis
NICE – National Institute for Health and Care Excellence
OARSI – Osteoarthritis Research Society International
ACR – American College of Rheumatology
AAOS – American Academy of Orthopaedic Surgeons
DDH – developmental dysplasia of the hip joint
FAI – femoroacetabular impingement
HHS – Harris Hip Score
WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index
HOOS – Hip disability and Osteoarthritis Outcome Score
LISH – Lequesne Index of Severity for Osteoarthritis of the Hip
TENS – transcutaneous electrical nerve stimulation
CBT – Cognitive behavioural therapy
NSAIDs – non-steroidal anti-inflammatory drugs
THA – total hip arthroplasty

Orthopaedic Surgeons (AAOS) guidelines to provide current recommendations on treatments options.

Prevalence

Most epidemiologic surveys of hip OA use both radiographic investigation and clinical presentation to establish disease prevalence [1, 6]. The age-standardized prevalence of hip OA was reported from 1% to 10% in large population-based studies [6–8]. A systematic review has shown a higher prevalence of hip OA in men before age 50, while women have higher prevalence in more advanced age [6]. Caucasian population with hip OA has prevalence rates between 3% and 6%, which is significantly higher than 1% or less found in Asians and East Indians [9].

Pathogenesis

Hip OA is a degenerative process with progressive loss of articular cartilage, followed by a reparative process such as reactive bone hypertrophy, which causes osteophyte formation and remodelling. The joint responds with subchondral and synovial inflammation. The degenerative process in Hip OA also includes muscle weakness and periarticular ligamentous laxity [10]. Abnormal biomechanical stress has the greatest impact on initiating OA changes in an osteoarthritic hip joint. Repetitive shear stress at the articular surface triggers decreased expression of type II collagen and proteoglycans. These changes lead to increased release of pro-inflammatory mediators and apoptotic cellular changes [11].

Risk factors

Primary OA is of idiopathic origin and often affects more than one joint mostly in elderly patients [1]. Secondary OA is a single joint disease, and is a result of a defined disorder which damages joint articular surfaces. These disorders include traumatic injury, infection, joint abnormalities, metabolic or endocrine diseases as well as neuropathic conditions. Risk factors for hip OA can be considered both local, acting on the joint level, and general, impacting the entire person [4, 12]. General factors include age, sex, obesity, genetics and occupation. Hip radiographies of elderly patients, often exhibit chondrocalcinosis which can be considered as a predisposing factor for OA by increased production of pro-inflammatory mediators [9]. Obesity increases the load on the hip joint and possibly causes metabolic changes that contribute to development of OA [13]. A twin study conducted by MacGregor et al. has shown 60% risk for hip OA that can be accounted by genetic factors [14]. Heavy manual labour can be associated with hip OA in older age. This is, however, mostly found in patients with pre-existing hip disorders [15]. Findings from a population based cohort study by Wise et al. suggest that hip OA can be associated with frailty with an odds ratio after adjusting for confounding variables of 1.57 (95% confidence interval 1.1 to 2.22) [16]. Developmental dysplasia of the hip joint (DDH) is characterized by a decreased femoroacetabular contact surface which results in abnormal distribution of shear forces on the acetabular rim. These forces in time cause degeneration of articular cartilage and acetabular labrum [4]. Femoroacetabular impingement (FAI) is a condition where parts of the proximal femur mechanically collide with the acetabular rim leading to adjacent and contrecoup acetabular damage. There is some evidence that supports relation between FAI and hip OA development. However, there is insufficient evidence that surgical intervention prevents further degeneration of the hip [17]. An acetabular labral tear is a frequent form of hip join injury, and is present in 66% of people with hip pain. With increasing age, acetabular labral tears can become an important risk factor for hip OA [18].

Symptoms

Patients with hip OA report pain in the groin area which can develop slowly and worsen over time. Pain is intermittent and activity related at first and can radiate into the buttocks or knee. Pain and stiffness is more common in the morning or after sitting or resting. Stiffness usually lasts up to 30 minutes [10, 19]. With the progression of the disease, range of motion of the affected hip is reduced, which alters the walk pattern and may cause a limp. Internal rotation is one of the most sensitive indicators of hip OA [20]. Several scoring systems are used to determine the severity of symptoms. Most commonly used are Harris Hip Score (HHS), Oxford Hip Score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Hip disability and Osteoarthritis Outcome Score (HOOS) and Lequesne Index of Severity for Osteoarthritis of the Hip (LISH) [21].

Diagnosis

When a patient has typical features of hip OA, diagnosis can be based upon clinical presentation [22]. However, plain radiography is useful to confirm a diagnosis, and to monitor the progression of the illness. It is also the simplest, least expensive and most commonly used evaluation method [23]. Based on Kellgren's classification system there are four grades of hip OA based on degree of join space narrowing, osteophyte formation, deformity of the

femoral head and acetabulum and subchondral sclerosis [24]. However, The Framingham Osteoartritis Study, showed that 15.6% of patients with hip pain had radiographic confirmation of hip OA, while only 20.7% of patients with radiographic evidence of hip OA had frequent pain [25]. The first step of the diagnostic process should be an evaluation of the patient's medical history, with emphasis on risk factors for the development of hip OA. The second step is a careful clinical examination of the hip. A physician should examine the range of motion of the affected hip and compare it to the contralateral side, assess the joint for contractures and deformity and evaluate gait abnormalities. The National Institute for Health and Care Excellence (NICE) guideline recommends a clinical approach to OA diagnosis if a patient is aged ≥ 45 and has activity related joint pain and minimal joint stiffness [22]. Conditions that are most often mistaken for hip OA include trochanteric bursitis, spinal symptoms, femoroacetabular impingement, rheumatoid arthritis, osteonecrosis and meralgia paresthetica [26].

Treatment options

Treatment plans should take into consideration the personal beliefs and preferences of the patient, as well as social and psychological factors such as quality of life, occupation, relationships and leisure activities. The clinician should assess each patient for certain comorbidities such as hypertension, cardiovascular disease, heart failure, gastrointestinal bleeding risk, chronic kidney disease that might increase the risk ofside effects from some pharmacological treatments. Patients with hip OA may suffer from mood disorders, altered sleep, chronic widespread pain and reduced coping skills due to pain and functional limitations. Interventions that are used in management of these conditions can be beneficial for patients with hip OA [27].

Non-pharmacological methods

Physical therapy

Structured land-based exercise programs are considered appropriate for the majority of patients with hip OA (Core Treatments) [28]. A Cochrane review by Fransen et al. showed that exercises reduce pain and reduce functional limitations in patients suffering from mild to moderate pain with hip OA. These improvements are modest, but have lasting effects for up to six months after treatment [29]. Exercising increase muscle strength, improve the biomechanical environment, and reduces joint load [30]. Aquatic exercise is recommended because it combines aerobic fitness exercises and exercises for increasing joint range of motion, in a low-impact environment. Tai chi is strongly advised for patients with hip OA. Tai chi combines gentle movements with deep diaphragmatic breathing and relaxation. Its holistic approach improves balance, muscle strength, functional outcome and reduces depression. Transcutaneous electrical nerve stimulation (TENS) is considered as adjunct to core treatments in patients with hip OA. Hot treatments enhance circulation and reduce stiffness. Cold treatments slow circulation, reduce swelling and ease acute pain. Both are conditionally recommended for patients with hip OA [27].

Weight reduction

Weight reduction is strongly recommended for overweight patients suffering from hip OA [22, 27, 28]. A loss of 5% or more of body weight in obese patients is associated with pain reduction and functional improvement. The most successful approach to weight loss is through reduction of calorie intake and non-weight-bearing activities such as swimming and individualized exercise program [31].

Other treatment options

According to the American College of Rheumatology (ACR) guideline self-efficacy and self-management-programs are strongly advised for patients with hip OA [27]. The benefits of participation in these programs were noted in various studies, and risks for the patients are minimal [27, 32]. Cognitive behavioural therapy (CBT) is conditionally recommended for patients with hip OA, since there is some evidence that it might reduce pain [33].

Patients with hip OA who have problems with daily activities, ambulation, joint stability and pain should use walking sticks or some other assistive device [22, 27, 28].

Pharmacological methods

Oral non-steroidal anti-inflammatory drugs (NSAIDs) remain the main pharmaceutical approach to hip OA [22, 27, 28]. There is some evidence suggesting that Diclofenac and Etoricoxib are the most efficient NSAIDs for pain relief in hip OA, with moderate to large effects. Findings of several studies imply that certain agents have a safer side effect profile than others [34–36]. NSAID doses should be as low as possible, and their use should be as short as possible so as to avoid potential gastrointestinal tract bleeding and adverse cardiovascular events that are associated with long term use [27, 28]. According to the current protocols Acetaminofen is recommend only conditionally for patients with hip OA [22, 27, 28]. Acetaminofen as a monotherapy has exhibited very small pain relief in clinical trials and meta-analysis, and long term treatment is no better than treatment with placebo for most individuals [37]. Recommendations for duloxetine use in patients with hip OA are conditional due to issues regarding tolerability and side effects [38]. Tramadol has very modest effects in the long term treatment of patients with hip OA. For some patients tramadol use remains a valid treatment option. Those are patients who have contraindications for use of NSAIDs, who have no available surgical options, and for whom other therapies were ineffective [39]. Topical NSAIDs and capsaicin are unlikely to have positive effects on paint relief due to the depth of the joint below the skin surface [27, 28]. Glucosamine and chondroitin sulphate are strongly counter indicated for patients with hip OA, since publicly funded studies show no important benefits over placebo [22, 27, 28].

Intra-articular injections

Intra-articular glucocorticoid injections offer short-term pain reduction in patients with hip OA, and current guidelines recommend their application with other non-surgical treatments [22, 27, 28]. The use of ultrasound guidance for intra-articular injection is strongly advised when treating the hip joint [27]. Intra-articular hyaluronic acid injections and platelet-rich plasma treatments are, according to current guidelines, strongly counter indicated in patients with hip OA. Multiple meta-analyses have shown that hyaluronic acid injections when compared to saline injections offer no effect difference. Concerning platelet-rich plasma application, there is heterogeneity in available preparations and techniques used which make it difficult to identify precisely what is injected [22, 27, 28, 40]. Guidelines for hip OA treatment advise strongly against the use of stem cell injections [22, 27, 28].

Surgical treatments

Total hip arthroplasty (THA) is one of the most frequently performed and most successful operations worldwide. It is estimated that 1 million THA procedures are performed every year [41]. THA is indicated for patients with advanced hip OA who have intractable pain, who have negative response to non-surgical treatment, and who have severe functional impairment [22, 40]. A determinant of THA success is how long it lasts, and the only measurable outcome is the need for revision of the operation. Current data suggests that the probability of THA revision operation is 6.20% at 11 years [41]. If a patient is in good general health condition, adopts a healthy lifestyle, exercises and is not overweight, 80% of prostheses can remain functional for 25 years after surgery [42]. The most common reason for revision of the operation is aseptic loosening of the prosthesis. The symptoms are thigh or groin pain, and diagnosis is confirmed by plain radiographies. Aseptic loosening can be caused by patient-related issues (age, activity level and body mass index), surgical technique and prosthesis design [43]. Physicians should encourage symptomatic patients with hip OA who are non-responsive to non-surgical treatment and have significant functional impairment and disability to avoid delaying THA procedure, because prolonged delays are associated with worse outcomes after THA [44, 45].

Hip arthroscopy is usually considered in the early stages of OA, it has temporary effect, and numerous patients after hip arthroscopy undergo THA later on (9.5-50%) [46]. Hip resurfacing is a valid treatment option for young active male patients with large femoral heads, as an alternative to THA [47].

Conclusion

Our belief is that the best course of action to reduce the global burden of hip osteoasthritis is to focus on risk factor modification in the early stages of the disease. It is important to identify risk factors while developing new treatment options and public health interventions for hip osteoasthritis. Approach to rehabilitation treatment for every patient should be multidisciplinary, multimodal and individualised, taking into account personal beliefs and preferences, social and psychological factors and prior medical history.

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CONTEMPORARY APPROACH TO OSTEOSARCOPENIA

SAVREMENI PRISTUP OSTEOSARKOPENIJI

Snežana TOMAŠEVIĆ TODOROVIĆ[1, 2] and Nataša ILIĆ[2]

Summary

Introduction. The elderly are at high risk of developing osteosarcopenia, which is characterized by the coexistence of osteoporosis and sarcopenia. There are many factors that affect the interaction between bones and muscles: genetics, hormones, nervous system, aging, cardiac rhythm, nutrition. **Pathophysiology of osteosarcopenia.** Risk factors include: age of 50 years and over, sex, Caucasian race, genetic predisposition, short stature, malnutrition, physical inactivity, amenorrhea, late menarche, early menopause, estrogen and androgen deficiency, alcohol consumption, cigarette smoking, calcium deficiency in the diet, use of some drugs. Complications of osteosarcopenia include frequent bone fractures, physical disability, and mortality in the elderly population. **Diagnostics**. The gold standard is magnetic resonance imaging and computed tomography to assess muscle tissue. Bioelectric impedance analyzes the composition of the body, based on the speed at which electricity moves through tissues. **Drug treatment of osteosarcopenia.** Modern treatment of osteosarcopenia includes application of bisphosphonates, selective estrogen-receptor modulators, monoclonal antibodies, hormonal therapy, estrogens, and supplementation with calcium preparations and vitamin D. **Prevention**. Lifestyle changes and non-pharmacological measures are most important for healthy bones and muscles. Physical activity, nutrition rich in calcium and vitamin D, smoking and alcohol consumption are of crucial importance for people of all ages, especially for the elderly. **The therapy should be reevaluated** at least annually, and the quality of life should be assessed.

Key words: Sarcopenia; Osteoporosis; Risk Factors; Diagnosis; Therapeutics; Quality of Life; Exercise

Sažetak

Uvod. Starije osobe su pod velikim rizikom za nastanak osteosarkopenije koju karakteriše istovremeno postojanje osteoporoze i sarkopenije. Brojni su faktori koji utiču na interakciju između kostiju i mišića: genetika, hormoni, nervni sistem, starenje, cikardijalni ritam, ishrana. **Patofizologija osteosarkopenije.** Glavni faktori rizika su starenje: 50 i više godina, bela rasa, genetska predispozicija, nizak rast, pothranjenost, fizička neaktivnost, amenoreja, kasna menarha, rana menopauza, stanja nedostatka estrogena i androgena, konzumiranje alkohola, pušenje cigareta, ishrana siromašna kalcijumom, upotreba nekih lekova. **Komplikacije osteosarkopenije** su učestali padovi, prelom kostiju, fizički invaliditet i mortalitet. **Dijagnostika**. Zlatni standard je magnetna rezonancija i kompjuterizovana tomografija za procenu mišićnog tkiva. Biolektrična impedansa kojom se analizira sastav tela, zasnovana na brzini kojom električna energija putuje kroz tkiva. Dvostruka apsorpciometrija X-zraka kuka i kičme je široko rasprostranjeni standard u dijagnostici osteoporoze. **Medikamentni tretman osteosarkopenije**. Savremeno lečenje osteosarkopenije uključuje primenu: bisfosfonata, selektivnih modulatora estrogenih receptora, monoklonalnih antitela, hormonske terapije, primenu estrogena i suplementaciju kalcijuma i vitamina D. **Prevencija.** Promena životnog stila i nefarmakološke mere su najznačajnije. Fizička aktivnost, adekvatna ishrana bogata kalcijumom i vitaminom D, izbegavanje pušenja i konzumiranja alkohola su od neprocenjivog značaja kod osoba svih uzrasta, naročito kod starijih osoba. **Reevaluacija terapije** najmanje jednom godišnje, uz procenu kvaliteta života.

Ključne reči: sarkopenija; osteoporoza; faktori rizika; dijagnoza; terapija; kvalitet života; fizička aktivnost

Introduction

A recently identified illness called osteosarcopenia combines the two age-related chronic musculoskeletal diseases osteoporosis and sarcopenia. In a frail segment of the elderly population, osteoporosis, which causes low bone mass and microarchitectural bone degeneration, and sarcopenia, which causes a loss of muscle mass, strength, and function, frequently coexist, leading to noticeably worse outcomes than found in either condition alone [1]. The definition of sarcopenia was updated by the European Working Group on Sarcopenia in Older People (EWGSOP2) in 2018. Sarcopenia, a muscle illness that commonly affects older people but can occasionally happen early in life, is caused by unfavorable muscle alterations that accumulate over a lifetime updates the clinical algorithm that can be used for case-finding, diagnosis and confirmation, and severity determination and provides clear cut-off points for measurements of variables that identify and characterize sarcopenia. The algorithm highlights low muscle strength as a key characteristic of sarcopenia, uses detection of low muscle quantity and quality to confirm the diagnosis, and identifies poor physical performance as indicative of severe sarcopenia. EWGSOP2 urges healthcare practitioners to take steps to support the early diagnosis and treatment of osteosarcopenia in light of these new recommendations [2]. Osteosarcope-

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Abbreviations

DXA – dual energy X ray absorptiometry
SPPB – short physical performance battery
TUG – time up and go test
FRAX – fracture risk assessment tool
BMD – bone mass density
EWGSOP 2 – European Working Group on Sarcopenia in Older People

nia is more common in women (2.5.5-82.6%) than in men (16.4-32%) with increasing age, with men experiencing an increase from 14.3 to 59.4 percent (60-64 years) and women experiencing an increase from 20.3 to 48.3 percent (60-64 years) respectively. The highest prevalence rates of osteosarcopenia are found in older people with minimal-trauma fractures (46%) or post-hip fractures (17.1–96.3%) [3]. An increased risk of falls, fractures, functional disability, and mortality is linked to osteosarcopenia. The disorder is widespread among older people. Given the high prevalence of sarcopenia in people with osteoporosis, screening for the second condition should be recommended whenever the first is suspected [4].

Pathophysiology of osteosarcopenia

Multiple factors contribute to the pathogenesis of osteosarcopenia. Sarcopenia is a condition caused by aging-related immunological changes such as hormonal imbalances, protein turnover (degradation) imbalances, chronic inflammation, an increase in oxidative stress, increases in adiposity (intra and intermuscular fat), a decrease in physical activity, and poor nutrition. Contrarily, osteoporosis is defined as the age-related loss of bone mineral density (BMD) and microarchitecture [5]. It is believed that imbalances between bone-forming (osteoblasts) and bone-resorbing (osteoclasts) cells, with the latter outnumbering the former over time, are the cause of decreases in bone density [6]. Traditional pathophysiologic models frequently highlighted endocrine mechanisms, estrogen deficiency and secondary hyperparathyroidism in the elderly due to estrogen deficiency, decreased dietary intake (low of intake protein, calcium), and widely prevalent vitamin D deficiency, as the key determinants of postmenopausal osteoporosis [7].

Risk factors for the onset of osteosarcopenia [8–11] are: genetic predisposition, age (> 50 years), female gender, undernourishment, short stature, physical inactivity, alcohol consumption, smoking, late menarche, early menopause, amenorrhea, estrogen deficiency, diet poor in calcium and proteins, certain drugs (steroids, insulin, heparin).

Osteosarcopenia complications

From the perspective of public health, it is crucial to recognize those who are at risk of fracture From a public health perspective, it is critical to identify those at risk of fracture so that early intervention and treatment can be given [12]. Trabecular Bone Score (TBS) was also decreased among those with osteosarcopenia, a sign of a worsening deterioration in bone microarchitecture [13]. Compared to individuals without osteosarcopenia, those with sarcopenia alone, and those with osteoporosis alone, those with osteosarcopenia were more likely to have previously suffered a fracture. Considerations of osteopenia and osteoporosis with high fracture risk may help to better understand the association between osteosarcopenia and fracture risk [14]. Osteosarcopenia has a negative impact on quality of life, morbidity, and mortality. It increases the risk of falls, fractures, disability, and hospitalization [15].

Diagnostics

An accurate and simple screening method for sarcopenia is SARC-F [16, 17]. This discovery supports the SARC-F recommendations of EWGSOP2 [18, 19]. The algorithm used by EWGSOP2 to identify cases, diagnose them, and assess the severity of sarcopenia has been updated. It is advised to evaluate muscles using DXA and BIA methods in routine clinical care, and that DXA, MRI, or CT in research and specialist care of individuals at high risk of negative consequences, to produce data that validates muscles of poor quantity or quality. SPPB, TUG, and 400-m walk tests are physical performance indicators used to gauge the degree of sarcopenia [20]. The first sarcopenia-specific quality of life survey, the Sarcol (SarQoL) questionnaire, has been developed and has been proven to be understandable to the targeted population. To assess the psychometric features (discriminative power, reliability, floor, validity, and ceiling effects), this questionnaire consists of 55 items that are divided into 22 questions and arranged into seven categories of quality of life [21–23]. DXA measurements of the hip and spine are the gold standard for diagnosis worldwide [24]. The measurement procedure is quick, allowing for a quick assessment of the mineral content of the entire body in a secure manner [25]. Quantitative computed tomography uses cross-sectional scans to measure thin layers. The computer analysis calculates BMD and determines the density of cortical and trabecular bone [26–28]. The advantages of ultrasound densitometry include lack of precision, portability, and avoidance of radiation [29].

Drug treatment of osteosarcopenia

Some substances' therapeutic effects on osteoporosis and sarcopenia suggest a potential dual effect on muscle and bone mass, suggesting that they may be helpful in for treating osteosarcopenia [30–32]. Pharmaceutical treatments that have an impact on both bone and muscle are necessary in these situations. Future (anti-myostatin antibodies, rapamycin, fatty acid synthase inhibitors) and present (denosumab, SARMs) drugs have demonstrated promising dual effects on bone and muscle that merit further study [33].

Prevention

Resistance training, adequate protein intake, calcium- and creatin-rich diets, avoidance of smoking and alcohol use, and resistance training have a dual favo-

rable effect on bone and muscle. These interventions may therefore minimize falls, fractures, and ultimately disability [34, 35].

According to Kanis and colleagues' meta-analysis, drinking more than two units of alcohol each day raises the risk of fracture tool [24]. Alcohol's complicated effects on bones and muscles raise the risk of slips and falls, calcium shortage, and liver overload. Similar to drinking, smoking cigarettes is bad for bones and muscles. It is believed to boost estrogen metabolism and have a direct impact on how cadmium affects bone metabolism. According to a meta-analysis by Law and Hackshaw, female smokers have worse bone health than non-smokers. Because they are both recognized risk factors for fracture, drinking alcohol and smoking are both part of the FRAX fracture risk assessment tool [36]. A meta-analysis of 14 prospective studies revealed a substantial inverse connection between older women's risk of hip fracture and the amount of physical activity [37]. Muscle-strengthening and weight-bearing exercise regimens should be the main emphasis of training, which should be tailored around the right dose, intensity, and frequency (at least three times per week for 30 minutes). Education to avoid falls and the ensuing fractures is a crucial concern [38]. An adequate intake of proteins, calcium, and vitamin D is guaranteed by a balanced and healthy diet. Lean mass, bone density, and fracture risk can all be reduced by eating enough protein (1.5 g/kg/day), vitamin D (800 IU/day), and calcium (1000 mg/day), all of which are well tolerated and effective treatments for osteosarcopenia. The American National Academy of Sciences advises that the recommended daily intake of vitamin D for healthy younger people be 400 IU. The recommended daily intake for people over 50 is 800 IU. The daily supplementation dose for patients with severe vitamin D deficiency should be up to 2000 IU. The lower limit for 25-hydroxyvitamin D is 30-32 ng/ml, whereas the upper limit is 60 ng/ml. The recommended daily calcium intake for people over 50 is 1200 mg (diet plus supplementation if necessary). Calcium supplements are required if the food falls short of meeting the body's needs 5 g/kg/day), 800 IU/day of vitamin D, and 1 mg/kg of calcium [39–41].

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EDITORIAL
UVODNIK

University of Novi Sad, Faculty of Medicine Novi Sad
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Orthopedic Surgery and Traumatology Clinic

Uvodnik
Editorial
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CONGRESS ACTIVITIES OF THE DEPARTMENT OF ORTHOPEDICS, UNIVERSITY CLINICAL CENTRE OF VOJVODINA

KONGRESNE AKTIVNOSTI KLINIKE ZA ORTOPEDIJU UNIVERZITETSKOG KLINIČKOG CENTRA VOJVODINE

Miroslav MILANKOV and Radmila MATIJEVIĆ

OsteoNS 2022 is a congress organized by ASTAS [1] (Association for Sports Traumatology and Arthroscopic Surgery of Serbia) in November (17-20.11.2022.) as a joint gathering of physiatrists, orthopedists, rheumatologists, endocrinologists, radiologists, pathophysiologists, general medicine doctors, i.e. all those who deal with diagnosis and treatment of patients with the pathology of the locomotor system. The secoAnd edition of this expert meeting has two parts - the 10th Balkan Congress of Arthroscopy and Sports Traumatology [2], which is followed by OsteoNS 2022, an annual multidisciplinary congress with topics in the field of osteoporosis, osteoarthritis and other musculoskeletal diseases [3].

This meeting was preceded by the 4th Basic Course in Knee Arthroscopy [4], which was held under the ESSKA support on November 17th, 2022. The course consisted of three parts. In the first part of the course, local lecturers held theoretical lectures covering the basic aspects of arthroscopic surgery. In the second part, course participants worked on models with eminent instructors. In the third part, each course participant took part in one arthroscopic surgery. Course participants were 15 orthopedic surgeons and residents from the West Balkan region - Serbia, Montenegro, North Macedonia, and Bosnia and Herzegovina. An expert team of lecturers from Serbia and North Macedonia conducted the theoretical and practical part of this course on knee models. Also, course participants had the opportunity to participate live in arthroscopy surgery at the Clinical Center of Vojvodina where the entirety of the course was organized.

Following, the latest trends in arthroscopic knee, ankle and shoulder surgery are presented at The 10th Congress Balkan Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (BASAKOS), with the participation of eminent lecturers from the Balkan countries as well as guests from Europe and the US. A large number of colleagues are expected both from the region and worldwide. As for the previous one, we strive to make this congress the best venue for the exchange of new knowledge and determination of new directions in maintenance and development of arthroscopic surgery, and certainly an occasion for strengthening collegial and friendly cooperation.

OsteoNS 2022 is the second of its kind that we organized with the aim to connect colleagues from different fields in medicine, but with one thing in common: patients suffering from osteo-muscular problems. We have lecturers from all over the world, leading experts in their area, who share their knowledge and experience on osteoarthritis - Jean Yves Reginster and Ali Mobasheri, management of hip fractures - Andreas Kurth and Olivier Bruyère, osteoporosis Polyzois Makaras and Kassim Javaid. Gathering lecturers and participants from the whole Balkan region contributes to very constructive discussions in every session, especially ones covering trauma and regenerative topics [5]. The most treasured outcome of OsteoNS 2022 is having orthopedic surgeons, rehabilitation medicine specialists, general practitioners, physiotherapists all in one place at the same time, trying to fully understand treatment approaches from one another's perspective and that is what OsteoNS 2023 continues to cherish [6].

ASTAS is a member of the European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) and the International Osteoporosis Foundation (IOF). The Clinic for Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina became an ESSKA Teaching Center [7]. The main goal of ASTAS is education, i.e. transfer of knowledge and experience of world-renowned experts in sports traumatology and arthroscopic sur-

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gery to the domestic professional public. The first President of ASTAS was Dr. Vaso Kecojević from the Clinic for Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina from Novi Sad.

I believe that young medical doctors in Serbia have the opportunity to be edified and perfected through various types of continuous education organized by the Medical Society of Vojvodina of the Serbian Medical Society [8, 9]. They also have the opportunity to participate in scientific research projects and at both national and international congresses. All of the above can help them achieve significant results on the domestic and international arthroscopic scene. I support and guide them in this as much as possible.

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OSTEO NS 2021

Institute for Rehabilitation, Belgrade

FRACTURE CONSOLIDATION IN PATIENTS WITH REDUCED BONE DENSITY

KONSOLIDACIJA PRELOMA KOD PACIJENATA SA SMANJENOM GUSTINOM KOSTIJU

Olivera ILIĆ STOJANOVIĆ

Summary

Introduction. The strategy of choosing drug therapy for patients with new low-energy fractures, is still ongoing discussed topic, particular problem and challenge for clinicians. **Material and Methods.** Analytic research method according to the PubMed relevant publications in the last 20 years. **Results.** It is considered that aging and osteoporosis are not correlated with the values of trabecular bone volume and the outcome of the operation. Elderly and osteoporotic patients with increased metabolic activity have a better outcome of osteosynthetic vertebral fusion and benefit the healing process. The patients with lower metabolic turnover, higher bone mineral density, and volume have worse results. The impaired ability of good fixation of osteosynthetic material due to the both thinned cortical layer and trabecular structure has been proven in rare publications. The lack of prospective clinical data studies, a shorter period of fracture repair in animal models, where the extrapolation of results is not safe, significantly complicates response accuracy. Elderly patients have lower trabecular density, lower volume and bone mineral density, higher intertrabecular space, but not a worse operative outcome compared to the age of 40-50. **Conclusion.** Therefore, osteoporosis may not in itself be a significant risk factor for an operative outcome or at least not to the expected extent. Contradictory, opinions regarding the effects of drug therapy primarily bisphosphonates, which are very often prescribed, indicate that the experience of clinicians and detailed individual approach of patients is crucial in the strategy of treating fractures in people with reduced bone density.

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THE ASSOCIATION OF EARLY MENOPAUSE AND OSTEOPOROTIC HIP FRACTURES

POVEZANOST RANE MENOPAUZE I PRELOMA KUKA KAO POSLEDICE OSTEOPOROZE

Ivana MINAKOVIĆ[1, 2], Ksenija BOŠKOVIĆ[1, 3] and Jelena ZVEKIĆ SVORCAN[1, 3]

Summary

Introduction. Postmenopausal osteoporosis is a frequent disease that increases fracture risk and represents a major public health problem. The aim of this study was to assess the impact of early menopause on the occurrence of hip fractures. **Material and Methods**. The retrospective cross-sectional study included 200 postmenopausal women aged ≥ 50 years who underwent bone mineral densitometry at the Special Hospital for Rheumatic Diseases Novi Sad, Serbia during 2015–2018. Patients were divided into two groups, the first group (N=107) was composed of women with spontaneous early menopause at the age of 40–45, and the second group (N=93) consisted of women in whom menopause occurred after age 45. The FRAX score for the Serbian population was calculated for each respondent. Women who have used hormone replacement therapy were excluded. **Results.** The groups were uniform by age and body mass index ($p > 0.005$), while the first group had a lower bone mineral density of the femoral neck (Me = 0.78 vs. Me = 0.86), $p < 0.001$. Respondents with early menopause had higher FRAX scores (higher risk) for hip fractures (Me 1.80) compared to women with menopause after the age of 45 (1.10), $p = 0.001$. Respondents with early menopause were more likely to have a high ten-year risk for hip fracture (32.2%) compared to women with menopause after the age of 45 (8.6%), $p < 0.001$. **Conclusion.** Our results suggest that early menopause could contribute to predicting future fractures.

General Hospital Subotica
Department of Orthopedic Surgery and Traumatology

RESULTS OF HIP PROSTHESIS IMPLANTATION IN PATIENTS ON DIALYSIS WITH OSTEOPOROSIS

REZULTATI UGRADNJE PROTEZE KUKA KOD PACIJENATA NA DIJALIZI SA OSTEOPOROZOM

Vladimir RISTIĆ

Summary
Introduction. Femoral neck fractures in dialyzed individuals occur due to: impaired bone metabolism, secondary hyperparathyroidism, low serum vitamin D levels and metabolic acidosis. The aim of this study is to present the results and complications of hip surgery in such patients. **Material and Methods**. Eleven persons with end-stage renal failure were surgically treated, 5 men and 6 women, mean age 57 years, with follow up of 3-10 years. We implanted a partial hip prosthesis in 7 of them due to: shorter duration of the operation, older age and shorter life expectancy, and in 4 patients on dialysis we used a total prosthesis. **Results**. In two cases, a deep infection occured despite the antibiotic therapy. One patient had a dislocation of the partial prosthesis, due to loosening and osteoporosis, so prosthesis was later removed and converted into a total endoprosthesis. The only lethal outcome occurred intrahospitally, due to post-operative complication of acute renal failure, with electrolyte imbalance and septic condition of a younger man, a chronic alcoholic. **Conclusion**. The success of treatment and reduction of complications of hip prosthesis implantation are influenced by: preoperative preparation, dialysis quality, surgical technique, choice of antibiotics, anticoagulant therapy, treatment of osteoporosis, postoperative care and rehabilitation. Serious complications have occurred in every third of our patients, but those who are successfully prevented can significantly improve their life expectancy, the quality of which is already impaired by renal insufficiency.

General Hospital, Vrbas

OUR COMPLICATIONS OF ARTHROSCOPIC KNEE SURGERY IN LOCAL ANESTHESIA

NAŠE KOMPLIKAKACIJE ARTOPSKOPSKE OPERACIJE KOLENA U LOKALNOJ ANESTEZIJI

Milan MILOVIĆ

Summary
Introduction. The advantages of arthroscopic knee surgery could be seen in a dramatic reduction in the duration of hospitalization and the time required for complete recovery and return to daily work and sports activities. This reduces treatment costs significantly, although low risk of complications still remains. After presenting our own results, they were compared with the data from the relevant professional literature in order to see the possibilities of preventing the complications, and the methods of resolving them, as well. **Material and Methods.** In the period from January 2016 to March 2020, 390 arthroscopic knee surgeries were performed under local anesthesia. There were 300 men (77%) and 90 women (23%) with an average age of 31 years (between 16-60 year-old). The left knee was operated 200 times, and the right 190 times. When diagnostic arthroscopies showed the presence of an isolated lesion of the anterior cruciate ligament in one patient and a change in the cartilage of the cup and the condyle of the femur, this was found in 113 patients, as well. A partial meniscetomy of the inner meniscus was performed in 211 patients, in 53 of the outer meniscus and in 12 free joint bodies were removed. The duration of the operation was 34 minutes on average (15-90 minutes). **Results**. A total of 140 complications (3.9%) were recorded, of which 35 (0.99%) were intraoperative (instrument fracture, loss of part of the meniscus, extravasation of fluid into the extremity) and 105 (2.98%) postoperative (infection, synovial fistula, thrombophlebitis, hemarthrosis, serous effusion in the knee and painful scarring). The average duration of surgery was 20 minutes (15-40 minutes). After diagnostic arthroscopies there were 10 (0.28%), while after various therapeutic arthroscopic procedures there were 13 (3.69%) complications. **Conclusion**. Crucial contributors to the occurrence of complications are insufficient professional training, improvisation in the application of routine techniques in work, rough handling and imprecise surgical approaches to the knee joint. The orthopedic surgeon must be familiar with all the potential complications of this technique in order to avoid them or at least reduce their number. The specifics of the instruments that are constantly improving and the rapid technological improvement of arthroscopy equipment necessarily require continuous education of surgeons who perform arthroscopic operations.

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STIFF KNEE AFTER ARTHROPLASTY – ISSUES IN REHABILITATION PRACTICE

UKOČENOST KOLENA POSLE ARTOPLASTIKE – PROBLEMI U REHABILITACIJSKOJ PRAKSI

Tatjana NOŽICA RADULOVIĆ[1, 2], Jelena STANKOVIĆ[1], Tamara POPOVIĆ[1, 2] and Željko JOVIČIĆ[1]

Summary
Total knee arthroplasty removes functional and aesthetic deformities caused by degenerative joint disease. Good functional results depend on good preoperative preparation, surgical treatment with a well trained surgical team and postoperative rehabilitation. The end result after total knee arthroplasty should be decreased pain, good functional ability and improved quality of life. Stiff knee occurs in 4-16% of patients with total knee arthroplasty and it is defined as a knee with postoperative range of motion less than 70 degrees. It presents great clinical issue because of greater postoperative pain intensity and limited function. Through review of the latest literature in the reduction of the risk of developing stiff knee, emphasis is given to prevention in terms of maximizing reduction of risk factors. If aggressive, rapid and effective physical therapy in combination with appropriate analgesia, motivation and active participation of the patient do not lead to satisfactory results, it is necessary to identify the cause of stiffness. Further treatment is in the domain of an orthopedic surgeon with possible manipulations (manipulation under anesthesia), arthroscopic arthrolysis, and finally revision knee surgery.

OSTEO NS 2022

Institute for Orthopedic Surgery “Banjica”, Beograd

HIP ARTHROSCOPY IN TREATMENT OF AVASCULAR NECROSIS OF THE FEMORAL HEAD

ARTROSKOPIJA KUKA U LEČENJU AVASKULARNE NEKROZE GLAVE FEMURA

Aleksandar CRNOBARIĆ

Summary
Avascular necrosis (AVN, osteonecrosis) of the femoral head is pathologic condition caused by proprietary vascular derangement, which very often leads to secondary degenerative changes in hip joint. It is considered that as much as 18% of all total hip replacements is performed due to treatment of consequences of Avascular necrosis. Core decompression of the femoral head is well known and widely accepted technique in treating this condition. Traditionally, it is performed using two-dimensional imaging, provided by AP and lateral X-ray projections of affected hip, which often results in lack of precision. Furthermore, due to two-dimensional visualization of the spheric shape of the femoral head, there is a possibility of damaging the articular cartilage when performing curettage of the necrotic tissue from underneath. To accomplish even better precision, we designed and 3d printed specific aimers, based on CT scans of individual patient’s hip. Therefore, we combined the best of two worlds, direct visualization of the femoral head provided by hip arthroscopy to enhance precision and direct visual control over femoral head while performing standard core decompression technique. Besides that, hip arthroscopy allowed us to further address intraarticular pathology caused by vascular necrosis (debridement, extraction of loose cartilage fragments if present, washing out etc.) which is not possible during standard core decompression procedure. We treated 12 patients during period June 2016. - March 2022. grading from Ficat II to IVa with described method (case reports).

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CONTROVERSIES IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

KONTROVERZE U REKONSTRUKCIJI PREDNJEG UKRŠTENOG LIGAMENTA

Aleksandar MATIĆ

Summary
Anterior cruciate ligament reconstruction is main tool for restoring knee stability after anterior cruciate ligament tear. Through years’ surgical technique advanced and many variations were developed in terms of graft selection, tunnel positioning, fixation devices, materials and even ligament repair. As there are many varieties in the same procedures, question is raised, are there some superiorities in some over others? Our aim is to try to present main items from surgical perspective and to provide pros and cons for each of them. Clinical studies provide information for wide range of those topics, yet, they are not uniform, and in some cases provide quite opposite results. We tried to provide objective opinion for various topics with clinical background, and as well to present our surgical preferences on anterior cruciate ligament reconstruction. By our opinion, for surgeon is the best to use the technique ones feels the best with and is the most familiar, as long as it is in standard practice worldwide.

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DILEMMAS IN THE DECISION MAKING PROCESS IN THE TREATMENT OF FEMORAL NECK FRACTURES – OUR EXPERIENCE AND METANALYSIS OF PAPERS DONE AT DIFFERENT CENTERS

DILEME U PROCESU ODLUČIVANJA LEČENJA PRLEOMA VRATA FEMURA - NAŠE ISKUSTVO I META ANALIZA RADOVA IZ RAZLIČITIH CENTARA

Antonio GAVRILOVSKI, Neron POPOVSKI, Teodora TODOROVA and Ilir SHABANI

Summary
Introduction. Fracture of the femoral neck is a challenging injury to treat properly. There is still a debate in the literature for the right treatment. We present to you our series of operated cases compared (in relation) to the published papers from different centers. In the period of 2016-2019, 314 cases were operated. All fractures analyzed were on the femoral neck. 39 cases required reoperation in the first year. There is a need for proper algorithm for treatment of these cases, and consensus is needed among the expert. It is crucial for surgeons to recognize fracture patterns and patient characteristics that will indicate use of right methods to manage these injuries effectively. Surgical options include in situ fixation, hemiarthroplasty, total hip arthroplasty, closed or open reduction and internal fixation. We present to you our series of operated cases compared (in relation) to the published papers from different centers. **Material and Methods.** This retrospective study was performed at the University Clinic for Orthopedic Surgery, Skopje, Republic of North Macedonia. The study was conducted in the period of 2016-2019. 314 patients with femoral neck fracture were treated surgically. **Results.** 39 cases required reoperation in the first year. Most common reason was fracture nonunion (68%) and avascular necrosis of the head of the femur (20%). **Conclusion.** There is a need for proper algorithm for treatment of these cases, and consensus is needed among the expert.

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INITIAL RESULTS FROM THE APPLICATION OF RADIAL EXTRACORPOREAL SHOCK WAVE THERAPY IN PATIENTS WITH KNEE OSTEOARTHRITIS

POČETNI REZULTATI PRIMENE TERAPIJE RADIJALNOM EKSTRA KORPORALNOM "SHOCK WAVE" TERAPIJOM KOD PACIJENATA SA OSTEROARTRITISOM KOLENA

Biljana KALCHOVSKA, Marija GOCEVSKA, Maja MANOLEVA, Valentina KOEVSKA, Biljana MITREVSKA, Cvetanka SAVEVSKA GERAKAROSKA, Erieta NIKOLIK DIMITROVA and Teodora JUGOVA

Summary
Introduction. Knee osteoarthritis is a common musculoskeletal disorder. Radial extracorporeal shock wave therapy comes as a new effective conservative method. **Material and Methods.** prospective, monocentric, interventional, non-randomized, controlled, clinical study of 50 patients divided in two groups: the examined group who was treated with radial extracorporeal shock wave therapy and kinesitherapy and the control group treated with conventional physical therapy and kinesitherapy. The patients' progress was monitored on the Numeric scale of pain, the WOMAC Index, and by clinical examination. The clinical findings were evaluated before the treatment started; immediately after its completion, and 3 months afterwards. **Results.** No statistically significant differences were found concerning the analyzed parameters at both group patients' physical examination at the beginning of physical treatment and at their first control. A statistically significant difference was found between the two groups at the second control in favour of the study group experiencing insignificantly less pain on palpation and pain when performing knee flexion; whereas regarding pain intensity, the control group patients experienced significantly stronger pain. Regarding the total value and the values of the three subscales of the WOMAC index, statistically significantly lower values were obtained in patients in the study group at the end of the first and second control. **Conclusion.** The results of this study demonstrate that radial extracorporeal shock wave therapy therapy has a better and longer-lasting effect on improving the knee joint movements, reducing pain and improving the functional ability of patients with knee osteoarthritis in comparison to patients treated with conventional physical therapy.

Institute for Orthopedic Surgery “Banjica”, Beograd

SECOND LOOK AFTER INITIAL SINGLE-BUNDLE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

‘’SECOND LOOK’’ INTERVENCIJA POSLE INICIJALNE ‘’SINGLE-BUNDLE’’ REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA

Boris VUKOMANOVIĆ, Dejan ALEKSANDRIĆ and Nikola BOGOSAVLJEVIĆ

Summary

Introduction. The ultimate goal of the surgery to reconstruct the injured anterior cruciate ligament is to restore its natural anatomy as much as possible, which would lead to the conditions that would ensure the longest survival of the replacement graft. To date, several reconstruction techniques have been described, but none of them have yet led to absolutely good results. The purpose of this work would be to arthroscopically evaluate the state of the reconstructed anterior cruciate ligament after arthroscopic assisted reconstruction with a single graft (ST/Gr, BPTB) based on anatomical versus non-anatomic principles of reconstruction in relation to synovial overlap, tension and damage. **Material and Methods.** The study included 28 patients who underwent second look after arthroscopic assisted single bundle anterior cruciate ligament reconstruction with autologous St/Gg or BTB graft. The position of the femoral and tibial graft insertion in relation to the natural anatomy was established and two groups of subjects were formed. The first group of subjects, of which there were 15, used a method of reconstruction based on the anatomical principles of graft placement in relation to the second group of 13 subjects where performed non-anatomic reconstruction of the anterior cruciate ligament. BioTransfik (Arthrek, Inc) or TightRope Button (Arthrek, Inc) was used for proximal femoral fixation, and PLLA Bioabsorbable Screw (Arthrek, Inc) was used for distal fixation in the tibia. All patients underwent a period of rehabilitation according to the same protocol. During the rearthroscopic procedure, synovial overlap of the graft, tension of the graft and damage to the graft were recorded. **Results.** It was observed that the reconstruction of the anterior cruciate ligament with a single bandle using the anatomical method of reconstruction showed better results compared to non-anatomical techniques. Synovial coverage of the graft occurred in 90.9% in anatomical reconstruction in ondos to 9.9% of good construction in non-anatomical reconstruction, in 71.4% with the anatomical reconstruction technique compared to 28.6% with the non-anatomical technique, and graft damage with the anatomical reconstruction was 15.4% compared to 84.6% with the non-anatomical reconstruction. **Conclusion.** The results showed that anatomical reconstruction is more effective than the non-anatomical method of anterior cruciate ligament reconstruction in terms of good synovial coverage, good tension and intactness of the graft, which puts arthroscopically assisted anatomical reconstruction of the anterior cruciate ligament in the place of the most acceptable way for survival.

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ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION AS AN OUTPATIENT SURGERY

REKONSTRUKCIJA PREDNJEG UKRŠTENOG LIGAMENTA KAO AMBULANTNI HIRURŠKI ZAHVAT

Dragan RADOIČIĆ

Summary

Introduction. Arthroscopic anterior cruciate ligament reconstruction performed as a one-day (day-case, one-day, outpatient surgery) intervention is a standard option in many orthopedic centers. The concept of one-day anterior cruciate ligament reconstruction, as any same-day surgery, has significant clinical and financial advantages primarily in regard to reduced hospital stay, reduced costs, higher hospital turnover and non-negligible patient satisfaction. **Material and Methods.** A retrospective series of a single surgeon consecutive arthroscopic anterior cruciate ligament reconstructions, performed as same-day surgeries. The reconstructions were performed in the period from 2016 to 2022. There were 89 patients in total. The aim was to determine complications related to the procedure, duration of pain, duration of recovery and general satisfaction with the one-day approach. Investigated factors additionally included patient age, gender, body mass index, primary or revision reconstruction. **Results.** No significant complications were recorded. After 6 months of reconstruction, 96.6% of patients were very satisfied with the result. 100% of patients declared that they were satisfied with the one-day intervention concept and 100% of operated patients would prefer the one-day option if they ever needed another similar surgical intervention. **Conslusion.** Rate of anterior cruciate ligament reconstructions as a day-case surgeries seems to remain low, despite an extremely low complication rate and high patient satisfaction. Anterior cruciate ligament reconstruction as a one-day intervention might an excellent option for adequately selected and prepared patients. Modern protocols, operative techniques and implants, allow safe and routine day-case anterior cruciate ligaments by all surgeons with adequate prior experience and knowledge.

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MULTIDISCIPLINARY REHABILITATION TREATMENT OF PATIENTS WITH SCIATICA

MULTIDISCIPLINARNA TERAPIJA REHABILITACIJE PACIJENATA SA IŠIJASOM

Dunja POPOVIĆ[1,2], Jana VASIN[1] and Larisa VOJNOVIĆ[1,2]

Summary
Introduction. Sciatica is pain that spreads from the lower back to the lower extremity below the knee. **Material and Methods.** The research included 51 subjects who were treated at the Clinic for Medical Rehabilitation of the Clinical Center of Vojvodina for chronic sciatica. Next to demographic data, we also gathered results from Numerical Rating Scale, The Oswestry Disability Index, Central Sensitization Inventory and Fear Avoidance Component Scale. Results were obtained at the start and at the end of the treatment. **Results.** The majority of the patients were women (34 (66.7%)). The duration of the stationary multimodal treatment od chronic pain was 20.48±5.89 days. The pain intensity measured by NRS had significantly lowered after the treatment (6.49±2.22 vs 5.00±2.22, t=5.629, p<0.001). Average ODI score (48.75±15.16 vs 42.24±14.13 (t=4.246, p<0.001), as well as FACS score (66.80±14.13 vs 62.47±16.49, t=2.086, p=0.042) had significant improvement after the tretament. The CSI score improved after the end of the treatment, but this difference did not reach statistical significance (t=1.446; p=0.155). **Conclusion.** Stationary multidisciplinary rehabilitation treatment leads to an improvement in the functional status of patients, a reduction in the level of activity avoidance due to fear, and a reduction in pain intensity.

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POSTERIOR APPROACH FOR MANAGEMENT OF POSTERIOR COLUMN TIBIAL PLATEAU FRACTURES IN THE PERIOD BETWEEN 02.2022-11.2022 IN THE UNIVERSITY CLINIC OF TRAUMATOLOGY - SKOPJE

POSTERIORNI PRISTUP U TERAPIJI 'PLATEAU' FRAKTURA POSTERIORNE KOLUMNE TIBIJE U PERIODU IZMEĐU 02.2022 I 11. 2022 NA UNIVERZITETSKOJ KLINICI SKOPJE

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Summary
Introduction. Posterior tibial plateau fractures are an uncommon type of fracures. Most surgeons are accustomed to operate in the supine position, however, surgery in the posterior knee region and operating in prone position can be challenging because of the presence of neurovascular structures including the tibial nerve, popliteal artery and vein,common peroneal nerve and also challenging to achieve effective reduction and fixation, thus, it is less commonly performed. **Material and Methods.** Between February and November 2022 four posterior tibial colum fractures were diagnosed and operated in our clinic within a six months follow-up (2 female and 2 male with mean age of 52 years). All were diagnosed with plain films and CT scans. All of the fractures were on the right leg. Posterior approach in prone position was used to reduce the tibial condyle and fix it with a plate. Radiographic evaluation included reduction quality and bone union. **Results.** All fractures healed within 6 months, without secondary displacement. Throughout the follow-up period, there were no incidences of post-traumatic osteoarthritis of the knee. No patient complained of knee instability. **Conclusion.** The posterior approach is challenging, it requires a thorough understanding of the anatomy of the neurovascular structures of the posterior knee. In terms of reduction and stable fixation, the prone position and posterior approach have significant advantages, producing positive outcomes.

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HYPERALGESIA IN PATIENTS WITH FIBROMYALGIA

HIPERALGEZIJA KOD PACIJENATA SA FIBRIMIJALGIJOM

Larisa VOJNOVIĆ[1,2], Jovana VIDIĆ[1] and Dunja POPOVIĆ[1,2]

Summary

Introduction. Chronic fatigue and widespread pain are some of the leading symptoms of fibromyalgia. Signs of central sensitization and hyperalgesia can often be observed in these patients. It is not clear if hyperalgesia is present for different painful stimuli such as pressure, heat and cold. Therefore, the aim of this study was to determine whether there are differences in pain pressure threshold, heat pain threshold and cold pressure threshold between healthy subjects and patients affected by fibromyalgia. **Material and Methods.** A retrospective study conducted at the Medical Rehabilitation Clinic of the University Clinical Center of Vojvodina included 45 subjects - a control group of healthy patients and a group of patients suffering from fibromyalgia in whom pain pressure threshold , heat pain threshold and cold pressure threshold were measured on the forearm and on the paraspinal musculature of the lumbosacral region of the spinal column. **Results.** The study included 45 patients (average age 54.60 ± 7.96 years, 88.9% females), of whom 23 (51.1%) were diagnosed with fibromyalgia, while 22 (48%) were the healthy control group. Patients with fibromyalgia have a significantly lower pain pressure threshold compared to the group of healthy subjects: 26.13 N/cm^2 vs 53.54N/cm^2, (Z=-4.439, p<0.001); heat pain threshold 39.70 °C vs 44.85 °C, (Z=-3.871, p<0.001); cold pressure threshold 20.51 °C vs 12.51 °C, (Z=-2.612, p=0.009). In the area of the paraspinal musculature, pain pressure threshold was 37.01 N/cm^2 vs 75.77 N/cm^2, (Z=-4.178, p<0.001); heat pain threshold - 38.18°C vs 44.13°C (Z=-3.758, p<0.001); cold pressure threshold - 21.52°C vs 11.16°C (Z=-2.737, p=0.006). **Conclusion.** In patients suffering from fibromyalgia, generalized hyperalgesia is present for various modalities including pain pressure threshold, heat pain threshold and cold pressure threshold.

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TREATMENT OF COMPLEX PSEUDOARTHROSIS OF THE SUPRACONDYLAR FEMUR WITH METHODS OF STANDARD OSTEOSYNTHESIS WITH BONE AUTOTRANSPLANT AND AUTOLOGOUS BIOREGENERATIVE SCAFFOLD AUGMENTATION – CASE REPORT AFTER MULTIPLE YEARS OF FOLLOW-UP

TERAPIJA KOMPLEKSNE PSEUDOARTROZE SUPRA KONDILARNOG FEMURA METODIMA STANDARNE OSTEOSINTEZE AUTOTRANSPLANTOM KOSTI I AUGMENTACIJOM AUTOLOGNOM BIOREGENERATIVNOM PODRŠKOM – PRIKAZ SLUČAJA POSLE VIŠEGODIŠNJEG PRAĆENJA

Milan TOŠIĆ[1], Nikola VUKOSAV[1], Milan MAJKIĆ[1], Branko BALJAK[1] and Oliver DULIĆ[1,2]

Summary

Introduction. Pseudoarthrosis of the supracondylar region of the femur represents one of the most difficult complications of femoral fracture treatment. These are patients who, most often, after undergoing numerous operations, developed a disability incompatible with everyday life and work activities. The local finding related to the local presence of biologically very "poor quality" tissue result in changes in anatomical relationships and the consequent impossibility of walking without aids, loss of range of motion of the knee and hypotrophy of the musculature. The aim of this case report is to present the method of treating these patients using the described technique. **Material and Methods.** After examination and evaluation of each patient condition, operative treatment was indicated for three patients admitted to our Clinic. After approaching the pseudarthrosis zone, tissue debridement and revascularization were performed. Overgrown medullary canals were opened and in situ produced cortical autotransplant and an autologous scaffold were implanted at the site of the bone defect. The fractures were fixed with an adequate locking plate. Patients underwent a special postoperative physical treatment protocol. **Results.** The average number of previous operations is 2.3 and the average time since the fracture was 15 months. The average age of the patients was 36.5 years. After the operation, there is an increase in the values both in the scores for the femur and the knee, as well as in the scores for the quality of life with a highly significant statistical difference. All operated patients were able to fully weight bare, walk without pain and without use of aids. All patiens had evident diagnostic confirmations of femoral union after 12 months postoperatively. **Conclusion.** The described method of treatment of femoral pseudarthrosis can be one of the options in achieving union and returning the patient to activities of daily living.

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OPEN BANKART PROCEDURE – STILL RELEVANT TODAY

OTVORENI BANKART ZAHVAT – ZNAČAJAN I DANAS

Milan TOŠIĆ[1], Nikola VUKOSAV[1], Milan MAJKIĆ[1], Branko BALJAK[1] and Srđan NINKOVIĆ[1, 2]

Summary
Introduction. The purpose of this study is to emphasize the benefits of using an open surgical technique in high-risk patients with anterior soft-tissue shoulder instability. **Material and Methods.** All patients were operated on at the Clinic for Orthopedic Surgery and Traumatology in Novi Sad in the period between January 2013 and September 2017. There were 40 patients enrolled in this study. The average age of the subjects was 27±6. Examination of the operated shoulder's range of motion and muscle strength was performed for all patients. The Constant-Murley score was used to evaluate the postoperative results. **Results.** The mean value of the Constant-Murley score following the operation was 90.3±11.5, while 87.5% patients had excellent and good results. In comparison with the opposite uninjured shoulder, there was a statistically significant difference ($p<0.05$) in the Constant-Murley score, in the external rotation of the shoulder in the abducted position (13.2°±10.4°), as well as in the adducted position (10.25°±9.7°). **Conclusion.** Despite the increasing popularity of arthroscopic Bankart repair, open Bankart repair remains an excellent surgical option for a select group of patients with risk factors for failure following arthroscopic stabilization.

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THE RESULTS OF TREATMENT OF ACROMIOCLAVICULAR JOINT INJURIES

REZULTATI LEČENJA POVREDA AKROMIOKLAVIKULARNOG ZGLOBA

Mile BJELOBRK[1,2], Milan TOŠIĆ[1], Milan MAJKIĆ[1], Nikola VUKOSAV[1], Branko BALJAK[1] and Srđan NINKOVIĆ[1,2]

Summary
Introduction. Arcomioclavicular joint occupies an important place in the function of the shoulder. Loss of joint function due to injury or disease disturbs the biomechanics of the shoulder. The aim of the research was to evaluate the results of operative treatment of acromioclavicular joint injuries, identify risk groups within the range of age and pointing out the most common mechanism of injury. **Material and Methods.** Retrospective study was conducted in the group of 20 patients treated because of an acromioclavicular injury. We assessed the results of surgically treated patients with acromioclavicular injury from January 2017 to January 2019. Patients were treated using Bosworth and Phemister operative techniques. In assessing the results of operations Constant shoulder score has been used. We compared the data of the operated and healthy shoulders for each patient. Statistical analysis was performed using Student's T-test and χ^2 test. **Results.** According to Constant's scoring scale 9 patients had an excellent result, 7 had a good result, 3 had satisfactory, and there were no patients with poor outcome. We compared the sum of Constant's scoring scale of the operated shoulder with the results of the opposite healthy shoulder, as well the range of motion of external rotation, and internal rotation range of motion of the operated and opposite healthy shoulder. There was a statistically significant difference ($p <0.05$) in all compared parameters. Sum of Constant's scale of the operated shoulder was 14% lower than in the healthy shoulder. **Conclusion.** The basic precondition of positive results of treatment is timely diagnosis and early surgical intervention. The function of the shoulder is surgically restored so that 95% of patients can perform all activities of daily living.

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LATERAL SURAL ARTERY PERFORATOR FLAP FOR SOFT TISSUE RECONSTRUCTION OF THE KNEE

LATERALNI SURALNI FACIO-KUTANI PERFORATORNI REŽANJ U REKONSTRUKCIJI MEKIH TKIVA KOLENA

Mladen JOVANOVIĆ, Marija MARINKOVIĆ, Miroslav TOMIĆ, Nenad ĐERMANOV and Sveto BJELAN

Summary

Introduction. Soft-tissue skin defects around the knee are most common caused by traffic accidents, burn, tumor resection or surgical site infection. Reconstruction of defects is considered as a challenging operation due to the needs for adequate skin coverage and restoration of knee function. Lateral sural flap is an ideal pedicled flap that is suitable for regional reconstruction around the knee for small and moderate defects. **Case reports NoI.** A 73 year-old male patient was admitted to our Department with skin defect and exposed prothesis after total arthroplasty of the wright knee. A month and a half after surgery, complete dehiscence of the suture line occured due to a direct fall on the right knee. The proximal part of the defect was covered with a skin graft, while the lateral sural flap was raised to cover the distal part of the defect (size 7 x 5 cm). **Case reports NoII.** A 22 years-old male patient was reffered to our Clinic three weeks after traffic accident with necrosis of soft tissue of the knee and exposed patella. Extensive wound debridement was done and elevation of the lateral sural flap – size 9 x 5.5 cm was performed to cover the defect. In both cases, flaps completely survived and direct closure of the donor site was possible. **Conclusion.** Proximally based lateral sural flap is a island fasciocutaneous flap with thin, pliable and sensate skin; which left minor donor-site morbidity. This surgical procedure is less technically demanding and could leed to excellent functional and aesthetic outcome.

City General Hospital 8-th of September Skopje, Republic of North Macedonia

DECISION MAKING FOR TREATMENT OF ROTATOR CUFF TEARS

POSTUPAK DONOŠENJA ODLUKE U TERAPIJI POVREDA ROTATORNE MANŽETNE

Nenad PETKOV

Summary

Introduction. Over the last 10 years, no reconstructive procedure of the shoulder has evolved more than the rotator cuff repair. Much of the impetus for this evolution has been the result of a better understanding of the anatomy and the patoanathomy of cuff patology provided by the artroscope. The primary function of the rotator cuff is to balance the force couples about the glenohumeral joint. Therefore, when faced with a rotator cuff tear, the primary goal of surgery is to balance the fource couples in the transverse and coronal planes. Our aim is to show the diferent cuff tear patterns and our experience with treatment of those tears. **Material and Methods.** During the period from 2014-2021, 290 patient were operated for cuff related problem. The average age of the patient at surgery was 52 years (range 24-84 years). Average follow up was 36 months. For evaluation we used the rating scale of UCLA, Constant and Murley and Simple Shoulder Test. **Results.** Taking in account the diversity of the group, it is difficult to draw conclusions from this numbers. In general 74% (217) of the patients had no pain, 22% (63) of the patients had slight pain without restriction of activities and 4% (10) of the patients had moderate pain with activity compromise. Average Constant Murley score was 76 of 100 points. A Yes response was given for an average of 9 of 12 questions on the Simple Shoulder Test. **Conclusion.** Clear understanding of the biomechanical role of the rotator cuff in shoulder function is imperative. Undestanding diferent tear patterns and treating them appropriately will be a step closer to achieving the gole of having a satisfied patient.

City General Hospital 8th of September, Skopje, Republic of North Macedonia

IMPORTANCE OF MUSCLE BALANCE IN REVERSE SHOULDER ARTHROPLASTY

ZNAČAJ RAVNOTEŽE MIŠIĆA KOD REVERZNE ARTROPLASTIKE RAMENA

Nenad PETKOV

Summary

Introduction. Since the introduction in the 1990 in Europe and 2003 in USA, reverse shoulder arthroplasty has been gaining more popularity as the surgeons and the patients see the improvements regarding pain, range of motion and functional results. The main candidates for reverse shoulder arthroplasty in the beginning were elderly patients with end stage cuff tear arthrosis. However, with the imrpovement in implant design, other indications emerged, like acute fractures and fracture sequelae of the proximal humerus and tumors of the proximal humerus. With these expansion in usage of the reverse shoulder arthroplasty, problems with muscle balancing started to occure. Reverse shoulder arthroplasty can succefully restore active elevation in rotator cuff deficient shouders. However, reverse shoulder arthroplasty cannot restore active external rotation. In absence of external rotator muscles, internal rotator muscles become dominant resulting in muscle imbalance. The combination of Latisimus dorsi and Teres Major transfer with reverse shoulder arthroplasty has been reported to restore both active elevation and external rotation. Our goal is to show that reverse shoulder arthroplasty can successfully be used not only in cuff tear arthropaties, but also for cominuted fractures of the proximal humerus, fracture sequelae, inflammatory arthropaties or tumors of the proximal humerus, and also to show that the combined procedure of reverse shoulder arthroplasty and tendon transfer can lead to good clinical outcome. **Material and Methods.** Between 2018 and 2021, 63 patient (64 shoulders), were treated with reverse shoulder arthroplasty. 12 patients were treated with reverse shoulder arthroplasty in combination with latisimus Dorsi/Teres major transfer in modified manner. All patients recived Delta Xtend Reverse Shoulder endoprosthesis. All patients were operated by the same surgeon and recived the same post operative protocol. For results evaluation we used "Constant score for functional results, Visual Analog Score for pain assesement. Literature citations were used regarding reverse shoulder arthroplasty and tendon transfer with the use of Pub Med. **Results.** We had improvement in functional scores as wel in the Visual Analog Score for pain assesement in all patients. **Conclusion.** As for the long term results we must say they are still pending, the mid term and short term results sugest that reverse shoulder arthroplasty is a reliable treatment for many previously very hard to treat proximal humerus pathologies, as for the combined approach of reverse shoulder arthroplasty and modified L'Episcopo transfer the literalure and our results show the importance of restoring muscle balance for optimal results.

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RECOVERY FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

OPORAVAK POSLE REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA KOLENA

Nikola VUKOSAV[1], Milan TOŠIĆ[1], Milan MAJKIĆ[1], Branko BALJAK[1] and Miroslav MILANKOV[1, 2]

Summary

Introduction. The frequency of anterior cruciate ligament injury has been steadily increasing in recent years. They occur mainly in young, sports-related individuals. The aim of this research is to carry out an analysis of returning to sports activities after the reconstruction of the anterior cruciate ligament. **Material and Methods.** The data from 795 patients who had reconstruction of the anterior cruciate ligament was analyzed included demographic data, the presence of associated meniscal injuries, the sports activity level before injury, time elapsed from injury to surgery, to start of running, to reaching full competition activity, and the level of sports activity in relation to pre-injury. **Results.** Half of patients returned to the intensity of training they had before injury. Just over half (57%) return to sports activities a year or more after of the operation. Younger than 30 years are returning faster than older. Patients with an associated meniscal injury, later return to sports activities and achieve lower levels of sports activity than those who had an isolated anterior cruciate ligament injury. Patients who wait longer for surgery, later return to sports activities. **Conclusion.** Half of patients returned to the intensity of training they had before injury. Just over half return to sports activities after a year or more of the operation. Sex has no impact on the time of return to full sports activities. Younger than 30 years are returning faster than older. Patients with an associated meniscal injury later return to sports activities. Patients who wait longer for surgery, later return to sports activities.

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Center for Physical Medicine and Rehabilitation

THE EFFECTIVENESS OF ELECTROTHERAPY MODALITIES AND KINESITHERAPY IN TREATMENT OF FROZEN SHOULDER IN ADULT PATIENTS

EFIKASNOST ELEKROTERAPIJSKIH MODALITETA I KINEZI TERAPIJE ZAMRZNUTOG RAMENA KOD ODRASLIH PACIJENATA

Sonja NEJKOV

Summary
Introduction. Frozen shoulder, sometimes also referred to as adhesive capsulitis, is a debilitating condition characterized by an insidious onset of shoulder pain, progressive stiffness, and significant restriction of range of motion. The prevalence is 2–5% although estimates range as low as 0.5% or as high as 10% adhesive capsulitis can be classified as primary (associated with other diseases, such as diabetes mellitus, hypothyroidism, Parkinson's disease) or secondary when the inflammation and fibrosis of the synovial joint can be triggered by trauma (e.g. rotator cuff tendon tear, subacromial impingement, biceps tenosynovitis and calcific tendonitis) or surgery to the joint. The aim of this work is to provide a systematic review of the evidence based literature on the need and place of physical therapy in treatment of frozen shoulder. **Material and Methods.** PubMed, Physiotherapy Evidence Database, and Cochrane databases of Systematic Reviews were searched for studies published in English since 2014. The search terms included: frozen shoulder, adhesive capsulitis, physical therapy, electrotherapy, kinesitherapy, rehabilitation, mobilization, exercise and education. **Results.** Low-level laser therapy is strongly suggested for pain relief. Electrotherapy can help in providing short term pain relief. Kinesitherapy and mobilization are strongly recommended for reducing pain, improving range of motion and function in patients with stages 2 and 3 of frozen shoulder. It is unclear whether a combination of manual therapy, exercise and electrotherapy is an effective adjunct to glucocorticoid injection or oral NSAID. Continuous passive motion is recommended for short-term pain relief but not for improving range of motion or function. Deep heat can be used for pain relief and improving range of motion. Ultrasound for pain relief, improving range of motion or function is not recommended. **Conslusion.** The evidence suggests that physical modalities and kinesitherapy are recommended for pain relief, improvement of range of motion, and function in patients with frozen shoulder.

University Clinic for Physical Medicine and Rehabilitation, Skopje, Republic of Macedonia
"St. Cyril and Methodius" University, Faculty of Medicine

KINESITHERAPY IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS

KINEZI TERAPIJA KOD ŽENA SA OSTEOPOROZOM U POSTMENOPAUZI

Valentina KOEVSKA

Summary
Introduction. Osteoporosis is most common in post-menopausal women, due to loss of trophic support for bone tissue from sex hormones. Osteoporosis and related fragility fractures are a global public health problem in which pharmaceutical agents targeting bone mineral density are the first line of treat-ment. However, pharmaceuticals have no effect on improving other key fracture risk factors, including low muscle strength, power and functional capacity, all of which are associated with an increased risk for falls and fracture, independent of bone mineral density. Regular exercise exercise training is the only strategy that can improves muscle strength and coordination, and reduces the risk of falls and improves mobility and quality of life. The role of exercises on bone mineral density and the quality of life in women with PMOs. **Material and Methods.** 92 women with PMOs were treated one year in University Clinic for Physical Medicine and Rehabilitation Skopje, Republic of Macedonia. The subjects were divided into three groups, the first group of 30 patients with exercise and physical pain procedures, the second group of 30 patients with exercise alone and the control group of 30 patients. Bone mineral density was determined by dual-energy x-ray absorptiometry, and quality of life was determined with Qualiifo-41 at baseline and after one year. **Results.** The average age was 60.64 ± 6.7, education: primary 23.9%, intermediate 48.91%, and higher 27.17%. Average BMI was insignificant in start ($p = 0.88$) and after research ($p=0.86$). The results of the comparison between the three groups showed that subjects had insignificantly different total bone mineral density at the lumbar spine ($p = 0.68$, vs $p = 0.72$), and at the femur ($p = 0.16$, vs $p = 0.06$), at the reception, and at the end of the follow-up. The subjects had insignificantly different t-score of the lumbar spine ($p=0.6$) and femur ($p=0.2$), at the reception, but the end of the follow-up subjects had significantly different t-score for the lumbal spine ($p = 0.04$) and for the femur ($p=0.018$). After one year there was a significant improvement in quality of life in the first and second groups compared to the control group ($p=0.001$). **Conclusion.** Regularly practicing exercises significantly improves the quality of life. In the treatment of PMOs, except drug therapy, suitable program of exercise is necessary.

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INJURIES OF THE ANTERIOR CRUCIATE LIGAMENT IN CHILDREN AND ADOLESCENTS – OUR EXPERIENCE

POVREDE PREDNJEG UKRŠTENOG LIGAMENTA KOD DECE I ADOLESCENATA – NAŠE ISKUSTVO

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Summary

Introduction. With the increase in children's participation in high-intensity sports activities, injuries characteristic of older age is becoming more common. One of these injuries is a tear of the anterior cruciate ligament. In the pediatric population, anterior cruciate ligament reconstruction represents a difficult and highly specialized intervention. Current evidence suggests that long delays in ligament reconstruction may predispose the patient to further episodes of instability, with consequent injuries to surrounding structures, such as meniscal and articular surface injuries. Understanding the pathology of anterior cruciate ligament injury and its treatment, due to the increasing frequency of this injury, is a necessity in order to prevent potential complications, reduce morbidity and restore the quality of life that children deserve. **Material and Methods.** In this retrospective study 51 patients that were operated on Institute for children and youth health care of Vojvodina from 2016 to 2022 were included. **Results.** Average patient age was 16 years. From time of the injury to definite of diagnosis, there was on average time delay of 4 months, and another 8 months until operative reconstruction of anterior cruciate ligament. In 84% of the patient's mechanism of injury was indirect. In almost all patients there was an magnetic resonance imaging verification of anterior cruciate ligament rupture. bone-patellar tendon-bone was a graft of choice for ligament reconstruction. 90% of the patients didn't have any associate injury. **Conclusion.** Anterior cruciate ligament injury is more and more common in pediatric population, with equal frequency in boys and girls. Most of these patients are skeletally mature, and could be treated using bone-patellar tendon-bone graft and interference screw fixation. Between injury and anterior cruciate ligament reconstruction there was a large time delay, almost one year, however, this did not affect increase in concomitant injuries of the knee.

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6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al.*

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Material and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.