

Резюмета на научните трудове на английски език

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Представени за участие в конкурс за академична длъжност „Доцент“ в област на висше образование 7. Здравеопазване и спорт, професионално направление 7.1. Медицина по научна специалност „Кардиология“ към Факултет „Медицина“, Първа катедра по вътрешни болести и Клиника по ревматология към УМБАЛ „Света Марина“ – ЕАД – Варна, съгласно публикувана обява в Държавен вестник бр. 61 / 23.07.2021 г.

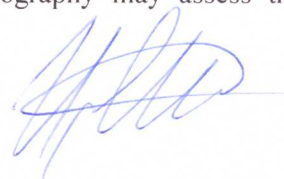
Г7. Публикации и доклади, публикувани в научни издания, реферирани и индексирани в световноизвестни бази данни с научна информация

Г7-1. Georgiev T., Stoilov R. Bulgarian rheumatology: science and practice in a cost-constrained environment. *Rheumatology International*. 2019; 39(3), 417–429. ISSN 1437-160X

Our aim was to appraise publications from Bulgaria, to assess their global impact, and to describe features and challenges unique to the rheumatology practice in Bulgaria characterized by stringent cost constraints. The Scopus database was queried on 25th July 2018 and data on the number of published documents, their Hirsch-indices and citations number were extracted. Published Bulgarian guidelines for the management of rheumatic diseases and the presented data on Bulgarian Rheumatology Society were identified based on prior knowledge of the authors. From all the identified 1082 document the most extensively researched areas were rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoporosis, and osteoarthritis (OA). For the last five years (from Jan 2013 to 25th July 2018) the number of publications was 293. We found that Bulgaria's international scientific collaboration in the field of rheumatology is focused on a handful of countries mainly from Europe. Although Bulgarian rheumatologists have access to costly biologic agents for treating their patients with rheumatic diseases, their funding may not be granted according to the current recommendations of European League against Rheumatism (EULAR) and national guidelines for the management of rheumatic diseases. Although the western world clearly dominates the production of scientific publications in rheumatology, Bulgarian rheumatology may present another perspective for diagnosis and management of patients with rheumatic diseases in a cost-stringent environment. Nevertheless, both rheumatology science and practice in Bulgaria still have a long way to go to take its deserved place among the other European countries.

Г7-2. Gerganov G., Georgiev T., Shivacheva T. AB0863 Radiography versus ultrasonography – which imaging modality tells us more about pain severity in knee osteoarthritis? *Annals of the Rheumatic Diseases* 2020;79:1738-1739. ISSN: 0003-4967

Osteoarthritis (OA) is a leading cause of disability worldwide and pain is its cardinal symptom. Ranging from structural injuries to central sensitization, multifactorial mechanisms play an important role in pain perception in patients with knee OA (KOA) defining a discrepancy between pain and structural damage. Imaging modalities such as radiography and musculoskeletal ultrasonography may assess those



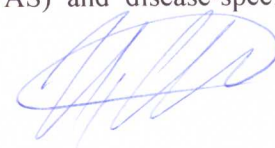
Imaging modalities such as radiography and musculoskeletal ultrasonography may assess those structural findings and both are well embedded in routine clinical practice. However, their association with pain severity is poorly studied. Objectives: To evaluate the place of X-ray- and ultrasound-derived parameters of structural damage for pain perception in knee osteoarthritis patients. Sixty-four knees from 38 patients with KOA fulfilling the ACR criteria were assessed. The pain severity was evaluated in all knees by 100-millimeters (mm) visual analogue scale (VAS). Anteroposterior radiographs of the fully extended knees in an upright weight-bearing position were obtained and images were evaluated according to the Kellgren-Lawrence (KL) and OARSI atlas. All patients were investigated with a portable MyLab 25 Gold system equipped with an LA435 transducer (Esaote SpA, Genoa, Italy) by two experienced ultrasonographers. The presence or absence of synovial thickening, effusion in the suprapatellar bursa, and popliteal cyst were assessed. Medial meniscal extrusion and medial and lateral femoral cartilage thickness (medial and lateral) were measured in mm in full extension and flexion position, respectively. Femoral osteophytes were semi-quantitatively scored using a scale consisted of four grades (0-3). The levels of pain differed significantly in the KL groups ($p = .001$) and in the groups classified according to the medial tibiofemoral compartment narrowing defined in line with the OARSI atlas ($p = .005$). The other knee osteoarthritis radiographic characteristics derived from the OARSI atlas did not correlate with the pain. From the assessed ultrasound parameters, medial meniscal extrusion and medial femoral cartilage showed a weak correlation with pain levels ($r = .254$, $p = .043$; $r = -.265$, $p = 0.034$, respectively). Nevertheless, in the multivariate analysis after adjusting for age and BMI, both variables did not reach significance for explaining the differences in VAS levels. No association between the presence of synovial effusion and popliteal cyst and pain severity was found. In conclusion, plain radiography and ultrasonography reflect different structural changes in osteoarthritis that may play an important role in pain perception. Both imaging modalities can complement each other in order to improve the evaluation of the patient with KOA.

Г7-3. Georgiev T., Angelov A.K. Complexities of diagnosis and management of COVID-19 in autoimmune diseases: Potential benefits and detriments of immunosuppression. *World Journal of Clinical Cases*. 2020 Sep 6;8(17):3669-3678. ISSN: 2307-8960

Recent advances in our understanding of coronavirus disease 2019 (COVID-19) and the associated acute respiratory distress syndrome might approximate the cytokine release syndrome of severe immune-mediated disease. Importantly, this presumption provides the rationale for utilization of therapy, until recently reserved mostly for autoimmune diseases (ADs), in the management of COVID-19 hyperinflammation condition and has led to an extensive discussion for the potential benefits and detriments of immunosuppression. Our paper intends to examine the available recommendations, complexities in diagnosis and management when dealing with patients with ADs amidst the COVID-19 crisis. Mimicking a flare of an underlying AD, overlapping pathological lung patterns, probability of higher rates of false-positive antibody test, and lack of concrete data are only a part of the detrimental and specific characteristics of COVID-19 outbreak among the population with ADs. The administration of pharmaceutical therapy should not undermine the physical and psychological status of the patient with the maximum utilization of telemedicine. Researchers and clinicians should be vigilant for upcoming research for insight and perspective to fine-tune the clinical guidelines and practice and to weigh the potential benefits and detrimental effects of the applied immunomodulating therapy.

Г7-4. Georgiev T. Clinical characteristics and disability in patients with knee osteoarthritis: real world experience from Bulgaria. *Reumatologia*. 2019;57(2):78–84. ISSN: 0034-6233

Objectives: Although knee osteoarthritis (KOA) is a leading cause of impaired functioning among older adults globally, little is still known about the complex mechanisms of disability accumulation in these patients. The aim of the study was to analyze the clinical parameters of patients with KOA in a Bulgarian population and to determine which of these clinical characteristics define disability to the greatest extent. Patients aged 40-80 years with symptomatic KOA were included. The assessment tools for pain, clinical disease severity, and disability were the pain visual analogue scale (VAS) and disease-specific



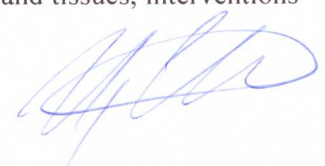
questionnaires: Algofunctional Index of Lequesne, Western Ontario and McMaster Universities OA Index (WOMAC), and the Health Assessment Questionnaire-Disability Index (HAQ-DI), respectively. Radiographs of the knees were obtained and graded according to the Kellgren-Lawrence (KL) system. One hundred and thirty-two patients (81% women) participated in the study. The median values of VAS (mm), WOMAC, Lequesne, and HAQ-DI scores were 52, 37.5, 11, 0.88, respectively. Men had milder disease, resulting in lower VAS, WOMAC, Lequesne, and HAQ-DI scores and less structural damage compared to women ($p < 0.05$). WOMAC index correlated positively with age of the patients but not with duration of the complaints. Patients with severe and very severe pain did not differ in their HAQ-DI, disease severity and KL grading. WOMAC physical function score and Lequesne index were independent predictors for the HAQ-DI in patients with KOA. To sum up, Bulgarian patients with KOA had moderate disability which showed a strong relationship with physical function of WOMAC and disease severity. Multiple layers of causality coexist to determine the knee pain in Bulgarian patients with KOA.

Г7-5. Georgiev T., Ivanova M., Velikova T., Stoilov R. Serum levels of matrix metalloproteinase-3 as a prognostic marker for progression of cartilage injury in patients with knee osteoarthritis. *Acta Reumatol Port.* 2020; 45: 207-213. ISSN 0303-464X

Our objective is to evaluate serum matrix metalloproteinase (MMP)-3 levels as a prognostic marker for the progression of cartilage damage in patients with knee osteoarthritis (KOA). Fifty-six patients, aged 40 to 80 years (62.59 ± 10.11 years) who met the ACR criteria for KOA, were included in a one-year observational prospective clinical study. Complete baseline and follow-up data were collected from 50 out of 56 patients. X-ray and magnetic-resonance images were carried out at baseline and after 12 months. They were evaluated according to the Kellgren-Lawrence and Whole-Organ magnetic Resonance iMaging Score (WORMS) semi-quantitative scales, respectively. Progression of cartilage damage in the medial tibiofemoral compartment was registered at the end of the follow-up using the change in WORMS. Serum levels of MMP-3 were measured during the baseline visit, using enzyme-linked immunosorbent assay. Significantly higher values of baseline MMP-3 levels were observed in patients with a registered progression of cartilage injury in the medial tibiofemoral compartment of the knee compared with patients with no progression ($p = 0.005$). Binary logistic regression analysis showed that levels of serum MMP-3 (ng/ml) were an independent predictor of subsequent progression of cartilage injury in the medial tibiofemoral compartment of the index knee (assessed by MRI) (OR = 1.042, CI 95%: 1.002-1.084). Receiver operating characteristic analysis was performed to delineate progressors from non-progressors. In conclusion, Serum MMP-3 levels may serve as a potential prognostic biomarker for cartilage injury in patients with KOA.

Г7-6. Georgiev T., Angelov A.K. Modifiable risk factors in knee osteoarthritis: treatment implications. *Rheumatology International.* 2019; 39(7): 1145–1157. ISSN 1437-160X

Optimal management of knee osteoarthritis (KOA) should include, where possible, modification of risk factors through targeted interventions. The objectives of the present narrative review were to identify, summarize, and cluster all the potentially modifiable risk factors that influence the course of KOA, and discuss their susceptibility to alteration via personal, clinical, and public strategy. For this purpose, Pubmed and Scopus databases were queried using the terms "knee osteoarthritis", "risk factors" and "improvement". Six main categories of modifiable risk factors were identified: (1) obesity and overweight, (2) comorbidity, (3) occupational factors, (4) physical activity, (5) biomechanical factors, (6) dietary exposures. In the era of age- and obesity-related diseases, the combined effects of local and systemic risk factors should be managed by combined measures. Femoral muscle-strengthening physical activities, complemented with proper diet, weight loss, vocational rehabilitation, management of comorbidities (especially diabetes and depression), and biomechanical support may add up to the holistic therapeutic approach towards the patient with KOA. An individual risk factor modification program should be developed in accordance with patient preferences and habits, workplace, medical history, and overall health condition. Due to its great impact on a wide range of functions and tissues, interventions



on modifiable risk factors improve not only the symptoms of KOA but also affect the osteoarthritic joint as a whole.

Г7-7. Bogdanova-Petrova S., **Georgiev T.**, Gerganov G., Hristova S., Dimitrov S., Shivacheva T. POS1224 RHEUMATIC MANIFESTATIONS IN COVID-19 PATIENTS - SINGLE-CENTER EXPERIENCE AMIDST THE PANDEMIC. *Annals of the Rheumatic Diseases* 2021;80:896. ISSN: 0003-4967

Background: Recently evolved from a monochromic flu-like disease to a polysyndromic “spectrum of disease”, our understanding of coronavirus disease 2019 (COVID-19) is still far from being complete. Hyperinflammation involving not only the lungs but also the musculoskeletal system, skin, cardiovascular, genitourinary systems is immune-mediated resembling the flares of a full-blown rheumatic disease. Objectives: To describe the prevalence and type of rheumatic manifestations in a cohort of COVID-19 patients hospitalized in the COVID-19 rheumatology department in University Hospital St. Marina, Varna, Bulgaria. In the present single-center cohort study, a retrospective database analysis was performed among all COVID-19 patients hospitalized from 1 Dec 2020 to 22 Jan 2021. All 243 patients (age 19 - 93 years) were treated for moderate or severe SARS-CoV-2 infection confirmed by laboratory tests, including positive polymerase chain reaction (PCR) test, and imaging modality. Inpatient treatment included antibiotics, dexamethasone, anticoagulants, and antiviral drug remdesivir (optional). Detailed disease history and clinical examination were carried out by a fully certified rheumatologist and/or specialist in internal medicine. Among all 243 COVID-19 patients, those with prominent self-reported myalgia and arthralgia were 26% (n = 63) and 21.3 (n = 52), respectively. We had 4 (1.6%) cases of newly developed cutaneous vasculitis and 2 (0.8%) cases of severe Raynaud’s phenomenon after SARS-CoV-2 infection onset. Two patients experienced severe muscle weakness, had elevated creatine phosphokinase, and were diagnosed with inflammatory myopathy secondary to COVID-19. Lupus-like syndrome was observed in 2 (0.8%) patients. In conclusion, rheumatic manifestations are part of the heterogeneous spectrum of COVID-19 disease. Amidst the COVID-19 crisis, each newly onset rheumatic manifestation warrants exclusion of SARS-CoV-2 infection. Therefore, a rheumatologist should be a part of a multidisciplinary approach towards the COVID-19 treatment.

Г7-8. Ангелов А., Копчев А., **Георгиев Ц.**, Иванова М. Сърдечно-съдови заболявания при пациенти с псориаичен артрит: корелация или каузалност? *Ревматология*. 2019; 27(1): 30-43. ISSN: 1310-0505

English title: Cardiovascular disease in patients with psoriatic arthritis: correlation or causation?

Psoriatic arthritis (PsA) is a pleiotropic inflammatory disease from the spectrum of spondyloarthritides which can potentially affect many organ systems. The chronic nature of the inflammatory milieu presented in rheumatic diseases, is similar to that of atherosclerosis, suggesting a common pathogenic basis. Effector cells of innate and adaptive immunity along with pro-inflammatory cytokines and other immune mediators may work together to potentiate endothelial damage and accelerate cardiovascular diseases (CVD). Thus, the risk of CVD and associated complications in PsA might be elevated, especially in patients with severe psoriasis, long-standing disease, and multiple comorbidities. This narrative review focuses on the prevalence of CVD in PsA patients, the overlapping molecular features in the pathogenesis of both conditions, and summarizes the benefits of the current treatments on impairments resolution. The ever-growing body of evidence confirms that increased CVD risk in PsA is present, especially in patients with severe psoriasis, longer disease duration, and multiple comorbidities. The prolonged inflammatory burden may be an important cause of early cardiovascular disease. It is difficult to conclude if the risk factors are caused by psoriasis and PsA or share a common pathogenesis, as risk factors are usually present even before diagnosis. Intricate overlapping features and mechanisms may work together to potentiate endothelial damage and progression of atherosclerosis. In all cases, risk factors should be identified and properly treated.



Г7-9. Georgiev T., Stoilov R. AB0791 One versus two injections of intra-articular highly cross-linked hyaluronan yearly in patients with knee osteoarthritis: insights from routine clinical practice. Annals of the Rheumatic Diseases 2019; 78: 1866-1867. ISSN: 0003-4967

Hyaluronic acid (HA) is a natural polysaccharide, which is an important structural component of synovial fluid and cartilage. There are different injectable forms of HA used for clinical application. Highly cross-linked/high-molecular-weight hyaluronans (HMWHA) provide additional stability and improve functionality, resulting in longer bioavailability in the knee joint and promoting viscoinduction. A direct comparison between the two most common injection protocols of HMWHA in our routine practice is of great practical interest, since viscosupplementation is among the most commonly used treatment modalities for patients with knee osteoarthritis (KOA) in Bulgaria. Our aim was to compare the clinical effectiveness of two different regimens for injecting intra-articular HMWHA in KOA patients under 'real-world' conditions in routine clinical practice. This prospective, open-label, observational study included 50 patients with KOA who were followed for a period of 1 year. They were divided into two therapeutic arms according to their preselected treatment regimen: patients injected once with HMWHA (n = 25; group 1) at baseline and patients injected twice 6 months apart with HMWHA (n = 25; group 2). A 100-mm visual analogue scale (VAS) for pain, disease-specific (Western Ontario & McMaster Universities Osteoarthritis index [WOMAC]) and generic (health assessment questionnaire – disability index [HAQ-DI]) questionnaires were used to evaluate patients at baseline, three months, six months, and one year later. Standardized radiographs were obtained at baseline and after one year. The response to the treatment was determined using the OMERACT-OARSI set of responder criteria. A single injection of HMWHA resulted in a statistically significant improvement in pain even at 12 months (Δ VAS = 10.12 \pm 14.5 mm, p < 0.05), although the effect progressively decreased after the third month when Δ VAS was 18 \pm 14.31 mm, p < 0.05 (Figure 1). If the two regimens of HA injections were directly compared, the mean difference of pain improvement for the year of follow-up was about 9 mm in favor of group 2, but this result was not "statistically" significant (10.12 vs 19.16 mm, p > 0.05). Physical function was statistically improved in both groups (p < 0.05) without any statistically significant difference. Responders in the first group in the end of the year were 40% (10/25) and 60% (15/25) in group 1 and group 2, respectively (p > 0.05). In the end of the follow-up period HAQ-DI did only statistically improve among patients in group 2.

Г8. Публикации и доклади, публикувани в нереферирани списания с научно рецензиране или публикувани в редактирани колективни томове

Г8-1. Георгиев Ц., Иванова М., Кабакчиева П., Коларов З., Стоилов Р. Остеоартроза: класификация, патогенеза, етиология, клинична картина и лечение. Tormedica 2016; 7(4): 18-23. ISSN: 1314-0434

English title: Osteoarthritis: classification, pathogenesis, etiology, clinical picture and treatment.

Osteoarthritis (OA) is the most common disease leading to joint pain, accompanied to varying degrees by functional deficits and reduced quality of life. OA is a slow, progressive and disabling process with a high frequency in the human population. According to statistics, it affects 12-15% of the adult population, and over the age of 75, 80% of the human population suffers from OA. OA is a chronic-progressive joint disease characterized by primary degeneration and destruction of articular cartilage with subsequent proliferation of bone tissue and the formation of osteophytes and subchondral bone sclerosis, changes in the synovium and joint capsule. The modern concept of OA presents the disease as a pathological process that affects all structures of the joint apparatus, including hyaline cartilage, synovial membrane, subchondral bone, ligaments and periarticular muscles. OA is a disease that is characterized by slow progression over years or even decades. During this period, the patient usually reduces his physical activity, which makes him more susceptible to diseases associated with a sedentary



lifestyle (including obesity and diabetes). The goals of osteoarthritis treatment include pain relief and improvement in functional deficits. Patients should receive an optimal combination of non-pharmacological and pharmacological treatment. In the present article, the recommendations of the European League Against Rheumatism (EULAR) for the treatment of the most common sites of osteoarthritis are presented.

Г8-2. Георгиев Ц. Съвременни аспекти на фармакологичната терапия при остеоартроза. Medinfo. 2019; 19(5); 64-68. ISSN: 1314-0345

English title: Modern aspects of pharmacological therapy in osteoarthritis.

Demographic trends in the aging population have turned osteoarthritis into a particularly pressing problem for modern society. Despite significant progress in recent years, the treatment of the disease is still a serious challenge for the modern clinician. In recent years, data have been accumulated from studies focused on the long-term effects of the use and safety of a number of oral agents in osteoarthritis. The purpose of this review is to analyze current ideas about the most commonly used in routine practice pharmacological agents for osteoarthritis, based on clinical studies and recommendations of world organizations. The article discusses oral agents often used in routine clinical practice from the group of chondroprotectors, analgesics, nonsteroidal anti-inflammatory drugs and opioids. They are an integral part of modern treatment of osteoarthritis, providing pain relief and improving joint function. Although, to date, there is no effective pharmacological therapy that has been shown to initiate joint regeneration and thus stop the progression of the disease, conservative treatment of osteoarthritis provides in most cases a reduction in pain and improvement in joint function. At present, however, a large proportion of patients with knee or hip osteoarthritis, regardless of pharmacological treatment, eventually end up with knee or hip arthroplasty, respectively. Given the irreversibility of joint arthroplasty, the limited life of prosthesis components, the risk of intra- and postoperative complications and long recovery, arthroplasty should be the last resort to restore mobility to patients with severe osteoarthritis.

Г8-3. Иванова М., Ангелов А.К., Димитров А., Георгиев Ц. Аксиален спондилоартрит. В светлината на съвременните познания. Medinfo 2020; 20(11): 72-75. ISSN: 1314-0345

English title: Axial spondyloarthritis in the light of current knowledge

Ankylosing spondylitis (AS) is the most common inflammatory disease of the spine worldwide, affecting a relatively high percentage of the population. It is a debilitating disease, the severe consequences of which for both patients and society require timely diagnosis in the early stages before the formation of structural changes in the axial skeleton. This is impossible to achieve using the generally accepted modified New York classification criteria for the disease from 1984, because they were created in the era before the introduction of magnetic resonance imaging and require the mandatory presence of sacroiliitis on radiography ≥ 2 nd degree bilaterally or 3-4 degrees unilaterally. The new classification criteria of the Assessment in Spondyloarthritis International Society (ASAS) expert group have broadened the spectrum of spondyloarthritis (SpA) by including early forms of the disease in addition to AS. The term non-radiographic axial spondyloarthritis (nr-axSpA) was introduced for patients with chronic back pain and sacroiliitis on magnetic resonance imaging (MRI) as a pre-phase of AS. In patients with normal sacroiliac joints or with an obscure / doubtful radiographic image but active sacroiliitis (nr-axSpA) on MRI, definitive radiographic sacroiliitis develops in a significant proportion of patients 3-7 years later. The scientific review presents current knowledge about axial SpA since the introduction of the ASAS classification criteria in 2009. There is a long delay of an average of about 8 years or more between the onset of symptoms and the diagnosis. This leads to the omission of early cases, which worsens the clinical results and contributes to the physical and occupational disability of patients. Vigilance is needed in this regard by rheumatologists, general practitioners, orthopedists and neurologists. Magnetic resonance imaging, which allows the objectification of active inflammation, is an important tool for early diagnosis of sacroiliitis, when it is not yet detected on radiography and should

be used in young individuals with long-term inflammatory back pain to diagnose nr-axSpA. This would lead to proper distribution of health care and adequate treatment in the early stages of this debilitating disease.

Г8-4. Kopchev A., Monov S., Kyurkchiev D., Ivanova I., **Georgiev T.** Vascular endothelial growth factor (VEGF), cartilage oligomeric protein (COMP) and matrix metalloproteinase 3 (MMP-3) as serum biomarkers in psoriatic arthritis. *International Journal of Pharmaceutical Science Invention*, 6(7), 08-12. ISSN: 2319-670X

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disorder characterized by axial and peripheral joint involvement as well as extra-articular manifestations such as skin and nail disease, enthesitis, dactylitis, uveitis, etc. Given the broad clinical spectrum, the assessment of the natural course, activity, therapeutic response and prognosis of PsA is difficult. The discovery and implementation of biomarkers would allow personalization of the management of PsA patients. **Materials and methods.** The serum levels of vascular endothelial growth factor (VEGF), cartilage oligomeric matrix protein (COMP) and matrix metalloproteinase 3 (MMP3) and C-reactive protein were measured in 106 patients with psoriatic arthritis – naive and treated with methotrexate and/or biologics (adalimumab, etanercept, infliximab, ustekinumab). Multiple clinical measures, indices and questionnaires used in PsA were also assessed. **Results.** Patients with achieved minimal disease activity, CPDAI and PASDAS remission had significantly lower serum VEGF concentrations (619.55 pg / ml vs 430.50 pg / ml, $p = 0.009$; 489.682 vs. 768.991 pg / ml, $p = 0.005$; and 459, 72 vs 726, 94 pg / ml, $p = 0, 004$ respectively). Serum levels of VEGF ($rs = 0.327$; $p = 0.015$), COMP ($rs = 0.328$; $p = 0.001$) and MMP-3 ($rs = 0,213$; $p = 0,028$) positively correlated with CRP. There was also a positive association of VEGF levels with PASI ($rs = 0.279$; $p = 0.004$), BSA ($rs = 0.225$, $p = 0.02$), PASDAS ($rs = 0.269$; $p = 0.005$), CPDAI ($rs = 0.213$; $p = 0.014$), HAQ-DI ($rs = 0.331$; $p = 0.001$), DLQI ($rs = 0.232$ $p = 0.017$) and PsAQoL ($rs = 0.256$; $p = 0.008$). Serum COMP levels were positively linked with the swollen joints number ($rs = 0.204$; $p = 0.035$), PASI ($rs = 0.205$; $p = 0.034$) and BSA ($rs = 0.247$; $p = 0.010$). MMP-3 correlated with the number of swollen joints ($rs = 0.255$; $p = 0.008$). **Conclusion.** COMP, MMP-3 and especially VEGF could be used as potential biomarkers in psoriatic arthritis.

Пълнотекстови публикации в научни списания и сборници, извън минималните наукометрични изисквания за заемане на АД „доцент“

1. Георгиев Ц., Тенева Цв. Оценка на атрофията и мастната дегенерация на паравертебралната мускулатура при аксиален спондилоартрит; *Ревматология*. 2020;28(3):25-38. ISSN: 1310-0505

English title: Evaluation of paravertebral muscle atrophy and fatty degeneration in patients with axial spondyloarthritis

Sarcopenia or muscle atrophy is a common feature of many chronic diseases of the musculoskeletal system including those accompanied by chronic low back pain (LBP). **Purpose.** The aim of the study was to evaluate the morphological changes of the muscles in the lumbosacral region in patients with axial spondyloarthritis (AxSpA) who underwent magnetic resonance imaging and to compare those changes with a group of patients with chronic low back pain of other etiology. A total of 82 patients with chronic LBP were studied, divided into three groups of interest - first group – controls with low back pain, the second group - patients with ankylosing spondylitis, and the third group - with non-radiographic AxSpA (nr-AxSpA). All patients underwent radiography and magnetic resonance imaging of the sacroiliac joints. The area of the following three paravertebral muscles was measured: lumbar multifidus muscle, erector spinae muscle, and psoas muscle. The available fatty infiltration of those muscles was graded (0-4). The area of the investigated paraspinal muscles did not differ significantly among the three study groups ($p > .05$). Multiple linear regression analysis determined that C-reactive

protein was a predictor of the measured area of multifidus muscle ($p < .001$). The study groups differ significantly in their fatty infiltration of multifidus muscle ($p = .02$), with 15/23 (65%) of patients with ankylosing spondylitis having a high degree of fatty degeneration (score ≥ 3) in comparison with 27.5% and 21% in the control and nr-AxSpA group, respectively. In conclusion, the imaging characteristics of multifidus muscle may be a useful marker for assessing muscle atrophy in patients with axial spondyloarthritis. Inflammation can play a certain role in multifidus sarcopenia in patients with low back pain. Its fatty infiltration is associated with radiographic changes and may distinguish patients with AS from those with nr-AxSpA and lumbosacral pain of another origin. To sum up, the imaging characteristics of multifidus muscle may be a useful marker for assessing muscle atrophy in patients with axial spondyloarthritis. Inflammation can play a certain role in multifidus sarcopenia in patients with low back pain. Its fatty infiltration is associated with radiographic changes and may distinguish patients with AS from those with nr-AxSpA and lumbosacral pain of another origin.

2. **Георгиев Ц.**, Стоилов Р., Бояджиева Вл., Иванова М. Хиалуронова киселина – исторически данни, класификация, механизъм на действие и съвременни препоръки, 2014, Ревматология 22(2):14-23. ISSN: 1310-0505

English title: Hyaluronic acid – historical data, classification, mechanism of action and recommendations

Intraarticular application of hyaluronans improves the biomechanical properties of the osteoarthritis synovial fluid restoring its viscosity and elasticity. Over the past years attention has also been paid to anti-inflammatory and anti-nociceptive properties of the hyaluronic acid which are not quite fully understood yet. The total clinical effect is alleviation of pain, improvement of joint function and eventually disease-modifying effect. Intraarticular application of hyaluronic acid is used for the treatment of symptoms associated with knee osteoarthritis with a good safety profile. Currently there are a large number of commercial products, characterized by different molecular weight, concentration and recommended number of injections per course of treatment. Due to the great heterogeneity of the studies and their results, there is no consensus that one product shows superiority over another. Cross-linked hyaluronates are designed to achieve a product with improved viscoelastic properties and greater resistance to intra-articular hyaluronidases. Studies show that the intra-articular half-life of low molecular weight hyaluronates is only 24 hours, while that of cross-linked molecules can reach several days and even weeks. The unique viscoelastic properties of HA, along with its biocompatibility and non-immunogenicity led to its clinical application in the form of intra-articular injection in rheumatology. Due to the great heterogeneity of the studies and their results, there is no consensus that a specific product shows superiority over another. Therefore, the right choice of hyaluronan depends on the physician's expert opinion and patient's preferences.

3. **Георгиев Г.**, **Георгиев Ц.**, Стоилов Р., Иванова М. Възможности и място на физикалната терапия в комплексното лечение на остеоартрозата. Ревматология. 2019; 27(3) 66-76. ISSN: 1310-0505

English title: Opportunities and place of physical therapy in the complex treatment of osteoarthritis

A significant place in the treatment of osteoarthritis (OA) is taken by physical therapy. Its modalities may be grouped into the following three categories, which could be used alone or in combination: 1) physiotherapeutic (preformed); 2) kinesiotherapeutic; 3) resort-climatic (natural) means. The purpose of this review is to outline the place of physical therapy in the treatment of OA. The choice of one or another preformed physical factor depends on the severity of the disease process, the sensitivity of the patient and the physiotherapist's experience. Among the most commonly used physiotherapeutic agents for pain and stiffness and joint function improvement are ultrasound, laser, magnetic therapy, and transcutaneous electrical nervous stimulation. Kinesiotherapy aims to soothe pain, strengthen, relax and stretch the muscles, increase the volume of movements, improve gait, joints with aids, and more.

Balneotherapy has an important place in the complex therapeutic program for diseases of the musculoskeletal system. Like other nonpharmacological and pharmacological treatments, the various means of physical therapy should be individually refined according to patient's condition and general health, disease stage and concomitant illnesses. This makes the problem interdisciplinary. Therefore, patients should be supervised and treated by a specialized team including: rheumatologist, orthopedic traumatologist, physiatrists, kinesiologist and, if necessary, associate specialists from other specialties.

4. **Georgiev T.** Coronavirus disease 2019 (COVID-19) and anti-rheumatic drugs. *Rheumatology International*. 2020 May; 40(5): 825-826. ISSN 1437-160X

Current pandemic of coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite drastic containment measures, the COVID-19 outbreak has taken lives of more than 12,000 people worldwide, with the number of those contracting the virus surpassing 300,000 (as of March 22, 2020). The seriousness of the situation necessitates urgent multidisciplinary strategy to contain the spread of the disease and prevent its complications. The affection of the lower airways in severe COVID-19 is driven by uncontrolled immune-mediated inflammatory response. T lymphocytes are the main target cells in severe acute respiratory syndrome (SARS) due to COVID-19, triggering cytokine storm with subsequent exhaustion of immune response. Importantly, there is no association between the viral load and severity of the disease. The cascade of the disease pathways is reminiscent of systemic immune disturbances, particularly those in severe rheumatic flare. Based on the current knowledge of COVID-19 pathophysiology and clinical manifestations, the rationale for searching specific antivirals along with immune-modulating drugs is justifiable. A quick search through the US National Library of Medicine Clinical Trials registry and the Chinese Clinical Trial Registry may help retrieve links to studies of anti-rheumatic drugs in COVID-19. Ongoing research brings about hope for developing evidence-based anti-rheumatic therapies for the viral disease. Systemic corticosteroids (CS) are known to potently dampen immune inflammation. Like in inflammatory rheumatic diseases, CS might serve as a "bridge" to specific efficient antiviral therapy for COVID-19. Despite the common fears of the virus replication, provisional recommendations for managing excessive inflammatory response in COVID-19 include intravenous CS. The World Health Organization (WHO), however, recommends to avoid routine administration of systemic CS for the treatment of viral pneumonia outside clinical trials.

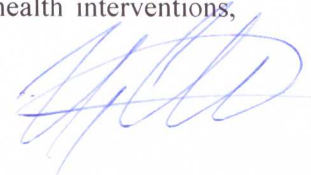
5. **Георгиев Ц., Иванова М., Стоилов Р.** Клинични методи за оценка на пациенти с гонартроза, *Ревматология*. 2018; 26(1): 3-10. ISSN: 1310-0505

English title: Clinical methods to evaluate patients with knee osteoarthritis: a review

There is a wide variety of tools to measure different aspects of health in patients with knee osteoarthritis (KOA). These include the visual analogue scale for determining pain intensity, disease-specific self-reported questionnaires or interviews, and generic questionnaires for overall health assessment, which evaluate quality of life and the degree of disability of patients with KOA. Follow-up of treatment response uses defined criteria that categorize patients as responders or non-responders. They are developed similarly to response criteria commonly used in other rheumatic diseases. Understanding, applying, and documenting these tools for clinical assessment may improve the course of the disease and the therapy. Given the heterogeneous manifestations of osteoarthritis and in particular knee osteoarthritis, a large number of clinometric instruments have been developed to evaluate each aspect of the disease. Their understanding, application, and documentation may be useful in tracking the course of the disease and assessing the response to therapy, both in research and in clinical aspects.

6. Velikova T., **Georgiev T.** SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. *Rheumatology International*. 2021;41:509–518. ISSN 1437-160X

Coronavirus disease 2019 (COVID-19) pandemic has become challenging even for the most durable healthcare systems. It seems that vaccination, one of the most effective public-health interventions,

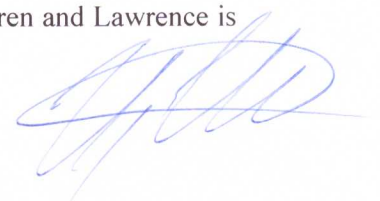


presents a ray of hope to end the pandemic by achieving herd immunity. In this review, we aimed to cover aspects of the current knowledge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines and vaccine candidates in the light of autoimmune inflammatory diseases (AIIDs) and to analyze their potential in terms of safety and effectiveness in patients with AIIDs. Therefore, a focused narrative review was carried out to predict the possible implications of different types of SARS-CoV-2 vaccines which confer distinct immune mechanisms to establish immune response and protection against COVID-19: whole virus (inactivated or weakened), viral vector (replicating and non-replicating), nucleic acid (RNA, DNA), and protein-based (protein subunit, virus-like particle). Still, there is uncertainty among patients with AIIDs and clinicians about the effectiveness and safety of the new vaccines. There are a variety of approaches towards building a protective immunity against SARS-CoV-2. Only high-quality clinical trials would clarify the underlying immunological mechanisms of the newly implemented vaccines/adjuvants in patients living with AIIDs. Establishing proper recommendations for the newly developed vaccines against SARS-CoV-2 would be challenging. Although vaccine administration has been associated with autoimmune manifestations in certain genetically predisposed individuals, it was demonstrated that vaccinations do not pose a more prominent danger than natural infections themselves. Both patients and clinicians are concerned about the potential risk for relapse or worsening of autoimmune diseases mainly because of insufficient data. At this stage of the trials, patients with rheumatic diseases are included only by exception. Clinical data extracted from these single cases cannot be applied to all patients with AIIDs. Experience with well-known vaccines can provide guidance and partial confidence for the use of the “new vaccines”. Still, AIID patients need to be included in the ongoing clinical trials to ensure vaccine safety and efficacy in the context of an autoimmune disease. The associated vaccination risk should not lead to vaccine refusal or major delay in rheumatic patients who will soon have at their disposal different vaccine platforms with variable safety and cost-effectiveness profiles. Furthermore, trials would clarify the underlying immunological mechanisms of the newly implemented vaccines/adjuvants in the AIIDs population.

7. Георгиев Ц., Стоилов Р., Пенков М., Иванова М. и Трифонов Ан. Рентгенографски методи за оценка на гонартроза. Ревматология 2016; 24(2): 48-58. ISSN: 1310-0505

English title: Radiographic methods for assessment of knee osteoarthritis

Plain film radiography still remains the “gold” standard in the assessment of knee osteoarthritis. It is a two-dimensional projection of three-dimensional joint structures. Radiographic changes include joint space narrowing, formation of osteophytes, subchondral osteosclerosis and cysts, deformity of the bone contour to complete ankylosis. These changes occur in various stages of development of osteoarthritis and are reflected in semiquantitative assessment scales. One of the most commonly used scale is the one created by Kellgren and Lawrence back in 1957, underwent many modifications over time. An atlas from the Osteoarthritis Research Society International (OARSI) offers another approach for semiquantitative evaluation. Measuring the distance between the femoral and tibial projected boundaries is the most common quantitative method for assessing knee osteoarthritis. One of the main disadvantages of conventional x-rays are the variations of the image depending on different positioning of the joint space. Radiographs at a fixed flexion provide reliable information about the joint space in patients with moderate knee osteoarthritis. Computerized tomography (CT) is a preferred method for the evaluation of knee osteoarthritis, when the area of interest includes bone changes such as subchondral osteosclerosis and cysts, osteophytes, and quality of the cortical bone. Despite the widespread use of joint ultrasonography and magnetic resonance tomography in clinical practice, conventional radiography of the knee remains the benchmark in the contemporary assessment of osteoarthritic knee. It is a two-dimensional projection of three-dimensional joint structures. This creates a prerequisite for variations of the image at different positioning of the joint space. X-ray at a fixed flexion provides reliable information about the joint space in patients with moderate knee osteoarthritis. In order to objectify the results of conventional radiography in clinical practice and studies, quantitative and semi-quantitative methods are used for assessing knee osteoarthritis. The scale of Kellgren and Lawrence is



widely used 5-point system for evaluating knee. It should be noted, however, that the patient complaints do not always correspond with the structural changes assessed by imaging studies. Therefore, in the diagnostic and treatment process complex approach is required to assess the severity of the disease.

8. **Георгиев Ц.**, Иванова М., Великова Ц., Куртева Е., Пенков М., Милошов А., Стоилов Р. Корелации между магнитнорезонансната находка и серумните нива на хрущялен олигомерен матриксен протеин при пациенти с гонартроза: крос-секционно проучване. Ревматология. 2018; 26(1): 22-32. ISSN: 1310-0505

English title: The relation of MRI-detected structural damage and serum levels of cartilage oligomeric matrix protein (COMP) in patients with knee osteoarthritis: a cross sectional study

Cartilage oligomeric matrix protein (COMP) is an oligomeric tissue-specific glycoprotein synthesized by chondrocytes. It represents structural damage in knee OA observed by imaging modalities such as radiography and MRI. Aim: The purpose of this study was to correlate serum COMP levels with MRI-detected structural damage of different joint elements in patients with knee osteoarthritis (KOA). Fifty-six patients with symptomatic KOA, meeting the ACR criteria, were included in the study. All of them filled in validated self-reported questionnaires. Their serum COMP levels were quantified using an enzyme-linked immunosorbent assay. Magnetic resonance tomography was evaluated using the Whole-Organ Magnetic Resonance Imaging Score. Serum levels of COMP correlated with bone marrow edema ($p < 0.001$, $r_s = 0.479$), changes in hyaline cartilage ($p < 0.001$, $r_s = 0.464$), osteophytosis ($p = 0.019$, $r_s = 0.312$) and synovitis ($p = 0,004$, $r_s = 0,383$) in patients with KOA. Stepwise multiple linear regression analysis was carried out to determine independent predictors of serum COMP levels. Conclusion: MRI-detected structural damage of the hyaline cartilage and bone marrow edema showed a positive correlation with the levels of COMP in the serum.

9. Бояджиева В., Стоилов Н., **Георгиев Ц.**, Стоилов Р., Петрова Г. Лечение на пациентите с ревматоиден артрит. Възможности и ползи от прилагане на фармакоикономическия анализ разход-ефективност. Ревматология. 2015; 23(3): 16-24. ISSN: 1310-0505

English title: How to treat patients with rheumatoid arthritis? Opportunities and benefits of the implementation of a pharmacoeconomic cost-effectiveness analysis.

During the last few years, the expenses for therapy with biological agents of patients with RA are progressively increasing due to the increased number of cases undergoing biological treatment. This pattern is one of the main causes for increased expenditure on the part of the National Health Insurance Fund. There are several problems that make the therapy process difficult. The insufficiency of funds in the health systems and in patients alike comes in first place. Secondly, there are a limited number of specialists in the field of rheumatology, the lack of patient education and general practicing physicians regarding RA, the lacking communication physician – patient and the insecurity in determining the proper treatment. Last but not least, the different government policies regulating the reimbursement of the expensive biological agents are present. This process can take up to several months slowing down the therapy thus causing increased direct and indirect expenses due to worsened patient conditions. By conducting randomized clinical trials and follow-up analysis of the type cost-effectiveness, pharmacoeconomics assists the evaluation of different types of therapies and their cost efficiency. In this way an optimal approach in treatment practices can be achieved also allowing for better access to biological treatment.

10. Kabakchieva P., **Georgiev T.**, Gateva A., Hristova J., Kamenov Z. Polycystic ovary syndrome and (pre)osteoarthritis: assessing the link between hyperandrogenism in young women and cartilage oligomeric matrix protein as a marker of cartilage breakdown. Clinical Rheumatology. 2021; 10.1007/s10067-021-05753-0. ISSN: 0770-3198



Our aim was to analyze the link between hyperandrogenism and early clinical manifestations of osteoarthritis (OA), knee cartilage thickness, and serum cartilage oligomeric matrix protein (sCOMP) levels in patients with polycystic ovary syndrome (PCOS) and to compare them with healthy volunteers. Methods: Fifty-four PCOS patients who met the Rotterdam criteria with phenotypes A, B, and C were included. They were compared with 26 age- and body mass index (BMI)-matched controls. Detailed anthropometric measurements and clinical evaluation for hyperandrogenism were performed for all participants who also filled in the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire. Furthermore, laboratory tests including sCOMP and hormone quantification were performed in a fasting stage. Finally, an ultrasound assessment was carried out in randomly selected 56 study participants. Results: PCOS women reported more prominent knee-related symptoms ($p = 0.035$) and more impaired activities of daily living (ADL) ($p = 0.001$) than controls. Cartilage thickness of the left and right medial condyle and left lateral condyle was significantly greater in PCOS group ($n = 41$) than in control group ($n = 15$) ($p = 0.05$, $p = 0.006$, and $p = 0.036$, respectively). COMP correlated significantly and negatively with testosterone levels ($p = 0.029$, $r = - 0.297$) in women with PCOS and the correlation remained significant after controlling for BMI. Conclusions: Women with PCOS may experience knee-related symptoms and impaired ADL. They had greater knee femoral cartilage thickness. Although sCOMP levels did not significantly differ between the groups, lower levels of sCOMP may be inherent to PCOS patients with higher testosterone levels. Lower sCOMP levels were related to higher testosterone levels.

