

***Lenac T, Budt M, Arapović J, Hasan M, Zimmermann A, Šimić H, et al. The herpesviral Fc receptor fcr-1 down-regulates the NKG2D ligands MULT-1 and H60. J Exp Med. 2006;203:1843-50.**

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Members of the alpha- and beta-subfamily of herpesviridae encode glycoproteins that specifically bind to the Fc part of immunoglobulin (Ig) G. Plasma membrane resident herpesviral Fc receptors seem to prevent virus-specific IgG from activating antibody-dependent effector functions. The authors show that the mouse cytomegalovirus (MCMV) molecule fcr-1 promotes a rapid down-regulation of NKG2D ligands murine UL16-binding protein like transcript (MULT)-1 and H60 from the cell surface. Deletion of the m138/fcr-1 gene from the MCMV genome attenuates viral replication to natural killer (NK) cell response in an NKG2D-dependent manner in vivo. A distinct N-terminal module within the fcr-1 ectodomain in conjunction with the fcr-1 transmembrane domain was required to dispose MULT-1 to degradation in lysosomes. In contrast, down-modulation of H60 required the complete fcr-1 ectodomain, implying independent modes of fcr-1 interaction with the NKG2D ligands. The results establish a novel viral strategy for down-modulating NK cell responses and highlight the impressive diversity of Fc receptor functions.

Baković D, Eterović D, Valić Z, Saratlija-Novaković Z, Palada I, Obad A, et al. Increased pulmonary vascular resistance and reduced stroke volume in association with CO₂ retention and inferior vena cava dilatation. J Appl Physiol. 2006;101:866-72.

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Changes in cardiovascular parameters elicited during a maximal breath hold are well described. However, the impact of consecutive maximal breath holds on central hemodynamics in the postapneic period is unknown. Eight trained apnea divers and eight control subjects performed five successive maximal apneas, separated by a 2-min resting interval, with face immersion in cold water. Ultrasound examinations of inferior vena cava (IVC) and the heart were carried out at times 0, 10, 20, 40, and 60 min after the last apnea. The arterial oxygen saturation level and blood pressure, heart rate, and transcutaneous partial pressures of CO₂ and O₂ were monitored continuously. At 20 min after breath holds, IVC diameter increased (27.6 and 16.8% for apnea divers and controls, respectively). Subsequently, pulmonary vascular resistance increased and cardiac output decreased both in apnea divers (62.8 and 21.4%, respectively) and the control group (74.6 and 17.8%, respectively). Cardiac output decrements were due to reductions in stroke volumes in the presence of reduced end-diastolic ventricular

volumes. Transcutaneous partial pressure of CO₂ increased in all participants during breath holding, returned to baseline between apneas, but remained slightly elevated during the postdiving observation period (approximately 4.5%). Thus increased right ventricular afterload and decreased cardiac output were associated with CO₂ retention and signs of peripheralization of blood volume. These results indicate that repeated apneas may cause prolonged hemodynamic changes after resumption of normal breathing, which may suggest what happens in sleep apnea syndrome.

***Letilović T, Vrhovac R, Verstovšek S, Jakšić B, Ferrajoli A. Role of angiogenesis in chronic lymphocytic leukemia. *Cancer*. 2006;107:925-34.**

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Angiogenesis is a physiologic process of new blood vessels formation mediated by various cytokines called angiogenic and angiostatic factors. Although its potential pathophysiologic role in solid tumors has been extensively studied for more than 3 decades, enhancement of angiogenesis in chronic lymphocytic leukemia (CLL) and other malignant hematological disorders has been recognized more recently. An increased level of angiogenesis has been documented by various experimental methods both in bone marrow and lymph nodes of patients with CLL. Although the role of angiogenesis in the pathophysiology of this disease remains to be fully elucidated, experimental data suggest that several angiogenic factors play a role in the disease progression. Biologic markers of angiogenesis were also shown to be of prognostic relevance in CLL. The current findings provide the rationale for investigating antiangiogenic agents in CLL. In the current review angiogenesis in CLL is discussed and its potential diagnostic and therapeutic applications.

***Barbalić M, Škarić-Jurić T, Cambien F, Barbaux S, Poirier O, Turek S, et al. Gene polymorphisms of the renin-angiotensin system and early development of hypertension. *Am J Hypertens*. 2006;19:837-42.**

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A case-control association study was conducted to investigate a possible involvement of polymorphisms of three renin-angiotensin system genes: ACE (I/D and T-3892C), AGT (M235T and T174M), and AT1R (A1166C) in the

early development of hypertension. One hundred nineteen hypertensive and 125 normotensive participants aged 18 to 40 years were selected from a broader sample representative of the general population of Croatia. The selection criteria for hypertensive cases were systolic blood pressure (BP) higher than 140 mm Hg or diastolic BP higher than 90 mm Hg and a history of hypertension according to patient interview. Among the polymorphisms investigated, only those located on the ACE gene were associated with hypertension. For ACE I/D, the odds ratio for hypertension of DD versus II homozygote individuals was 2.50 (95% confidence interval [CI] 1.19-5.25) and for ACE T-3892C, the odds ratio of CC versus TT individuals was 2.32 (95% CI 1.05-5.10). Both polymorphisms of the ACE gene were in tight linkage disequilibrium. Of the investigated risk factors for hypertension, only body mass index (BMI) showed an influence on the early development of hypertension, acting independently of the ACE polymorphism. Their additive effect gives rise to 86% of hypertensives in subjects having both the DD genotype and BMI ≥ 30 kg/m². The present study provides evidence of the association of the ACE gene polymorphisms and premature hypertension. In addition, BMI proved to be another important predictor of the disorder acting independently of the ACE gene.

Boraska Jelavić T, Barišić M, Drmić Hofman I, Boraska V, Vrdoljak E, Peruzović M, et al. Microsatellite GT polymorphism in the toll-like receptor 2 is associated with colorectal cancer. *Clin Genet*. 2006;70:156-60.

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Factors underlying genetic predisposition for development of sporadic colorectal cancer are largely unknown. The fact that this cancer is more common in patients suffering from inflammatory bowel disease raises the question of the relationship between chronic inflammation and cancer. Toll-like receptors 2 (TLR2) and 4 (TLR4) are critical in initiating innate immune response and inflammation toward various bacteria commonly found in the intestine. Recent evidence about the association of polymorphisms in these genes with ulcerative colitis and Crohn's disease, as well as other inflammatory conditions, was the basis for our investigation of their role in sporadic colorectal cancer. We assessed genotype and allele frequencies of TLR2 GT microsatellite polymorphism, TLR2 Arg753Gln, TLR4

Asp299Gly and TLR4 Thr399Ile polymorphisms in 89 colorectal cancer patients and 88 age- and sex-matched controls. The frequency of TLR2 GT microsatellite alleles with 20 and 21 GT repeats was decreased ($p = 0.0044$ and $p = 0.001$, respectively), while the frequency of the allele with 31 GT repeats was increased ($p = 0.0147$) in patients. The mutant allele Asp299Gly of TLR4 gene was slightly more frequent in colorectal cancer patients ($p = 0.0269$). In conclusion, we report an association of microsatellite GT polymorphisms of TLR2 gene and Asp299Gly polymorphism of the TLR4 gene with sporadic colorectal cancer among Croatians.

Filipović V, Viskić-Štalec N. The mobility capabilities of persons with adolescent idiopathic scoliosis. *Spine*. 2006;31:2237-42.

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The aim of this study was to analyze differences in dynamic balance among adolescents with a variety of postural statuses and verify the sensitivity value of the Cobb angle. The participants' balance (left and right step test) was estimated using electromyography and the reaction of base power on the platform. Discriminant analysis confirmed a significant difference between the participants with AIS and healthy persons on the left step test. The values of the lumbar erector muscles, right gluteus, and side-to-side reaction of the force platform are more pronounced than the other variables. There is no significant difference among the participants with various Cobb angles. The dynamic balance tests contribute to the AIS screening process. The pathologic form of AIS and lateralization highly affect dynamic balance. The study confirmed the neurophysicians' claims of the neuroplasticity of the central nervous system. In addition, the research illustrated the compensational functioning of mobility, especially when there is a lack of normal mobility forms, and there are weak postural control mechanisms and proprioception. There was no proof of the value of the Cobb angle as a clinical method and a measurement of the functional capabilities of the participants in the screening process.

Reiner Ž, Mihatov S, Miličić D, Bergovec M, Planinc D; on behalf of the TASPIC-CRO Study Group Investigators. Treatment and secondary prevention of

ischemic coronary events in Croatia (TASPIC-CRO study). *Eur J Cardiovasc Prev Rehabil*. 2006;13:646-54.

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The objective of this study is to determine the status of major risk factors for coronary heart disease in patients with established coronary heart disease in Croatia and whether the Joint European Societies' recommendations on coronary heart disease prevention are being followed in Croatia and whether secondary prevention practices have improved between 1998 and 2003. Five surveys were undertaken in 35 centers covering the geographical area of the whole of Croatia between 1 June, 1998 and 31 March, 2003. Consecutive patients of both sexes were identified after coronary-bypass grafting or a percutaneous transluminal coronary angioplasty or a hospital admission with acute myocardial infarction or ischaemia. Data collection was based on a review of medical records and the methodology used was similar to the one used in the EUROASPIRE study. Fifteen thousand, five hundred and twenty patients were enrolled (64.6% men); 35% of patients smoked cigarettes, 66% had raised blood pressure, 69% elevated serum total cholesterol, 69% elevated serum low-density lipoprotein (LDL) cholesterol, 42% low high-density lipoprotein (HDL) cholesterol, 37% elevated triglycerides, 30% diabetes and 34% family history of coronary heart disease. More men were smokers and had low HDL cholesterol, but more women had elevated total and LDL cholesterol, hypertension and diabetes. More men had Q wave acute myocardial infarction, but more women had angina. Over 5 years, the prevalence of hypercholesterolemia decreased substantially from 82.7% to 65%. Eighty-three percent of patients received aspirin and this percentage did not change during the study. The use of diuretics, calcium antagonists and nitrates did not change either. The reported use of statins, angiotensin-converting enzyme inhibitors and beta-blockers increased significantly. This survey shows a high prevalence of modifiable risk factors in Croatian patients with coronary heart disease. Although the higher use of statins, angiotensin-converting enzyme inhibitors and beta-blockers is encouraging, the fact that most coronary heart disease patients are still not achieving the recommended goals remains a concern. There is real potential to reduce the very high coronary heart disease morbidity and mortality in Croatia.

Šagud M, Mihaljević-Peješ A, Mück-Šeler D, Jakovljević M, Pivac N. Quetiapine augmentation in treatment-resistant depression: a naturalistic study. *Psychopharmacology (Berl)*. 2006;187:511-4.

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Treatment-resistant depression (TRD) is a common clinical problem, often complicated with suicidal ideations and greater lifetime functional impairment, and represents a considerable challenge to management and treatment. The aim of a prospective, open-label, noncomparative, flexible-dosed 20-week study was to evaluate the effects of quetiapine, as an add-on therapy, in patients with TRD who were refractory to previous treatments. Eighteen patients with major depressive disorder (DSM-IV criteria) were treated for 20 weeks with quetiapine (mean dose 315 ± 109 mg/day). Patients were evaluated at baseline, weekly from 1 to 9 weeks, and then after 12, 16, and 20 weeks of treatment, using Hamilton rating scale for depression-17 items (HAMD) scale. Fourteen patients with TRD completed the 20-week open trial with quetiapine. The augmentation with quetiapine significantly reduced total scores and scores listed in the anxiety subscale on the HAMD, and these effects were observed after the fourth week of treatment, while the depressed mood scores were significantly reduced after the fifth week of treatment. Quetiapine add-on treatment significantly decreased the scores listed in the insomnia subscale on the HAMD subscale after the second week of treatment. These preliminary data indicate that quetiapine add-on therapy appears to have beneficial effects in the treatment of patients with TRD.

Ivković A, Bojanić I, Pećina M. Stress fractures of the femoral shaft in athletes: a new treatment algorithm. *Br J Sports Med*. 2006;40:518-20.

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Femoral shaft stress fractures in athletes are not common but pose a great diagnostic challenge to clinicians. Because of few clinical signs, diagnosis and treatment are often delayed. Furthermore, if not treated correctly, these fractures are well known for complications and difficulties. The aim of this study was to develop a well structured and reproducible treatment algorithm for athletes with femoral shaft

stress fractures. The proposed algorithm is carried out in four phases, each lasting three weeks, and the move to the next phase is based on the result of the tests carried out at the end of the previous phase. Over nine years, the authors treated seven top level athletes, aged 17-21. In all athletes, diagnosis was based on physical examination, plain radiographs, and bone scan. As a result of the treatment method, all the athletes were fully engaged in athletic activity 12-18 weeks after the beginning of treatment. After completion of the treatment, the athletes were followed up for 48-96 months. During the follow up, there was no recurrence of discomfort or pain, and all the athletes eventually returned to competition level. These results and data available from the literature suggest that the algorithm is the optimal treatment protocol for femoral shaft stress fractures in athletes, avoiding the common complications and difficulties.

Miškulin M, Maldini B. Outpatient arthroscopic knee surgery under multimodal analgesic regimens. *Arthroscopy*. 2006;22:978-83.

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The aim of this study was to investigate whether diclofenac could be used in preemptive and multimodal fashion with local anesthesia (LA) during arthroscopic knee surgery. A cohort of 628 patients (age range, 14 to 60 years) underwent outpatient arthroscopic knee surgery under LA with 15 mL of 2% lidocaine with epinephrine. Diclofenac 1 mg/kg was administered immediately before the procedure was performed. Pain was intraoperatively assessed with a 10-cm visual analogue scale (VAS). Patients' and surgeons' satisfaction with the quality of anesthesia was estimated by a special questionnaire and VAS score. From the technical point of view, arthroscopic procedures were successfully completed in 98.2% of patients. Pain experienced during injection of lidocaine (VAS score: median, 2.9; mean, 3.4; standard deviation [SD], 3.2; range, 0 to 10) was more severe ($p=0.0001$) than pain experienced during the surgical procedure itself (VAS score: median, 1.8; mean, 2.4; SD, 2.2; range, 0 to 5.2). Arthroscopy was well tolerated by most patients (98.5%), and only 1.4% of procedures had to be terminated prematurely because of patient discomfort. Almost 95.7% of patients reported that they would undergo the same procedure again under the same type of anesthesia. In 4.7% of

patients, LA was not considered optimal by the performing surgeon. In conclusion, arthroscopic knee surgery with diclofenac and LA with no premedication is an efficient and well-tolerated method used in outpatient practice with no major adverse effects.

Tamarut T, Kovačević M, Glavičić S. Influence of the length of instrumentation and canal obturation on the success of endodontic therapy. A 10-year clinical follow-up. *Am J Dent.* 2006;19:211-6.

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The aim of this study was to clinically test the periapical healing of the method of recurrent electronic root canal measurement and the method of root canal obturation by the guttapercha-eucapercha method. During 10 years of endodontic practice of the first author, endodontic interventions were performed on approximately 4500 patients, aged 12-75 years. The success of therapy was followed-up in 257 teeth with diagnosis K04.0 to K04.5 (according to the X international classification of diseases) for whom a preoperative and control radiograph during the investigation period existed. Root canal preparation started with the "crown-down pressureless technique" and proceeded with the method of recurrent electronic root canal measurement. Obturation was done by the guttapercha-eucapercha method up to the apical constriction. The result of therapy success was approximately 95% overall (t-test, ANOVA); for the diagnosis: necrosis and pulp gangrene (K04.1): 64%; for the acute apical periodontitis (K04.4): 88%; for the inflamed pulp (K04.0) and pulp degeneration (K04.2) 95%; chronic apical periodontitis (K04.5): 98%, and abnormally formed hard tissue in the pulp (K04.3):100%.

Grčević D, Lukić IK, Kovačić N, Ivčević S, Katavić V, Marušić A. Activated T lymphocytes suppress osteoclastogenesis by diverting early monocyte/macrophage progenitor lineage commitment towards dendritic cell differentiation through down-regulation of receptor activator of nuclear factor-kappaB and c-Fos. *Clin Exp Immunol.* 2006;146:146-58.

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Activated T lymphocytes either stimulate or inhibit osteoclastogenesis from haematopoietic progenitors in different experimental models. To address this controversy, we used several modes of T lymphocyte activation in osteoclast differentiation--mitogen-pulse, anti-CD3/CD28 stimulation and in vivo and in vitro alloactivation. Osteoclast-like cells were generated from non-adherent immature haematopoietic monocyte/macrophage progenitors in murine bone marrow in the presence of receptor activator of nuclear factor (NF)-kappaB ligand (RANKL) and monocyte-macrophage colony-stimulating factor (M-CSF). All modes of in vivo and in vitro T lymphocyte activation and both CD4(+) and CD8(+) subpopulations produced similar inhibitory effects on osteoclastogenesis paralleled by enhanced dendritic cell (DC) differentiation. Osteoclast-inhibitory effect was associated with T lymphocyte activation and not proliferation, and could be replaced by their culture supernatants. The stage of osteoclast differentiation was crucial for the inhibitory action of activated T lymphocytes on osteoclastogenesis, because the suppressive effect was visible only on early osteoclast progenitors but not on committed osteoclasts. Inhibition was associated specifically with increased granulocyte-macrophage colony-stimulating factor (GM-CSF) expression by the mechanism of progenitor commitment toward lineages other than osteoclast because activated T lymphocytes down-regulated RANK, CD115, c-Fos and calcitonin receptor expression, and increased differentiation towards CD11c-positive DC. An activated T lymphocyte inhibitory role in osteoclastogenesis, confirmed in vitro and in vivo, mediated through GM-CSF release, may be used to counteract activated bone resorption mediated by T lymphocyte-derived cytokines in inflammatory and immune disorders. We also demonstrated the importance of alloactivation in osteoclast differentiation and the ability of cyclosporin A to abrogate T lymphocyte inhibition of osteoclastogenesis, thereby confirming the functional link between alloreaction and bone metabolism.