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MEĐUSOBNA POVEZANOST EPIDEMIOLOŠKE SITUACIJE I LABORATORIJSKE DIJAGNOSTIKE

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SAŽETAK

Globalna epidemiološka situacija, naročito u oblasti zaraznih oboljenja se danas, u odnosu na periode u prošlosti, mijenja znatno brže. Pojava novih infekcija povezana je sa nizom faktora kao što su: gustina naseljenosti, putovanja i trgovina, klimatske promjene te promjene u pripremi i konzumiranju hrane. Evidentan je povećan rizik izloženosti uzročnicima zoonoza, ali i sve veći broj imunkompromitovanih osoba te pojava mikroorganizama otpornih na postojeće antimikrobna sredstva što rezultira pojavom emergentnih i reemergentnih oboljenja.

Nadzor nad zaraznim bolestima je od vitalnog značaja za ranu identifikaciju prijetnji javnom zdravlju i u najvećoj mjeri je zavisan od dijagnostike. Osnovni preduslov za pravilnu ocjenu epidemiološke situacije je postavljanje etiološke dijagnoze, odnosno dokazivanje uzročnika oboljenja, a to zahtijeva postojanje i funkcionalnost laboratorijsko dijagnostičkih kapaciteta. Osposobljenost laboratorijsko-dijagnostičkih kapaciteta je ključna u procjeni sposobnosti i brzog odgovora na pojavu oboljenja kao i daljem nadzoru i kontroli oboljenja.

Značajan problem kod pojave novih oboljenja je nepostojanje jasno definisanih dijagnostičkih metoda i pouzdanih dijagnostičkih testova. Evidentne su razlike u osposobljenosti dijagnostičkih kapaciteta u različitim sredinama (veliki centri i mala mjesta) što za posljedicu ima iskrivljenu epidemiološku sliku prema kojoj se oboljenja javljaju znatno češće u većim centrima (gdje postoji mogućnost dijagnostike) u odnosu na male sredine

Nove dijagnostičke tehnologije omogućavaju brzu molekularnu identifikaciju patogena,te su pogodne za preciznije praćenje aktivnosti zaraznih bolesti kako na regionalnom tako i na globalnom nivou. Zahvaljujući vještačkoj inteligenciji i razvijanju epidemioloških modela moguće je predviđanje, a i preveniranje budućih prijetnji izazvanih zaraznim bolestima kao i modeliranje epidemija te shodno tome i planiranje potreba za dijagnostičkim kapacitetima.

Dobra uvezanost epidemioloških i laboratorijskih službi je preduslov tačne procjene epidemiološke situacije i adekvatnog planiranja razvoja laboratorijsko-dijagnostičkih kapaciteta na nekom području.

Ključne riječi: epidemiologija, laboratorijska dijagnostika, saradnja

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INTERRELATION BETWEEN THE EPIDEMIOLOGICAL SITUATION AND LABORATORY DIAGNOSTICS

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ABSTRACT

The global epidemiological situation, especially in the field of infectious diseases, is changing much faster today, compared to periods in the past. The emergence of new infections is associated with a number of factors such as: population density, travel and trade, climate change and changes in food preparation and consumption. There is an evident increased risk of exposure to zoonotic agents, but also an increasing number of immunocompromised persons and the appearance of microorganisms resistant to existing antimicrobial agents, which results in the appearance of emergent and re-emergent diseases.

Surveillance of infectious diseases is vital for the early identification of threats to public health and is largely dependent on diagnostics. The basic prerequisite for a proper assessment of the epidemiological situation is establishing an etiological diagnosis, that is, proving the cause of the disease, and this requires the existence and functionality of laboratory diagnostic capacities. The qualification of laboratory-diagnostic capacities is crucial in assessing the ability and rapid response to the occurrence of diseases, as well as further monitoring and control of diseases.

A significant problem with the emergence of new diseases is the lack of clearly defined diagnostic methods and reliable diagnostic tests. There are evident differences in the competence of diagnostic capacities in different environments (large centers and small places), which results in a distorted epidemiological picture, according to which diseases occur significantly more often in larger centers (where there is a possibility of diagnosis) compared to small environments

New diagnostic technologies enable rapid molecular identification of pathogens, and are suitable for more precise monitoring of the activity of infectious diseases both on a regional and global level. Thanks to artificial intelligence and the development of epidemiological models, it is possible to predict and prevent future threats caused by infectious diseases, as well as modeling epidemics and, accordingly, planning the need for diagnostic capacities.

A good connection between epidemiological and laboratory services is a prerequisite for an accurate assessment of the epidemiological situation and adequate planning of the development of laboratory-diagnostic capacities in an area.

Key words: epidemiology, laboratory diagnostics, colaboration

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PREDNOSTI I NEDOSTACI KONVENCIONALNOG TESTIRANJA ANTIMIKROBNE OSJETLJIVOSTI I NOVE METODE ODABIRA ANTIBIOTIKA

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SAŽETAK

Usprkos velikom broju antibiotika i testova za ispitivanje osjetljivosti u svijetu umire 5 milijuna ljudi godišnje od bakterijskih infekcija. Antimikrobna rezistencija (AMR) će u slijedećim decenijama postati vodeći uzrok smrti u svijetu. Problem je nedostatak potpuno pouzdane metode testiranja osjetljivosti bakterija na antibiotike. Neka istraživanja su pokazala nedostatak povezanosti između rezultata *in vitro* testiranja i kliničkog odgovora. Kliničke opservacije su utvrdile pravilo 90-60.To znači da 90% "osjetljivih" infekcija reagira na antibiotik i 60% "rezistentnih". Iz toga proizlazi da rezistencija nije jedini uzrok lošeg terapijskog ishoda kod teških infekcija. Nameće se pitanje: Zašto konvencionalno testiranje osjetljivosti često ne izabere pravi antibiotik kod uzoraka koji nisu primarno sterilni? To se odnosi na infekcije mokraćnog sustava, dišnog sustava, kože i mekih tkiva. Konvencionalno testiranje se bazira na testiranju osjetljivosti dominantnog patogena u uzorku i koristi se čista kultura dominantnog patogena umjesto da se analizira čitava mikrobna zajednica. Uzorci kao što je sputum, BAL, obrisak rane ili urin se procesuiraju tako da se dobije čista kultura uzročnog agensa kultiviranjem na neselektivnim i selektivnim podlogama a taj proces traje 24 do 48 h. Danas postoje automatizirane metode koje daju rezultat brže od konvencionalnih tehnika ali isto zahtjevaju čistu kulturu izoliranog soja. Te metode uključuju i identifikaciju i testiranje osjetljivosti (VITEK 2, PHOENIX, MALDI-TOF). Nove tehnike koje ispituju odgovor bakterija na antibiotik uključuju morfološke promjene, metaboličke promjene, inhibiciju ranog bakterijskog rasta i detekciju razgradnih produkata antibiotika. Molekularnim metodama možemo dokazati gene rezistencije direktno u bolesničkom uzorku bez prethodne kultivacije. Nedostaci molekularne dijagnostike su što dokaz gena ne znači rezistenciju jer ne moraju biti ekspremirani. PCR ne dokazuje funkcionalnost gena. Nije moguće dokazati da su geni rezistencije od uzročnika (mogu biti od popratne mikrobiote). Terapija bazirana na dokazu gena je često preširoka što propagira razvoj rezistencije. Konvencionalno testiranje svrstava izolate u osjetljive (S), intermedijarne ili osjetljivi uz povećanu izloženost (I), ili rezistentne bazirano na veličine inhibicijske zone ili vrijednosti MIK-a. Prijelomne točke se baziraju na koncentracijama antibiotika u krvi a ne uzimaju obzir sposobnost penetracije antibiotika u tkiva i organe i ulazak u stanice. Koncen-

tracija slobodnog antibiotika u krvi se bitno razlikuje od koncentracije u plućima, urinu ili mekim tkivima. Greške nastaju zbog toga što se prijelomne točke baziraju na farmakodinamskih i farmakokinetskim parametrima antibiotika u krvi.Drugi problem je to što je izolat tijekom testiranja izložen konstantnoj koncentraciji antibiotika što nije slučaj tijekom terapije.Antibiotici se dijele u tri skupine: ovisni o koncentraciji (cmax>MIC), ovisni o vremenu iznad MIK-a (t>MIC) i ovisni o totalnom izlaganju antibiotiku (AUC/MIC). Ti parametri se ne uzimaju u obzir kod konvencionalnog *in vitro* testiranja što dovodi do precijenjivanja ili podcijenjivanja učinkovitosti antibiotika. Osjetljivost bakterija na antibiotike u biofilmu je tisuću puta manje u odnosu na planktonske bakterije. Bakterije se unutar biofilma sporije umnožavaju, usporava se metabolizam nastaju perzisteri koji nisu osjetljivi na antibiotike. Kada koncentracija antibiotika padne perzisteri ponovno stvaraju biofilm i to dovodi do kroničnih i rekurentnih infekcija. Jedna od novih metoda je ATB finder. Ne zahtjeva čistu kulturu nego analizira odgovor čitave polimikrobne populacije.Baziran je na uzgoju bakterija na TGV agaru koji omogućuje rast različitih vrsta bakterija u obliku miješanog biofilma s formiranjem ekstracelularnog matriksa i površinskog filma.To oponaša polimikrobnu zajednicu i modulaciju QS i tezR moduliranu antibiotsku rezistenciju.Ta podloga omogućuje rast teško-uzgojivih bakterija znatno bolje od uobičajenih bogatih podloga kao što je BHI bujon ili LB bujon to omogućuje analizu bakterijske raznolikosti. ATB finder je pločica s 48 jažica ispunjena TGV agarom.Za razliku od konvencionalnog testiranja ne bazira se na MIK-u i prijelomnim točkama za evaluaciju učinkovitosti antibiotika nego određuje učinkovitost bazirano na kvantificiranju penetracije antibiotika u različita tkiva koja su mjesto infekcije. Dodaje se koncentracija antibiotika ovisna o mjestu infekcije. Budućnost razvoja metoda testiranja antimikrobne osjetljivosti se bazira na tehnikama koje uzimaju u obzir cijelu antimikrobnu zajednicu i uzimaju u obzir i osjetljivost bakterija u biofilmu.

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ADVANTAGES AND DISADVANTAGES OF CONVENTIONAL ANTIMICROBIAL SUSCEPTIBILITY TESTING AND NOVEL METHODS FOR ANTIBIOTIC SELECTION

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ABSTRACT

Despite of the high number of antibiotics and antimicrobial susceptibility tests there are five millions of people dying from bacterial infections. Antimicrobial resistance (AMR) will become a leading cause of death in the following decades. The main issue is the lack of reliable antimicrobial susceptibility testing method. Some studies have shown a disconcordance between *in vitro* testing results and clinical response. Clinical observational studies have confirmed the rule 90-60, meaning that 90% of „susceptible" and 60% of resistant infections are likely to respond to an antibiotic. Thus, resistance is not the only reason for therapeutic failure. There is a question: Why does the conventional antibiotic susceptibility testing fail to choose the appropriate antibiotic? This pertains to urinary tract infections, respiratory infections and skin and soft tissue infections with specimen which are not primarily sterile. Conventional antimicrobial susceptibility testing is focused on the dominant pathogen instead of analyzing the whole microbial community. The specimens like sputum, BAL, wound swab and urine are processed in order to get the pure culture of the dominant pathogen by culturing on selective and non-selective media, lasting 24 to 48 h. Nowdays, we have faster automated systems which provide results in the shorter time, but still require the pure culture of the isolated strain. These methods perform identification and antibiotic susceptibility testing (Vitek 2, Phoenix, MALDI-TOF). However, there are new techniques being developed now which monitor morphologic and metabolic changes, inhibition of early bacterial growth and detection of antibiotic degradation products. Using molecular methods, it is possible to detect genes encoding resistance directly in the patient's sample, without previous cultivation. The drawback of molecular diagnostic is that the presence of genes does not mean that they are expressed. The genes are not necessarily functional. Moreover, the resistance genes can be from the concomitant microbiota. Therapy based on detection of resistance genes is to broad and can propagate resistance development. Conventional testing classifies isolates into susceptible (S), intermediate susceptible or susceptible at increased exposure (I) or resistant (R) based on the size of the inhibition zone or MIC value. Breakpoints are

based on the peak concentrations achieved in the blood, without taking into account tissue penetration and cell entry. Concentration of free antibiotic in blood is different from that in lungs, urine or soft tissue. Errors are due to the fact that breakpoints are based on the pharmacodynamic and pharmacokynetic parameters of the antibiotic in the blood and not in the tissue. The other problem is that during antibiotic susceptibility testing the isolate is exposed to the constant antibiotic concentration, which is not the case during therapy. Antibiotics are divided into three categories: concentration-dependent (cmax>MIC), time-dependent (tmax>MIC) and total antibiotic exposure dependent /AUC/MIC). These parameters are not taken into account with standard antimicrobial susceptibility testing leading to underestimating or overestimating of antibiotic efficacy. The antibiotic susceptibility of bacteria in biofilm is 1000 fold less than in planctonic bacteria. Bacteria in the biofilm multiply slowlier, the metabolism slows down and persisters develop which are not susceptible to antibiotics. When antibiotic concentration falls below MIC, persisters start to produce biofilm, leading to chronic and recurrent infections. One of the newly developed method for antibiotic selection is ATB finder. It does not require pure culture, instead it analyses the response of the whole microbial community. The method is based on bacterial culture on TGV agar which enables the growth of various bacterial species in the form of mixed biofilm with extracellular matrix and surface film. This mimics polymicrobial community and QS and tezR modulated antibiotic resistance. The medium enables the growth of fastidious bacteria much better than conventional rich media such as BHI or LB broth allowing analysis of bacterial diversity. ATB finder is a 48 well microtiter tray filled with TGV agar. In contrary to conventional testing, it is not based on MICs and breakpoints for evaluation of antibiotic efficacy, but determines antibiotic efficacy based on the antibiotic tissue penetration, depending on the infection site. Antibiotic concentration added in the wells depends on the infection site. The future of antimicrobial susceptibility testing methods is based on techniques which analyse the whole microbial community and take into account susceptibility of biofilm bound bacteria.

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LABORATORIJSKA DIJAGNOSTIKA INVAZIVNIH GLJIVIČNIH INFEKCIJA

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LABORATORY DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS

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IMPLEMENTACIJA NOVIH TEHNOLOGIJA U IDENTIFIKACIJI LEGIONELLA

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SAŽETAK

Legionella spp. su bakterije koje su široko rasprostranjene u vodenim ekosustavima. Iz ovih prirodnih rezervoara, ovaj oportunistički patogen može se proširiti i kolonizirati umjetne vodene sustave, što predstavlja značajan javnozdravstveni problem zbog povezanosti s legionarskom bolešću i Pontijačnom groznicom. Tradicionalne metode za identifikaciju legionela iz okolišnih uzoraka (filtracija, inokulacija, inkubacija i metode identifikacije) imaju ograničenja u smislu osjetljivosti, specifičnosti i vremena obrade.

Zbog promjena u propisima i razvoja turističkog sektora, pritisak na laboratorije raste. Odgovor na ovaj pritisak mogu biti nove metode identifikacije, poput lančane reakcije polimerazom u stvarnom vremenu (qPCR) i masene spektrometrije (MALDI-TOF), koje se smatraju obećavajućim tehnologijama za brzu i točnu identifikaciju mikroorganizama.

U Laboratoriju za mikrobiologiju voda Nastavnog zavoda za javno zdravstvo Primorsko-goranske županije obrađeno je 673 uzoraka vode na *Legionella* spp. u 2023. godini, od kojih je 75 uzoraka bilo pozitivno. Ove godine broj uzoraka se značajno povećao zbog izmjena zakonskih propisa, te se očekuje da će broj pozitivnih uzoraka na *Legionella* spp. također višestruko porasti.

Primjena MALDI-TOF metode u identifikaciji sojeva *Legionella* spp. značajno je ubrzala proces identifikacije, a time i izdavanje rezultata analize.

IMPLEMENTATION OF NEW TECHNOLOGIES IN THE IDENTIFICATION OF LEGIONELLA

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ABSTRACT

Legionella spp. are ubiquitous bacteria that are widely distributed in aquatic ecosystems. From these natural reservoirs, this opportunistic pathogen can spread to and colonize artificial aquatic environments, posing a significant public health concern due to their association with Legionnaires' disease and Pontiac fever. The traditional methods for the identification of *Legionella* from environmental samples (filtration, inoculation, incubation, and identification methods) suffer from limitations in terms of sensitivity, specificity, and turnaround time.

Due to changes in regulations and the development of the tourism sector, the pressure on laboratories is increasing. The answer to this pressure can be new identification methods such as Real Time Polymerase Chain Reaction (qPCR) and Mass Spectrometry (MALDI-TOF), as promising technologies for rapid and accurate microbial identification.

In the Laboratory for Water Microbiology of the Teaching Institute of Public Health of Primorje-Gorski Kotar County, in 2023, 673 water samples were processed for Legionella spp., of which 75 samples were positive. This year, the number of samples has increased significantly due to changes in legal regulations, and it is to be expected that the number of positive samples for *Legionella* spp. will also be many times higher.

The use of the MALDI-TOF method in the identification of *Legionella* spp. strains significantly accelerated the identification process, and thus the release of analysis results.

VRIJEDNOSTI LABORATORIJSKIH POKAZATELJA UPALNE AKTIVNOSTI U BOLESNIKA S COVID-19

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SAŽETAK

Uvod: COVID-19 je okarakteriziran kao vrlo zarazna i smrtonosna bolest za koju ne postoji vjerodostojan i prikladan prognostički biomarker. Uloga laboratorijske dijagnostike je ključna u suzbijanju i praćenju bolesti upotrebom već dobro poznatih laboratorijskih parametara. Kliničke studije pokazale su da bi promjene vrijednosti nekih krvnih biljega mogle biti povezane sa stupnjem ozbiljnosti i smrtnosti COVID-19 bolesnika. U većini studija, C-reaktivni protein (CRP) je nađen kao važan biljeg koji se značajno mijenja u bolesnika s teškom kliničkom slikom COVID-19.

Cilj istraživanja: Usporediti vrijednosti upalnih biljega u COVID-19 bolesnika koji su preminuli i onih koji su preživjeli.

Ispitanici i metode: U ovo istraživanje uključeno je 1043 COVID-19 bolesnika hospitaliziranih u Klinici za infektivne bolesti "Dr. Fran Mihaljević" u Zagrebu, podijeljenih u dvije skupine. U prvu skupinu je uključeno 712 (68,3%) bolesnika koji su preživjeli, a u drugu skupinu 331 (31,7%) bolesnika koji su preminuli. Podaci su prikupljeni iz povijesti bolesti uz odobrenje Etičkog povjerenstva ustanove. Vrijednosti laboratorijskih pokazatelja (leukociti, CRP, fibrinogen, prokalcitonin, D-dimeri) prikazane su u dvije različite vremenske točke (prva - prilikom primitka u Kliniku i druga - u najtežem trenutku bolesti) i statistički obrađene. Za usporedbu numeričkih varijabli korišten je Mann-Whitney U test. Razina statističke značajnosti postavljena je na $p<0,001$ (ns: $p>0,05$).

Rezultati: Statistički značajno povišene vrijednosti broja leukocita, CRP-a, prokalcitonina i D-dimera, određenih prilikom primitka na liječenje, pronađene su u bolesnika koji su kasnije preminuli ($p<0,001$), dok su vrijednosti fibrinogena bile više u skupini COVID-19 bolesnika koji su preživjeli. Laboratorijski parametri određeni u najtežem trenutku bolesti također su pokazali statistički značajne razlike u vrijednostima broja leukocita, CRP-a, prokalcitonina i D-dimera u COVID-19 bolesnika koji su preminu-

li ($p<0,001$), dok su vrijednosti fibrinogena bile statistički nesignifikantne ($p=0,782$). Skupina COVID-19 bolesnika-preživjeli, u usporedbi sa skupinom bolesnika-preminuli, imala je značajno niže vrijednosti D-dimera (medijan 1,2 ng/mL vs. 3,7 ng/mL; $p<0,001$), CRP-a (medijan 98 mg/L vs. 317 mg/L; $p<0,001$) i broja leukocita (medijan $10,2x10^9$/L vs. $32,7x10^9$/L; $p<0,001$).

Zaključak: Preminuli COVID-19 bolesnici imali su značajno više vrijednosti laboratorijskih pokazatelja upalne aktivnosti (broj leukocita, CRP, D-dimeri) u usporedbi s COVID-19 bolesnicima koji su preživjeli.

Ključne riječi: COVID-19; CRP; D-dimeri; prokalcitonin; upalni biljezi

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VALUES OF LABORATORY INDICATORS OF INFLAMMATORY ACTIVITY IN PATIENTS WITH COVID-19

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ABSTRACT

Introduction: COVID-19 is characterized as a highly contagious and and lethal; however, there is no credible and convenient biomarker to predict the severity of the disease. The role of laboratory diagnostics is crucial in the prevention and monitoring of diseases using already well-known laboratory parameters. Clinical studies have shown that changes in the values of some blood markers could be related to the degree of severity and mortality in COVID-19 patients. In most studies, C-reactive protein (CRP) has been reported as an important marker that changes significantly in patients with a severe COVID-19.

Research goal: To compare the values of inflammatory markers in COVID-19 patients who died and those who survived.

Subjects and methods: 1043 COVID-19 patients hospitalized in the University Hospital for infectious Diseases (UHID) in Zagreb, divided into two groups. The first group included 712 (68.3%) patients who survived, and the second group included 331 (31.7%) patients who died. Data were collected from the medical records with the approval of the institutional Ethics Committee. The values of laboratory indicators (leukocytes, CRP, fibrinogen, procalcitonin, D-dimers) were shown at two different time points (first - at the admission at UHID, and second - at the most severe moment of the disease) and statistically processed. The Mann-Whitney U test was used to compare numerical variables. The level of statistical significance was set at $p<0.001$ (ns: $p>0.05$).

Results: Statistically significantly increased leukocytes, CRP, procalcitonin and D-dimer, determined at the time of admission at UHID, were found in patients who later died ($p<0.001$), while fibrinogen values were higher in the group of COVID-19 patients who survived. Laboratory parameters determined at the most severe moment of the disease also showed statistically significant differences in leukocytes, CRP, procalcitonin and D-dimer in the COVID-19 patients with lethal outcome ($p<0.001$),

while the values of fibrinogen were statistically insignificant (p =0.782). The group of COVID-19 patients-survivors, compared to the group of patients with lethal outcome, had significantly lower values of D-dimer (median 1.2 ng/mL vs. 3.7 ng/mL; $p<0.001$), CRP (median 98 mg/L vs. 317 mg/L; $p<0.001$) and leukocyte (median $10.2x10^9$/L vs. $32.7x10^9$/L; $p<0.001$).

Conclusion: COVID-19 patients with lethal outcome had significantly higher values of laboratory indicators of inflammatory activity (leukocytes, CRP, D-dimers) compared to surviving COVID-19 patients.

Keywords: COVID-19; CRP; D-dimers; inflammatory markers; procalcitonin

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TEŠKI METALI U MESU - RIZICI ZA POTROŠAČE

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SAŽETAK

Uvod: Meso je ključni izvor hranjivih materija i mikroelemenata, ali istovremeno može biti kontaminirano teškim metalima poput olova i kadmija, koji predstavljaju ozbiljan rizik za ljudsko zdravlje. Ovi metali su toksični, imaju sposobnost bioakumulacije i biomagnifikacije u prehrambenom lancu, što može imati dugoročne negativne posljedice na zdravlje potrošača. Cilj ovog istraživanja bio je ispitati sadržaj olova i kadmija u pilećem i goveđem mesu, ribi, te njihovim proizvodima, s posebnim fokusom na uticaj vrste proizvoda, porijekla, ambalaže i godišnjeg doba na koncentracije ovih metala.

Materijal i metode: Ispitana su 72 uzorka mesa i ribe na sadržaj olova i kadmija metodom atomske apsorpcione spektrometrije- grafitnom tehnikom. Analize su rađene u skladu sa standardima BAS EN 13804:2015 i BAS EN 14084:2005.

Rezultati: Srednje koncentracije olova i kadmija bile su: za pileće meso i proizvode 12,40 µg/kg i 12,76 µg/kg, za goveđe meso i proizvode 29,06 µg/kg i 13,74 µg/kg, te za ribu i proizvode 14,63 µg/kg i 40,96 µg/kg. Nisu uočene statistički značajne razlike među vrstama mesa i ribe, ali je najveća koncentracija olova izmjerena u proizvodima od goveđeg mesa (297,63 µg/kg), dok je najviša koncentracija kadmija zabilježena u proizvodima od ribe (262,93 µg/kg).

Zaključak: Koncentracija olova u jednom uzorku je bila iznad maksimalno dopuštene količine, dok su koncentracije kadmija u svim uzorcima bile ispod dozvoljenih vrednosti. Istraživanje nije pokazalo značajnu razliku u koncentracijama olova i kadmija između domaćih i uvoznih proizvoda, ali je statistički značajna razlika uočena u proizvodima različitih vrsta ambalaže. Procijenjeni sedmični unos kadmija i olova iz mesa i ribe koje prosječan građanin konzumira bio je ispod preporučenog maksimuma, što ukazuje na relativno nisku izloženost ovim metalima, ali ukazuje na potrebu za daljim nadzorom i kontrolom. Ova istraživanja naglašavaju važnost praćenja prisustva teških metala u hrani, s ciljem smanjenja rizika po zdravlje potrošača.

Ključne riječi: teški metali, meso, riba, rizici, ljudsko zdravlje

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HEAVY METALS IN MEAT - RISKS FOR CONSUMERS

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ABSTRACT

Introduction: Meat is a key source of nutrients and trace elements, but it can also be contaminated with heavy metals such as lead and cadmium, which pose a serious risk to human health. These metals are toxic and have the ability to bioaccumulate and biomagnify in the food chain, which can have long-term negative consequences for consumer health. The aim of this study was to examine the content of lead and cadmium in chicken and beef meat, fish, and their products, with a particular focus on the influence of product type, origin, packaging, and season on the concentration of these metals.

Materials and Methods: A total of 72 meat and fish samples were tested for lead and cadmium content using atomic absorption spectrometry with graphite furnace technique. The analyses were conducted in accordance with the standards BAS EN 13804:2015 and BAS EN 14084:2005.

Results: The average concentrations of lead and cadmium were as follows: for chicken meat and products, 12.40 μg/kg and 12.76 μg/kg; for beef meat and products, 29.06 μg/kg and 13.74 μg/kg; and for fish and products, 14.63 μg/kg and 40.96 μg/kg. No statistically significant differences were observed between meat and fish types, but the highest lead concentration was measured in beef products (297.63 μg/kg), while the highest cadmium concentration was found in fish products (262.93 μg/kg).

Conclusion: The concentration of lead in one sample exceeded the maximum allowable limit, while cadmium concentrations in all samples were below the permitted values. The study did not show significant differences in lead and cadmium concentrations between domestic and imported products, but a statistically significant difference was found in products with different types of packaging. The estimated weekly intake of cadmium and lead from meat and fish consumed by the average citizen was below the recommended maximum, indicating relatively low exposure to these metals, but emphasizing the need for continued monitoring and control. This research highlights the importance of monitoring the presence of heavy metals in food to reduce the health risks for consumers.

Keywords: heavy metals, meat, fish risks, human health

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DETEKCIJA HIMERIZMA NAKON ALOGENE TRANSPLANTACIJE HEMATOPOETSKIH MATIČNIH ĆELIJA

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SAŽETAK

Alogena transplantacija hematopoetskih matičnih ćelija predstavlja ključnu terapiju za mnoge hematološke maligne i nemaligne bolesti. Jedan od glavnih izazova nakon transplantacije je identifikacija prisustva himerizma – postojanja mješavine donorskih i pacijentovih hematopoetskih ćelija. Pravovremena detekcija himerizma omogućava rano otkrivanje potencijalnih komplikacija, kao što su bolest *Graft-versus-host disease* (GvHD) i odbacivanje grafta, što može uticati na izbor terapije.

Ovaj pregled prikazuje metode detekcije himerizma, uključujući primjenu STR analize, kvantitativne PCR tehnike (STR-PCR) i nove molekularne pristupe, te analizira njihovu osjetljivost, specifičnost i kliničku primjenjivost.

Razumijevanje i primjena ovih metoda od ključne su važnosti za optimizaciju post-transplantacionog praćenja i poboljšanje ishoda pacijenata.

Ključne riječi: himerizam, alogena transplantacija, hematopoetske matične ćelije, STR analiza, kvantitativna PCR, post-transplantaciono praćenje, graft-versus-host bolest

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DETECTION OF CHIMERISM AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation is a key therapy for various hematologic malignant and non-malignant diseases. One of the main challenges post-transplantation is identifying the presence of chimerism – a mixture of donor and recipient hematopoietic cells. Timely detection of chimerism allows for the early identification of potential complications, such as Graft-versus-Host Disease (GvHD) and graft rejection, which can influence therapy choices.

This review presents chimerism detection methods, including the application of STR analysis, quantitative PCR techniques (STR-PCR), and new molecular approaches, and analyzes their sensitivity, specificity, and clinical applicability.

Understanding and applying these methods are crucial for optimizing post-transplant monitoring and improving patient outcomes.

Keywords: chimerism, allogeneic transplantation, hematopoietic stem cells, STR analysis, quantitative PCR, post-transplant monitoring, graft-versus-host disease

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POLIMORFIZMI GENA *MTNR1B* I RAZINE PROTUTIJELA NA TIREOGLOBULIN KOD HASHIMOTOVE BOLESTI

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SAŽETAK

Hashimotova bolest je autoimuni poremećaj štitne žlijezde koji uzrokuje kroničnu upalu i može dovesti do hipotireoze. Definirana je smanjenim razinama hormona štitne žlijezde tj. slobodnog tiroksina (fT4) uz sniženu ili normalnu razinu slobodnog trijodtironina (fT3) s posljedičnim porastom vrijednosti tireotropnog hormona (TSH) koji se sintetizira u hipofizi. Hashimotova bolest praćena je poremećajem humoralne imunosti (povećano stvaranje protutijela na tireoidnu peroksidazu (anti-TPO) i tireoglobulin (anti-Tg)), i u većoj mjeri, stanično posredovanim imunološkim procesima koji dovode do poticanja apoptoze folikularnih stanica štitne žlijezde. Melatonin, hormon koji regulira ciklus spavanja i budnosti, također ima ulogu u imunološkom sustavu. Njegov receptor, MTNR1B, sudjeluje u modulaciji imunoloških odgovora. Cilj ovog istraživanja je ispitati povezanost polimorfizama gena *MTNR1B* s Hashimotovom bolešću, uzimajući u obzir razine anti-Tg. U istraživanje su uključeni pacijenti s Hashimotovom bolesti koji su bili podijeljeni u dvije skupine na temelju razine anti-Tg – pacijenti s negativnim anti-Tg (manjim od 115 kIU/L) i pacijenti s pozitivnim anti-Tg (većim od 115 klU/L). Napravljena je analiza tri polimorfizma gena *MTNR1B* rs10830963, rs1387153 i rs4753426 TaqMan metodologijom. Polimorfizam rs10830963 nalazi se unutar jednog introna gena *MTNR1B* te nema vidljiv učinak na vezanje transkripcijskog čimbenika ili prekrajanje. Polimorfizam rs1387153 je nekodirajući polimorfizam smješten 28 kb uzvodno od 5' regije *MTNR1B* na kromosomu 11q21-q22. Polimorfizam rs4753426 (−1193T>C) nalazi se u promotorskoj regiji gena *MTNR1B* te utječe na transkripcijsku modulaciju ekspresije *MTNR1B*. Analizom navedenih polimorfizama i njihovog utjecaja na razvoj Hashimotove bolesti, otkriveno je da određeni polimorfizmi mogu povećati rizik od bolesti kod osoba s pozitivnim anti-Tg. Pokazano je da su razine anti-Tg bile povezane s rs10830963 polimorfizmom gena *MTNR1B,* dok polimorfizmi rs1387153 i rs4753426 nisu bili povezani s Hashimotovom bolešću na temelju razina anti-Tg. Rezultati sugeriraju da genetski čimbenici u kombinaciji s razinama anti-Tg mogu imati važnu ulogu u patogenezi Hashimotove bolesti, što otvara nove mogućnosti za personalizirane pristupe liječenju.

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Ključne riječi: autoimunost, melatonin, štitna žlijezda

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MTNR1B GENE POLYMORPHISMS AND THYROGLOBULIN ANTIBODY LEVELS IN HASHIMOTO'S DISEASE

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ABSTRACT

Hashimoto's disease is an autoimmune disease of the thyroid gland that causes chronic inflammation and can lead to hypothyroidism. It is defined by decreased levels of thyroid hormones, i.e., free thyroxine (fT4) with decreased or normal levels of free triiodothyronine (fT3), with a resulting increase in thyroid stimulating hormone (TSH) synthesized in the pituitary gland. Hashimoto's disease is associated with a disturbance of humoral immunity (increased production of antibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg)) and, to a greater extent, with cell-mediated immune processes that lead to the induction of apoptosis of thyroid follicular cells. Melatonin, the hormone that regulates the sleep-wake rhythm, also influences the immune system. Its receptor, MTNR1B, is involved in the modulation of immune responses. This study aimed to investigate the association of polymorphisms of the *MTNR1B* gene with Hashimoto's disease, taking into account the Ab-Tg levels. The study included patients with Hashimoto's disease who were divided into two groups based on Ab-Tg levels – patients with negative Ab-Tg (less than 115 kIU/L) and patients with positive Ab-Tg (more than 115 kIU/L). Three polymorphisms of the *MTNR1B* gene, rs10830963, rs1387153, and rs4753426, were analyzed using the TaqMan method. The rs10830963 polymorphism is located in an intron of the *MTNR1B* gene and has no apparent effects on transcription factor binding or splicing. The rs1387153 polymorphism is a non-coding polymorphism located 28 kb upstream of the 5' region of *MTNR1B* on chromosome 11q21-q22. The rs4753426 polymorphism (−1193T>C) is located in the promoter region of the MTNR1B gene and affects the transcriptional modulation of *MTNR1B* expression. Analysis of the above polymorphisms and their effects on the development of Hashimoto's disease revealed that specific polymorphisms may increase the risk of disease in individuals with positive Ab-Tg. Ab-Tg levels were found to be associated with the rs10830963 polymorphism of the *MTNR1B* gene, while the rs1387153 and rs4753426 polymorphisms were not associated with Hashimoto's disease based on Ab-Tg levels. The results suggest that genetic factors in combination with Ab-Tg levels may play an important role in the pathogenesis of Hashimoto's disease, opening up new possibilities for personalized treatment approaches.

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Keywords: autoimmunity, melatonin, thyroid gland

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KORELACIJA SERUMSKIH VRIJEDNOSTI TUMORSKIH MARKERA AFP I CEA KOD BENINGNIG I MALIGNIH OBOLJENJA JETRE

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SAŽETAK

UVOD
Tumorski markeri AFP i CEA veoma su bitni pri otkrivanju benignih i malignih stanja jetre. Određivanje koncentracije može pomoći upostavljanju rane dijagnoze (posebno u visoko rizičnim skupinama), tijeka i prognoze maligne bolesti, kao i praćenja terapije. Tumorski marker je tvar koja se nalazi u tumoru ili ga stvara tumor a koristi se za razlikovanje tumora od normalnog tkiva. Njihovo određivanje je značajno u prognozi te u liječenju malignih bolesti. Određivanje AFP-a služi općenito kao screening test različitih tumora, ali može biti od velike koristi kao dodatno mjerilo prilikom određivanja rizičnih grupa za nastanak primarnog karcinoma jetre. Povišene vrijednosti CEA najčešće se nalaze u kolorektalnom karcinomu, ali i kod benignih.

HIPOTEZE
Radne hipoteze: 1. Osjetljivost i specifičnost tumorskih markera AFP i CEA je statistički značajna kod malignih i benignih oboljenja jetre. 2. Kombinacijom tumorskih markera CEA i AFP omogućuje se razlikovanje metastatskog karcinoma jetre i hepatocelularnog karcinoma. Nulte hipoteze: 1. Osjetljivost i specifičnost tumorskih markera AFP i CEA nije statistički značajna kod malignih i benignih oboljenja jetre 2. Kombinacijom tumorskih markera AFP i CEA ne omogućuje se razlikovanje metastatskog karcinoma jetre i hepatocelularnog karcinoma.

CILJEVI ISTRAŽIVANJA
1. Utvrditi vrijednosti koncentracija tumorskih markera AFP i CEA kod pacijenata sa dijagnosticiranim malignim i benignim oboljenjima jetre. 2. Komparirati vrijednosti tumorskih markera AFP i CEA kod pacijenata sa dijagnosticiranim malignim i benignim oboljenjima jetre. 3. Utvrditi povezanost serumskih koncentracija tumorskih markera AFP i CEA sa metastatskim oboljenjima jetre i hepatocelularnim karcinomom.

MATERIJAL I METODE ISTRAŽIVANJA
Istraživanje je provedeno u Hrvatskoj bolnici „Dr fra Mato Nikolić" u Novoj Biloj u periodu između 01.01.2018. do 31.12.2020. godine. Znanstvena metoda ovog istraživanja jeste deskriptivno- analitička, retrospektivna studija. Istraživanje je uključivalo 120 pacijenata, u dobi između 2 i 93 godine života, uključujući oba spola.

REZULTATI ISTRAŽIVANJA
U obradi podataka koristili smo deskriptivnu statistiku, parametrijske i neparametrijske

testove signifikantnosti. U našem istraživanju rezultati mjerenja su u odnosu na potvrđenu dijagnozu oboljenja potvrdili zaista pozitivne i negativne rezultate. Testovima AFP i CEA dobili smo određeni udio lažno pozitivnih i negativnih rezultata. Ispitivanu populaciju je činilo 60 (50%) žena i 60 (50% muškaraca). Odnos muškaraca naspram žena iznosio je 1.0.

ZAKLJUČAK

1. Urađena je kontrola kvalitete testa TM koja je uključivala niske, srednje i visoke vrijednosti kontrolnih seruma. Vrijednosti kontrolnih seruma TM su bile u okviru jedne od dvije standardne devijacije. 2. Utvrđena je osjetljivost TM AFP iznosila 48%, dok je osjetljivost TM CEA iznosila 86%. 3. Utvrđena specifičnost TM AFP je iznosila 94.29%, a specifičnost TM CEA je iznosila 80%. 4. Utvrđena je točnost TM AFP od 75.31%, a točnost TM CEA je bila 82.46%. 5. Komparacijom TM AFP i CEA došli smo do zaključka da u određivanju postojanja malignih oboljenja kombinacija testova AFP i CEA ima senzitivnost 92%, specifičnost 95.71% sa točnošću od 94.19%, što su znatno više vrijednosti od bilo kojeg testa pojedinačno.

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SERUM VALUES CORRELATION OF CEA AND AFP TUMOR MARKERS IN BENIGN AND MALIGNANT LIVER DISEASES

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ABSTRACT

INTRODUCTION

AFP and CEA are very important in diagnosing benign and malignant liver conditions. Determining the concentration of these markers can help in early diagnosis of diseases (especially in risk groups), monitoring and prognosis of the disease and monitoring of therapy efficiency. A tumor marker is a substance contained in or being produced by the tumor which is being used to differentiate tumor from surrounding tissue.
Determining tumor marker concentration is significant in prognosis and treatment of malignant diseases. AFP concentration level is commonly used as a screening test of various tumors, but can be of great use as an additional criterion in determining risk groups for primary liver carcinoma. Elevated CEA levels are commonly found in colorectal carcinoma, but also in various benign tumors.

HYPOTHESIS

Working hypothesis: 1. Sensibility and specificity of AFP and CEA tumor markers is statistically important with malignant and benign liver diseases. 2. Combining determination of CEA and AFP tumor marker levels it's possible to differentiate between metastatic liver carcinoma and hepatocellular carcinoma. Zero hypothesis: 1. Sensibility and specificity of AFP and CEA tumor markers is not statistically important with malignant and benign liver diseases. 2. Combining determination of CEA and AFP tumor marker levels it's not possible to differentiate between metastatic liver carcinoma and hepatocellular carcinoma.

RESEARCH OBJECTIVES

1. Determine AFP and CEA concentration levels with patients diagnosed with malignant and benign liver disease. 2. Compare AFP and CEA tumor marker levels among patients diagnosed with malignant and benign liver disease. 3. Determine correlation between AFP and CEA tumor marker concentration levels and metastatic liver carcinoma and hepatocellular carcinoma.

MATERIALS AND METHODOLOGY

The research was conducted in the Croatian Hospital "Dr. fra Mato Nikolić" in Nova Bila between 1st of January, 2018 and 31st of December, 2020.. The scientific method used to conduct this research was descriptive-analytical retrospective study. The research included 120 patients between ages of 2 and 93 both male and female.

RESEARCH RESULTS

Descriptive statistics, and parametrized and non–parametrized significancy test were used in processing research data. The research measurements confirmed both positive and negative results although there was a certain number of falsely positive and negative results gotten through AFP and CEA tests. Research population included 60 (50%) female and 60 (50%) male patients. Male to female ratio was 1.0.

CONCLUSION

1. Verification of tumor marker tests which included low, medium and high concentration levels concluded that the levels were inside the standard deviation limits. 2. AFP tumor marker sensitivity was 48%, while CEA sensitivity was 86%. 3. Specificity of AFP tumor marker was 94.29%, while CEA specificity was 80% 4. AFP accuracy was 75.31% while CEA accuracy was 82.46%. 5. Combining the two tests sensitivity of 92%, specificity of 95.71% and accuracy of 94.14% was achieved which are significantly higher than any other single test.

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MOŽE LI TROMBOCITOZA BITI PROGNOSTIČKI MARKER U METASTATSKOM KARCINOMU DEBELOG CRIJEVA?

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SAŽETAK

Uvod: Karcinom debelog crijeva treća je najčešće dijagnosticirana maligna neoplazma i drugi uzrok smrti od raka u svijetu. Povišeni broj trombocita (trombocitoza) uočen je u bolesnika s različitim vrstama raka i prijavljeni su u obrnutoj korelaciji s preživljenjem. Ovi dokazi pokazuju da bi trombociti mogli biti jednostavan i robustan prognostički marker za prepoznavanje visokorizičnih pacijenata.

Cilj: Prikazati utjecaj trombocitoze kao prognostičkog markera na preživljenje pacijenata sve do potencijalne progresije bolesti u metastatski karcinom debelog crijeva, također povezujući trombocitozu s ukupnim preživljenjem bolesnika kod kojih metastaze nisu operirane.

Ispitanici i metode: Istraživanje je provedeno po principu retrospektivne studije iz baze podataka Klinike za onkologiju, Kliničkog bolničkog centra Osijek. Uključeni ispitanici bili su pacijenti kojima je dijagnosticiran metastatski karcinom debelog crijeva, te smo iste pacijente pratili tijekom petogodišnjeg preživljenja. Korišten je $\chi 2$-test, dok je statistička analiza napravljena pomoću programskog sustava MedCalc (inačica 14.12.0, MedCalcSoftware) uz razinu značajnosti od $P < 0,05$. Kod usporedbe ponovljenih numeričkih mjerenja korišten je Wilcoxon test, za analizu utjecaja trombocita na preživljenje Kaplan-Meier test preživljenja, te Cox proporcionalna hazard regresija (s odabranom metodom - Forward) kod analize prognostičkih parametara.

Rezultati: Statističkom analizom obradili smo 179 pacijenata, koji su imali dijagnozu metastatskog karcinoma debelog crijeva. Dobiveni rezultati analize pokazali su statistički značajan utjecaj trombocitoze na preživljenje promatranih pacijenata (P = 0,002), kao i povezanost s lošijom prognozom kod bolesnika s metastatskim karcinomom debelog crijeva, dok statistički značajan utjecaj trombocitoze na vrijeme do progresije u metastatski karcinom debelog crijeva nije dokazan.

Zaključak: Trombocitoza se u ovom istraživanju pokazala kao vrijedan prognostički čimbenik kod pacijenata s metastatskim karcinomom debelog crijeva.

Ključne riječi: karcinom debelog crijeva, metastaze, trombociti, trombocitoza

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CAN THROMBOCYTOSIS BE A PROGNOSTIC MARKER IN METASTATIC COLORECTAL CANCER?

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ABSTRACT

Introduction: Colorectal cancer is the third most commonly diagnosed malignant neoplasm and the second cause of death due to cancer worldwide. Elevated platelet count (thrombocytosis) is observed in patients with various kinds of cancer and reported inversely correlated with survival. This evidence indicated that platelet could be a simple and robust prognostic marker to identify high risk patients.

Aim: To demonstrate the impact of thrombocytosis as a prognostic marker on the survival of patients up to potential disease progression into metastatic colorectal cancer, also linking thrombocytosis with overall survival of patients whose metastases were not surgically removed.

Participants and methods: This study was conducted retrospectively using data from the Department of Oncology at the Clinical Hospital Center Osijek. The subjects were patients diagnosed with metastatic colorectal cancer, who were followed for up to five years. The $\chi 2$ test was used, while statistical analysis was performed using the MedCalc software (version 14.12.0, MedCalc Software) with a significance level of $P<0.05$. Wilcoxon test was used for comparing repeated numerical measurements, Kaplan-Meier survival test for the analysis of the impact of platelets on survival, and Cox proportional hazards regression (with the Forward method selected) for the analysis of prognostic parameters.

Results: A total of 179 patients from the Department of Oncology and Radiotherapy of the Clinical Hospital Center Osijek, diagnosed with metastatic colorectal cancer,

were analyzed. The obtained results of the analysis showed a statistically significant impact of thrombocytosis on the survival of observed patients (P = 0.002), as well as an association with a poorer prognosis in patients with metastatic colorectal cancer. However, a statistically significant impact of thrombocytosis on the time to progression to metastatic colorectal cancer was not proven.

Conclusion: Thrombocytosis was identified as a valuable prognostic factor for patients with metastatic colorectal cancer in this study.

Keywords: colorectal cancer; metastases; platelets, thrombocytosis

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RANA DETEKCIJA KARCINOMA DOJKE POMOĆU AI-a SA FOKUSOM NA LABORATORIJSKU DIJAGNOSTIKU

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SAŽETAK

UVOD: Karcinom dojke je jedan od najčešćih oblika raka koji pogađa žene širom svijeta. Rano otkrivanje ovog tipa raka je ključno, jer omogućava pravovremeno liječenje, što značajno poboljšava izglede za oporavak. Umjetna inteligencija može pomoći radiolozima i laboratorijskom osoblju u donošenju odluka nakon dijagnostike pomoću tradicionalnih metoda kao što su: mamografija i ultrazvuk kao i analiza biomarkera što može poboljšati mogućnost postavljanja dijagnoze u ranijem stadiju kada je terapija najefektivnija.

MATERIJAL I METODE ISTRAŽIVANJA: Istraživanje je provedeno kao pregledna studija sa najnovijim saznanjima iz literature.

REZULTATI: Umjetna inteligencija (AI) donosi nove mogućnosti u području laboratorijske dijagnostike karcinoma dojke. Pomoću naprednih modela mašinskog učenja i dubokog učenja, AI može analizirati složene podatke kao što su hormonski profili, kao i upalne i molekularne biomarkere uključujući: CEA, CA 15-3, CA 27-29, NLR, LMR, CTCs itd. Ključni aspekti primjene AI u laboratorijskoj dijagnostici karcinoma dojke obuhvataju: identifikaciju biomarkera, predikcija i personalizacija, optimizacija protokola skrininga, integracija sa postojećim dijagnostičkim sistemima. Analiza patohistoloških preparata ima ulogu u kasnijoj fazi kao potvrda dijagnoze.

ZAKLJUČCI: U ovom kontekstu, potencijal umjetne inteligencije u unapređenju laboratorijske dijagnostike karcinoma dojke je ogroman. AI predstavlja ključnu tehnologiju koja može poboljšati dijagnostičke procese, dovodeći do ranijeg otkrivanja i boljih ishoda za pacijente. Kako se primjena ovih tehnologija širi, istraživači i kliničari moraju se fokusirati na etičke aspekte, validaciju i integraciju AI rešenja u svakodnevnu praksu.

KLJUČNE RIJEČI: karcinom dojke; umjetna inteligencija; laboratorijska dijagnostika.

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EARLY DETECTION OF BREAST CANCER USING AI WITH FOCUS ON LABORATORY DIAGNOSTICS

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ABSTRACT

INTRODUCTION: Breast cancer is one of the most common forms of cancer women worldwide. Early detection of this type of cancer is crucial, as it allows for timely treatment, significantly improving recovery prospects. Artificial intelligence can assist radiologists and laboratory personnel in decision-making following diagnostics using traditional methods such as mammography and ultrasound, as well as biomarker analysis, which can enhance the likelihood of diagnosing at an earlier stage when therapy is most effective.

MATERIALS AND METHODS: The research was conducted as a review study with the latest findings from the literature.

RESULTS: Artificial intelligence (AI) brings new opportunities in the field of laboratory diagnostics for breast cancer. Using advanced machine learning and deep learning models, AI can analyze complex data including hormonal profiles, as well as inflammatory and molecular biomarkers including: CEA, CA 15-3, CA 27-29, NLR, LMR, CTCs etc. Key aspects of AI application in laboratory diagnostics for breast cancer include: biomarker identification, prediction and personalization, optimization of screening protocols, and integration with existing diagnostic systems. Analysis of pathohistological slides plays role in later phase as diagnosis confirmation.

CONCLUSIONS: In this context, the potential of artificial intelligence in enhancing laboratory diagnostics for breast cancer is immense. As research continues, AI represents a key technology that can improve diagnostic processes, leading to earlier detection and better outcomes for patients. As the application of these technologies expands, researchers and clinicians must focus on ethical aspects, validation, and integration of AI solutions into everyday practice.

KEYWORDS: breast cancer; artificial intelligence; laboratory diagnostics

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EUROPSKA UDRUGA BIOMEDICINSKIH ZNANSTVENIKA

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Odjel za zaštitu okoliša i zdravstvenu ekologiju, Nastavni Zavod za javno zdravstvo Primorsko-goranske županije, Rijeka, Hrvatska
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SAŽETAK

Europska udruga biomedicinskih znanstvenika (En. European Association of Biomedical Scientists - EPBS) od svog osnutka 1999. godine predstavlja temelj za unapređenje biomedicinskih znanosti i profesionalni razvoj diljem Europe. Ova prezentacija pruža detaljan pregled misije, postignuća i strateških inicijativa EPBS-a s ciljem osnaživanja biomedicinskih znanstvenika.

Ključne teme uključuju razvoj europskih smjernica za obrazovanje, obuku i kontinuirani profesionalni razvoj, zajedno s naporima EPBS-a u usklađivanju standarda i promicanju etičkih praksi. Naglašavajući suradnje s međunarodnim i europskim organizacijama, prezentacija ističe predanost udruge oblikovanju budućnosti biomedicinskih znanosti, uz suočavanje s izazovima dinamičnog zdravstvenog sustava.

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ABSTRACT

The European Association of Biomedical Scientists (EPBS) has been a cornerstone in advancing biomedical sciences and fostering professional growth across Europe since its establishment in 1999. This presentation provides an in-depth overview of EPBS's mission, achievements, and strategic initiatives aimed at empowering biomedical scientists.

Key topics include the development of European policy guidelines for education, training, and continuous professional development, along with EPBS's efforts to harmonize standards and promote ethical practices. Highlighting collaborations with international and European organizations, the presentation underscores the association's commitment to shaping the future of biomedical sciences while addressing the challenges of a dynamic healthcare landscape.

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INTEGRACIJA JCI, AKAZ I ISO STANDARDA U MEDICINSKIM LABORATORIJAMA-TEMELJI ZA OSIGURANJE KVALITETA I POUZDANOSTI USLUGA

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SAŽETAK

Primjena različitih standarda, poput JCI (Joint Commission International), AKAZ (Agencija za kvalitet i akreditaciju u zdravstvu u FBiH) i ISO standarda, ima ključan značaj u medicinskim laboratorijama, pružajući strukturu za osiguranje kvaliteta i pouzdanost usluga. Integracija ovih standarda laboratorijima omogućava unapređenje operativnih procesa, smanjenje rizika i postizanje konzistentnosti rezultata, što doprinosi sigurnosti pacijenata i jačanju povjerenja u zdravstveni sistem. JCI standardi, koji su namijenjeni međunarodnim zdravstvenim ustanovama, fokusirani su na podizanje nivoa kvaliteta i sigurnosti putem detaljnih smjernica i procjene usklađenosti. Ovi standardi posebno naglašavaju upravljanje rizicima, kontrolu infekcija, sigurnost pacijenata i stalno unapređenje kvaliteta. U BiH ne postoji nijedna zdravstvena ustanova akreditovana prema JCI(neke počinju proces). S druge strane, AKAZ, kao entitetska akreditaciona agencija, razvija standarde koji su prilagođeni lokalnim potrebama i zakonodavnim okvirom, definišući osnovne zahtjeve za kvalitet u zdravstvu kroz smjernice za postupke, nadzor i evaluaciju kvaliteta rada laboratorija, objavljen u 2024 godini.

ISO standardi, poput ISO 15189 (specifičan za medicinske laboratorije) i ISO 9001 (sistem upravljanja kvalitetom), pružaju međunarodno priznate smjernice i zahtjeve za postizanje konzistentnosti, sljedivosti i efikasnosti. Na primjer, ISO 15189 fokusira se na tehničke aspekte i stručnost osoblja u laboratorijima, što je od ključnog značaja za pouzdane rezultate testiranja. U BiH je ukupno 6 laboratorija akreditirano, a u FBiH postoje 2 akreditovane laboratorije prema BAS EN ISO 15189.

Sinergijom ovih standarda medicinske laboratorije mogu uspostaviti čvrste sisteme upravljanja kvalitetom. Ova integracija omogućava laboratorijama da ispune zahtjeve nacionalnih i međunarodnih akreditacija, kao i da primjenjuju najbolje prakse kroz sve faze rada – od prikupljanja uzoraka do tumačenja rezultata. Ključne prednosti ovakve integracije uključuju bolju sljedivost, smanjenje grešaka, veću transparentnost i poboljšano iskustvo pacijenata.

Ipak, uvođenje integrisanog sistema standarda može biti izazovno zbog potrebe za obukom osoblja, tehničkim usklađivanjem i efektivnim upravljanjem resursima. Uspješna implementacija zahtijeva strateški pristup i kontinuirano praćenje kako bi se postigla usklađenost svih aspekata rada laboratorija s najvišim standardima kvaliteta. Na taj način, integracija JCI, AKAZ i ISO standarda u medicinskim laboratorijama postaje osnov za osiguranje kvaliteta, doprinoseći pouzdanosti usluga i povjerenju pacijenata u zdravstvenu zaštitu.

Ključne riječi: standard, laboratorije, sigurnost pacijenta, kompetentnost

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INTEGRATION OF JCI, AKAZ, AND ISO STANDARDS IN MEDICAL LABORATORIES – FOUNDATIONS FOR QUALITY ASSURANCE AND SERVICE RELIABILITY

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ABSTRACT

Application of various standards, such as JCI (Joint Commission International), AKAZ (Agency for Quality and Accreditation in Healthcare in FBiH), and ISO standards, is of critical importance in medical laboratories, providing a framework for quality assurance and service reliability. Integration of these standards allows laboratories to enhance operational processes, reduce risks, and achieve consistency in results, thereby contributing to patient safety and strengthening trust in the healthcare system. JCI standards, designed for international healthcare institutions, focus on raising the level of quality and safety through detailed guidelines and compliance assessment. These standards emphasize risk management, infection control, patient safety, and continuous quality improvement. In Bosnia and Herzegovina, no healthcare institution is JCI-accredited yet (some are beginning the process). On the other hand, AKAZ, as an entity-level accreditation agency, develops standards adapted to local needs and legislative frameworks, defining basic quality requirements in healthcare through guidelines for procedures, supervision, and evaluation of laboratory work quality.

ISO standards, such as ISO 15189 (specific to medical laboratories) and ISO 9001 (quality management system), provide internationally recognized guidelines and requirements for achieving consistency, traceability, and efficiency. For example, ISO 15189 focuses on technical aspects and personnel competence in laboratories, which is essential for reliable test results. In Bosnia and Herzegovina, a total of 6 laboratories are accredited, with 2 accredited laboratories in the FBiH according to BAS EN ISO 15189.

Through the synergy of these standards, medical laboratories can establish robust quality management systems. This integration enables laboratories to meet the requirements of both national and international accreditations and apply best practices across all work stages—from sample collection to result interpretation. Key benefits of such integration include improved traceability, error reduction, greater transparency, and enhanced patient experience.

However, implementing an integrated standards system can be challenging due to the need for staff training, technical alignment, and effective resource management. Successful implementation requires a strategic approach and continuous monitoring to achieve compliance with the highest quality standards across all laboratory operations. Thus, the integration of JCI, AKAZ, and ISO standards in medical laboratories becomes a foundation for quality assurance, contributing to service reliability and patient trust in healthcare.

Keywords: standards, laboratories, patient safety, competence

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IMPLEMENTACIJA SUSTAVA UPRAVLJANJA KVALITETOM PREMA NORMI ISO 15189 - ISKUSTVO MIKROBIOLOŠKOG LABORATORIJA

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SAŽETAK

Svakodnevno smo svjedoci razvoja mikrobioloških laboratorija koji nude usluge korisnicima što je povezano s potrebom povjerenja u nalaze, odnosno rezultate ispitivanja. Upravo je uspostava sustava upravljanja ta koja potvrđuje kompetentnost mikrobiološkog laboratorija za dosljednu i pouzdanu provedbu postupaka ispitivanja s nalazima koji su prepoznatljivi kao valjani, sljedivi i točni.

U ovom radu prikazano je iskustvo Službe za mikrobiologiju Nastavnog zavoda za javno zdravstvo Osječko-baranjske županije u uspostavi, primjeni i održavanju sustava upravljanja, odnosno akreditaciji prema normi HRN EN ISO 15189, te prednosti i nedostatci uspostave sustava upravljanja.

Proces akreditacije započeo je osiguranjem potrebnih resursa, definiranjem opsega akreditacije i imenovanjem ključnog osoblja. Slijedila je usporedba postojećeg stanja sa zahtjevima norme, definiranje potrebnih promjena, definiranje sustava upravljanja, izrada potrebne dokumentacije, njena primjena, ocjena sustava i podnošenje prijave za akreditaciju. Nakon provedene akreditacije za izabrane pretrage, uspostava sustava upravljanja je završila, ali se i dalje redovito preispituje u cilju uočavanja prilika za poboljšavanjem. Za održavanje sustava kontinuirano se prate sve faze rada, provode postupci unutarnje i vanjske kontrole kojima se nadziru postupci ispitivanja, te se uvažavaju povratne informacije dobivene od korisnika.

Akreditacija je poboljšala procese u laboratoriju, povećala se kvaliteta u svim fazama ispitivanja, a greške su se smanjile. Uložen je maksimalan trud da se zadovolje svi zahtjevi za resurse, procese i sustav upravljanja. Uz dodatne troškove, dodatne poslove i mnoštvo dokumentacije još uvijek ne postoji adekvatno vrednovanje akreditiranih pretraga. Iako su rezultati akreditacije međunarodno priznati, te se nakon završenog procesa akreditacije postiže cilj „jednom ispitano – svuda prihvaćeno" i dalje ostaje pitanje "Akreditacija je prilika za mikrobiološki laboratorij ili ipak nije?".

Ključne riječi: akreditacija, sustav upravljanja, mikrobiološki laboratorij.

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IMPLEMENTATION OF THE QUALITY MANAGEMENT SYSTEM ACCORDING TO ISO 15189 - MICROBIOLOGY LABORATORY EXPERIENCE

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ABSTRACT

On a daily basis we witness the development of microbiological laboratories that offer services to users, which is connected with confidence in a test report. The established management system is a confirmation of competence microbiological laboratory for consistent and reliable implementation of examination processes with valid, traceable and accurate the tests reports.

This article presents experience the Department of Microbiology of the Teaching Institute for Public Health of Osijek-Baranja County in the establishment, application and maintenance of the management system, i.e. accreditation according to HRN EN ISO 15189, advantages and disadvantages of the establishment of the management system.

The accreditation process began with securing the necessary resources, defining the scope of accreditation and appointing key personnel. This was followed by a comparison of the existing situation with the requirements of the standard, definition of the necessary changes, definition of the management system, preparation of the necessary documentation, application of documentation, evaluation of the system and submission of the application for accreditation. After the accreditation process for the selected tests, the establishment of the management system was completed, but it is still regularly reviewed in order to identify opportunities for improvement. In order to maintain the system, all phases of work are continuously monitored, internal and external controls are carried out for test monitoring, and feedback received from users is taken into account.

Accreditation improved processes in the laboratory, increased quality in all phases of testing, and reduced errors. Maximum effort has been made to fulfill requirements for resource, process and management system. With additional costs, additional work and a lot of documentation, there is still no adequate evaluation of accredited tests. Accreditation results are internationally recognized, the goal "tested once - accepted everywhere" has been achieved, but still remains the question "Is accreditation an opportunity for a microbiological laboratory or isn't?".

Key words: accreditation, management system, microbiological laboratory

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ULOGA BILJNIH PRIPRAVAKA U SPRJEČAVANJU NASTANKA INFEKCIJA

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SAŽETAK

Stavljanjem u uporabu prvog antibiotika, salvarsana, a potom otkriće penicilina 1928. godine, te njegovo stavljanje u uporabu, značajno su promijenili modernu medicinu. Posebno treba naglasiti, da su produžili prosječan životni vijek za 23 godine. Period od otkrića penicilina, 1928. godine, smatra se zlatnom erom u otkriću prirodnih antibiotika pri čemu je vrhunac bio sredinom pedesetih godina, od kada se značajno smanjuju otkrića novih antibiotika. Evolucija rezistencije na antimikrobne lijekove kod značajnog broja ljudskih patogena dovodi do pojave otpornosti pri čemu značajan doprinos daje neracionalna uporaba istih.

Problem antimikrobne rezistencije, u biti, jest globalan problem čovječanstvu jer se sve češće javljaju otporni bakterijski sojevi za koje su značajno smanjene mogućnosti liječenja. Bitni čimbenici rizika za nastanak antimikrobne rezistencije je nepravilna uporaba antimikrobnih lijekova kako u ljudskoj medicini tako i u životinjskoj prehrambenoj industriji. Alarmantni su podaci koji govore da je broj umrlih, kao posljedica antimikrobne rezistencije, na godišnjoj razini u Europi oko 25 000, a u Sjedinjenim Američkim Državama oko 23 000.

Narečeni problemi nalažu iznalaženje novih antimikrobnih sredstava, pa su tako česta meta istraživača i biljni pripravci koji su se dugo kroz povijest , kao dio narodne medicine, koristili kao prirodna sredstva za sprječavanje nastanka infekcija.

Dakle, iskustveno je poznato da pripravci brojnih biljaka, između ostalih, imaju i antimikrobne učinke, ali je zbog njihove složene građe teško zaključiti koji su spojevi zaslužni upravo za njih. Budući da ti spojevi imaju različite mehanizme djelovanja u odnosu na tradicionalne antibiotike, očekuje se smanjena mogućnost nastanka antimikrobne rezistencije. Dokazano antimikrobno djelovanje imaju spojevi koji se mogu naći u raznim biljnim pripravcima poput fenolnih spojeva u koje spadaju podrazredi poput fenolnih kiselina, flavonoida, kumarina i tanina. Oni djeluju inhibicijom deoksiribonukleinske kiseline ili sinteze proteina, razaranjem stanične membrane, ali i drugim mehanizmima. Značajno je naglasiti i njihov obećavajući antibiofilmski potencijal.

Antimikrobno djelovanje biljnih pripravaka, uz ostale metode, moguće je ispitati na mikroorganizama, metodom disk difuzije, dok se za otkrivanje bioaktivnih spojeva koristi HPLC analiza.

Projekt IP – FDMZ -2024.2025 – 08

Ključne riječi: antimikrobno djelovanje**,** biljni pripravci, infekcija

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THE ROLE OF HERBAL REMEDIES IN THE PREVENTION OF INFECTIONS

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ABSTRACT

The introduction of the first antibiotic, salvarsan, and the discovery of penicillin in 1928 and its introduction into use have significantly changed modern medicine. It should be emphasized that they extended the average life expectancy by 23 years. The period since the discovery of penicillin in 1928 is considered a golden era in the discovery of natural antibiotics, with a peak in the mid-1950s when discoveries of new antibiotics declined significantly. The development of resistance to antimicrobial drugs in many human pathogens leads to the emergence of resistance, with their irrational use making a significant contribution.

The problem of antimicrobial resistance is a global problem for humanity, as resistant strains of bacteria are increasingly appearing, for which treatment options have been significantly restricted. The inappropriate use of antimicrobial drugs, both in human medicine and in the animal feed industry, is a significant risk factor for the emergence of antimicrobial resistance. Alarming data indicate that the number of deaths due to antimicrobial resistance in Europe is around 25,000, and in the United States, around 23,000 per year.

These problems require discovering new antimicrobial agents, so researchers often target herbal preparations that have long been used as natural remedies to prevent infections.

It is, therefore, known from experience that preparations of numerous plants also have antimicrobial effects. However, due to their complex structure, it is difficult to say which compounds are responsible for this. As these compounds have different mechanisms of action than conventional antibiotics, the possibility of antimicrobial resistance will likely be lower. Compounds found in various herbal preparations, such as phenolic compounds, which include subclasses such as phenolic acids, flavonoids, coumarins, and tannins, have been shown to have antimicrobial activity. They act by inhibiting deoxyribonucleic acid or protein synthesis, destroying the cell membrane and other mechanisms. Their promising potential for combating biofilms should also be emphasized.

The antimicrobial activity of herbal preparations can be tested on microorganisms using the disk diffusion method, while HPLC analysis is used to detect bioactive compounds.

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Key words: antimicrobial activity, herbal preparations, infection

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EFEKTI SREBRO NITRATA I SREBRENIH NANOČESTICA NA SPOSOBNOSTI FORMIRANJA BIOFILMA U *STAPHYLOCOCCUS AUREUS*

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SAŽETAK

Problem pojavljivanja biofilmova predstavlja problem u mnogim sferama medicine i industrije. Sama pojava biofilmova predstavlja izazov gdje u sferi medicine se može pripisati sposobnosti mikroorganizama da pokažu mogućnosti rezistencije ka konvencionalnim metodama njihove kontrole i suzbijanja sa antibioticima i biocidima. Mnogi pristupi su ispitivani a medju njima su i metode ''zelene nanotehnologije'' koja je pružila ohrabrujuće rezultate u cilju da se pronadje način da se bakterije ''zamrznu'' u svom planktonskom stanju. Zbog historijske primjene srebra ova studija je sprovedena koristeći sub-inhibitorne koncentracije srebro nitrata i srebrenih nanočestica na bakterijske sojeve kako bi se odredila mogućnost da srebrene nanočestice služe kao blokatori genske ekspresije za formiranje biofilma.

Cilj studije: Cilj ove studije je bio da se odredi efekat srebro nitrata i srebrenih nanočestica na sposobnosti formiranja biofilma u sojevima *S.Aureus*. Srebro nitrat je služio kao glavni izvor za sintezu srebrenih nanočestica koje su inokulirane u tečnu bakterijsku kulturu. Glavna uloga nanočestica je bila ta da se odredi njihova koncentracija i efekti po koncentraciji na formiranje biofilma u periodu od 24 sata i 48 sati.

Materijal i metode: Korišteni sojevi za studiju su bili *S.Aureus* (ATCC 25923), klinički soj Methycillin senzitivni *Staphylococcus aureus* (MSSA) i klinički soj Methycilin resistentni *Staphylococcus aureus* (MRSA). Srebro nitrat je redukovan na dva načina: zelenom sintezom uz pomoć Aloe Vera biljke te hemijskom redukcijom uz pomoć natrijum borohidrida (natrijum tetrahidroborat) sa stabilizirajućim reagensima. Nanočes-

tice su potom inokulirane u tečne kulturue u koje su dodati sojevi bakterija te su ploče inkubirane u periodu od 24 i 48 sati. Nakon inkubacije ploče su obojene sa 0.1% kristalnim violetom kako bi se utvrdilo prisustvo biofilmova. Biofilmovi koji su prisutni su očitani na ELISA čitaču kako bi se odredila njihova gustoća.

Rezultati: Rezultati studije su pokazali da formacija biofilma smanjena kod *S. aureus* (ATCC 25923) koristeći srebro nitrat na koncentraciji od 0.625 mM gdje je smanjena sa srednje na ne prijanjajuću dok pri koncentracijama od 0.3125 mM, 0.15625 mM, 0,0781 mM, 0.039 mM i 0.0195 mM sa srednje koncentracije na nisku.

Kod *S. aureus* (MSSA) biofilm se formirao na slabu formaciju na koncentraciji od 0.3125 mM, 0,00061 mM i 0.00030 mM dok MRSA nije formirala biofilm na bilo kojoj testiranoj koncentraciji.

Za nanočestice koje su dobivene zelenom sintezom *S. aureus* (ATCC 25923) formacija biofilma se promijenila na koncentracijama 1 mM, 0.5 mM i 0.25 mM gdje je intenzitet formiranja pao sa srednjeg nivo na ne prijanjajući, te formacija biofilma se povratila na koncentraciji od 0.125 mM. MSSA i MRSA nisu formirali biofilm na bilo kojoj testiranoj koncentraciji.

Za nanočestice koje su dobivene procesom hemijske redukcije formirajne biofilma za soj *S. aureus* (ATCC 25923) se desila promjena u formaciji biofilma sa srednjeg intenziteta na koncentraciji od 0.00098 mM gdje se formirao biofilm blagog intenziteta dok pri višim koncentracijama nije bilo formiranja biofilma. MSSA i MRSA nisu formirali biofilm na bilo kojoj testiranoj koncentraciji.

Zaključak: Srebro nitrat i srebrene nanočestice su potvrdili svoje dejstvo na testirane bakterijske sojeve *S.Aureus* kao što je već ranije testirano u literaturi. Jedan od ključnih principa ovog istraživanja je bio da se utvrdi dejstvo nanočestica dobivenih zelenom sintezom koje su pokazale pozitivne efekte na suzbijanje formiranja biofilma te da su komparativno pokazali slične rezultate kao nanočestice dobivene hemijskom redukcijom. U oba slučaja srebro nitrat i srebrene nanočestice su imali efekta na suzbijanje formiranja biofilma u bakterijskim kulturama.

Ključne riječi: Srebro, Srebrene nanočestice, *S. aureus*, Zelena sinteza, Biofilm

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EFFECT OF SILVER NITRATE AND SILVER NANOPARTICLES ON BIOFILM FORMATION IN STAPHYLOCOCCUS AUREUS

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ABSTRACT

Biofilms have become a major issue in different spheres of medicine and industry. Source of the issue revolves around increasing resistance of microorganisms towards conventional antibiotics which is even more elevated within biofilms that are difficult to eradicate by means of biocides and antibiotics. Multiple approaches were applied to deal with this issue amongst which green nanotechnology gave promising results and the search for molecules that "freeze bacteria" in the planktonic state. Since silver was used as an antimicrobial agent since ancient times. Considering this a study which deals with the effect of sub-inhibitory concentrations of silver nitrate and silver nanoparticles on biofilm forming capacity of bacteria would yield valuable information to evaluate the effect these substances have on the phenotypical expression of biofilm formation in bacteria as potential biofilm gene expression stoppers.

Aim of the study: The aim of the study conducted was to determine the effects of silver and silver nitrate on biofilm forming capacity of *S.Aureus* strains. The silver nitrate was used as a main source of production for nano-silver particles which were inoculated in the median to which bacterial culture was introduced. The purpose of nano-silver was to examine its properties and effects of biofilm and biofilm forming microorganisms in order to present nano-silver as a means of combating the everlasting threat of microbial quorums which are presented in the biofilm.

Materials and methods: The tested bacterial strains included: *Staphylococcus aureus ATCC* (25923), clinical strain of *Methycillin sensitive Staphylococcus aureus* (MSSA)

and clinical strain of *Methyciline resistant Staphylococcus aureus* (MRSA). Silver nitrate was reduced with two methods: Green synthesis which involved usage of Aloe Vera plant and chemical reduction with use of sodium borohydride alongside stabilizing agents. The obtained nanoparticles were introduced into culture media alongside the strains which then were incubated for periods of 24 and 48 hours.

Results: The results of the study indicate that the biofilm formation was quenched in the case of

S. aureus (ATCC 25923) using silver nitrate and at the concentration of 0.625 mM it was reduced from medium to non-adherent, while at concentration of 0.3125 mM, 0.15625 mM, 0.0781 mM,

0.039 mM and 0.0195 mM and it was reduced from medium to weak, biofilm returned its intensity back to medium at concentration of 0.00975 mM.

For the case of *S. aureus* (*MSSA*) biofilm was increased from non-adherent to weak at concentrations 0.3125 mM and 0.00061 Mm and 0.00030 mM, while MRSA did not form biofilm at any of the given concentrations.

For the nanoparticles synthesized with green synthesis method *S. aureus* (ATCC 25923) at concentrations 1 mM, 0.5 mM and 0.25 mM the intensity of biofilm has changed from medium to non-adherent, the intensity returned at concentration 0.125 mM. *MSSA* and *MRSA* did not form biofilm on any tested concentrations.

In case of silver nanoparticles produced with chemical reduction *S. aureus* (ATCC 25923) from medium biofilm has changed at concentration of 0.00098 mM where weak biofilm has formed, in higher concentrations no biofilm has formed. Both *S. aureus MSSA* and *MRSA* did not form biofilm in any of the concentrations.

Conclusion: Silver nitrate and silver nanoparticles have produced results similar to the previous studies which were conducted in literature. One of the key concepts was the nanoparticles obtained with green synthesis also provided satisfactory results when compared to those obtained with chemical reduction. Both silver nitrate and silver nanoparticles have hindered bacterial biofilm forming capacity when tested within the concentrations.

Key words: Silver, Silver nanoparticles, S. aureus, Green synthesis, Biofilm

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DIJAGNOZA KRIPTOKOKNOG MENINGITISA: POGLED KROZ MIKROSKOP

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SAŽETAK

Cryptococcus neoformans je kvasac iz roda *Cryptococcus.* Blastokonidija je ovalnog ili okruglog oblika s malim pupoljkom na uskoj peteljci i obavijena je polisaharidnom kapsulom. Kapsula je najvažniji čimbenik virulencije kriptokoka jer ometa fagocitozu neutrofilima i makrofagima. Nama je najznačajniji zato što uzrokuje kriptokokozu čovjeka. *C. neoformans* ulazi u tijelo inhalacijom kroz respiratorni trakt, širi se hematogeno i može inficirati bilo koji organ u tijelu, ali ima sklonost za pluća i središnji živčani sustav (SŽS). Meningitis je najčešća manifestacija kriptokokoze, a smrtnost ostaje visoka, čak i u razvijenim zemljama. Stoga je potrebno brzo prepoznavanje i dijagnoza kako bi se smanjile stope smrtnosti.

Kriptokokni meningitis je česta oportunistička infekcija i bolest koja definira AIDS u bolesnika s HIV infekcijom u kasnom stadiju, ali se javlja i u bolesnika s drugim oblicima imunosupresije i u očito imunokompetentnih osoba. Citološka procjena cerebrospinalne tekućine (likvora) učinkovito je sredstvo za dijagnosticiranje mnogih poremećaja koji zahvaćaju SŽS. Citološki pregled često pokazuje prisutnost gljivičnih elemenata nakon izravnog pregleda u komorici za brojanje stanica i na obojenim stakalcima nakon citocentrifugiranja.

U bolesnika s kriptokoknim meningitisom, upalni odgovor pokazuje različite stupnjeve ovisno o imunokompetenciji domaćina. Dok se nalazi likvora imunokompetentnih pacijenata obično manifestiraju kao pleocitoza, nalazi u imunokompromitiranih pacijenata često pokazuju veliki broj stanica kvasca bez upalnog odgovora. Konačna dijagnoza ovisi o otkrivanju uzročnika kulturom; stoga je uvijek potrebno potvrditi pozitivne citološke nalaze s kulturama.

U bolesnika s kriptokoknim meningitisom, citološki pregled likvora je vrlo težak jer se stanice kvasca mogu lako previdjeti, osobito kada ih je malo, i mogu se zamijeniti s eritrocitima ili artefaktima. Štoviše, kriptokoki ponekad pokazuju neobičnu citomorfologiju koja može uzrokovati dijagnostičke poteškoće. Stoga, dobro educirani i iskusni

laboratorijski tehnolozi/citotehnolozi moraju biti dostupni za prepoznavanje ovih neobičnih organizama.

Ključne riječi: *Cryptococcus neoformans*, kriptokokni meningitis, likvor

DIAGNOSIS OF CRYPTOCOCCAL MENINGITIS: A VIEW THROUGH THE MICROSCOPE

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ABSTRACT

Cryptococcus neoformans is a yeast from the genus *Cryptococcus*. Blastoconidia are oval or round in shape, with a small bud on a narrow stalk encased in a polysaccharide capsule. The capsule is the most important cryptococcal virulence factor because it inhibits neutrophil and macrophage phagocytosis. It is particularly important to us because it causes human cryptococcosis. *C. neoformans* enters the body by inhalation through the respiratory tract, spreads hematogenously and can infect any organ in the body, but has a predilection for the lung and the central nervous system (CNS). Meningitis is the most frequent manifestation of cryptococcosis, and mortality remains high, even in developed countries. Therefore, rapid recognition and diagnosis are required to decrease mortality rates.

Cryptococcal meningitis is a common opportunistic infection and AIDS-defining illness in patients with late-stage HIV infection, but also occurs in patients with other forms of immunosupression and in apparently immunocompetent individuals. Cytological evaluation of cerebrospinal fluid (CSF) is an effective means for diagnosing many disorders involving the CNS. A cytological examination frequently shows the presence of the yeast upon direct examination in a cell counting chamber, and on stained slides after cytocentrifugation.

In patients with cryptococcal meningitis, the inflammatory response shows different degrees depending on the immunocompetence of the host. While CSF findings in immunocompetent patients usually manifest as pleocytosis, findings in immunocompromised patients often show large numbers of yeast cells without an inflammatory response. The final diagnosis depends on the detection of the causative agent by culture; therefore, it is always necessary to confirm positive cytological findings with cultures. In patients with cryptococcal meningitis, cytological examination of the CSF is very difficult as the yeast cells can be easily overlooked, particularly when few in number, and can be confused with erythrocytes or artefacts. Moreover, cryptococci sometimes show un-

usual cytomorphology that can cause diagnostic difficulty. Therefore, well trained and experienced laboratory technologists/cytotechnologists must be available to recognize these unusual organisms.

Key words: *Cryptococcus neoformans*; Cryptococcal meningitis; cerebrospinal fluid

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ZNAČAJ PREDANALITIČKE I ANALITIČKE FAZE U LABORATORIJSKOJ DIJAGNOSTICI

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SAŽETAK

UVOD Laboratorijska medicinska dijagnostika je multidisciplinarna nauka koja obuhvata: mikrobiologiju, hematologiju, transfuziju, histopatologiju, kliničku biohemiju, citologiju, imunologiju i molekularnu dijagnostiku. Važnost laboratorijske dijagnostike je u postavljanju dijagnoze i procijeni stanja pacijenta. Segmenti laboratorijskog procesa sastoje se od predanalitičke, analitičke i postanalitičke faze. Uočeno je da predanalitičke greške čine više od dvije trećine svih laboratorijskih grešaka. Sistem kontrole kvaliteta standardizira laboratorijske analize, postupke te osigurava sigurno radno okruženje za pacijente i osoblje.

CILJ Ukazati na najčešće potencijalne greške u predanalitičkoj i analitičkoj fazi rada u laboratoriju, kao i na dobre prakse i usklađenost s novim strategijama kontrole kvaliteta za sprječavanje i značajno smanjenje predanalitičkih pogrešaka.

ZAKLJUČAK Iako je smatrano da se najviše grešaka u laboratorijskom radu odvija u analitičkom dijelu procesa, nakon dosadašnjih poboljšanja te faze, zaključeno je da se najviše grešaka događa u predanalitičkoj fazi, a nešto manje u postanalitičkoj fazi. To se prvenstveno dešava zbog poteškoća u postizanju standardiziranih postupaka za prikupljanje uzoraka.

KLJUČNE RIJEČI Laboratorijska dijagnostika; konrotola kvaliteta; predanalitička faza; analitička faza

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THE SIGNIFICANCE OF THE PRE-ANALYTICAL AND ANALYTICAL PHASES IN LABORATORY DIAGNOSIS

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ABSTRACT

INTRODUCTION Laboratory medical diagnostics is a multidisciplinary science that includes: microbiology, hematology, transfusion, histopathology, clinical biochemistry, cytology, immunology, and molecular diagnostics. The importance of laboratory diagnostics is in establishing a diagnosis and assessing the patient's condition. The segments of the laboratory process consist of pre-analytical, analytical, and post-analytical phases. It has been observed that pre-analytical errors account for more than two-thirds of all laboratory errors. The quality control system standardizes laboratory analyses, and procedures and ensures a safe working environment for patients and staff.

OBJECTIVE To indicate the most common potential errors in the pre-analytical and analytical phase of laboratory work, as well as good practices and compliance with new quality control strategies to prevent and significantly reduce pre-analytical errors.

CONCLUSION Although laboratory work is primarily performed in the analytical phase, previous improvements in that phase have resulted in the conclusion that the majority of errors occur in the pre-analytical phase and somewhat less in the post-analytical phase. This is primarily due to difficulties in achieving standardized procedures for collecting samples.

KEY WORDS Laboratory diagnostics; quality control; pre-analytical phase; analytical phase

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UTICAJ TEŠKIH METALA NA POJAVU *LEGIONELLA* SPP. U VODI BAZENA, LJEČILIŠTA I SPA CENTARA NA PODRUČJU FEDERACIJE BOSNE I HERCEGOVINE

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SAŽETAK

Uvod*: Legionella spp.* su bakterije koje izazivaju ozbiljne respiratorne infekcije, prisutne u vodenim sistemima poput bazena, lječilišta i spa centara. Prisutnost teških metala (željezo, mangan, cink, bakar) može smanjiti efikasnost dezinfekcije i filtracije, stvarajući povoljne uvjete za njihov rast.

Cilj: Procijeniti uticaj koncentracija teških metala na pojavu *Legionella spp.* u vodi objekata u Federaciji Bosne i Hercegovine.

Materijali i metode: Analiza je obuhvatila mikrobiološku detekciju *Legionella spp.* prema BAS EN ISO 11731:2018 metodi, koristeći membransku filtraciju i selektivne agare. Koncentracije teških metala određene su metodom plamene atomske apsorpcijske spektrofotometrije. Uzorci su prikupljeni i obrađeni uz osiguranje kvaliteta u akreditiranim laboratorijima prema ISO 17025:2018 standardu.

Rezultati: Od analiziranih uzoraka *Legionella spp.* je otkrivena u 28,3% uzoraka. Prosječne koncentracije teških metala u pozitivnim uzorcima bile su: željezo 57,78±41,25 µg/L, mangan 4,97±4,19 µg/L, cink 3,40±2,12 µg/L, bakar 45,03±35,27 µg/L. Statistički značajne razlike između pozitivnih i negativnih uzoraka zabilježene su za željezo ($p<0,001$), mangan ($p=0,0004$) i bakar ($p=0,0077$), dok za cink nije utvrđena značajna razlika ($p=0,7921$).

Zaključak: Visoke koncentracije teških metala značajno koreliraju s prisutnošću *Legionella spp.* u vodi, posebno željeza, mangana i bakra. Redovni monitoring, kontrola teških metala i optimalna dezinfekcija ključni su za prevenciju *Legionella spp.* i sigurnost korisnika bazena, lječilišta i spa centara.

Ključne riječi: *Legionella spp.*, teški metali, bazenska voda

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THE IMPACT OF HEAVY METALS ON THE PRESENCE OF *LEGIONELLA SPP.* IN POOL, SPA, AND HEALTH RESORT WATER IN THE FEDERATION OF BOSNIA AND HERZEGOVINA

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ABSTRACT

Introduction: *Legionella spp.* are bacteria that cause serious respiratory infections and are present in water systems such as pools, health resorts, and spas. The presence of heavy metals (iron, manganese, zinc, copper) can reduce the efficiency of disinfection and filtration, creating favorable conditions for their growth.

Objective: To assess the impact of heavy metal concentrations on the occurrence of *Legionella spp.* in water from facilities in the Federation of Bosnia and Herzegovina.

Materials and Methods: The analysis included microbiological detection of *Legionella spp.* using the BAS EN ISO 11731:2018 method, employing membrane filtration and selective agars. Heavy metal concentrations were determined using flame atomic absorption spectrophotometry. Samples were collected and processed with quality assurance in accredited laboratories according to the ISO 17025:2018 standard.

Legionella spp. was detected in 28.3% of the samples analyzed. The average concentrations of heavy metals in positive samples were: iron 57.78±41.25 µg/L, manganese 4.97±4.19 µg/L, zinc 3.40±2.12 µg/L, copper 45.03±35.27 µg/L. Statistically significant differences between positive and negative samples were observed for iron ($p<0.001$), manganese ($p=0.0004$), and copper ($p=0.0077$), while no significant difference was found for zinc ($p=0.7921$).

Conclusion: High concentrations of heavy metals significantly correlate with the presence of *Legionella spp.* in water, particularly iron, manganese, and copper. Regular monitoring, control of heavy metals, and optimal disinfection are essential for the prevention of *Legionella spp.* and the safety of pool, spa, and health resort users.

Key words: *Legionella spp.*, heavy metals, pool water

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FENOTIPSKA REZISTENCIJA IZOLATA *ESCHERICHIA COLI* PORIJEKLOM IZ LOKALNIH VODOVODA

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SAŽETAK

Brojna istraživanja ukazuju da je vodeni okoliš rezervoar multirezistentnih bakterija, gena otpornosti i mobilnog genetskog materijala. Prema navodima Svjetske zdravstvene organizacije (WHO - World Health Organization) 80% svih bolesti u svijetu prouzrokovano je zagađenom vodom ili nedostupnošću pitkoj vodi. Ispitivanje antimikrobne osjetljivosti izolata *Escherichia coli* iz lokalnih sistema vodoopskrbe, na području Zeničko-Dobojskog kantona (ZDK), imalo je za cilj utvrdi prevalencu antimikrobne rezistencije, prevalencu multirezistentih sojeva i eventualnu sumnju na ESBL producirajuće sojeve (Extended-spectrum beta-lactamase). Antimikrobna osjetljivost ispitana je disk difuzionom metodom na 22 antibiotika iz 10 grupa antimikrobnih sredstava, a dvostruki disk-sinergički test (DDST) korišten je za ispitivanje prisustva sumnjivih ESBL sojeva. Ukupno je izolovano 50 sojeva *E. coli* od kojih je 78% (n=39) pokazlao osjetljivost prema svim testiranim antibioticima, 18% je ispoljilo rezistenciju na jednu grupu antimikrobnih srdstava, 2% na dvije grupe i 2% na sedam grupa antibiotika. Najčešća rezistencija (42% izolata) ispoljena je prema β-laktamskim antibioticima, i to ukupno 34% na cefalosporine, 6% na amoksicilin u kombinaciji sa klavulanskom kisilinom i 2% na aztreonam. Ukupno 6% izolata ispoljilo je rezistenciju na tracikline, 4% na fluorokinolone i 2% na hloramfenikole, kao i na kombinovane sulfonamide i streptogramine. Obrazac rezistencije multirezistentnog soja obuhvatio je otpornost na β–laktamske antibiotike, tertracikline, polimiksine, kombinovane sulfonamide, aminoglikozide i streptogramine. Rezultati DDS testa, kod ovog izolata, ukazuju na prisutnost betalaktamaza proširenog spektra zbog čega ne smijemo zanemariti rizik prenosa antimikrobne rezistencije u vodenom okolišu. Možemo zaključiti da vode iz lokalnih sistema vodoopskrbe često ne ispunjavaju mikrobiološke kriterije propisane Pravilnikom o zdravstvenoj ispravnosti vode za piće, zbog čega predstavljaju veliki javnozdravstveni problem. Nedovoljna snabdjevenost stanovništva ZDK zdravstveno ispravnom vodom za piće predstvalja rizik po zdravlje ljudi, a osim ovog lokalnog problema predstavlja i globalni problem zbog mogućnosti horizontalnog prenosa rezistentnih gena. Rješavanje ovog problema trebao bi biti jedan od pripritetnih zadataka općinskih i kantonalnih vlasti ZDK.

Ključne riječi: Multirezistencija, vodeni okoliš, „Jedno zdravlje"

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PHENOTYPIC RESISTANCE OF ESCHERICHIA COLI ISOLATES ORIGINATING FROM LOCAL WATER SUPPLY SYSTEMS

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ABSTRACT

Numerous studies suggest that the aquatic environment serves as a reservoir of multi-drug-resistant bacteria, resistance genes, and mobile genetic material. According to the World Health Organization (WHO), 80% of all diseases worldwide are caused by contaminated water or lack of access to potable water. This study aimed to determine the prevalence of antimicrobial resistance, the prevalence of multidrug-resistant strains, and the potential presence of extended-spectrum beta-lactamase (ESBL)-producing strains among Escherichia coli isolates from local water supply systems in the Zenica-Doboj Canton (ZDC). Antimicrobial susceptibility was tested using the disk diffusion method on 22 antibiotics from 10 groups of antimicrobial agents, while the double-disk synergy test (DDST) was used to detect suspected ESBL-producing strains. A total of 50 E. coli strains were isolated, of which 78% (n=39) were sensitive to all tested antibiotics, 18% showed resistance to one group of antimicrobials, 2% to two groups, and 2% to seven groups of antibiotics. The most common resistance (42% of isolates) was observed against β-lactam antibiotics, with 34% showing resistance to cephalosporins, 6% to amoxicillin combined with clavulanic acid, and 2% to aztreonam. Overall, 6% of isolates were resistant to tetracyclines, 4% to fluoroquinolones, and 2% to chloramphenicol, as well as to combined sulfonamides and streptogramins. The resistance pattern of the multidrug-resistant strain included resistance to β-lactam antibiotics, tetracyclines, polymyxins, combined sulfonamides, aminoglycosides, and streptogramins. Results of the DDST for this isolate suggest the presence of extended-spectrum beta-lactamases, highlighting the risk of antimicrobial resistance transmission in aquatic environments. We conclude that water from local water supply systems often fails to meet microbiological criteria outlined in the Ordinance on the Health Safety of Drinking Water, posing a significant public health issue. The insufficient supply of safe drinking water for the ZDC population represents a health risk and, in addition to being a local issue, poses a global concern due to the potential for horizontal transfer of resistance genes. Addressing this problem should be one of the priority tasks for municipal and cantonal authorities in ZDC.

Key words: Multidrug-resistant, aquatic environment, „One health"

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KORELACIJA IZMEĐU PRISUSTVA POLONIJUMA-210 U DUVANSKOM DIMU I UČESTALOSTI KARCINOMA PLUĆA

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SAŽETAK

Polonijum-210 (Po-210) je radioaktivni izotop koji nastaje kao posljedica sagorjevanja duvana, pri čemu se oslobađa u obliku aerosola i čestica koje se mogu inhalirati i dospjeti direktno u pluća. Zbog emisije alfa-čestica, Po-210 izaziva ozbiljna oštećenja tkiva i DNK te stvara ozbiljne zdravstvene rizike za pušače, uključujući rizik razvoja karcinoma pluća. Istraživanja su pokazala da Po-210 ne samo da doprinosi razvoju karcinoma pluća, već uzrokuje i promjene histološkog tipa bolesti, dovodeći do povećane učestalosti adenokarcinoma u odnosu na skvamozni karcinom. Ova promjena može biti rezultat povećane izloženosti radioaktivnim česticama, što dodatno komplikuje dijagnostiku i liječenje. Podaci o incidenciji i mortalitetu karcinoma za 2020. godinu, koje je pripremila Međunarodna agencija za istraživanje raka (IARC) u okviru projekta GLOBOCAN, pokazuju da karcinom pluća i dalje predstavlja vodeći uzrok smrti od karcinoma, sa procijenjenih 1,8 miliona smrtnih slučajeva globalno (18%) u 2020. godini. Podaci Instituta za javno zdravstvo Republike Srpske za period 2016–2020. godine pokazuju da je stopa smrtnosti od karcinoma pluća znatno viša kod muškaraca nego kod žena. Najviša stopa smrtnosti kod muškaraca zabilježena je 2016. godine (41,6/100.000), dok je kod žena najviša stopa registrovana 2017. godine (11,6/100.000). S druge strane, podaci o klinički liječenim pacijentima pokazuju kontinuirani porast broja oboljelih od karcinoma pluća u periodu 2021–2023. godine. Ukupan broj oboljelih porastao je sa 4.062 u 2021. godini na 4.868 u 2023. godini, pri čemu je značajno veći broj oboljelih muškaraca u odnosu na žene (68% naprema 32%). Uzimajući u obzir navedeni porast učestalosti karcinoma pluća, potrebno je podrobnije istražiti uticaj Po-210, sa ciljem razvoja efikasnijih preventivnih mjera i strategija liječenja, što može značajno poboljšati javno zdravlje.

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CORRELATION BETWEEN THE PRESENCE OF THE POLONIUM-210 IN TOBACCO SMOKE AND THE INCIDENCE OF LUNG CANCER

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ABSTRACT

Polonium-210 (Po-210) is a radioactive isotope that is released as a result of tobacco combustion, forming aerosols and particles that can be inhaled and directly reach the lungs. Due to its emission of alpha particles, Po-210 causes severe tissue and DNA damage, posing significant health risks to smokers, including an increased risk of developing lung cancer. Research has shown that Po-210 not only contributes to the development of lung cancer but also causes changes in the histological type of the disease, leading to a higher incidence of adenocarcinoma compared to squamous cell carcinoma. This shift may result from increased exposure to radioactive particles, further complicating diagnosis and treatment. Data on cancer incidence and mortality for 2020, prepared by the International Agency for Research on Cancer (IARC) as part of the GLOBOCAN project, indicate that lung cancer remains the leading cause of cancer-related death, with an estimated 1.8 million deaths globally (18%) in 2020. Data from the Public Health Institute of the Republic of Srpska for the period 2016–2020 show that lung cancer mortality rates are significantly higher in men than in women. The highest mortality rate among men was recorded in 2016 (41.6/100,000), while the highest rate for women was observed in 2017 (11.6/100,000). On the other hand, data on clinically treated patients show a continuous increase in the number of lung cancer cases during the period 2021–2023. The total number of cases rose from 4,062 in 2021 to 4,868 in 2023, with a significantly higher proportion of male patients compared to female patients (68% versus 32%). Given the observed increase in lung cancer incidence, it is essential to further investigate the impact of Po-210 to develop more effective preventive measures and treatment strategies, which could significantly improve public health outcomes.

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VAŽNOST MINERALA ZA LJUDSKI ORGANIZAM

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SAŽETAK

Uvod: Za mnoge procese u organizmu su neophodni minerali, a svakodnevnim unosom hrane koja nije zdrava sve više se gubi tih bitnih nutrijenata. Minerali i vitamini potrebni su za: rast, razvoj, izgradnju kostiju, energiju, pravilan rad bubrega,mišića i nerava, transport kiseonika kao i mnoge druge metaboličke procese koji su međusobno povezani. Nedostatak minerala ima loš uticaj na ljudsko zdravlje.

Cilj rada: Naučnim pregledom literature **(**izdvajanjem ključnih studija, kodiranjem izdvojenih studija i tumačenjem evidencije) utvrditi važnost minerala za ljudski organizam. Da li treba unositi minerale na preporuku TV reklama i farmako industrije ili za upotrebu minerala treba konsultacija liječnika ili nutricioniste.

Materijal i metode: Istraživački dio rada je oblikovan kao neeksperimentalno kvalitativno istraživanje (naučni pregled literature) koji tumači značajnost minerala za ljudski organizam, kao i štetno djeleovanje na organizam kod pretjeranog unosa minerala.

Rezultati: U radu je prikazano 10 studija koje govore o značajnosti minerala za organizam u: dječijem uzrastu, srednjoj životnoj dobi u starosti, važnost minerala kod trudnica kao i kod osoba oboljelih od dijabetesa. Prikazana je značajnost minerala kroz ishranu. Tokom trudnoće povećane su nutritivne potrebe, s toga se trebaju uključivati suplementi da bi se spriječili razni defekti kod novorođenčadi. Prikazana je važnost magnezija posebno kod osoba pri aerobnoj tjelesnoj aktivnosti. Istakla se važnost hepcidina koji se smatra regulatorom ravnoteže željeza. Koncentracije Cu, Fe, Mo, Se i Zn u venskoj krvi majke u prosjeku su bile 2,156, 2,020, 13, 102 i 656 μg/L kod kontrolne grupe žena (n=17), dok je u grupi dijabetičara (n=14), odgovarajuće vrijednosti za elemente u tragovima su u prosjeku iznosile 3,135, 3,675, 15, 85 i 628 μg/L retrospektivno. Vrijednosti bakra i molibdena bile su značajno veće ($p<0,05$) u ispitivanoj grupi u odnosu na kontrolnu grupu. U skupini analiziranih osoba u postmenopauzi uočena je nepravilno uravnotežena prehrana. Navedeno je da dnevni unos svih procijenjenih minerala nije bio ovisan o BMI za ženske jedinke u postmenopauzi, ali je gustoća hranjivih tvari u prehrani(za natrij, kalij i magnezij) povezana s BMI.

Zaključak: Kroz ovaj rad naučnici su dokazali i ukazali na značaj upotrebe minerala

kroz ishranu. Upoznali smo se sa izvorima minerala, njihovim značajem za naše zdravlje, rast i pravilan razvoj. Takodje smo ukazali na posljedice prekomjernog unosa minerala, kao i nedostatka. . Upotreba minerala sve više dobiva na značenju u preventivi, ali i terapiji određenih bolesti i stanja. Kako bi se smanjili toksični učinci i štetno djelovanje minerala u dodacima prehrani, potrebno je savjetovati se s farmaceutom ili ljekarom prije njihova korištenja.

Ključne riječi: minerali, ljudski organizam, značaj

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THE IMPORTANCE OF MINERALS FOR THE HUMAN BODY

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ABSTRACT

Introduction: Minerals are necessary for many processes in the body, and with the daily intake of unhealthy food, more and more of these essential nutrients are lost. Minerals and vitamins are necessary for: growth, development, bone building, energy, proper functioning of kidneys, muscles and nerves, oxygen transport as well as many other metabolic processes that are interconnected. Lack of minerals has a bad effect on human health.

The aim of the work: to determine the importance of minerals for the human body through a scientific review of the literature (selecting key studies, coding selected studies and interpreting records). Do you need to take minerals on the recommendation of TV commercials and the pharmaceutical industry, or do you need to consult a doctor or nutritionist to use minerals?

Material and methods: The research part of the paper is designed as a non-experimental qualitative research (scientific review of the literature) that interprets the importance of minerals for the human body, as well as the harmful effects on the body of excessive intake of minerals.

Results: The paper presents 10 studies that talk about the importance of minerals for the body in: children's age, middle life in old age, the importance of minerals in pregnant women as well as in people suffering from diabetes. The importance of minerals through nutrition is shown. During pregnancy, nutritional needs are increased, with this supplements should be included to prevent various defects in newborns. The importance of magnesium, especially in people with aerobic physical activity, is shown. The importance of hepcidin, which is considered a regulator of iron balance, was highlighted. Concentrations of Cu, Fe, Mo, Se and Zn in maternal venous blood were on average 2,156, 2,020, 13, 102 and 656 μg/L in the control group of women (n=17), while in the group of diabetics (n=14) , the corresponding values for trace elements averaged 3.135, 3.675, 15, 85 and 628 μg/L retrospectively. Copper and molybdenum values were significantly higher ($p<0.05$) in the tested group compared to the control group. An improperly balanced diet was observed in the analyzed group of

postmenopausal people. It was stated that the daily intake of all assessed minerals was not dependent on BMI for postmenopausal women, but the density of nutrients in the diet (for sodium, potassium and magnesium) was related to BMI.

Conclusion: Through this work, scientists have proven and pointed out the importance of using minerals through nutrition. We got acquainted with the sources of minerals, their importance for our health, growth and proper development. We also pointed out the consequences of excessive intake of minerals, as well as a lack of them. The use of minerals is becoming more and more important in the prevention and treatment of certain diseases and conditions. In order to reduce the toxic effects and harmful effects of minerals in dietary supplements, it is necessary to consult a pharmacist or doctor before using them.

Key words: minerals, human organism, significance

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ISHOD IVF POSTUPKA KOD PACIJENTICA SA POVIŠENIM VRIJEDNOSTIMA FSH

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SAŽETAK

Cilj ovog rada je prikazat ishod vantjelesne oplodnje u ovisnosti od vrijednosti FSH hormona. Poznato je da je FSH indirektni pokazatelj funkcije jajnika. Njegove vrijednosti osciliraju unutar menstrualnog ciklusa, a često je u direktnoj koorelaciji sa godinama žene. Dokazano je da su vrijednosti veće što su ovarijalne rezerve manje, a shodno godinama vrijednosti su također veće kod starijih žena. Jos uvijek nije klinički potvrđeno koja je idealna vrijednosti FSH da bi se započeo postupak stimulacije jajnika. U praksi je dokazano da žene sa nižim vrijednostima FSH imaju bolji odgovor na terapiju stimulacije jajnika, da je potrebna manja doza lijekova za stimulaciju, te da je broj jajnih stanica veći. Nažalost, sve veći broj žena koje ulaze u postupka IVF-a su u kritičnoj starosnoj skupini, što za posljedicu imamo lošije vrijednosti FSH-a. U ovom radu cemo prikazati dvije skupine ispitanica. Prva skupina će biti 30 pacijentica koje su imale FSH manji od 17 mlIU, a drugu skupinu cine isti broj ispitanica sa FSH >17 mIU. Prikazat cemo učestalost i vrste protokola za stimulaciju, ukupno potrošenu hormonalnu terapiju po stimuliranom ciklusu, dužina trajanja stimulacije, broj dobivenih jajnih stanica nakon punkcije, zrelost iistih, te krajnji ishod samog postupka, tj. učestalost trudnoća.

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OUTCOME OF THE IVF PROCEDURE IN PATIENTS WITH ELEVATED FSH VALUES

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ABSTRACT

The aim of this paper is to show the outcome of in vitro fertilization depending on the value of the FSH hormone. FSH is known to be an indirect indicator of ovarian function. Its values oscillate within the menstrual cycle, and it is often in direct correlation with the age of the woman. It has been proven that the values are higher when the ovarian reserves are smaller, and according to age, the values are also higher in older women. It is still not clinically confirmed what is the ideal FSH value to start the ovarian stimulation procedure. In practice, it has been proven that women with lower FSH values have a better response to ovarian stimulation therapy, that a smaller dose of stimulation drugs is needed, and that the number of egg cells is higher. Unfortunately, an increasing number of women entering IVF procedures are in the critical age group, which results in worse FSH values. In this paper, we will present two groups of respondents. The first group will be 30 patients who had FSH less than 17 mlIU, and the second group will consist of the same number of patients with FSH >17 mIU. We will present the frequency and types of stimulation protocols, the total amount of hormonal therapy consumed per stimulated cycle, the duration of stimulation, the number of oocytes obtained after puncture, the maturity of the oocytes, and the final outcome of the procedure itself, i.e. frequency of pregnencies.

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LABORATORIJSKE TEHNOLOGIJE U HUMANOJ REPRODUKCIJI

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SAŽETAK

Neplodnost je ozbiljan globalni medicinski problem. Stajališta o reprodukciji veoma su se promijenila, kako u svijetu, zapadnim zemljama, tako i kod nas. Izuzev cijelog niza medicinskih faktora koji bitno doprinose neplodnosti, veliku ulogu imaju i različiti nemedicinski faktori: socijalni i ekonomski faktori, te današnji brzi način života.

Svjetska zdravstvena organizacija (SZO) definiše neplodnost kao stanje tokom kojeg spolno aktivni muškarac i žena ne uspijevaju začeti dijete, a da pritom ne koriste kontraceptivna sredstva u razoblju od jedne godine.

Etiološki razlikujemo pretestikularne, testikularne i posttestikularne uzroke neplodnosti. Pretestikularne razloge nalazimo u poremećenoj osovini hipotalamus – hipofiza – testis pri čemu posljedično dolazi do smanjene sinteze testosterona i poremećaja spermatogeneze. Testikularni uzroci odnose se na patološke promjene u testisu te čine polovinu svih uzroka neplodnosti, a najčešće se radi o varikoceli, kriptorhizmu, Klinefelterovom sindromu. Posttestikularni uzroci obuhvataju ona stanja koja ometaju odvod spermija od testisa do uretre, a mogu biti na nivou funkcije spermatozoida, kanalnog sistema, ejakulacije ili erekcije . Dijagnostika neplodnosti temelji se na anamnezi, kliničkom pregledu, hormonskom statusu, analizi ejakulata, radiološkim pretragama, biopsiji testisa.

Analiza ejakulata (spermiogram) je najvažniji dijagnostički parameter.

Ejakulat se prikuplja u sterilnu bočicu, kvaliteta spermatozoida je održiva je u rasponu od 20ºC do 37ºC. Ejakulat je najbolje dati nakon apstinencije od tri do pet dana jer je tada kvaliteta spermatozoida najbolja.

Analiza podliježe makroskopskom i mikroskopskom pregledu.

Svrha evaluacije muške neplodnosti je otkriti ireverzibilne uzroke i liječiti ih.

Ključne riječi: Muška neplodnost, pretestikularni uzroci, testikularni uzroci, posttestikularni uzroci, spermiogram

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IMPORTANCE AND ROLE OF LABORATORY TECHNOLOGIES IN HUMAN REPRODUCTION

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ABSTRACT

Infertility is a serious global medical problem. Attitudes about reproduction have changed a lot, both in the world, in Western countries, and in our country. Apart from a whole series of medical factors that significantly contribute to infertility, various non-medical factors also play a major role: social and economic factors, and today's fast-paced lifestyle.

The World Health Organization (WHO) defines infertility as a condition in which a sexually active man and woman fail to conceive a child without using contraceptives within one year.

Etiologically there are pretesticular, testicular and posttesticular causes of infertility. Pretesticular causes are related to hypothalamus – pituitary axis disturbance, resulting in insufficient testosteron production or abnormal spermatogenesis. The testicular causes are related to pathological changes in the testicle. Varicocele, cryptorhism, Klinefelter syndrome are the most common testicular reason for infertility. Posttesticular causes include conditions that interfere with sperm transport from the testicle to the urethra, and can be due to sperm motility malfunction, duct obstruction, disorders of ejaculation or due to erectile dysfunction. Diagnosis of infertility is based on anamnesis, clinical examination, hormonal status, semen analysis, radiological examinations, testicular biopsy.

The semen analysis is the most important diagnostic parameter.

The ejaculate is collected in a sterile bottle, the sperm quality is sustainable in the range from 20ºC to 37ºC. The ejaculate is best given after abstinence for three to five days because then the sperm quality is the best.

The analysis is subject to macroscopic and microscopic examination.

The purpose of male infertility evaluation is to detect irreversible causes and treat them.

Key words: Men infertility, pretesticular causes, testicular causes, posttesticular causes, semen analysis;

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NOVE SMJERNICE EVROPSKOG KARDIOLOŠKOG UDRUŽENJA- UTICAJ NA LABORATORIJSKU PRAKSU

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SAŽETAK

Arterijska hipertenzija ostaje vodeći uzrok smrti u većini zemalja u svijetu. Smjernice donose brojne novosti, od kojih su neke značajne i za laboratorijsku praksu. Izdvajamo najvažnije: Prema novim smjernicama evropskog kardiološkog udruženja broj pacijenata se povećao, jer je granica normale spuštena i mnogi pacijenti koji su do sad smatrani urednim ulaze u kategoriju hipertoničara. Visoki nivoi lipida, posebno LDL, doprinosu razvoju ateroskleroze. Preporuke ESC-a ističu važnost rano prepoznavanje povišenih razina glukoze jer visoka koncentracija glukoze u krvi (hiperglikemija) dugoročno može dovesti do brojnih kardiovaskularnih komplikacija, uključujući bolesti srca, moždani udar i periferne vaskularne bolesti. Elektroliti se često analiziraju zajedno s hormonima (kao što su aldosteron, renin i kortizol), jer hormonalni disbalansi mogu izazvati promjene u ravnoteži elektrolita, što zauzvrat može povećati krvni pritisak. Na primjer, hiperaldosteronizam može dovesti do zadržavanja natrijuma i smanjenja kalijuma, što doprinosi hipertenziji. Uključivanje testova za funkciju štitne žlijezde u rutinske preglede hipertenzivnih pacijenata ključno je za holistički pristup liječenju i prevenciji kardiovaskularnih komplikacija.

Ključne riječi: Evropsko kardiološko udruženje (ESC), hipertenzija, LDL holesterol, Hiperglikemija; Elektroliti, Aldosteron, Renin, Kortizol, Hiperaldosteronizam, Funkcija štitne žlijezde, Laboratorijska praksa

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NEW GUIDELINES FROM THE EUROPEAN SOCIETY OF CARDIOLOGY – IMPACT ON LABORATORY PRACTICE

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ABSTRACT

Arterial hypertension remains the leading cause of death in most countries worldwide. The guidelines introduce several updates, some of which are significant for laboratory practice. We highlight the most important points: According to the new guidelines from the European Society of Cardiology (ESC), the number of patients has increased as the normal blood pressure threshold has been lowered, and many patients who were previously considered normal now fall into the category of hypertensives. High lipid levels, particularly LDL, contribute to the development of atherosclerosis. The ESC guidelines emphasize the importance of early recognition of elevated blood glucose levels, as high glucose concentration in the blood (hyperglycemia) can lead to numerous cardiovascular complications in the long term, including heart disease, stroke, and peripheral vascular diseases. Electrolytes are often analyzed alongside hormones (such as aldosterone, renin, and cortisol), as hormonal imbalances can cause changes in electrolyte balance, which in turn can increase blood pressure. For example, hyperaldosteronism can lead to sodium retention and potassium depletion, contributing to hypertension. Including thyroid function tests in routine screening of hypertensive patients is crucial for a holistic approach to the treatment and prevention of cardiovascular complications.

Keywords: European Society of Cardiology (ESC), hypertension, LDL cholesterol, hyperglycemia, electrolytes, aldosterone, renin, cortisol, hyperaldosteronism, thyroid function, laboratory practice.

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UTICAJ LIJEČENJA HEMODIJALIZOM BOLESNIKA SA BUBREŽNOM INSUFICIJENCIJOM NA NIVOE KALCIJA,KALIJA,FOSFORA I ALKALNE FOSFATAZE

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SAŽETAK

Hronična bubrežna insuficijencija, sa prevalencom od oko 9 - 13% značajno doprinosi svjetskom morbiditetu i mortalitetu od nezaraznih bolesti, te je nezavisni faktor rizika razvoja kardiovaskularnih bolesti i to u svim fazama bolesti. Hemodijaliza je jedan od najčešćih terapeutskih postupka nadomještanja bubrežne funkcije u pacijenata sa hroničnom bubrežnom insuficijencijom. Ipak, morbiditet i moralitet tako liječenih bolesnika i dalje je visok, a vodeći uzrok smrtnosti su kardiovaskularne bolesti i hiperkalemija. Mineralno koštana pregradnja jedna je od komplikacija višegodišnje terapije dijalizom koja se manifestuje biohemijskim poremećajima uključujući kalcij, fosfor, PTH, vitamin D, te patološkim kalcifikacijama koje za posljedicu imaju kardiovaskularne bolesti. Osnovni cilj našeg istraživanja bio je utvrditi serumske koncentracije kalcija, kalija, fosfora i alkalne fosataze u bolesnika sa hroničnom bubrežnom insuficijencijom liječenih hemodijalizom prije početka terapije i u okviru posljednje biohemijske obrade, te utvrditi promjene navedenih parametara ovisno o dužini trajanja liječenja hemodijalizom.

Istraživanje je provedeno kao „case control" studija u koju je bilo uključeno 40 pacijenata sa hroničnom bubrežnom insuficijencijom na dugotrajnom liječenju hemodijalizom u hemodijaliznom centru JZU Opća bolnica "dr. Mustafa Beganović" Gračanica. Vrijednosti kalcija, kalija, fosfora i alkalne fosfataze određivane su u serumu pacijenata prilikom posljednje rutinske biohemijske obrade pacijenta. Kao kontrolni uzorci korištene su serumske vrijednosti kalcija, kalija, fosfora i alkalne fosfataze istih pacijenata određene prije početka liječenja, a uzete iz medicinske dokumentacije. Za statističku obradu podataka korišteni su Wilcoxon-ov test za zavisni uzorak i Spearmanov test korelacije primjenom SPSS/WIN programa (Release 26.0, SPSS Inc., Chicago, IL, USA.).

Utvrđeno je da je došlo do statistički značajnog povećanja koncentracija Ca (p=0,002), K (p=0,001) i ALP (p=0,014) u odnosu na vrijednosti utvrđene prije početka liječenja hemodijalizom, ali ne i statistički značajna promjena u koncentracijama P u odnosu na početak terapije. Takođe, rezultati su pokazali statistički značajnu korelaciju nivoa ALP sa dužinom terapije (p=0,001).

Dobiveni rezultati mogu doprinijeti boljem razumijevanju biohemijskih promjena mineralno koštanog metabolizma u pacijenata sa hroničnom bubrežnom insuficijencijom liječenih hemodijalizom.

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INFLUENCE OF HEMODIALYSIS TREATMENT OF PATIENTS WITH RENAL FAILURE ON THE LEVELS OF CALCIUM, POTASSIUM, PHOSPHORUS AND ALKALINE PHOSPHATASE

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ABSTRACT

Chronic renal failure, with a prevalence of about 9-13%, significantly contributes to global morbidity and mortality from non-communicable diseases, and it is an independent risk factor for the development of cardiovascular disease in all stages of the disease. Dialysis is one of the most common therapeutic procedures for renal function replacement in patients with chronic renal failure. Nevertheless, the morbidity and mortality of such treated patients remains high, and the leading causes of mortality are cardiovascular disease and hyperkalemia. Mineral bone remodeling is one of the complications of long-term dialysis therapy, which is manifested by biochemical disorders including calcium, phosphorus, PTH, vitamin D, and pathological calcifications that result in cardiovascular disease. The primary aim of our study was to determine serum concentrations of calcium, potassium, phosphorus and alkaline phosphatase in patients with chronic renal failure treated with hemodialysis before therapy and during the last biochemical treatment, and to determine changes in these parameters depending on the duration of hemodialysis treatment.

The study was conducted as a "case control" study involving 40 patients with chronic renal failure on long-term hemodialysis treatment at the hemodialysis center PHI General Hospital "Dr. Mustafa Beganović" Gračanica. Calcium, potassium, phosphorus and alkaline phosphatase values were determined in the serum of the patients during the last routine biochemical treatment of the patient. Serum values of calcium, potassium, phosphorus and alkaline phosphatase of the same patients determined before the start of treatment and taken from medical documentation were used as control samples. Wilcoxon's dependent sample test and Spearman's correlation test using the SPSS / WIN program (Release 26.0, SPSS Inc., Chicago, IL, USA) were used for statistical data processing.

Obtained results showed that there was a statistically significant increase in the concentrations of Ca ($p = 0.002$), K ($p = 0.001$) and ALP ($p = 0.014$) compared to values determined before the start of hemodialysis treatment, but no statistically significant change in P concentrations in relationto the start of therapy. Also, the results showed a

statistically significant correlation of ALP levels with the length of therapy ($p = 0.001$).

The obtained results may contribute to a better understanding of biochemical changes in bone mineral metabolism in patients with chronic renal failure treated with hemodialysis.

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