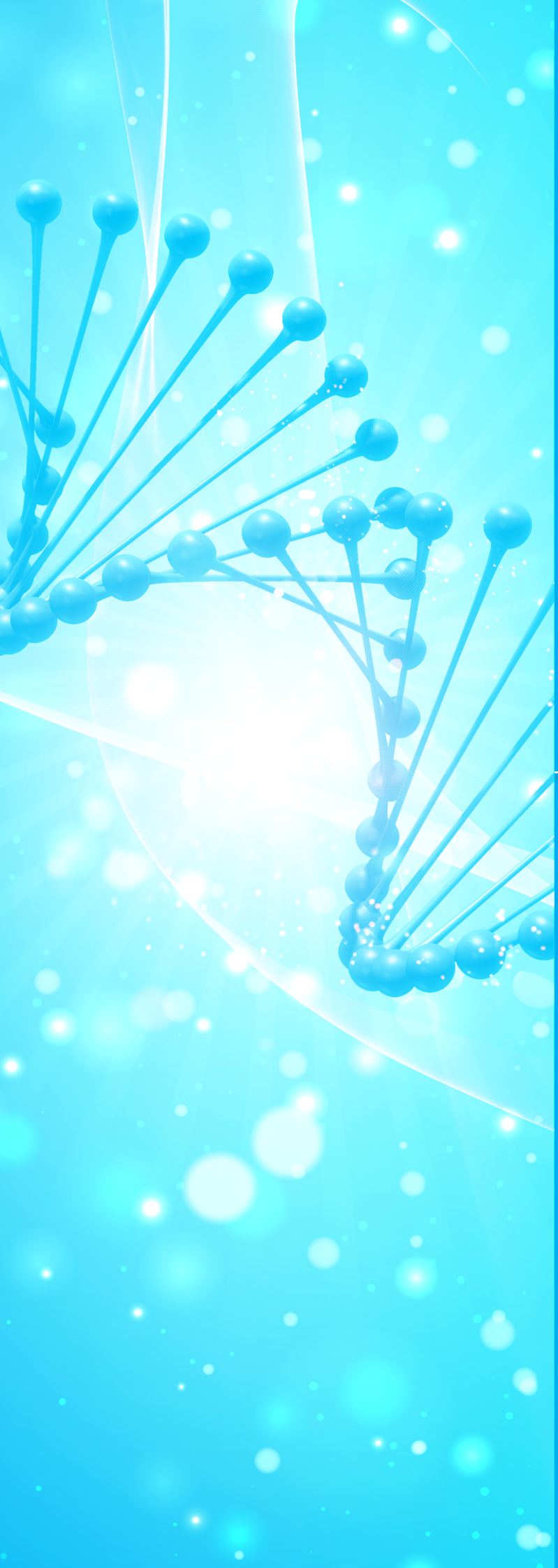

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NAUKA O MEDICINSKOJ MARIHUANI I IZAZOVI U ISTRAŽIVANJU

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SAŽETAK

Endokanabinoidi su retrogradni neurotransmiteri na bazi lipida koji se vežu za kanabinoidne receptore, od kojih su trenutno dva opisana: CB1 i CB2. Dve glavne aktivne komponente kanabisa su tetrahidrokanabinol (THC) i kanabidiol (CBD), koji se na različite načine vežu za receptore, time omogućavajući različite sistemske efekte, kao i modifikaciju sopstvenih efekata. Zbog ovih različitih osobina, terapijski efekat marihuane direktno zavisi od srazmere THC: CBD u određenoj formulaciji. Trenutno se sintetički i proizvodi nastali iz kanabisa koje je odobrila Uprava za hranu i lekove Sjedinjenih Američkih Država koriste za lečenje epileptičnih napada, mučnine izazvane hemoterapijom, i anoreksije kod pacijenata sa HIV infekcijom. Istraživanja su pružila dokaze niskog do srednjeg kvaliteta o koristima kanabinoida koji se koriste za lečenje hroničnog neuropatskog bola i bola izazvanog kancerom. Međutim, veliki su izgledi da će se oni koristiti kao alternativa opiodima. Ostaju izazovi u medicinskim istraživanjima kanabisa, naročito u smislu nekonzistentnog hemijskog sastava i izvora, malih uzoraka, slabih kontrola, i kratkog kliničkog istraživanja. Najveće medicinske ustanove pozivaju na rigorozna istraživanja da bi se dalje istražila bezbednost i efikasnost marihuane.

Ključne reči: medicinska marihuana, mehanizmi delovanja, indikacije, bezbednost, efikasnost

Uvod

Korišćenje kanabisa u medicinske svrhe se prvi put pominje u drevnoj kineskoj farmakopeji napisanoj u prvom veku pre nove ere, koja opisuje lekove koji su se koristili tokom prethodna dva milenijuma (1). Reumatski bol, konstipacija, malarija i ginekološki poremećaji bili su navedeni u medicinskoj upotrebi kanabisa. U drevnoj Indiji, kanabis se brzo širio zbog svoje sposobnosti da izazove sreću. Takođe je korišćen za lečenje nesanice, gastrointestinalnih poremećaja i različitih vrsta bolova. Antički Grci i Arapi su koristili kanabis za slične medicinske svrhe, i naglašavali su njegovu efikasnost u borbi protiv upala, edema i reumatizma. Kanabis su u Novi svet doneli robovi iz Južne Amerike u 16. veku, uglavnom zbog njegovih psihoaktivnih efekata. Ubrzo je uvedena upotreba u medicinske svrhe i biljka je korišćena da izazove san i leči napade, reumatizam i urinarne probleme (1,2). Interesovanje za marihuanu u medicinske i rekreativne svrhe je poraslo tokom prethodnih godina, naročito nakon njene legalizacije u 36 država Sjedinjenih Američkih Država, Kanadi i nekoliko zemalja Evrope. U ovom radu su prikazani mehanizmi delovanja, trenutne indikacije i budući pravac istraživanja medicinske marihuane.

Kanabinoidni receptori

Endokanabinoidi su retrogradni neurotransmiteri na bazi lipida koji se vežu za kanabinoidne receptore, od koji su do sada dva opisana: CB1 i CB2 (3). CB1 receptori se nalaze u centralnom nervnom sistemu (CNS): naročito u hipokampusu (koji je odgovoran za kratkoročno pamćenje), korteksu, bazalnim ganglijama (motoričke sposobnosti), malom mozgu (motorička koordinacija), hipotalamusu, limbičkom sistemu, kičmenoj moždini. U mozgu, kanabinoidi utiču na funkcije poput kognitivne, na pamćenje, motoriku i percepciju

ACTUAL TOPIC

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THE SCIENCE BEHIND MEDICAL MARIJUANA AND RESEARCH CHALLENGES

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SUMMARY

Endocannabinoids are lipid-based retrograde neurotransmitters that bind to cannabinoid receptors, two of which are currently described: CB1 and CB2. The two main active components of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD), have differing binding affinities to the receptors, allowing them to mediate different systemic effects as well as modulate each other's effects. Due to these varied properties, the therapeutic effect of marijuana is directly correlated with the THC:CBD ratio in a particular formulation. Current FDA-approved synthetic and cannabis-derived products are indicated for the treatment of nausea induced by chemotherapy, seizure disorders, and anorexia in AIDS patients. Regarding the treatment of chronic neuropathic pain and cancer pain, research has shown a low-to-moderate quality evidence for use of cannabinoids, but greatly promising in providing alternatives to opioids. Challenges in medical research on cannabis remain, particularly in terms of inconsistent chemical composition and sourcing, small sample sizes, poor controls, and short duration of trials. Major medical institutions call for more thorough research and further investigation of marijuana safety and efficacy.

Keywords: medical marijuana, mechanisms of action, indications, safety, efficacy

Introduction

The first reference to a cannabis product use for medicinal purposes was found in ancient Chinese pharmacopoeia, in 1. BC, which describes remedies used over the previous two millennia (1). Among the reported medical uses of cannabis were constipation, rheumatic pain, gynecological disorders, and malaria. In ancient India, cannabis spread rapidly for its ability to elicit happiness. It was also used to treat insomnia, gastrointestinal disorders, and different forms of pain. The ancient Greeks and Arabs used cannabis for similar medicinal purposes, and highlighted its efficacy at fighting inflammation, edema, and rheumatisms. Cannabis was brought into the New World through South America in the 16th century by African slaves, largely for its psychoactive effects. Medicinal uses were soon introduced and the plant was used to induce sleep and treat seizures, rheumatisms, and urinary afflictions (1,2). Interest in marijuana use for both medicinal and recreational purposes has increased in recent years, especially following its legalization in 36 U.S.A. states, Canada, and several European countries. Here, we provide an outline of the mechanisms of action, indications, and future directions of study for medical marijuana.

Cannabinoid receptors

Endocannabinoids are lipid-based neuro-transmitters that bind to cannabinoid receptors retrogradely, of which two are currently described: CB1 and CB2 (3). CB1 receptors are present throughout the central nervous system (CNS): particularly in the hippocampus (responsible for short-term memory), cortex, basal ganglia (motor activity), cerebellum (motor coordination), hypothalamus, limbic system, and spinal cord. In the brain, cannabinoids affect cognition, memory, motor movement, and the perception of pain. This is due to the inhibitory-mediated action of the CB1 receptor's continuous release of many excitatory and inhibitory neurotransmitter systems at the terminals of central and peripheral neurons (4). CB2

bola. Ovo je posledica inhibitorne aktivnosti CB1 receptora koji utiču na dalje oslobađanje jednog broja ekscitatornih i inhibitornih sistema neurotransmitera na vrhovima centralnih i perifernih neurona (4). CB2 receptori su najviše izraženi u imunskim ćelijama: CB2A u B limfocitima, NK ćelijama, monocitima, testisima; CB2B u slezini i gastrointestinalnom sistemu. Ovo ukazuje da kanabinoidi posredstvom receptora imaju specifičan uticaj na imunski sistem, posebno putem CB2 receptora (5).

Kanabidiol i THC

Dve glavne komponente kanabisa su tetrahidrokanabinol (THC) i kanabidiol (CBD). Oni imaju slične efekte u određenim domenima, ali potpuno suprotne u drugim. THC deluje kao delimični agonist CB1 i CB2 receptora. S obzirom da ima osobinu vezivanja sličnu CB1 receptorima, THC se pripisuju psihoaktivne osobine, koje uključuju prolazne psihotičke simptome, kao i povišeni nivo uznemirenosti, intoksikaciju i sedaciju. Takođe, utvrđeno je da THC proizvodi, u zavisnosti od doze, hipoaktivnost, hipotermiju, narušenu prostornu i verbalnu kratkoročnu memoriju (6,7). Analgetsko dejstvo THC-a je dokazano u stanjima poput fibromialgije i reumatoidnog artritisa. Takođe, može da pojača analgetska svojstva opioida (8).

Pokazano je da je CBD efikasan u blokiranju većine efekata THC-a, kada se oba leka daju istovremeno. CBD nije imao značajnog uticaja na ponašanje, ali kada su primenjivani zajedno sprečavao je privremene psihotičke simptome koje je izazvao THC. Anksiolitičko dejstvo CBD-a nastaje zbog njegovog uticaja na limbički i paralimbički sistem (9). Takođe, smatra se da CBD ima antipsihotički efekat, s obzirom da je to potencijalno antipsihotički lek, ali i da je to mogući lek za druga stanja poput inflamacije, dijabetesa, kancera, i neurodegenerativnih bolesti (10). CBD se ne dovodi u vezu sa analgezijom, u stvari, on je u negativnoj korelaciji sa oslobađanjem od nekih oblika bola (11).

Zbog ovih raznolikih svojstava THC-a i CBD-a, terapeutsko dejstvo marihuane je u direktnoj vezi sa sadržajem THC-a u određenoj formulaciji, kao i sa odnosom THC:CBD. Potrebna su dodatna istraživanja da bi se odredio terapijski indeks u smislu doziranja i srazmere THC:CBD. Na primer, u reklamama za većinu proizvoda dostupnih na tržištu se navodi da imaju >15% THC-a, što može biti neodgovarajuće za lečenje neuropatskog bola (12).

S obzirom da je marihuana legalizovana zakonima nekih država u Sjedinjenim Američkim Državama, na tržištu se pojavilo mnoštvo CBD proizvoda izvedenih od marihuane poput CBD ulja u kapima, kapsulama, prehrambenim proizvodima, topikalnim losionima i dijetetskim suplementima. Tvrdnje o dobrobitima ovih proizvoda često su preterane i neosnovane, a variraju od lečenja anksioznosti i nesanice do lečenja demencije i kancera. Uprava za hranu i lekove Sjedinjenih Američkih Država (eng. *FDA*) je osudila dodavanje lekova u prehrambene proizvode za ljude i životinje. FDA je odobrila *Epidiolex* (kanabidiol), CBD lek izveden iz kanabisa za lečenje napada koji se povezuju sa *Lennox-Gastaut* sindromom ili Dravet sindromom kod pacijenata starih dve godine ili više. Takođe, odobrena su još tri sintetička THC leka: *Marinol* (dronabinol), *Syndros* (dronabinol) i *Cesamet* (nabilone). Oni su dostupni uz recept i koriste se za mučninu koja je povezana sa hemioterapijom i za lečenje anoreksije koja se povezuje sa gubitkom težine kod pacijenata koji imaju sidu.

Indikacije i neželjena dejstva

Dokazi srednjeg kvaliteta podržavaju korišćenje kanabinoida za lečenje hroničnog bola i mišićnog spasticiteta, dok je kvalitet dokaza bio nizak za rezultate koji se povezuju sa kanabinoidima u slučaju mučnine i povraćanja u hemoterapiji, dobijanja težine kod HIV infekcije, poremećaja sna i Turetovog sindroma.

Sistematski pregled i meta-analiza medicinske upotrebe kanabisa dati su u studiji koju su sproveli Vajting i saradnici, a koja je uključila 79 kliničkih istraživanja. Većina njih je pokazala poboljšanje simptoma koje se povezuje sa kanabinoidima, ali ova veza nije dostigla statističku značajnost u svim istraživanjima. Najčešće kratkoročne nus pojave kanabinoida bile su vrtoglavica, suva usta, mučnina, zamor, pospanost, euforija, povraćanje, dezorijentisanost, konfuzija, gubitak ravnoteže i halucinacije (13). U Tabeli 1 su sažeto prikazana poznata neželjena dejstva marihuane.

Još jedna negativna posledica marihuane je njeno dejstvo na mlađu populaciju. Dugoročna upotreba kanabisa predstavlja predispoziciju za promene u beloj masi mozga u razvoju. Narušene veze u mozgu kod korisnika kanabisa mogu da

receptors are mostly expressed in immune cells: CB2A in B lymphocytes, NK cells, monocytes, testes; CB2B in the spleen and gastrointestinal system. This suggests that cannabinoids act on the immune system specifically through CB2 receptors (5).

Cannabidiol and THC

The two main components of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). They have similar effects on certain areas while having almost opposite effects in others. THC acts as a partial agonist to both CB1 and CB2 receptors. As a result of its high binding affinity with CB1 receptors, THC is attributed psychoactive properties, which may include transient psychotic symptoms as well as increased levels of anxiety, intoxication, and sedation. THC was also found to produce hypoactivity, hypothermia, spatial and verbal short-term memory impairment depending on the dose (6,7). Analgesic effects of THC have been shown in conditions including fibromyalgia and rheumatoid arthritis. It may also enhance the analgesic properties of opioids (8).

CBD was shown to be efficient in blocking most of the effects of THC, when both drugs were administered together. CBD had no significant effect on behavior, and when administered together it could prevent the temporary psychotic symptoms caused by THC. CBD's anxiolytic effect is produced through its activity on limbic and paralimbic system (9). CBD is also considered to have antipsychotic properties, being considered as a potential antipsychotic medicine, and a possible remedy for other conditions such as diabetes, neurodegenerative diseases, cancer, and inflammation (10). CBD is not associated with analgesia, in fact it has a negative correlation with relief from certain forms of pain (11).

Due to these varied properties of THC and CBD, the therapeutic effect of marijuana is directly correlated with the THC content in a particular formulation, as well as the THC:CBD ratio. More research is needed to determine the safe therapeutic index in terms of dosing and THC:CBD ratio. For example, the majority of products available on the market are advertised as >15% THC, which could be unsuitable for treating neuropathic pain (12).

Since the legalization of marijuana under some USA state laws, markets have seen an expanse of marijuana-derived CBD products such as CBD oil in drops, capsules, food products, topical lotions, and dietary supplements. Claims about the benefits of these products are often exaggerated and unfounded, varying from the treatment of anxiety and insomnia to the treatment of dementia and cancer. The addition of drug products to human and animal food products based on insufficient scientific evidence was condemned by the US Food and Drug Administration (FDA). The FDA approved Epidiolex (cannabidiol), a cannabis-derived CBD drug product for treating seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years and older. Three synthetic THC drug products have also been approved: Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone). The products are available with a prescription for use in nausea associated with chemotherapy side effects and for the treatment of anorexia correlated with weight loss in AIDS patients.

Indications and side effects

There is moderate-quality evidence that supports the use of cannabinoids for treating spasticity and chronic pain, and low-quality evidence supported cannabinoid-associated improvement in chemotherapy induced nausea, increase of appetite in HIV, Tourette's and some sleep disorders.

A systematic review and meta-analysis for the medical use of cannabis performed by Whiting PF et al. included 79 trials. Most of them showed positive progress in symptoms associated with cannabinoids, however, without reaching statistical significance in all included trials. The most common short-term adverse effects with cannabinoids included drowsiness, dizziness, euphoria, fatigue, somnolence, nausea, vomiting, dry mouth, confusion, disorientation, and hallucination(13). Table 1 summarizes the known systemic side effects of marijuana.

Another negative consequence of marijuana is its effect on the younger population. Long-term cannabis use predisposes white matter alterations in the brain as it develops. Cognitive impairment and susceptibility to anxiety, depression, and psychosis may be due to disturbed brain connectivity in chronic users of marijuana (14). Cannabis utilization during imperative phrases of

Tabela 1. Sistemski neželjeni efekti inhalacije marihuane

Kardiovaskularni	Povećana stopa infarkta miokarda; Povezanost sa povećanim kardiovaskularnim mortalitetom (18).
Cerebrovaskularni	Moždani udar (19); Prolazni ishemijski napad.
Gastrointestinalni	Kada se marihuana koristi na dnevnoj osnovi to je faktor rizika za razvoj fibroze jetre kod pacijenata sa virusnim hepatitisom C, uprkos činjenici da se marihuana nekada preporučuje pacijentima sa virusnim hepatitisom C (20,21).
Respiratorni	Hronični kašalj i bronhitis; Inhalacija pirolitičkih nus proizvoda; Povećani rizik za pneumoniju kod imunokompromitovanih pacijenata (22).
Reproduktivni	Sprečava oogenezu; Povezuje se sa atrofijom testisa; Povezuje se sa abnormalnom pokretljivošću spermatozoida; Delta-9-THC blokira oslobađanje LHRH iz hipotalamusa, i proizvodnju LH iz adenohipofize (23). THC prolazi kroz placentu. Prenatalna izloženost kanabisu se povezuje sa redukcijom rasta fetusa (24).

budu osnova za kognitivna oštećenja i osetljivost na psihoze, depresiju i poremećaje anksioznosti (14). Upotreba kanabisa tokom kritičnih faza u razvoju mozga može ozbiljno da naruši endokanabinoidni sistem i na kraju bazične funkcije mozga. Na PET skeneru je pokazano da ispitanici koji su počeli da koriste marihuanu pre sedamnaeste godine imaju manju moždanu masu, kao i manji procenat centralne sive mase u poređenju sa pojedincima koji su počeli da je koriste nakon tog uzrasta (15). Nasuprot tome, magnetna rezonanca kod mlađih ljudi koji često koriste marihuanu nije pokazala atrofiju ili opštu promenu zapremine tkiva (16). Strukturalne promene mozga na jedrima akumbensu i amigdale su pokazane na magnetnoj rezonanci visoke rezolucije kod mladih koji rekreativno koriste marihuanu u poređenju sa onima koji je ne koriste (17).

Hemijski sastav i kontrola kvaliteta

Kanabis je složena biljka sa više od 400 sastojaka od kojih su više od 60 kanabinoidna jedinjenja. Smatra se da je THC glavni psihoaktivni sastojak, dok je pokazano da kanabidiol ima anksiolitička i antipsihotička svojstva, narušavajući efekte THC-a (10). Velika većina proizvoda od marihuane ne ispunjava osnovne standarde za farmaceutske proizvode. Sadržaj THC-a ili CBD-a u testiranim proizvodima je često značajno manji nego što je navedeno. Takvi proizvodi ne obezbeđuju željeni medicinski benefit ili stavljaju pacijente u povećani rizik od neželjenih dejstava. CBD je na osnovu informacija o proizvodu manje štetan zbog manje mogućnosti za zloupotrebu ili za ozbiljna neželjena dejstva, dok THC s druge strane, može da izazove intoksikaciju ili oštećenje, naročito ako nema suprotnog dejstva CBD-a (25,26).

Primena kanabisa raste širom sveta u zadnje vreme (27). Povećana primena THC-a tokom vremena izaziva zabrinutost po pitanju pouzdanosti i primenjivosti benefita i neželjenih dejstava marihuane koji su dokazani u starijim istraživanjima, naročito u studijama koje su procenjivale dugoročne ishode (28). Potreban je regulatorni sistem, na koji bi zdravstveni stručnjaci mogli da se oslone kako bi uverili pacijente i javnost generalno da je kanabis bezbedan i efikasan. Možda je marihuana manje štetna od drugih supstanci koje imaju potencijal za zloupotrebu, ali je potrebno istraživanje podataka o hroničnoj toksičnosti u proceni rizika, koji može biti potcenjen u složenim jedinjenjima sa niskom akutnom toksičnosti poput kanabisa. Ovaj zadatak predstavlja izazov zbog velikih varijacija THC-a u svakom proizvodu, što ga čini teškim za praćenje (29). Jedan od potrebnih koraka u obezbeđivanju bezbednosti marihuane je standardizacija i kontrole kvaliteta kulture. Biljka bi trebalo da bude gajena organski, bez genetskih modifikacija, na osnovu dobre poljoprivredne prakse i prerađena na osnovu Vodiča za dobru proizvođačku praksu. Ovaj proizvod takođe treba da ima sertifikat da je bez pesticida, da nije kontaminiran mikrobima i teškim metalima (30).

Tabela 1. Systemic side effects of marijuana inhalation

Cardiovascular	Increased rates of acute MI; Association with increased cardiovascular mortality (18).
Cerebrovascular	Stroke(19); Transient ischemic attack.
Gastrointestinal	Daily smoked marijuana is a risk factor for progression of liver fibrosis in Hepatitis C patients, despite the fact that marijuana is sometimes recommended in Hepatitis C patients (20,21).
Respiratory	Chronic cough and bronchitis; Inhalation of pyrolytic by-products; Increased risk of pneumonia in immunocompromised patients (22).
Reproductive	Suppresses oogenesis; Associated with testicular atrophy; Associated with abnormal sperm motility; Delta-9-THC blocks the release of LHRH from the hypothalamus, and LH production by the adenohypophysis (23). THC crosses the placenta barrier. Prenatal cannabis exposure was associated with fetal growth reduction (24).

brain growth can lead to a strong disturbance of the endocannabinoid system and cause inappropriate hardwiring in the brain. People who consumed marijuana at a young age (<17) have a grossly smaller brain, as well as the percent of central gray matter compared to individuals who began using it after the age of 17, as shown on a PET scan (15). In contrast, Block et al. showed that young, frequent cannabis users had no significant changes in tissue volume or atrophy on MRI images (16). A more recent study showed structural brain changes on high-resolution MRI in young recreational cannabis users when compared to non-users, particularly in the nucleus accumbens and the amygdala (17).

Chemical composition and quality control

Cannabis has over 400 active chemical substances and more than 60 of them are cannabinoids, increasing the complexity of the plant. THC is perceived as the main psychoactive ingredient, while cannabidiol has been shown to have anxiolytic and antipsychotic properties, antagonizing the effects of THC (10). The big majority of marijuana products are far from meeting the basic label accuracy standards for pharmaceuticals. The THC or CBD content in the tested products is often found to be significantly less than the labeled dose. Those products may not assure the anticipated medical benefit, or place patients at increased risk for side effects. CBD under labeling is less concerning due to low abuse liability or serious adverse events, while THC on the other hand, can produce intoxication or impairment, especially in the absence of antagonizing effects of CBD (25,26).

Recently, there has been an increase in marijuana potency throughout the world (27). The THC potency increase over time raises concerns about the reliability and applicability of the benefits and side effects of marijuana use discovered in older studies, especially studies that assessed long-term outcomes (28). A regulatory system is needed upon which health care professionals can rely on to assure the patients, and the public in general, that cannabis itself is safe and effective. Perhaps marijuana is less harmful than other substances with potential for abuse, but nevertheless, the investigation of chronic-toxicity data is necessary in estimating the risk, which may be underestimated in compounds with low acute toxicity such as cannabis. This task is also challenging to perform because of the wide variations of THC in every product, making it difficult to be monitored (29). One of the required steps in assuring safety of marijuana products is the standardization and quality control of culture. The plant should be cultivated organically, without genetic modification, following Good Agricultural Practice, and processed by following guidelines of Good Manufacturing Practice. The product should also be accompanied by certification that it has no pesticides, microbial or heavy metal contamination (30).

Novi naučni dokazi: stanje bola

Medicinska marihuana je sve više popularna kao alternativa tradicionalnim lekovima protiv bolova. Dokazi ukazuju na malo analgetičko dejstvo u lečenju hroničnog neuropatskog bola (31,32). Jedno randomizirano kliničko istraživanje je pokazalo da medicinska marihuana, naročito THC, izaziva značajno povećanje praga bola (33). Kao alternativa, CBD može imati sinergističke farmakokinetičke interakcije, povećavajući koncentracije THC u plazmi, ali i antagonističke farmakokinetičke interakcije, smanjujući analgeziju izazvanu THC-om (33). U jednom sistematskom pregledu, u kome su istraživani specifični mehanizmi kojima kanabinoidi moduliraju bol, pokazano je kako kanabinoidi povećavaju prag bola, povećavaju toleranciju bola, i smanjuju neprijatnost koju izaziva eksperimentalni bol. Međutim, kanabinoidi nisu smanjili intenzitet eksperimentalnog bola ili mehaničku hiperalgeziju (34).

Kod pacijenata sa hroničnim bolom, kojima je prepisano da puše medicinsku marihuanu, doziranje je bilo u visokoj pozitivnoj korelaciji sa incidencijom depresije. Međutim, srednji nivo bola i stepen anksioznosti nisu bili u korelaciji sa dozom (35).

U lečenju bola koji izaziva kancer, dokazi iz sistematskih pregleda nisu bili ubedljivi, verovatno zbog niskog kvaliteta dostupnih dokaza. Randomizirana klinička istraživanja koja se tiču ove teme nisu pokazala razliku između kanabinoida i placeba po pitanju smanjenja bola, problema sa nesanicom, doziranja opioida i učestalosti kombinovanog odgovora, ozbiljnih neželjenih dejstava, i psihijatrijskih poremećaja. Treba istaći da su studije imale ograničenja u smislu loših kontrola i pristrasnosti u objavljenim istraživanjima (36,37).

Izazovi koji se tiču legalizacije marihuane uključuju rizik od zloupotrebe, fizičke i mentalne zavisnosti koje se povezuju sa dugoročnim korišćenjem, i potencijal za neželjena dejstva. Marihuana se povezuje sa neželjenim efektima koji imaju veze sa centralnim nervnim sistemom (psihoza, kognitivno oštećenje) i neželjena dejstva povezana sa gastrointestinalnim sistemom (suva usta, mučnina, sindrom kanabinoidne hiperemeze). Dugotrajno korišćenje se povezuje sa fizičkom i mentalnom zavisnošću (31). Međutim, pokazano je da su ozbiljna neželjena dejstva bila slična između grupa kod kojih je korišćen kanabinoid i placebo grupa (32).

Novi naučni dokazi: zamena za opioide

Pronalaženje alternative opioidima u lečenju hroničnog bola bi predstavljalo najveći napredak u borbi protiv opioidne krize. Na primer, nakon što je Kolorado legalizovao marihuanu, oni su bili svedoci značajnog pada u distribuciji opioida, što je bio veći pad nego u državama bez zakona o rekreativnom korišćenju marihuane (38). Među korisnicima opioida koji su patili od hroničnog bola, korišćenje marihuane na dnevnoj bazi povezivano je sa značajno nižom upotrebom nelegalnih opioida na dnevnoj bazi (39). Istraživanje među ljudima koji su koristili i opioide i marihuanu u proteklih godinu dana pokazalo je da je 41% njih prijavilo smanjenje ili prestanak korišćenja opioida zbog upotrebe marihuane (40). Postoji nekoliko drugih istraživanja koje prijavljuju da konzumiranje marihuane dovodi do značajnog smanjenja korišćenja opioida (41,42). Ono što obećava je činjenica da korišćenje marihuane nije povezivano sa dozom opioida ili zloupotrebom opioida (43). U stvari, emotivni simptomi su se poboljšali kod pacijenata koji su koristili medicinsku marihuanu (44). Međutim, dokazi ne podržavaju uvek korišćenje kanabinoida kao zamenu za opioide. Jedno randomizirano kliničko istraživanje na malom broju ispitanika pokazalo je da dronabiol nije umanjio ili nije promenio analgeziju koju je izazvao oksikodon, već da je povećao zloupotrebu ili subjektivne efekte povezane sa oštećenjem koji se pripisuju oksikodonu (45).

Metodologija i izazovi u istraživanju

Ima mnogo razlika u metodologiji istraživanja marihuane kojima se treba baviti kako bi se poboljšao kvalitet dokaza i omogućilo donošenje boljih zaključaka. Jedan sistematski pregled pokazao je da su rezultati studija generalno pozitivniji u studijama bez kontrolnih grupa, i da je 15 od 21 primarne studije o marihuani bilo bez kontrolnih grupa. Pored toga, oni su pronašli da su studije koje su koristile više doze marihuane vodile ka zaključku da je marihuana efikasna, što predstavlja jedno od pitanja zato što su se lekovi i protokoli primene u velikoj meri razlikovali u studijama (46).

Česta nedoslednost u istraživanju medicinske marihuane se tiče srazmere THC: CBD i doziranja. Generalno, <10% THC imalo je najvišu efikasnost u lečenju neuropatskog bola, pa ipak, velika većina dostupnih proizvoda kanabisa imaju >15% THC, na-

New scientific evidence: pain conditions

Medical marijuana is gradually becoming a popular alternative to traditional pain-relieving medications. Evidence points to a small analgesic effect in the treatment of chronic neuropathic pain (31,32). One randomized controlled trial has found that medical marijuana, THC in particular, causes a noteworthy increase in the pressure pain threshold (33). Alternatively, CBD may have synergistic pharmacokinetic interactions, by increasing THC plasma concentrations, but antagonistic pharmacodynamic interactions, by decreasing THC-induced analgesia (33). A systematic review also investigating the specific mechanisms by which cannabinoids modulate pain has found that cannabinoids increase pain thresholds, increase pain tolerance, and reduce the unpleasantness of ongoing experimental pain. However, cannabinoids didn't decrease experimental pain intensity or mechanical hyperalgesia (34).

In patients prescribed smoked medical marijuana for chronic pain, the dosage was found to be highly positively correlated with the incidence of depression. Mean level of pain and severity of anxiety, however, were not correlated to the dosage (35).

In cancer pain treatment, evidence from systematic reviews has been inconclusive, most likely due to the very low quality of evidence available. RCTs on the topic have typically found no difference between placebo and cannabinoids in reducing pain, dose of opioids, sleep issues, as well as serious adverse events, or other side effects such as psychiatric-like disorders. Most notably, studies carried design limitations, such as poor controls, and publication bias (36,37).

Challenges when it comes to legalizing marijuana include the risk of misuse, dependence, and addiction which have been associated with long-term duration of use, and the potential for adverse effects. Marijuana has been associated with psychiatric disorder like side effects (psychosis, cognitive impairment) and GI-related adverse effects (dry mouth, nausea, vomiting). Long-term duration of use has been associated with dependence and addiction (31). Severe adverse effects, however, were found to be similar between cannabinoid and placebo treatment groups (32).

New scientific evidence: opioid replacement

Finding an opioid alternative to treating chronic pain would constitute major progress in the battle against the opioid crisis. For instance, in the years after Colorado legalized marijuana, they witnessed a significant drop in opioid distribution, a larger decrease than seen in states without recreational marijuana policies (38). Among chronic pain sufferers using opioids, daily marijuana use was linked with significantly lower odds of daily illicit opioid use(39). A survey among people who used both opioids and marijuana in the past year showed that 41% reported a reduction of opioid dose or completely stopping use as a result of marijuana use(40). There are several other new reports of marijuana consumption leading to a significant reduction in opioid consumption (41,42). Promisingly, marijuana use was not associated with opioid dose or opioid misuse behavior (43). In fact, emotional symptoms improved in patients taking medical marijuana (44). Nonetheless, the evidence does not always align in using cannabinoids as an opioid adjuvant. A small RCT found that dronabinol decreased or did not change oxycodone-induced analgesia, rather, it augmented oxycodone related side effects(45).

Methodology and challenges in research

There is much variability in marijuana research methodology which needs to be addressed in order to improve the quality of evidence and enable better informed conclusions to be drawn. A systematic review into the topic found that study deductions were generally more positive in non-controlled studies, and that 15 of 21 primary studies on marijuana were noncontrolled. Additionally, they found that studies using greater doses concluded that marijuana was effective, which is an issue because drugs and protocols of administrations ranged greatly across studies (46).

A common inconsistency in research on medical marijuana revolves around the THC:CBD ratio and dosing. Overall, <10% THC has demonstrated the highest efficacy in treating of neuropathic pain, yet the great majority of cannabis products available are >15% THC, most likely to appeal to the recreational use realm (12). Currently, none of the states with legalized medical or recreational marijuana deliberate the THC:CBD

jverovatnije da bi bili privlačni u domenu upotrebe u rekreativne svrhe (12). Trenutno se nijedna od država sa legalizovanom medicinskom ili rekreativnom marihuanom ne bavi odnosom THC:CBD u regulativama. Uz to, u objavljenim studijama, ta srazmera često nije navedena ili je trivijalizovana zbog dostupnosti (47).

Takođe, postoji velika potreba za dodatnim istraživanjem upotrebe marihuane u populacijama specifičnih pacijenata uključujući trudnoću, gerijatrijsku i pedijatrijsku poplaciju. Kada je u pitanju pedijatriska populacija, trenutno postoje samo dve objavljene studije o medicinskoj marihuani koja se koristi za lečenje bola u pedijatriji, od kojih je jedna studija slučaja (48).

Postoji i velika potreba za dugoročnim studijama koje bi se bavile procenom rizika i benefita koji su povezani sa dugoročnim korišćenjem. Do sada, dugoročno, hronično korišćenje kod ljudi mlađih od 25 godina se povezuje sa gubitkom pamćenja, kognitivnom disfunkcijom, psihozom koja rano počinje ili šizofrenijom (49).

Zaključak

Medicinska marihuana ima brojne potencijalne medicinske efekte, kao i moguće rizike po zdravlje ljudi. Vodiči koje izdaju institucije poput Uprave za hranu i lekove (eng. *Food and Drug Administration*, FDA), Američkog lekarskog društva (eng. *American Medical Association*, AMA), Svetskog lekarskog udruženja (eng. *World Medical Association*, WMA) i Društva za kancer Sjedinjenih Država podržavaju rigoroznija istraživanja. Dokazi o benefitima kanabinoida u poremećajima koji izazivaju bolna stanja su niskog do srednjeg kvaliteta, ali ima izgleda da će obezbediti alternativu opioidima. Većina studija je uključivala mali broj ispitanika, neadekvatne kontrole i bile su kratkotrajne, tako da je potrebno dalje istraživanje kako bi se ispitala bezbednost i efikasnost marihuane. Važno je istaći da se postojeći dokazi baziraju na evaluaciji upotrebe sintetičkih kanabinoida, ili nekomercijalno dostupnih proizvoda koji imaju kontrolisane i regulisane sastojke. Nažalost, proizvodi koji su dostupni na tržištu ne mogu biti uključeni u istu kategoriju kontrolisanih i regulisanih komponenti, stoga lekari koji se bave bolnim stanjima moraju biti oprezni kada preporučuju medicinsku marihuanu pacijentima.

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ratio in protocols. Moreover, in published studies, the ratio is often not listed or trivialized based on availability (47).

There is also a need of additional research into marijuana use in specific patient populations including pregnancy, geriatric, and pediatric populations. Concerning the latter, for instance, there are currently only two published studies on medical marijuana on pediatric pain, of which one is a case report (48).

There is also a great need of more long-term studies to assess the risks and benefits associated with long-term use. To date, long-term chronic use in the younger population was associated with serious cognitive impairment, memory loss, and early onset of psychotic symptoms(49).

Conclusions

Medical marijuana has many potential medical benefits, as well as possible health risks. Emerging guidelines from institutions such as the FDA, AMA, WMA, and the American Cancer Society encourage more rigorous research. The evidence of cannabinoids' benefit in pain disorders is of low-to-moderate quality, but greatly promising in providing alternatives to opioids. Most studies were comprised of small populations, poor controls and short duration, and further research is necessary to examine marijuana safety and efficacy. Of note, the existing evidence is based on the evaluation of synthetic cannabinoids' use, or non-commercially available products that have controlled and regulated components. Unfortunately, the products available on the market cannot be included in the same category of controlled and regulated components, therefore pain medicine physicians must be cautious when suggesting medical marijuana to patients.

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URINARNI METABOLITI KAO INDIKATORI IZLOŽENOSTI LJUDI HEMIJSKIM KARCINOGENIMA

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SAŽETAK

Izloženost stanovništva hemijskim karcinogenima iz životne sredine prestavlja sve veći javnozdravstveni problem. Kancerogene hemikalije mogu se klasifikovati u dve grupe: genotoksične i ne-genotoksične. Genotoksična hemikalija ima potencijal da indukuje nastanak karcinoma, bilo u direktnoj interakciji sa DNK ili sa ćelijskim strukturama odgovornim za očuvanje integriteta genoma. Negenotoksična hemikalija ima potencijal da indukuje rak na indirektan način ulazeći u procese etiopatogeneze karcinoma. Dosadašnja istraživanja ukazuju da se neorganska jedinjenja arsena mogu dovesti u vezu sa nizom malignih bolesti (rakom pluća, mokraćne bešike, kože, bubrega, jetre i prostate). Neorganski arsen pretežno se nalazi u mesu, mlečnim proizvodima i žitaricama, a organski arsen (arsenobetain) u morskim plodovima, voću i povrću. Metaboliti benzena dovode se u vezu sa različitim vrstama leukemija i limfomima, benzidin sa rakom mokraćne bešike, nikl sa rakom pluća, a jedinjenja hroma sa rakom pluća, rakom nosa i nazalnih sinusa. Najveća profesionalna izloženost benzenu je u industriji (kože, elektronskih uređaja, obuće, sportske opreme), a sa benzidinom osobe mogu doći u kontakt preko robe široke potrošnje (proizvodi od kože, odeća i igračke). Najviše koncentracije nikla izmerene su u pasulju, orasima i žitaricama. Kadmijum i kadmijumova jedinjenja uzrokuju rak pluća, a utiču i na pojavu raka bubrega i prostate. Rizik od hepatocelularnog karcinoma značajno je povišen kod ispitanika sa visokim koncentracijama urinarnih metabolita aflatoksina (adukti aflatoksin-N7-gvanina). Izomeri lindana nalaze se u mlečnim proizvodima, mesu, ribi, živini, baštenskom voću, uljima i mastima, lisnatom i korenovskom povrću i šećeru, a kod ljudi uzrokuju ne-Hodgkinov limfom. Postoji pozitivna veza između konzumiranja biljaka aristolohia i pojave urotelnih karcinoma. Ne postoje skrininzi za identifikaciju osoba koje su u velikom riziku da dobiju maligno oboljenje u narednih 10 ili 20 godina. U prevenciji nastanka malignih bolesti neophodno je staviti akcenat na pronalaženje adekvatnih metoda za određivanje koncentracija urinarnih metabolita za najtoksičnije hemijske karcinogene i definisati njihove rizične vrednosti.

Ključne reči: urinarni metaboliti, hemijski karcinogeni, maligne bolesti

Uvod

Tokom Rimskog carstva uvedena je nagrada za rimsko plemstvo ukoliko rano stupe u brak i steknu potomstvo. Razlog uvođenja ove nagrade je bio čest sterilitet kod rimskog plemstva usled premazivanja/izrađivanja kuhinjskog posuđa olovom. Bilo je neophodno gotovo dva milenijuma za razumevanje uzroka ovog steriliteta.

Izloženost stanovništva štetnim hemikalijama iz okoline prerasta u sve veću zabrinutost na globalnom nivou. Postojeći skrininzi prepoznaju bolesti u ranoj fazi svog razvoja (mamografija, Papanikolau test itd). S obzirom na veliki broj različitih malignih bolesti, broj takvih skringa je mali. Međutim, ne postoje skrininzi za osobe koje su u velikom riziku da u narednih 10 ili 20 godina dobiju maligno oboljenje. Određivanjem koncentracije urinarnih metabolita hemijskih karcinogena moglo bi da pomogne u identifikovanju najviše eksponiranih osoba ili grupa osoba. Znači, nedostatak skrininga za određivanje osoba u velikom riziku za nastanak malignih bolesti, sputava preventivnu onkologiju i povećava zdravstveni rizik. Mnoge regulatorne mere su u toku ili su već primenjene za opasne hemikalije, ali bi brz, jeftin, neinvazivan, pouzdan skrining, dostupan bilo gde i bilo kada velikom delu populacije, bio koristan u prevenciji izloženosti karcinogenim hemikalijama i smanjenju zdravstvenog rizika.

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URINARY METABOLITES AS INDICATORS OF HUMAN EXPOSURE TO CHEMICAL CARCINOGENS

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SUMMARY

Population exposure to environmental chemical carcinogens is a growing public health problem. Carcinogenic chemicals may be classified into two groups: genotoxic and non-genotoxic. A genotoxic chemical has a potential to induce the development of cancer, either in direct interaction with DNA or with cell structures, which are responsible for the maintenance of genome integrity. A non-genotoxic chemical has a potential to induce cancer indirectly by entering the processes of cancer etiopathogenesis. Previous research studies indicate that inorganic arsenic compounds may be associated with various malign diseases (lung cancer, urinary bladder cancer, skin, kidney, liver and prostate cancer). Inorganic arsenic is mainly present in meat, dairy products and grains, while organic arsenic (arsenobetaine) is present in seafood, fruit and vegetables. Benzene metabolites are associated with different types of leukemias and lymphomas, benzidine with bladder cancer, nickel with lung cancer, chromium compounds with lung cancer, nose and nasal sinus cancer. The greatest occupational exposure to benzene is in industry (leather, electronic device, shoes, sports equipment), while people may come into contact with benzidine through consumer goods (leather products, clothes, toys). The highest concentrations of nickel were measured in the beans, walnuts and grains. Cadmium and cadmium compounds cause lung cancer, and influence the occurrence of renal and prostate cancer. The risk of hepatocellular carcinoma is significantly increased in respondents with high concentrations of urinary metabolites of aflatoxin (aflatoxin N7-gvanine adducts). Lindane isomers are present in dairy products, meat, fish, poultry, garden fruit, oils and lipids, leaf and root vegetables and sugar, and they cause noon-Hodgkin lymphoma. There is a positive correlation between the consumption of aristolochia plants and the occurrence of urothelial carcinoma. There are no screening examinations for the identification of persons who are at great risk of developing malign disease in the next 10 or 20 years. As for the prevention of malign diseases, it is necessary to put an accent on finding the adequate methods for determining the concentrations of urinary metabolites for the most toxic chemical carcinogens and define their risk values.

Key words: urinary metabolites, chemical carcinogens, malign diseases

Introduction

In the Roman Empire, an award was introduced to encourage marriage and having children in Roman aristocracy. The reason for this award was frequent infertility in Roman aristocracy, which was caused by their pottery that was made using a lead glaze. Two millennia were necessary to realize the cause of this infertility.

Population exposure to harmful environmental chemicals is a growing concern globally. The existing screenings recognize early stage diseases (mammography, Papanicolaou test). Having in mind a great number of different malign diseases, the number of such screenings is small. However, there are no screenings for persons who are at a higher risk of developing certain malign diseases in the next 10 or 20 years. Determining the concentration of urinary metabolites of the most toxic chemical carcinogens could help in identifying the most exposed individuals or groups. Thus, the lack of screening to determine persons at a higher risk of malign diseases restrains preventive oncology and increases the health risk. Many regulations are ongoing or they have already been applied. However, a fast, cheap, non-invasive,

Kancerogene hemikalije mogu se klasifikovati u dve grupe: genotoksične i ne-genotoksične. Genotoksična hemikalija (GTkH) ima potencijal da indukuje nastanak karcinoma, bilo u direktnoj interakciji sa DNK ili sa ćelijskim strukturama odgovornim za očuvanje integriteta genoma (2). Negenotoksična hemikalija (NGTkH) ima potencijal da indukuje rak na indirektan način ulazeći u procese etiologije i patogeneze karcinoma (2).

Prema Svetskoj zdravstvenoj organizaciji odnosno njenoj Međunarodnoj agenciji za istraživanje karcinoma, postoji 121 hemijsko jedinjenje svrstano u Grupu 1 (dokazani vrlo opasni kancerogeni). U Grupu 2A svrstano je 89 verovatnih hemijskih kancerogena, a u Grupu 2B, 318 mogućih kancerogenih (1). Kod nekih hemijskih karcinogena metabolizmom ne nastaju metaboliti koji se mogu detektovati u urinu (formaldehid, acetaldehid, etil alkohol). Izloženost ljudi najopasnijim hemijskim kancerogenima mogla bi se verovatno otkriti detektovanjem urinarnih metabolita odgovarajućim instrumentalnim metodama (indukovana kuplovana plazma, tečna hromatografija-masena spektrometrija).

Nekoliko supstanci iz Grupe 1 karcinogena su lekovi koji se trenutno koriste u kliničkoj praksi u terapiji karcinoma (ciklosporin, busulfan, tiotepa, ciklofosfamid, hlornafazin, azatioprin, etopozid u kombinaciji sa cisplatinom i bleomicinom, etopozid, hlorambucil, treosulfan, metoksalen (8-metoksipsoralen), melfalan, sredstva za alkilovanje, semustin), ali tu su i lekovi slični hormonima (estrogena terapija u postmenopauzi; estrogen-progestogena terapija menopauze (kombinovana), estrogen-progestogeni oralni kontraceptivi (kombinovani), dietilstilbestrol), i analgetičke smeše koje sadrže paracetamol (uzrok tzv. „fenacetinskih bubrega“).

Određeni industrijski procesi pri kojima se koriste ili nastaju supstance svrstane u Grupu 1 karcinogena mogu izrazito doprineti nastanku raka. Nepoznato je kako takvi procesi utiču na pojavu maligniteta (proizvodnja izopropil alkohola upotrebom jake kiseline, proizvodnja aluminijuma, proizvodnja auramina, livenje gvožđa i čelika, industrija gume, zavarivanje).

Postoje karcinogeni iz Grupe 1 koji metabolizmom ne daju jedinjenja koja mogu biti detektovana u urinu: pare jakih neorganskih kiselina (sumporne kiseline i hlorovodonične kiseline), bis (hlormetil) etar hlormetil metil etar, nitrati, nitriti i nitrozoamini. Za razliko od prethodno navedenih jedinjenja postoje i ona poput aristoholičnih kiselina, aflatoksina i nekih drugih karcinogena (u mnogo manjim razmerama) koja daju DNK adukte, koji se mogu smatrati vrstom urinarnih metabolita.

Karcinogeni entiteti navedeni kao „zagađenje vazduha na otvorenom“, „čađ“, „boje“, „emisije u zatvorenom prostoru usled sagorevanja u domaćinstvu“, „proizvodnja koksa“, „plinifikacija uglja“, „destilacija ugljenog katrana“ i „smola ugljenog katrana“ su prilično složeni procesi za analizu indikatora karcinogena u vidu urinarnih metabolita.

Metaboliti hemijskih karcinogena u urinu obično odražavaju nedavnu izloženost ljudskim kancerogenima i mogu dovesti u zabludu u slučaju povremene izloženosti (ako se meri koncentracija urinarnih metabolita neposredno ili ubrzo po zadesnoj izloženosti hemijskim karcinogenima). Zato je preporučljivo tri puta ponoviti merenje supstanci u urinu u normalnom fiziološkom stanju organizma. Izlučivanje urinarnih metabolita varira i zavisi od demografskih karakteristika, telesne težine i hidratacije organizma, pa je neophodno uzeti u obzir ove parametre pri određivanju urinarnih metabolita (3,4).

Metode

Pretraga literature je sprovedena u bazi podataka „PubMed advanced“ za period od 1. januara 2000. do 15. avgusta 2021. godine, kako bi se dobili potrebni podaci prema pretraživanim terminima. Vodeća pitanja u pregledu literature bila su izloženost ljudi hemijskim kancerogenima i mogućnost detekcije njihovih metabolita u urinu. Korišćeni su radovi koji su u celosti objavljeni u časopisima sa recenzijom, na engleskom jeziku, iz kategorija: „*Books and Documents*”, “*Clinical Trials*”, “*Meta-Analyses*”, “*Randomized Controlled Trials*”, “*Reviews*“ и „*Systematic Reviews*“. Kriterijumi za uključivanje ovih radova bile su sledeće ključne reči: hemijski kancerogeni, izloženost ljudi, prevencija raka, karcinogeni indikatori i metaboliti u urinu. Korišćena je strategija izbora članaka pretraživanje korak po korak. Prvi korak, termini u okviru za upit: hemijski kancerogeni I izloženost ljudi = 1760 referenci; Drugi korak, termini u okviru za upit: hemijski kancerogeni I izloženost ljudi I metaboliti u urinu = 29 referenci; Treći korak, termini u okviru za upit: hemijski kancerogeni I izloženost ljudi I metaboliti u urinu I kancerogeni indikatori = 6 referenci; Četvrti korak, termini u okviru za upit:

reliable screening, available to a great part of the population anywhere and anytime, would be useful in the prevention of exposure to carcinogenic chemicals and decrease of health risk.

Carcinogenic chemicals can be classified into two groups: genotoxic and non-genotoxic. A genotoxic chemical (GTcH) has a potential to induce cancer, either in a direct interaction with DNA or cell structures, which are responsible for the maintenance of genome integrity (2). A non-genotoxic chemical (NGTcH) has a potential to induce cancer indirectly by entering into processes of cancer etiology and pathogenesis (2).

According to the World Health Organization, that is, its International Agency for Cancer Research, there are 121 chemical compounds that are classified into Group 1 (proved as very dangerous carcinogens). There are 89 possible chemical carcinogens that are classified into Group 2A, while 318 possible carcinogens are in Group 2B (1). In some chemical carcinogens, metabolism does not produce metabolites that can be detected in urine (formaldehyde, acetaldehyde, ethyl alcohol). Human exposure to the most dangerous chemical carcinogens could possibly be found by detecting urinary metabolites with the help of appropriate instrumental methods (inductively coupled plasma, liquid chromatography - mass spectrometry).

Several substances from the Group 1 are currently used in the clinical practice for the treatment of cancer (cyclosporine, busulfan, thiotepa, cyclophosphamide, chlornaphazine, azathioprine, etoposide in combination with cisplatin and bleomycin, etoposide, chlorambucil, treosulfan, methoxsalen (8-methoxypsoralen), melphalan, alkylating agents, semustine), and there are also drugs which are similar to hormones (estrogen therapy in postmenopausa; estrogen-progesterone postmenopausal therapy (combined), estrogen-progesterone oral contraceptives (combined), diethylstilbestrol, and compound analgesic preparations containing paracetamol (cause of "phenacetin nephropathy").

Certain industrial processes, during which substances from Group 1 of carcinogens are used or produced, can contribute to cancer development. It is not known how these processes influence malignancy (the production of isopropyl alcohol with the help of strong acid, the production of aluminum, auramine, iron and steel casting, rubber products industry, welding). In some carcinogens from Group 1, metabolism does not produce compounds that can be detected in urine: strong inorganic acid mists (containing sulfuric acid and hydrochloric acid), bis (chloromethyl) ether, chloromethyl methyl ether, nitrates, nitrites, and nitrosamines. In contrast to previously mentioned compounds, some compounds, such as aristolochic acids, aflatoxin and other carcinogens (in smaller percentages) give DNA adducts, which can be considered as urinary metabolites.

Carcinogenic entities, which are marked as "outdoor air pollution", "carbon black dust", "paints", "indoor emissions from the household combustion", "fuel coke production", "gas production from coal", "distillation of coal tar" and "coal tar pitch", are very complex processes for the analysis of indicators of carcinogens in the form of urinary metabolites.

Metabolites of chemical carcinogens in urine usually reflect the recent exposure to human carcinogens and they can mislead us in case of periodical exposure (if the concentration of urinary metabolites is measured immediately after or soon after the accidental exposure to chemical carcinogens). Therefore, substances in urine in the normal physiological state of the body should be measured three times. The secretion of urinary metabolites varies and depends on demographic characteristics, body weight, and hydration, and therefore, all these parameters should be taken into account when urinary metabolites are determined (3,4).

Methods

The literature was searched in the data base "PubMed advanced" from 1 January 2000 to 15 August 2021, in order to get necessary data according to the searched terms. The leading questions during this search were human exposure to chemical carcinogens and the possibility of detection of their metabolites in urine. We used full-text articles that were published in the peer-reviewed scientific journals in the English language, from the categories: "Books and Documents", "Clinical Trials", "Meta-Analyses", "Randomized Controlled Trials", "Reviews" and "Systematic Reviews". Criteria for the inclusion of these studies were the following key words: chemical carcinogens, human exposure, prevention of

hemijski kancerogeni I izloženost ljudi I metaboliti u urinu I indikatori kancerogena I preventivna onkologija = 1 referenca.

Prva grupa članaka izostavljena je od daljeg razmatranja nakon uvida u naslove članaka. Nakon čitanja sažetaka članaka, druga i najbrojnija grupa članaka je izostavljena od daljeg razmatranja. Treća grupa članaka isključena je nakon uvida u metode i rezultate naučnih publikacija. Četvrta grupa članaka izostavljena je nakon analize celokupne publikacije. Konačno, peta grupa članaka nije uključena nakon upoređivanja sa ostalim člancima prema kriterijumima: naučna informativnost i naučna pouzdanost publikacija o najtoksičnijim predstavnicima hemijskih karcinogena i njihovih metabolita u urinu.

Arsen, organska jedinjenja arsena i neorganska jedinjenja arsena

Arsen i njegova neorganska jedinjenja svrstavaju se među najznačajnije hemijske karcinogene. Arsen je 20. najčešći element u zemljinoj kori i prisutan je u više od 200 mineralnih vrsta. Primarni put izlaganja arsenu za opštu populaciju je konzumiranje kontaminirane hrane ili vode. Dnevni unos arsena iz hrane i pića uglavnom se kreće u rasponu 20–300 µg/dan. Dnevni unos udisanjem može iznositi oko 20–200 ng u ruralnim područjima, 400–600 ng u gradovima bez značajne industrijske emisije arsena, oko 1 µg/dan kod nepušača, a u zagađenim područjima kod pušača i do približno 10 µg/dan (5,6). Neorganski arsen pretežno se nalazi u mesu, mlečnim proizvodima i žitaricama, a organski arsen (arsenobetain) u morskim plodovima, voću i povrću (5,6).

Metaboliti arsena u urinu, koji se koriste kao indikatori skore izloženosti, su: ukupni neorganski arsen, arsenobetain, monometilarsenska kiselina (MMAK) i dimetilarsenska kiselina (DMAK). Vlada Kanade pokrenula je 2007. godine nacionalno istraživanje na reprezentativnom uzorku opšte populacije, kod oko 30.000 stanovnika. Za ukupni neorganski arsen, MMAK i DMAK, određene su koncentracije u urinu od po 20 µgAs/L (95. percentil 15-26) (7).

Poznato je da neorganska jedinjenja arsena dovode u vezu sa rakom pluća, mokraćne bešike i kože. Takođe, primećena je povezanost između izloženosti arsenu i njegovim neorganskim jedinjenjima sa rakom bubrega, jetre i prostate.

Benzen

Benzen se uglavnom koristi za proizvodnju organskih hemikalija (stiren, fenol, cikloheksan, anilin, anhidrid maleinske kiseline, alkilbenzen i hlorobenzen), odnosno za proizvodnju lekova, boja, insekticida, deterdženata i plastike (8). Prirodno se javlja u naftnim proizvodima (sirova nafta i benzin), a dodaje se i bezolovnom benzinu. Koncentracija benzena u ovim gorivima je 1-2% (9).

Opšta populacija je najviše izložena benzenu putem duvanskog dima, vazduha u oblastima gde je gust saobraćaj, oko benzinskih pumpi, konzumiranjem zagađene vode i hrane iz područja kontaminiranih velikim količinama izduvnih gasova iz vozila ili toplana na tečna goriva (mazut). Najveća profesionalna izloženost je u industriji kože, industriji elektronskih uređaja, industriji obuće, industriji sportske opreme, pri radu s mašinama i sa kancelarijskim materijalom.

Metaboliti benzena imaju kancerogeni potencijal (10,11). Metaboliti benzena mogu uzrokovati akutnu mijeloidnu leukemiju i akutnu ne-limfocitnu leukemiju. Primećena je povezanost između izloženosti benzenu i akutne limfocitne leukemije, hronične limfocitne leukemije, multiplog mijeloma i ne-Hodgkinovog limfoma. Uobičajeni nivoi metabolita benzena u urinu su: 70–85% fenola, 5–10% hidrohinona, trans-mukonske kiseline i katehola i manje od 1% S-fenilmerkapturne kiseline (12,13).

Benzidin

Proizvodnja i upotreba benzidina u industriji boja zabeležena je u nekim zemljama u razvoju. Američka administracija za hranu i lekove ograničava sadržaj benzidina u bojama za hranu na 1 deo na milijardu (*parts per billion* - ppb) ili mg/kg. Iako se izlaganje benzidinu oralnim putem smatra malo verovatnim, ali nečistoće u sintetičkim sredstvima za bojenje mogu se metabolisati u benzidin nakon gutanja (14).

Opšta populacija može biti izložena benzidinu pri kontaktu sa robom široke potrošnje koja sadrži benzidin ili boje na bazi benzidina, poput proizvoda od kože, odeće i igračaka (15,16). Neke boje za hranu, u ograničenom broju proizvoda i na bezbednim nivoima, mogu sadržavati benzidin u tragovima (17). Benzidin uzrokuje rak mokraćne bešike, a indikatori karcinogena u urinu su benzidin i njegovi konjugati (monoacetilbenzidin).

cancer, carcinogenic indicators and metabolites in urine. Strategy step by step was used in order to choose the articles. The first step included terms in search lines: chemical carcinogens and human exposure = 1760 references; the second step included terms in search lines: chemical carcinogens and human exposure and metabolites in urine = 29 references; the third step included terms in search lines: chemical carcinogens and human exposure and metabolites in urine and carcinogenic indicators = 6 references; the fourth step included terms in search lines: chemical carcinogens and human exposure and metabolites in urine and indicators of carcinogens and preventive oncology = 1 reference.

The first group of articles was not left open for further consideration after reading the titles. After reading the abstracts, the second group, which was the most numerous group of articles, was not further considered. The third group of articles was excluded after the insight into the methods and results of scientific papers. The fourth group of articles was excluded after the analysis of the whole publication. Finally, the fifth group of articles was not included after the comparison with other articles according to the following criteria: scientific informativeness and scientific reliability of publications about the most toxic representatives of chemical carcinogens and their urinary metabolites.

Arsenic, organic and inorganic arsenic compounds

Arsenic and its inorganic compounds are classified as the most important chemical carcinogens. Arsenic is the twentieth element among the elements in the earth's crust and it is present in more than 200 mineral species. The primary path of exposure for the general population is the consumption of contaminated food or water. The daily intake of arsenic from food and beverages ranges from 20-300 µg/day. The daily intake due to inhalation can amount to 20-200 µg in rural regions, 400-600 µg in cities without significant industrial emissions of arsenic, around 1µg/day in non-smokers, and up to 10µg/day in polluted areas in smokers (5,6). Inorganic arsenic is mainly present in meat, dairy products, grains, while organic arsenic (arsenobetaine) is present in seafood, fruit and vegetables (5,6).

Metabolites of arsenic in urine, which are used as indicators of recent exposure, are the following: total inorganic arsenic, arsenobetaine, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). The government of Canada launched the study on the representative sample of general population in 2009, which included around 30000 inhabitants. Concentrations of urine of 20 µgAs/L were determined for the total inorganic arsenic, MMA and DMA (95th percentiles 15-26) (7).

It is known that inorganic arsenic compounds are associated with lung cancer, urinary bladder cancer and skin cancer. Also, the relation between the exposure to arsenic and its inorganic compounds and kidney cancer, liver cancer and prostate cancer was noticed.

Benzene

Benzene is mainly used for the production of organic chemicals (styrene, phenol, cyclohexane, aniline, anhydride of maleic acid, alkylbenzene and chlorobenzene), that is, for the production of drugs, paints, insecticides, detergents and plastic (8). In nature, it appears in petroleum products (crude oil and petrol), and it is added to unleaded fuel. The concentration of benzene in these fuels is 1-2% (9).

The general population is most exposed to benzene through tobacco smoke, air in areas with heavy traffic, around petrol stations, the consumption of polluted water and food from regions, which are contaminated by high amounts of exhaust gases from vehicles or power plants that use liquid fuels (mazut fuel oil). The greatest occupational exposure is in leather industry, industry of electronic devices, shoe industry, sporting equipment industry, when working with machines and office supplies.

Benzene metabolites have a carcinogenic potential (10,11). Metabolites of benzene cause acute myeloid leukemia and acute non-lymphocyte leukemia. The connectedness between the exposure to benzene and acute lymphocyte leukemia, chronic lymphocyte leukemia, multiple myeloma, and non-Hodgkin lymphoma was noticed. The usual levels of metabolites of benzene in urine are: 70-85% of phenol, 5-10% of hydroquinone, trans, trans-muconic acid and catechol and less than 1% of S-phenylmercapturic acid (12,13).

Polihlorobifenili (*PCB*)

U zavisnosti od položaja i broja atoma hlora, postoji 209 pojedinačnih kongenera *PCB*-a (srodnih jedinjenja). Grupu „dioksinu sličnih (DS)“ čini dvanaest *PCB*-a. *PCB* se nikada nisu koristili kao pojedinačna jedinjenja, već kao složene smeše. *Frame* i koautori i *Johnson* i koautori navode oko 130 od 209 *PCB*-a u komercijalnim proizvodima. U takvim komercijalnim proizvodima koncentracije PCB-a bile su iznad 0,05% (18,19).

Prehrambeni proizvodi se redovno analiziraju na *PCB*-e u nacionalnim (Skandinavija, Finska) i međunarodnim programima za nadzor kvaliteta hrane (Evropska agencija za bezbednost hrane – EFSA) (20,21), s fokusom analize na *PCB*-a, koji se analiziraju zajedno sa dioksinima i furanima. Jaja se obično analiziraju na PCB, s fokusom na žumance (22,23). Voće i povrće se analizira ređe od prehrambenih proizvoda koji su bogati lipidima. *PCB* se koriste i u vojne svrhe. *PCB* se uglavnom primenjuju u dielektričnim tečnostima u kondenzatorima i transformatorima. Takođe se koriste kao zaptivači, plamenotporni premazi, u mastilima, lepkovima, mikrokapsulacijama boja za kopiranje papira bez ugljenika, transportnim trakama, gumenim proizvodima, bojama, punilima pesticida, plastifikatorima, poliolefinskim nosačima katalizatora, uljima za mikroskope, površinskim premazima, izolatorima od žice i metalnim premazima (24,25). Nepravilno rukovanje elektronskim otpadom identifikovano je kao izvor zagađenja životne sredine *PCB*-ima, posebno za staru opremu (26).

PCB se mogu naći širom sveta u merljivim koncentracijama u svim komponentama životne sredine (zemljište i sedimenti, voda, vazduh), u divljim životinjama i telu svakog čoveka. Izloženost ljudi *PCB*-ima uglavnom se javlja konzumiranjem kontaminirane hrane, ali i udisanjem i dermalnom apsorpcijom. *PCB* se apsorbuje putem organskog ugljenika u zemljište, a kad se jednom upije, relativno je postojan (27). Hrana je glavni put za konzumiranje *PCB*-a .

PCB su decenijama dospevali u vazduh iz industrijskih objekata, vojnih lokacija, deponija opasnog otpada, elektrolučnih peći, spaljivanja i drugih oblika sagorevanja, mulja iz kanalizacije, građevinskog materijala, boja, zaptivača, zaptivnih masa za pod, lepkova i plastifikatora kod starijih zgrada (28,29). *PCB* iz tla, sedimenata, vazduha i vode ulazili u lanac ishrane bioakumulacijom u biljkama i životinjskim mastima. *PCB* se akumuluraju u masnim tkivima svih životinja, u svim mlečnim proizvodima koji sadrže masti i u jajima (23,30). Koncentracije *PCB*-a su obično najviše kod mesožderskih riba koje dolaze iz zagađenih voda (31). Opšta populacija je decenijama bila izložena višestrukim izvorima *PCB*-a, retko jednom komercijalnom proizvodu. Izloženost opšte populacije *PCB*-ma je verovatno moguća kod slabo razvijenih i slabo kontrolisanih afričkih i azijskih zemalja ili zadesno u drugim delovima planete.

Sagorevanjem uglavnom starog otpada i drugim procesima na visokim temperaturama nastaju *PCB*. Biljno lišće (kupus i salata) bioakumulira organske zagađivače i može služiti za biomonitoring pomoću vrlo osetljivih instrumentalnih metoda za procenu zagađenja *PCB*-om (32-34). Tokom višedecenijskog perioda neograničene primene PCB-ova upijali su se u okolne materijale, poput betona ili drveta, i kontaminirali naročito vazduh u zatvorenom prostoru (29).

Dospevanje *PCB*-a u vodu se uglavnom odigrava putem ispuštanja kućne kanalizacije, industrijskih otpadnih voda, ulične kišne kanalizacije, procednih voda sa deponija čvrstog otpada, atmosferskog taloženja i oticanja vode sa njiva i voćnjaka uglavnom obsolentnih pesticida ili njihovih jedinjenja (35,36). Tokom ranih 1990-ih, hrana je identifikovana kao glavni put čovekove izloženosti lipofilnim i postojanim *PCB*-ima (20,37,38). U evropskoj opštoj populaciji više od 90% izloženosti PCB-ima bilo je putem hrane, (mleko i mlečni proizvodi za gotovo sve grupe novorođenčadi i mališana), proizvodi od ribe i morskih plodova za većinu adolescenata, odraslih i starijih (19,39-43). Područje Baltičkog mora bilo je veoma kontaminirano *PCB*-ima, što je bilo jasno potvrđeno uzorcima masne ribe sa istočne obale Švedske (44). Jetra je glavni organ za metabolizam *PCB*-a, a zatim intestinum. PCB se dovodi u vezu sa nastankom malignog melanoma, ne-Hodžkinovog limfoma i karcinoma dojke. Visoko hlorisani PCB opstaju u telu, sa poluživotom u od 8 do 15 godina, dok manje hlorisani PCB imaju kraći poluživot (45).

Nikl i jedinjenja nikla

Nikl je široko rasprostranjen u prirodi i nalazi se u životinjama, biljkama i zemljištu. To je 24. element po zastupljenosti, koji čini oko 0,008% zemljine kore (46). Zbog otpornosti na koroziju i

Benzidine

The production and usage of benzidine in dye industry was noted in some developing countries. The Food and Drug Administration of the United States of America limited the contents of benzidine in color additives to 1 part per billion (ppb). Although exposure to benzidine via ingestion is considered highly unlikely, impurities in synthetic coloring agents may be metabolized to benzidine after ingestion (14).

The general population can be exposed to benzidine in contact with consumer goods containing benzidine or benzidine-based dyes, such as leather products, clothes and toys (15,16). Some food colorants, in the limited number of products and at safe levels, can contain trace amounts of benzidine (17). Benzidine causes urinary bladder cancer, while benzidine and its conjugates (monoacetylbenzidine) are indicators of urinary carcinogens.

Polychlorobiphenyls (PCBs)

Depending on the position and number of chlorine atoms, there are 209 congeners of PCBs (similar compounds). A group of dioxine-like (DS) PCBs is made of twelve PCBs. PCBs have never been used as separate compounds, but as complex mixtures. Frame et al. and Johnson et al. state that around 130 of 209 PCBs are in commercial products. In such commercial products, concentrations of PCBs are above 0.05% (18,19).

Food products are analyzed regularly for PCBs (Scandinavia, Finland) and international programs for the supervision of food quality (European Food Safety Agency) (20,21), while this analysis is focused on dioxine-like PCBs, which are analyzed together with dioxins and furans. Eggs are usually analyzed for PCBs, especially yolks (22,23). Fruit and vegetables are analyzed more rarely than food products that are rich in lipids. PCBs are used for military purposes, as well. Also, they are used as sealants, fire retardants, in caulks, adhesives, carbonless copy paper, transport systems, rubber products, paints, pesticide extenders, plasticizers, wire coatings and metal coatings (24,25). The improper handling of electric waste has been identified as a source of pollution with PCBs, especially for older devices (26).

PCBs can be found across the world in concentrations that can be measured in all components of the environment (soil and sediments, water, air), in wild animals and human bodies. The human exposure to PCBs mainly happens via the consumption of contaminated food, as well as via inhalation and dermal absorption. PCBs are absorbed via organic carbon in the soil, and once they are absorbed, they remain relatively stable (27). Food is the main path of ingestion of PCBs.

For decades, PCBs have reached air from industrial facilities, military locations, hazardous waste landfills, electric arc furnace, burning and other forms of combustion, mud from sewage, construction materials, dyes, sealants, sealing floor masses, adhesives, plasticizers in older buildings (28,29). PCBs from soil, sediments, air and water entered the food chain by bioaccumulation in plants and animal fats. PCBs are accumulated in adipose tissues of all animals, in all dairy products containing fats, and eggs (23,30). Concentrations of PCBs are usually the highest in carnivorous fish, which come from polluted waters (31). The general population has been exposed to the multiple sources of PCBs for decades, rarely via one commercial product. The exposure of general population to PCBs is likely in less developed and weakly controlled African and Asian countries or accidentally in other parts of the world.

PCBs appear during the combustion of mainly old waste and other processes at high temperatures. Leaves of plants (cabbage and salad) bioaccumulate organic pollutants and may be used for biomonitoring with the help of very sensitive instrumental methods for the assessment of pollution with PCB (32,34). During the unlimited application of PCBs over decades, they have been absorbed by materials, such as concrete or wood, and they have particularly contaminated the indoor air (29).

PCBs get into water via drainage systems, industrial waste waters, rainwater drains, processed water from solid waste landfills, atmospheric sedimentation, and water discharge from agricultural fields and fruit gardens with obsolete pesticides or their compounds (35,36). During the early 1990s, food was identified as the main source of human exposure to lypophilic and stable PCBs (20,37,38). In the European general population, more than 90% of exposure to PCBs was via food (milk and dairy products for almost all groups of newborns and children), fish products

na toplotu, tvrdoće i čvrstoće, nikl je deo mnogih legura, a koristi se za galvanizaciju, keramiku, pigmente i međuprodukte (katalizatori, stvaranje drugih jedinjenja nikla). Feronikal se koristi za pripremu čelika, a nerđajući čelici sadrže čak 25–30% nikla. Sagorevanje fosilnih goriva je najviše doprinelo da se nikl nađe u atmosferi, čineći 62% antropogenih emisija tokom 1980-ih (47,48). Konzumiranje nikla putem hrane i u manjoj meri pijaće vode, primarni su načini ekspozicije niklu opšte populacije (nepušači).

Najviše koncentracije nikla izmerene su u pasulju, orasima i žitaricama. Iako se koncentracije nikla razlikuju u zavisnosti od vrste hrane, prosečne vrednosti su uglavnom u opsegu od 0,01 do 0,1 µg/g. Jedinjenja nikla i metal nikl uzrokuju rak pluća, nosne šupljine i paranazalnih sinusa. Rastvorljiva jedinjenja nikla se brzo apsorbuju kroz pluća i izlučuju se urinom kao nikl. Dovode se u vezu sa karcinomom pluća, nosne šupljine i paranazalnih sinusa.

Šestovalentni hrom (Cr6+) i jedinjenja šestovalentnog hroma

Hrom (Cr6+) se retko javlja u prirodi. Do 2013. godine njegova jedinjenja su se široko koristila kao: pigment za tekstilne boje, kao i za boje uopšte, za mastila i plastiku, antikorozivna sredstva, sredstva za zaštitu drveta, za završnu obradu metala i hromiranje, za štavljenje kože, u pesticidima i kao nečistoća u cementu (49). Jedinjenja šestovalentnog hroma izazivaju rak pluća, a utiču i na pojavu karcinoma nosa i nazalnih sinusa. Njihov urinarni metabolit je hrom.

Kadmijum i jedinjenja kadmijuma

Zemljina kora u proseku sadrži 0,1–0,2 mg/kg kadmijuma, veće koncentracije se nalaze u rudama cinka, olova i bakra. Prirodni nivoi kadmijuma u okeanskoj vodi su uglavnom do 5 ng/l, pa čak i do 110 ng/l (50-52). Kadmijum se koristi za pigmente, staklo, glazure, keramiku, gumu, emajle, umetničke boje, vatromete, premaze i oplate (gvožđe, čelik, aluminijum i obojeni metali), stabilizatore za plastiku, legure obojenih metala (bakar, cink, olovo, kalaj, srebro i drugi plemeniti metali), poluprovodnike i fotonaponske uređaje, automobilske sisteme, vojnu opremu i morske/priobalne instalacije (51). Nikl-kadmijumske baterije se široko primenjuju u železničkoj i avionskoj industriji, za bežične električne alate, mobilne telefone, prenosne računare, kućne aparate i igračke (51). Kadmijum je takođe prisutan kao nečistoća u fosilnim gorivima (ugalj, nafta, gas, drvo), cementu i fosfatnim đubrivima.

Dnevni unos kadmijuma za američku populaciju putem hrane se procenjuje na 18,9 µg/dan po osobi (52). Prosečne procene nedeljnog unosa putem hrane u Evropskoj uniji 2,3 µg/kg telesne težine. Bilo kakav unos kadmijuma u organizam je neprihvatljiv, jer je izuzetno karcinogen. Kadmijum i kadmijumova jedinjenja uzrokuju rak pluća, a utiču i na pojavu raka bubrega i prostate. Urinarni metaboliti su beta 2-mikroglobulin i N-acetil-β-D-glukozaminidaza.

1,3-butadien

1,3-butadien nastaje isključivo antropogeno. Široko se koristio u proizvodnji sintetičke gume i polimera, kao važne komponente automobila, građevinskog materijala, delova računara, telekomunikacione opreme, odeće, zaštitne odeće, ambalaže i predmeta za domaćinstvo. Takođe se koristio kao međuprodukt u proizvodnji osnovnih petrohemikalija (53). Butadien je sveprisutni zagađivač životne sredine koji uglavnom potiče od proizvoda sagorevanja (emisije motornih vozila i duvanskog dima). Postoji uzročna veza između izloženosti 1,3-butadienu i nastanku leukemije, kao i ne-Hodgkinovog limfoma (54). Njegovi urinarni metaboliti su: 1,2-dihidroksibutil merkapturna kiselina i monohidroksi-3-butenil merkapturna kiselina. Ovi urinarni metaboliti su važni kao pokazatelji izloženosti 1,3-butadienu, vrlo opasnom karcinogenu.

4,4'-metilenbis (2-hloroanilin)

4,4'-metilenbis (2-hloroanilin) je veštački proizvod. Čist 4,4'-metilenbis (2-hloroanilin) se ne koristi komercijalno, osim za laboratorijske radove (55), ali 4,4'-metilenbis (2-hloroanilin) čini do 90–92% proizvedenih komercijalnih hemikalija (anilinske boje) za premaze i livene poliuretane. Opšta populacija može biti izložena anilinskim bojama ako živi na području kontaminiranom ovim jedinjenjima. Anilinske boje uzrokuju karcinom mokraćne bešike kod izloženih osoba (56). Urinarni metaboliti za 4,4'-metilenbis (2-hloroanilin) su anilini i njihovi konjugati.

and seafood for the majority of adolescents and older people (19, 39-43). The region of the Baltic Sea was very contaminated by PCBs, which was clearly confirmed by the samples of fatty fish from the Swedish east coast (44). Liver is the main organ for the metabolism of PCBs, and then intestinum. PCBs are associated with the occurrence of malign melanoma, non-Hodgkin lymphoma and breast cancer. Highly chlorinated PCBs remain in the body, with the half-life of 8 to 15 years, while less chlorinated PCBs have shorter half-life (45).

Nickel and nickel compounds

Nickel is widely present in nature, in animals, plants and soil. It is the 24th most abundant element, which makes up about 0.008% of the earth's crust (46). Due to its resistance to corrosion and heat, due to its hardness, nickel is part of many alloys, and it is used for galvanization, ceramics, pigments and intermediates (catalyzers, creation of other nickel compounds). Ferronickel is used for the preparation of steel, while stainless steel contains 20-25% of nickel. The combustion of fossil fuels contributed most to atmospheric nickel concentrations, making 62% of anthropogenic emissions in 1980s (47,48). The consumption of nickel via food, and to the lesser extent, via drinking water, is the primary way of exposure of the general population to nickel (non-smokers).

The highest concentrations of nickel have been measured in beans, walnuts and grains. Although nickel concentrations depend on the type of food, average values mainly range from 0.01 to 0.1 µg/g. Nickel compounds and metal nickel cause lung cancer, nose and paranasal sinus cancer. Soluble nickel compounds are quickly absorbed through lungs and excreted via urine as nickel. They are associated with lung cancer, nose cancer and paranasal sinus cancer.

Hexavalent chromium (Cr+) and hexavalent chromium compounds

Chromium (Cr+) rarely appears in nature. Until 2013, its compounds have been widely used as: the pigment for textile colors, as well as colors in general, for inks and plastics, anti-corrosive agents, wood preservatives, metal finishers and chromium plating, for tanning, in pesticides, and as impurities in cement (49). The hexavalent chromium compounds cause lung cancer, nose and nasal sinus cancer. Chromium is its urinary metabolite.

Cadmium and cadmium compounds

The earth's crust contains 0.1-0.2 mg/kg of cadmium on average, while higher concentrations are in the ores of zinc, lead and copper. The natural level of cadmium in the oceans ranges from 5 ŋg/L to even 110 ŋg/L (50-52). Cadmium is used for pigments, glass, glaze, ceramics, rubber, stainless products, artistic colors, fireworks, coatings and plating (iron, steel, aluminum, and colored metals), stabilizers for plastics, alloys of colored metals (copper, zinc, lead, tin, silver and other precious metals), semiconductors and photovoltaic devices, vehicle systems, art equipment and sea/coastal installations (51). Nickel-cadmium batteries are widely used in rail industry and aviation, for wireless electric tools, mobile phones, laptops, home appliances and toys (51). Cadmium is also present in impurities in fossil fuels (coal, petroleum, gas, wood), cement and phosphate fertilizers.

The daily intake of cadmium for the American population via food is estimated at 18.9 µg/day per person (52). The average weekly intake in the European Union is 2.3 µg/kg/body weight. Any intake of cadmium into the organism is not tolerable, because it is highly carcinogenic. Cadmium and cadmium compounds cause lung cancer, and it influences kidney cancer and prostate cancer. Urinary metabolites are beta 2-microglobulin and N-acetyl-ß-D-glucosaminidase.

1,3-Butadiene

1,3-butadiene is released from the anthropogenic sources. It has been widely used in the production of synthetic rubber and polymers, as important components of cars, construction materials, computer parts, telecommunication equipment, clothes, protective clothes, packaging and household utensils. Also, it has been used as an intermediate in the production of basic petrochemicals (53). Butadiene is the omnipresent environmental pollutant, which mainly originates from combustion products (emissions from vehicles and tobacco smoke). There is a causal relationship between the exposure to 1,3-butadiene and occurrence of leukemia and non-Hodgkin lymphoma (54). Its urinary

2,3,7,8-tetrahlorodibenzo-para-dioksin (2,3,7,8-*TCDD*)

2,3,7,8-tetrahlorodibenzo-para-dioksin (2,3,7,8-*TCDD*) nema komercijalne primene, ali se zbog svoje izuzetno velike karcinogenosti razmatra u onkologiji. Izvori ispuštanja 2,3,7,8-*TCDD*-a u životnu sredinu su: mesta spaljivanja (komunalni otpad, bolnički otpad, opasni otpad), izvori sagorevanja (cementne peći, drva za gorivo, dizel vozila, peći na ugalj), industrijski izvori (fabrike celuloze i papira, hemijska industrija, metalna industrija) i drugi izvori (kanalizacijski mulj, biohemijski procesi, fotolitički procesi, šumski požari, slučajna ispuštanja) (57). 2,3,7,8-*TCDD* je postojan u životnoj sredini i akumulira se u životinjskoj masti (mesu, mleku, jajima, ribi). Dioksin je potpuni karcinogen, može da podstiče pojavu bilo kog karcinoma kod ljudi, ali su dokazi najjači za nastanak raka pluća.

Polihlorovani dibenzofurani (*PCDF*)

Najznačajniji polihlorovani dibenzofuran (*PCDF*) je pentahlorodibenzofuran (*PeCDF*). *PeCDF* se može oslobađati tokom nekontrolisanog sagorevanja. Ranije se oslobađao i tokom rafiniranja i obrade metala; hemijske proizvodnje hlorofenola, *PCDF*-a, vinil-hlorida i beljenja pulpe (58,59). *PCDF* se mogu akumulirati u masnom tkivu životinja, pa su se tokom ranijih decenija najveće koncentracije *PCDF* nalazile u ribi, mesu, jajima i mlečnim proizvodima (60,61). Urinarni metaboliti za 2,3,4,7,8-pentahlorodibenzofuran su metoksi-pentahlorodibenzo furan i dimetoksi-pentahloro-bifenil.

Bis (hlorometil) etar (*BCME*) i hlorometil metil etar (*CAMEO*)

BCME se koristi u proizvodnji plastike, jonoizmenjivačkih smola i polimera (62). *BCME* se koristi kao industrijski rastvarač, vodoodbojni sastojak, sastojak jonoizmenjivačke smole i polimera (62). Izloženost ljudi *BCME* i *CAMEO* je putem udisanja i dermalnog kontakta, jer se *BCME* i *CAMEO* oslobađuju tokom proizvodnje u vazduh (63). *BCME* i *CAMEO* uzrokuju rak pluća. U biološkim tečnostima ove supstance se brzo hidrolizuju na hlorovodoničnu kiselinu, metanol i formaldehid (64), zato ne postoje njihovi pouzdani urinarni metaboliti.

1,2-dihloropropan

1,2-dihloropropan je isključivo sintetički proizvod. Koristio se u proizvodnji propilena, tetrahloridnog ugljenika i tetrahloretilena, kao i u proizvodnji sredstava za uklanjanje mrlja na tekstilu, zatim ekstrakata ulja i parafina, jedinjenja za ribanje, sredstava za čišćenje metala, odmašćivača na bazi rastvarača, lepkova i insekticida (65,66). Glavni put unosa u ljudski organizam je kroz respiratorni trakt. Koncentracije u urinu koreliraju sa koncentracijama u udahnutom vazduhu. 1,2-dihloropropan izaziva rak bilijarnog trakta (holangiokarcinom). 1,2-dihloropropan se nepromenjen izlučuje urinom.

Lindan

Komisija za ekološku saradnju (67,68) predstavila je podatke da je lindan zabranjen za upotrebu u 52 zemlje, a u 33 zemlje je ograničena ili strogo ograničena upotreba, a u 10 zemalja nije registrovan. Lindan proizvodi nekoliko proizvođača širom sveta, uglavnom u Indiji i Kini (69). Ljudi su izloženi lindanu koji se nalazi u prašini domaćinstva. U studiji sprovedenoj širom SAD lindan je izmeren u prašini domaćinstava u količini 5,85 ppm (69). U Singapuru, uzorci prašine u zatvorenom prostoru iz 31 doma sadržali su lindan u rasponu od 2,23 ng/g do 2,9 ng/g (70). Izomeri lindana nalaze se u mlečnim proizvodima, mesu, ribi, živini, baštenskom voću, uljima i mastima, lisnatom i korenovskom povrću i šećeru. Kod ljudi lindan uzrokuje ne-Hodgkinov limfom. Hlorfenoli su urinarni metaboliti lindana.

Aflatoksini

Postoji najmanje 13 različitih vrsta prirodnih aflatoksina. Aflatoksin B1 se smatra najčešćim i najmoćnijim aflatoksinom, a proizvode ga gljivice Aspergilus Flavus i Aspergilus parasiticus (71). Aspergilus Flavus je posebno zastupljen u tropskim predelima, a glavni domaćini su mu: kukuruz, kikiriki i seme pamuka, dok su orašasti plodovi ređe kontaminirani. Pojedini začini mogu ponekad sadržavati aflatoksine. Zbog trgovine poljoprivrednim proizvodima širom sveta, nijedan region sveta nije bezbedan od aflatoksina (71). Aflatoksini B1, B2, G1 i G2 mogu se sakupljati u prašini u pogonima za preradu hrane (kakao, kafa i začini) (72). Rizik od hepatocelularnog karcinoma značajno je povišen kod ispitanika sa visokim koncentracijama

metabolites are the following: 1,2-dihydroxybutyl mercapturic acid and monohydroxy-3-butenyl mercapturic acid. These urinary metabolites are important indicators of exposure to 1,3-butadiene, which is a very dangerous carcinogen.

4,4'-methylenebis (2-chloroaniline)

4,4'-methylenebis (2-chloroaniline) is a synthetic product. Pure 4,4'-methylenebis (2-chloroaniline) is not used commercially, except for laboratory work (55), but 4,4'-methylenebis (2-chloroaniline) makes 90-92% of produced commercial chemicals (aniline colors) for dyes and cast polyurethanes. The general population may be exposed to aniline colors if people live in the regions contaminated by these compounds. Aniline colors cause cancer of urinary bladder in exposed persons (56). Urinary metabolites for 4,4'-methylenebis (2-chloroaniline) are anilines and their conjugates.

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD)

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) has no commercial application, but due to its high carcinogenicity, it is examined in oncology. The sources of release of TCDD into the environment are: locations of combustion (municipal waste, hospital waste, hazardous waste), sources of combustion (cement furnace, wood for fuel, diesel vehicles, coal furnace), industrial sources (paper and cellulose factories, chemical industry, metal industry) and other sources (sewage mud, biochemical processes, photolytic processes, forest fires, accidental release) (57). TCDD is constant in the environment and it is accumulated in animal fats (meat, milk, eggs, fish). Dioxin is a complete carcinogen, and it can cause any cancer in humans, but the strongest proofs are for the development of lung cancer.

Polychlorinated dibenzofurans (PCDFs)

The most common polychlorinated dibenzofuran (PCDF) is pentachlorodibenzofuran (PeCDF). PeCDF can be released during the uncontrolled combustion. Previously it was released during refining and processing of metals, chemical production of chlorophenol, PCDB, vinyl chloride and bleaching of pulp (58,59). PCDF can be accumulated in the adipose tissue of animals, and therefore, during the previous decades, the highest concentrations have been in fish, meat, eggs and dairy products (60,61). Urinary metabolites for 2,3,4,7,8-pentachlorodibenzofuran are methoxy-pentachlorodibenzofuran and dimethoxy-pentachloro-biphenyl.

Bis (chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME)

BCME is used in the production of plastics, ion-exchange resins and polymers (62). CMME is used as an industrial solvent, water repellent, component of the ion-exchange resin, and polymers (62). The human exposure to BCME and CMME is via inhalation and dermal contact, because BCME and CMME are released during the production into the air (63). BCME and BCME cause lung cancer. In biological fluids, these substances are quickly hydrolyzed to hydrochloric acid, methanol and formaldehyde (64), and therefore, there are no reliable urinary metabolites.

1,2-dichloropropane

1,2-dichloropropane is a synthetic product. It has been used for the production of propylene, carbon tetrachloride and tetrachloroethylene, as well as in the production of agents used for the removal of stains on textile, then in the oil and paraffin extraction, compounds used for cleaning, agents used for cleaning of metal, degreasers based on solvents, adhesives and insecticides (65,66). It is inhaled via respiratory tract mainly. Concentrations in urine correlate with the concentrations in the inhaled air. 1,2-dichloropropane causes cancer of biliary tract (holangiocancer). 1,2-dichloropropane is excreted via urine in the unchanged form.

Lindane (hexachlorocyclohexane, γ-HCH)

The Commission for Environmental Cooperation (67,68) presented data that lindane is prohibited in 52 countries, while its usage is limited or strictly limited in 33 countries and not registered in 10 countries. Lindane is produced by a few manufacturers, mainly in India and China (69). Humans are exposed to lindane which is present in household dust. In a study conducted in the USA, lindane was measured in household dust in concentrations 5.85 ppb (ppb – parts per billion) (69). In Singapore, samples of indoor dust from 31 households contained γ-HCH and ß-HCH that

urinarnih metabolita aflatoksina (adukti aflatoksin-N7-gvanina) (73-75).

2-naftilamin

Opšta populacija može biti izložena 2-naftilaminu iz: duvanskog dima, različitih isparenja koja sadrže 2-naftilamin, nekih boja i boja za kosu kontaminiranih 2-naftilaminom i izduvnih gasova dizel goriva. 2-naftilamin izaziva rak mokraćne bešike kod ljudi. Njegovi urinarni metaboliti su: 2-naftilamin, N- (2-naftil) -hidroksilamin, bis- (2-amino1-naftil) fosfat, 2-aminobifenil i 4-aminobifenil.

4-aminobifenil

4-aminobifenil se formira tokom sagorevanja duvana (glavni izvor izloženosti za opštu populaciju). Ostali potencijalni izvori su: kozmetički aditivi u boji, boje za kosu, fungicidi koji se koriste za jabuke, isparenja od ulja i rafinirane svinjsknj masti (76). Život u blizini mesta zagađenih benzidinom može rezultirati izlaganjem 4-aminobifenilu, jer određene bakterije mogu razgraditi benzedin na 4-aminobifenil (77). Verovatno postoje i drugi izvori izlaganja iz okoline, jer su biomarkeri izvedeni iz aromatičnih amina (adukti hemoglobina, urinarni metaboliti) identifikovani kod nepušača koji nisu profesionalno izloženi ovim hemikalijama. 4-aminobifenil uzrokuje rak mokraćne bešike (56). Njegovi urinarni metaboliti su: N-hidroksi-4-aminobifenil, N-glukuronidi i 4-aminobifenil - DNK adukti.

Aristolohična kiselina

Aristolohična kiselina I i II su alkaloidne komponente iz brojnih vrsta porodice Aristolochiaceae (Aristolochia, Asarum) (71). Koristile su se u tabletama za mršavljenje i u razvijenim zemljama su zabranjene. Ali, biljke su sveprisutne u svetu i uzrokuju fibrozu i otkazivanje bubrega (hronična bolest) sa fatalnim ishodima (nefropatija kineskog bilja). Postoji pozitivan odnos između konzumiranja biljaka aristolohia i pojave urotelnih karcinoma. U uzorcima urotela kod svih pacijenata sa urotelijskim karcinomom pronađeni su DNK adukti aristolohične kiseline (71). Njihovi urinarni metaboliti su urinarni DNK adukti aristolohične kiseline (71).

Etilen oksid

Etilen oksid se koristi kao osnovna supstanca za proizvodnju važnih derivata kao što su: di-, tri- i poli- (etilen) glikoli, celuloza i poli- (propilen) glikol, etri etilen glikola, etanol-amini, alkoholi i masni amini, alkil fenoli. Veoma malo etilen oksid se koristi direktno u gasovitom obliku kao sredstvo za sterilizaciju, fumigant i insekticid (sam ili u smeši sa azotom, ugljen-dioksidom ili dihlorofluorometanom). On se koristi za sterilizaciju lekova, bolničke opreme, medicinskih predmeta za višekratnu upotrebu, ambalažnog materijala, hrane, knjiga, muzejskih predmeta, naučne opreme, odeće, krzna, vagona, aviona i košnica. Postoji uzročno-posledična veza između izloženosti etilen oksidu i pojave limfnog i hematopoetskog karcinoma (ne-Hodgkinov limfom, multipli mijelom i hronična limfocitna leukemija) i raka dojke kod ljudi (54). Njegovi urinarni metaboliti su: S-(2-hidroksietil) glutation i N-acetil-S-(2-hidroksietil)-L-cistein [hidroksietil merkapturna kiselina (HEMA)] - konjugati sa glutationom, kao i etilen glikol (54).

Zaključak

Većina ljudi ne zna koliki broj kancerogenih hemikalija i u kojoj meri dospeva svakodnevno u organizam čoveka. Karcinomi su uglavnom multikauzalne bolesti, ali kod postojanja intenzivne izloženosti prethodno pomenutim hemijskim karcinogenima, vrlo verovatno da su upravo te hemikalije i glavni etiološki faktori. Nažalost, mnogi od ovih karcinogena imaju kumulativni efekat. Nije moguće eliminisati kancerogene materije iz našeg života, ali možemo unaprediti njihovo otkrivanje u organizmu ljudi i na taj način redukovati ili eliminisati njihovo prisustvo u životnom okruženju. To je zadatak preventivne onkologije.

Savremene metode poput tečne hromatografije visokih performansi mogu otkriti oko nekoliko hiljada različitih jedinjenja u ljudskom urinu. Ali ova i slične metode zahtevaju posebne laboratorijske uslove, toksikološke laboratorije, obučeno osoblje, specijaliste toksikološke hemije i izuzetno su skupe. Urinarni metaboliti karcinogena mogu se otkriti kvalitativnim i kvantitativnim analizama, koje bi trebale biti razvijene tako da sa sigurnošću predstavljaju biomarkere ekspozicije hemijskim karcinogenima.

ranged from 2.23 ηg/g to 2.9 ηg/g (70). LIndane isomers are present in dairy products, meat, fish, poultry, fruit, oils and fats, leaf and root vegetables and sugar. In humans, lindane causes non-Hodgkin lymphoma. Chlorophenols are urinary metabolites of lindane.

Aflatoxins

There are at least 13 different species of natural aflatoxins. Aflatoxin B1 is deemed to be the most common and most powerful aflatoxin. It is produced by the fungus Aspergillus Flavus and Aspergillus Parasiticus (71). Aspergillus Flavus is present in tropical regions, while its main hosts are: corn, peanuts, and cotton seeds, while nuts are more rarely contaminated. Certain spices may contain aflatoxins. Due to the agricultural products trade around the world, there is no region in the world which is safe (71). Aflatoxins B1, B2, G1 and G2 can be present in the dust in food processing industry (cacao, coffee, spices) (72). The risk of hepatocellular carcinoma is significantly higher in respondents with high concentrations of urinary metabolites of aflatoxin (aflatoxin-N7-gvanine adducts) (73,75).

2-Naphthylamine (2-NA)

The general population may be exposed to 2-NA from: tobacco smoke, steams that contain 2-NA, some colors and hair dyes contaminated by 2-NA, and exhaust gas of diesel fuels. 2-Naphthylamine causes urinary bladder cancer in humans. Its urinary metabolites are: 2-Naphthylamine, N-(2-naphthyl)-hydroxilamine, bis- (2-aminol-naphthyl) phosphate, 2-aminobiphenyl, and 4-aminobiphenil.

4-aminobiphenyl

4-aminobiphenyl is formed during the combustion of tobacco (the main source of exposure for the general population). Other potential sources are: cosmetic additives in colors, hair dyes, fungicides that are used for apples, steams from oils and refined lard (76). Living near the place, which is contaminated by benzidine, may result in the exposure to 4-aminobiphenyl, because certain bacteria can dissolve benzedine to 4-aminobiphenyl (77). Probably there are other sources of environmental exposure, because biomarkers that are derived from aromatic amines (hemoglobin adducts, urinary metabolites) have been identified in non-smokers, who have not been exposed to these chemicals professionally. 4-aminobiphenyl causes urinary bladder cancer (56). Its urinary metabolites are the following: N-hydroxy-4-aminobiphenyl, N-glucuronides and 4-aminobiphenyl-DNA adducts.

Aristolochic acid

Aristolochic acids I and II are alkaloid components from numerous species from the family Aristolochiaceae (Aristolochia, Asarum) (71). They were used in weight loss pills and they were prohibited in developed countries. However, these plants are omnipresent in the world and they cause fibrosis, and kidney failure (chronic disease) with fatal outcomes (Chinese herbs nephropathy). There is a positive relationship between the consumption of aristolochia plants and the development of urothelial carcinoma. In the samples of urothelia in all patients with urothelial carcinoma, DNA adducts of aristolochic acid were found (71). Their urinary metabolites are urinary DNA adducts of aristolochic acid (71).

Etylene oxide

Etylene oxide is used as the main substance for the production of important derivatives, such as di-, tri- and poly- (ethylene) glycols, ethers of ethylene glycol, ethanol amines, alcohol and fatty amines, alkyl phenols. Ethylene oxide is barely used directly in the gaseous state as an agent for sterilization, fumigant and insecticide (alone or in mixture with nitrogen, carbon dioxide or dichloromethane). It is used for the sterilization of drugs, hospital equipment, reusable medical devices, scientific equipment, clothes, fur, railroad cars, planes and beehives. There is a causal relationship between the exposure to ethylene oxide and the development of lymphoma and hematopoietic carcinoma (non-Hodgkin lymphoma, multiple myeloma, chronic lymphocyte leukemia) and breast cancer (54). Its urinary metabolites are: S-(2-hydroxyethyl) glutation and N-acetyl-S-(2-hydroxyethyl)-L-cysteine [hydroxyethyl mercapturic acid (HEMA)] – conjugates with glutation, as well as ethyl glycol (54).

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Conclusion

The majority of people does not know how many carcinogenic chemicals, and to what extent, enter the human organism every day. Cancers are mainly multicausal diseases, but in case of intense exposure to the previously mentioned chemical carcinogens, it is very likely that these chemicals are the main etiological factors. Unfortunately, many of these carcinogens have a cumulative effect. It is not possible to eliminate carcinogenic substances from our lives, but we can improve their detection in the human organism and thus, reduce or eliminate their presence in the environment. This is a task of preventive oncology.

Contemporary methods such as high performance liquid chromatography can detect a few thousands of different compounds in human urine. However, this and similar methods demand special laboratory conditions, toxicology laboratories, trained personnel, toxicology specialists and they are very expensive. Urinary metabolites of carcinogens may be detected with the help of qualitative and quantitative analyses, which should be developed to represent biomarkers of exposure to chemical carcinogens.

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STUDIJE PRESEKA: PREDNOSTI I NEDOSTACI

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SAŽETAK

Studija preseka pripada grupi opservacionih studija. Neki autori studiju preseka svrstavaju u analitičke studije, a drugi u deskriptivne studije. Nazivi za ovu studiju su i studija prevalencije i transverzalna studija. U okviru ove studije, istovremeno se određuje izloženost faktorima rizika i postojanje bolesti. Ove studije predstavljaju "snimak" trenutne situacije. Najpogodnije su za javnozdravstvena planiranja, etiološka ispitivanja i testiranje dijagnostičkih testova. Ne koriste se za istraživanje bolesti koje kratko traju i za retke poremećaje zdravlja, a glavni njihov nedostatak je što ne može da se odredi smer uzročno-posledične veze. S druge strane, ove studije su jeftinije, brže i jednostavnije se izvode i u okviru njih ne dolazi do osipanja podataka u odnosu na kohortne studije, a u odnosu na studije slučajeva i kontrola izvode se na reprezentativnom uzorku i nije prisutna pristrasnost prisečanja o izloženosti faktorima rizika.

Ključne reči: studija preseka, prednosti, nedostaci, unakrsni odnos

Uvod

Epidemiologija je nauka o učestalosti, rasprostranjenosti i determinantama stanja ili događaja povezanih sa zdravljem u nekoj populaciji, kao i o sprečavanju i suzbijanju zdravstvenih problema. Specifični ciljevi epidemiologije su: identifikacija etiologije ili uzroka bolesti; određivanje opterećenosti društva/zajednice bolestima; ispitivanje prirodnog toka bolesti i prognoze bolesti; evaluacija postojećih i novih preventivnih i terapijskih mera i načina pružanja zdravstvene zaštite; obezbeđivanje osnova za razvoj javne politike u vezi sa ekološkim problemima, genetskim pitanjima i razmatranja vezana za prevenciju bolesti i promociju zdravlja (1-6). Epidemiološke studije (tabela 1) se koriste u cilju realizacije postavljenih epidemioloških ciljeva (3,5). Deskriptivne (engl. *descriptive studies*) i analitičke studije (engl. *analytic studies*) pripadaju opservacionim studijama (engl. observational studies), jer se realizuju bez intervencije istraživača. Nazivaju se i neeksperimentalne studije. Nasuprot njima eksperimentalne (engl. *experimental studies*) ili interventne studije (engl. *interventional studies*) sprovode se pod direktnom kontrolom istraživača.

Studija preseka (engl. *cross-sectional study*) pripada grupi analitičkih studija, mada je neki istraživači svrstavaju u deskriptivne studije (1-3). Ova studija ima i sledeće nazive: studija prevalencije (jer se u njoj izračunava prevalencija zbog identifikovanja prevalentnih slučajeva) i transverzalna studija (jer se sprovodi u jednom trenutku, tj. predstavlja snimak trenutne situacije) (slika 1). To znači da se u definisanoj populaciji, ili njenom reprezentativnom uzorku, istovremeno određuje izloženost faktorima rizika i postojanje bolesti (slika 2). One predstavljaju "snimak" trenutne situacije. U njima se ispituje povezanost između posmatranih obeležja. Najčešće se koriste za sagledavanje potreba zdravstvene zaštite, postavljanje hipoteze o etiologiji i za evaluaciju dijagnostičkih testova.

Razlike između studija preseka i longitudinalnih studija

U studijama preseka prikupljaju se podaci o izloženosti određenom faktoru rizika i postojanju bolesti u određenom trenutku, a u longitudinalnim studijama prikupljanje podataka sprovodi se više

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CROSS-SECTION STUDIES: ADVANTAGES AND DISADVANTAGES

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SUMMARY

The cross-sectional study belongs to the group of observational studies. Some authors classify cross-sectional studies as analytical studies and others as descriptive studies. The names for this study are both the prevalence study and the transversal study. In this study, the exposure to risk factors and the existence of the disease is determined simultaneously. These studies are a "snapshot" of the current situation. They are most suitable for public health planning, etiological testing, and diagnostic testing. They are not used for research on short-term diseases and rare health disorders, and their main drawback is that the direction of the cause-and-effect relationship cannot be determined. On the other hand, these studies are cheaper, faster, and easier to perform and do not scatter data compared to cohort studies, and compared to case studies and controls, they are performed on a representative sample, and there is no recall bias regarding exposure to risk factors.

Keywords: cross-sectional study, advantages, disadvantages, odds ratio

Introduction

Epidemiology is the science of the frequency, prevalence, and determinants of health-related conditions or events in a population and the prevention and suppression of health problems. The specific objectives of epidemiology are: identification of the etiology or cause of the disease; determining the disease caused burden to society/community; examination of the natural course of the disease and its prognosis; evaluation of existing and new preventive and therapeutic measures and ways of providing health care; providing a basis for policy development related to environmental issues, genetic issues, and considerations related to disease prevention and health promotion (1-6). Epidemiological studies (Table 1) are used in order to achieve the set epidemiological goals (3,5). Descriptive and analytical studies belong to observational studies because they are conducted without researchers' intervention. They are also called non-experimental studies. In contrast, experimental or interventional studies are conducted under the direct control of researchers. The cross-sectional study belongs to the group of analytical studies, although some researchers classify it as descriptive studies (1-3). This study also has the following names: prevalence study (because it calculates prevalence due to the identification of prevalence cases) and transversal study (because it is conducted at one time, i.e., it is a snapshot of the current situation) (Figure 1). This means that in a defined population or its representative sample, exposure to risk factors and the existence of disease are simultaneously determined (Figure 2). They are a "snapshot" of the current situation. They examine the connection between the observed features. They are most often used to assess health care needs, hypothesize the etiology, and evaluate diagnostic tests.

Differences between cross-sectional studies and longitudinal studies

Cross-sectional studies collect data on exposure to a certain risk factor and the existence of a disease at a certain time, and in longitudinal

Tabela 1. Epidemiološke studije (7)

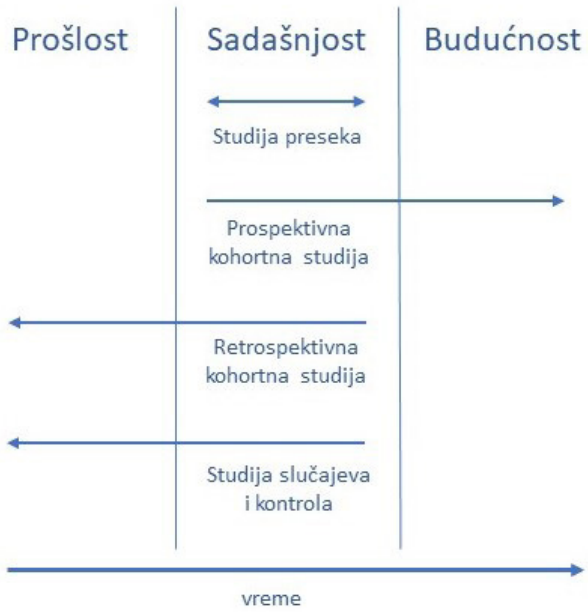
Opservacione studije
1. deskriptivne studije i 2. analitičke studije: a) studije slučajeva i kontrola (anamnestičke studije), b) retrospektivne i prospektivne kohortne studije, c) studije preseka (studije prevalencije).
Interventne (eksperimentalne) studije:
a) klinički eksperimenti, b) terenski eksperimenti, c) eksperimenti u društvenoj zajednici.

puta iz istog uzorka tokom dužeg vremena (slika 3) (6,8). Studija preseka predstavlja osnov za dalje longitudinalne studije. Ako želimo da ispitamo vezu između gojaznosti i bola u donjem delu leđa, onda je dobro prvo da se sprovede studija preseka. Među svim gojaznim studentima medicinskog fakulteta u trenutku sprovođenja studije preseka možemo ispitati da li neko u trenutku sprovođenja istraživanja (npr. tokom jednog dana) ima bol u donjem delu leđa (trenutna prevalencija)? Ukoliko dobijemo da je gojaznost u vezi sa bolom u donjem delu leđa samo kod muškaraca, onda možemo sprovesti longitudinalnu studiju kako bi ispitali ovu vezu samo među muškarcima. Bez prethodnog sprovođenja studije preseka ne bi mogli da se fokusiramo samo na mušku populaciju.

Način izvođenja studije i izračunavanje unakrsnog odnosa

Koraci u izvođenju studije preseka su: definisanje populacije (cela populacija ili njen reprezentativan uzorak), prikupljanje podataka o izloženosti potencijalnim faktorima i prisustvu poremećaja zdravlja, i analiza prikupljenih podataka (3,6,8).

U studijama preseka izračunamo unakrsni odnos (UO) ili odnos šansi tako što šansu da su



Slika 1. Studija preseka i ostale analitičke studije u odnosu na vreme izvođenja studije

Table 1. Epidemiological studies (7)

Observational studies:
1. descriptive studies and
2. analytical studies:
a) case studies and controls (anamnestic studies)
b) retrospective and prospective cohort studies
c) cross-sectional studies (prevalence studies)
Intervention (experimental) studies:
a) clinical experiments,
b) field experiments,
c) experiments in the social community

studies, data collection is carried out several times from the same sample over a long time (Figure 3) (6,8). The cross-sectional study is the basis for further longitudinal studies. If we want to examine the connection between obesity and lower back pain, it is good to conduct a cross-sectional study first. Among all obese medical students at the time of the cross-sectional study, we can examine whether someone has lower back pain at the time of the study (e.g., during one day; current prevalence)? If we find that obesity is related to lower back pain only in men, we can conduct a longitudinal study to examine this relationship only among men. Without prior cross-sectional studies, we would be unable to focus only on the male population.

Study conduction method and cross-relationship calculation

The steps in conducting a cross-sectional study are: defining the population (whole population or its representative sample), collecting data on exposure to potential factors and the presence of health disorders, and analyzing the collected data (3,6,8).

We calculate the cross-ratio (OR) or chance ratio in cross-sectional studies by dividing the

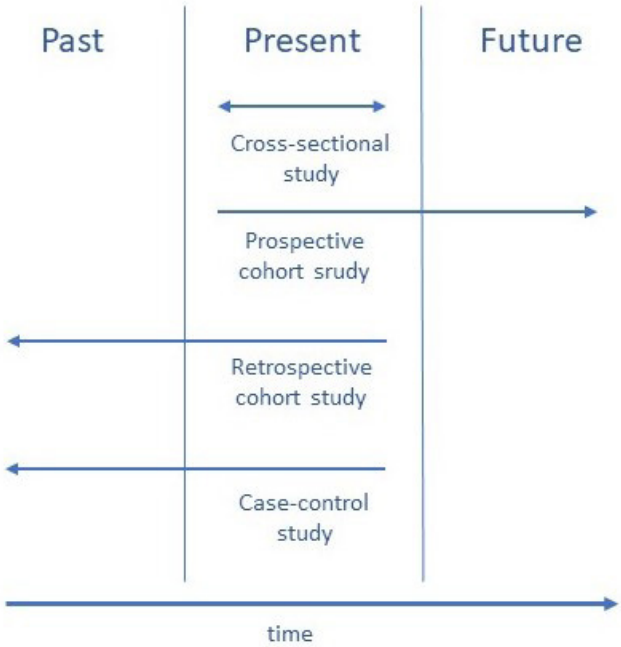
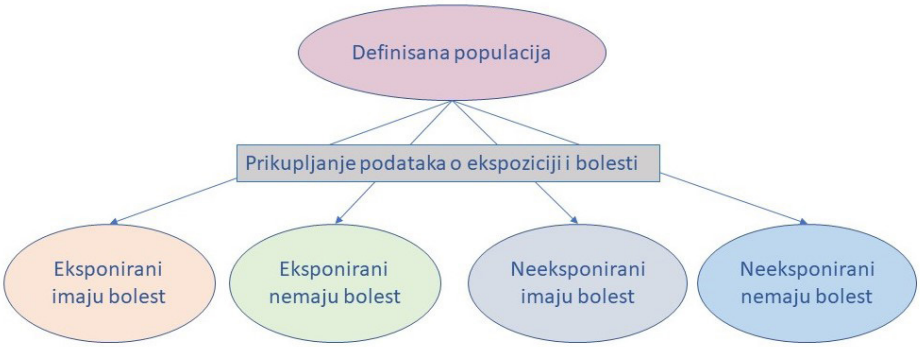


Figure 1. Cross-sectional study and other analytical studies in relation to the time of the study



Slika 2. Dizajn studije preseka

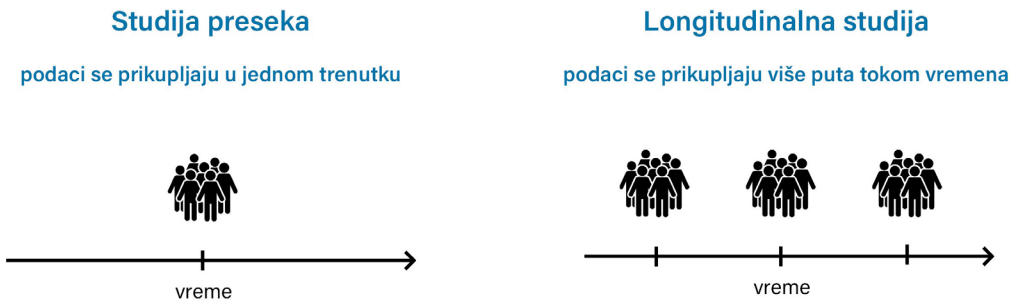
oboleli izloženi (a/c) delimo sa šansom da su kontrole bile izložene (b/d). Ukoliko je vrednost UO jednaka 1 to znači da nema veze između ispitivane ekpozicije i bolesti, ako je manja od 1 onda je ekspozicija negativno povezana sa bolešću (protektivni efekat), a ako je veća od 1 onda je ekspozicija pozitivno povezana sa bolešću (faktor rizika).

U ovim studijama povezanost između izloženosti nekom faktoru i pojave bolesti može se ispitati određivanjem prevalencije bolesti (bol u donjem delu leđa) u odnosu na izloženost (gojaznost) ili izračunavanjem prevalencije izloženosti (gojaznosti) u odnosu na postojanje bolesti (bol u donjem delu leđa) (5,6).

Izračunavanje veličine uzorka

U studijama preseka može da se procenjuje prevalencija neke bolesti u populaciji ili prosečna vrednost neke kvantitativne varijable u populaciji (9).

Dakle, potrebna je adekvatna veličina uzorka da bi se procenila prevalencija u populaciji sa dobrom preciznošću. Za izračunavanje veličine uzorka koristi se sledeća formula za kvalitativne varijable: $n=(Z^2 P (1 - P))/d^2)$. U ovoj formuli *n* je veličina uzorka, *Z* je koeficijent poverenja (za 5% grešku prve vrste iznosi 1,96, a za 1% grešku prve vrste iznosi 2,58), *P* je očekivana prevalencija (koja se može dobiti iz istih studija ili pilot istraživanja sprovedenih od strane istraživača), i *d* je preciznost (odgovara veličini efekta). Pretpostavljena vrednost prevalencije je veoma važna, jer se preciznost (*d*) bira prema vrednosti *P*. Greška prve vrste (greška I vrste ili alfa greška) zavisi od naše arbitrarne odluke kako ćemo definisati granicu statističke značajnosti. Nema dovoljno smernica za izbor odgovarajuće d vrednosti. Neki autori preporučuju da se izabere preciznost od 5% ako je prevalencija bolesti između 10% i 90%. Međutim, kada je pretpostavljena prevalencija mala (ispod 10%), preciznost od 5% je neodgovarajuća. Na primer, ako je pretpostavljena prevalencija 1%, preciznost od 5% očigledno može dovesti do odabira neprikladne



Slika 3. Razlika između studije preseka i longitudinalnih studija

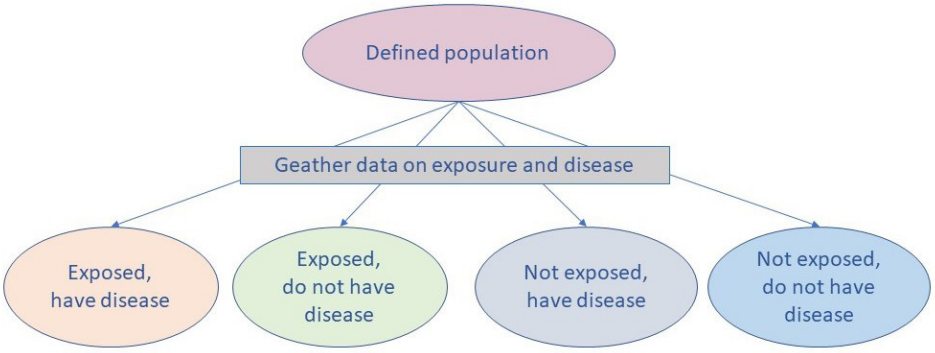


Figure 2. Cross-sectional study design

chance patients were exposed (a/c) by the chance that controls were exposed (b/d). If the value of the OR is equal to 1, it means that there is no connection between the examined exposure and the disease, if it is less than 1, then the exposure is negatively related to the disease (protective effect), and if it is greater than 1, then the exposure is positively related to the disease (risk factor).

In these studies, the association between exposure to a factor and disease onset could be examined by determining disease prevalence (lower back pain) versus exposure (obesity) or calculating exposure prevalence (obesity) versus disease (lower back pain) (5.6).

Sample size calculation

Cross-sectional studies can estimate the prevalence of a disease in a population or the average value of a quantitative variable in a population (9).

Therefore, adequate sample size is required to estimate the prevalence in the population with good precision. The following formula for qualitative variables: $n=(Z^2 P (1 - P))/d^2$ is used To calculate the sample size. In this formula, n is the sample size, Z is the confidence coefficient (It is 1.96 for 5% type I error, and 2.58 for 1% type I error), P is the expected prevalence (which can be obtained from the same studies or pilot research conducted by researchers), and d is precision (corresponds to the size of the effect). The assumed value of prevalence is very important because precision (d) is chosen according to the value of P. The error of the first type (type I error or alpha error) depends on our arbitrary decision on how we will define the limit of statistical significance. There are not enough guidelines to select the appropriate d value. Some authors recommend choosing an accuracy of 5% if the prevalence of the disease is between 10% and 90%. However, when the assumed prevalence is low (below 10%), an accuracy of 5% is inadequate. For example, if a prevalence of 1% is assumed, it is obvious that an accuracy of 5% can lead to the selection of an

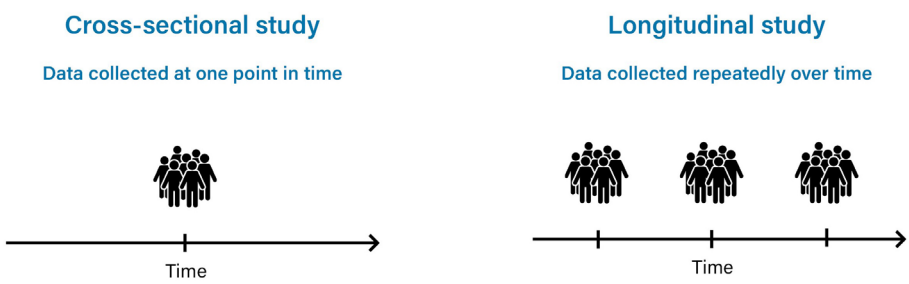


Figure 3. Difference between cross-sectional study and longitudinal studies

veličine uzorka. Konzervativan izbor bi bio jedna četvrtina ili jedna petina prevalencije kao vrednost preciznosti u slučaju male *P*.

Na primer, kolika je adekvatna veličina uzorka ako želimo da procenimo proporciju pacijenata sa dijabetesom tip 2 kod školske dece u jednoj opštini. Na osnovu podataka drugih studija prevalencija dijabetesa tip 2 nije veća od 15% kod školske dece. Pored ovog podatka definišemo da ćemo koristiti preciznost od 5% i 5% grešku tipa I. Prema gore navedenoj formuli neophodna veličina uzorka je 196 ispitanika $n=(1{,}96^2\ 15\ (1 - 0{,}15))/0{,}05^2)=196$.

Kada je u pitanju određivanje prosečne vrednosti neke kvantitativne varijable u populaciji onda koristimo sledeću formulu: $n=(Z^2\ SD^2)/d^2$ (9). U ovoj formuli SD je standardna devijacije koja može biti preuzeta iz prethodnih istraživanja ili iz sprovedenog pilot istraživanja. Na primer, odrediti neophodnu veličinu uzorka da bi se procenila prosečna vrednost glikemije dece jednog grada. Za izračunavanje opredeljujemo se za preciznost od 5%, 5% grešku tipa I i SD = 25 iz nekog predhodnog istraživanja. Prema gore navedenoj formuli, istraživač treba da meri glikemiju kod najmanje 96 dece da bi odredio prosečnu vrednost glikemije kod dece $n=(1{,}96^2\ 25^2\ )/5^2=96$.

Prednosti i nedostaci

Ove studije su najpogodnije za ispitivanje veze između bolesti i stalnih karakteristika ispitanika (npr. genetske karakteristike), kao i za hronične bolesti (1-7). One su jeftine, brzo i jednostavno se izvode, i u okviru njih ne dolazi do osipanja podataka u odnosu na kohortne studije. U odnosu na studije slučajeva i kontrola izvode se na reprezentativnom uzorku populaciji i ne postoji pristrasnost prisećanja (engl. *recall bias*) o izloženosti potencijalnim faktorima. Često se koriste za testiranje efektivnosti dijagnostičkih testova. Nedostaci studije preseka su: ne koriste se za bolesti koje kratko traju i za retke poremećaje zdravlja, u njima se može utvrditi veza, ali ne i vremenski sled između ekspozicije i bolesti (ne zna se šta je uzrok, a šta posledica bolesti), ne obuhvataju sve obolele npr. osobe sa ranim smrtnim ishodom, ne može se razmatrati izloženost koja brzo nestaje, procena incidencije nije moguća, i ispitivane grupe na kraju istraživanja mogu imati različiti broj ispitanika, što doprinosi gubitku statističke efikasnosti (1-6). Ne koriste se za analizu ponašanja tokom određenog vremenskog perioda ili utvrđivanje dugoročnih trendova. Na primer, sagledavanje koristi od neke psihoterapije na depresiju (9), ne može se sagledati studijom preseka koja se izvodi posle dva dana od primenjene terapije. To znači da bi na osnovu studije preseka došli do pogrešnog zaključka da terapija dovodi do depresije, čak i ako je ona efikasna posle dužeg vremenskog perioda.

Kada možemo koristiti studije preseka

Studija preseka može se koristiti za populaciona istraživanja (8). U ovim studijama možemo da budemo zainteresovani da saznamo kolika je prevalencija dijabetesa tipa 2 u nekom gradu X. Neophodno je prvo da formiramo reprezentativan uzorak ciljne populacije. Važno je da opišemo tačan način formiranja reprezentativnog uzorka. Zatim je potrebno da kontaktiramo sve članove izabranih domaćinstva koja treba da budu uključena u reprezentativan uzorak. Ako se ukupan ispitivani uzorak sastoji od 7.897 i ako od njih 112 osoba ima dijabetes tip 2, onda će prevalencija dijabetesa u gradu X iznositi: 112/7897 ili 14,2/1000 stanovnika.

Studije preseka mogu se koristiti za procenu prevalencije u kliničkim istraživanjima (8). Ukoliko želimo da odredimo prevalenciju hipovitaminoze D kod pacijenata sa prelomima koji se sukcesivno hospitalizuju na odeljenju traumatologije. Na primer, ako je u studiju uključeno 250 pacijenata sa traumom iz Klinike za ortopediju i ako od svih uzmemo anamnestičke podatke i uzorak krvi (za određivanje vrednosti vitamina D) onda možemo da procenimo kolika je prevalencija hipovitaminoze kod ljudi sa traumom. Ako 93 pacijenta od 250 hospitalizovanih zbog povreda ima nedostatak vitamina D, onda je prevalencija hipovitaminoze vitamina D 37,2%. Ne treba zaboraviti da je ovo klinička studija i da može imati sva ograničenja koja kliničke studije mogu da imaju. Stoga, generalizacija podataka o prevalenciji iz ovih studija može biti ograničena.

Mogu se koristiti kada se ispituje prevalencija određenog poremećaja zdravlja tokom vremena (serija studija preseka). U Engleskoj je sprovedena serijska studija preseka i to 1994, 1998, 2003, 2006. i 2011. (9). Istraživanje je bilo bazirano na reprezentativnom uzorku populacije uzrasta ≥16 godina. Rezultati istraživanja su pokazali da se vrednosti srednjeg nivoa krvnog pritiska muškaraca i žena u opštoj populaciji i među pacijentima sa

inappropriate sample size. A conservative choice would be one quarter or one-fifth of the prevalence as a value of precision in the case of small P.

For example, what is the adequate sample size to estimate the proportion of patients with type 2 diabetes in school children in one municipality? According to other studies, the prevalence of type 2 diabetes is no more than 15% in school children. In addition to this data, we define that we will use a precision of 5% and 5% type I error. According to the above formula, the required sample size is 196 subjects $n=(1{,}96^2\ 15\ (1 - 0{,}15))/0{,}05^2)=196$.

When it comes to determining the average value of a quantitative variable in the population, then we use the following formula: $n=(Z^2\ SD^2\ )/d^2$ (9). In this formula, SD is a standard deviation taken either from previous research or from a conducted pilot study. Take the example of determining the necessary sample size to estimate the average glycemic value of children in a city. For the calculation, we opt for an accuracy of 5%, 5% type I error, and SD = 25 from a previous study. According to the above formula, the researcher should measure glycemia in at least 96 children to determine the average glycemic value in children $n=(1{,}96^2\ 25^2\ )/5^2=96)$.

Advantages and disadvantages

These studies are most suitable for examining the relationship between disease and persistent characteristics of subjects (e.g., genetic characteristics), as well as for chronic diseases (1-7). They are cheap, quick, easy to perform, and do not scatter data compared to cohort studies (Table 2). In comparison to case studies and controls, they are performed on a representative population sample, and there is no recall bias regarding the exposure to potential factors. They are often used to test the effectiveness of diagnostic tests. The disadvantages of the cross-sectional study are: they are not used for short-term diseases and rare health disorders, they can establish a relationship, but not the time sequence between exposure and disease (it is not known what the cause is and what the consequence is), they do not include all patients, e.g., individuals with early death, rapidly disappearing exposure cannot be considered, incidence cannot be estimated, and study groups at the end of the study may have different numbers of subjects, contributing to a loss of statistical efficacy (1-6). They are not used to analyze behavior over a period of time or to identify long-term trends. For example, the benefits of some psychotherapy for depression (9) cannot be seen in a cross-sectional study performed two days after the therapy, this is because a cross-sectional study would lead to the erroneous conclusion that therapy leads to depression, even if it is effective after a long time period.

Cases when we can use cross-sectional studies

A cross-sectional study can be used for population surveys (8). In these studies, we may be interested to find out the prevalence of type 2 diabetes in city X. First, it is necessary to form a representative sample of the target population. It is important to describe the exact way of forming a representative sample. We then need to contact all members of the selected households for inclusion in the representative sample. If the total sample surveyed consists of 7,897 and 112 have type 2 diabetes, then the prevalence of diabetes in city X will be 112/7897 or 14.2 / 1000 inhabitants.

Cross-sectional studies can be used to assess prevalence in clinical trials (8). If we want to determine the prevalence of hypovitaminosis D in patients with fractures who are successively hospitalized in the trauma department. For example, if 250 patients with trauma from the Orthopedic Clinic were included in the study and if we take anamnestic data and a blood sample (to determine the value of vitamin D) from all of them, we can estimate the prevalence of hypovitaminosis in people with trauma. If 93 patients out of 250 hospitalized due to injuries have vitamin D deficiency, then the prevalence of vitamin D hypovitaminosis is 37.2%. One must not forget that this is a clinical study and that it may have all the limitations that clinical studies may have. Therefore, the generalization of prevalence data from these studies may be limited.

They can be used when examining the prevalence of a particular health disorder over time (a series of cross-sectional studies). A serial cross-sectional study was conducted in England in 1994, 1998, 2003, 2006, and 2011. (9). The study was based on a representative sample of the population aged ≥16 years. The research results showed that the values of the average blood

lečenom hipertenzijom progresivno poboljšavaju u period od 1994. do 2011. godine.

Studije preseka se mogu koristiti i za određivanje unakrsnog odnosa (OR) (8). Na primer, hoćemo da ispitamo povezanost između pola i deficita vitamina D (iz prethodnog primera). Napravićemo tabelu kontingencije 2 × 2. Od 250 pacijenata, 175 su žene, a 75 muškarci. Od 50 pacijenata sa deficitom vitamina D, 40 su žene a 10 muškarci (tabela 2). Unakrsni odnos (UO) računa se kao a × b/c × d, odnosno 40 × 65/ 10 × 135, što iznosi 4. Interpretacija ove vrednosti unakrsnog odnosa jeste da žene imaju 4 puta veću šansu da imaju deficit vitamina D nego muškarci. Pošto je OR veći od 1 ishod je verovatniji kod žena nego kod muškaraca. Međutim, potrebni su nam intervali poverenja za dalje tumačenje unakrsnog odnosa.

Populaciona istraživanja

Cilj studije bio je da se proceni prevalencija povišenog krvnog pritiska i nivo svesti, lečenja i kontrole hipertenzije u populaciji Srbije. Istraživanje je sprovedeno po tipu studije preseka, na teritoriji cele Srbije 2006. godine (11). Ispitivanu populaciju činili su muškarci i žene starosti 20 i više godina. Osobe koje su se nalazile u domovima za penzionere, socijalnim institucijama, zatvorima i psihijatrijskim ustanovama su isključene iz studije. Uzorak je trebalo da predstavlja sva domaćinstva u okviru Popisa stanovništva Srbije 2002. godine. Primenjeno je stratifikovano dvostepeno uzorkovanje. Uključeno je stanovništvo iz 3 regiona: Beograda, Vojvodine i Centralne Srbije. Dalja stratumska analiza bila je na urbano i ruralno stanovništvo. Odabran je reprezentativan uzorak. U studiju je bilo uključeno 6156 domaćinstava, odnosno 14.204 ispitanika. Intervjui i merenja krvnog pritiska obavljeni su u domovima ispitanika. Krvni pritisak je meren ispitanicima koji su bili u sedećem položaju, nakon što su odmarali najmanje 5 minuta. Urađena su tri merenja, sa intervalom od 1 minuta između merenja. Za vrednost krvnog pritiska uzeta je srednja vrednost prva dva merenja. Međutim, ako je razlika između prvog i drugog čitanja bila veća od 10 mm Hg, korišćena je srednja vrednost 2 najbliža merenja. Hipertenzija (HBP) je definisan kao prosečan sistolni krvni pritisak (SBP) od 140 mm Hg ili više, dijastolni krvni pritisak (DBP) od 90 mm Hg ili više, ili upotreba antihipertenziva. Hipertenzija je klasifikovana kao stadijum 1, kada je SBP od 140 do 159 mm Hg ili DBP od 90 do 99 mm Hg, a kao stadijum 2 kada je SBP od 160 mm Hg ili više ili DBP od 100 mm Hg ili više. Kategorije HBP su definisane kao nelečeni HBP i lečeni HBP. Kontrola HBP je definisana kao farmakološki tretman HBP koji dovodi do SBP manjeg od 140 mm Hg i DBP manjeg od 90 mm Hg. Procena razloga za nelečenje od HBP je bila procenjena upitnikom. Svest o HBP je podrazumevala da je ispitaniku lekar rekao da ima povišen krvni pritisak. Ukupno, 47% odrasle populacije Srbije imalo je hipertenziju: 25,3% je imalo hipertenziju prvog stadijuma, 18,1% je imalo hipertenziju drugog stadijuma. Samo 58,0% osoba se hipertenzijom je bilo svesno da ima bolest, a 60,4% je bilo na lečenju. Među onima koji su bili na lečenju, samo 20,9% je imalo krvni pritisak u granicama normale. Jedan od 10 učesnika sa hipertenzijom nije lečen, između ostalog iz razloga što smatraju da je lečenje nepotrebno (55,3%) ili im nedostaje novac za lekove (19,3%). Prevalencija nedijagnostikovane i nelečene hipertenzije je visoka u odrasloj populaciji Srbije. Potrebne su dalje mere da bi se ubrzalo otkrivanje i lečenje visokog krvnog pritiska. Pažnju treba usmeriti prema programima koji unapređuju znanje, stavove i svest o hipertenziji kod odraslih.

Panel studija

Panel studija je definisana kao studija koja prikuplja informacije o istim pojedincima u različitim vremenskim periodima. Drugim rečima, panel studiju čine najmanje dve studije preseka sprovedene na istim ispitanicima u dve ili više tačaka u vremenu. To je longitudinalna studija koju treba

Tabela 2. Fiktivni primer za izračunavanje unakrsnog odnosa

Pol	Deficit vitamina D	Zadovoljavajući nivo vitamina D	Ukupno
Žene	40 (a)	135 (b)	175
Muškarci	10 (c)	65 (d)	75
Ukupno	50	200	250

pressure level of men and women in the general population and among patients with treated hypertension progressively improved from 1994 to 2011.

Cross-sectional studies can also be used to determine cross-ratio (OR) (8). Take the example that we want to examine the relationship between gender and vitamin D deficiency (previously used). We will make a contingency table of 2 × 2. Out of 250 patients, 175 are women, and 75 are men. Of the 50 patients with vitamin D deficiency, 40 are women, and 10 are men (Figure 2). Cross-ratio (OR) is calculated as a × b / c × d, or 40 × 65/10 × 135, which is 4. The interpretation of this value of cross-ratio is that women are four times more likely to have vitamin D deficiency than men. Since the OR is greater than 1, the outcome is more likely in women than in men. However, we need confidence intervals to interpret the cross-relationship further.

Population research

The study aimed to assess the prevalence of high blood pressure, the level of awareness, the treatment, and control of hypertension in the population of Serbia. The research was conducted as a cross-sectional study encompassing the entire territory of Serbia in 2006 (11). The study's population consisted of men and women aged 20 and over. Individuals in retirement homes, social institutions, prisons, and psychiatric institutions were excluded from the study. The sample was supposed to represent all households within the 2002 Census of Serbia. Stratified two-stage sampling was applied. Population from 3 regions was included: Belgrade, Vojvodina, and Central Serbia. Further stratum analysis differentiated urban and rural populations. A representative sample was selected. The study included 6156 households or 14,204 respondents. Interviews and blood pressure measurements were performed in the respondent's homes. The subjects' blood pressure was measured in sitting position after at least 5 minutes of rest. Three measurements were made, with an interval of 1 minute between measurements. The mean value of the first two measurements was taken as the blood pressure value. However, if the difference between the first and second readings was greater than 10 mm Hg, the mean value of the two closest measurements was used. Hypertension (HBP) is defined as average systolic blood pressure (SBP) of 140 mm Hg or more, diastolic blood pressure (DBP) of 90 mm Hg or more, or the use of antihypertensives. Hypertension is classified as stage 1 when SBP is 140 to 159 mm Hg or DBP 90 to 99 mm Hg, and as stage 2 when SBP is 160 mm Hg or more or DBP 100 mm Hg or more. Categories of HBP are defined as untreated HBP and treated HBP. Control of HBP is defined as the pharmacological treatment of HBP that results in SBP of less than 140 mm Hg and DBP of less than 90 mm Hg. The reasons for the non-treatment of HBP were assessed by a questionnaire. Awareness of HBP meant that the doctor informed the respondent regarding the respondent's high blood pressure. In total, 47% of the adult population of Serbia had hypertension: 25.3% had first-degree hypertension, 18.1% had second-degree hypertension. Only 58.0% of people with hypertension knew they had the disease, and 60.4% were in treatment. Among those who were treated, only 20.9% had blood pressure within normal limits. One in 10 participants with hypertension was not treated, among other things, because they believe that treatment is unnecessary (55.3%) or they lack money for medicines (19.3%). The prevalence of undiagnosed and untreated hypertension is high in the adult population of Serbia. Further measures are needed to speed up the detection and treatment of high blood pressure. Attention should be directed to programs that promote knowledge, attitudes, and awareness of hypertension in adults.

Table 2. Fictitious example for calculating the cross-relationship

Sex	Vitamin D deficiency	Satisfactory vitamin D levels	Total
Women	40 (a)	135 (b)	175
Men	10 (c)	65 (d)	75
Total	50	200	250

razlikovati od drugih studija koje prikupljaju informacije tokom vremena, kao što su vremenske serije i kohortne studije.

Primer panel studije

Cilj studije je bio da se proceni uticaj zagađenja vazduha na dnevne respiratorne simptome dece osnovne škole u Seulu (12). Koristeći dizajn panel studije, prikupljeni su podaci iz dnevnika za respiratorne simptome dece tokom 1. i 15. dana aprila, jula, oktobra i decembra 2003. godine kod učenika 2. i 3. razreda osnovne škole. Podaci o respiratornim simptomima spojeni su sa podacima o zagađenju ambijentalnog vazduha koje je pratilo Ministarstvo životne sredine. Zatim je procenjen odnos između dnevnih simptoma ispitanika i izloženosti zagađenju vazduha, nakon kontrole na različite potencijalne konfaunding faktore. Izloženost azot-dioksidu (NO_2) u toku dana značajno je povećala simptome gornjih disajnih puteva (UO=1,12, 95% IP=1,01-1,24) i donjih disajnih puteva (UO=1,18, 95% IP= 1.06-1.31) u toku istog dana. Izloženost sumpor dioksidu (SO_2) i ugljen monoksidu (CO) u toku dana bila je povezana sa simptomima donjih respiratornih organa (UO =1,12, 95% IP=1,01-1,25 za SO2; UO=1,16, 95% IP=1,02-1,32 za CO). Može se zaključiti da izloženost zagađenju vazduha utiče na dnevne respiratorne simptome kod dece. Ova studija sugeriše da kratkoročne promene nivoa zagađenja vazduha imaju značajan efekat na zdravlje dece i da ih treba smatrati važnim javnozdravstvenim problemom.

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Panel study

A panel study is defined as a study that collects information about the same individuals in different time periods. In other words, a panel study consists of at least two cross-sectional studies conducted on the same subjects at two or more points in time. It is a longitudinal study that should be distinguished from other studies that collect information over time, such as time series and cohort studies.

Panel study example

The study aimed to assess the impact of air pollution on the daily respiratory symptoms of primary school children in Seoul (12). Using the panel study design, data from the diary for children's respiratory symptoms were collected during the 1st and 15th April, July, October, and December 2003 in students of the 2nd and 3rd grade of primary school. Data on respiratory symptoms were combined with the data about ambient air pollution monitored by the Ministry of Environment. After controlling for various potential confounding factors, the relationship between the subjects' daily symptoms and exposure to air pollution was then assessed. Exposure to nitrogen dioxide (NO_2) during the day significantly increased the symptoms of the upper respiratory tract (UO = 1.12, 95% IP = 1.01-1.24) and lower respiratory tract (UO = 1.18, 95% IP). = 1.06-1.31) during the same day. Exposure to sulfur dioxide (SO_2) and carbon monoxide (CO) during the day was associated with lower respiratory symptoms (UO = 1.12, 95% IP = 1.01-1.25 for SO_2; UO = 1.16, 95% IP = 1.02-1.32 for CO). It can be concluded that exposure to air pollution affects daily respiratory symptoms in children. This study suggests that short-term changes in air pollution levels significantly affect children's health and should be considered an important public health problem.

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INSTITUT ZA HISTOLOGIJU I EMBRIOLOGIJU „PROF. DR ALEKSANDAR Đ. KOSTIĆ" KROZ PRIZMU SUDBINE NJEGOVOG OSNIVAČA POVODOM 100 GODINA OD OSNIVANJA INSTITUTA

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SAŽETAK

Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić" ove godine obeležava jedan vek postojanja. Osnivač Instituta, prvi profesor histologije i embriologije i prvi upravnik Instituta bio je prof. dr Aleksandar Kostić, jedna od poslednjih renesansnih ličnosti XX veka. Ogromnim trudom, zalaganjem i entuzijazmom je od prostorije u kojoj osim zidova, poda i plafona ničega nije bilo, doveo Institut do zgrade koja se krajem 1920-ih smatrala jednom od najmodernijih zgrada naučnih instituta u jugoistočnoj Evropi i koja je imala, za to doba, izvanredne uslove za obavljanje nastavne delatnosti, izuzetno posvećen kadar, ali i visoko razvijen istraživački potencijal, bogatu stručnu biblioteku, terminološki seminar i fotografsko odeljenje. Nakon bombardovanja Beograda i same zgrade Instituta 6. aprila 1941, Kostić je po drugi put podigao zgradu i postavio osnove za rad, a zatim, zbog ideoloških neslaganja, po sili zakona penzionisan i udaljen sa fakulteta. Moralno je rehabilitovan posthumno, zajedno sa grupom nastavnika Medicinskog fakulteta, na sednici Nastavno-naučnog veća održanoj 24. januara 2001. godine.

Ključne reči: istorijat, Institut za histologiju i embriologiju, prof. dr Aleksandar Đ. Kostić

Uvod

Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić" (stari naziv Histološki institut) ove godine obeležava prvi vek postojanja. Osnivač Instituta, dr Aleksandar Đ. Kostić (slika 1), bio je prvi profesor histologije i embriologije na Medicinskom fakultetu Univerziteta u Beogradu i prvi upravnik Histološkog Instituta. Rođen je u Beogradu 19. marta (6. marta po Julijanskom kalendaru) 1893. godine. U Beogradu je završio osnovnu školu i Drugu mušku gimnaziju. Paralelno sa gimnazijom, pohađao je i Srpsku muzičku školu (klavir i kompoziciju), u kojoj je direktor bio Stevan Mokranjac, a nastavnici Petar Krstić, Stevan Hristić, Stanislav Binički. U septembru 1912. godine upisao je Medicinski fakultet u Nansiju (Francuska). Studije medicine je u dva navrata prekidao, radi učešća u Balkanskim ratovima i u Prvom svetskom ratu. Diplomirao je i doktorirao 1921. godine na Medicinskom fakultetu u Strazburu (1,2)

Predlog za njegovo angažovanje na novoosnovanom Medicinskom fakultetu u Beogradu potekao je od dr Miloša Đ. Popovića, lekara i prvog Srbina specijaliste stomatologa, osnivača Saveza trezvene mladeži i Saveza izviđača Srbije. Naime, krajem 1920. godine, prodekan Medicinskog fakuleta prof. Vojislav Subbotić je u razgovoru sa dr Popovićem izrazio zabrinutost zbog teškoća u pronalaženju profesora za predmet histologija (3). Dr Popović je tada predložio mladog studenta iz Beograda, koji uspešno privodi kraju studije medicine u Strazburu, i već pokazuje veliko interesovanje za histologiju. O tom razgovoru obavestio je i Kostića, koji je na njegovu inicijativu ubrzo stupio u kontakt sa prof. Subbotićem i započeo prepisku o pripremama za angažovanje na budućem Institutu za histologiju i embriologiju (3, 4, 5). U međuvremenu, dr Subbotić je sa nestrpljenjem očekivao odgovor i prof. Eugena Ludviga (nem. *Eugen Ludwig*) sa Univerziteta u Bazelu, kome je pisao sa molbom da prihvati poziciju profesora histologije i embriologije na Medicinskom fakultetu u Beogradu (6). U dostupnoj arhivskoj

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INSTITUTE OF HISTOLOGY AND EMBRYOLOGY "PROF. DR ALEKSANDAR Đ. KOSTIĆ" THROUGH THE PRISM OF ITS FOUNDER'S FATE MARKING THE 100th ANNIVERSARY OF THE INSTITUTE

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SUMMARY

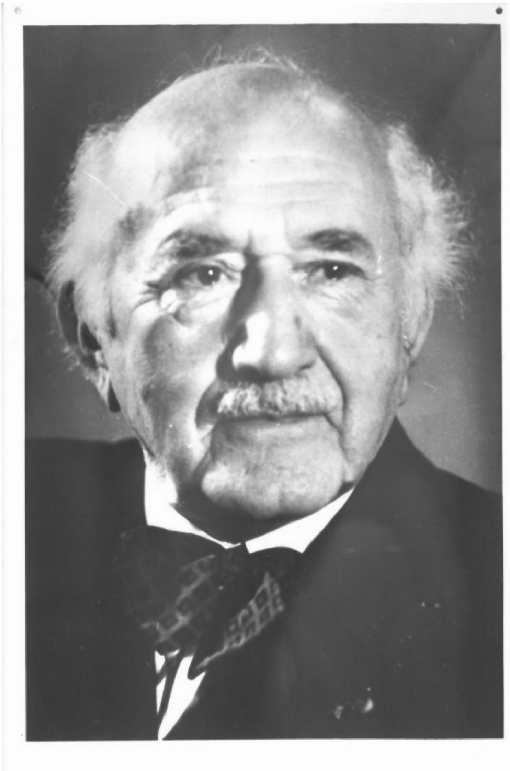
The Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić" is celebrating its 100th anniversary this year. The founder of the Institute, the first Professor of Histology and Embryology, and the first Director of the Institute was Professor Aleksandar Đ. Kostić, PhD, one of the last Renaissance figures of the XX century. Investing tremendous effort and enthusiasm he developed the Institute, from a bare room, with only four walls, a floor, and a ceiling, into a building which was, in the late 1920s, considered to be one of the most modern buildings housing a scientific institute in South-East Europe, which, for that time, had exceptionally good conditions for research and teaching, a very dedicated staff, but also a highly developed research potential, a rich library, terminology unit, and a photography department. After the bombing of Belgrade and of the Institute, on April 6, 1941, he rebuilt the building and reestablished the Institute, yet once more, during his lifetime, and then, due to ideological differences, he was forced into retirement and removed from the Faculty. He was morally rehabilitated posthumously, together with a group of teachers from the Faculty of Medicine, at the session of the Academic Council of the Faculty of Medicine held on January 24, 2001.

Keywords: history, Institute of Histology and Embryology, Professor Aleksandar Đ. Kostić

Introduction

The Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić", previously the Institute of Histology, is celebrating its 100th anniversary. The founder of the Institute, Dr. Aleksandar Đ. Kostić (Photo 1), was the first Professor of Histology and Embryology at the Faculty of Medicine of the University of Belgrade and the first Director of the Institute of Histology. He was born on March 19, 1893 (March 6, 1893, according to the Julian calendar), in Belgrade. He finished primary school and the Second Male Gymnasium in Belgrade. In parallel with high school, he attended the Serbian Music School (piano and composition), where, at the time, Stevan Mokranjac was the headmaster, while Petar Krstić, Stevan Hristić, and Stanislav Binički were teachers. In September 1912, Aleksandar Đ. Kostić enrolled at the Faculty of Medicine in Nancy (France). He interrupted his studies twice in order to take part in the Balkan Wars and the First World War. He graduated from the faculty and defended his PhD thesis, in 1921, at the Faculty of Medicine in Strasbourg (1, 2).

Dr. Miloš Đ. Popović, the first Serbian dental specialist and the founder of the Temperance Youth Association and the Scout Association of Serbia, was the one who proposed that Aleksandar Đ. Kostić should be invited to work at the newly founded Faculty of Medicine in Belgrade. Namely, near the end of 1920, in a conversation with Dr. Popović, the Vice Dean of the Faculty of Medicine, Professor Vojislav Subbotić, expressed his concern regarding the difficulties of finding a professor for the subject - Histology (3). Dr Popović proposed a young student from Belgrade who was about to graduate from the Faculty of Medicine in Strasbourg and who had already shown a great interest in Histology. Dr. Popović informed Aleksandar Kostić about this conversation, whereupon, encouraged by Dr. Popović, Dr. Kostić soon made contact with Dr. Subbotić and started correspondence about



Slika 1. Prof. dr Aleksandar Đ. Kostić, dokumentacija Instituta za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić", zaostavština Foto-filmskog zavoda

dokumentaciji se ne nalazi odgovor prof. Ludviga, tako da razlozi njegovog neprihvatanja pozicije na novoosnovanom fakultetu ostaju nepoznati. Imajući u vidu tu činjenicu, prof. Subbotić je nastavio prepisku sa Kostićem, ali je pisao i prof. Polu Buenu (fran. *Pol Bouin*), profesoru histologije na Univerzitetu u Strazburu, sa kojim je Aleksandar Kostić već ostvario saradnju. On je, sa svoje strane, molio prof. Buena da pomogne Kostiću da se pripremi za nastavu citologije, histologije i embriologije, koja je planirana za letnji semestar 1922. godine (5). Inače, konkurs za „nastavnika za katedru Normalne Histologije na Medicinskom Fakultetu Beogradskog Univerziteta" Medicinski fakultet je objavio 21. decembra 1920. godine u Službenim novinama Kraljevine Srba, Hrvata i Slovenaca.

U tekstu o istorijatu Histološkog instituta iz 1935. godine, objavljenom povodom 15 godina od osnivanja Medicinskog fakulteta, navodi se da je Histološki institut osnovan izborom dr Kostića za honorarnog profesora histologije i embriologije 29.10.1921. godine (7). Autor teksta je sam prof. Kostić koji je, možemo pretpostaviti, tekst pisao po sećanju i zato pogrešio, ili je do greške došlo prilikom pripreme rukopisa za štampu. U svakom slučaju, taj datum je široko zastupljen u različitim tekstovima jer su ga brojni autori kasnije direktno preuzimali (8-12). Međutim, nedavnim istraživanjima došlo se do više dokumenata koji pokazuju da je ministar prosvete potpisao rešenje o izboru dr Aleksandra Kostića za honorarnog profesora histologije i embriologije na Medicinskom fakultetu Univerziteta u Beogradu 21. novembra 1921. godine (1,13-15) i da je on tog dana i zvanično stupio na dužnost (13-15). U svetlu novih saznanja, upravo ovaj datum bi trebalo usvojiti kao zvaničan datum osnivanja Instituta.

U vreme imenovanja za honorarnog profesora histologije i embriologije, Aleksandar Kostić je još uvek bio u Strazburu, radio kao saradnik prof. Buena, i po preporuci prof. Subbotića pripremao zbirku histoloških preparata koja je poslužila kao osnovno nastavno sredstvo prvoj generaciji studenata. Zahvaljujući podršci koju je dobio od prof. Buena, dr Kostić je uspeo da do kraja decembra 1921. godine pripremi kolekciju između 2000 i 3000 histoloških preparata različitih tkiva i organa (2,7). Bila je to prva tekovina i prvi inventar novog, Histološkog instituta.

Po povratku u Srbiju, u januaru 1922. godine, dr Kostić se javio na dužnost i dobio na raspolaganje prvu prostoriju za potrebe rada Instituta. Bila je to jedna soba u prizemlju upravne zgrade Glavne vojne bolnice (Danas Uprava Kliničkog

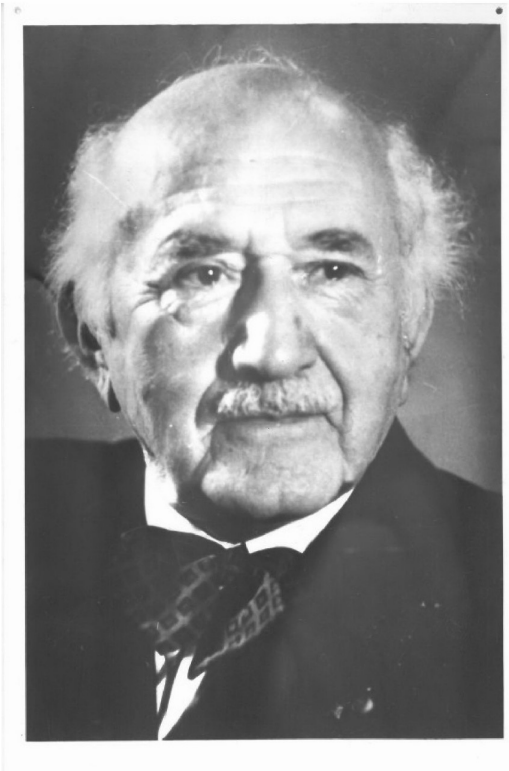


Figure 1. Prof. dr Aleksandar Đ. Kostić, documentation of the Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić", the legacy of the Photo-Film Institute

preparations for his engagement at the future Institute of Histology and Embryology (3, 4, 5). In the meantime, Dr. Subotić was impatient to receive a reply from Professor Eugen Ludwig of the University in Basel, whom he had written to with an appeal to accept the position of Professor of Histology and Embryology at the Faculty of Medicine in Belgrade (6). The reply from Professor Ludwig is not in the available archive documents, and therefore, his reasons for not accepting the position at the newly established faculty remain unknown. Bearing this fact in mind, Professor Subbotić continued his correspondence with Kostić, but he also wrote to Professor Pol Bouin, Professor of Histology at the University of Strasbourg, with whom Aleksandar Kostić had already collaborated. He appealed to Professor Bouin to help Kostić prepare for the curriculum of cytology, histology and embryology, which was planned for the summer semester of 1922 (5). The vacancy for “lecturer at the Department of Normal Histology at the Faculty of Medicine, University of Belgrade” was announced by the Faculty of Medicine on December 21, 1920, in the Official Gazette of the Kingdom of Serbs, Croats and Slovenes.

A text about the history of the Institute of Histology, from 1935, which was published in celebration of the 15th anniversary of the Faculty of Medicine, states that the Institute of Histology was founded when Dr. Kostić was appointed Adjunct Lecturer of Histology and Embryology, on October 29, 1921 (7). The author of the text was Professor Kostić himself, who, as we may assume, wrote this text from memory, and therefore, made a mistake, or the mistake was made during preparation for printing. In any case, this date is widely present in various texts, as numerous authors directly referenced the date from the above-mentioned text (8 - 12). However, several documents have been discovered in recent research showing that the Minister of Education signed the decision on appointing Dr. Aleksandar Kostić Adjunct Lecturer of Histology and Embryology at the Faculty of Medicine, University of Belgrade, on November 21, 1921 (1, 13 - 15), and also showing that he officially took up his duties (13-15) on the same day. In light of this new information, this date should be taken as the official date when the Institute was founded.

At the time when he was appointed Adjunct Lecturer of Histology and Embryology, Aleksandar

centra Srbije). Koliki napor i rad pojedinaca se u to vreme zahtevao i očekivao, u cilju osposobljavanja prostora za početak rada, uz svu neophodnu pripremu samih nastavnika i edukativnog materijala, može se zaključiti iz reči prof. Subbotića prilikom primopredaje prostorije „Dragi *amice*, evo, ovo je sada Vaš Institut. Za ostalo, *debrouillez-vous*[1] kako znate i umete" i komentara samog prof. dr Kostića zapisanog u spomenici Fakulteta iz 1935. godine „Primio sam sobu u kojoj osim četiri zida, poda i plafona, ničega nije bilo" (7). Prvu stolicu dobio je od obližnjeg Doma za sirotnu decu, a sto od komandira Dunavske bolničarske čete, sanitetskog kapetana Dimitrija Jovčića (7).

Neposredno pre početka nastave, u februaru 1922. godine, prof. Kostiću se javio student medicine Momčilo Milojević sa molbom da bude primljen i pomogne u praktičnom radu. Ova pomoć je u tom momentu bila dragocena, a Momčilo je bio prvi „pomoćni službenik" (16), iz perspektive današnjeg angažovanja studenata možemo reći demonstrator na Histološkom institutu. Na osnovu dostupnih podataka može se zaključiti da je bio angažovan samo u prvoj školskoj godini (Inače, Milojević je prerano preminuo, 1925. godine u Skoplju) (16). Fakultet je već 1. marta 1922. godine na Histološkom institutu zaposlio i prvo tehničko lice (najpre u zvanju služitelja). Bio je to Dimitrije Veličković, koji je naredne 23 godine, sve do penzionisanja 1945. godine, vršio dužnost domaćina Instituta (16,17).

Uprkos nedostatku osnovnih sredstava za rad, pripreme za početak nastave trebalo je obaviti do početka marta, odnosno, početka letnjeg semestra. Prof. Kostić je pozajmio klupe i radne stolove od Dunavske bolničke čete, koja se nalazila u krugu Glavne Vojne bolnice, a mikroskope sa Instituta za patologiju i Instituta za fiziologiju. Paralelno sa aktivnostima na nabavci neophodnog inventara, pripremio je i prvo predavanje, koje je održao 7. marta 1922. godine u slušaonici jedne od fakultetskih baraka na Guberevcu (nekadašnji naziv za padinu između kruga Opšte državne bolnice i ulice Kneza Miloša) (18). Prvom predavanju prisustvovali su, pored studenata i profesora Medicinskog fakulteta, i profesori Univerziteta u Beogradu. Ovim predavanjem praktično je počela nastava histologije i embriologije na Medicinskom fakultetu (7), o čemu je dekan Medicinskog fakulteta izvestio rektora Univerziteta u Beogradu 14. marta 1922. godine (18). Ubrzo po otpočinjanju nastave, ukazom od 2. maja 1922. godine, honorarni profesor Aleksandar Kostić postavljen je za docenta na Medicinskom fakultetu Univerziteta u Beogradu (1).

Već u novembru iste godine Institut je preseljen u novu zgradu Univerziteta, u prostorije namenjene Fizičkom institutu Filozofskog fakulteta, gde su bili bolji uslovi za izvođenje nastave, a stigli su i novi mikroskopi, koje je prof. Kostić poručio još dok je bio u Strazburu (7,16). Pored toga, formirana je i laboratorija za izradu histoloških preparata. Međutim, nedostajala je literatura o praktičnom laboratorijskom radu i histološkim tehnikama na našem jeziku. Zbog toga je prof. Kostić pripremio i već sledeće, 1923. godine, objavio priručnik „Osnovi histološke tehnike".

Po preseljenju, prof. Kostić je dobio i pomoć u radu sa studentima. Naime, dr Smilja Kostić-Joksić, njegova supruga, takođe francuski đak, postavljena je za prvog ukaznog asistenta histologije i embriologije oktobra 1922. godine (2). Na toj poziciji bila je sve do 1924. godine, kada je prešla na novoosnovanu Katedru pedijatrije, gde je kasnije, 1939. godine, izborom za docenta, postala prva žena u tom zvanju na Medicinskom fakultetu (2). Pored dr Smilje Kostić-Joksić, u izvođenju nastave pomagao je i student-demonstrator Stevan Vasojević (7). Na kraju zimskog semestra u vežbaonici Fizičkog instituta održan je i prvi ispit iz histologije, a ispitnom komisijom je predsedavao prof. Đorđe Joannović, tadašnji dekan Medicinskog fakulteta. Prof. Kostić je u spomenici Fakulteta iz 1935. godine zapisao svoju impresiju tim povodom „Uspeh je bio osobit" (7).

U iščekivanju završetka izgradnje namenske zgrade, Histološki institut se u januaru 1924. još jednom seli, ovoga puta u Školu za nudilje Društva Crvenog krsta. U novom prostoru prof. Kostić dobija i priliku da iskustvo u izradi mikrofotografija koje je stekao u Francuskoj dalje razvija. Naime, zahvaljujući boljim prostornim i tehničkim mogućnostima, upravo je 1924. godine u prostorijama Škole za nudilje počelo sa radom i fotografsko odeljenje (7,16). Glavna tekovina tog odeljenja i Kostićeve aktivnosti bio je Mikrofotografki atlas normalne histologije, koji je izašao iz štampe već sledeće, 1925. godine. Celokupan rad na pripremi preparata, kao i samih mikrofotografija, prof. Kostić je izneo sam. Samo tri mikrofotografije urađene su na osnovu histoloških preparata koje su pripremili

1 snađite se

Kostić was still in Strasbourg working as an assistant to Professor Bouin, and, in keeping with Professor Subbotić's recommendations, preparing the collection of specimens, which served as teaching aids for the first generation of students. Thanks to Professor Bouin's support, by late December 1921, Dr. Kostić managed to prepare a collection of between 2.000 and 3.000 specimens of different tissues and organs (2, 7). It was the first acquisition and the first property of the Institute of Histology.

When he returned to Serbia, in January 1922, Dr. Kostić took up his duties and was allocated the first premises for the needs of the Institute. It was one room on the ground floor of the administration building of the Main Military Hospital (today, the administration building of the Clinical Center of Serbia). How much effort was expected in the preparation of the premises for the beginning of work, as well as in completing all the necessary preparations of teachers and educational materials, one may conclude from Professor Subbotić's words, spoken when the premises were officially being handed over to the Institute: "Dear *amice*, here, this is your Institute now. For the rest, *debrouillez-vous*[1] on your own.", as well as from the comment written by Professor Kostić in the Faculty's commemorative volume from 1935: "I received a room with nothing in it but four walls, a floor and a ceiling" (7). He got the first chair from the nearby orphanage, and a desk from the Commander of the Danube Medical Company, Medical Corps Captain Dimitrije Jovčić (7). Before classes started, in February 1922, one of the medical students, Momčilo Milojević, approached Professor Kostić requesting to be engaged in assisting with the practical work. Such assistance was precious at that time, and Momčilo was the first "assisting employee" (16), one could say, from today's perspective of the way students are engaged, that he was the first student demonstrator at the Institute of Histology. According to available data, one may conclude that he was engaged only during the first academic year (Milojević passed away prematurely, in 1925, in Skoplje) (16). The Faculty employed the first member of support staff at the Institute of Histology, on March 1, 1922 (first as an attendant). It was Dimitrije Veličković, who served as the custodian of the Institute during the following 23 years, until he retired, in 1945 (16, 17).

Despite the lack of basic conditions, the preparations for the beginning of lectures needed to be made until the beginning of March, i.e., the beginning of the spring semester. Professor Kostić borrowed desks and benches from the Danube Medical Company, which was stationed at the Main Military Hospital, and microscopes from the Institute of Pathology and Institute of Physiology. In parallel with these activities, which included finding the necessary fixtures and fittings, he prepared the first lecture, which he delivered on March 7, 1922, at the lecture hall in one of the portable buildings belonging to the Faculty, on *Guberevac* (former name for the slope between the area of the General State Hospital and Kneza Miloša Street) (18). The first lecture was attended by students and professors from the Faculty of Medicine, as well as professors from the University of Belgrade. It is with this lecture that the Histology and Embryology classes commenced at the Faculty of Medicine (7), of which the Dean of the Faculty of Medicine informed the Rector of the University of Belgrade, on March 14, 1922 (18). Soon after this, Adjunct Lecturer Aleksandar Kostić was appointed Assistant Professor at the Faculty of Medicine of the University of Belgrade, by a decree issued on May 2, 1922, (1).

In November 1922, the Institute was moved to the new University building, to the premises intended for the Physics Institute of the Faculty of Philosophy, where the conditions for teaching were better, and where the new microscopes, which Professor Kostić had ordered while still in Strasbourg, also arrived (7, 16). In addition, a laboratory for making specimens was formed. However, there was a lack of literature about practical laboratory work and histological techniques, in the Serbian language. This is why Professor Kostić prepared and published the handbook Basic Histological Techniques (1923).

After the move, Professor Kostić got help in working with students. Namely, Dr. Smilja Kostić-Joksić, his wife, who had also studied medicine in France, was appointed the first Teaching Assistant of Histology and Embryology, in October 1922 (2). She occupied this position until 1924, when she transferred to the newly established Department of Pediatrics, where later, in 1939, she was elected for the position of Assistant Professor, becoming the first woman with that title at the Faculty of Medicine in Belgrade (2). Together with Dr. Smilja

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njegovi saradnici, studenti Aleksandar Telebaković i Svetislav Popović (19). Pored njih dvojice, u periodu rada u Školi za nudilje, kao i nakon preseljenja u novu zgradu Instituta, prof. Kostiću su u radu pomagali studenti viših godina studija: Božidar Ristić, Georgije Pastelj, Stanojka Ivanović, Draginja Stojanović, Bosiljka Prljinčević (7).

Duboko uveren u značaj fotografije za nauku i nastavu, ne samo za potrebe histologije, već i Medicinskog fakulteta i Univerziteta, prof. Kostić je u projektu buduće zgrade Instituta, koji je u to vreme bio u pripremi, predvideo veliki prostor za Fotografsko odeljenje. Pored toga, na njegov predlog je 1. marta 1925. godine u službu primljen Aleksandar Šafranski, ruski vojni i avijatičarski fotograf (16,17), koji je značajno doprineo radu i daljem razvoju fotografskog odeljenja Instituta.

Kompletnu opremu za Fotografsko odeljenje prof. Kostić je nabavio od Znanstvenog zavoda prof. dr Breslera, sa kojim je i u kasnijim godinama nastavio saradnju, i koji je opremio i prostor Fotografskog odeljenja u novoj zgradi Instituta. Pored toga, Zavod prof. Breslera je, na osnovu negativa koje je pripremio prof. Kostić, napravio i veliku kolekciju crno-belih dijapozitiva (19). Dijapozitivi su korišćeni kao nastavna sredstva za vežbe i predavanja, a projektovani su iz posebnih komora.

Tokom 1924. godine prof. Kostić je pored svih navedenih aktivnosti napisao i nekoliko radova, štampanih uglavnom u Srpskom arhivu, objavio je prevod svoje doktorske disertacije u Glasniku Ministarstva narodnog zdravlja, kao i Rečnik histoloških izraza (1924), prvi rečnik svoje vrste na srpskom jeziku. Istovremeno, bio je to i početak njegove aktivnosti vezane za medicinsku terminologiju, a sam Rečnik histoloških izraza bio je preteča prvog Medicinskog rečnika koji je objavio skoro trideset godina kasnije, 1956. godine. Sve navedeno doprinelo je njegovom unapređenju, te je ukazom od 23. maja 1924. godine postavljen za vanrednog profesora histologije i embriologije (1).

U novu zgradu Histološki institut se preselio u januaru 1927. godine, i to je bilo poslednje i definitivno preseljenje (7,16). Institut se i danas nalazi na istom mestu, mada na različitoj adresi. Naime, tadašnja adresa Instituta bila je Resavska br. 92 (stari naziv Zrinjska), dok je danas adresa iste zgrade Višegradska br. 26. Zgradu je projektovao arhitekta Svetozar Jovanović. Plan je bio da se u njoj organizuje rad dva instituta: fiziološkog i histološkog. Zbog toga su u procesu projektovanja i gradnje, vrlo aktivno učestvovali i upravnici tih instituta, prof. Rihard Burijan i prof. Aleksandar Kostić (20). Tim povodom je 7. septembra 1923. godine potpisan i dogovor između prof. Burijana, prof. Kostića i prof. Đorđa Joannovića, tadašnjeg dekana, o rasporedu instituta u novoj zgradi koja bi imala zajednički amfiteatar i dva krila, za svaki

Slika 2. Zgrada Fiziološkog i Histološkog instituta podignuta 1927. godine, dokumentacija Instituta za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić", zaostavština Foto-filmskog zavoda

Kostić-Joksić, a student demonstrator, Stevan Vasojević, also helped with the classes (7). At the end of the fall semester, the first Histology exam was held, in the classroom for practical classes of the Physics Institute. The Head of the Examination Committee was Professor Đorđe Joannović, Dean of the Faculty of Medicine. In 1935, in the commemorative volume of the Faculty, Professor Kostić wrote his impressions of that occasion: "The success was remarkable." (7).

While waiting for the completion of the construction of facilities specifically designed for the Institute of Histology, the Institute moved once again, in January 1924, to the Red Cross Society Nursing School. At the new premises, Professor Kostić had the opportunity to further develop his experience of microphotography that he had gained in France. Namely, thanks to better spatial and technical conditions, in 1924, the Photography Department started its activities within the premises of the Nursing School (7, 16). The main legacy of that Department and Professor Kostić's activities was the Microphotographic Atlas of Normal Histology, which was published in 1925. The complete work on the specimens, as well as on the microphotographs, was done by Professor Kostić himself. Only three microphotographs were produced on the basis of the specimens that his assistants, students Aleksandar Telebaković and Svetislav Popović had prepared (19). In addition to these two students, the following senior students assisted Professor Kostić while the Institute was housed at the Nursing School, and also after it was moved to the new building: Božidar Ristić, Georgije Pastelj, Stanojka Ivanović, Draginja Stojanović, Bosiljka Prljinčević (7).

Professor Kostić was deeply convinced of the significance of photography in science and teaching, not only for Histology, but also for the Faculty of Medicine and the University of Belgrade, which is why he included a large space for the Photography Department within the plans for the future building of the Institute. In addition to this, the Professor's proposal to engage Aleksandar Šafranski, a Russian military and aviation photographer, was accepted on March 1, 1925. Aleksandar Šafranski significantly contributed to the work and further development of the Photography Department at the Institute (16, 17).

Professor Kostić obtained the complete equipment for the Photography Department from Professor Bresler's Scientific Institute. He had continued cooperation with professor Bresler throughout the years, and Professor Bresler was the one who equipped the facilities of the

Figure 2. Building of the Institute of Physiology and Histology built in 1927, documentation of the Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić", the legacy of the Photo-Film Institute

od instituta (Fiziološki i Histološki) (1). Sam proces izgradnje tekao je u dve faze. U prvoj fazi je adaptirana Bolnica za tuberkulozne bolesnike, koju je projektovala Jelisaveta Načić (1912). Ona je ušla u sastav krila namenjenog Institutu za fiziologiju. U drugoj fazi je izgrađen amfiteatar i krilo namenjeno Institutu za histologiju (21). Nova zgrada Fiziološkog i Histološkog instituta omogućila je najsavremenije uslove za rad sa studenatima. Bila je prema inicijalnim preporukama i uputstvima prof. dr Subbotića, u to vreme „najmodernije zamišljena" i „po svom uređenju … najmodernija u Evropi" (3) (slika 2).

U prizemlju Instituta je bila velika vežbaonica sa 90 radnih mesta. Dugački stolovi su bili orjentisani ka prozorima, a svaki naredni sto je u odnosu na prethodni bio za 20 cm na višem nivou, kako bi svetlost nesmetano dopirala do svih mikroskopa (22). Svako radno mesto bilo je opremljeno mikroskopom i lampom, a po dva susedna radna mesta su delila sudoperu i bateriju za bojenje preparata. Vežbaonica je dobila naziv Pol Buen. Nakon uvodnih časova projektovani su crno-beli dijapozitivi *„par transparence*" iz komore koja se nalazila pored vežbaonice. Pored projekcija slajdova tokom uvodnih časova, studentima je prepoznavanje preparata olakšavao i veliki broj postera na zidovima. Ukupan broj preparata je postepeno rastao do broja od nekoliko hiljada (4).

U okviru vivarijuma bile su tri prostorije: jedna za čuvanje i razmnožavanje životinja, druga za životinje u eksperimentu i treća za operacije na životinjama. Kavezi su bili ugrađeni u zidove od armiranog betona, sa gvozdenim rešetkama i istovremeno su se vrlo lako mogli čistiti i dezinfikovati. Kapacitet vivarijuma je bio u to vreme za 1000 miševa, 500 pacova, 200 zamorčića i 20 zečeva. Sve životinje su sistematski obeležavane specijalnim pločicama na ušima u vidu „minđuša", žutih tj. mesinganih za mužjake i belih tj. cinkanih za ženke. Pored ovog obeležavanja, postojala je i detaljnija evidencija za svaku eksperimentalnu životinju (7, 16,22).

Odmah po useljenju, u jednoj od prostorija u prizemlju je obrazovana biblioteka, za koju je namenski izrađen impresivan nameštaj od hrastovog drveta, sa policama od poda do plafona i stepenicama koje se mogu pomerati duž polica (7,16). Do 1935. godine, u biblioteci već bilo oko 1.300 knjiga, preko 2.000 svezaka časopisa, uglavnom na nemačkom i francuskom, 850 separata, a postojao je i uredni centralni katalog knjiga i časopisa svih ustanova Medicinskog fakulteta (7,16). Kartoni, koji sadrže osnovne podatke o svakoj bibliografskoj jedinici, uključujući i poziciju u ormanima i na policama čuvaju se i danas u biblioteci Instituta, mada je taj redosled davno narušen.

Kadar Histološkog instituta je u savremenim uslovima rada, po preseljenju u novu zgradu 1927. godine, stekao i mogućnost za intenzivan razvoj i napredovanje u svakom pogledu, i u skladu sa tim razvijao je i svaku od svojih aktivnosti: nastavnu, istraživačku, terminološku, fotografsku, bibliotečku.

Godine 1928. na Institutu su bila četiri asistenta-dnevničara: dr Nikola Mirjanić, koji je kasnije otišao na ginekologiju, kao i bivši demonstratori dr Aleksandar Telebaković, koji je prešao na hirurgiju, dr Bosiljka Milošević-Prljinčević, koja je postala profesor na Katedri ginekologije i bila upravnik Klinike za ginekologiju i akušerstvo i Evgenije Meljnikov, o čijem kasnijem profesionalnom radu nisu pronađeni podaci (17). Godine 1930. primljen je još jedan asistent, dr Branko Vlatković, koji je u proleće 1937. godine prešao na novoosnovani Veterinarski fakultet i počeo da razvija i unapređuje Katedru histologije i embriologije na tom fakultetu. Ogromnu pomoć i podršku u tom poslu pružio mu je prof. dr Kostić, koji je bio i jedan od osnivača Veterinarskog fakulteta 1936. godine (2,17). Pored asistentskog, proširen je i tehnički kadar Instituta prijemom novih laboranata, ali je i broj pomoćnog osoblja povećan. Po podacima iz službene arhive iz 1935. godine, na Institutu su bila dva laboranta-dnevničara: Đorđe Purković i Vladimir Sokolov, obojica inače studenti Medicinskog fakulteta. Pored domaćina Instituta Dimitrija Veličkovića, služitelji su bili Ivan Lazić i Jelisije Radojević (17). Većina zaposlenih, uključujući i sam bračni par Kostić, u to vreme je i stanovala u Institutu. Takođe, u periodu od 1. decembra 1931. do 1. juna 1932. u Fotografskom odeljenju je volontirala i Elfrida Grasl (17), koja se u kasnijim dokumentima službene arhive Instituta ne pominje.

Godine 1927. izašao je iz štampe i prvi udžbenik histologije prof. dr Kostića Osnovi histologije I deo: ćelije i tkiva. Ovaj udžbenik je u narednom periodu proširen, dopunjen i štampan pod nazivom Osnovi normalne histologije (1942), a doživeo je još 4 dopunjena i prerađena izdanja (1946, 1957, 1963. i 1968.).

Opšti trend razvoja i napretka Instituta i svih njegovih delatnosti u to vreme odrazio se i na

Photography Department in the new Institute building. In addition, Professor Bresler's Scientific Institute made a big collection of black and white diapositives, on the basis of negatives prepared by Professor Kostić (19). The diapositives were used as teaching aids for practical classes and for lectures and they were projected from special chambers.

During 1924, in addition to the above-mentioned activities, Professor Kostić wrote several scientific papers, published mainly in the Serbian Archives of Medicine. He published the translation of his doctoral dissertation in the Gazette of the Ministry of People's Health, as well as the Dictionary of Histological Terms (1924), which was the first dictionary of its kind in Serbian. At the same time, this was the beginning of his activities related to medical terminology, while the Dictionary of Histological Terms was the forerunner of the first Medical Dictionary, published almost thirty years later, in 1956. All of the above-mentioned contributed to his promotion, and therefore, by a decree from May 23, 1924, he was appointed Associate Professor of Histology and Embryology (1).

The Institute of Histology moved to the new building in January 1927, and that was the last and definitive move (7, 16). The Institute is located in the same building today, although the address is now different. Namely, the address at that time was 92 Resavska Street (formerly Zrinjska Street), while today, it is 26 Višegradska Street. Architect Svetozar Jovanović drew up plans for the building. Two institutes were planned to operate there: The Institute of Physiology and the Institute of Histology. Therefore, the directors of these institutes, Professor Rihard Burijan and Professor Aleksandar Kostić, participated actively in the project and the building process (20). Thus, on September 7, 1923, an agreement was signed between Professor Burijan, Professor Kostić, and Professor Đorđe Joannović, who was Dean at the time, about the arrangement of the institutes in the new building – the institutes would be sharing a lecture hall, while each of them would have a separate wing (the Physiology wing and the Histology wing) (1). The building process evolved in two stages. In the first stage, the Tuberculosis Hospital, designed by Jelisaveta Načić in 1912, was adapted and incorporated into the wing intended for the Institute of Physiology. In the second stage, the lecture hall was built, as well as the wing intended for the Institute of Histology (21). The new building was designed in such a way as to enable the most modern working and teaching conditions. It had, according to the initial recommendations and instructions, given by Professor Subbotić, „the most modern plan" and at that time it was "the most modern …… in all of Europe" (3) (Photo 2).

On the ground floor, there was a big classroom, with 90 seats, for carrying out practical classes. Long desks were oriented towards the windows, while each desk was elevated by 20 cm in relation to the one before it, so that light would reach each microscope (22). Each working place was equipped with a microscope and a lamp, while two workstations shared a sink and glass staining jars used for staining specimens. The classroom was named after Pol Bouin. After introductory classes, black and white diapositives "par-transparence" were projected from a chamber next to the classroom. In addition to the projection of slides, during introductory classes, a great number of posters enabled students to recognize preparations more easily. The total number of specimens gradually increased to several thousand (4).

There were three rooms within the vivarium: one for keeping and breeding the animals, the second for animal experiments, and the third for operations performed on animals. Cages were built into impregnated concrete walls, they had iron bars, and were designed in such a way as to make them easy to clean and disinfect. The capacity of the vivarium, at the time, was 1,000 mice, 500 rats, 200 guinea pigs and 20 rabbits. All the animals were systematically marked with special plates on the ears in the form of 'earrings' – yellow, i.e., brass for males, and white, i.e., zinc for females. In addition to this type of labelling, there was a detailed documentation for each experimental animal (7, 16, 22).

As soon as the move was complete, a library was created in one of the rooms on the ground floor, and striking oak furniture was made especially for this library, with shelves from floor to ceiling and steps that could be moved along the shelves (7, 16). Until 1935, there were around 1,300 books, more than 2,000 volumes of journals, mainly in German and French, 850 copies of articles, and there was a neatly organized central catalogue of books and journals of all the institutions of the Faculty of Medicine (7, 16). Catalog cards, which

status prof. dr Kostića. U tri mandata, u periodu od 1936. do 1939. godine, bio je na poziciji dekana Medicinskog fakulteta. Neposredno pre prvog izbora za dekana, Kostić je ukazom od 2. januara 1936. godine unapređen u zvanje redovnog profesora (1). Godine 1938. Institut je dobio još jednog ukaznog asistenta, dr Jovana Čankovića, a 1940. godine primljen je i dr Dragoljub Mršević, kao asistent-dnevničar (23). Upravo su dr Čanković i dr Mršević u posleratnom periodu izneli veliki teret nastave, posebno nakon udaljavanja prof. Kostića sa fakulteta. Godine 1940. prof. Kostić je dobio i orden Legije časti, kojim ga je odlikovao predsednik Francuske republike za doprinos u razvoju medicinske nauke (2).

Već sledeće, 1941. godine, ogroman potencijal Instituta i svih zaposlenih srušen je u jednom danu. Naime, 6. aprila 1941. godine, za vreme bombardovanja Beograda, pogođen je i Institut. Jedini deo zgrade koji je ostao neoštećen bio je centrali deo, u kome su se nalazili amfiteatar i fotografsko odeljenje. U te prostorije i podrume su krajem aprila službenici Instituta preneli biblioteku, mali deo preostalog neoštećenog inventara i 76 mikroskopa (24). Za vreme okupacije Medicinski fakultet je radio u značajno izmenjenom i smanjenom obimu (12), a Nemci su zaplenili sačuvane mikroskope i drugi sitan inventar (24).

Nakon tih nemilih događaja, usledio je još jedan. Naime, prof. Kostić je 1942. godine bio udaljen sa Medicinskog fakulteta. Često se u pojedinim tekstovima može naći pogrešna interpretacija dešavanja iz 1941. godine koja su tome prethodila. Pojedini autori navode da je profesor navodno udaljen sa fakulteta jer je odbio da potpiše Apel srpskom narodu (10,25), koji je obznanjen 13. avgusta 1941. godine u dnevnim novinama Novo vreme. Međutim, najveći broj nastavnika Medicinskog fakulteta, kao i prof. Kostić, nije potpisao Apel, i niko od njih direktno zbog toga nije udaljen. Inače, Apel srpskom narodu bio je jedna vrsta propagandnog pamfleta, odnosno, antikomunističkog proglasa, u kome se tražila lojalnost okupacionoj vladi, i koji je imao za cilj da smanji podršku srpske javnosti ustanku protiv okupatora (12,26).

Međutim, 16. oktobra 1941. godine Velibor Jonić, ministar prosvete u Vladi narodnog spasa Milana Nedića, doneo je Osnovnu uredbu o Univerzitetu. Prema toj uredbi, razrešeni su dužnosti i stavljeni na raspolaganje ministru prosvete svi dosadašnji nastavnici, kao i sve osoblje Univerziteta. Cilj uredbe bio je da se sa Univerziteta uklone nacionalno i ideološki nepodobni nastavnici, jer se znalo za prisutnu komunističku i antifašističku aktivnost na Univerzitetu kako pre početka II svetskog rata, tako i za vreme rata (26). U skladu sa tim, na osnovu Osnovne uredbe o Univerzitetu, doneta je i Opšta uredba o Univerzitetu, kojom su definisani principi reorganizacije Univerziteta, a samim tim i Medicinskog fakulteta (12,26). Prema toj uredbi, tokom 1942. godine raspisivani su konkursi za prijem nastavnika i nenastavnog osoblja, ali su sve odluke prosleđivane ministru prosvete, koji je postavljao nastavnike bez predloga Univrzitetskog saveta, određivao i kontrolisao rad rektora i u potpunosti kontrolisao rad Univerziteta (26). Time je u potpunosti urušena autonomija Univerziteta, izbor nastavnika stavljen pod kontrolu ministarstva, i direktno otvoren put ka ukanjanju nepodobnih, bez obzira na sadržaj i zaključak referata.

Prof. Aleksandar Kostić se, takođe, javio na konkurs za izbor redovnog profesora histologije i embriologije. Za referente su određeni prof. Kosta Todorović i prof. Milovan Milovanović. U pripremljenom referatu su, pored pohvala na račun nastavnih i naučnih kvalifikacija prof. Kostića, izneli i kritike na račun njegovih tekstova iz oblasti seksologije, a koji su, kako oni navode, često bili tumačeni u javnosti kao pornografski i štetni za javni moral. Takođe, naveli su i da je prof. Kostić počeo da obrazuje „klike" u Savetu Medicinskog fakulteta, koje su štetile ugledu Medicinskog fakulteta i Univerziteta (12). U zaključku referata stoji sledeći tekst: ,,Ako bi se g. prof. A. Kostić obavezao da se ubuduće neće više baviti objavljivanjem popularnih članaka i publikacija ovakve vrste, osobito iz seksologije, i da od sada neće više obrazovati klike na Medicinskom fakultetu, onda bi mogao biti predložen za redovnog profesora" (27). Referat je potpisan 17. jula 1942. godine (2) i prosleđen Ministarstvu prosvete. Krajnji ishod cele procedure bilo je penzionisanje prof. Kostića u 49. godini života (2).

Nakon penzionisanja prof. Kostića, za vršioca dužnosti upravnika Instituta, postavljen je doc. dr Branko Vlatković, Kostićev bivši asistent, a tada docent na Veterinarskom fakultetu (24). U ratnim okolnostim Institut je, kao i ceo fakultet, radio u redukovanom obimu, a ispiti su se održavali po dobijenoj saglasnosti Nemačke vrhovne komande (12,26).

contained the main data on each bibliographic unit, including its position in bookcases and on the shelves, have been kept until the present day at the library of the Institute, although that order was disrupted a long time ago.

After moving to the new building, in 1927, with the new, modern working environment, the employees of the Institute of Histology were given the opportunity for intensive professional development and progress in every sense, and thereby, they developed each of their activities related to teaching, research, terminology, photography, and the library.

In 1928, there were four teaching assistants: Dr. Nikola Mirjanić, who later transferred to gynecology, as well as former student demonstrators, Dr. Aleksandar Telebaković, who transferred to surgery, Dr. Bosiljka Milošević-Prljinčević, who became Professor at the Department of Gynecology and who was the director of the Clinic for Gynecology and Obstetrics, and Evgenije Meljnikov, about whose later professional work data were not found (17). In 1930, one more assistant was employed, Dr. Branko Vlatković, who transferred to the newly established Faculty of Veterinary Medicine, in the summer of 1937, where he went on to develop and improve their Department of Histology and Embryology. In this respect, he was given great help and support Professor Kostić, who was one of the founders of the Faculty of Veterinary Medicine, in 1936 (2, 17). In addition to the assistants, the number of technical personnel was increased, and new laboratory technicians were employed, as well as support staff. According to the data from official archives, from 1935, there were two laboratory technicians: Đorđe Purković and Vladimir Sokolov, students of the Medical Faculty. Apart from the Custodian of the Institute, Dimitrije Veličković, the support staff were also: Ivan Lazić and Jelisije Radojević (17). Most employees, including the Kostićes – husband and wife, lived in the Institute building, at that time. Also, from December 1, 1931 to June 1, 1932, Elfrida Grasl was a volunteer at the Department of Photography, however, she was not mentioned in later documents of the official archives of the Institute.

In 1937, the first Histology textbook, written by Professor Kostić, was published, under the title: Basics of Histology Part I: Cells and Tissues. This textbook was later expanded and published under the title: Basics of Normal Histology (1942), with four revised and expanded editions (1946, 1957, 1963, 1968).

The general trend of development and progress of the Institute and all its activities also had an impact on Professor Kostić's status. He was Dean of the Faculty of Medicine during three terms, between 1936 and 1939. Kostić was promoted to the rank of Full Professor, by decree, issued on January 2, 1936, just before he was elected Dean (1). In 1938, the Institute employed one more permanent assistant, Dr. Jovan Čanković, while in 1940, Dr. Dragoljub Mršević was employed as an assistant (23). In the postwar period, Dr. Čanković and Dr. Mršević carried the burden of teaching after Professor Kostić was removed from the Faculty. In 1940, Professor Kostić was awarded the medal of the Legion of Honor by the president of France for his contribution to the development of medical science (2).

As soon as 1941, the immense potential of the Institute and of all its employees was destroyed in a day. Namely, on April 6, 1941, during the bombing of Belgrade, the Institute was hit. The only part of the building that was not damaged was the central part, where the lecture hall and Photography Department were located. In late April, the employees moved the library, the remaining undamaged materials and furniture, as well as 76 microscopes to these premises and to the basement (24). During the German occupation, the Faculty of Medicine significantly changed and reduced its scope of work (12), while Germans seized the preserved microscopes and other lesser items (24).

After these unfortunate events, came another. Namely, Professor Kostić was removed from the Faculty of Medicine in 1942. A misinterpretation of events from 1941, which preceded this removal, can often be found in different texts. Some authors claim that the Professor was allegedly removed from the Faculty because he refused to sign the Appeal to the Serbian People (10, 25), which was proclaimed on August 13, 1941 in the daily newspaper Novo vreme. However, a majority of teachers from the Faculty of Medicine, including professor Kostić, did not sign the Appeal and none of them were removed directly for that reason. Besides, the Appeal to the Serbian People was a form of propaganda pamphlet, i.e., an anticommunist proclamation, in which loyalty

Nakon oslobođenja Beograda, 20. oktobra 1944. godine, formirani su novi komunistički organi u gradu i na Univerzitetu, a prof. Kostić je vraćen na dužnost upravnika Instituta već 8. decembra 1944. godine. Ubrzo je otpočela obnova, izgradnja i rad Fakulteta (12,17,24). Nastava histologije se najpre održavala u garderobi očuvanog dela zgrade Histološkog i Fiziološkog instituta i na Veterinarskom fakultetu (24). Dogradnja i rekonstrukcija oštećene zgrade Instituta je završena 1948. godine. Oba krila zgrade i fasada su dobili potpuno nov izgled, u duhu tadašnjih pravaca u arhitekturi, čime su mnogo izgubili od svoje prvobitne lepote. Takođe, značajno je izmenjen i unutrašnji raspored, kvadratura i spratnost. Umesto nekadašnje vežbaonice Pol Buen, Institut je dobio manju vežbaonicu sa 60 mesta. Svoj prostor u obnovljenoj zgradi i salu za vežbe dobio je i Institut za humanu genetiku (raniji naziv Biološki institut). Pokretni inventar je u početku bio različitog porekla i ne uvek odgovarajućih dimenzija i namene. Deo je dobijen na poklon, a deo nameštaja, kao i oprema za fotografsko odeljenje su otkupljeni od privatnih lica. Tek su 1954. godine ugrađeni dugački radni stolovi u vežbaonici, po uzoru na predratne (24), a koji se i danas koriste. U tom periodu malobrojni kolektiv Instituta je proširen prijemom asistenta pripravnika dr Stevana Popovića 1950. godine i dr Olge Piletić 1954. godine (23,24).

Međutim, obnovljen rad Medicinskog fakulteta, pratila su i dalje turbulentna dešavanja na ideološkom i političkom planu, što je kulminiralo ponovnim udaljavanjem prof. Kostića sa fakulteta 25. marta 1952. godine (2). Toga dana je dobio rešenje po kome mu „prestaje služba po sili zakona". Naime, on je u martu napunio 59 godina i time stekao jedan od uslova za penzionisanje, što je iskorišćeno kao osnova za navedeno rešenje. Međutim, razlozi za njegovo udaljavanje sa fakulteta su bili mnogo dublji. Naime, bili su političke prirode, a jedan od direktnih povoda za to je bio i dopis koji je uputio Savetu Medicinskog fakulteta 4. februara 1952. godine „O načinu izbora nastavnog osoblja" (1). U tom dopisu se zalaže za tajno glasnje pri izboru nastavnog osoblja i odbacivanje kriterijuma političke podobnosti (2). Prof. Kostić je inače bio okarakterisan kao najveći „neprijatelj" na Univerzitetu još od 1945. godine, jer nije bio spreman na kompromis sa novom vlašću, a smatralo se i da oko sebe organizuje „reakciju" (26).

U kojoj meri je Kostić smetao tadašnjem komunističkom rukovodstvu, govori i činjenica da je penzionisan uprkos velikom nedostatku kvalifikovanog naučnog i stručnog kadra. Da bi prevazišao takav deficit fakultet je ili ostavljao nastavnike da rade preko svih starosnih granica za odlazak u penziju, poput prof. oftalmologije dr Đorđa Nešića, upravnika Očne klinike, ili birao u zvanja profesora ljude bez odbranjenog doktorata. Za docenta na Institutu za histologiju i embriologiju je te iste, 1952. godine izabran dotadašnji asistent dr Jovan Čanković (23). On se, nakon demobilizacije, vratio na Institut i u periodu od 1946. do 1948. godine bio na stručnom usavršavanju u Sovjetskom Savezu, na Katedri histologije i embriologije II Moskovskog državnog medicinskog instituta (rus. *2-й Московский государственный медицинский институт*, danas *Росси́йский национа́льный иссле́довательский медици́нский университе́т и́мени Н. И. Пирого́ва*). Po povratku iz Moskve, publikovao je dva rada u Arhivu bioloških nauka 1951. godine, koji su bili osnova za izbor u zvanje docenta (23).

Dva dana po dobijanju rešenja o penzionisanju, tj. 27. marta, Kostić je razrešen dužnosti upravnika Instituta. Istog dana mu je dekan pismenim putem naložio da odmah ukloni „pismenu objavu" kojom poziva svoje studente na oproštajno predavanje, jer za „isto nije tražio prethodno odobrenje" (1,2).

Jedini koji se usudio da mu uputi oproštajno pismo zbog odlaska sa Medicinskog fakulteta, bio je njegov bivši student, tada upravnik Histološkog instituta u Sarajevu, prof. Radivoje Milin (1,2).

Za novog upravnika Instituta 27. marta 1952. godine postavljen je profesor anatomije Siniša Radojević, ali je već 31. marta usledila promena rukovodioca – za vršioca dužnosti upravnika imenovana je prof. Marija Višnjić Frajnd sa Patološkog instituta. Sledeće, 1953. godine, 16. februara, za upravnika Instituta je postavljen docent Jovan Čanković (23,24). On je na toj poziciji bio do odlaska u penziju 1978. godine (23). Pored Čankovića, na Institutu je u to vreme bio i asistent Dragoljub Mršević, koji je 1954. godine odbranio habilitacioni rad i postao docent 1957. godine (23).

Pored udaljavanja sa Instituta, prof. dr Kostić je 27. marta 1952. godine razrešen i dužnosti upravnika Foto-filmskog zavoda. Zavod je nastao iz prvobitnog Fotografskog odeljenja, koje je početkom 1950-ih pripojeno stručnim službama fakulteta (2).

to the occupation government was demanded, and whose aim was to decrease the support of the Serbian public for the uprising against the occupiers (12, 26).

However, on October 16, 1941, Velibor Jonić, the Minister of Education in Milan Nedić's Government of National Salvation issued the Basic Ordinance on the University. According to this Ordinance, all former teachers and personnel from the University were released from duty and put at the disposal of the Minister of Education. The aim of this Ordinance was to remove unsuitable teachers, in terms of ideology and nationality, from the University, because communist and antifascist activity was present at the University even before the Second World War, as well as during the war (26). In keeping with the Basic Ordinance on the University, the General Ordinance on the University was also adopted, defining the principles of the reorganization of the University, and therefore, the Faculty of Medicine, as well (12, 26). According to this Ordinance, during 1942, the Faculty announced openings for teaching and non-teaching staff, however, all decisions had to be sent to the Minister of Education, who appointed teachers without the participation of the University Council. The Minister defined and controlled the mandate of the Rector and completely controlled the work of the University (26). Thus, the autonomy of the University was completely disrupted, the selection of teachers was controlled by the Ministry, and therefore, it was made possible to remove those deemed unsuitable regardless of the contents and the conclusion of the report on their qualifications.

Professor Aleksandar Kostić also applied for the position of Full Professor of Histology and Embryology. Professor Kosta Todorović and Professor Milovan Milovanović were appointed to be members of the selection committee. In the report that they wrote, besides commendations for Professor Kostić's teaching and scientific qualifications, they also criticized his texts in the field of sexology, which, as they claimed, were often interpreted by the public as pornographic and harmful to public morality. They also stated that Professor Kostić had started to create "cliques" within the Council of the Faculty of Medicine, which did harm to the reputation of the Faculty of Medicine and the University, as well (12). The following text was in the conclusion of the report: "If Professor A. Kostić would pledge not to publish such popular articles and publications in the future, especially in the field of sexology, and not to form cliques at the Faculty of Medicine, then he might be proposed for the position of Full Professor" (27). The report was signed on July 17, 1942 (2) and sent to the Ministry of Education. The final outcome of the whole procedure was the retirement of Professor Kostić at the age of 49 (2).

After Professor Kostić's retirement, Assistant Professor Branko Vlatković, Professor Kostić's former assistant and Assistant Professor at the Faculty of Veterinary Medicine at the time, was appointed to the position of Acting Director of the Institute (24). In the circumstances of war, the Institute, as well as the whole Faculty, reduced its scope of work, while exams were held when approval was obtained from the German Supreme Command (12, 26).

After the liberation of Belgrade, on October 20, 1944, new communist authorities were established not only at the level of the City of Belgrade but also at the level the University, and Professor Kostić was reinstated as the Director of the Institute on December 8, 1944. Soon, the reconstruction, rebuilding and renewal of regular operation of the Faculty began (12, 17, 24). The Histology course was held first in the cloakroom of the preserved part of the building of the Institute of Histology and Physiology and at the Faculty of Veterinary Medicine. Building and reconstruction of the damaged building was completed in 1948. Both wings of the building had a completely new appearance, in keeping with the architectural style of that time, thus, losing a lot of its original beauty. Also, the inner arrangement, size and number of floors were significantly changed. Instead of the former classroom for practical classes named after Pol Bouin, the Institute got a smaller classroom with 60 seats. The Institute of Human Genetics (previously the Institute of Biology) got its space in the reconstructed building as well as a room for practical classes. The furniture and fittings were, at first, obtained from different places and they often did not meet the necessary requirements as to size and purpose. Some of it was received as a present, while other furniture and equipment for the Department of Photography was purchased from private persons. Long desks were built in the classroom in 1954, based on the model of the pre-war desks (24), which are used even today. In

Inače, Fotografsko odeljenje je u samom početku svoga postojanja daleko prevazišlo okvire Instituta. Fotografije je izrađivalo kako za potrebe medicinske dokumentacije i zaposlenih na celom Medicinskom fakultetu, tako i za potrebe Univerziteta u Beogradu, ali i drugih institucija širom zemlje. Podaci iz perioda pre Drugog svetskog rata ukazuju na to da je prof. Kostić pod okriljem Fotografskog odeljenja uspostavio saradnju sa čak 47 institucija u zemlji (7).

Nakon Kostićevog razrešenja sa svih dužnosti, uključujući i dužnost upravnika Terminološkog seminara, njemu je ipak učinjen jedan „ustupak". Naime, nakon nekoliko molbi, 23. avgusta 1952. dekan mu je odobrio korišćenje jedne kancelarije u prostorijama Terminološkog seminara radi završavanja rada na započetom rečniku (1). Narednih sedam godina, sve do 17. januara 1959. godine kada je rešenjem dekana deo prostorija Terminološkog seminara, uključujući i tu kancelariju, ustupljen Institutu za epidemiologiju, Kostić je redovno dolazio u Institut (1,28). Pomenutim rešenjem prof. Kostić se za sve eventualne potrebe u vezi rečnika upućuje na Centralnu biblioteku u koju je planirano premeštanje sadržaja Terminološkog seminara (1,28).

Od tog datuma prof. Kostić više nije dolazio na Institut, niti na Medicinski fakultet, sve do marta 1982. godine, kada mu je uručena plaketa Medicinskog fakulteta u znak priznanja za dugogodišnji doprinos razvoju Medicinskog fakulteta i medicinske nauke (11). Ovaj presedan je učinio uprkos stavu koji je imao prema Fakultetu zbog dve decenije duge bezuspešne borbe protiv nepravde koja mu je naneta i na koju je stavio tačku pismom upućenim rektoru Beogradskog Univerziteta septembra 1971. godine sa godišnjeg odmora u Nici. U njemu je jasno stavio do znanja da njegova rehabilitacija mora da prethodi svečanosti pedesetogodišnjice osnivanja Medicinskog fakulteta, na kojoj on ne može da učestvuje „okaljana obraza" (2). Nažalost, to nije doživeo.

Moralno je rehabilitovan posthumno, na svečanoj sednici Nastavno-naučnog veća Medicinskog fakulteta održanoj 24. januara 2001. godine, zajedno sa svojom suprugom i grupom nastavnika koji su doživeli sličnu sudbinu. Sednici je prisustvovao i njegov sin Vojislav Voki Kostić. Odluka Nastavno-naučnog veća kojom se stavljaju van snage sva rešenja, odluke i naredbe koje se odnose na odstranjivanje nastavnika Medicinskog fakulteta u Beogradu u periodu od 1944. do 1953. doneta je jednoglasno (2,29).

Udaljavanje prof. dr Kostića bio je veliki gubitak za Institut i Fakultet. Za samog profesora Kostića bila je to samo prva u nizu nepravdi, koje su se nastavile najpre zabranom održavanja oproštajnog skupa sa studentima, zatim razrešenjem statusa saradnika na Institutu za fiziologiju razvića, genetiku i selekciju Srpske akademije nauka, zabranom održavanja solističkog koncerta u sali Kolarčeve zadužbine 1969. godine, oduzimanjem Vukove nagrade dan uoči same dodele priznanja 1973. godine i mnogih drugih zbog čega je sve do svoje smrti 19. januara 1983. godine živeo „život sa neprebolnim bolom u duši".

Generacije nastavnika su radile i razvijale svoje potencijale, na čvrstim temeljima koje je uspostavio i ostavio za sobom prof. Kostić. Institut za histologiju i embriologiju, koji je osnovao i u dva navrata gradio iz temelja, od 1980. godine nosi njegovo ime.

U periodu od udaljavanja prof. Kostića do danas, rad Instituta je unapređivan u skladu sa razvojem nauke i tehnologije. Na inicijativu prof. Milorada Japundžića, 1979. godine formirana je Laboratoriju za obradu tkiva za elektronsku mikroskopiju, a prof. Japundžić je bio i direktor Laboratorije za elektronsku mikroskopiju na Univezitetu. Angažovanjem prof. Vesne Lačković, Foto-filmski zavod je vraćen u sastav samog Instituta 1998. godine, ali je na veliku žalost zaposlenih u januaru 2006. godine ugašen. Bio je to danak širokoj dostupnosti i jednostavnosti korišćenja savremenih fotografskih tehnologija, a Medicinski fakultet nije našao način i rešenje za modernizaciju, osavremenjavanje i nastavak rada ustanove sa tako velikim istorijskim značajem, potencijalom i skoro vekovnom tradicijom. Stari mikroskopi su zamenjeni 1979-1980. binokularnim mikroskopima, 1997. je uvedena zdravstvena delatnost za potrebe elektronsko-mikroskopske analize, ali je kasnije ukinuta, istraživački rad je osavremenjen nabavkom elektronskog i konfokalnog mikroskopa. Članovi katedre su bili angažovani na brojnim važnim pozicijama na Fakultetu i Unverzitetu, akademik Vladimir Bumbaširević je bio dekan i u dva mandata rektor Univerziteta u Beogradu. U duhu savremenih trendova u edukaciji studenata, na inicijativu prof. Miloša Bajčetića i asistenta Kirila Gligorovskog, na Institutu se počelo sa realizacijom *online* nastave još početkom 2000-ih. Upravo

that period, the small group of employees at the Institute was enlarged when teaching assistants Dr. Stevan Popović, in 1950, and Dr. Olga Piletić, in 1954, were employed (23, 24).

However, the work of the Faculty of Medicine was still disturbed by turbulent events, related to ideology and politics, which again culminated in the removal of Professor Kostić from the Faculty, on March 25, 1952 (2). On that day, he received the decision, according to which his duty ended 'by force of law'. Namely, since, in March of that year, he turned 59, thus fulfilling one of the conditions for retirement, this was used as the basis for the aforementioned decision. However, reasons for his removal from the Faculty ran a lot deeper. Namely, they were political in nature, and one of direct motives was the letter that the Professor sent to the Council of the Faculty of Medicine on February 4, 1952 "about the manner of selecting the teaching staff" (1). In this letter, he advocated secret voting in the selection of the teaching staff and the rejection of the criterion of political suitability (2). Professor Kostić was characterized as the biggest "enemy" of the University since 1945 because he was not ready to make a compromise with the new authorities, and it was deemed that he organized "reactionist activity" around him (26).

To which extent Kostić disturbed the communist authorities at that time was clear when he was retired although there was a lack of qualified scientific and professional personnel. In order to overcome such lack in staff, the Faculty allowed teachers to work over the age limit for retirement, as was the case with Professor of Ophthalmology Dr. Đorđe Nešić, Director of the Ophthalmology Clinic, or even appointed persons who had not defended their PhD thesis to the position of Professor. Dr. Jovan Čanković, former assistant was appointed the position of Assistant Professor at the Institute of Histology and Embryology, in 1952. After he was demobilized, he returned to the Institute, and from 1946 to 1948 was away for advanced professional development in the Soviet Union, at the Department of Histology and Embryology of the II Moscow State Medical Institute (*2-й Московский государственный медицинский институт*, today – *Росси́йский национа́льный иссле́довательский медици́нский университе́т и́мени Н. И. Пирого́ва*). After he returned from Moscow, he published two research papers in the Archives of Biological Sciences, in 1951, which were the basis for his being appointed Assistant Professor (23).

Two days after he had received the decision on retirement, i.e., on March 27, Kostić was released from his duty of Director of the Institute. On the same day, the Dean ordered him, in written form, to remove his "written announcement" which invited his students to his farewell lecture because "he did not ask permission for it" (1, 2).

The only one who dared send him a farewell letter was his former student, Professor Radivoje Milin, who was the Director of the Institute of Histology in Sarajevo (1, 2).

The Professor of Anatomy, Siniša Radojević was appointed to the post of the new Director of the Institute on March 27, 1952, but as soon as March 31, he was replaced by Professor Marija Višnjić Frajnd from the Institute of Pathology, who was appointed Acting Director. In 1953, on the February 16, Assistant Professor Jovan Čanković was appointed the position of Director of the Institute (23, 24). He occupied this post until he retired in 1978 (23). Together with Jovan Čanković, Assistant Dragoljub Mršević was employed at the Institute at that time, and, in 1954, he defended the habilitation thesis and became Assistant Professor in 1957 (23).

In addition to his removal from the Institute, on March 27, 1952, Professor Kostić was released from the duty of Director of the Photo-Film Institute. The Institute originated from the initial Department of Photography, which was adjoined to the professional services of the Faculty, in the early 1950s (2).

The Department of Photography exceeded the scope of the Institute even at the beginning of its existence. It developed photographs for medical documentation and for employees at the level of the entire Faculty of Medicine, as well as for the University of Belgrade and other institutions across the country. Data from before the Second World War indicate that Professor Kostić had established cooperation with as many as 47 institutions in the country (7).

After Kostić's release from all of his duties, including the duty of the Director of the Terminology Unit, the Professor was allowed one 'concession'. Namely, after repeated requests, the Dean allowed him to use one office in the Terminology Unit in order to complete his work on the dictionary he was writing (1). Over the

ovo iskustvo i već razrađen *online* kurs bili su od ključne važnosti u aktuelnoj epidemiološkoj situaciji, a sama Katedra je bila primer mnogim drugim institutima i katedrama.

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following seven years, until January 17, 1959, when by the Dean's decision, one part of the premises of the Terminology Unit, including the said office, was given to the Institute of Epidemiology, Kostić used to come regularly to the Institute (1, 28). In the above-mentioned decision, Professor Kostić was referred to use the Central Library, for all his future needs, and this was where the contents of the Terminology Unit were planned to be moved (1, 28).

As of that day, Professor Kostić ceased coming to the Institute and to the Faculty of Medicine altogether, until March 1982, when he received an award from the Medical Faculty, in recognition of his long-standing contribution to the development of the Faculty of Medicine and of medical science (11). He made this precedent in spite of his attitude towards the Faculty, which was the result of his twenty-year long and unsuccessful struggle against the injustice inflicted upon him. He put an end to it with the letter he sent to the Rector of the Belgrade University which he wrote while on holiday in Nice, in 1971. In that letter he clearly stated that his rehabilitation should precede the celebration of the 50th anniversary of the Faculty of Medicine, which he could not take part in with a 'tarnished reputation' (2). Unfortunately, he did not live to see his name cleared and his reputation restored.

He was morally rehabilitated posthumously, together with his wife and a group of teachers who shared a similar fate, at the session of the Academic Council of the Faculty of Medicine, held on January 24, 2001. His son Vojislav Voki Kostić was present at this session. The decision of the Academic Council of the Faculty of Medicine, which revoked all decisions, acts and orders relating to the removal of teachers from the Faculty of Medicine in Belgrade from 1944 to 1953, was made unanimously (2, 29).

The removal of Professor Kostić from the Faculty was a great loss for the Institute as well as for the Faculty. For professor Kostić it was the first in a series of injustices, which continued, first with the prohibition of his farewell meeting with students, then with his dismissal from the status of Associate at the Institute of the Physiology of Development, Genetics and Selection of the Serbian Academy of Sciences, followed by the prohibition of a solo concert at the concert hall of the Kolarac Endowment, in 1969, as well as with the withdrawing of the 'Vuk' Award, one day before the prize awarding ceremony, in 1973, and continuing with many other injustices, due to which he lived with an "everlasting pain in his soul", until his death, on January 19, 1983.

Generations of teachers worked and developed their potential on the firm foundations laid by Professor Kostić. The Institute of Histology and Embryology, which he founded and built from the ground, twice, has borne his name, since 1980.

The work of the Institute has improved, in accordance with the development of science and technology, since the Professor's removal. The Laboratory for Tissue Analysis and Electron Microscopy was formed on the initiative of Professor Milorad Japundžić, in 1979, and Professor Japundžić himself was the Director of the Laboratory for Electron Microscopy at the University. At the initiative of Professor Vesna Lačković, the Photo-Film Institute was reinstated within the Institute in 1998, but was closed in January 2006, to the regret of all the employees. This was the consequence of the wide availability and simplicity of using modern photographic technologies, and the Faculty of Medicine did not find ways and solutions for modernizing and maintaining an institution of such great historical significance, such potential and a tradition lasting almost a whole century. Old microscopes were replaced between 1979 - 1980 with binocular microscopes. In 1997, a health service for the needs of electron-microscopic analysis was introduced and later cancelled, and research work was modernized with the purchase of an electron and a confocal microscope. The members of the Department of Histology and Embryology were engaged in numerous important positions at the Faculty and University, while academician Vladimir Bumbaširević was elected the Rector of the Belgrade University, twice. In light of modern trends related to students' education, at the initiative of Professor Miloš Bajčetić and Teaching Assistant Kiril Gligorovski, online courses started in the early 2000s. It is precisely this experience and an already developed online course that were of great significance in the current epidemiological situation, where the Department served as an example to other Institutes and Departments.

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PROIZVODNJA RENDGEN APARATA U SRBIJI

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SAŽETAK

Rendgen dijagnostika ima nezamenljivo mesto u okviru radiologije i pored drugih savremenih dijagnostičkih metoda. Zato je proizvodnja savremenih rendgen aparata strateški bitna za svaki zdravstveni sistem. Srbija ima tradiciju dugu preko 70 godina u proizvodnji rendgen aparata. Od prvog aparata, proizvedenog u Srbiji 1953. godine, u tehničko-tehnološkom pogledu, išlo se u korak sa svetom. Rendgen aparate je proizvodila državna kompanija Jugorendgen iz Niša. Nažalost, kompanija Jugorendgen je zaustavila proizvodnju pre nego što je uspela da napravi digitalni rendgen aparat. Poslednjih 17 godina, ove uređaje proizvodi kompanija *Visaris*. *Visaris* je privatna kompanija iz Beograda, koja se bavi razvojem i proizvodnjom digitalnih rendgen aparata i softverskih sistema od 2003. godine. Njen značaj došao je do izražaja u vreme pandemije SARS-CoV-2 infekcije, kada je u kratkom vremenskom roku zdravstvenom sistemu Srbije bilo potrebno više stacionarnih i mobilnih rendgen aparata.

Ključne reči: rendgen aparat, proizvodnja, zdravstveni sistem

Uvod

Rendgen dijagnostika je opstala i razvija se i pored razvoja drugih savremenih dijagnostičkih metoda koje se primenjuju u medicinskoj praksi. Stanje se verovatno neće promeniti u skoroj budućnosti, s obzirom na dostupnost, brzinu, kvalitet i cenu rendgen dijagnostike u odnosu na druge dijagnostičke metode. Savremene tehničke inovacije u proizvodnji rendgen aparata omogućavaju minimalno zračenje pacijenata i profesionalno izloženih lica u odnosu na period odmah posle otkrića X-zraka, uz visoku dijagnostičku vrednost. Sve to pomaže očuvanju zdravlja ljudi.

Doza jonizujućeg zračenja koja je potpuno bezopasna ne postoji, kao što ne postoji zaštitno sredstvo, koje bi u potpunosti otklonilo štetan efekat X-zraka (1). Opravdanost upotrebe X-zraka u medicini postoji kada je šteta koju može prouzrokovati manja u odnosu na koristi koju donosi po zdravlje pacijenta. Ovo pravilo se primenjuje i na skrining programe (2). Jedan od preduslova za poštovanje pomenutog pravila, odnosno pravilan izbor i sprovođenje radiološke procedure je posedovanje kvalitetnih rendgen aparata. Ulaganjem u razvoj i proizvodnju rendgen aparata svaka država obezbeđuje svom stanovništvu optimalno izlaganje X-zracima, ukoliko je to potrebno u cilju izlečenja pojedinaca ili periodične provere zdravstvenog stanja stanovništva (3).

Istorijat proizvodnje rendgen aparata u javnom sektoru Srbije

Neposredno po završetku II svetskog rata uvidela se potreba za nabavkom novih ili rezervnih delova za stare rendgen aparate. Već 1947. godine, uspostavljena je saradnja sa firmom Simens (*Siemens*) iz Nemačke. Napravljen je dogovor o preuzmanju postrojenja za kompletnu proizvodnju rendgenskih cevi, radio-cevi i aparata, što je rezultiralo formiranjem Instituta za proizvodnju radio-opreme i rendgenskih aparata 1948. godine i kompanije RR Zavod Niš, koji je 1950. prerastao u Elektronsku industriju (Ei) Niš. Pri Elektronskoj industriji u Nišu

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MANUFACTURE OF X-RAY APPARATUS IN SERBIA

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SUMMARY

X-ray diagnostics has an irreplaceable place in radiology despite other modern diagnostic methods. That is why the production of modern X-ray machines is strategically important for every health system. Serbia has a tradition of over 70 years in the production of X-ray machines. From the first device manufactured in Serbia in 1953, it kept pace with the world in technical and technological terms. X-ray machines were produced by the state company Jugorendgen from Nis. Unfortunately, the company Jugorendgen stopped production before it managed to make a digital X-ray machine. For the past 17 years, these devices have been manufactured by Visaris. Visaris is a private company from Belgrade, which has been developing and manufacturing digital X-ray machines and software systems since 2003. Its importance came to the forefront during the pandemic SARS-CoV-2 infection when the health system of Serbia needed more stationary and mobile X-ray machines in a short time period.

Key words: X - ray machine, production, health system

Introduction

X-ray diagnostics has survived and is developing despite the development of other modern diagnostic methods applied in medical practice. The situation is unlikely to change in the near future, given the availability, speed, quality, and cost of X-ray diagnostics compared to other diagnostic methods. Modern technical innovations in the production of X-ray machines enable minimal radiation of patients and professionally exposed persons compared to the period immediately after the discovery of X-rays and possess a high diagnostic value. All this helps to preserve people's health.

There is no dose of ionizing radiation that is completely harmless, just as there is no protective agent that would completely eliminate the harmful effect of X-rays (1). The justification for using X-rays in medicine exists when the damage it can cause is less than its benefits to the patient's health. This rule also applies to the screening program (2). One of the preconditions for respecting the mentioned rule, i.e., the correct choice and implementation of the radiological procedure, is the presentation of quality X-ray machines. By investing in the development and production of X-ray machines, each country provides its population with optimal exposure to X-rays, if necessary, in order to cure individuals or periodically check the health of the population (3).

History of X-ray machine production in the public sector of Serbia

Immediately after the end of World War II, there was a need to purchase new or spare parts for old X-ray machines. As early as 1947, cooperation was established with Siemens from Germany. An agreement was made to take over the plant for the complete production of X-ray tubes, radio tubes, and apparatus, which resulted in the formation of the Institute for the production of radio equipment and X-ray apparatus in 1948 and the company "RR Zavod Nis," which in 1950 grew into the Electronic Industry Nis. At the Electronic Industry in Nis, the

Institut za proizvodnju rendgen aparata od 1952. godine posluje kao samostalna radna jedinica Jugorendgen. Prvi radnici ove fabrike obučavali su se u Simensovim pogonima u Nemačkoj. Dobijena Simensova licenca bila je temelj proizvodnje rendgen aparata u Srbiji.

Pored pomenute licence fabrika je posedovala i kvalitetan visokoškolski kadar, tako da je ulaganje u razvoj dovelo do toga da je Srbija bila jedina zemlja na Balkanu koja je proizvodila rendgen aparate polovinom prošlog veka. Prva rendgenska cev u Nišu proizvedena je 1952. godine, dok je prvi rendgen aparat proizveden i instaliran 1953. godine. Aparat je nosio naziv Moravica, i proizveden je u 1.500 primeraka. Pored jugoslovenskog tržišta, ovaj rendgen aparat je plasiran i u zemljama u okruženju. Zbog razvoja proizvodnje kompleksnih rendgen aparata i osvajanja novih tržišta kompanija je sarađivala sa vodećim svetskim proizvođačima rendgen aparata i zapošljavala je oko 700 radnika (4,5). U jednom trenutku većina (oko 75%) rendgen aparata koji su se koristili u Srbiji u okviru medicinske radiologije, bila je proizvedena u Jugorendgenu.

Sve do 1992. godine, kada je uveden embargo Srbiji (tada SR Jugoslaviji) od strane Saveta bezbednosti Ujedinjenih nacija, u Nišu su se proizvodili rendgen aparati za ceo svet. Najviše se izvozilo u Francusku, Poljsku, Holandiju, Rusiju, Australiju i Afriku. Stanje se međutim vrlo brzo promenilo, zbog ratova i ekonomske krize koji su zadesili državu, kao i druge domaće velike kompanije i Jugorendgen krajem XX veka stagnira. Na samom početku XXI veka bilo je više pokušaja da se kompanija reorganizuje uz nove strateške partnere iz inostranstva, međutim svi ti pokušaji su bili kratkog daha (6). Ispostavilo se da su gubici bili nenadoknadivi, tako da je kompanija Jugorendgen zaustavila proizvodnju rendgen aparata pre nego što je uspela da napravi digitalni rendgen aparat. To znači da nije uspela da uhvati korak sa konkurencijom na svetskom tržištu.

Proizvodnja rendgen aparata u privatnom sektoru Srbije

U novonastalim okolnostima, u Srbiji je 2003. godine osnovana privatna kompanija *Visaris* koja se bavi razvojem i proizvodnjom digitalnih rendgen aparata i softverskim rešenjima za prateće uređaje u okviru radiološke dijagnostike (7).

Redgen aparati koje proizvodi ova firma primenjuju se za dijagnostiku i upotpunjeni su informatičkim rešenjima za kompletno elektronsko poslovanje radioloških odeljenja. Potpuno je robotizovano kretanje uređaja, razvijeni su digitalni prihvat i akvizicija slike, upravljački softveri i napredni alati za obradu dijagnostičkih snimaka. Na taj način, u duhu tradicije duge pola veka, kompanija *Visaris* u potpunosti prati svetske trendove i standarde Sertifikovanjem svojih proizvoda. Zahvaljujući ovoj kompaniji proizvodnja rendgen aparata u Srbiji je izašla iz nacionalnih okvira. Kompanija je uspela da uspostavi saradnju sa preko 30 zemalja u svetu (8).

Pored toga, kompanija *Visaris* je postala i nastavna baza za studente Studijskog programa za strukovne medicinske radiologe sa Visoke zdravstvene škole strukovnih studija iz Beograda.

Studenti tradicionalno svake godine u okviru predmeta Aparati za radiološku dijagnostiku odlaze u *Visaris*, gde su u prilici da prisustvuju procesu proizvodnje rendgen aparata (slika 1).

U vreme pandemije SARS-CoV-2 infekcije 2020. godine kompanija *Visaris* je pokazala ogroman potencijal kada je u kratkom vremenskom roku zdravstvenom sistemu Srbije obezbedila više stacionarnih i mobilnih rendgen aparata. Ovi aparati bili su namenjeni kako velikim centrima koji su bili najviše opterećeni tokom pandemije, tako i drugim manjim centrima u Srbiji (9,10).

Perspektiva proizvodnje rendgen aparata u Srbiji

Perspektiva proizvodnje rendgen aparata u Srbiji, gledano iz društveno-političkog i ekonomskog aspekta, je da se najverovatnije rendgen aparati neće proizvoditi u javnom sektoru. Izuzetak mogu da budu, eventualno, neki pojedinačni delovi potrebni za sklapanje rendgen aparata. S druge strane, malo je verovatno da će se pojaviti još neka domaća ili strana privatna kompanija za proizvodnju rendgen aparata, s obzirom na potrebne resurse da bi se pokrenula proizvodnja i uspostavio neophodan nivo. U prilog ovoj pretpostavci je i činjenica da je Srbija malo tržište i za Visaris, kao trenutno jedina kompanija koja u Srbiji proizvodi rendgen aparate.

Analizom podataka o zastupljenosti rendgen aparata u Srbiji i podataka kompanije *Visaris* o zastupljenosti rendgen aparata na srpskom tržištu

Institute for the Production of X-ray machines has been operating as an independent working unit of Jugorendgen since 1952. The first workers of this factory were trained in Siemens' plants in Germany. The obtained Siemens license was the basis for the production of X-ray machines in Serbia.

In addition to the mentioned license, the factory also had quality higher education staff, so that the investment in development led to the fact that Serbia was the only country in the Balkans that produced X-ray machines in the middle of the last century. The first X-ray tube in Nis was produced in 1952, while the first X-ray machine was manufactured and installed in 1953. The device was called "Moravica" and was produced in 1,500 copies. In addition to the Yugoslav market, this X-ray machine has also been marketed in the surrounding countries. Due to the development of complex X-ray machines and the conquest of new markets, the company cooperated with the world's leading manufacturers of X-ray machines and employed about 700 workers (4.5). At one point, most (about 75%) of X-ray machines used in Serbia in medical radiology were manufactured in Jugorendgen.

Until 1992, when the United Nations Security Council imposed the embargo on Serbia (then FR Yugoslavia), X-ray machines for the whole world were produced in Nis. Most were exported to France, Poland, the Netherlands, Russia, Australia, and Africa. However, the situation changed quickly due to the wars and economic crisis that hit the country and other large domestic companies, and Jugorendgen stagnated at the end of the 20th century. At the very beginning of the 21st century, there were several attempts to reorganize the company with new strategic partners from abroad, but all these attempts were short-lived (6). It turned out that the losses were irreparable, so the company Jugorendgen stopped the production of X-ray machines before it managed to make a digital X-ray machine. This means that it failed to catch up with the competition on the world market.

Production of X-ray machines in the private sector of Serbia

In the new circumstances, a private company Visaris was founded in Serbia in 2003, which deals with developing and producing digital X-ray machines and software solutions for ancillary devices within radiological diagnostics (7).

The X-ray machines produced by this company are used for diagnostics and are complemented by IT solutions for the complete electronic business of radiology departments. The device's movement is completely robotized, while digital image reception and acquisition, control software, and advanced tools for processing diagnostic images have been developed. In this way, in the spirit of a half-century-long tradition, Visaris fully follows world trends and standards by certifying its products. Thanks to this company, the production of X-ray machines in Serbia has gone beyond the national framework. The company has managed to establish cooperation with over 30 countries worldwide (8).

In addition, the company Visaris has become a teaching base for students of the Study Program for Professional Medical Radiologists from the College of Health Professional Studies in Belgrade.

Students traditionally go to Visaris every year as part of the Radiological Diagnostic Apparatus course, where they have the opportunity to attend the X-ray apparatus production process (Figure 1).

At the time of the pandemic SARS-CoV-2 infection in 2020, the company Visaris showed huge potential when in a short time, it provided the health care system of Serbia with more stationery and mobile X-ray machines. These devices were intended for large centers that were the busiest during the pandemic and other smaller centers in Serbia (9,10).

Prospects for the production of X-ray machines in Serbia

The perspective of X-ray machine production in Serbia, seen from the socio-political and economic aspect, is that most likely, X-ray machines will not be produced in the public sector.

Exceptions may be some individual parts required for assembling the X-ray machine. On the other hand, it is unlikely that another domestic or foreign private company will appear for the production of X-ray machines, given the resources needed to start production and establish the necessary level. In support of this assumption is that Serbia is a small market for Visaris, as the only company currently producing X-ray machines in Serbia.

An analysis of data on the presence of X-ray machines in Serbia and data from Visaris on the

Slika 1. Studenti Odseka visoke zdravstvene škole u kompniji Visaris

došlo se do saznanja da je 2018. godine samo oko 7% rendgen aparata koji se koriste u Srbiji u okviru medicinske radiologije proizvedeno u *Visaris*-u u Beogradu. Ako se uzme u obzir starost tj. period montaže rendgen aparata u Srbiji (od ukupnog broja rendgen aparata u Srbiji, 40-50% je montirano u poslednjih 15 godina) onda se može reći da je oko 15% rendgen aparata koji se koriste u Srbiji, a mlađi su od 15 godina, proizvedeno u *Visaris*-u (11). Interesantan je podatak da je kompanija *Visaris* mnogo više svojih rendgen aparata izvezla u inostranstvo nego što je plasirala na domaće tržište. *Visaris* je 2018. godine obeležio 15 godina uspešnog poslovanja, o čemu govore rendgen aparati ove kompanije na kojima je urađeno oko 1.000.000 ekspozicija.

Zaključak

Proizvodnja rendgen aparata u Srbiji ima dugu tradiciju. Tradicija se nije prekidala od 1953. godine bez obzira na ozbiljne društveno-političke i ekonomske probleme na prostoru naše zemlje i u bliskom okruženju. Pola veka od prvog proizvedenog rendgen aparata u Srbiji u korak sa svetom rendgen aparate proizvodila je državna kompanija Jugorendgen iz Niša. Poslednjih 17 godina rendgen aparate proizvodi privatna kompanija *Visaris*. Obe kompanije su svojim kvalitetom dostigle svetsko tržište, što je od ogromnog značaja za samu državu Srbiju. Zahvaljujući dugoj tradiciji proizvodnje kvalitetnih rendgen aparata u Srbiji građani Srbije imaju uvek dostupnu rendgen dijagnostiku. Njihov značaj posebno je uočen tokom pandemije SARS-CoV-2 infekcije.

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Figure 1. Students of the Department of Higher Health School in the company Visaris

presence of X-ray machines on the Serbian market revealed that in 2018 only about 7% of X-ray machines used in Serbia in medical radiology were manufactured at Visaris in Belgrade. If we take into account age, i.e., period of installation of X-ray machines in Serbia (of the total number of X-ray machines in Serbia, 40-50% have been installed in the last 15 years), then it can be said that about 15% of X-ray machines used in Serbia are younger than 15 years, produced in Visaris (11). It is interesting to note that Visaris has exported many more of its X-ray machines abroad than it has placed on the domestic market. In 2018, Visaris marked 15 years of successful business, which is evidenced by the X-ray machines of this company, on which about 1,000,000 expositions were made.

Conclusion

The production of X-ray machines in Serbia has a long tradition. The tradition has not been interrupted since 1953, regardless of the serious socio-political and economic problems in our country and the immediate vicinity. Half a century since the first X-ray machine was produced in Serbia, in step with the world, X-ray machines have been produced by the state company Jugorendgen from Nis. For the last 17 years, X-ray machines have been produced by the private company Visaris. Both companies have reached the world market with their quality, which is of great importance for Serbia itself. Thanks to the long tradition of producing quality X-ray machines in Serbia, the citizens of Serbia always have X-ray diagnostics available. Their importance was especially noticed during the pandemic of SARS-CoV-2 infection.

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PROCENA UTICAJA PREKOMERNE TELESNE TEŽINE I GOJAZNOSTI NA NASTANAK PREDHIPERTENZIJE I HIPERTENZIJE KOD DECE UZRASTA 6-15 GODINA

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SAŽETAK

Uvod/Cilj: Prekomernu telesnu težinu ili gojaznost ima 41 milion dece mlađe od 5 godina i 340 miliona dece i adolescenata uzrasta od 5 do 19 godina. Gojaznost dece i adolescenata predstavlja najvažniji prediktor povišenog krvnog pritiska. Cilj istraživanja je bio da se ispita učestalost javljanja prekomerne telesne težine i gojaznosti kod dece uzrasta 6-15 godina, kao i da se proceni učestalost javljanja predhipertenzije i hipertenzije kod dece sa prekomernom telesnom težinom i gojaznošću.
Metode: Ovom studijom bilo je obuhvaćeno 85 od ukupno 86 dece iz Osnovne škole u Krupi na Uni. Podaci su prikupljeni upitnikom, a telesna težina i krvni pritisak su mereni. U statističkoj analizi podataka korišćeni su hi kvadrat test i t-test.
Rezultati: Studijom preseka je bilo obuhvaćeno 85 dece, i to 45 (52,9%) dečaka i 40 (47,1%) djevojčica prosečne starosti 10,87 ± 2,70 godina. Normalna uhranjenost utvrđena je kod 54 (63,5%) ispitanika, pothranjenost u 12 (14,1%), prekomerna uhranjenost kod 5 (5,9%), a gojaznost kod 14 (16,5%). Normalne vrednosti krvnog pritiska imalo je 76 (89,4%) ispitanika, predhipertenzivno stanje 5 (5,9%), arterijsku hipertenziju 4 (4,7%). Između mlađe i starije dece nije bilo značajne razlike u odnosu na stepen uhranjenosti (p=0,477) i visinu krvnog pritiska (p=0,453). Deca sa prekomernom telesnom težinom i gojaznošću bila su značajno češće sa predhipertenzijom i hipertenzijom (p<0,001).
Zaključak: Kod svakog petog deteta utvrđena je prekomerna uhranjenost ili gojaznost, a kod svakog desetog predhipertenzija i hipertenzija. Pravovremena promena načina ishrane i fizičke aktivnosti, kao i svih drugih životnih navika, može doprineti regulaciji ne samo telesne težine nego i regulaciji krvnog pritiska.
Ključne riječi: prekomerna telesna težina, gojaznost, predhipertenzija, hipertenzija, studija preseka, deca

Uvod

Gojaznost se, po Međunarodnoj klasifikaciji bolesti (eng. *International classification of diseases, eleventh revision,* ICD-11), svrstava u endokrine bolesti, bolesti ishrane i metabolizma (ICD-XI; E66) (1). To je hronična bolest praćena prekomernim nakupljanjem masnog tkiva i povećanjem telesne težine, a nastaje kao rezultat uticaja brojnih faktora (prekomeran kalorijski unos, fizička neaktivnost i drugo) (1-4). Svetska zdravstvena organizacija (SZO) opisuje epidemiju dečije gojaznosti kao ozbiljan javno zdravstveni izazov 21. veka (5-7). Prema podacima SZO, u vremenskom periodu od 1975. godine do 2016. godine došlo je do porasta prevalencije gojaznosti za tri puta, tako da danas 41 milion dece mlađe od 5 godina i 340 miliona dece i adolescenata uzrasta od 5 do 19 godina ima prekomernu telesnu težinu ili gojaznost (5). Oko 31 milion dece živi u zemljama u razvoju (6). Gojaznost može imati značajan uticaj na zdravstveno stanje, blagostanje (socijalno i psihološko), samopoštovanje, akademski uspeh i kvalitet života svakog deteta (8).

Gojazna deca imaju tri puta veću verovatnoću da dobiju hipertenziju u odnosu na normalno uhranjenu decu (9). Uzroci koji vode gojaznosti su brojni, a najčešće se ističe značaj genetskih, endokrinih, bihevioralnih i sredinskih faktora (10). Kod gojazne dece sa hipertenzijom može postojati subklinička ateroskleroza sa zadebljenjem arterijskog zida i ugroženom arterijskom elastičnošću (11). Osim toga, promene u geometriji i funkciji miokarda kod ovih osoba (povećanjem leve i desne srčane komore, zadebljanjem zida leve komore, povećanjem mase leve komore) ukazuju

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ASSESSMENT OF THE INFLUENCE OF OVERWEIGHT AND OBESITY ON THE DEVELOPMENT OF PREHYPERTENSION AND HYPERTENSION IN CHILDREN AGED 6-15

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SUMMARY

Introduction/Aim: 41 million children under the age of 5 and 340 million children and adolescents aged 5 to 19 are overweight or obese. Obesity in children and adolescents is the most important predictor of high blood pressure. The aim of the study was to examine the incidence of overweight and obesity in primary school children aged 6 to 15 years, as well as to examine the incidence of prehypertension and hypertension in children who were overweight and obese.
Method: The study included 85 of 86 children from the Primary School „Krupa na Uni“. Data were collected with the help of a questionnaire, while body weight and blood pressure were measured. The chi-square test and t-test were used for the statistical analysis of data
Results: The cross-sectional study included 85 children, 45 (52.9%) boys and 40 (47.1%) girls with an average age of 10.87 ± 2.70 years. Normal weight was found in 54 (63.5%) subjects, underweight in 12 (14.1%), overweight in 5 (5.9%), and obesity in 14 (16.5%). 76 (89.4%) subjects had normal blood pressure values, 5 (5.9%) pre-hypertensive state, and 4 (4.7%) arterial hypertension. There was no significant difference between younger and older children regarding their nutritional status (p=0.477) and blood pressure levels (p=0.453). Children who were overweight and obese had prehypertension and hypertension significantly more often (p<0.001).
Conclusion: Every fifth child was overweight or obese, while prehypertension and hypertension were found in every tenth child. The timely change of diet and physical activity could contribute to the regulation of body weight and the regulation of blood pressure, as well.

Keywords: obesity, hypertension, screening, primary school.

Introduction

According to the International Classification of Diseases, Eleventh Revision (ICD-11), obesity is classified into endocrine, nutritional and metabolic diseases (ICD-XI; E66) (1). It is a chronic disease accompanied by the excessive fat accumulation and the increase in body weight, and it appears due to numerous factors (excess calories, physical inactivity etc.) (1-4). The World Health Organization (WHO) describes an epidemic of childhood obesity as a serious public health challenge of the 21st century (5-7). According to the WHO data, the prevalence of obesity nearly tripled between 1975 and 2016, and therefore, today 41 million children under the age of 5 and 340 million children and adolescents aged 5-19 are overweight or obese (5). Around 31 million children live in developing countries (6). Obesity may have a significant influence on the health condition, well-being (social and psychological), self-respect, academic success and the quality of life of each child (8).

Obese children are three times more likely to develop hypertension in comparison to normal weight children (9). Factors that lead to obesity are numerous, however, the significance of genetic, endocrine, behavioral and environmental factors is most common (10). In obese children with hypertension, subclinical atherosclerosis with arterial wall thickening and impaired arterial elasticity may arise (11). Besides, changes in the cardiac geometry and function in these persons (left and right ventricular hypertrophy, thickening of the wall of the left ventricle, increase in

na rani početak potencijalno nepovoljnih promena u mišićnom tkivu srca (12).

Gojaznoj deci sa navršene tri godine se preporučuje merenje krvnog pritiska (3,13). Međutim, kod dece mlađe od tri godine merenje krvnog pritiska se preporučuje u slučaju postojanja pozitivne anamneze za neonatalne komplikacije, srčane malformacije, genetsku bolest, stečenu ili urođenu bolest bubrega, neoplazmu, upotrebu lekova (kortikosteroida, teofilina, nazalnih dekongestiva) i bolesti koje uzrokuju povećani intrakranijalni pritisak (3,13). Dijagnoza hipertenzije zahteva neke laboratorijske analize (npr. analizu vrednosti uree, kreatinina, glukoze, lipida i elektrolita u krvi, pregled urina, dokazivanje malih količina proteina u urinu, merenje glomerularne filtracije) i ehokardiografski pregled (3,13).

Cilj ove studije preseka je bio da se ispita učestalost javljanja prekomerne telesne težine i gojaznosti kod osnovnoškolske dece i da se ispita da li postoji veza između hipertenzije i prekomerne telesne težine i gojaznosti.

Metode

Urađena je epidemiološka studija preseka u periodu od 30 dana, od 15.07.2021. do 15.08.2021. Studijski uzorak (ispitanici) bili su učenici Osnovne škole u Krupi na Uni, 85 od ukupno 86 učenika koliko ima škola.

Telesna težina je merena antropometrijskom vagom u kilogramima (dete bez obuće, sa laganom odećom, u ortostatskom položaju na sredini vage). Telesna visina je merena stadiometrom u centimetrima, na najbližih 0,1 cm (dete bez obuće, okrenuto leđima prema zidu, paralelnih, spojenih stopala, u uspravnom položaju i pogledom prema napred u liniji horizonta).

Indeks telesne mase (engl. *Body Mass Index*, BMI) je dobijen deljenjem telesne težine u kilogramima i telesne visine u kvadratnim metrima. Stratifikacija statusa uhranjenosti utvrđena je iz percentila u odnosu na indeks telesne mase, uzrast i pol. Status uhranjenost ispod 5. percentila označen je kao pothranjenost, od 5. do 85. percentila kao normalna uhranjenost, od 85. do 95 percentila kao prekomerna uhranjenost, a iznad 95. percentila kao gojaznost (14,15).

Merenje krvnog pritiska je izvršeno aparatom za merenje krvnog pritiska, živinim sfingomanometrom. Dete je sedelo leđima naslonjeno na naslon stolice i bilo sa mirno položenim nogama. Ruke su bile oslobođene odeće, ekstendirane, oslonjene na podlogu u visini srca, laktovi ispruženi, dlanovi okrenuti prema gore. Distalni rub manžete je postavljen 2 do 3 cm iznad kubitalne jame, sa balonom narukvice na volarnoj strani. Merenje je izvršeno na obe ruke. Ukoliko je postojala razlika u izmerenim vrednostima na levoj i desnoj ruci, viša vrednost je uzeta za relevantnu. Arterijska hipertenzija kod dece definisana je kao sistolni i/ili dijastolni krvni pritisak jednak ili veći 95. percentila za uzrast i pol. Sistolni i/ili dijastolni krvni pritisak od 90. do 95. percentila za odgovarajuću dob i uzrast predstavljalo je predhipertenziju (16-18).

Za obradu i analizu prikupljenih podataka korišćena odgovarajuća softverska podrška u vidu programa *Microsoft Excel*, te 21 verzije statističkog programa za društvene naukeIBMSPSS Statistics (engl. *Statistical Package for the Social Science*, SPSS).U statističkoj analizi korišćeni su hi kvadrat test i Fisherov test.

Rezultati

Istraživanje je obuhvatilo 85 osnovnoškolske dece. Među njima je bilo 40 (47,1%) devojčica i 45 (52,9%) dečaka. Prosečna starost ispitivane populacije iznosila je 10,87 ± 2,70 godina (najmlađe dete imalo je 7, a najstarije 16 godina) (Tabela 1).

Table 1. Distribucija dece osnovne škole prema uzrastu i polu

Uzrast (godine)	Dečaci Broj (%)	Devojčice Broj (%)	Ukupno Broj (%)
6-9	22 (25,9)	16 (18,8)	38 (44,7)
10-15	23 (27,0)	24 (28,2)	47 (55,2)
Ukupno	45 (52,9)	40 (47,1)	85 (100,0)
$\bar{x}$ ± SD	10,44 ± 2,64	10,35 ± 2,80	10,87 ± 2,70

$\bar{x}$ -srednja vrednost; SD-standardna devijacija.

muscle mass of left ventricle) indicate the early development of potentially serious changes in the cardiac muscle tissue (12).

Blood pressure measurements are recommended in obese children aged 3 and above (3,13). However, in children younger than three, blood pressure measurements are recommended in case of positive anamnesis for neonatal complications, heart malformations, genetic diseases, congenital or acquired diseases of kidneys, neoplasma, usage of medications (corticosteroids, theophylline, nasal decongestants) and diseases that cause intracranial pressure (3,13). The diagnosis of hypertension demands certain laboratory analyses (e.g. analysis of urea levels, creatinine, glucose, lipids and electrolytes in blood, urine analysis, proving a small amount of proteins in urine, measuring glomerular filtration) and echocardiographic assessment (3,13).

The aim of this cross-sectional study was to examine the incidence of overweight and obesity in primary school children, as well as to determine the connection between hypertension and overweight, that is, obesity.

Methods

An epidemiological cross-sectional study was conducted from 15th July 2021 to 15th August 2021. The sample (respondents) included students from the Primary School in Krupa on the river Una, that is, 85 students of 86 students of this school.

Body weight was measured with the help of anthropometric scale in kilograms (a child was without shoes, with light clothes, in the orthostatic position in the middle of the board). Body height was measured with the help of a stadiometer in centimeters, to the nearest 0.1 cm (a child was without shoes, standing against the wall, with heels together, in the upright position, eyes looking straight ahead).

Body mass index was obtained by dividing the body weight in kilograms by the body height in meters squared. The stratification of nutritional status was determined in percentiles according to body mass index, age and sex. The nutritional status below the fifth percentile was marked as underweight, from the 5th to the 85th percentile as normal, from the 85th to the 95th as overweight, and above the 95th percentile as obesity (14,15).

The measurement of blood pressure was done with the help of the apparatus for measuring blood pressure, mercury sphygmomanometer. Children were in the seated position with their back leaning against the chair's back and with their legs sitting still. Upper arms were bare, extended, supported at the same vertical height as the heart; elbows were stretched out, palms upward. Distal edge of the cuff was placed 2 to 3 cm above the cubital fossa with the inflated cuff on the volar side. The measurement was done on both arms. If there was a difference between the values on the left and the right hand, higher value was deemed to be relevant. Arterial hypertension in children was defined as systolic and/or diastolic blood pressure equal to or higher than the 95th percentile for certain age and sex. Systolic and/or diastolic blood pressure from the 90th to the 95th percentile for certain sex and age was prehypertension (16-18).

The appropriate software support, such as Microsoft Excel program, and IBM SPSS Statistics 21.0 (Statistical Package for the Social Science, SPSS) were used for the analysis of collected data. The chi-square test and Fisher's test were used for the statistical analysis.

Results

The study included 85 primary school children. There were 40 (47.1%) girls and 45 (52.9%) boys among them. The average age of the examined population was 10.87+2.70 years (the youngest

Table 1. Distribution of primary school children by sex and age

Age (years)	Boys Number (%)	Girls Number (%)	Total Number (%)
6-9	22 (25.9)	16 (18.8)	38 (44.7)
10-15	23 (27.0)	24 (28.2)	47 (55.2)
Total	45 (52.9)	40 (47.1)	85 (100.0)
$\bar{x}$ ± SD	10.44 ± 2.64	10.35 ± 2.80	10.87 ± 2.70

$\bar{x}$ -mean; SD-standard deviation.

Tabela 2. Distribucija dece osnovne škole prema uzrastu i stepenu uhranjenosti

Uzrast (godine)	Pothranjenost (< 5,00) Broj (%)	Normalna uhranjenost (5,00 – 84,99) Broj (%)	Prekomerna uhranjenost (85,00 – 94,99) Broj (%)	Gojaznost (≥ 95,00) Broj (%)	Ukupno Broj (%)	p vrednost*
6-9	8 (9,4)	20 (23,5)	4 (4,7)	6 (7,1)	38 (44,7)	0,477
10-15	4 (4,7)	34 (40,0)	1 (1,2)	8 (9,4)	47 (55,3)	
Ukupno	12 (14,1)	54 (63,5)	5 (5,9)	14 (16,5)	85 (100,0)	

*p prema χ^2 testu

Normalna uhranjenost utvrđena je kod 54 (63,5%) dece, pothranjenost kod 12 (14,1%), prekomerna uhranjenost kod 5 (5,9%) i gojaznost kod 14 (16,5%). Između mlađe i starije dece nije bilo značajne razlike u odnosu na stepen uhranjenosti (p=0,477) (Tabela 2).

Normalne vrednosti krvnog pritiska imalo je 76 (89,4%) ispitanika, predhipertenziju 5 (5,9%) i arterijsku hipertenziju 4 (4,7%). Između mlađe i starije dece nije bilo značajne razlike u odnosu na vrednosti krvnog pritiska (p=0,453) (Tabela 3).

Deca sa prekomernom telesnom težinom i gojaznošću su značajno (p<0,001) češće imala predhipertenziju i hipertenziju (Tabela 4).

Diskusija

Gojaznost dece predstavlja globalni javnozdravstveni problem (14). Širom sveta broj gojazne dece raste alarmantnom brzinom (14). Globalna telesna uhranjenost raste 0,32 kg/m^2/10 godina kod devojčica, odnosno 0,40 kg/m^2/10 godina kod dečaka (20). Udeo dece u najvišim percentilima telesne uhranjenosti je u periodu rasta (7). Najvišu prevalenciju gojaznosti imaju zemlje Severne Amerike (u prvom redu Sjedinjene Američke Države i Meksiko) i Bliskog Istoka (6). Nešto nižu prevalenciju imaju zemlje jugoistočne Azije i zapadnog Pacifika, uključujući Indiju, Maleziju, Vijetnam, Kinu, Australiju, Južnu Koreju i Japan (21). Najniža stopa prevalencije utvrđena je u zemljama Afrike

Tabela 3. Distribucija dece osnovne škole prema uzrastu i vrednostima krvnog pritiska

Uzrast (godine)	Normotenzija Broj (%)	Predhipertenzija Broj (%)	Arterijska hipertenzija Broj (%)	Ukupno Broj (%)	p vrednost*
6-9	33 (38,8)	2 (2,4)	3 (3,5)	38 (44,7)	
10-15	43 (50,6)	3 (3,5)	1 (1,2)	47 (55,3)	0,453
Ukupno	76 (89,4)	5 (5,9)	4 (4,7)	85 (100,0)	

*p prema χ^2 testu

Tabela 4. Distribucija dece osnovne škole prema stepenu uhranjenosti i vrednostima krvnog pritiska

		Pothranjenost ili normalna uhranjenost Broj (%)	Prekomerna uhranjenost ili gojaznost Broj (%)	Ukupno Broj (%)	p vrednost*
Krvni pritisak (mmHg)	Normotenzija	63 (74,1)	13 (15,3)	76 (89,4)	<0,001
	Predhipertenzija ili hipertenzija	3 (3,5)	6 (7,1)	9 (10,6)	
Ukupno		66 (77,6)	19 (22,4)	85 (100)	

*p prema *Fisher*-ovom testu

Table 2. Distribution of primary school children by age and nutritional status

Age (years)	Underweight (< 5.00) Number (%)	Normal weight (5.00 – 84.99) Number (%)	Overweight (85.00 – 94.99) Number (%)	Obesity (≥ 95.00) Number (%)	Total Number (%)	p value*
6-9	8 (9.4)	20 (23.5)	4 (4.7)	6 (7.1)	38 (44.7)	
10-15	4 (4.7)	34 (40.0)	1 (1.2)	8 (9.4)	47 (55.3)	0.477
Total	12 (14.1)	54 (63.5)	5 (5.9)	14 (16.5)	85 (100.0)	

*p value according to χ^2 test

child was 7, while the oldest was 16) (Table 1).

Normal weight was found in 54 children (63.5%), 12 children (14.1%) were underweight, 5 children (5.9%) were overweight and 14 (16.5%) were obese. There was no significant difference between younger and older children regarding their nutritional status (p=0.477) (Table 2). Normal values of blood pressure were found in 76 (89.4%) respondents, prehypertension in 5 (5.9%) and arterial hypertension in 4 (4.7%). There was no significant difference between younger and older children regarding the blood pressure values (p=0.453) (Table 3).

Prehypertension and hypertension were found significantly more often (p<0.001) in children who were overweight and obese (Table 4).

Discussion

Childhood obesity is a global public health problem (14). The number of obese children worldwide rises at alarming speed (14). Global body weight grows 0.32 kg/m^2/10 years in girls, that is, 0.40 kg/m^2/10 years in boys (20). The share of children in the highest percentiles of body weight is in the period of growth (7).

The countries of the North America (first of all the United States of America and Mexico) and the Middle East have the highest prevalence of obesity (6). Somewhat lower prevalence is in the countries of Southeast Asia and West Pacific, including India, Malaysia, Vietnam, China, Australia, South Korea and Japan (21). The lowest prevalence is in Africa (16). In the European countries, almost every

Table 3. Distribution of children by age and blood pressure levels

Age (years)	Normotension Number (%)	Prehypertension Number (%)	Arterial hypertension Number (%)	Total Number (%)	p value*
6-9	33 (38.8)	2 (2.4)	3 (3.5)	38 (44.7)	
10-15	43 (50.6)	3 (3.5)	1 (1.2)	47 (55.3)	0.453
Total	76 (89.4)	5 (5.9)	4 (4.7)	85 (100.0)	

*p value according to χ^2 test

Table 4. Distribution of primary school children by nutritional status and blood pressure levels

		Underweight or normal weight Number (%)	Overweight or obesity Number (%)	Total Number (%)	p value*
Blood pressure (mmHg)	Normotension	63 (74.1)	13 (15.3)	76 (89.4)	<0.001
	Prehypertension or hypertension	3 (3.5)	6 (7.1)	9 (10.6)	
Total		66 (77.6)	19 (22.4)	85 (100)	

*p value according to Fisher test

(16). U zemljama Evrope gotovo svako četvrto dete ima prekomernu uhranjenost ili gojaznost (22).

Naše istraživanje je pokazalo postojanje prekomerne uhranjenostikod 5,9% (n=5) ispitanika, a gojaznosti kod 16,5% (n=14) ispitanika. Između mlađih i starijih uzrasta nije bilo značajne razlike u odnosu na stepen uhranjenosti.

Patofiziologija uključuje genetske, endokrine, bihevioralne i sredinske faktore (15,23). Disfunkcija adipocita predisponira rezistenciju na insulin (vaskularnu i sistemsku), disfunkciju simpatičkog nervnog sistemai sistema renin angiotenzinaldosteron (23).

Gojazna deca imaju viši nivo aktivnosti renina, angiotenzinogena, angiotenzin konvertujućeg enzima i aldosterona (23,24). Kompresija bubrega prekomernom masnoćom (visceralnom i retroperitonealnom) i prekomerna aktivnost simpatičkog nervnog sistema povećavaju oslobađanje renina iz jukstaglomerularnih ćelija bubrega (24). Adipociti luče angiotenzinogen, angiotenzin II, stimulišu proizvodnju aldosterona iz nadbubrežne žlezde (nezavisno od angiotenzina II) (24). Angiotenzin II povećava proizvodnju aldosterona, uzrokuje sistemsku vazokonstrikciju, direktno zadržavanje natrija i vode i povećanu proizvodnju aldosterona (25). Aldosteron modulira ekspresiju natrijumovog kanala endotelnih ćelija (povećava endotelnu krutost), aktivira nikotinamid adenin dinukleotid fosfat-oksidazu (pospešuje oksidativni stres) i smanjuje bioraspoloživost azotnog oksida (23-25).

Abnormalno lučenje adipokina iz masnog tkiva, disfunkcija renin angiotenzin aldosteron sistema, insulinska rezistencija i disfunkcija baroreceptora u gojazne dece povećavaju aktivnost simpatičnog nervenog sistema (19,24). Stimulacije α-adrenergičnih i β-adrenergičnih receptora povećava minutni volumen, brzinu otkucaja srca i bubrežnu tubularnu reapsorpciju natrijuma (19,24).

Pojavi hipertenzije u gojazne dece mogu doprinjeti genetski i epigenetski faktori (promene u metilaciji deoksiribonukleinske kiseline, modifikaciji histona i regulaciji mikronukleinske kiseline) (25). U našem istraživanju, deca sa prekomernom telesnom težinom i gojaznošću su značajno češće imala predhipertenziju i hipertenziju (p<0,001).

Skrinining hipertenzije među 5.000 učenika Osnovne škole u Sjedinjenim Američkim Državama utvrdio je gojaznost kao najvažniji prediktor povišenog krvnog pritiska kod dece (26,27). Hipertenzije je ustanovljena kod 11,1% gojazne dece (26). Druga studija koja je obuhvatila 9.167 dece uzrasta od 5 do 17 godina ustanovila je da gojazna deca imaju 2,4 puta veću verovatnoću za povišen dijastolni pritisak i 3,0 puta veću verovatnoću za povišen sistolni pritisak (28). Studija preseka, sprovedena u Kini, koja je obuhvatila 78.114 ispitanika starosti od 7 do 20 godina identifikovala je 2,2% veću verovatnoću razvoja hipertenzije u gojaznih ispitanika (29). Istraživanje 1.626 dece uzrasta od 7 do 16 godina u četiri velika kineska grada (Peking, Šangaj, Nanjing, Xi'an) utvrdilo je 5,94 puta veću verovatnoću hipertenzije kod dece s opštom gojaznošću i 3,45 puta veću verovatnoću hipertenzije kod dece s centralnom gojaznošću (30). Istraživanje koje je obuhvatilo 2.650 učenika u osnovnoj školi (uzrast od 5 do 15 godina) u Indiji otkrilo je značajno češće prisustvo hipertenzije kod gojazne dece (13,7% naspram 0,4% u normalno uhranjene dece) (31). Studija preseka u Severnoj Karnataki među 19.263 dece uzrasta od 5 do 16 godina utvrdila je prisustvo hipertenzije u 18,2% gojazne dece (32). Kod normalno uhranjene dece hipertenzija je bila značajno ređa (10,10% ukupno, 5,18% sistolna hipertenzija, 6,15% dijastolna hipertenzija) (32). Istraživanje u Italiji među 1.310 dece uzrasta od 5 do 14 godina identifikovalo je gojaznost kao najznačajniji prediktor hipertenzije (unakrsni odnos = 2,63; 95% interval poverenja = 2,12-3,28) (33). Prospektivna kohortna studija u Sjedinjenim Američkim Državama u kojoj je učestvovalo 242 ekstremno gojazne dece uzrasta od 13 do 19 godina i koji su bili podvrgnuti barijatrijskoj hirurgiji hipertenzija je postojala kod čak 49,5% ispitanika (34). Identifikacija gojazne dece s trajno povišenim krvnim pritiskom zahteva kontinuirano merenje krvnog pritiska u dužem vremenskom periodu (35). Kod gojazne dece s hipertenzijom utvrđeno je prisustvo oštećenja ciljnih organa (povećanje mase leve i desne srčane komore, zadebljanje zida leve komore, zadebljeaje arterijskog zida i smanjena arterijska elastičnost) koje ukazuju na rani početak potencijalno nepovoljnih promena miokarda i endotela krvnih sudova (36,37). U cilju ranog otkrivanja ovih patoloških promena koristi se ehokardiografija (36,37).

Glavni nedostatak ove studije ogleda se u malom broju ispitanika, kao i u korišćenju studije preseka u kojoj ne možemo da definišemo uzročno posledičnu vezu. Neophodna su dalja istraživanja u ovoj oblasti.

fourth child is overweight or obese (22).

Our study showed that 5.9% of participants (n=5) were overweight, while 16.5% (n=14) were obese. There was no significant difference between younger and older children regarding the nutritional status.

Pathophysiology includes genetic, endocrine, behavioral and environmental factors (15,23). Dysfunction of adipose tissues may result in insulin resistance (vascular and systemic), dysfunction of sympathetic nervous system and system of renine angiotensine aldosterone (23).

Obese children have higher levels of the activity of renine, angiotensinogene, angiotensin converting enzyme and aldosterone (23,24). Kidney compression because of excess fat (visceral and retroperitoneal) and excessive activity of the sympathetic nervous system increase the release of renine from juxtaglomerular renal cells (24). Adipocytes secrete angiotensinogene, angiotensin II, stimulate the production of aldosterone from the adrenal gland (independently from angiotensin II) (24). Angiotensin II increases the production of aldosterone, causes systemic vasoconstriction, increases body water and sodium content and production of aldosterone (25). Aldosterone modulates the expression of sodium channel of endothelial cells (increases the endothelial stiffness), activates nicotinamide adenine dinucleotide phosphate-oxidase (activates oxidative stress) and decreases bioavailability of nitric oxide (23-25).

The abnormal secretion of adipokines from adipose tissues, dysfunction of renine angiotensin aldosterone system, insulin resistance and dysfunction of baroreceptors in obese children increase the activity of sympathetic nervous system (19,24). The stimulation of α-adrenergic and ß-adrenergic receptors increases the minute volume, the heart rate and renal tubular reabsorption of sodium (19,24).

Genetic and epigenetic factors (changes in the methylation of deoxyribonucleic acid, modification of histones and regulation of micronucleic acid) may contribute to hypertension in obese children (25). In our study, children who were overweight and obese had prehypertension and hypertension significantly more often ($p<0.001$).

Screening for hypertension among 5000 students of one primary school in the United States of America found that obesity was the most significant predictor of hypertension in children (26,27). Hypertension was found in 11.1% of obese children (26). Another study, which included 9.167 children aged 5 to 17, found that obese children were 2.4 times more likely to develop elevated diastolic pressure and 3.0 times more likely to develop elevated systolic pressure (28). A cross-sectional study, which was conducted in China and which included 78.114 respondents aged 7 to 20 years, identified that obese respondents were 2.2% more likely to develop hypertension (29). A study, which included 1.626 children aged 7 to 16 years in four big cities in China (Beijing, Shanghai, Nanjing, Xi`an) identified that children with general obesity were 5.94 times more likely to develop hypertension and that children with central obesity were 3.45 times more likely to develop hypertension (30). A study, which included 2.650 students in one primary school (aged 5 to 15) in India, found that hypertension was present significantly more often in obese children (13.7% in comparison to 0.4% in children with normal weight) (31). A cross-sectional study conducted in North Karnataka, which included 19.263 children aged 5 to 16, found hypertension in 18.2% of obese children (32). In children with normal nutritional status, hypertension was significantly rarer (10.10% total, 5.18% systolic hypertension, 6.15% diastolic hypertension) (32). A study, which was conducted in Italy among 1.310 children aged 5 to 14, identified obesity as the most significant predictor of hypertension (odds ratio = 2.63; 95% confidence interval = 2.12-3.28) (33). A prospective cohort study, which was conducted in the United States of America and which included 242 extremely obese children aged 13 to 19 who underwent bariatric surgery, showed that hypertension was present in 49.5% of respondents (34).

The identification of obese children with permanently elevated blood pressure demands the continuous monitoring of blood pressure during a long period of time (35). In obese children with hypertension, damage of target organs was found (left and right ventricular hypertrophy, thickening of the left ventricular wall, thickening of the arterial wall, decreased arterial elasticity), which pointed to the early development of potentially unfavorable myocardial changes and changes in the endothelium of blood vessels (36,37). Echocardiography is used in order to detect these pathological changes early (36,37).

Zaključak

Kod osnovnoškolske dece sa prekomernom telesnom težinom i gojaznošću značajno češće dolazi do pojave predhipertenzije i hipertenzije. Predhipertenziju i hipertenziju imalo je 10,6% učenika, a 7,1% i prekomernu telesnu težinu i gojaznost. Pravovremena promena ishrane, fizičke aktivnosti i drugih životnih navika doprineće kako redukciji prekomerne telesne težine i gojaznosti, tako i regulaciji vrednosti krvnog pritiska. Pozitivni ishodi iziskuju multidisciplinarni pristup, a to znači uključivanje kako porodice, tako i svih nivoa obrazovnog i zdravstvenog sistema, nadležnih ministarstava, šire društvene zajednice, medija, prehrambene i farmaceutske industrije.

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The main shortcoming of this study is the small number of participants, as well as the fact that it is the cross-sectional study, in which we cannot define a causal relationship. Further research is needed in this field.

Conclusion

In primary school children, who are overweight and obese, prehypertension and hypertension develop significantly more often. 10.6% of students had prehypertension and hypertension, while 7.1% were overweight and obese, as well. Timely change of diet, physical activity and other life habits would contribute to the reduction of overweight and obesity, as well as the regulation of blood pressure levels. Positive outcomes demand a multidisciplinary approach, including the participation of family, and all levels of educational and health care system, competent government departments, wider social community, media, food and pharmaceutical industry.

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ORIGINALNI RAD

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DA LI POSTOJI VEZA ANKSIOZNOSTI KAO CRTE LIČNOSTI SA CRTAMA DEPRESIVNE LIČNOSTI?

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SAŽETAK

Uvod/cilj: Rezultati dosadašnjih istraživanja ukazuju da postoji povezanost između simptoma depresije i anksioznosti, kao i da je javljanje ovih simptoma delimično uslovljeno crtama ličnosti. Cilj ovog istraživanja je bio da se ispita da li postoji veza između anksioznosti kao crte ličnosti sa crtama depresivne ličnosti među odraslim ispitanicima iz Crne Gore, kako bi dobili smernice za primenu programa za očuvanje mentalnog zdravlja.
Metode: U okviru ove studije preseka bilo je uključeno 355 ispitanika. Podaci od svih ispitanika iz Crne Gore prikupljeni su onlajn putem, kroz *Google Forms* platformu. Pored opšteg upitnika, korišćeni su upitnici za ispitivanje crta ličnosti anksioznosti (engl. *Anxiety Trait* 29 – AT29) i depresivnosti („Depresivna ličnost" – DL). U statističkoj analizi podataka korišćen je *Pearson*-ov koeficijent korelacije i jednofaktorska analiza varijanse.
Rezultati: Od 355 ispitanika, uzrasta od 18 do 68 godina, 74,6% su činile žene. Značajna visoka pozitivna korelacija dobijena je između crta anksioznosti i crta depresivne ličnosti (r=0,82, p<0,01). Pored toga, obe ove crte ličnosti bile su značajno više ispoljene kod žena, osoba sa nižim stečenim stepenom obrazovanja i lošim socio-ekonomskim stanjem. Mlađi i nezaposlena lica su imali značajno više izražene crte anksioznosti, ali značajna razlika nije utvrđena u pogledu izraženosti crta depresivne ličnosti. Nije bilo značajne ispoljenosti anksioznih i depresivnih crta ličnosti u odnosu na bračni status i zaposlenost.
Zaključak: Kada znamo da se u značajnom broju slučajeva crte anksioznosti i depresivnosti javljaju zajedno, onda možemo osmisliti programe prevencije i podrške kod osoba kod kojih bi se rano detektovale ove crte, kako bi se sprečilo da poteškoće u funkcionisanju prerastu u anksioznost ili depresiju.

Ključne riječi: anksionost kao crta ličnosti, depresivne crte ličnosti, demografske karakteristike

Uvod

Anksioznost možemo posmatrati u skladu sa Splibergerovom teorijom koja definiše razliku između crte i stanja anksioznosti (1). Anksioznost kao crta ličnosti predstavlja sklonost da se odgovori stanjem anksioznosti pri anticipaciji pretećih situacija (čak i kada su situacije objektivno bezopasne), dok je stanje anksioznosti subjektivno, svesno opaženo stanje straha i zebnje, koje može biti isprovocirano nekim spoljašnjim ili unutrašnjim stimulusom opaženim kao opasnost ili pretnja. Osnovna razlika je u tome što je anksioznost kao crta stabilna dispozicija, koja se ispoljava kroz više situacija tokom vremena, dok je anksioznost kao stanje tranzitorna, vezana za date okolnosti u datom trenutku.

Depresivna ličnost se opisuje kao ličnost koja je dominantno tužna, sumorna, obeshrabrena, preozbiljna, sa sniženim samopouzdanjem i izraženom sklonošću ka osećanju krivice, a ostali aspekti funkcionisanja se mogu označiti kao normalni (2). Po Šnajderu sledećih 7 crta ličnosti sačinjava depresivnu ličnost ili depresivnu psihopatiju: mirna, introvertna, pasivna i neasertivna; turobna, pesimistična, ozbiljna i nesposobna za šalu; samokritična, samooptužujuća i samoomalovažavajuća; skeptična, hiperkritična i teško udovoljava; savesna, odgovorna i samodisciplinovana; zamišljena i zabrinuta; preokupirana negativnim događajima, osećanjem neadekvatnosti i sopstvenim nedostacima (2).

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IS THERE A CONNECTION OF ANXIETY AS A PERSONALITY TRAIT WITH DEPRESSIVE PERSONALITY TRAITS?

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SUMMARY

Introduction/Aim: The results of previous research indicate that there is a connection between the symptoms of depression and anxiety, and that the occurrence of these symptoms is partly conditioned by personality traits. The aim of this study was to examine the correlation between anxiety as a personality trait and depressive personality traits among the respondents from Montenegro, in order to obtain guidance for the application of mental health programs.
Method: The cross-sectional study included 355 respondents. Data were collected online, through the Google Forms platform In addition to the general questionnaire, questionnaires for the evaluation of anxiety-related traits and depressive personality traits (DP) were used.
Results: Of 355 respondents, aged 18 to 68, 74.6% were women. A high positive correlation between the anxiety-related traits and depressive personality traits was significant ($r = 0.82$, $p < 0.01$). In addition, we found that both of these traits were more pronounced in women, in respondents with lower educational levels and poorer material status. Younger respondents and unemployed persons had significantly more pronounced anxiety-related traits, but there was no significant difference regarding depressive personality traits. There was no significant difference regarding the pronounced anxious and depressive personality traits related to marital status and employment.
Conclusion: Having in mind the fact that anxious and depressive personality traits occur simultaneously in a significant number of cases, it is important to detect these traits early and implement prevention programs in order to prevent them from developing into anxiety or depression.

Key words: anxiety trait, depressive personality traits, gender, age

Introduction

Anxiety can be observed from the perspective of Spielberger's theory, which defines the difference between trait and state anxiety (1). Anxiety as a personality trait is a tendency to respond with the state of anxiety when threatening situations are anticipated (even when situations are objectively harmless), while state anxiety is a subjective, consciously perceived state of fear and worry, which may be provoked by some outer or inner stimuli, which are seen as threatening or dangerous. The basic difference is that anxiety as a trait is a stable disposition, which is manifested through different situations over time, while anxiety as a state is transitory, connected with certain circumstances at the given moment.

A depressive person is described as a person, who is dominantly sad, gloomy, discouraged, too serious, with low self-confidence and pronounced inclination to the feeling of guilt, while other aspects of functioning may be marked as normal (2). According to Shneider, the following seven personality traits make a depressive personality or depressive psychopathy: calm, introvert, passive and non-assertive; gloomy, pessimistic, serious unable to joke; self-critical, self-reproaching and self-scornful; skeptical, hypercritical and hard to please; conscientious, responsible and self-disciplined; pensive and worried; preoccupied with negative events, feeling of inadequacy and their own shortcomings (2).

Certain pathological personality traits (such as self-sacrifice, avoiding the criticism, distrust, impulsive behavior, unstable behavior) correlate with the symptoms of depression and anxiety

Pokazalo se da određene patološke crte ličnosti (kao što su samo-žrtvovanje, izbegavanje kritike, nepoverenje, impulsivnost, nestabilnost raspoloženja) koreliraju sa simptomima depresije i anksioznosti (3). Anksioznost kao crta pozitivno korelira sa ruminacijom i depresijom, dok mentalna fleksibilnost negativno korelira sa anksioznošću, ruminacijom i depresijom (4). Moguće je da mentalna fleksibilnost moderira vezu između anksioznosti kao crte i depresije, pri čemu ruminacija ima medijatorski efekat. Pored toga, kao medijator između ranije anksioznosti i kasnije depresivnosti registruje se izbegavajuće ponašanje (5).

Rezultati sugerišu da je depresija u vezi sa crtama kao što su neuroticizam/negativna emocionalnost, ekstraverzija/pozitivna emocionalnost i savesnost. Šta više, izgleda da karakteristike ličnosti doprinose početku i toku depresije različitim putevima (6). Visok neuroticizam je dokazano prediktor psiholoških problema, što nam govori da su crte ličnosti korisni indikatori za skrining psiholoških problema i efektivan put ka prevenciji u opštoj populaciji (7). Postavlja se pitanje da li rane intervencije kod osoba sa visokim neuroticizmom mogu biti efektivne u preveniranju kasnijeg bola i doživljaja nesposobnosti povezanih sa anksioznim i depresivnim poremećajima (8).

Cilj ovog istraživanja je bio da se ispita da li postoji veza između anksioznosti kao crte ličnosti sa crtama depresivne ličnosti među odraslim ispitanicima iz Crne Gore, kako bi dobili smernice za primenu programa za očuvanje mentalnog zdravlja.

Metode

U studiju je uključeno 355 ispitanika koji su pristupili upitniku onlajn preko *Google Forms* platforme. Link za pristup upitniku je: https://docs.google.com/forms/d/e/1FAIpQLSdygvpFmMpY-HlK9oMTDeMJYKPyKiuKehLbmSyveHRSsPERsnQ/viewform. Upitnik su popunjavala punoletna lica iz Crne Gore koja su pristupila linku tokom septembra i oktobra 2020. godine.

Opštim upitnikom prikupljeni su od ispitanika sledeći podaci: pol (ženski i muški), starost (numerička varijabla, transformisana u dve kategorije mlađi - od 18 do 43 godine i stariji - od 44 do 68 godina), regija u kojoj osoba živi (jug, centralna regija i sever Crne Gore), stečeno obrazovanje (srednja škola, fakultet, magistarske ili doktorske studije), radni status (nezaposlen, zaposlen), bračni status (neudata/neoženjen, bračna zajednica, vanbračna zajednica, razveden/a, udovac/udovica) i socio-ekonomski status (loš, prosečan, dobar).

Za ispitivanje anksioznosti kao crte ličnosti korišćen je standardni upitnik pod nazivom Crta ličnosti – 29 (engl. *Anxiety Trait* 29 – AT 29) (2), koju su konstruisale i standardizovale Snežana Tovilović i Zdenka Novović, 2009. godine. Skala se sastoji od 29 ajtema, a ukupan skor je suma pojedinačnih skorova. Skala je konstruisana kao petostepena skala Likertovog tipa. Na ispitivanom uzorku dobijena je izrazito visoka interna konzistentnost skale – Krombah alfa je iznosio 0,96.

Za ispitivanje depresivne ličnosti korišćena je standardizovani upitnik pod nazivom Depresivna ličnost (DL) (2), koju su konstruisale i standardizovale Zdenka Novović, Ljiljana Mihić i Snežana Tovilović, 2008. godine. Skala sadrži 26 ajtema, a ukupan skor je suma pojedinačnih skorova. U pitanju je petostepena skala Likertovog tipa. Na ispitivanom uzorku dobijene su visoke interne konzistentnosti – u studentskom i opštem uzorku: 0,90, i kliničkom: 0,84.

Podaci su obrađivani u statističkom programu SPSS, a za statističku analizu podataka korišćen je Pearsonov koeficijent linearlne korelacije i jednofaktorska analiza varijanse.

Rezultati

U istraživanju je učestvovalo 355 ispitanika, od čega 265 (74,8%) žena i 90 (25,4%) muškaraca (tabela 1). Starost ispitanika se kretala od 18 do 68 godina. Najveći procenat ispitanika je bio iz centralne regije Crne Gore (72,1%), a zatim sa juga (17,5%) i severa Crne Gore (10,4%). Po pitanju obrazovanja, 40% ispitanika je bilo sa završenom srednjom školom, 47,9% sa fakultetom i 12,1% sa magistarskim ili doktorskim studijama. Zaposleni su činili 59,7% ispitanika, a nezaposleni 40,3%. Skoro svaka druga osoba je bila neudata/neoženja, 26,2% je bilo u bračnoj zajednici, 24,8% u vanbračnoj vezi, a 2,5% je bilo razvedeno. Čak 82,3% ispitanika se izjasnilo da ima prosečno socio-ekonomsko stanje, 9,9% loše, a 7,9% dobro.

Žene su, u poređenju sa muškarcima, imale značajno izraženije crte anksioznosti ($F=13,34$; $p < 0,01$) i crte depresivnosti ($F=5,35$; $p<0,05$) (tabela 1). Pokazalo se da starost nije značajan faktor koji utiče na ispoljavanje depresivnih crta, ali je crta anksioznosti bila značajno više izražena kod

(3). Anxiety as a trait correlates positively with rumination and depression, while mental flexibility correlates negatively with anxiety, rumination and depression (4). Mental flexibility may possibly moderate the relationship between trait anxiety and depression (4), while rumination has a mediating effect. In addition, avoidance behavior has been registered as a mediator between previous anxiety and later depression (5)

The results suggest that depression is connected with personality traits such as neuroticism/negative emotionality, extravert behavior/positive emotionality and conscientiousness. Moreover, it seems that personality traits contribute to the onset and course of depression in different ways (6). High neuroticism was proved to be the predictor of psychological problems, which speaks of the fact that personality traits are useful indicators for the screening of psychological problems and efficient way towards the prevention in general population (7). The question arises whether early interventions in persons with high neuroticism can be efficient in preventing the later pain and emotions of incapacity related to anxiety and depressive disorders (8).

The aim of this study was to examine the connection between trait anxiety and depressive personality traits among adult respondents from Montenegro, in order to get directions for the application of programs for the maintenance of mental health.

Methods

The study included 355 respondents, who completed the questionnaire online via Google Forms platform. The link that was used to access the questionnaire was: https://docs.google.com/forms/d/e/1FAIpQLSdygvpFmMpYHlK9oMTDeMJYKPyKiuKehLbmSyveHRSsPERsnQ/viewform. The questionnaire was completed by adult persons from Montenegro, who accessed the link in September and October 2020.

The following data were collected from the respondents with the help of the general questionnaire: sex (female and male), age (numerical variable transformed into two categories: younger – from the age of 18 to 43 and older – from the age of 44 to 68), region where the person lived (south, central region and north of Montenegro), education (high school, faculty, master or doctoral studies), employment status (unemployed, employed), marital status (not married, married, common-law marriage, divorced, widow/widower), socio-economic status (poor, average, good).

For the assessment of anxiety as a personality trait, we used a standard questionnaire Anxiety Trait 29 (AT-29), which was designed and standardized by Snezana Tovilovic and Zdenka Novovic in 2009. The scale consists of 29 items, while the total score is the sum of individual scores. The scale was designed as a 5-point Likert scale. Particularly high consistency of the scale was obtained for this sample – Cronbach's alpha amounted to 0.96.

For the assessment of depressive personality we used the standardized questionnaire Depressive Personality (DP), which was made and standardized by Zdenka Novovic, Ljiljana Mihic and Snezana Tovilovic in 2008. The scale consists of 26 items, while the total score is the sum of individual scores. It is a 5-point Likert scale. High internal consistency was obtained for the examined sample – for the students' and general sample: 0.90, and clinical: 0.84.

Data were analyzed with the help of SPSS statistical program, while Pearson's linear correlation coefficient and one-factor analysis of variance were used for the statistical analysis of data.

Results

The study included 355 respondents, 265 women (74.8%) and 90 men (25.4%) (Table 1). The respondents' age ranged from 18 to 68 years. The highest percentage of respondents was from the central region of Montenegro (72.1%), and then from the south (17.5%) and north (10.4%). As far as their education is concerned, 40% of respondents finished high school, 47.9% of them graduated from the faculty, while 12.1% of them graduated from master or doctoral studies. 59.7% of them were employed, while 40.3% were unemployed. Almost every other person was not married, 26.2% were married, 24.8% in common-law marriage, and 2.5% were divorced. Even 82.3% of them stated that they had average socio-economic status, 9.9% poor and 7.9% good.

Women, in comparison to men, had significantly more pronounced anxiety-related personality traits ($F=13.34$; $p<0.01$) and depressive traits ($F=5.35$; $p<0.05$) (Table 1). It was shown that

Tabela 1. Distribucija ispitanika Crne Gore prema izraženosti anksioznih (AT29) i depresivnih (DL) crta ličnosti u odnosu na njihove demografske karakteristike

Varijable	AT29 skala $\bar{x}$ ±SD	Jednofaktorska analiza varijanse	DL skala $\bar{x}$ ±SD	Jednofaktorska analiza varijanse
Ukupno (N=255)	49,40±25,49		38,48±18,37	
Pol				
Žene (N=265)	52,23±26,17	F=13,34 p<0,001	39,79±18,34	F=5,35 p=0,02
Muškarci (N=90)	41,07±21,43		34,63±18,01	
Uzrast (godine)				
Mlađi (18-43) (N=320)	50,40±25,65	F=5,09 p=0,03	38,98±18,53	F=2,35 p=0,13
Stariji (44-68) (N=35)	40,23±22,23		33,97±16,40	
Stepen obrazovanja				
Srednja škola (N=142)	55,77±24,90	F=8,42 p<0,001	43,96±17,80	F=11,63 p<0,001
Fakultet (N=170)	46,18±25,72		35,41±18,76	
Magistarske ili doktorske studije (N=43)	41,09±21,96		32,51±13,71	
Mesto stanovanja				
Jug Crne Gore (N=62)	51,26±26,00	F=0,20 p=0,82	38,23±19,11	F=0,18 p=0,83
Centralna Crna Gora (N=256)	49,03±25,50		38,29±18,23	
Sever Crne Gore (N=37)	48,84±25,08		40,22±18,54	
Bračni status				
Slobodan (N=165)	50,28±26,67	F=0,54 p=0,65	40,19±19,22	F=1,31 p=0,26
Vanbračna zajednica (N=88)	49,75±23,52		37,59±15,98	
Bračna zajednica (N=93)	48,43±25,30		37,06±18,94	
Razveden/a (N=9)	39,78±25,88		30,44±17,25	
Radni status				
Nezaposlen (N=143)	53,83±25,28	F=7,35 p=0,01	40,67±16,87	40,67±16,87
Zaposlen (N=212)	46,42±25,25		37,00±19,22	37,00±19,22
Socio-ekonomski status				
Loš (N=35)	60,17±25,57	F=4,45 p=0,01	48,66±20,13	F=6,28 p<0,001
Prosečan (N=192)	48,81±25,29		37,54±17,91	
Dobar (N=28)	42,07±24,29		35,57±17,47	

$\bar{x}$ -aritmetička sredina; SD-standardna devijacija.

mlađih ispitanika (F=5,09; p<0,05). Kada pogledamo obrazovni nivo, najslabije izražena crta anksioznosti bila je prisutna kod osoba sa završenim magistarskim ili doktorskim studijama, nešto veća kod osoba sa završenim fakultetom, a najveća kod osoba sa završenom srednjom školom (F=8,42; p<0,01). Slično je dobijeno u pogledu izraženosti crta depresivne ličnosti kod osoba različitih obrazovnih nivoa (F=11,63; p<0,01). Anksiozne crte (F=4,45; p<0,05) i crte depresivne ličnosti (F=6,28; p<0,01) su bile značajno više kod osoba sa lošim, nego kod osoba sa prosečnim i dobrim socio-ekonomskim stanjem. Zaposleni i nezaposleni ispitanici se nisu značajno razlikovali u pogledu izraženosti crta depresivne ličnosti, ali su se razlikovali u pogledu crte anksioznosti, koja je bila značajno više izražena kod nezaposlenih ispitanika nego kod zaposlenih (F=7,35; p<0,05). Regija iz koje ispitanici dolaze i bračni status nisu se pokazali kao faktori koji značajno utiču na izraženost anksioznih i depresivnih crta ličnosti.

Statistički značajna visoka pozitivna korelacija dobijena je između crte anksioznosti i crta depresivne ličnosti (r=0,82; p<0,01) (tabela 2).

Diskusija

U našem istraživanju uočena je značajna visoka pozitivna korelacija između crta ličnosti anksioznosti i crta depresivne ličnosti. Rezultat našeg istraživanja je u skladu sa rezultatima ranije sprovedenih istraživanja (4,9), koja su pokazala da postoji pozitivna veza između simtoma anksioznosti i depresije, ako se na osnovu brojnih rezultata anksiozne i depresivne crte shvate kao predisponirajući faktori za razvoj neurotskih simptoma (3,5,8). Anksioznost kao crta ličnosti predstavlja sklonost da se odgovori stanjem anksioznosti onda kada anticipiramo opasnost, bilo da je ona stvarna ili

Table 1. Distribution of respondents from Montenegro regarding anxious (AT-29) and depressive (DP) personality traits according to their demographic characteristics

Variables	AT29 scale x̄ ±SD	Jednofaktorska analiza varijanse	DL skala x̄ ±SD	Jednofaktorska analiza varijanse
Total (N=255)	49.40±25.49		38.48±18.37	
Pol				
Women (N=265)	52.23±26.17	F=13.34 p<0.001	39.79±18.34	F=5.35 p=0.02
Men (N=90)	41.07±21.43		34.63±18.01	
Uzrast (godine)				
Mlađi (18-43) (N=320)	50.40±25.65	F=5.09 p=0.03	38.98±18.53	F=2.35 p=0.13
Stariji (44-68) (N=35)	40.23±22.23		33.97±16.40	
Stepen obrazovanja				
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Razveden/a (N=9)	39.78±25.88		30.44±17.25	
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Loš (N=35)	60.17±25.57	F=4.45 p=0.01	48.66±20.13	F=6.28 p<0.001
Prosečan (N=192)	48.81±25.29		37.54±17.91	
Dobar (N=28)	42.07±24.29		35.57±17.47	

x̄ -mean; SD-standard deviation.

age was not a significant factor which influenced the manifestation of depressive traits, whereas anxiety-related traits were significantly more pronounced in younger respondents (F=5.09; p<0.05). As for the level of education, the most weakly pronounced trait anxiety was present in persons with master's or doctoral degree, somewhat higher in persons with bachelor's degree, and the highest in persons with high school diploma (F=8.42; p<0.05). The similar results were obtained for depressive personality traits depending on the level of their education (F=11.63; p<0.01). Anxiety-related traits (F=4.45; p<0.05) and depressive personality traits (F=6.28; p<0.01) were significantly higher in persons with poor than in persons with average and good socio-economic status. There was no significant difference between employed and unemployed respondents regarding depressive personality traits, while difference was noted regarding trait anxiety, which was more pronounced in unemployed respondents in comparison to employed respondents (F=7.35; p<0.05). Region, where the respondents came from, and marital status were not factors that significantly influenced anxious and depressive personality traits.

The high positive correlation between trait anxiety and depressive personality traits was statistically significant (r=0.82; p<0.01) (Table 2).

Discussion

In our study, the high positive correlation between anxiety-related personality traits and depressive personality traits was significant. The results of this study are in accordance with the results of previously conducted studies (4,9), which showed the positive correlation between the symptoms of anxiety and depression, if according

Tabela 2. Deskriptivna statistika na skali anksioznosti (AT29) i na skali depresivnosti (DL)

Skale	Min	Max	x̄	SD	Skjunis	Kurtozis
AT29	2	114	49,40	25,49	0,23±0,13	-0,86±0,26
DL	0	101	38,48	18,37	0,41±0,13	-0,16±0,26

x̄ -aritmetička sredina; SD-standardna devijacija.

ne (10). Stanje anksioznosti podrazumeva svesno opaženo stanje straha i strepnje, koje je subjektivno i može biti isprovocirano nekim spoljašnjim ili unutrašnjim stimulusom opaženim kao opasnost ili pretnja. Crte depresivne ličnosti uključuju pesimističnost, pasivizaciju, samokritičnost, samooptuživanje, zabrinutost, preokupiranost negativnim događajima, osećanjem neadekvatnosti i sopstvenim nedostacima i ove crte su relativno trajne karakteristike ličnosti. Stanje depresivnosti može imati različit tok i trajanje, a karakteriše ga doživljaj intenzivne tuge, potištenosti, bezvoljnosti, beznađa i bespomoćnosti, neretko uz usporenost, iscrpljenost, razdražljivost i probleme koncentracije i pažnje.

Ono što je zajedničko i za jedne i za druge crte jeste psihološka vulnerabilnost, odnosno ranjivost, koja podrazumeva preosetljivost i smanjenu otpornost na različite podražaje koji prete da ugroze stanje psihološke ravnoteže, pa se prisustvo ovih crta može smatrati značajnim preduslovom za razvoj simptoma anksioznosti i depresije (3,5,11). Upravo bi zato bilo poželjno rano identifikovati pojedince sa ovim tendencijama (moguće tokom školovanja) i osmisliti tretmane za prevenciju poremećaja.

Iako se ove crte ličnosti formiraju tokom ranog razvoja, značajno je obratiti pažnju na uticaj pojedinih demografskih karakteristika na njihovu izraženost. Naši rezultati ukazuju da su ove crte izraženije kod žena, kod ispitanika nižeg obrazovnog statusa i lošijeg socio-ekonomskog stanja. Činjenica da su kod žena izraženije anksiozne i depresivne crte mogu se donekle objasniti kulturološkim obrascima crnogorskog društva, gde je emocionalna ekspresija neuobičajena i neočekivana od muškaraca, pa će oni, čak i ako poseduju ove crte, biti manje skloni da ih pokažu. Sa druge strane, jasno je da niži obrazovni nivo i lošiji materijalni status mogu uticati na kvalitet života pojedinca, te bi to moglo biti obrazloženje veće izraženosti anksioznih i depresivnih crta kod ovih ispitanika.

Kod ispitanika koji su nezaposleni, jače je bila izražena crta anksioznosti nego kod zaposlenih. Takođe, anksiozne crte značajno su izraženije kod mlađih ispitanika nego kod starijih, što je u skladu sa rezultatima istraživanja Varme i saradnika, gde su mlađi ispitanici pokazivali značajno veće nivoe anksioznosti, deprimiranosti i distresa nakon izbijanja pandemije COVID 19 nego što je to bio slučaj sa starijim ispitanicima (10). Jedno od mogućih objašnjenja ovog fenomena može da bude to što su mlađi ispitanici otvoreniji za izražavanje svojih emocionalnih stanja u situaciji ispitivanja, ali su neophodna dalja istraživanja koja bi ovu problematiku detaljno ispitala.

Kada znamo da postoje crte ličnosti koje predstavljaju predispozicije za razvoj određenih simptoma i poremećaja, kao što je to slučaj sa crtama merenim u ovom istraživanju, posebno kada znamo da se u značajnom broju slučajeva te crte javljaju zajedno, onda možemo osmisliti programe prevencije i podrške kod osoba kod kojih se rano detektuju ove crte, kako bi se sprečilo da poteškoće u funkcionisanju prerastu u anksioznost ili depresiju.

Zaključak

Crte ličnosti koje predstavljaju predispoziciju za razvoj simptoma aksioznosti i depresivnosti su značajno više ispoljene kod žena, osoba sa nižim stepenom obrazovanja i lošijeg socio-ekonomskog stanja. Kod mlađih ispitanika i onih koji su nezaposleni, značajno je jače izražena crta anksioznosti u odnosu na starije i zaposlene ispitanike, ali se nije pokazalo da starost i radni status utiču na ispoljenost depresivnih crta ličnosti. Nije pronađen značajan uticaj bračnog statusa i zaposlenosti na ispoljenost crta ličnosti merenih u ovom istraživanju. Uočena je značajna visoka pozitivna korelacija između crta anksioznosti i crta depresivne ličnosti, što može doprineti osmišljavanju adekvatnih preventivnih programa za očuvanje mentalnog zdravlja kod rizičnih kategorija osoba.

Table 2. Descriptive statistics on the anxiety scale (AT29) and depression scale (DP)

Skale	Min	Max	$\bar{x}$	SD	Skewness	Kurtosis
AT29	2	114	49.40	25.49	0.23±0.13	-0.86±0.26
DL	0	101	38.48	18.37	0.41±0.13	-0.16±0.26

$\bar{x}$ -mean; SD-standard deviation.

to numerous results, anxious and depressive traits are considered to be predisposing factors for the development of neurotic symptoms (3,5,8). Anxiety as a personality trait is a tendency to respond with the state anxiety when danger is anticipated, no matter whether it is real or not (10). State anxiety is a consciously perceived state of fear and worry, which is subjective and can be provoked by some outer or inner stimuli, which are perceived as a threat or danger. Depressive personality traits include pessimism, passive behavior, self-criticism, self-reproach, worry, preoccupation with negative events, feeling of inadequacy and shortcomings and these traits are relatively constant personality traits. Depressive state can have different course and duration, and it is characterized by the feeling of intensive sorrow, fatigue, irritability and problems with concentration and attention.

What is common for both trait anxiety and depressive personality traits is psychological vulnerability, that is, high sensitivity and lowered resistance to different stimuli, which threaten to endanger the state of psychological balance, and therefore, the presence of these traits is deemed to be a significant precondition for the development of symptoms of anxiety and depression (3,5,11). Therefore, it is important to identify persons with such tendencies early (possibly during schooling) and work on the treatments for the prevention of these disorders.

Although these personality traits are formed during early development, it is important to pay attention to the influence of certain demographic characteristics on their distinctiveness. The results of our study point to the fact that these traits are more pronounced in women, respondents with lower educational status and poorer socio-economic status. The fact that anxiety-related traits and depressive traits are more pronounced in women may be explained, to some extent, by cultural patterns of Montenegrin society, where emotional expression is unusual and not expected from men, and even if they have these traits, they do not tend to show them. On the other hand, it is clear that lower educational status and poorer material status may influence the quality of life, and therefore, this might be the explanation of higher distinctiveness of these traits in these respondents.

In respondents, who are unemployed, trait anxiety was more pronounced than in employed respondents. Also, anxiety-related traits are significantly more pronounced in younger respondents than in older ones, which is in accordance with the results of Varma and associates, where younger respondents showed significantly higher levels of anxiety, depression and distress after the onset of COVID-19 pandemic in comparison to older respondents (10). One of the possible explanations of this phenomenon may be that younger respondents are more open to express their emotional state in the examination situation, but further research is needed to examine this issue in detail.

Having in mind the fact that some personality traits may be the predisposition for the development of certain symptoms and disorders, as in the case of traits measured in this study, especially when we know that they may appear simultaneously in a significant number of people, we can create programs of prevention and support when these traits are detected early, in order to prevent these problems from developing into anxiety or depression.

Conclusion

Personality traits, which are the predisposition for the development of symptoms of anxiety and depression are significantly more pronounced in women, people with lower educational status and poorer socio-economic status. In younger and unemployed respondents, trait anxiety is significantly more pronounced than in older and employed respondents, but age and employment

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status were not shown to influence depressive personality traits. The influence of marital status and employment on personality traits measured in this study was not significant. The positive correlation between trait anxiety and depressive personality traits was significantly high, which may contribute to the creation of adequate prevention programs for the maintenance of mental health in risk categories.

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In this section, the authors describe how the study was conducted, explain the choice of methods and design of the research. The sub-sections of the methods may be: study design (eg quantitative or qualitative research, descriptive or analytical or experimental study, etc.), choice of respondents (inclusion and exclusion criteria from the study), ethical aspects (the number under which the study was approved by the ethics committee), research instruments (method of data collection, specificity of instruments used), and statistical analysis of the data (types of tests). It is important to provide literature data for known methods, including statistical methods.

The results

Describe the results of the research presented in a logical order through tables, charts and illustrations (appendices are cited after the Literature).

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Acknowledgment

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Appendices

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