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Plenarne sekcije/Plenary Sessions
Apstrakti/Abstracts

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Plenarno predavanje
Opening lecture

LABORATORY MEDICINE IN THE ERA OF COVID-19: LESSONS FOR THE FUTURE

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The lockdown due to the coronavirus disease 2019 (COVID-19), a major healthcare challenge, is a worldwide threat to public health, social stability, and economic development. The pandemic has affected all aspects of society, dramatically changing our day-to-day lives and habits. It has also changed clinical practice, including practices of clinical laboratories. After two years, it is time to rethink what has happened, and is still happening, in order to learn lessons for the future of laboratory medicine and its professionals. The first issue is the increased visibility of the central role of clinical laboratories in modern healthcare. Before the pandemic, several documents, papers and initiatives emphasized the importance of laboratory testing in numerous clinical pathways, but the pandemic further raised awareness of the essential contribution made by clinical laboratories to diagnostic reasoning and the management of cases of suspected or confirmed SARS-CoV-2 infection. These include etiological diagnosis, patient monitoring, and epidemiological surveillance. Further evidence of the importance of laboratory medicine is being gained thanks to serological testing for SARS-CoV-2 antibodies in vaccine(s) clinical trials, in properly monitoring vaccinated subjects (eventually with different vaccines and different clinical histories), and in better understanding the effects of virus variants from both diagnostic and clinical viewpoints. The second lesson is that »speed must never compromise quality, and a marriage between accuracy, reliability and quickness should be assured«. A thrid lesson is that we have to »assure and monitor quality in all phases of the testing process and measure clinical and economical outcomes to provide evidence of the effectiveness of laboratory services. The IFCC Model of Quality Indicators (MQI) is a valuable tool for achieving this goal«. A fourth lesson is that laboratory professionals have to evaluate all well-developed and promising technologies, validate and deploy them according to established guidelines and recommendations focusing on patient needs. And we have to integrate different diagnostic approaches in a clear and reliable report so that the information is conducive to diagnostic accuracy, effective therapy and the best possible clinical outcome. However, the most important lesson is to move slinical laboratories out of the silo, avoid isolation and integrate laboratory testing in diagnostic and clinical pathways that effectively prevent disease, and provide early diagnosis, valuable monitoring, personalized therapy and epidemiological surveillance. The ultimate goal is, in fact, effectiveness, not just efficiency.

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Plenarno predavanje
Plenary Lecture

LABORATORY MANAGEMENT IN THE NEW NORMAL

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Laboratory leadership is a skill mostly learned by experience and intuition (often referred to as emotional inteligence). The art of leadership is akin to the art of living – we learn as we go along. Preanalytical, analytical and postanalytical processes need to be constantly monitored and optimized, with no visible disruptions in the service. It is often presumed that the most prominent sign of a smoothly operated laboratory are happily oblivious customers who never give a laboratory a second thought, which means that results are always delivered as requested, in an efficient and timely manner. This notion might be true in a fee for service oriented laboratory, but not neccessarily in the one which aspires to provide an added value. An "added value" laboratory is the one where not all requests are uniformely received as unquestionable orders to be fullfilled, where results are not only numbers but may and should contain meaningful and informative comments and where laboratory people bear names and faces known to their users.This presentation therefore deals with all the additional chalenges faced by hospital laboratory leaders during the two years of the Covid 19 pandemic. All the hospital laboratories needed to promptly adapt to the sudden unprecedented demands, not only related to SARS CoV-2 diagnostic, but also to all the other challenges connected to swift and often chaotic hospital workflow and case mix changes. Staff routines were adapted to accomodate the highest priority – no disruption of laboratory services due to within laboratory infection spread. Preanalytical workflow suddenly became crucial in terms of timely and safe specimen delivery while minimising human contact, both from emergency departements and intensive care units dealing with covid patients. Any process changes which were not carefully talked through have resulted in serious TAT delays, as will be discussed in detail with practical examples. New tests (SARS CoV2 PCR and antibodies, IL-6) needed to be quickly added to the existing STAT routine. But, above all, throughout this period laboratory technicians and other employees had to feel safe and cared for. As in any emergency situation, people's individual vulnerabilities became visible and needed immediate attention. All this had to be done by the laboratory leader, who simultaneously held an 24 hours' open hotline with hospital administration and their various questions and demands. Finally, the laboratory remains as usual the only voice of reason to be heard regarding excessive unnecessary testing conected with Covid and suspected post Covid sydromes.

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Plenarne sekcije
Plenary sessions

MEETING THE LEADERSHIP CHALLENGE OF DISRUPTIVE INNOVATION

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The 20th century digital revolution has seen the introduction of faster, innovative and easier to use technologies that have taken laboratory medicine services closer to patients in primary and community care. For the 21st century artificial intelligence driven algorithms are increasingly supporting evidence-based decision making that is reducing the need for expert human resource and opening opportunities for global, information technology providers to disrupt conventional ways of working at the point of care. A new leadership challenge emerges for specialists in laboratory medicine. Perhaps no longer laboratory-based specialists will extend their knowledge, skills and competence to a) guiding appropriate services for local environments based on clinical need, b) ensuring technology solutions are cost-effective, safe and reliable, c) developing the business acumen to market, negotiate and manage change d) getting a better understanding of imaging technologies, genomics, and health information science (data mining and health economics) that also drive the changing landscape. In providing examples of the new ways of working this talk will also emphasise the potential to exploit specialist leadership to ensure effective use of resource across the diagnostics and information technology industries, service commissioners, academia and policy related healthcare organisations.

ADDED VALUE BY INTERPRETATIVE COMMENTING

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EFLM Working Group »Patient Focused Laboratory Medicine«

Consultation by adding interpretative comments to reports has long been recognized in laboratory medicine as one of the activities that can support physicians and help to improve patient treatment outcomes. Interpretation of laboratory test results might in some cases considerably be supported when additional tests are performed on the available samples. This activity was named reflective testing-where the reflection is done by the laboratory specialist - and that can improve the diagnostic efficiencyconsiderably. Both the need, clinical value and appreciation by stakeholders of these forms of consultation have been proven by a diversity of studies. Both general practitioners and medical specialists have been shown to value interpretative commenting. Other forms of consultation are emerging: reporting of laboratory results to patients is becoming the rule. Most patients have little understanding of these results, and consultation of patients could add a new dimension to the service of the laboratory. These developments have been recognized by the European Federation of Clinical Chemistry and Laboratory Medicine, which has established the working group on Patient Focused Laboratory Medicine for work on the matter. Providing proper interpretative comments is, however, labor intensive. Harmonization is necessary to maintain quality between individual specialists. In present-day high-volume laboratories, there are few options on how to generate high-quality, patient-specific comments for all the relevant results without overwhelming the laboratory specialists. Automation and application of expert systems could be to only solution.

SMARTPHONE APPLICATIONS USING LABORATORY MEDICINE DATA – RELIABILITY AND BENCHMARKING

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Thanks to their accessibility, many of smartphone mobile applications (apps) are used for delivering health interventions to clinicians and patients. However, the burning issue is the quality of health related apps and how to evaluate it. The content of most of them is not officially regulated, unless they function as part of a medical device. Mobile App Rating Scale (MARS) is a multidimensional tool for classifying and rating the quality of mobile health apps. Its quality criteria consider engagement, functionality, aesthetics, and information quality of the app content. The project of EFLM Patient Focused Laboratory Medicine Working Group was to analyze the number and quality of smartphone apps available on the market using in any way laboratory medicine data. Seven categories were distinguished: 1) apps that offer medical advice about symptoms and health queries with the possibility to upload laboratory test results, which can be seen, stored and shared; 2) reference ranges of selected analysis with basic information about the causes of increase or decrease designed for patients; 3) quick reference for laboratory tests for medical students and doctors; 4) apps for monitoring the state of user's health through a wide range of health parameters, including glucose and/or cholesterol as laboratory data, 5) apps that provide access to patients' laboratory results to physicians; 6) apps that enable patients to access their laboratory test results directly from the diagnostic center; and 7) electronic health records apps that include laboratory test results. MARS score values revealed the poorest performance and quality of the apps intended for patients, with significant issues of security of personal information used by the apps, and the questionable affiliation of developers, without referencing the source of information cited. The working group also analyzed the users' (i.e. patients') opinion on selected apps, which pointed out the trustworthiness, the adequate style of presenting information the graphics, and the appearance of the app as the key issues of the app quality.

THE PROFESSIONAL DEVELOPMENT OF LABORATORY MEDICINE PROFESSIONALS IN/THROUGH EFLM COUNTRIES: WHAT TOOLS AND OPPORTUNITIES DO WE HAVE?

Evgenija Homšak
EFLM Professional Committee, Chair

University Clinical Centre Maribor, Slovenia

The International Federation of Clinical Chemistry and Laboratory medicine (IFCC), and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) are two essential professional organizations in a field of Clinical Chemistry and Laboratory Medicine (CCLM), that join and linking together Professional National societies (NSs) and their members through Europe and all over the world. In a scope of both organizations, professionals as NSs representatives are actively involved through different roles and issues in various professional working groups and committees. EFLM has several essential Committees: for Education and Training (C-ET), Communication (C-C), Quality and Regulation (C-QR), Science (C-S) and Professional Committee (C-P). C-P is responsible for several important issues, to represent the professional interests of specialists in laboratory medicine across Europe. One of the most important is the effort to achieve recognition of professional qualifications under European Union (EU) legislation based on the principles of free movement of professionals within Europe. According to the »EU Directive 2013/55/EU on recognition of professional Qualifications«, this effort could be achieved with the harmonization of our profession on EFLM level through Common Training Framework (CTF) and confirmed exit qualifications. This process/approach is started almost 20 years ago, with the established European Communities Confederation of Clinical Chemistry and Laboratory Medicine (EC4) who put the base for rules and minimal criteria for harmonization of our diverse education system through EU Countries. Since 2016 EC4 has been transferred to the EFLM C-P. Through these years, several (5) versions of the Syllabus for post-graduate training in CCLM was prepared, which present the education/training program, with important areas of knowledge and essential competencies for our profession. It represents the cornerstone for later established Equivalents of standards (EoS) for European Specialist in Laboratory Medicine. According to determined criteria, first EoS have been delivered to the Countries whose education program/system for specialization post-graduate training fulfil and include all important parts of these established rules for EoS: education/training duration, program (polyvalent), final exam/exit qualification.

Equivalence of Standards in Education and Training (EoS)

- Minimum 9 years (ideally 10): years academic (4 or 5 years) and specialist training (5 years);
- Education and training to standards set in the EFLM syllabus version 5;
- A Master's degree in Medicine, Pharmacy or Science;
- An EFLM Profession Committee recognised 'Equivalence of Standards' exit qualification;
- Evidence of participation in continuous professional development (CPD).

It requires curriculum content to include:

- General chemistry of at least 35%;
- General chemistry plus haematology of at least 65%;
- Flexibility as to the remaining 35%, including general chemistry, haematology, microbiology, and genetics and IVF in a proportion consistent with the requirements in the country of destination.

For the recognition and legislation of our profession, on the EU level through Directive, it is essential to obtain EoS of post-graduate education and training and confirmation of CTF on government level at least in 33% of EU Member States. Once the recognition and legislation of our profession would be accepted there is an EU requirement for all Member States to implement it. This is important especially for non-medical specialists since the specialists who are medical doctors have been already recognised on EU level. Now we have already 15 countries with achieved/confirmed EoS and the number still growing. To support the Profession Committee in its strategy to achieve recognition of Specialists in Laboratory Medicine, EFLM has established the EFLM Register of European Specialists in Laboratory Medicine (EuSpLM). It was first established in 1997 by EC4, the merger of EC4 with FESCC culminated in 2016 with the transfer of the Register to EFLM. Through the standards it sets and the code of conduct it expects from its registrants, the Register has identified a cohort of nearly 3000 individuals with unique knowledge, skills and competencies for leading/delivering high-quality laboratory medicine services. EFLM members in this register who already fulfil and have confirmed exit qualification according to the EoS criteria obtain the common title EuSpLM. However, the goal of our efforts and for our profession is to achieve EoS in all EFLM countries and raising the level of professional knowledge and skills in all field of Laboratory Medicine. To achieve this goal, EFLM through activities of their professional units have developed several tools and

opportunities. Education Committee through important efforts and work of their working groups (WG) offer several possibilities for additional education and training. WG: Congresses and Postgraduate Education has launched post-graduate courses, that NSs can apply for them, to offer their members additional knowledge in two fields: Biostatistics, How to write a good professional article. Another very important tool is EFLMLabX project of exchanging practical knowledge and skills through EFLM web-platform (https://eflmlabx.eflm.eu/en), where potential users can search and apply for practice/visiting/research in different laboratories/institutions through EFLM countries and get direct contacts. WG: Distance Education and e-Learning offer several different webinars on different topics and recordings of conferences/congresses. Lately, under Task Group: EFLM Syllabus Course it has been launched first webinars also on Syllabus topics, which could be an important additional tool for the trainees/specialists, for their professional development. Science Committee with several and different WGs provide evidence and recommendations for harmonization of knowledge and practice of our profession on different field of LM. In 2019 EFLM has, next to EuSpLM Register, established EFLM-Academy. Its memberships offer/bring a lot of benefits not only to already registered EuSpLM but also to all other (non-EuSpLM) members who want to be a part of »big EFLM family« and show the interest for Laboratory Medicine (from non- EFLM countries, other profession (medical doctors, nurses), engineers on field of LM..).

The important benefits of EFLM-Academy are:

- Free on-line subscription to CCLM, the official EFLM journal;
- Unlimited access to all documents (laboratory standards) of the CLSI (Clinical and Laboratory Standards Institute) database;
- Regular e-mail notifications of all EFLM activities, programmes and opportunities;
- Eligibility to apply for EFLM travel grants (subordinated to application's criteria of each specific EFLM initiative)
- Reduced registration fee to all EFLM conferences and courses
- Free access to EFLM webinars
- Enrollment in the EuSpLM Register for those who meet the Educational and Training EFLM Equivalence of Standards (subordinated to the evaluation of the requested documentation by the EFLM Profession Committee).
- With all the activities, efforts, opportunities and benefits that come and grow with the enthusiastic work of experts in EFLM WGs and committees and across EFLM countries, we help to create the tools for expanding our knowledge of Laboratory Medicine. By using these tools and opportunities, we also rising the strength of our profession for present and for the future.

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ACCREDITATION OF LABORATORIES

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An actual contribution of accreditation certificate to day to day laboratory routine is not easily measurable. Does it represent an objective, independent confirmation of the quality of laboratory practice and reliability of laboratory test reports, or is it a mere formality to be fulfilled and carefully followed? How does accreditation contribute towards minimizing error occurences and risks? In the past, the quality of laboratory practice was traditionally and exclusively demonstrated by means of external quality assessment (EQA) results. When considering eligibility of a laboratory for participation in clinical studies, EQA certificates are even today still the most often required and sufficient proof of quality.Increasingly, however, this approach does not allways suffice as EQA covers only some (mostly analytical) aspects of laboratory practice.Therefore, in 2003 the first version of the international standard for implementation of the quality management system in medical laboratories was adopted and published, i.e. ISO 15189: Medical laboratories – Requirements for quality and competence. A new and somewhat altered and updated version of this standard was published in 2012.This specific standard consists of a number of regulations and requirements to be met by an accredited laboratory, and is intended for all medical laboratories that perform biological, microbiological, immunological, chemical, immunohematological, hematological, biophysical, cytological, pathological and other examinations of human material. ISO 15189 standard was adopted as a national standard in the Republic of Croatia in 2006, and so far 13 medical diagnostic laboratories have been accredited (domains of work: medical biochemistry, microbiology and transfusion). Accreditation of laboratories in Croatia (and of one laboratory in Slovenia) has been carried out by the Croatian Accreditation Agency, an independent and non-profit public institution founded according to the Croatian Governmentdecree based on the Accreditation Act. Accreditation of Croatian laboratories is voluntary and for the time being it does not confer any particular privileges to accredited as compared to unaccredited laboratories in public healthcare system. The only advantage worth mentioning is a comparatively simpler acceptance of laboratories for participation in clinical studies, however laboratories with acceptable EQA results are included without problems as well. Accreditation of medical biochemistry laboratories according to ISO 15189 standard requires continuous monitoring, surveillance and improvements of all laboratory processes (preanalytical, analytical, postanalytical), active interpretation of laboratory test results, and establishment of full laboratory users' trust in the quality of reported results. It should be stated that the aim of an accredited laboratory is not only to issue accurate results based on physician's request, but also to participate in correct test selection and in interpretation of results, to respect patients' rights to privacy and to focus its attention on patient safety and on laboratory practice according to ethical principles. All these requirements are put in place in order to elevate the role of the laboratory from mere anonymus service towards diagnostic partnership. A question whether a fully accredited medical laboratory achieves this goal, remains to be answered.

IMPORTANCE OF LABORATORY GUIDELINES FOR MEDICAL LABORATORY PRACTICAL WORK

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Despite recent progress towards laboratory test standardization and harmonization, there are still huge problems that have to be addressed. Since in clinical guidelines only the laboratory parameters are defined, in different countries are useddiverse laboratory methods for the same diagnoses. In order to improve the quality of treatment and achieve standardization in treatment along with using of resources properly, there is a need for formulation of common laboratory guidelines for European countries and beyond. On this way, problems which can be found in developing laboratory guidelines on national or hospital level can be avoided and update of the new scientific advances would be faster. One of the first steps towards laboratory guidelines development is creation of guideline's frame that incorporate essential information related preanalytical, analytical and postanalytical process, clinical benefit and cost-effectiveness data. The most guidelines enclose data related to sample collection, biological variations, sample type, transport and storage of the sample. For most methods, analytical information (reference material, total error, bias, inaccuracies and interferences) is also known. From the postanalytical information, measurement units, reference interval, maximum allowed TAT is available. Future laboratory guidelines should focus on laboratory tests that may influence the decision-making process, treatment optimization, disease prediction and improvement of patient outcome while also be cost – effective. Laboratory results are critical to ensuring the treatment of most patients. A number of locally accepted laboratory guidelines remain too vague with respect to new scientific information and optimal analytical approaches. In order to develop a laboratory guideline, many obstacles need to be overcome. It should consider different patients' needs and reimbursement systemsin different countries. Also, laboratory guidelines should be synchronized with clinical guidelines. Guidelines should be translated into national languages and be accepted by the most European countries.

MANAGING THINGS AND LEADING PEOPLE

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What is a Leadership?

It is the process through which leaders influence the values, behavior and attitude of others. Leadership qualities can either be innate or also can be acquired. A Leader is someone who shows a direction, influences, motivates and inspires. A Leader is a person who can bring constructive change. Core values of a Leader are moral courage, integrity, decisiveness and assertiveness. Good Leader has to have: knowledge and skills, sense of priority, focus, vision, judgment, charisma, trust and emotional intelligence. A Leader motivates the team members in any situation, if they perform well or in case of failure. A good Leader applies the following approaches to lead: strategic approach, human assets approach, expertise approach, unbox approach, change approach. A Leader does the right thing at the right time, in right place. Manager does things right. A Manager is someone who plans, organizes and allocates resources, controls and solves problems. Manager administers while Leader innovates. Manager focuses on system processes, a Leader focuses on people; Manager relies on control, a Leader inspire trust; Manager has a short range view; a Leader has a long-range perspective. A Leader knows the way, goes the way and shows the way. All Managers are not Leaders but all Leaders can be Managers.

PRIMENA TEHNIKA KONTROLE KVALITETA RADA U REALNOM VREMENU KOJE KORISTE REZULTATE PACIJENATA U MEDICINSKIM LABORATORIJAMA

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Tehnike kontrole kvaliteta u realnom vremenu (Patient-Based Real Time Quality Control, PBRTQC) koje koriste rezultate pacijenata u medicinskim laboratorijama koriste izračunate parametre iz uzoraka pacijenata u realnom vremenu kao oblik kontrole kvaliteta (QC). Upotreba uzoraka pacijenata široko se koristi u hematologiji kao QC alat vec četrdeset godina. U medicinskim laboratorijama, mada se QC tehnike koje koriste rezultate pacijenata opisane pre više od pedeset godina, ovaj koncept se smatra zanimljivim, ali zbog praktičnih problema nije široko korišcen. Strategije QC koje koriste rezultate pacijenata, kao što su delta provere (delta check), prosečna vrednost normala (average of normals, AON), pokretni prosek (moving average, MA) i prosečna delta vrednost (average of delta, AOD) su sve češće zasupljeni u medicinskim laboratorijama zbog dostupnosti laboratorijskog informacionog sistema (LIS)/middleware. U poređenju sa »konvencionalnim« QC strategijama (interna kontrola kvaliteta, IQC), PBRTQC ima više prednosti i postoji sve veća zabrinutost da IQC nije dovoljna za brzo otkrivanje analitičke greške. Tradicionalni QC materijali nisu komutabilni, neki IQC materijali navode samo takozvane »ciljne« vrednosti koje su specifične za anlizatore umesto prave koncentracije analita. Danas su analizatori pouzdaniji i medicinske laboratorije određuju manji broj QC uzoraka što povecava broj rezultata iz uzoraka pacijenata koji se izveštavaju pre nego što se otkrije sistematska greška ili »odstupanje« (bias) se otkrije tek naknadnim neodgovarajućim rezultatom QC. AON i MA tehnike kontinuirano prate performanse određivanja u medicinskim laboratorijama. Srednja vrednost ili medijana za grupe rezultata pacijenata koje se prate u određenim vremenskim intervalima mogu da se koriste u statističkoj QC. AoN ili MA pristup je više zasnovan na riziku koji koristi karakteristike populacije pacijenta da otkrije pomeranje u izmerenoj prosečnoj vrednosti za populaciju. U medicinskim laboratorijama PBRTQC predstavlja QC nove generacije, ali njena implemntacija nije jednostavna kao što je to za »konvencionalnu« QC. Postoje određeni zahtevi za LIS/middlware-a koji su ključni za primenu PBRTQC. Potrebne su sledeće neophodne karakteristike LIS/middlware softvera za uspešnu

IMPLEMENTATION OF PATIENT-BASED REAL TIME QUALITY CONTROL TECHNIQUES IN MEDICAL LABORATORIES

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Patient-Based Real Time Quality Control (PBRTQC) techniques in medical laboratories use parameters calculated from patient samples in real time as a form of quality control (QC). The use of patients samples have been widely used in haematology as QC tool for over forty years. In medical laboratories, even patient-based QC techniques have been described for more than fifty years, the concept were seen as interesting, however, because of practical issues it has not been widely utilized. Patient based QC strategies such as the delta check, average of normal (AON), moving average (MA) and average of delta (AOD) are becoming more commonplace in medical laboratories because of availability of laboratory information system (LIS)/middleware programs. There are many advantages of PBRTQC in comparison with »conventional« QC strategies (internal quality control, IQC) and there is growing concerns that IQC alone is not sufficient to rapidly detect analytical error. Traditional QC materials may be non-commutable, some IQC materials state only so-called assay targets that are specific to anlyzers instead of the true analyte concentration. Today analyzers are more reliable and medical laboratories run fewer QC samples which increases the number of patients samples reported before systematic error or bias event is detected by a subsequent QC failure. The AON and MA techniques continuously monitor assay performance in medical laboratories. The mean or median for groups of patient results is tracked over sequential time intervals can be used in a statistical QC process. An AoN or MA approach is more of risk based approach using the patient population characteristics to detect a shift in the measured population mean. PBRTQC is next generation medical laboratory QC, but is not as simple to implement as conventional QC. There are some requirements of LIS/middleware that are crucial for adoption of PBRTQC. The essential features of LIS/middleware for successful implantation and operational application of PBRTQC are: data capture and storage, data extraction, analysis, visualization, exploration and transformation, statistical analysis and testing environment, live application and reporting. Also, a software has to have some additional features: advanced data visualization, for-

implantaciju i operativnu primenu PBRTQC-a: prikupljanje i čuvanje podataka, ekstrakcija podataka, analiza, vizualizacija, istraživanje i transformacija, statistička analiza i okruženje za testiranje, aplikacija u realnom vremenu i izveštavanje. Takođe, softver mora da poseduje neke dodatne karakteristike: naprednu vizualizaciju podataka, formalnu statističku analizu i mogucnost da se inkorporiraju podaci unutrašnje kontrole kvaliteta rada. QC programi koji koriste rezultate pacijenata trenutno se široko koriste i primena PBRTQC je u fazi brzog rasta. Međutim, softverska podrška je ograničena, a za sprovođenje programa PBRTQC potrebno je dosta vremena i statističkih veština. PBRTQC tehnike ne mogu u potpunosti da zamene tradicionalnu IQC. One su superiornije u odnosu na klasičnu QC za veliki broj određivanja, ali za određivanja u malim serijama, konvencionalna QC je pogodnija. Kombinacija tehnika QC omogućava najbolju zaštitu protiv pogrešnih rezultata koji se izveštavaju.

DA LI SE *MOVING AVERAGE* PROCEDURE MOGU KORISTITI KAO KONTINUIRANA KONTROLA KVALITETA RADA U MEDICINSKIM LABORATORIJAMA?

Vera Lukić

Odeljenje za laboratorijska ispitivanja,
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Tradicionalno se kontrola kvaliteta analitičkog rada u medicinskim laboratorijama sprovodi analiziranjem komercijalno dostupnih kontrolnih uzoraka u određenim vremenskim intervalima, kao i učešćem u spoljašnjim programima kontrole kvaliteta. Nedostaci tradicionalne kontrole su intermitentnost i nekomutabilnost. Zbog toga se javlja potreba za uvođenjem dodatnih kontrolnih mehanizama koji bi mogli prevazići ove nedostatke i obezbediti kontinuirani nadzor nad analitičkim procesom. U tu svrhu u savremenoj laboratorijskoj praksi se razmatra ideja kontrole kvaliteta zasnovane na rezultatima pacijenata. Jedan od mogućih načina korišćenja rezultata pacijenata u svrhu kontrole kvaliteta analitičkog rada jeste pokretni prosek (eng. moving average, MA). MA podrazumeva izračunavanje prosečne vrednosti iz dobijenog seta rezultata pacijenata i dalje korišćenje te vrednosti u kontrolne svrhe. Naziva se pokretnim, jer se vrši rekalkulacija MA vrednosti svaki put kada se primi novi rezultat, odnosno podaci se kontinuirano ažuriraju i evaluiraju, kako se uzorci pacijenata analiziraju. Najčešće korišćeni algoritmi za izračunavanje MA vrednosti su: prosti MA, eksponencijalno ponderisani MA i Bulov algoritam. Iako je konmal statistical analysis and possibility to incorporate internal quality data. Patient-based QC programs are currently widely used and PBRTQC is in rapid growth phase. However, there is only limited software support, and to implement a PBRTQC program requires considerable time and statistical skills. PBRTQC techniques cannot totally replace traditional IQC. For high volume assays they are superior to conventional QC, but for small batch type assays, conventional QC has a place. A combination of techniques QC will provide the best protection against erroneous results being reported.

CAN *MOVING AVERAGE* PROCEDURES BE USED AS A CONTINUOUS QUALITY CONTROL IN MEDICAL LABORATORIES?

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Traditionally, the analytical quality control in medical laboratories is conducted by analysing commercially available control materials in certain time intervals, as well as by participating in external quality control programs. The disadvantages of traditional control are intermittency and non-commutability. Therefore, there is a need to introduce additional control tools that can overcome these shortcomings and ensure continuous control of the analytical process. In this light, the idea of quality control based on patient results is being considered in modern laboratory practice. One of possible methods of using patient results for control purposes is the moving average (MA). MA involves calculating the average value from the obtained set of patient results and further using that value for the purpose of continuous quality control. It is called «moving« because the MA value is recalculated every time a new result is received, that is, the data is continuously updated and evaluated as patient samples are analysed. The most commonly used algorithms for calculating MA values are: simple MA, exponentially weighted MA and Bull's algorithm. Although the concept of MA has been known for decades, it has never been wide-

cept MA poznat već decenijama, on nikada nije ušao u širu primenu u medicinskim laboratorijama iz više razloga. Jedan je složenost definisanja optimalnih MA procedura koje su specifične za svaki test i svaku laboratoriju i stoga ne mogu biti generalizovane niti preuzete iz nekog drugog izvora, već zahtevaju pojedinačni izbor, optimizaciju i validaciju. Drugi razlog koji ograničava primenu MA procedura jeste nepoznavanje detalja sposobnosti odabrane MA procedure da otkriva klinički značajan bias, pri čemu se posebno nameće pitanje da li je ovim procedurama moguće otkriti pojavu bias-a za ređe zahtevane testove i u laboratorijama koje imaju mali dnevni broj uzoraka i urađenih testova. Poslednjih godina ponovo raste interesovanje istraživača za ovu temu, sa novim predlozima za načine na koje bi se MA procedure mogle optimizovati za rutinsku upotrebu.

ly adopted in medical laboratories for many reasons. One is the complexity of defining optimal MA procedures that are specific to each test and each laboratory and therefore cannot be generalized or downloaded from another source, but require individual selection, optimization, and validation. Another reason limiting the use of MA procedures is the lack of insight in the ability of selected MA procedures to detect clinically significant bias, especially their ability to detect the occurrence of bias for less frequently required tests and in laboratories with a small daily number of samples and tests performed. In recent years, there has been a renewed interest of researchers in this topic, with new suggestions for ways in which MA procedures could be optimized for routine laboratory use.

KORIŠĆENJE REZULTATA PACIJENATA ZA IZRAČUNAVANJE REFERENTNIH VREDNOSTI

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U cilju interpretacije rezultata u medicinsko biohemijskim laboratorijama, najčešće se kvantitativni rezultat posmatra u odnosu na referentni interval (RI), koji predstavlja fiksni procenat referentne populacije u intervalu koje opisuju donje i gornje referentne granice. Preporučeno određivanje RI ili direktno određivanje, podrazumeva predhodan odabir referentne populacije po tačno definisanim kriterijumima, uzorkovanje biološkog materijala i analiziranje uzoraka. Alternativni pristup određivanju RI ili indirektno određivanje podrazumeva korišćenje velikog broja postojećih, odrađenih rezultata iz uzoraka koji se sakupljaju u rutinske svrhe, iz kojih se biohemijski parametri određuju u svrhu skrininga, postavljanja dijagnoze ili praćenja, i koji se čuvaju u bazama laboratorijskih informacionih sistema. Veliki broj objavljenih radova ukazuje na prednost indirektno određenih RI uz uslov pravilne selekcije »nezdravih« osoba, kao i razlikovanja hospitalizovanih od ambulantnih pacijenata, ali i korišćenje složenih statističkih algoritama za dobijanje krajnjeg RI. Trenutne smernice i vodiči ne podržavaju indirektni metod kao primarni zbog činjenice da većina podataka možda ne potiče od zdravih osoba. Takođe, statistička analiza koja se koristi za obradu velikog broja podataka je primarno namenjena za direktno određivanje RI, tj. analizu preporučenih 120 rezultata referentne popu-

THE USE OF PATIENT RESULTS FOR CALCULATION OF REFERENCE INTERVALS

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In order to interpret the results in the medical biochemical laboratories, the quantitative result is most often viewed in relation to the reference interval (RI), which represents a fixed percentage of the reference population at the interval described by the lower and upper reference limits. Recommended RI determination, or direct determination, involves preselecting a reference population according to well-defined criteria, sampling biological material and analyzing samples. An alternative approach to RI determination, or indirect determination, involves the use of a large number of existing, extracted results from samples collected for routine purposes, from which biochemical parameters are determined for screening, diagnosis or monitoring purposes, and stored in the laboratory information system databases. The large number of published papers points to the advantage of indirectly determined RIs with the condition of proper selection of "unhealthy" persons, as well as separation of hospitalized from outpatients, as well as the use of complex statistical algorithms to obtain the ultimate RI. Current guidelines and documents do not support the indirect method as primary, due to the fact that most data may not come from healthy individuals. Also, the statistical analysis used to process large amounts of data is primarily intended to directly determine RI, i.e. analysis of the recom-

lacije. Međutim, postoje posebni staistički programi i tehnike kojima je omogućena pravilna statistička analiza velikog broja podataka za indirektno određivanje RI. Preporuka da svaka laboratorija definiše sopstvene RI, a da to bude ekonomično i minimalno kompleksno, daje prednost indirektnom određivanju RI, u smislu korišćenja postojećih baza podataka. Takođe, nijedan RI nije apsolutno tačan i predstavlja samo procenu. Buduća ispitivanja bi trebalo da regulišu etičke aspekte indirektnog određivanja, kao i pravilnu verifikaciju na ovaj način definisanih RI.

mended 120 results of the reference population. However, there are special statistical programs and techniques that allow proper statistical analysis of a large amount of data for indirect RI determination. The recommendation that each laboratory defines its own RIs, while being cost-effective and minimally complex, favors indirectly determining RIs, in terms of using existing databases. Also, no RI is absolutely correct and is only an estimate. Future trials should regulate the ethical aspects of indirect determination as well as the proper verification of RIs defined in this way.

NOVI BIOMARKERI AKUTNOG OŠTEĆENJA BUBREGA

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Akutno oštećenje bubrega (AOB) je često i po život opasno stanje. AOB se u detinjstvu najčešće javlja tokom prve godine života. Deca sa epizodom AOB imaju povecan rizik od razvoja hronične bolesti bubrega. AOB je reverzibilno ako se prepozna u ranoj fazi i ako se brzo preduzmu terapijske mere. Kreatinin u serumu kao tradicionalni biomarker koji se koristi za definisanje i ocenjivanje stepena AOB nije dovoljno senzitivan biomarker. Naime, potrebno je neko vreme nakon oštećenja bubrega odnosno smanjenja diureze, da bi se nivo kreatinina u serumu povisio, pa je kreatinin kasni marker AOB. Pored toga, kreatinin u serumu zavisi od uzrasta, pola, mišicne mase i upotrebe lekova. Potrebni su nam dakle bolji biomarkeri od kreatinina, koji bi trebali biti senzitivniji i specifičniji, omogucujuci bržu dijagnozu AOB i upotrebu odgovarajuce kliničke intervencije koja može zaustaviti ili preokrenuti AOB. Ograničenja serumskog kreatinina podstakla su istraživanja koja su razvila biomarkere AOB, uključujuci cistatin C, lipokalin povezan sa želatinazom neutrofila, molekul oštećenja bubrega 1, interleukin-18, protein koji veže masne kiseline u jetri, inhibitor tkiva metaloproteinaza-2 i protein 7-vezujuci protein. U poređenju sa kardiologijom, klinička upotreba novih biomarkera u nefrologiji je ograničena. Iako je intenzivna istraživačka aktivnost otkrila nekoliko novih biomarkera AOB, potrebna su dodatna istraživanja kako bi se odredila njihova klinička uloga. Činioci koji utiču na upotrebu biomarkera AOB uključuju cenu, dostupnost u lokalnoj laboratoriji ili na mestu lečenja i jednostavnu upotrebu. Primena inovativnog učenja i veštačke inteligencije može omoguciti brže otkrivanje

NEW BIOMARKERS OF ACUTE KIDNEY INJURY

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Acute kidney injury (AKI) is a common and life-threatening condition. AKI in childhood is most common during the first year of life. Infants with an episode of AKI have increased risk of developing chronic kidney disease. AKI is reversible when recognized early and promptly treated. Serum creatinine as traditional biomarker used to define and grade AKI is not sensitive enough. Furthermore, it takes some time after kidney injury or decrease in urine output until serum creatinine level rises, so creatinine is a late marker of AKI. In addition, serum creatinine depends on age, gender, muscular mass and medication. Better biomarkers than creatinine should be more sensitive and specific, allowing faster diagnosis of AKI, and use of appropriate clinical intervention that may stop or reverse AKI. Limitations of serum creatinine stimulated research that developed biomarkers of damage in AKI including cystatin C, neutrophil gelatinase–associated lipocalin, kidney injury molecule 1, interleukin-18, liver type fatty acid–binding protein, tissue inhibitor of metalloproteinase-2, and IGF-binding protein 7. In comparison to cardiology, clinical use of novel biomarkers in nephrology has been limited. Although intensive research activity identified several new AKI biomarkers further investigation is needed to define their clinical role. Factors influencing use of AKI biomarkers include price, availability at the local lab or point of care, and simple use. Application of innovative learning and artificial intelligence may allow faster detection and earlier treatment of AKI.

ZAKASNELI PUBERTET – IZAZOVI U DIJAGNOSTICI

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Zakasneli pubertet se viđa kod približno 5% adolescenata oba pola, a u diferencijalnoj dijagnozi, pored konstitucionalnog zakasnelog puberteta kao najčešćeg uzroka, na drugom mestu se nalazi hipogonadotropni hipogonadizam. Veliki broj urođenih i stečenih uzroka mogu dovesti do hipogonadotropnog hipogonadizma, koji takođe može nastati i usled intenzivnih sportskih treninga, poremećaja u ishrani ili u sklopu kliničke slike hroničnih sistemskih bolesti. Razlikovanje izolovanog hipogonadotropnog hipogonadizma od konstitucionalnog zakasnelog puberteta predstavlja veliki dijagnostički izazov u pubertetskom uzrastu i zasniva se na kliničkom nadzoru, izuzev kada postoje jasne udružene fenotipske odlike hipogonadotropnog hipogonadizma, poput anosmije ili hiposmije u sklopu Kallmannovog sindroma. Poslednjih godina sve značajniju ulogu u diferenciranju konstitucionalnog zakasnelog puberteta u odnosu na hipogonadotropni hipogonadizam ima određivanje koncentracija inhibina B, a sa sve dostupnijim genetskim analizama metode molekularne dijagnostike dobijaju sve veću ulogu ne samo u istraživačkom, već i u kliničkom kontekstu. U terapijskom pogledu, bez obzira da li se radi o izolovanom hipogonadotropnom hipogonadizmu ili konstitucionalnom zakasnelom pubertetu, kod dečaka koji imaju psihološke tegobe zbog kašnjenja ili zastoja u pubertetskom razvoju treba razmotriti kratkoročnu primenu depo preparata testosterona. Kod najvećeg broja dečaka sa hipogonadotropnim hipogonadizmom je moguća dalja indukcija pubertetskog razvoja i fertiliteta, uključujući razvoj i porast testisa uz uspostavljanje spermatogeneze u periodu adolescencije upotrebom humanog horionskog gonadotropina i rekombinantnog folikulo-stimulišućeg hormona.

DELAYED PUBERTY – DIAGNOSTIC CHALLENGES

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Delayed puberty can be observed in approximately 5% of the adolescent population, with majority of the affected youth having a benign variant of pubertal development - constitutional delay of puberty, with hypogonadotropic hypogonadism being the most frequent differential diagnosis. Multitude of congenital and acquired etiologies can lead to hypogonadotropic hypogonadism, including the development of »functional« hypogonadotropic hypogonadism due to secondary causes, such as vigorous exercise, eating disorders or systemic chronic illnesses. Distinguishing between constitutional delay of puberty and isolated hypogonadotropic hypogonadism remains a major clinical challenge during adolescence, and is mainly based on watchful waiting, unless specific features suggestive of hypogonadotropic hypogonadism are present, such as anosmia or hyposmia in Kallmann syndrome. During the recent years, inhibin B levels are proving more useful in distinguishing between constitutional delay of puberty and isolated hypogonadotropic hypogonadism, and with the genetic analyses becoming more available, molecular diagnostics are becoming increasingly important in both research and clinical practice. Regarding treatment approach, whether the aetiology is constitutional delay of puberty or hypogonadotropic hypogonadism, in boys with psychosocial complaints resulting from delayed or arrested pubertal development, short-term treatment with testosterone should be considered. In most of the boys with hypogonadotropic hypogonadism, complete pubertal development including the testicular growth and spermatogenesis during adolescence can be acquired by the use of human chorionic gonadotropin and follicle-stimulating hormone subcutaneous injections.

NOVI MARKERI SEPSE U NEONATOLOGIJI

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Morbiditet i mortalitet u neonatalnoj sepsi su značajni uprkos kontinuiranom napretku u neonatologiji i izboru novih generacija antibiotika. Preterminska novorođenčad veoma niske telesne mase su posebno osetljiva zbog imunske nezrelosti, teškog opšteg stanja i česte potrebe za primenom invazivnih procedura u toku lečenja. Kod ovih pacijenata je povećan rizik od razvoja sepse, antibiotske toksičnosti i lošeg ishoda lečenja. Hemokultura je »zlatni standard« u dijagnostici bakterijske sepse, ali na rezultate treba čekati 24–48 sati. Rezultati mogu biti lažno negativni u slučaju postojanja pneumonije ili meningitisa. Tradicionalni laboratorijski pokazatelji sepse pokazuju nedostatke, kao što je širok opseg referentnih vrednosti za hematološke testove, zbog čega su nekad teški za interpretaciju, ili spadaju u kasne markere sepse, kao što je C-reaktivni protein. Razvoj novih tehnologija je omogućio bolje upoznavanje neonatalnog imuniteta i odgovora na infekciju kao i otkrivanje novih biomarkera koji bi mogli da poboljšaju rano otkrivanje infekcije i pravovremeno započinjanje terapije. Pored biomarkera koji su već u upotrebi, kao što su C-reaktivni protein i prokalcitonin, u fazi ispitivanja ili u početnim fazama primene su presepsin, neki citokini, serumski amiloid A, lipopolisaharid-vezujući protein i površinski leukocitni antigeni. Za novorođenče bi bila veća šteta da infekcija nije dijagnostikovana i lečena, nego lažno dijagnostikovana i nepotrebno lečena. Zato je važnija osobina dijagnostičkog testa za neonatalnu infekciju visoka osetljivost i negativna prediktivna vrednost blizu 100%, nego visoka specifičnost. Mnogi autori smatraju da kombinacija serumskih markera infekcije pokazuje bolju dijagnostičku specifičnost i osetljivost nego pojedinačni markeri. Kad je u pitanju neonatalna populacija pri izboru biomarkera sepse se vodi računa o fiziološkim varijacijama njihovih koncentracija u prvim danima života, kao i o vrsti i zapremini uzorka koji se koristi za analizu.

NEW MARKERS FOR SEPSIS IN NEONATOLOGY

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Morbidity and mortality in neonatal sepsis are significant, regardless of the continuous advancement in neonatology and emerging new-generation antibiotics. Preterm infants of very low weight are particularly sensitive due to immune immaturity, serious general condition and frequent necessary application of invasive procedures in the course of treatment. The risks of development of sepsis, antibiotic toxicity and poor treatment outcomes are increased in these patients. Blood culture is considered the gold standard for diagnosis of bacterial sepsis, but the results are available after 24–48 hours. Additionally, they can be false-negative in the case of pneumonia or meningitis. Traditional laboratory indices of sepsis have certain shortcomings, such as wide reference intervals for haematological tests, which make them difficult to interpret, or belong to late sepsis markers, such as C-reactive protein. The development of new technologies has enabled better understanding of neonatal immunity and response to infection, as well as the discovery of new biomarkers which could improve early detection of infection and timely initiation of therapy. In addition to biomarkers already in use, such as C-reactive protein and procalcitonin, presepsin, some cytokines, serum amyloid A, lipopolysaccharide-binding protein and surface leukocyte antigens are in the phase of investigation or initial application phases. It would be more harmful for the newborn if the infection was not diagnosed and treated, than to have false diagnosis and unnecessary treatment. Therefore, a more important feature of the diagnostic test for neonatal infection is the high sensitivity and negative predictive value near 100%, than the high specificity. Many authors consider that the combination of serum markers of infection shows better diagnostic specificity and sensitivity than individual markers. When it comes to the selection of sepsis biomarkers in neonatal population, physiological variations in their levels in the first days of life and the types and volume of the sample for analysis have to be taken into account.

ULOGA LABORATORIJE U DIJAGNOSTICI I PRAĆENJU KOMORBIDITETA TIP 1 DIJABETES MELITUSA

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Deca i adolescenti, oboleli od tip 1 dijabetes melitusa (T1DM), imaju povećan rizik za razvoj jedne ili više pridruženih autoimunskih bolesti. Autoimunski tireoiditis i celijačna bolest imaju najveću prevalencu, a slede autoimunske bolesti vezivnih tkiva, gastrointestinalnog sistema, kože i primarna adrenalna insuficijencija. Laboratorijski skrining na funkciju tiroidne žlezde i celijačnu bolest je neophodan pri postavljanju dijagnoze T1DM i kasnije u redovnim intervalima, u cilju ranog otkrivanja i lečenja bolesti. Prema preporukama, skrining na autoimunski tireoiditis uključuje određivanje tireostimulirajućeg hormona i antitela na tiroidnu peroksidazu. Kod asimptomatskih pacijenata, skrining se ponavlja svake druge godine posle dijagnostikovanja dijabetesa, odnosno češće u prisustvu karakterističnih simptoma bolesti. Određivanje antitela na tkivnu transglutaminazu (anti-tTG IgA i/ili anti-tTG IgG) je primarno u dijagnostici celijačne bolesti kod asimptomatskih pacijenata sa T1DM. Laboratorijski skrining se ponavlja svake druge, odnosno svake pete godine, posle dijagnostikovanja dijabetesa. Frekventnost analiziranja zavisi od ispoljenih simptoma, uzrasta i genetske predispozicije pacijenta. Preporučuje se i skrining na deficit vitamina D, posebno kod dece sa pridruženom celijačnom bolešću ili promenama na koži. Autoimunske bolesti udružene sa T1DM predstavljaju dodatni rizik za mikro- i makrovaskularne komplikacije. Hronična inflamacija, koja je pratilac autoimunskih poremećaja i inflamacija u aterosklerozi imaju slične karakteristike, pri čemu patofiziološki činioci karakteristični za autoimunsku bolest mogu da ispolje nezavisno ili sinergističko dejstvo na razvoj ateroskleroze i povećanje kardiovaskularnog rizika. Laboratorijska evaluacija potencijalnog proaterogenog efekta autoimunskog tireoiditisa i celijačne bolesti, kao udruženih autoimunskih bolesti, mogla bi da identifikuje dijabetičare sa povećanim kardiovaskularnim rizikom u detinjstvu i adolescenciji. Određivanje markera inflamacije, indeksa ateroskleroze uz standardni lipidni profil i brzine izlučivanja albumina, ukazalo bi na eventualni disbalans u proaterogenim i antiaterogenim komponentama kod obolelih

THE ROLE OF LABORATORY IN DIAGNOSIS AND MONITORING OF CO-MORBIDITIES IN TYPE 1 DIABETES MELLITUS

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Children and adolescents with type 1 diabetes mellitus are at increased risk for developing one or more associated autoimmune diseases. Autoimmune thyroiditis and celiac disease have the highest prevalence, followed by autoimmune diseases of connective tissue, gastrointestinal system and skin, and primary adrenal insufficiency. Therefore, laboratory screening for thyroid function and celiac disease is necessary at the diagnosis of T1DM, and later, at regular intervals, in order to early detect and treat the disease. According to the recommendations, screening for autoimmune thyroiditis involves determination of thyroid stimulating hormone and antithyroid peroxidase antibodies. In asymptomatic patients, screening is repeated every second year after diabetes is being diagnosed, or more frequently in the presence of characteristic symptoms of the disease. Determination of tissue transglutaminase antibodies (tTG IgA and/or tTG IgG) is primary in the diagnosis of celiac disease in asymptomatic patients with T1DM. Laboratory screening is repeated every second or every fifth year after diagnosis of diabetes. The frequency of analysis depends on clinical symptoms, age and the genetic predisposition of the patient. Screening for vitamin D deficiency is also recommended, especially in children with coexisting celiac disease or skin disorders. Autoimmune diseases associated with T1DM pose an additional risk for microvascular and macrovascular complications. Chronic inflammation, that accompanies autoimmune disorders and inflammation in atherosclerosis have similar characteristics. Pathophysiological factors related to autoimmune disease, can have independent or synergistic effect on the development of atherosclerosis and increase cardiovascular risk. A laboratory evaluation of the potential proatherogenic effect of autoimmune thyroiditis and celiac disease, as associated autoimmune diseases, could identify diabetics at increased cardiovascular risk in childhood and adolescence. Determination of inflammatory markers, atherosclerosis indexes, standard lipids profile and albumin excretory rate could indicate possible imbalance between proatherogenic and antiatherogenic components in patients.

LABORATORIJSKA DIJAGNOSTIKA ALERGIJA KOD DECE

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Alergijska reakcija predstavlja neočekivan i neadekvatan odgovor imunološkog sistema na različite faktore (alergene) iz spoljašnje sredine. Najčešće se ispoljava kao reakcija rane preosetljivosti (tip I) i posredovana je alergen-specifičnim IgE antitelima. Alergijske bolesti su danas najčešća hronična oboljenja kod dece i odraslih, posebno u razvijenim zemljama. Procenjeno je da 20% svetske populacije boluje od neke vrste alergije. Za razliku od drugih hroničnih bolesti, alergijske bolesti počinju još u najranijem detinjstvu, a prema mišljenju nekih autora čak i prenatalno. Alergije na nutritivne alergene se sreću kod 2–8% dece i to najčešće u uzrastu odojčeta i malog deteta. Sa druge strane, rezultati velike Internacionalne studije astme i alergija kod dece (ISAAC) pokazali su da je najveća prevalenca simptoma astme kod dece predškolskog i školskog uzrasta. Laboratorijska dijagnostika alergija uključuje čitav niz testova koji se koriste da potvrde alergijsku reakciju, odrede tip/mehanizam reakcije (posredovana imunoglobulinima ili ćelijama), identifikuju pokretača/uzročnika senzibilizacije (alergen), i za praćenje uspešnosti terapije. Određivanje tipa/mehanizma alergijske reakcije uključuje merenje koncentracije ukupnog serumskog IgE (skrining za atopiju, kao i razlikovanje atopijskih-alergija od neatopijskih bolesti-intolerancija), broja eozinofilnih granulocita u cirkulaciji, perifernom razmazu krvi i razmazu brisa nosa (pomoć u proceni trenutne izloženosti alergenu i fenotipizaciji astme), te bazofilnih granulocita (dodatni parameter u proceni alergijske bolesti) i serumske koncentracije eozinofilnog katjonskog proteina – ECP (marker aktivacije eozinofila, pogodan za praćenje stepena inflamacije kod astmatičara i efikasnosti terapije). Uzročnik alergijske reakcije se određuje posredno merenjem serumske koncentracije alergen-specifičnog IgE. U tu svrhu se koriste različite imunohemijske metode: semikvantitativne (imunoblot metoda, paneli koji sadrže nutritivne/inhalatorne alergene) i kvantitativne metode (imunohemijske metode koje odlikuje velika dijagnostička specifičnost i osetljivost). Određivanje alergen-specifičnog IgE u serumu se koristi i kada se ne mogu primeniti kožni testovi (atopijski dermatitis) ili testovi provokacije (opasnost od anafilakse – nutritivni alergeni), kao i za praćenje efikasnosti terapije. Iako je laboratorijsko ispitivanje

LABORATORY DIAGNOSIS OF ALLERGIES IN CHILDREN

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An allergic reaction is an unexpected and inadequate response of the immune system to various environmental factors (allergens). It is most commonly manifested as a hypersensitivity reaction (type I) and is mediated by allergen-specific IgE antibodies. Today, allergies are the most common chronic diseases in children and adults, especially in developed countries. It is estimated that 20% of the world's population has some type of allergy. Unlike other chronic diseases, allergies begin in the earliest childhood, even prenatal according to some authors. Food allergy affects 2–8% of children, most often infants and children under three years of age. Results of a major International Study of Asthma and Allergies in Children (ISAAC) have shown that the highest prevalence of asthma is determined in preschool and school-age children. Laboratory diagnosis of allergies includes a battery of tests that should verify an allergic reaction, determine the type/mechanism of reaction (mediated by immunoglobulins or cellular mediators), identify triggers of allergic reaction and follow up therapy. Assessment of the type/mechanism of allergic reaction involves measuring of total serum IgE concentration (screening for atopy, as well as differentiation of atopic disease-allergy from non-atopic disease-intolerance), the eosinophilic granulocyte count in the blood and nasal swab (assessment of current allergen exposure and asthma phenotyping), basophilic granulocyte count (additional parameter in assessment of allergic disease) and the eosinophil cationic protein – ECP concentration (eosinophil activation parameter, for monitoring the level of inflammation in asthma and the therapy). The trigger of the allergic reaction is determined indirectly by measuring the allergen-specific IgE concentration. Different immunoassays are in use: semi-quantitative (immunoblot method with panels containing food/inhalative allergens) and quantitative methods (immunoassays characterized by high diagnostic specificity and sensitivity). Determination of allergen-specific IgE in serum is also used when skin tests or provocation tests cannot be administered, as well as to monitor the effectiveness of therapy. Although laboratory testing of allergies is necessary for the diagnosis of allergic diseases, there are limitations that affect the accuracy of the test results. Preanalytical problems

alergija neophodno za postavljanje dijagnoze alergijskih bolesti, postoje ograničenja koja utiču na tačnost rezultata primenjenih testova. Preanalitičke greške uključuju vreme uzorkovanja krvi za određivanje ukupnog IgE, specifičnog IgE, ECP i broja eozinofilnih granulocita (sezonske alergije, alergije na lekove i otrove insekata, uticaj brzine koagulacije i temperature na koncentraciju ECP). Analitički problemi odnose se na primenu standardizovanih imunohemijskih metoda za određivanje ukupnog i specifičnog IgE. Post-analitički problemi odnose se na korelaciju između rezultata in vitro testova sa rezultatima in vivo testova (kožni testovi, provokacijski testovi) kao i sa kliničkim podacima. Pomenuta korelacija je najvažnija za dijagnozu i kontrolu alergijske bolesti.

include time of blood collection for the measurement of total IgE, specific IgE, ECP and eosinophilic granulocyte count (seasonal allergies, insect sting allergies, drug allergies, influence of coagulation time as well as temperature on ECP levels). Analytical problems are related to the use of standardized immunoassays for the determination of total and specific IgE. Post-analytical problems are related to the correlation between in vitro test results with the in vivo test results (skin tests, provocation tests), as well as with clinical data. This correlation is most important for the diagnosis and control of allergic disease.

ZNAČAJ BIOHEMIJSKIH MARKERA U PROCENI RIZIKA ZA RAZVOJ KOMPLIKACIJA U TRUDNOĆI

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Razvoj komplikacija u trudnoći, kao što su preeklampsija, gestacijski dijabetes, prevremeni porođaj, intrauterini zastoj u razvoju ploda, ukazuje na sve veću potrebu za što jasnijim definisanjem potencijalnih biomarkera čijim bi određivanjem u ranom prvom trimestru trudnoće bilo moguće predvideti rizičan tok Time se omogućavaju pravovremena klinička ispitivanja i intervencije kod visoko rizičnih trudnoća, u cilju prevencije ili adekvatnijeg tretmana komplikacije. Danas se u cilju predikcije određenih komplikacija trudnoće uglavnom koriste kombinacije nekoliko biomarkera čime se postiže veća dijagnostička tačnost. Kada je preeklampsija u pitanju, koriste se kombinacije placentalnog faktora rasta (PLGF), tirozin solubilnog proteina (sFlt-1) i vaskularnog endotelnog faktora rasta (VEGF), zatim PAPP-a i plazma protein 13 (PP13) i drugi proteini placentalnog porekla kao što je inhibin A i aktivin A. Procena rizika za razvoj prevremenog porođaja i intrauterinig zastoja u rastu, pored navedenih testova koriste još i free beta human chorionic gonadotropin (free β-HCG) i metaloproteazu (ADAM12). Procena rizika za razvoj aneuploidija uključuje takođe screening ranog prvog trimestra kojim se određuje PAPP-a i free β-hCG. Navedeni biohemijski parametri kombinuju se sa ultrazvučnim parametrima kao i karakteristikama i faktorima rizika majke (godine starosti, težina, pušenje i dr.), što se obrađuje adekvatnim sofwaer-om za procenu rizika.U narednom periodu trebalo bi i dalje unapređivati

BIOCHEMICAL PARAMETERS IN PREGNANCY COMPLICATIONS RISK ASSESSMENT

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Pregnancy complications development as preeclampsia, gestational diabetes, preterm birth, foetal intrauterine growth restriction, indicates necessity of definition and identification of specific early pregnancy biomarkers for pregnancy complication prediction. Those biomarkers would be used in order to preventing or treating these complications more appropriately. Nowadays, combinations of several biomarkers are generally used to predict certain complications of pregnancy, thus achieving greater diagnostic accuracy. In preeclampsia, combinations of placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and vascular endothelial growth factor (VEGF) are used, followed by PAPP-A and plasma protein 13 (PP13) and other proteins of placental origin, including inhibin A and activin A. Risk assessment for preterm birth and intrauterine growth restriction, beside mentioned tests, use free beta human chorionic gonadotropin (free β-HCG) and metalloprotease (ADAM12). An aneuploidy risk assessment also includes early first trimester screening for PAPP-A and free β-hCG. These biochemical parameters are combined with ultrasound parameters as well as risk factors parameters associated with mother (age, BMI, smoking, etc.), which are processed by an adequate software for risk assessment. The aim of further investigations will be addressed to development of some new combinations of biomarkers with associated software that would be integrate

kombinacije biomarkera uz prateće sofwear-e koji bi objedinili i kvalitetan screening za procenu rizika za razvoj navedenih komplikacija, kao i screening za aneuploidije. Rezultati naših studija su izdvojili aterogeni indeks palzme (AIP) i markere lipidne peroksidacije kao potencijalne markere predikcije komplikacija u trudnoći (preeklampsija, gestacijski dijabet, IUGR).

DIJAGNOSTIČKA TAČNOST TESTOVA ZA PROCENU OVARIJALNE REZERVE

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Ovarijalna rezerva podrazumeva veličinu, kao i kvalitet ovarijalnog pula žene određene životne dobi. Ona predstavlja funkcionalni kapacitet jajnika, odnosno njihovu biološku starost i mogućnost jajnika da proizvedu kvalitetne jajne ćelije. Radi se o veoma kompleksnom kliničkom parametru koji je pre svega uslovljen godinama starosti žene, ali i različitim genetskim, kao i fakorima okruženja. Idealni test za procenu ovarijalne rezerve trebao bi da bude visoko osetljiv, ponovljiv, bez varijacija u rezultatima između ciklusa, kao i visoko specifičan, čime bi se izbegli lažno pozitivni, kao i lažno negativni rezultati. Testovi su bazirani na specifičnim hormonskim analizama i ultrazvučnim pregledima. Broj antralnih folikula i koncentracija anti-Mullerian (AMH) hormona se prema većini autora smatraju testovima koji pokazuju veću specifičnost i osetljivost u odnosu na ostale biohemijske testove, bazalnu koncentraciju folikostimulirajućeg hormona (FSH), koncentraciju estradiola, kao i u odnosu na dinamički test sa klomifen citratom. Većina ovih testova se međusobno dopunjuje i kombinuje, međutim analize su pokazale da upotreba više različitih testova za ispitivanje ovarijalne rezerve ne dovodi do značajnog poboljšanja dijagnostičke tačnosti. Rezultati se razlikuju u zavisnosti od upotrebljenih graničnih (cut-off) vrednosti testova, kao i u zavisnosti od toga koji ishod testa se prati (najčešće je to odgovor na stimulaciju jajnika u procesu vantelesne oplodnje). Rezultati testova koji ukazuju na oslabljenu ovarijalnu rezervu mogu pružiti ženi informacije značajne za pravovremenu intervenciju i ranije planiranje trudnoće, ali ne ukazuju i na nemogućnost začeća.

TESTS OF OVARIAN RESERVE – DIAGNOSTIC ACCURACY

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Ovarian reserve is a term that is refers to imply the capacity of the ovary to produce quality egg cells. It is a functional capacity of the ovaries that is their biological age. Ovarian reserve is a very complex clinical parameter that is primarily associated with the woman's age, but also with different genetic and environmental factors. The respectable test for the ovarian reserve evaluation should be highly sensitive, repeatable, with no variations between menstrual cycles and highly specific, to avoid false positives, as well as false negative results. Ovarian reserve tests are based on specific hormonal analyses and ultrasound examinations. According to current expert's opinions, antral follicles count (AFC) and the concentration of anti-Mullerian (AMH) hormone provides more sensitive and specific results than other biochemical tests, basal follicle stimulating hormone (FSH) concentration, estradiol concentration and dynamic clomiphene citrate test. Most of these tests are complementary and combined. However, analyses have shown that the use of multiple different tests for ovarian reserve evaluation does not significantly improve diagnostic accuracy. The results vary depending on the cut-off test used and the tests outcome (usually the response to ovarian stimulation in the process of in vitro fertilization). Test results suggesting a declining ovarian reserve might be helpful in pregnancy planning. However, these results are not reliable

ULOGA POLNIH STEROIDA KOD ŽENA I MUŠKARACA POSLE 50. GODINE

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Menopauza predstavlja period u zivotu žene koji se javlja godinu dana posle poslednje menstruacije i traje do kraja života. Involutivni hopoandrogenizam u muškaraca odlikuje se padom testosterona i pojavom tipičnih simptoma i znakova. Insuficijencija estradiola u žena i testosterona u muškaraca dovodi do valunga, promena raspolozenja, depresije, nervoze, loše koncentracije, nesanice, kardiovaskulnih bolesti, osteoporoze, metaboličkog sindroma, dijabetesa i značajno smanjuje kvaliteta života i dovodi do većeg mortaliteta. Najčešći uzrok smrti svih ljudi su kardiovaskulne bolesti. Upravo pad gonadnih steroida dovodi do dislipidemije, vazokontrikcije, promene u simpatktikusnom sistemu, hipertenzije, aritmija, uslovljavajući infarkt miokarda ili srčanu insuficijenciju. Najveći denzitet receptora za testosterone je u miokardu. Dve trećine težine mozga čine krvni sudovi, a na njima su prisutni receptori za polne steroide. Takodje, receptori su prisutni i u kardiomiocitima. Sa padom polnih steroida pojačava se inflamacija preko interleukina , citokina i brojnih faktora inflamacije. Adaptivni mehanizmi slabe, a stresori dovode do sloma adaptacije i brojnih bolesti koje predstavljaju stresogeno stanje. Osteoporoza je izazvana nedovoljnošću gonadnih steroida. Povećava se broj fraktura. Seksualnost se značajno menja odlikujući se smanjenom seksualnom željom kod žena i impotencijom kod muškaraca. U cilju prevencije bolesti neophodno je oko 50. godine uraditi sistematski pregled koji obuhvata odredjivanje hormonskog statusa, internistički nalaz, nalaz ginekologa/urologa, osteodenzitometriju, ultrasonografske preglede. Posle obavljene dijagnostike i isključivanja apsolutnih kontraindikacija neophodno je uvesti supstitcionu terapiju svih insuficijentnih hormona. Na taj način se sprečavaju brojne bolesti, invaliditeti, smanjuju morbiditet, mortalitet i poboljšava kvalitet života.

THE ROLE OF SEXUAL STEROIDS IN WOMEN AND MEN OLDER THAN FIFTY YEARS OF AGE

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Menopause represents a period in woman's life starting one year after the last menstruation and continuing all life. Involutive hypoandrogenism in male is characterized by insufficient testosterone and typical symptoms and signs. Estradiol insufficiency in women and testosterone insufficiency in male are characterized by hot flushes, changes in psychic status, depression, irritability, lack of concentration, insomnia, cardiovascular diseases, osteoporosis, metabolic syndrome, diabetes, significantly decreasing quality of life and increasing mortality rate. Cardiovascular diseases are the most frequent cause of all deaths. Gonadal steroid insufficiency induce dislipidaemia, vasocontriction, changes in symphaticus system, hypertension, arrhythmias, leading to myocardial infarction and heart insufficiency. In the myocard the greatest density of gonadal steroid receptors are found. Two thirds of brain weight are blood vessels and gonadal steroid receptors are present on them. As well, the same receptors are present on cardiomyocytes. Gonadal steroid insufficiency increase inflammation by inducing cytokines and other inflammatory factors. Adaptive mechanism are becoming more fragile, stressores brake adaptation and induce diseases, as a stress status. Low levels of gonadal steroid induce osteoporosis. Number of fractures are increasing. Sexuality changes are characterized by typical hypoactive sexual desire in women and erectile dysfunction in male. In order to do a prevention complete examination are needed about the age of 50 years of age. Hormonal analysis, internal examination, gynecological/urological examination, osteodensitometry, ultrasonography, mammography are needed. After excluding absolute contraindications hormone replacement therapy of all insufficient hormones are needed. In such an approach many diseases can be prevented, morbidity and mortality rate reduced and better quality of life obtained.

METABOLIZAM GVOŽĐA I ISHOD TRUDNOĆE

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Poremećaj homeostaze gvožđa se često javlja u trudnoći, kada su potrebe za gvožđem povećane. Nivo peptidnog hormona hepcidina, koji je ključni regulator metabolizma gvožđa, opada tokom trudnoće, čime se omogućavaju optimalna apsorpcija i bioraspoloživost gvožđa. Nedostatak gvožđa je najčešći tip nutritivne deficijencije i uglavnom se manifestuje anemijom. Anemija usled deficijencije gvožđa je česta kod žena u reproduktivnom periodu: između 30 i 70% žena nema dovoljno gvožđa u depoima pre začeća, dok je oko polovine trudnica anemično. Fetus dobija gvožđe isključivo iz krvi majke, te svaki poremećaj homeostaze gvožđa kod majke ima posledice i po fetus. Nedostatak gvožđa povezan je sa povećanim rizikom za prevremeni porođaj, poremećajima u rastu i razviću fetusa, povećanim rizikom ka nastanku infekcija, anemijom, ali i komplikacijama u odraslom dobu. Primena suplemenata gvožđa je uobičajena u praksi, ali je veoma važno utvrditi da li je zaista potrebna, proceniti odnos koristi i eventualnih rizika, odnosno pravilno utvrditi dozu koja se primenjuje. Iako je neophodno za pravilno funkcionisanje organizma, višak gvožđa može biti štetan. Povećan sadržaj gvožđa doveden je u vezu sa poremećajima u metabolizmu glukoze i mogao bi imati veze sa razvojem gestacijskog dijabetes melitusa. Povišene vrednosti gvožđa u serumu majke imaju veze sa preeklampsijom (PE), stanjem koje je specifično za trudnoću, a ima za posledicu visok morbiditet i mortalitet i majke i novorođenčeta. Slobodni radikali, nastali usled viška gvožđa, mogu indukovati oksidativni stres, strukturno i funkcionalno oštećenje endotela, što može doprineti razvoju PE. U odnosu na zdrave trudnice, povećane vrednosti hepcidina su izmerene tokom infekcije, kao i kod gojaznih trudnica, što može imati negativan uticaj na dostupnost gvožđa. Deo istraživanja Laboratorije za biologiju reprodukcije usmeren je na ispitivanje uloge metabolizma gvožđa na ishod trudnoće, kao i na eventualni značaj hepcidina kao biomarkera u komplikacijama vezanim za trudnoću.

IRON METABOLISM AND PREGNANCY OUTCOME

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Dysregulation of iron homeostasis is commonly seen during pregnancy, when iron needs are increased. In non-complicated pregnancy, levels of peptide hormone hepcidin, a key regulator of iron homeostasis, decline through the pregnancy course, in order to ensure optimal iron absorption and bioavailability. Iron deficiency, the most common nutritional deficiency, is often manifested by anaemia. Iron deficiency anaemia is frequent in women of reproductive age: 30-70% of women have insufficient iron reserves before conception and around 50% of pregnant women are anaemic. Foetus is completely dependent on mother's serum iron, so any disturbance of maternal iron homeostasis, reflects on the developing foetus. Iron deficiency is related to increased risk for preterm birth, inadequate foetal growth and development, anaemia, increased risk for infection, but also to complications in adult life. Iron supplementation is common in routine practice, but it is important to assess is it really necessary, to estimate potential benefits and possible risks and to optimise dosage. While iron is essential for optimal organism functioning, its excess might be deleterious. Higher body iron content is linked to impairment of glucose metabolism and might be involved in development of gestational diabetes mellitus. Elevated iron levels were reported in preeclampsia (PE), pregnancy specific condition, related to high mortality and morbidity of both mother and the newborn. The free radicals, released in the presence of iron excess, might lead to oxidative stress and endothelial damage and dysfunction, contributing to the PE development. Higher hepcidin concentrations in maternal serum, compared to healthy controls, are seen in infection and obesity and might adversely affect the iron bioavailability. One of the topics addressed by the Laboratory for Biology of Reproduction is impact of iron metabolism on pregnancy outcome, and the potential role of maternal hepcidin as biomarker of pregnancy-related complications.

FARMAKOGENETIKA U ONKOLOGIJI – MOĆNO ORUĐE PRECIZNE MEDICINE

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Moderna farmakogenetika je u potpunosti transformisala lečenje onkoloških pacijenata omogućavajući preciznu upotrebu molekularno-ciljanih terapija u odabranim pacijentima i u specifičnom trenutku evolucije njihovih tumora. Centralizovani farmakogenomski Servis je oformljen naInstitutu za onkologiju i radiologiju Srbije sa ciljem da se omogući personalizovani molekularni pristup svakom srpskom onkološkom pacijentu. Testiranje pojedinačnih gena je započeto 2008. godine i prošireno na NGS panele i testiranje tečnih biopsija 2016. godine. Trenutno, u Servisu se uspešno obavljaju analize KRAS/NRAS mutacija u metastatskom karcinomu kolorektuma (osetljivost na anti-EGFR monoklonska antitela), primarnih i stečenih EGFR mutacija u uznapredovalom adenokarcinomu pluća iz FFPE i tečnih biopsija (osetljivost na prvu i treću generaciju tirozin kinaznih inhibitora), BRAF mutacija u metastatskom melanomu (osetljivost na tirozin kinazne inhibitore) i BRCA1/2 mutacija u karcinomu ovarijuma (osetljivost na PARP inhibitore). Budući planovi uključuju uvođenje prediktivnog NGS testiranja za imunoterapiju određivanjem nivoa mutacionog opterećenja, mikrosatelitske nestabilnosti i deficijencije mismatch mehanizma popravke DNK, kao idetekciju klinički značajnih onkogenih genetičkih rearanžmana kao što su ALK, NTRK, RET, ROS1 fuzije i sl. Prateća farmakogenetička dijagnostika je najvišepomogla pacijentima čiji tumori imaju onkogene vodič-promene kada se uzmu uobzir preživljavanje i kvalitet života. Dalji razvoj eksperimentalnih tehnika i bioinformatičkih analiza doprineće boljoj nezi onkoloških pacijenata i smanjenju troškova lečenja.

CANCER PHARMACOGENETICS – A MIGHTY PRECISION MEDICINE TOOL

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Modern pharmacogenetics has completely transformed oncological patient care enabling the precise use of molecularly targeted therapies in selected patients and in a specific evolution point of their tumors. A centralized pharmacogenetics Service was formed at the Institute for Oncology and Radiology of Serbia (IORS) with the purpose of providing a personalized molecular approach to each Serbian cancer patient. Single-gene testing was initiated in 2008 and expanded to NGS panels and liquid biopsy testing in 2016. Currently, metastatic colorectal cancer samples are successfully tested for the presence of KRAS/NRAS mutations (sensitivity to anti-EGFR monoclonal antibodies), as well as advanced lung adenocarcinoma patients for the presence of primary and acquired EGFR mutations from FFPE biopsies and/or liquid biopsy (sensitivity to first and third generation tyrosine kinase inhibitors), metastatic melanoma patients for the presence of BRAF mutations (sensitivity to tyrosine kinase inhibitors), and ovarian cancer patients for the presence of somatic BRCA1/2 mutations (sensitivity to PARP inhibitors). Future plans include the introduction of immunotherapy predictive NGS tests for the level of tumor mutational burden, microsatellite instability and mismatch repair deficiency, and also for clinically actionable oncogenic gene rearrangements as ALK, NTRK, RET, ROS1 fusions etc. Patients with oncogenically driven cancers benefit strongly from this companion diagnostic approach when both survival and quality of life are taken into account. Further development of experimental techniques and bioinformatics data analyses will improve overall cancer patient care management and lower treatment costs.

BIOMARKERI PROŠIRENOG LIPIDNOG STATUSA U KOLOREKTALNOM KARCINOMU

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Kolorektalni karcinom se svrstava među maligne bolesti sa najvećom učestalošću u savremenom svetu, te su brojna biomedicinska istraživanja posvećena otkrivanju i evaluaciji prediktivnih i dijagnostičkih biomarkera za ovo oboljenje. S obzirom da bolest ima kompleksnu etiopatogenezu, koja uključuje širok spektar metaboličkih poremećaja, parametri lipidnog statusa bi mogli imati značajnu ulogu u dijagnostici i predikciji nastanka kolorektalnog karcinoma. Rutinsko određivanje serumskih lipidnih parametara kod ovih pacijenata najčešće pokazuje tipičan profil koji se karakteriše sniženim koncentracijama ukupnog holesterola, triglicerida, te holesterola sadržanog u česticama lipoproteina niske (LDL) i visoke gustine (HDL). Ovakav nalaz se objašnjava stanjem kaheksije i anoreksije, ali i povećanim preuzimanjem holesterola iz cirkulacije u maligno izmenjene ćelije. Osim toga, opsežna ispitivanja markera proširenog lipidnog statusa u kolorektalnom karcinomu ukazala su na prisustvo specifičnih promena metabolizma holesterola i lipoproteinskih čestica. U našim istraživanjima u ovoj oblasti izdvojio se niz parametara sa potencijalno značajnim prediktivnim ili dijagnostičkim kapacitetom u koje se ubrajaju: markeri sinteze i apsorpcije holesterola, markeri metabolizma HDL čestica i pojedini metaboliti vitamina D. Ipak, pojedinačni lipidni parametri u pravilu ne zadovoljavaju sve kriterijume koji se podrazumevaju za pouzdane i efikasne biomarkere. U tom smislu, predložen je »multimarkerski pristup«, odnosno formiranje adekvatnih kombinacija individualnih biomarkera, čijim bi se određivanjem unapredila postojeća dijagnostika i predviđanje nastanka bolesti. Ovakav pristup u analizi parametara proširenog lipidnog statusa otvara brojne mogućnosti za definisanje panela lako dostupnih analita, čijom bi se primenom mogla poboljšati kako dijagnostika, tako i skrining. Osim toga, integrativni »multimarkerski pristup« u istraživanjima ukazuje na kritične tačke lipidnog metabolizma značajne za nastanak kolorektalnog karcinoma, što unapređuje razumevanje samog patofiziološkog procesa i omogućava bolju prevenciju nastanka ove bolesti.

ADVANCED LIPID STATUS BIOMARKERS IN COLORECTAL CANCER

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Colorectal cancer is among the most prevalent malignant diseases worldwide. Therefore, numerous biomedical researches are focused to identification and evaluation of predictive and diagnostic markers of this disease. Given the fact that colorectal cancer has complex aetiology, which includes a wide spectrum of metabolic disturbances, lipid status parameters might have a role in its prediction and diagnosis. Routine determination of serum lipid parameters in these patients usually reveals a typical profile, characterized by decreased levels of total cholesterol, triglycerides, low density lipoprotein (LDL) – cholesterol and high density lipoprotein (HDL) – cholesterol. Such findings could be explained by the cachexia – anorexia syndrome, which is frequently seen in these subjects. However, decreased cholesterol concentration might as well develop as a consequence of its increased uptake by malignant cells. Moreover, detailed investigations of advanced lipid status parameters in colorectal cancer pointed towards characteristic changes in cholesterol and lipoprotein metabolism. Our research in this area revealed a range of parameters with possibly significant predictive and diagnostic capacity, including markers of cholesterol synthesis and absorption, markers of HDL particles metabolism and several vitamin D metabolites. Yet, single lipid parameters usually do not meet the criteria for reliable and efficient biomarkers of colorectal cancer. Therefore, a novel multimarker approach is proposed, which comprises clustering and simultaneous determination of several individual biomarkers. It is considered that such approach might significantly improve diagnostics and prediction of various diseases. Namely, determination of selected lipid status parameters, within carefully designed diagnostic panels, could enhance both diagnosis and screening of colorectal cancer. In addition, integrative multimarker approach in biomedical investigations could shed light on critical points of lipid metabolism during cancerogenesis, thereby enhancing the understanding of its pathophysiological basis and consequently, improving the prevention of this disease.

GALEKTINI KAO BIOMARKERI: POTENCIJAL I PERSPEKTIVE

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Galektini pripadaju široko rasprostranjenoj familiji proteina koju karakteriše prisustvo očuvanog domena (engl. carbohydrate recognition domain – CRD) odgovornog za vezivanje glikana koji sadrže β-galaktozidne strukture. U ćeliji mogu biti prisutni u jedru, citoplazmi, na površini ćelije kao i u vanćelijskom matriksu. Galektini mogu delovati unutar ćelije kroz interakcije sa drugim proteinima (protein-protein) i izvan ćelije, pokazujući lektinsku aktivnost. Na taj način učestvuju u regulaciji i modulaciji ćelijskih događaja i bioloških procesa. U skladu sa učešćem u raznovrsnim biološkim funkcijama, promenjena ekspresija i/ili funkcija se često povezuje sa različitim patološkim stanjima. Veliki broj studija identifikovao je članove ove familije proteina kao relevanne biomarkere u karcinomima, bolestima srca, bubrega, jetre i infekcijama. Promene u ekspresiji galektina mogu pomoći u dijagnozi različitih bolesti, mogu se povezati sa ishodom lečenja i terapijskim pristupima.Veliki broj studija je ispitivao promene galektina-1 i galektina-3 u tkivnoj ekspresiji ili u cirkulaciji kod različitih bolesti. Većina istraživanja je izvedena na uzorcima pacijenata obolelih od karcinoma i često je ukazivala na postojanje veze između uočenih promena u cirkulaciji i tkivnoj ekspresiji galektina. Takođe, akumulirani podaci ukazuju na sve veći značaj otkrivanja i određivanja galektina kod koronarnih bolesti, reproduktivnih poremećaja, bubrežne insuficijencije i drugih oboljenja. Uprkos nekim odstupanjima, postoji dovoljno dokaza koji pokazuju značaj galektina kao biomarkera. Međutim, ispitivanje galektina kod raznih bolesti je ukazalo na potrebu razvijanja adekvatnih metoda koje bi osigurale poboljšanu osetljivost i tačnost kod detekcije galektina, konsenzus između laboratorija i uspostavljanje referentnog opsega. Dalji napredak na ovom polju zahteva integrativni i sistematski pristup, kojim bi se dodatno potkrepio klinički značaj određivanja galektina.

GALECTINS AS BIOMARKERS: POTENTIAL AND PERSPECTIVES

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Galectins are members of a widely distributed protein family defined by specificity for β-galactoside containing glycans and presence of conserved carbohydrate recognition domain (CRD). They can be found in the nucleus, cytoplasm, at the cell surface as well as in the extracellular matrix. Galectins can act inside the cell mainly through protein-protein interactions and outside the cell displaying lectin activity, thereby regulating and modulating cellular events in biological processes. In line with this multifunctionality, altered expression and/or function of galectins has often been associated with various pathologies. An increasing number of studies have identified members of this protein family as relevant biomarkers in cancer, heart, renal and liver disease, as well as in infections. To date, detected changes in galectin expression may aid in diagnosis of various diseases, can be linked to patient outcome, and galectin-based therapeutic approaches. Increasing number of studies are mainly focused on galectin-1 and galectin-3 in different diseases, whether expressed in tissue or present in circulation. The majority were performed on cancer patients, often showing correlation between changes in circulating galectin and altered tissue expression. Accumulated data also indicates increasing importance of galectin detection and measurement in coronary diseases, reproductive disorders, renal failure and others. Despite some discrepancies, there is ample evidence showing significance of galectins as biomarkers. However, screening for galectin family members in various diseases has pointed out a need for additional studies in order to develop adequate galectin detection methods insuring improved sensitivity and accuracy, enabling consensus between laboratories and establishment of normal reference range. Further progress in the field requires integrative and systematic approach in support of galectin determination clinical utility.

IZAZOVI U LABORATORIJSKOJ DIJAGNOSTICI BOLESTI TIROIDNE ŽLEZDE

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Laboratorijski testovi imaju ključnu ulogu u postavljanju dijagnoze i lečenju bolesti tiroidne žlezde. Imunohemijske metode su danas metoda izbora za određivanje koncentracije hormona u krvi, zahvaljujući potpunoj automatizaciji, kratkom vremenu obrade i visokoj specifičnosti i osetljivosti prema velikom panelu heterogenih molekula. Pri svakodnevnom korišćenju ovih, naizgled jednostavnih, testova javljaju se brojne interferencije koje ometaju dobijanje tačnih rezultata, te zahtevaju veliko poznavanje interferencija od strane biohemičara, kako bi se broj netačnih rezultata sveo na minimum. Tačni rezultati testiranja su neophodni za uspešnu dijagnostiku i uspešno lečenje pacijenata. Pored obezbeđivanja tačnih rezultata postoje i drugi ključni izazovi koji se javljaju u laboratorijskoj endokrinologiji, a svakako danas su najveći izazovi standardizacija i harmonizacija imunohemijskih testova koje, bez obzira na ogromne napore koji se ulažu, nisu još uvek potpune. Za uspešnu dijagnostiku i uspešno lečenje pacijenata neophodno je izrada referentnih vrednosti za hormone štitne žlezde u sopstvenoj populaciji, koja se uglavnom ne sprovodi u našem okruženju, nego se koriste referentne vrednosti po preporuci proizvođača reagenasa. Takođe, potrebno je analizirati i nivoe TSH koje se koriste kao granice kliničkih odluka za hipotireozu, a koje su ovisne između ostalog, o metodi koju laboratorija koristi za merenje TSH. I na kraju, pri interpretaciji rezultata moralo bi se uzeti u obzir i vreme uzimanja krvi za analizu TSH, imajući u vidu da je nivo TSH najviši u vreme sna, a najniži u kasnim poslepodnevnim satima. Sve gore pomenuto, bez dovoljnog razumevanja i dovoljne pažnje biohemičara, moglo bi dovesti do pogrešne procene funkcionalnog stanja štitne žlezde sa velikim posledicama za pacijenta.

CHALLENGES IN LABORATORY DIAGNOSTICS OF THYROID DISORDERS

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Laboratory testing plays a key role in the diagnosis and treatment of thyroid disease. Today, immunochemical methods are methods of choice for determining the level of hormones in the blood, due to complete automatization, short processing time, and high specificity and sensitivity to a large panel of heterogeneous molecules. When using these, seemingly simple tests on a daily basis, numerous interferences occur, interfering with the obtaining accurate results and requiring a high level of knowledge in order to minimize inaccuracy. Accurate testing results are essential for successful diagnosis and successful treatment of patients. In addition, there are other key challenges that arise in laboratory endocrinology. Today, it is certainly the greatest challenge to standardize and harmonize immunochemical assays, which is still uncompleted task, regardless the enormous efforts. For successful diagnosis and treatment of patients, it is necessary to determine reference values for thyroid hormones, which is rarely done in our country. Instead, we use the reference values obtained by the reagents manufacturers. It is also necessary to reconsider the levels of TSH which are significant for clinical decisions in case of hypothyroidism and which strongly depend on the method used by the laboratory to measure TSH. Finally, when interpreting the results, blood sampling time for TSH analysis should be considered, because TSH levels are the highest during sleep and the lowest in the late afternoon. All of the above mentioned, without enough understanding and enough attention of biochemists, could lead to the wrong assessment of thyroid functional condition, with substantial consequences for the patient.

DOKTORI NAUKA U IVD INDUSTRIJI – OČEKIVANJA I MOGUĆNOSTI

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Poslednjih nekoliko decenija zapaža se značajan rast i razvoj u oblasti industrije koja se bavi medicinskim sredstvima. Prema definiciji, *in-vitro* dijagnostička sredstva (IVD) obuhvataju neinvazivne testove koji se izvode na različitom biološkom materijalu sa ciljem postavljanja dijagnoze, radi skrininga pacijenata ili praćenja terapije. IVD industrija nudi širok opseg različitih rešenja počevši od onih najjednostavnijih poput *point-of-*care testova za praćenje nivoa glukoze, preko uređaja namenjenih za rutinski rad kliničkih laboratorija do sofisticiranih tehnologija za molekularna testiranja poput *real-time* PCR tehnologije. Paralelno sa intenzivnim razvojem ove industrijske grane raste i potreba za stručnim kadrovima unutar kompanija. Poseban akcenat se stavlja upravo na visokokvalifikovano stručno osoblje koje može pružiti adekvatnu stručnu podršku kliničkim laboratorijama i pomoći kliničarima u odabiru i primeni adekvatnih testova sa ciljem postavljanja brze i tačne dijagnoze. Stoga je veoma važno dati prave smernice doktorantima o mogućnostima koje im se otvaraju u ovom segmentu, po završenom doktoratu, i pružiti informacije na koji način znanja i veštine stečene tokom doktorskih studija mogu biti prepoznate od strane budućih poslodavaca i implementirane u svakodnevni rad. Ne samo da mogu da rade u sektoru za istraživanje i razvoj, već mogu konkurisati za pozicije u okviru naučnog marketinga i stručne podrške. Rad u IVD kompanijama, bilo da su u pitanju multinacionalne kompanije ili kompanije lokalnog tipa, pred mlade ljude postavlja izazove sa kojima se nisu susretali ranije. Pored stručnog znanja iz oblasti za koje su se školovali, zahteva se posedovanje dodatnih veština. Neke od njih, poput upravljanja projektima i vremenom, su veštine kojima su doktori nauka već ovladali. Osim njih posebno značajne za rad u IVD industriji su komunikacione veštine važne za komunikaciju kako sa krajnjim korisnicima tako i sa menadžmentom, sposobnost upravljanja finansijama i budžetima, kao i sposobnost primene marketinških principa za pravilno i uspešno pozicioniranje proizvoda na tržištu.

PHD IN IVD INDUSTRY – EXPECTATIONS AND POSSIBILITIES

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Over the last few decades there have been noticed considerable rise and development in medical devices industrial segment. According to definition, *in-vitro* diagnostics (IVD) are non-invasive tests performed on biological samples used for diagnose, screening or therapy monitoring. IVD industry offers wide range of different solutions, from the simplest ones like the *point-of-care* tests for glucose monitoring, over the analyzers intended for routine clinical laboratories, up to the sophisticated solutions for molecular testing like the *real-time* PCR technology. Together with the intensive development of this industry area, there is a growing need for professionals within the companies. There is a special demand for highly qualified employees who could offer adequate professional support to clinical laboratories and help clinicians to choose and implement appropriate assays in order to get timely and accurate diagnose. Therefore, it is of the great importance to give the right guidelines to PhD students about employment possibilities in this segment after graduation, as well to inform them how skills and knowledge, that they have already gained during studies, can be recognized by employers and implemented into their everyday work routine. Not only can they work in research and development department, but they can also apply to positions in scientific marketing and scientific support. The work in both multinational and local IVD companies can put in front of the young people great challenges they have not faced before. Parallel to the professional knowledge for the area they have been educated for, it demands certain additional skills. Some of them, like project and time management, are skills PhDs have already acquired. Except them, the skills that are of special value for the work in IVD industry are communication skills, which are necessary for effective communication both with end-users and management, financial and budget management skills, as well marketing skills necessary for appropriate and successful positioning of the final product at the market.

DOKTORSKE STUDIJE KAO SVEOBUHVATNA NADOGRADNJA ZA USPEŠAN RAZVOJ KARIJERE U IN VITRO DIJAGNOSTICI

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Globalni strateški prioriteti u in vitro dijagnostici su transformacija zdravstvene zaštite na globalnom nivou i bolji rezultati kroz inovacije u efikasnosti testiranja, kliničkoj vrednosti i digitalnim rešenjima. Inovacije u kliničkoj vrednosti podrazumevaju razvoj kliničkih rešenja, koja se odnose na medicinske potrebe koje još uvek nisu rešene i koja obezbeđuju pravi benefit za pacijenta. Inovacije u kliničkim rešenjima, bilo da su novi biomarkeri, nove indikacije postojećih biomarkera ili digitalna rešenja, ostvaruju se kroz klinicke studije. U ulozi globalnog menadžera za medicinske poslove, kandidat mora da bude sposoban da prepozna, kombinuje, analizira i interpretira različite grupe kliničkih podataka, uključujući podatke iz randomizovanih kliničkih studija kao i iz opservacionih studija, elektronskih kartona, i novijih tipova podataka, kao sto su genomika, u kombinaciji sa inovativnim načinima interpretacije tih podataka. Doktorat je esencijalan za uspešno kreiranje novih podataka kao i za analizu interpretaciju već postojećih. On omogućava odgovarajuće implementiranje medicinskog znanja kao i znanja iz translacionog istraživanja, epidemiologije i biostatistike. Doktorat bi dodatno trebalo da omogući kandidatu fokus na inovativan način kreiranja novih kliničkih dokaza (maksimalno iskoristiti opservacione studije, korisiti alternativne robusne kredibilne izvore preko digitalnih kanala za publikacije) i fokus na transformaciju medicinskog angažovanja za odgovarajuće prenosenje kliničkih informacija (globalni pristup medicinskom angažovanju sa sofisticiranom kvalitetnom funkcijom, rigorozni analitički pristup u identifikaciji i prioritizaciji ključnih uticajnih osoba na globalnom nivou i prioritizacija između država, pravilna upotreba digitalnih sredstava, saradnja sa nezavisnim edukativnim platformama i digitalnim programima). Menadžer medicinskih poslova sa doktoratom bi trebalo da ima jasno razumevanje potreba korisnika I da bude u stanju da generiše i dalje promoviše solidan sadržaj koji kreira. To može biti pokretačka snaga jedinstvenog pristupa kompanije u IVD u predstavljanju vrednosti svojim korisnicima.

PHD AS A COMPREHENSIVE UPGRADE FOR SUCCESSFUL CARRIER DEVELOPMENT IN IVD

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Global IVD strategic priorities are transformation of global healthcare and improvement of outcomes through innovation in testing efficiency, medical value and digital insights. Innovation in medical value considers development of medically differentiated solutions, which address unmet needs and provide a real and superior benefit for patients. Medically differentiated solutions (either new biomarkers, new indications of existing biomarkers or clinical algorithms) bring the innovation with breakthrough clinical studies. In the role of Global Medical Affairs Manager, candidate needs to be able to select, combine, analyze and interpret the data from different data sets, including randomized clinical trials as well as real-world evidence (RWE), electronic medical records, and novel sources of data, such as genomics in combination with innovative ways of mining and interpreting that data. PhD background is essential for the generation of new data as well as analysis and interpretation of already existing data. It allows person to implement properly medical knowledge together with knowledge in translational sciences and most importantly biostatistics and epidemiology. PhD should furthermore enable candidate to focus on innovative evidence generation (leverage on RWE generation, use of other robust, credible evidence available on digital channels for publications) and transformation of medical engagement for proper dissemination of medical information (global approach to medical stakeholder engagement with robust medical excellence function, rigorous analytical approach for identification and prioritization of the key opinion leaders globally and coordination across countries, proper use of digital tools, e-congresses and other innovative methods, collaboration with independent medical education platforms and digital programs). Medical Affairs Manager with PhD should have clear understanding of stakeholder needs and be able to generate and disseminate strong value story to support it. It can be the driving force behind IVD Company's one unified collaborative approach to delivering value to its stakeholders.

GENSKA EKSPRESIJA ADIPONEKTINSKIH RECEPTORA KOD PACIJENATA SA KOLOREKTALNIM KARCINOMOM

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Neadekvatan imuni odgovor je prepoznat kao jedan od faktora koji doprinose složenoj etiopatogenezi kolorektalnog karcinoma (CRC). Nova istraživanja ukazuju na značaj različitih adipocitokina u imunološkom odgovoru. Adiponektin se ovde posebno izdvaja, s obzirom na njegovu ulogu u plastičnosti i polarizaciji makrofaga, pri čemu istovremeno utiče i na nivo cirkulišućeg faktora nekroze tumora alfa (TNF-alfa). Cilj naše studije je bio ispitivanje nivoa informacione ribonukleinske kiseline (iRNK), TNF-alfa i adiponektinskih receptora 1 i 2 (adipor 1 i 2) u mononuklearnim ćelijama periferne krvi (MĆPK). Pored toga smo ispitali i njihovu povezanost sa lipidima kao pokazateljima narušene metaboličke kontrole.U istraživanje su bile uključene dve grupe: pacijenti sa CRC-om (N= 73) i kontrolna grupa (KG) (N = 80). Za procenu relativnih nivoa ekspresije iRNK upotrebljena je lančana reakcija polimeraze (PCR), dok je beta aktin korišćen kao konstitutivno eksprimiran gen za normalizaciju podataka. Parametri lipidnog statusa određeni su korišćenjem komercijalno dostupnih enzimskih metoda na automatskom analizatoru ILAB 300+. Normalizovani nivoi adipor 1 i TNF-alfa iRNK su bili sniženi u CRC (p <0,001; p<0,050), dok se nivo adipor 2 iRNK-a nije značajno razlikovao između grupa (p = 0,442). Uočena je značajna pozitivna korelacija između TNF-alfa iRNK i koncentracije holesterola lipoproteina visoke gustine (HDL-H) u CRC (ρ = 0,242; p <0, 05), dok je koncentracija HDL-H negativno korelirala sa adipor 1 iRNK (ρ = -0,262; p <0, 05). Osim toga, nivo adipor 1 iRNK je pozitivno korelirao sa adipor 2, kako u CRC tako i u KG (ρ = 0,268; p <0, 05, ρ = 0,498; p <0,001). U KG ukupni holesterol je negativno korelirao sa TNF-alfa i sa adipor 1 iRNK (ρ = -0.228; p <0, 05; ρ = -0,230; p<0,05). Naši rezultati ukazuju da je narušena metabolička kontrola povezana sa složenom genetskom deregulacijom imuniteta. Dobijeni rezultati mogli bi predstavljati novu, važnu informaciju u istraživanjima karcinoma, koja bi mogla biti posebno značajna u razvijanju individualizovanog pristupa u dijagnozi i prognozi bolesti. Stoga dobijeni rezultati mogu predstavljati temelj za buduća istraživanja.

GENE EXPRESSION OF ADIPONECTIN RECEPTORS IN PATIENTS WITH COLORECTAL CANCER

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Immune irregularity is recognized as one of the factors that contribute to complex etiopathogenesis of colorectal cancer (CRC). Novel studies imply significance of different adipocytokines in immune response. Adiponectin can be singled out, considering its role in macrophages' plasticity and polarization, while also influencing tumor necrosis factor alpha (TNF alpha) circulating levels. The aim of our study was to investigate messenger ribonucleic acid (mRNA) levels of TNF alpha and adiponectin's receptors 1 and 2 (adipor 1 and adipor 2), in peripheral blood mononuclear cells (PBMCs). Additionally, we explored their association with lipids as indicators of impaired metabolic control. This study included two cohorts: CRC patients (N=73) and control group (CG) (N=80). Polymerase chain reaction (PCR) was employed for evaluation of relative mRNA expression levels, while beta actin was used as a constitutively expressed gene for normalization of data. Lipid status parameters were obtained by using commercially available enzymatic methods on automated analyzer ILAB 300+. Normalized adipor1 and TNF alpha mRNA levels were reduced in CRC ($p<0.001$; $p<0.050$; respectively), while adipor 2 mRNA didn't differ between our two groups ($p=0.442$). Significant positive correlation was observed between TNF alpha mRNA and high density lipoprotein cholesterol (HDL-C) in CRC ($\rho = 0.242$; $p<0.05$), while HDL-C levels negatively correlated with adipor 1 mRNA ($\rho = -0.262$; $p<0.05$). Furthermore, adipor 1 mRNA positively correlated with adipor 2 in CRC, as well as in CG ($\rho = 0.268$; $p<0.05$, $\rho = 0.498$; $p<0.001$; respectively). In CG total cholesterol correlated negatively with TNF alpha and adipor1 mRNA ($\rho = -0.228$; $p<0.05$; $\rho = -0.230$; $p<0.05$, respectively). Our results suggest that disrupted metabolic control is associated with complex genetic dysregulation of immunity. The observed relationship could represent important novel information for cancer research, which could be especially significant for more individualized approach in patients' diagnosis and prognosis. Therefore our results warrant future studies.

MARKERI HOMEOSTAZE HOLESTEROLA U VISOKORIZIČNOJ TRUDNOĆI

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Dislipidemija koja se razvija kod žena sa pre-eklampsijom (PEK) po nekim autorima se smatra značajnim činiocem razvoja endotelne disfunkcije i ne-potpune invazije trofoblasta koje se nalaze u osnovi razvoja ove komplikacije trudnoće. Molekularni mehanizmi nastanka ove dislipidemije nisu u potpunosti razjašnjeni, tako da je cilj naše studije bio da ispitamo promjene u koncentraciji ne-holesterolskih sterola (NHS), surogat markera sinteze i apsorpcije holesterola, i da definišemo metabolički profil holesterola kod žena sa visoko-rizičnom trudnoćom. Devedeset trudnica koje su na osnovu važećih preporuka bile u riziku da razviju PEK uključeno je u studiju i praćeno longitudinalno u 4 tačke tokom trudnoće. Dvadeset trudnica je razvilo PEK. Uzorci krvi su uzimani jednom u svakom trimestru i ne-posredno prije porođaja. Tečnom hromatografijom sa tandem masenom spektrometrijom (LC-MS/MS) određena je koncentracija NHS. U grupi sa visokim rizikom od 2. trimestra je uočen značajan porast dezmosterola ($p<0,001$), 7-dehidroholesterola ($p<0,05$) i latosterola ($p<0,001$), tj. markera sinteze holesterola, a vrijednosti su ostale visoke do kraja trudnoće. Kod trudnoće komplikovane PEK-om značajan porast je uočen samo za latosterol ($p<0.05$) i to od 3. trimestra. Latosterol u 1. trimestru je bio viši u grupi žena sa PEK-om u poređenju sa grupom sa visokim rizikom ($p<0,05$), ukazujući da je sinteza holesterola bila povećana od samog početka trudnoće komplikovane PEK-om. Značajan pad β-sitosterola, markera apsorpcije holesterola, je uočen samo u grupi sa visokim rizikom u tački prije porođaja ($p<0,05$). β-sitosterol u 1. trimestru je bio niži u grupi sa PEK-om u poređenju sa grupom sa visokim rizikom ($p<0,05$). Međutim, pozitivna korelacija između dezmosterola i β-sitosterola u 1. trimestru u grupi sa PEK-om ($\rho=0,459$; $p<0,05$) ukazuje da je a-psorpcija holesterola bila povišena u prisustvu povišene sinteze holesterola, tj. da je homeostaza holesterola bila narušena rano u trudnoći komplikovanoj PEK-om. Dakle, dobijeni metabolički profil holesterola sugeriše da je sinteza holesterola povišena, a homeostaza holesterola narušena već u prvom trimestru kod žena sa PEK-om.

CHOLESTEROL HOMEOSTASIS MARKERS IN HIGH-RISK PREGNANCY

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Dyslipidemia observed in women with pre-eclampsia (PEC) is considered to be a significant factor in the development of endothelial dys-function and incomplete trophoblast invasion that underlie the development of PEC. Molecular mechanisms of this dyslipidemia have not been fully elucidated so our study aimed to investigate changes in non-cholesterol sterols (NCSs), cholesterol synthesis and absorption surrogate markers, and to define the cholesterol metabolic profile in a high-risk pregnancy. Ninety pregnant women who were at risk of developing PEC based on valid recommendations were included in the study and monitored longitudinally. Twenty pregnant women developed PEC. Blood samples were taken once in each trimester and before delivery. Circulating profiles of NCSs were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS). In a high-risk group a significant increase in desmosterol ($p<0.001$), 7-de-hydrocholesterol ($p<0.05$) and lathosterol ($p<0.001$), i.e. cholesterol synthesis markers, were observed from the 2nd trimester. In PEC complicated pregnancy, a significant increase was observed only for lathosterol ($p<0.05$) from the 3rd trimester. First trimester latosterol was higher in the PEC compared to the high-risk group ($p<0.05$), indicating cholesterol synthesis was higher from the onset of PEC complicated pregnancy. A significant decrease in β-sitosterol, cholesterol absorption marker, was observed only in the high-risk group before delivery ($p<0.05$). First trimester β-sito-sterol was lower in the PEC group compared to the high-risk group ($p<0.05$). However, a positive corre-lation between desmosterol and β-sitosterol in the PEC group in the 1st trimester ($\rho=0.459$, $p<0.05$), implied cholesterol absorption was increased in presence of increased cholesterol synthesis, i.e. cholesterol homeostasis was disrupted early in PEC complicated pregnancy. In conclusion, the cholesterol metabolic profile obtained suggests increased cholesterol synthesis and impaired cholesterol homeostasis in women with PEC as early as the first trimester.

LONGITUDINALNE PROMENE LIPOPROTEINSKIH ČESTICA VISOKE GUSTINE I ENZIMA PARAOKSONAZE 1 TOKOM RIZIČNE TRUDNOĆE

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Preeklampsija (PE) je komplikacija trudnoće koja se karakteriše de novo razvojem hipertenzije i proteinurije posle 20-te nedelje gestacije kao i prestankom svih simptoma do 6-te nedelje nakon porođaja. Incidenca PE je od 3% do 7% i predstavlja jedan od glavnih uzročnika smrtnosti kako fetusa tako i majke tokom trudnoće i porođaja. Osnovni patogenetski mehanizam nastanka PE je neadekvatno vaskularno remodelovanje koje je neophodno za adekvatnu perfuziju placente i razvoj fetusa. Posledično dolazi do neadekvatne perfuzije placente, oksidativnog stresa, inflmacije i disfunkcije majčinog endotela. U PE kod trudnica se razvija dislipidemija, pri čemu lipoproteinske čestice visoke gustine (HDL) gube svoja antiaterogena i antioksidativna svojstva, doprinoseći progresiji endotelne disfunkcije. Cilj ovog rada bio je praćenje raspodele subfrakcija HDL čestica i antioksidativnog kapaciteta ovih čestica preko aktivnosti enzima paraoksonaze 1 (PON1), trudnica koje su u visokom riziku da razviju PE. Studija je uključila 91 trudnicu sa jednim ili više faktora rizika za nastanak PE. Krv je uzorkovana u četiri tačke, od prvog do trećeg trimestra (T1, T2, T3), kao i u 37-oj nedelji gestacije pre porođaja (T4). Aktivnost PON1 je određena preko brzine razgradnje supstrata paraoksona, dok je razdvajanje HDL subfrakcija vrseno metodom vertikalne elektroforeze na poliakrilamidnom gradijent gelu. Rezultati su pokazali da je relativni udeo HDL 2b subfrakcije statistički značajno veći u T2 u odnosu na T1 kod obe grupe ispitanica, trudnica koje su razvile PE i kod trudnica koje su bile u riziku da razviju PE ($p<0.05$). Relativni udeo velikih HDL 2a čestica se smanjivao tokom trudnoće, sa značajnom razlikom u T2 u odnosu na T1 ($p<0.05$). Takođe, relativni udeo HDL 3a čestica je bio manji u T2 u odnosu na T1 ($p<0.001$). Aktivnost enzima PON1 od početka trudnoće kreće da raste i statistički je značajno veća u T2 u odnosu na T1 kada posmatramo sve ispitanice zajedno ($p<0.05$), s tim da trudnice koje su razvile PE, u startu imaju znatno veću

LONGITUDINAL CHANGES OF HIGH DENSITY LIPOPROTEIN PARTICLES AND PARAOXONASE 1 ENZYME DURING RISK PREGNANCY

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Preeclampsia (PE) is a pregnancy complication, characterized by de novo development of hypertension and proteinuria after 20th weeks of gestation and disappearance of all symptoms by the 6th week postpartum. The incidence of PE ranges from 3% to 7% and is one of the leading causes of mortality for both the fetus and the mother during pregnancy and childbirth. The pathogenetic mechanism of PE formation is inadequate vascular remodeling, which is necessary for adequate placental perfusion and fetal development. Consequently, inadequate placental perfusion, oxidative stress, inflammation and dysfunction of the maternal endothelium occur. Dyslipidemia develops in PE, with high density lipoprotein (HDL) particles losing their antiatherogenic and antioxidant properties, progressing endothelial dysfunction. The aim of this study was to monitor the distribution of HDL particle subfractions and antioxidant capacity of these particles via the activity of the enzyme paraoxonase1 (PON1), pregnant women at risk of developing PE. The study included 91 pregnant women with one or more risk factors for PE. Blood was sampled sequentially in four points, from the first to third trimesters (T1, T2, T3) as well as at the 37th week of gestation before birth (T4). PON1 activity was determined by the rate of degradation of the paraoxonase substrate, while the separation of HDL subfractions was performed by vertical electrophoresis on a polyacrylamide gradient gel. The results showed that relative proportion of HDL2b subfractions was significantly higher in T2 compared to T1 in both groups of pregnant women who developed PE as well as in high-risk group ($p<0.05$). The relative proportion of large HDL2a particles was lower in T2 compared to T1 ($p<0.05$). Also, relative proportion of HDL3a particles was lower in T2 compered to T1 ($p<0.05$). The activity of PON1 enzyme from the beginning of pregnancy starts to grow and it is significantly higher in T2 compered to T1 when we look at all subject together, but

aktivnost ovog enzima kroz T1, T2 i T4 tačku u odnosu na trudnice koje su bile u visokom riziku od razvoja PE ($p<0.05$). Na osnovu rezultata ove studije može se zaključiti da su trudnoće komplikovane PE praćene kvalitativnim i kvantitativnim promenama HDL čestica.

pregnant women who developed PE, at start having significantly higher activity of this enzyme trough T1, T2 and T4 point compered to pregnant women who were in high risk. Based on the results of this study, it can be concluded that the pregnancies complicated with PE are accompanied by qualitative and quantitative changes in HDL particles.

GAMA-GLUTAMIL TRANSFERAZA KAO MARKER EKSTRAĆELIJSKIH VEZIKULA U SEMENOJ PLAZMI ČOVEKA

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Ekstraćelijske vezikule (EV) su membranske strukture nano veličine, koje se sastoje od proteina, lipida i nukleinskih kiselina. Njihov složen sastav u velikoj meri odslikava ćeliju od koje vode poreklo, a dodatno može biti promenjen u zavisnosti od fizioloških i patoloških procesa. Upotreba EV u kliničkoj dijagnostici kao oruđa »tečne biopsije« je, stoga, sve više u porastu. Naše istraživanje se bavi EV, poznatim kao prostazomi, koje su izolovane iz semene plazme muškaraca sa normospermijom i oligospermijom. Uporedna analiza molekulskih svojstava površine prostazoma sa aspekta glikanskog sastava, bila je usmerena na moguće razlike u manozilovanim i sijalinizovanim glikoproteinima. Posebna pažnja je bila posvećena praćenju membranskog glikoproteina, gama-glutamil transferaze (GGT; EC 2.3.2.2.). U oblasti reproduktivne fiziologije, GGT se, do sada, nije ispitivala kao marker prostazoma. Sticanjem uvida u obrasce distribucije GGT na različitim supopulacijama ili domenima EV, može se povećati njen biomarkerski potencijal u rutinskoj laboratorijskoj dijagnostici. Intaktni ili solubilizovani prostazomi, izolovani diferencijalnim centrifugiranjem i gel filtracijom, okarakterisani su pomoću elektronske mikroskopije, afinitetne hromatografije, određivanjem aktivnosti GGT i blota korišćenjem lektina konkavalina A, lektina iz pšeničnih klica i antitela na tetraspanine. Dobijeni rezultati su pokazali da distribucija GGT, generalno, prati distribuciju CD63 i N-glikana. U odnosu na ko-distribuciju ostalih ispitivanih membranskih glikoproteina, molekulski obrasci povezani sa GGT su odražavali razlike u prostazomima muškaraca sa normospermijom i oligospermijom. Dobijeni rezultati su otkrili GGT na EVs kao analit i referentni parametar.

GAMMA-GLUTAMYL TRANSFERASE AS A MARKER OF EXTRACELLULAR VESICLES IN HUMAN SEMINAL PLASMA

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Extracellular vesicles (EVs) are nano-sized membranous structures, carrying diverse cargoes including proteins, lipids and nucleic acids. Their complex composition largely reflects the cells which they originated from and can be changed in physiological and pathological processes. With the emerging interest in the use of EVs for clinical and diagnostic purposes, its application as a 'liquid biopsy' tool have exponentially growed. Our research deals with EVs, known as prostasomes, isolated from human seminal plasma of normozoo- and oligozoospermic men. Comparative examination of molecular properties of prostasomal surface, exemplified by glycan compositions as possible distinction factor, was focused on mannosylated and sialylated glycoproteins. Specifically, membranous glycoprotein gamma-glutamyl transferase (GGT; EC 2.3.2.2.) was monitored. So far, GGT was not studied as a prostasomal marker in relation to reproductive physiology. Getting insight into distribution patterns of GGT on different EVs subpopulation or domains can add new value to its common use as a biomarker by raising its laboratory diagnostic potential. Intact or detergent-treated prostasomes, isolated by differential centrifugation and gel filtration, were characterized by electron microscopy, affinity chromatography, GGT activity and blotting using concanavalin A, wheat germ lectin and antibodies to tetraspanins. The results obtained indicated that GGT distribution generally overlapped distribution of CD63 and N-glycans. In relation to co-distribution of individual membrane glycoproteins studied, distinct GGT-associated molecular patterns were found to reflect differences in prostasomes from normozoo- and oligozoospermic men. Consequently, GGT on EVs as an analyte and new reference parameter emerged.