

dies doctorandorum
BOOK OF ABSTRACTS

2018



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BOOK OF ABSTRACTS

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Foreword

Faculty of Medicine of Osijek, organizes for the fourth time – *Dies doctorandorum* 2018. (Days of Ph.D. candidates). This annual event is reserved for doctoral students and their mentors to give them a platform to present the results of their research.

The primary objective of this event is to give PhD students a professional environment in which they can discuss their scientific achievements. This also gives them the opportunity to subject their research interests to a critique by their peers and provides a valuable experience to improve their communication and argumentation abilities in presenting their further research.

Dies doctorandorum is designed as a way to monitor the progress of PhD students in an encouraging, professional environment that will eventually lead to scientific excellence.

In addition, giving the opportunity to PhD students to meet world renowned scientists has an informative character as well and enables them to form contacts for future scientific collaboration.

As has been the case in previous years, the best poster presentations will be selected by the Members of the Committee for Doctoral Studies and awarded by the Dean's award.

Professor Jure Mirat, M.D., Ph.D.
Dean, Faculty of Medicine Osijek

Abstracts of
annual seminars





Title of abstract: Acute Dietary Salt Modulation Induces Changes in Dynamics and Activation of Leukocyte and Monocyte Subpopulations in Young Healthy Women

Dissertation Proposal Title: Role of Oxidative Stress in High Salt Diet-Induced Endothelial Dysfunction in Young Healthy Subjects

PhD candidate: Lidija Barić, MD, Health Center Osijek

Mentor: Assist. Prof. Ana Stupin, MD, PhD, Assistant Professor, Department of Physiology and Immunology, Faculty of Medicine, J. J. Strossmayer Osijek

Introduction: It has been proposed that inflammation has an important role in the mechanisms underlying endothelial dysfunction (altered vascular response and oxidative stress) induced by high-salt (HS) intake, and that the leukocyte-endothelial cell interactions are important for this process.

Aims: This study aimed to assess the effect of 7-days salt intake modulation on leukocytes and monocyte subpopulations distribution and activation defined by CD11a expression (part of LFA-1/Leukocyte Function Antigen 1, which is ligand of ICAM-1-5/Intercellular Adhesion Molecules 1-5) in young healthy women.

Materials/Participants and Methods: 15 young healthy women who all took 7-days low-salt (LS) diet (<3.2 g salt/day) followed by 7-days HS diet (~14 g salt/day) participated in this study. Blood pressure (BP) was measured, and 24h urine samples were analyzed for sodium, potassium, urea and creatinine levels before and after diet protocols. Also, before and after diet protocols, measurement of circulating leukocytes and monocyte subpopulations ('classical' CD14++CD16-, 'non-classical' CD14+CD16++ and 'intermediate' monocytes CD14++CD16+) distribution, and its activation (CD11a expression) was performed using flow cytometry (BD FACS Canto II cytometer). Results were analyzed using the FlowLogic software (Inivai Technologies) and presented as mean fluorescence intensity. This study was approved by the Ethical Committee of the Faculty of Medicine University of Osijek (Class: 602-04/17-08/12, No: 2158-61-07-17-42).

Results: Changes in 24h urinary sodium confirmed that subjects conformed to the diet protocol. BP was reduced after LS diet, but not changed after HS diet protocol. Total frequency of CD16high granulocytes, monocytes and lymphocytes, as well as

of CD14⁺⁺CD16⁺ (intermediate) and CD14⁺⁺CD16⁻ (classical) gated monocytes was not significantly changed due to HS loading compared to LS diet. CD14⁺CD16⁺⁺ gated (non-classical) monocytes significantly decreased after HS diet compared to the LS diet. HS diet significantly decreased CD11a expression on CD16^{high} granulocytes, monocytes and lymphocytes in peripheral blood, compared to LS diet. CD11a expression on all three gated monocyte subpopulations was significantly decreased after HS diet compared to LS diet.

Conclusions: The results of the present study demonstrated that 7-days HS loading decreased CD14⁺CD16⁺⁺ (non-classical) monocytes subpopulation which usually acts as endothelium housekeepers, and also significantly decreased expression of CD11a on CD16^{high} granulocytes, monocytes (all three subsets) and lymphocytes when compared to LS diet in young healthy women. It is possible that such decrease in activated leukocytes expressing high-level of CD11a provoked by short-term HS loading occurs due to activated leukocytes adhesion and migration through endothelial layer at the place of vascular injury.

Keywords: endothelium, high salt diet, leukocytes, monocyte subsets, CD11a

Acknowledgement: This study was funded by Croatian Science Foundation project #IP-2016-06-8744 (RAS-AdrenOX).



Dissertation Proposal Title: Public Health Importance of the National Colon Cancer Screening Programme in Osijek-Baranja County

PhD candidate: Maja Čebohin, Faculty of Medicine Osijek

Mentor: Assist. Prof. Senka Samradžić, Department of Public Health, Institute of Public Health for the Osijek -Baranja County

Introduction: Colorectal cancer is the third most common among malignant neoplasms in the world, but it is one of the rare tumours that allows for timely prevention. It is known as a 'silent disease' because many people lack clinical symptoms until the disease becomes difficult to treat. It is an important public health problem due to its growing incidence. In the last thirty years its incidence and mortality has been on the rise with an annual increase rate of new cases around 3%, it is the third most common cancer in the world and the second most common cause of death in the developed countries.

Hypothesis:

1. The incidence of carcinoma and advanced adenomas in O-B County* is high and greatly important for public health
2. National colon cancer screening programme has revealed a significant number of newly detected carcinoma and advanced adenomas in O-B County*
3. Incidence of carcinoma and advanced adenomas is higher in men
4. Incidence of carcinoma and advanced adenomas is higher in older age groups, over 65.

Aims:

1. To identify the response rate to the 3rd cycle National colon cancer screening programme in O-B County* (colonoscopy examination performed)
2. To identify the proportion of findings about advanced adenomas and carcinoma
3. To explore findings about advanced adenomas and carcinoma with regard to age and gender of study participants

Participants and methods: The target population are persons included in the National Colon Cancer Screening Programme in O-B County* from 2013 to July 2017. The anticipated sample is 692 participants aged 50 to 74 with a positive test for occult

blood. The screening method used for early detection of colon cancer is the guaiac test for hidden blood.

Research plan: Study participants received a notification letter and a consent form sent by the Croatian Institute of Public Health (first phase of the Programme). After the receipt of the signed consent, three samples of the test were delivered to the participants' home address with guidelines for use. The tests were returned by regular mail to the Institute of Public Health of O-B County* and analysed (second phase of the Programme). Colonoscopy exam was performed on the participants with positive occult blood test at the Clinical Hospital Osijek (third phase of the Programme).

Scientific contribution: The study on the response rate and findings about advanced adenomas and carcinoma provides an estimate of burden of this public health problem in O-B County*. Results will point at the significance of the Programme for the specific local population of the County by taking into account local characteristics of the population. The results will contribute to the improvement of the Programme, thus leading to a decrease in incidence and prevalence of carcinoma in the population.

Keywords: National programme, selection, colon cancer, occult bleed test, colonoscopy



Title of abstract: Effect of different combination of maternal and postnatal diet on adipose tissue morphology in female rat offspring.

Dissertation proposal title: Effect of different combination of maternal and postnatal diet on ovarian and adipose tissue morphology in female rat offspring.

PhD candidate: Nenad Čekić, Department of Surgery, General hospital Vukovar, Department of Anatomy and Neuroscience, Faculty of Medicine, University of Osijek

Mentor: Assist. Prof. Anđela Grgić, Department of Anatomy, Histology and Embriology, Pathological anatomy and Patological histology, Faculty of Dental Medicine and Health, University of Osijek

Introduction: Two main types of adipose tissue in mammals are white (WAT) and brown (BAT) adipose tissue. Recent researches show that mechanisms leading to adipose tissue expansion could be an important factor in development of metabolic syndrome in obesity. The expansion of adipose tissue is possible through enlargement of existing fat cells (hypertrophy) or through formation of new adipocytes (hyperplasia). WAT is organized in two compartments: subcutaneous and visceral fat pad. Visceral adipose tissue expansion is associated with a higher risk of insulin resistance, dyslipidaemia, and diabetes type 2, hypertension, and all-cause mortality. Subcutaneous adipose tissue is associated with preserved insulin sensitivity. In animal studies high-fat fed mothers produce offspring with a phenotype resembling human metabolic syndrome and induce hyperleptinemia, hyperinsulinemia, insulin resistance, hyperphagia, and hyperlipidaemia in the offspring.

Aim: To investigate how different combination of maternal and postnatal diet affects female offspring subcutaneous and perigonadal WAT morphology.

Materials and Methods: Ten female rats were randomly divided in two groups. One group was fed with high content of saturated fatty acid food (HFD) and the other one with standard laboratory chow (CD). Female offspring from both groups were randomly divided in two subgroups after coupling and lactation period, subsequently there were four groups of offspring (n=5 each) with different feeding protocol: a) CD-CD, b) CD-HFD, c) HFD-CD and d) HFD-HFD. At the age of 18 weeks offspring were sacrificed and adipose tissue morphometry was studied. On tissue sections, histomorphometric

analysis was conducted using CellProfiler program. Statistical analysis was performed using IBM SPSS Statistics software (version 21, IBM Corporation, NY).

Results: In subcutaneous adipose tissue the largest surface area was measured in CD-CD group, which was significantly higher than surface area in CD-HFD and HFD-CD group ($p < 0.05$). In perigonadal adipose tissue the largest surface area was measured in CD-HFD group which was significantly higher than surface in HFD-CD group ($p < 0.05$). Significantly higher adipocyte surface area compared to HFD-CD group was also measured in CD-CD group ($p < 0.05$).

Conclusion: Our results lead to the conclusion that alteration of postnatal diet can lead to adipocyte morphology changes.

Keywords: obesity, high fat diet, white adipose tissue, epigenetics, morphometry



Title of abstract: The association between brain derived neurotrophic factor and cognition in veterans with posttraumatic stress disorder

Dissertation Proposal Title: The association between brain derived neurotrophic factor and cognition in veterans with posttraumatic stress disorder

PhD candidate: Sandra Domitrović, General Hospital Karlovac

Mentor: Assist. Prof. Suzana Uzun, Psychiatric Clinic Vrapče

Introduction: Combat - related posttraumatic stress disorder (PTSD) is frequently comorbid with cognitive decline and various cognitive symptoms. The comorbid cognitive disturbances complicate its pharmacotherapy and worsen clinical picture of PTSD. Brain derived neurotrophic factor (BDNF) is a neurotrophin with important role in modulation of neuronal survival, differentiation, synapse formation, brain plasticity and neurotransmission. In addition, BDNF is significantly associated with cognitive processes including learning, memory, and response to stress, all processes that are altered in PTSD. A common single-nucleotide polymorphism (SNP) has been identified in the human BDNF gene (BDNF Val66Met) that leads to decreased BDNF secretion and impairments in specific forms of learning in humans.

Aims: to prove the association between BDNF Val66Met (rs6265) and BDNF C270T (rs56164415) polymorphism and cognitive decline in veterans with PTSD

Materials / Participants and Methods: 333 male Caucasian war veterans with combat-related PTSD were included. They were consecutively sampled in Department for Biological Psychiatry and Psychogeriatric University Hospital Vrapče, Zgreb, Croatia, from September 2015 to July 2017. Diagnosis: current and chronic combat – related PTSD (structured clinical interview, DSM V criteria; APA 2013). Evaluations were done using different scales: PANSS, CAPS; and PANSS cognitive subscales. PANSS Cognition subscale 1: 5 items P2, N5, G5, G10, G11 and PANSS Cognition subscale 2: 4 items; P2, N5, G10, G11.

Genotyping: BDNF Val66Met (rs6265) and BDNF C270T (rs56164415) were genotyping using real PCR for DNA isolated from blood samples with a salting method (Miller et al., 1988.).

Results: conformation with BDNF C270T polymorphism; TT carriers had the most severe symptoms and pronounced cognitive decline vs. Carriers of the CT and CC genotypes

Conclusion: These preliminary data confirmed our hypothesis that BDNF is related to cognition and also revealed for the first time a significant association between BDNF C270T and cognition in PTSD

Keywords: Brain derived neurotrophic factor, cognition, PTSD, stress, polymorphism



Title of abstract: Correlation of folate receptor alpha expression with histological grade and size of triple negative breast carcinoma

Dissertation proposal title: Folate receptor alpha expression in triple negative breast carcinoma

PhD candidate: Irena Fröhlich, MD, Clinical Hospital Center Osijek, Faculty of Medicine Osijek

Mentor: Assoc. Prof. Branka Lončar, MD, PhD, Clinical Hospital Center Osijek, Faculty of Medicine Osijek

Introduction: Breast cancer is the most prevalent neoplasm in women. According to Croatian Institute of Public Health, in 2015 there were 2748 newly registered cases. Triple negative breast cancer (TNBC) is a molecular subtype of breast cancer shown to have more aggressive course and lower survival rates, with no guided therapy, compared to other breast cancer subtypes. Recently, folate receptor alpha (FRA) took central stage in cancer therapy research, and is shown to be overexpressed in epithelial malignancies, including breast cancer.

Aims: To determine the correlation of FRA expression with clinicopathological parameters in TNBC.

Participants and Methods: This preliminary study included 29 women diagnosed with breast cancer, between January 1, 2008 and December 31, 2017, in Clinical Hospital Center Osijek. Including factor was the TNBC subtype with positive FRA membranous staining (regardless of cytoplasmic stain), while excluding factors were diagnosis of other molecular subtype and TNBC with negative FRA membranous staining. Clinicopathological parameters were determined using immunohistochemistry methods and correlated afterwards with FRA expression, which was scored with H-score ranging 0-300 (the critical level of statistical significance was accepted when $p < 0.05$).

Results: Our study involved 29 women, between ages 34-87 (at the time of diagnose). 20 women were diagnosed with grade III TNBC (graded using the Bloom-Richardson grading system), 9 with grade II and none with grade I carcinoma. Size of the tumor

was assessed using TNM criteria and our examinees were evaluated as T1 (n=20) and T2 (n=9). Aforementioned clinicopathological criteria were correlated with H-score of FRA expression, and we showed that there is a correlation between FRA expression and tumor grade, as well as with the size of tumor, with p values of 0.634 and 0.812 respectively.

Conclusion: Our study reports, although limited by a small sample size, that high grade TNBCs, as well as the larger tumors, express high levels of FRA, making them a potential target for anti-FRA therapy.

Keywords: breast cancer, TNBC, FRA, histological grading, immunohistochemistry



Dissertation Proposal Title: Tracking eye movements as a biomarker for early detection of cognitive disorders and autonomic dysfunction in patients with focal cervical dystonia

PhD candidate: Tihana Gilman Kuric, MD, Neurology Clinic, University Hospital Center Osijek

Mentor: Assist. Prof. Svetlana Tomić, MD, PhD, Neurology Clinic, University Hospital Center Osijek

Introduction: Dystonia is the third most frequent motion illness, whose pathology and pathophysiology has not been fully clarified. The main clinical feature is the abnormal function of a body part and non-motor symptoms: depression, anxiety, sleep disturbance, pain and cognitive impairment.

Recent research suggests that focal dystonia is a disturbance of communication between basal ganglia and cerebellum, therefore, new research has recently focused on the examination of eye movements as biomarkers for early detection of symptoms and monitoring of neurodegenerative diseases.

Given that the cerebral pathway for conduction of ocular movements extends from the cerebral cortex to the cerebral trunk it is logical to assume the interdependence of higher cortical functions and ocular motor movement.

As mentioned, the cerebral pathway for ocular movements includes brain stem, which is largely responsible for autonomic nerve function. Most symptomatology of disautonomy is present in basal ganglia disorders, so this study will also attempt to identify the possible existence of autonomous nonmotor symptomatology in patients with cervical dystonia.

Hypothesis: Monitoring of ocular movements can be used as a biomarker for early detection of cognitive and autonomic disorders in a group of patients with focal cervical dystonia.

Aims: Main Objective of Research:

- (a) Behavior of biomarkers in patients with diagnosed focal dystonia compared to a control group
- (b) behavior of biomarkers in patients with diagnosed focal dystonia before and after treatment

- (c) co-existence of biomarker with motor and non-motoric symptoms
- (d) linkage of biomarkers with duration of cervical dystonia symptoms
- (e) Determine the frequency and degree of cognitive impairment in relation to the control healthy group
- (f) To determine the frequency and extent of autonomic function impairment in relation to the control healthy group
- (g) Determine the correlation between ocular movements and cognitive function disorders
- (h) Determine the connection between ocular movements and autonomic function disorders

Participants and Methods: The study will include 50 patients with focal cervical dystonia before and after botulinum toxin application and 50 healthy individuals. Respondents will be recruited from the dispensary for motion sickness disorders. As a research tool will be performed standardized questionnaires of the Montreal Cognitive Assessment, Adenbrooke's Cognitive Examination, COMPASS 31 and a general data questionnaire. We will use the Tobii TX300 model of the Swedish eye-vision device. Statistical processing will be done using the SPSS 17.0 statistical program.

Research Plan: The research would be carried out in cooperation with the Faculty of Computer and Information Technology (Laboratory for Artificial Intelligence) from the University of Ljubljana. Part of the research will be conducted at University Hospital Center Osijek, at the Neurology Clinic. The planned study time is 18 months / until the planned number of examinees is tested.

Expected scientific contribution: Confirmation of the hypothesis that eye movement testing could serve as a biomarker for early detection of cognitive and autonomic disorders in patients with focal cervical dystonia.

Keywords: (6) focal dystonia; eye movements; biomarker; cognitive functions; autonomous functions; botulinum toxin



Title of abstract: Immunochemical methods for determination of glutathione peroxidase (GPX) 1/2, 3 and 4

Dissertation proposal title: Oxidative stress in gestational diabetes mellitus (GDM): role of glutathione (GSH) and glutathione peroxidases (GPXs)

PhD candidate: Martin Gredičak, M.D., General Hospital Zabok

Mentor 1: Assist. Prof. Rajko Fureš, M.D., General Hospital Zabok

Mentor 2: Marija Ljubojević, Ph.D. Institute for Medical Research and Occupational Health, Zagreb, Croatia.

Introduction: Oxidative stress in pregnancy affected by GDM may be cause or consequence of that pathology. GSH and GPXs are involved in organism protection against peroxidation reactions. GPX1/2, GPX3 and GPX4 enzymes may be stress induced, and possible changed in GDM. GPXs are small (about 20 kDa) cytosolic proteins. They are usually homotetramers that break peroxides using GSH with necessary and specific amino acid selenocysteine (Sec) in active site of enzymes. Immunochemical detection of human GPXs depends on specific antibodies (Abs) both for western blot analysis (WB) and immunohistochemistry (IHC). Getting right protein band by WB in homogenates of human placenta (hhP) and pattern with IHC staining is starting point for further analysis of proposed correlations between GPXs, GSH and Se in control compared to GDM pregnancies.

Aims: For that purpose, first aim was to establish reliable results of immunochemical methods for detection of GPXs that will be used in further investigations.

Participants and Methods: GDM is estimated on basis of fasting glucose > 5.1 mM and criteria of standard oral glucose tolerance tests (OGTT), that are globally accepted. Samples of blood and urine for biochemical and other analysis were collected late in pregnancy (about 36 week) of glycemic normal (control) and only diet regulated GDM women (at least 10 samples from each group). Future mothers were informed in advance and voluntary involved in samples collecting during regular pregnancy control. Placentas after childbirths from all women were collected for Se analysis (ICP-MS) and for immunochemical studies of GPXs as tissue parts in liquid nitrogen and piece in fixative for IHC. For present study of immunochemical methods, homogenates

of human placenta (hhP) were prepared from collected tissue to be tested in which conditions specific antibodies (Ab) works best and after staining result in specific protein bands.

Results: WB resulted in specific protein bands of expected molecular weight (MW) for monoclonal Abs GPX1/2 (~ 23 kDa) and GPX4 (~ 20 kDa) in reducing conditions and polyclonal GPX3 Ab gave strong protein bands but not expected size of tetramer (92 kDa) and its use is not reliable without further examination with another Ab against GPX3 as stabile dimers in placental tissue are optional explanation of lower MW. IHC must be further resolved through antigen retrieval as present staining and distribution of for example GPX1/2 is not prominent.

Conclusion: At the present we have reliable tools to investigate proposed relations between GPXs (GPX1/2 and GPX4), GSH and Se in GDM.

Keywords: Gestation diabetes mellitus (GDM), glutathione (GSH), glutathione peroxidases (GPXs), immunohistochemistry (IHC), inductively coupled plasma mass spectrometry (ICP-MS)



Suggested dissertation title: The correlation between specific education and the development of students' professional identity during their studies within nursing education system

PhD candidate: Ivana Gusar, Department of Health Studies, University of Zadar

Mentor1: Assist.Prof. Robert Lovrić, PhD, MSN, RN, Faculty of Dental Medicine and Health, Osijek

Mentor 2: Assist.Prof. Andrea Tokić, Department of Psychology, University of Zadar

Introduction: Professional identity (PI) implies knowledge, skills, attitudes, values and beliefs that we share with the members of a particular group of people and that, at the same time, distinguish us from other groups. PI develops not only throughout work, but also during education and the preparation of students for future work. The professional identification of nurses begins at the early stage of professional education and it is a precondition for quality health care. By researching the available relevant literature, a lack of a reliable instrument in the Croatian language for the assessment of the PI level of nursing students and nurses has been noticed.

Hypotesis: Specific education correlates with the development of students' PI during their studies.

Aims: The main objective is to gain an insight into the contribution of specific education to the development of the PI within the same generation of students during their studies.

The following matters are to be measured:

- the reliability and validity of the PI level assessment questionnaire
- the PI level of the test group and the control group of students during their studies
- the differences in the levels of the PI between the test group and the control group of students in the beginning, throughout and in the end of their studies
- the correlation between specific education and the PI level of students in the test group during their studies

Materials/participants and methods: For the purpose of the questionnaire validation, the following instruments will be used: Nurses Professional Identity Tools (NPIT), Professional Identity Five-Factor Scale (PIFFS) and Identity. The questionnaires

will be given to first, second and third year students of the undergraduate nursing studies in Zadar, Osijek, Rijeka, Split and Dubrovnik. The three-year research will include one generation of nursing students in Zadar (test group) and Osijek (control group).

Research plan: This research will be conducted longitudinally in the duration of three years:

- Phase 0: psychometric analysis of three standardized questionnaires for the PI level assessment. Selection of the most reliable questionnaire for future application.
- Phase 1: (beginning of the studies) the first PI level assessment of the students in the test group and the control group.
- Phase 2: (beginning of the second year) repeated PI level assessment of the students in the test group and the control group. Implementation of specific education for the students in the test group.
- Phase 3: (end of studies) final PI level assessment of the students in the test group and the control group.

Expected scientific contribution: This research will provide a reliable instrument for the PI level assessment of nursing students in the Croatian language. The results of the research could point out the significant contribution of specific education to the development of the students' PI during their studies, as well as the possible need for the implementation of specific education programs in the undergraduate nursing education system.

Keywords: professional identity, students, nursing, education



Dissertation Proposal Title: Epidemiology of fractures in the elderly, early, middle and very old age

PhD candidate: Dijana Hnatešen, MSc, RN, University Hospital Center Osijek/Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Mentor: Prof. Roman Pavić, MD, PhD, University Hospital „Sisters of Mercy“, Traumatology Clinic, Zagreb/Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Introduction: Increasing the life age increases the frequency of fractures that is more common in older people. The incidence of geriatric trauma requiring hospitalization increases as a result of the increase in the number of elderly people in the total population. World changes in life expectancy and natality are likely to increase the number of elderly people in EU member states, thereby increasing the need to allocate funds for age-related diseases. Fractures caused by the action of the minimum force are a major public health problem around the world, and as the population grows by the number of older persons, it is likely that the number of fractures will increase accordingly. By prolonging life expectancy, they become more frequent, and research has shown that 30% of fractures in men and 66% in women can be classified as a fracture due to bone fragility. Hip fractures have become an international benchmark for osteoporosis because these are related to low bone mineral density. The fractures of the proximal part of the upper arm bone are the third most common type of fracture after the fracture of the hip and the distal part of the thumb bone in elders. As a common denominator, according to a survey in Finland, there is a decline in injuries occurring in older persons and in the number of total fractures, as opposed to traffic accidents that were the main cause of the fracture in the total number of fractures. In 2011, the population of the Republic of Croatia was averagely 41.7 years old (men - 39.9 years old and women - 43.4 years old), making it one of the oldest nations in Europe. There is an increase in the number of persons of very high ages, e.g. the share of the population aged 80 and over in 2011 was 3.9%, while in 1953 it was only 0.8%.

Hypotesis: The number and types of fractures in elders of earlier, middle and deep life age from 65 to 85 and more years occupy a significant proportion in the total number of fractures.

The number and types of fractures in elders of earlier, middle and deep life age from

65 to 85 and more years grows proportionally.

The number of fractures in the hip area in elders of earlier, middle and deep life age from 65 to 85 and more years grows proportionally.

The most common cause of fractures among persons older than 65 years is fall.

Aims: The aim is to examine the number and type of fractures in elders of earlier, middle and deep life age from 65 to 85 and more years divided into five age groups from 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years and 85 years of age and more over the total number of fractures.

Specific aims

- Examine the number and type of fractures regarding to gender and age
- Examine the number of patients with more than one fracture regarding to gender and age
- Examine the number and types of open fractures regarding to gender and age
- Examine the number and types of pathological fractures regarding to gender and age
- Examine the way and mechanism how the fracture occurred
- Examine the number of hospitalized patients treated operatively and conservatively regarding to gender and age
- Examine the length of hospitalization
- Examine the number of patients treated ambulatory
- Examine the total number of fractures

Materials/Participants and Methods: Respondents of research - elders of earlier, middle and deep life age from 65 to 85 and more years divided into five age groups from 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years and 85 years of age and more who were hospitalized and treated ambulatory at the Surgery Clinic, Department of Traumatology, KBC Osijek in period from 01.01.2013. until 31.12.2017. As a retrospective study tool I will use the available medical documentation of the Surgery Clinic, Department of Traumatology, KBC Osijek to prove the necessary research parameters about age, sex, type of fracture, number of patients with more than one fracture, number and type of open fractures, number and type of pathological fractures, mode and mechanism of injury, hospitalized patients treated conservatively and operationally, length of hospitalization, number of patients treated with ambulatory care and about the total number of fractures. The category variables will be described by absolute and relative frequencies. The differences between the category variables will be tested by χ^2 test and Fisher's exact test. In order to evaluate the importance of the obtained results, the level of significance of $\alpha = 0.05$ will be chosen.

Research plan: A retrospective study of ambulatory and hospitalized treated elders patients of earlier, middle and deep life age divided into different age groups, will be performed using available medical documentation. The data obtained will be statistically processed.

Expected scientific contribution: Highlight the number and types of fractures at elders of earlier, middle and deep life age from 65 to 85 and more years divided into five age groups from 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years and 85 years of age and more for the purpose of insight into significant health, social and economic issues, which have a tendency to increase with regard to the increase in life expectancy and accordingly the number of elderly patients for whom health care will be needed.

Key words: epidemiology of fractures, fractures in adults, osteoporotic fractures.



Dissertation Proposal Title: The effect of simvastatin and metformin on the regulation of adipogenesis in vitro

PhD candidate: Jelena Jakab, MD; Faculty of Dental Medicine and Health Osijek

Mentor: Professor Aleksandar Včev, MD, PhD; Faculty of Dental Medicine and Health Osijek; Faculty of Medicine Osijek

Mentor 2: Associate Professor Martina Smolić, M.D., Ph.D.; Faculty of Medicine Osijek; Faculty of Dental Medicine and Health Osijek

Introduction: Obesity is one of the major public health problems and presents a risk factor for chronic diseases such as type 2 diabetes and coronary heart disease. On the cellular level, obesity is characterized by adipocyte hyperplasia and hypertrophy. Adipogenesis begins as a physiological response to energy disbalance. Prevention of adipogenesis may be one of the approaches to obesity treatment. The first phase of adipogenesis involves the accumulation of C/EBP- β and c/EBP- δ during the first 24 hours, which directly promotes expression of PPAR- γ and C/EBP- α , key transcriptional differentiation factors. Statins inhibit differentiation in adipocytes through reduced expression of genes specific to lipocytes such as PPAR- γ and aP2. Previous studies have shown that the presence of metformin improves this effect of statin.

Hypothesis: The use of small doses of simvastatin and metformin leads to inhibition of adipogenesis transcription factors in vitro.

Aims: The aim of this study is to establish a model of adipogenesis in vitro and to evaluate the effect of different doses and time periods of simvastatin and metformin therapy on the expression of the main modulators and transcription factors in the adipogenesis process.

Materials and Methods: Murine 3T3-L1 cells (Sigma Aldrich, Missouri, USA) is a cell line of preadipocytes that can adopt a rounded adipocyte phenotype and accumulate lipid droplets of triacylglycerols after appropriate stimulus. A combination of dexamethasone (DEX) (Sigma Aldrich, Missouri, USA), isobutylmethylxanthine (IBMX) (Sigma Aldrich, Missouri, USA) and insulin (Sigma Aldrich, Missouri, USA) will be used for the induction of adipogenesis. Simvastatin (Sigma Aldrich, Missouri, USA) and metformin (Sigma Aldrich, Missouri, USA) will be used to reduce adipocyte

differentiation. Adipogenesis will be visualised by the Oil Red O staining. The expression and activity of transcriptional factor will be determined by PCR Array Human Adipogenesis (Qiagen, Hilden, Germany) and Chemiluminescent Substrate Reagent Kit (Invitrogen, California, USA), respectively. Proteins will be detected using primary antibodies against target proteins and Goat Anti-Rabbit IgG secondary antibody (Abcam, Cambridge, UK).

Research plan: Murine 3T3-L1 preadipocytes will be grown in 10% CS/FBS-DMEM with 1% antibiotic solution (penicillin/streptomycin) at 37C and 5% CO₂. After full confluence, cell differentiation will be induced by adding 0.5 mM IBMX, 0.25 µM DEX and 1 µg/ml insulin to DMEM with 10% FBS. Cell differentiation will be visualized by the Oil Red O which accumulates in intracellular lipid droplets, visible by a light microscope. Cell culture medium will be supplemented with different concentrations of simvastatin and metformin as monotherapy or concomitant therapy to examine their effect on adipocyte differentiation and to find the most effective drug concentration. 3T3-L1 adipocytes of all differently treated groups will be lysed after 3, 5, and 7 days of treatment for the analysis of PPAR γ , C/EBP α and SREBP transcription factor and STAT3 and TGF β /Smad3 signaling cascades by RT-PCR to find a time period in which the effect of drugs is the highest. Adipogenesis in all differently treated groups will be visualized by the Oil Red O staining, and the expression of transcriptional factors will be determined by RT-PCR and their activity confirmed by immunocytochemical or Western blot method.

Expected scientific contribution: The results of this study will contribute to the understanding of the effect of simvastatin and metformin on the adipogenesis process in vitro and to determine the dosage and time period of their most effective anti-adipogenic activity in 3T3-L1 preadipocytes. Regulation of the expression of main adipogenesis modulators and targeted cascade signaling genes could be an attractive target for obesity treatment and lead to the development of new therapeutic paradigms.

Keywords: Obesity, Adipogenesis, Simvastatin, Metformin, Transcriptional factors



Dissertation Proposal Title: Rumination and impairment of cognitive control in internalizing and externalizing mental disorders in adolescents.

PhD candidate: Sanja Jandrić, Clinical Hospital Center Osijek, Unit for Child and Adolescent psychiatry

Mentor: Professor Pavo Filaković, M. D., Ph.D., Faculty of Dental Medicine and Health, University of J.J.Strossmayer Osijek

Introduction: Adolescence marks the transition from childhood to adulthood. Physical changes occurs first and happens much faster than in any other developmental period. These changes are associated with hormonal changes during puberty and the appearance of adult sexuality. The process of psychological maturation during puberty affects shifting from dependence on parents to increased involvement with peers and others. Also it affects taking responsibility for making decisions about two important aspects of adult age, work and love. This transition is accompanied by more important roles of peer group and newly discovered cognitive ability that allows adolescents to think about future events and develop their own identity.

Our cognitive skills are integrated into a higher level of executive system. Executive functions direct and regulate cognitive functions. They select and successfully monitor behaviors that facilitate the attainment of chosen goals. Executive functions include basic cognitive processes such as attention control, cognitive inhibition, working memory, cognitive flexibility and cognitive control. In recent years there are more researches of executive functions, both in children with normal development and children with deviations in the development. Results has shown that changes in executive functions can be associated with maturation and as well with damages in the central nervous system.

Cognitive control is the process that allows information processing and behavior to vary adaptively from moment to moment depending on current goals, rather than remaining rigid and inflexible. Cognitive control processes include a broad class of mental operations including goal or context representation and maintenance, and strategic processes such as attention allocation and stimulus-response mapping. Cognitive control is associated with a wide range of processes and is not restricted to a particular cognitive domain. The presence of impairments in cognitive control functions may be associated with specific deficits in attention, memory, language comprehension and emotional processing. Also, it can be manifested through the

impaired planning, execution or monitoring of cognitive tasks and the performance of particular phases involved in a particular activity. Furthermore, the damage may include selfcare deficit and disturbed social relationships. Personality changes, such as impaired self-control and self-directedness, emotional lability, impulsiveness, disinhibition, irritability, specific thinking and difficulty in moving attention, are also common. Also, it is possible that person physically neglect or may have a lack of motivation and energy.

Within the Response Styles Theory (Nolen-Hoeksema) rumination is defined as a stress reaction that involves repeated and passive focusing on the symptoms of stress, the causes of the symptoms, their significance and consequences. When people ruminate they focus on negative effects of problems which prevents them from active problem solving. In other words, rumination foster negative thinking and behavior that are associated with negative feelings.

In the last three decades, the traditional view of mental illness as distinct categories of disorder is experiencing numerous changes. It has been shown that many disorders occur in comorbidity and exist on continuum in different dimensions. A large number of studies have confirmed that certain mental disorders in adulthood share a certain percentage of common factors and that they exist on two dimensional continuum: on an externalized dimension, transferring the risk to disinhibited, antisocial disorders and behavioral disorders caused by psychoactive substances use; on an internalized dimension, transferring the risk of mood disorders and anxiety disorders. Furthermore, these findings of the two-dimensional model of psychopathology have been confirmed in recent researches of child and adolescents psychopathology, suggesting the structure stability function during the development.

Recent researches of comorbidity of mental illness are focused on the identification of neurocognitive processes and deficits that can affect appearance and formation of mental disorders. So far little attention has been given to processes of rational-emotional control, such as the process of rumination. Although rumination in most studies is related to depression, several studies have confirmed a connection between ruminations and other forms of psychopathology, such as anxiety, eating disorders, and psychoactive substance abuse. Likewise, some researches has shown that rumination is associated with abnormalities in the functioning of neural circuits associated with emotional regulation and executive functions, particularly cognitive control.

Previous researches has examined rumination and cognitive control in adult population, while only few studies have examine it with youth. A small number of empirical studies lighted the influence of rumination and poor cognitive control on the development of internalizing mental disorders in adolescents, while there is no data of the influence on the development of externalizing psychopathology in adolescents. Considering the limited number of findings, especially in clinical

adolescent samples, further researches is needed. Consequently, with the principle that rumination and cognitive control show a stable structure of development in time, this research has a significant scientific contribution. The obtained results can provide valuable information for creating the goals of therapeutic interventions.

Hypothesis: There is a correlation between high levels of rumination and low cognitive control with internalizing and externalizing mental disorders in adolescents where the rumination is a mediator between poor cognitive control and psychopathological symptoms in both groups.

Aims:

Main aim

Determine the relationship between rumination and impairment of cognitive control in internalizing and externalizing mental disorders in adolescents.

Secondary aims

1. Determine rumination and cognitive control in a group of adolescents with internalizing mental disorders.
2. Determine rumination and cognitive control in a group of adolescents with externalizing mental disorders.
3. Investigate the association between rumination and cognitive control with symptoms of anxiety and depression in a group of adolescents with internalizing mental disorders.
4. Investigate the association between rumination and cognitive control with symptoms of aggression in a group of adolescents with externalizing mental disorders.

Materials/Participants and Methods:

Participants:

The participants will come from the region of Eastern Croatia, indicated for the psychological testing after the first psychiatric examination at the Unit for Child and Adolescent psychiatry at the Clinical Hospital Center Osijek. The participants will be divided into two groups, experimental and control group. An experimental group is consisting of adolescents with externalizing mental disorders (eg, F90 Hyperkinetic disorders and F91 Conduct disorders). The control group is consisting of internalizing mental disorders (eg. F92 Mixed disorders of conduct and emotions, F93 Emotional disorders with onset specific to childhood and F98 Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence). The study will involve a minimum of 200 participants, 100 per each group. Prior to the beginning of the research, each potential participant will be given oral and written explanation to the purpose of the research and the manner of its implementation. Then they will be

asked for written consent to participate in the research, which will sign adolescents, as well as one of the parents.

Methods:

The subjects will be psychologically tested within the routine psychodiagnostic assessment indicated by the psychiatrist for child and adolescent psychiatry in the order referred to psychologist during the period from October 2018 to March 2019.

The following psychodiagnostic procedures will be used:

1. The participants will complete the Croatian version of the Youth Self-Report (YSR) which consists of 113 items leading to the following primary subscales: social withdrawal, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent behaviour, and aggressive behaviour. Two second-order scales reflecting internalizing and externalizing and a total problem score can be calculated. The time frame of symptoms includes the past 6 months. Reliability and validity have been shown to be good both for the original version and the Croatian version of the YSR.
2. The participants will complete selected tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, Cambridge, United Kingdom), an Intra-Extra Dimensional Set Shift. The Intra-Extra Dimensional Set Shift test (IED) is a computerized analogue of the Wisconsin Card Sorting Test and will be used to examine general cognitive control. The dimensions include color- filled shapes and white lines, with simple stimuli including only one of these dimensions and complex stimuli including both. Participants will be presented with two color-filled shapes and must indicate the correct response by touching it on the screen. The correct response is learned through feedback, and after six correct responses, the rule and/or stimuli change. Shifts are intra-dimensional first (i.e., only color-filled shapes) and then switch to extra-dimensional (ED, i.e., white lines).
3. The participants will complete the Croatian version of The Children's Response Styles Questionnaire (CRSQ; Abela, Brozina, & Haigh, 2002) which is a 25-item scale that assess the extent to which children respond to sad feelings with rumination (defined as self-focused thought concerning the causes and consequences of depressed mood), distraction, or problem solving. The measure is modeled after the Response Styles Questionnaire (Nolen-Hoeksema & Morrow, 1991) that was developed for adults. For each item, youths are asked to rate how often they respond in a particular way when they feel sad on a 4-point Likert scale ranging from almost never (1) to almost always (4). Sample items include, "Think about a recent situation wishing it had gone better" and "Think 'Why can't I handle things better?'"
4. The participants will complete the Croatian version of The Beck Depression Inventory, which is a 21 question multiple choice self report inventory, one of the

most widely used psychometric test for measuring the severity of depression. Its development marked a shift among mental health professionals. It is designed for individuals ages 13 and over, and is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Scale contains 21 questions, each answer being scored on a scale value of 0 (not at all) to 3 (severely). Higher total scores indicate more severe depressive symptoms.

5. The participants will complete the Croatian version of The Beck Anxiety Inventory which is a 21 question multiple choice self report inventory that is used for measuring the severity of anxiety in children and adults. The questions used in this measure ask about common symptoms of anxiety that the subject has had during the past week (including the day you take it) (such as numbness and tingling, sweating not due to heat, and fear of the worst happening). It takes 5 to 10 minutes to complete. Scale contains 21 questions, each answer being scored on a scale value of 0 (not at all) to 3 (severely). Higher total scores indicate more severe anxiety symptoms.
6. The participants will complete Aggressive Scale (SNOP) (Vulić-Prtorić, 2008) which consists of 40 questions: 9 for the subscale of Oppositional defiant disorder, 15 for the subscale of Conduct, 9 for the subscale of the Victim and 7 for the Subscale Tormentor. Respondents record their responses to the 5-degree Lykert scale by estimating how much behavior described in the claims often occurred in the last 6 months: (1 = never, 2 = rarely, 3 = sometimes, 4 = frequently, 5 = very often. Coefficients of internal consistency (Cronbach alpha coefficients) were determined on a normative sample of children and adolescents and for the entire SNOP scale were 0.93 and for the subscales ranged from 0.81 to 0.88.

Statistical Methods:

Statistical data analysis will be calculated using the program package SPSS 21. for Windows. In the case of categorical variables, measurements of nonparametric statistics (frequencies, percentages, media, mod) will be used for the description of the sample, and in other cases, parametric statistics will be used (arithmetic mean, variance, standard deviation, standard error of arithmetic mean).

The normal distribution of the numerical variables will be tested by the Kolmogorov-Smirnov test. Categorical variables will be described in absolute and relative frequencies.

To investigate differences in rumination and cognitive control in both groups of adolescents it will be used t test for independent samples (in the case of normal distribution) or Mann-Whitney test. For comparison of more than two independent groups, it will be used the ANOVA or Kruskal Wallis test, depending on the normality of the distribution.

The differences between the category variables will be tested by chi-square (χ^2) test. The associations between variables will be checked by the Pearson correlation coefficient or Spearman's correlation coefficient.

In order to evaluate the significance of the obtained results, it was chosen the level of significance of $p < 0.05$.

Research plan:

Conducting research:

The study is planned as a cross-sectional study.

The inclusion criteria are:

- A) Adolescents between the ages of 12 and 18, both gender
- B) Adolescents indicated for the psychological testing after the first psychiatric examination under dg.:

- a) F90 Hyperkinetic disorders and F91 Conduct disorders

- b) F92 Mixed disorders of conduct and emotions, F93 Emotional disorders with onset specific to childhood and F98 Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

The exclusion criteria are:

- A) Adolescents whose IQ, diagnosed through psychological testing, is lower than 70
- B) Adolescents having a adolescent crisis with psychotic symptoms
- C) Adolescents and parents who refuse to sign informed consent for participation in the study.

Significance/Expected scientific contribution: The scientific contribution of this research will illuminate the role of rumination and impairment of cognitive control in the formation of a clinical picture of mental disorders in adolescents and their figuration in an internalizing or externalizing form. Namely, there is still a small number of researches that investigate rumination and executive functions in adolescents in general, especially in those with internalizing psychopathology, and in adolescents with externalizing psychopathology such data on a clinical sample almost do not exist. The research will also make contributions to improving the dimension aspects of classifying the examined mental disorders, within the existing categorical ICD and DSM classification systems for mental disorders, which already accept dimension qualifiers to a degree that does not change the affiliation of the category disorder.

Keywords: (5) Internalizing, externalizing, rumination, cognitive control, adolescents



Dissertation Proposal Title: The ability of community health nursing interventions on response improvement to the colon cancer screening

PhD candidate: Sanja Kanisek, MSN, RN, Health Center Osijek

Mentor: Prof. Rudika Gmajnić, MD, PhD, Health Center Osijek

Introduction: Results of the first cycle of the National program for early detection of colon cancer (CC) showed that responses to screening at the national level were 21%, and in Osijek-Baranja County (OBC) 20.3%, which is significantly less than acceptable (45%) and desirable response (60%). The population is made up of individuals of different ages, cultures, values and levels of education, which can aggravate their understanding of the information provided and influence motivation for participating in the screening so that the written information should be supplemented with verbal interventions. The activities of community health nursing in the team of the National preventive program for early detection of CC are home visits to motivate participation by distributing tests.

Hypothesis: By interdisciplinary approach, The national program of early detection of CC in the Republic of Croatia can be significantly improved in a way that the responsiveness of invited citizens is significantly higher than it is to date, ie that it is brought closer to European standards. The response can be increased by coordinating the activities of the Institute of Public Health (IPH), family medicine teams, community health nursing and the interested population. In the process of increasing the response, the community health nursing can play a significant role as it contacts the invited citizens as part of their everyday tasks.

Aims: The main goal is to examine the possibilities of intervention by community health nursing to improve the response of the population who did not respond to the written call to the national preventive screening of CC. The specific aim is to examine the possibility of intervention by community health nursing to improve the response of the population in urban and rural environments.

Materials/Participants and Methods: The intervention group will consist of 250-300 persons from five family medicine practices in urban and rural areas willing to participate in research, who were called for screening but failed to respond in

the period of 2 months (random selection of two birth years in the call cycle). A questionnaire designed for the National program for early detection of CC will be used as a research tool. The question of why a person has not responded to the screening so far, would be added for the purposes of this research. The effectiveness of conducted community health nursing interventions will be evaluated by comparing the data extracted from the computer program of the community health nursing (test group - home visit with delivery test) from IPH database of persons from the examined and control group who sent the test, 2 months after the intervention.

Research plan: Data on patients who did not respond to a written call within the national National program for early detection of CC and who are patients in the selected family medicine teams, will be extracted from IPH database. Based on the submitted patient information, community health nurses will plan their home visits along with the preparation of the required materials (through a cooperation with the IPH bring a letter of invitation and test material in a home visit). During a home visit, a community health nurse will indicate the importance of the need for testing to the target person and their family and try to motivate the person to participate (get the consent through the signing of the invitation letter), interview the person using the questionnaire in the attachment of the invitation letter, educate them about filling out the test card and deliver the necessary materials. Community health nurses will record their visits in their computer program and the signed letter of invitation will be forwarded once a week to the IPH of OBC.

Expected scientific contribution: The results would point the ability of community health nursing interventions on response improvement to the CC screening, the need to implement these interventions at the OBC level as well as the importance of IT connectivity of community health nursing, IPH and family medicine practices with the purpose of improving the organization of the implementation of the National preventive program for early detection of CC. Through the establishment of a special team at the IPH, with the aim of coordinating activities of community health nursing, general practitioner and the IPH, with a highly educated nurse being a carrier, it would be possible to extend and intensify activities of the community health nursing. This team could also encourage and advocate various civil society associations in implementing activities aimed at motivating the population to participate in early detection of CC

Key words: colon cancer, screening, community health nursing



Disertation proposal title: Effects of PRGF on soft tissue and bone healing

PhD candidate: Matej Karl, D.M.D.

PhD Student Advisor: Assit. Prof. Marko Matijević, D.M.D., PhD., Faculty of Dental Medicine and Health

Introduction: Plasma rich with growth factors (PRGF) has a high therapeutical potential in various clinical cases in field of oral surgery. Due to its biocompatibility, safety and variety of apply this method can be used for socket preservation after tooth extraction, guided bone regeneration, soft tissue healing after mucogingival surgery and maxillary sinus augmentation following sinus lifting surgery. Due to high concentration of growth factors in PRGF, rate of wound healing could increase multiple times. PRGF helps easier integration of transplanted material, wound maturing and epitelization. That makes operational wounds less painfull, swelling is decreased and scar formation is less probable in comparison to healing process without PRGF.

Hypothesis: Use of PRGF in oral surgery can facilitate healing proces through faster soft tissue and bone regeneration resulting in shorter postoperative period with less pain and swelling.

Aims:

1. Assesment of soft tissue healing with and without using PRGF
2. Assesment of bone healing with and without using PRGF
3. Determine clinical value of PRGF usage in tissue defects after third molar extraction

Materials/Participants and methods: Materials to be used include alloplastic materials, kits for the preparation of plasma membranes, nonresorptive membranes, laboratory consumable materials and other excipients required to achieve research goals.

Targeted number of participants is 60 patients. Inclusive criteria will be presence of both third lower molars, indication for third lower molar extraction, completed skeletal growth and development. Exclusive criteria will be significantly different position of molars and systemic diseases.

Research plan: Patients with indication for the extraction of both mandibular wisdom teeth will undergo surgery after which tissue defect will be filled with PRGF clot and covered with nonresorptive membrane. After two weeks, the same patients will undergo extraction of wisdom teeth on the contralateral side of the mandibula. The second defect will be augmented with autologus bone material and also covered with nonresorptive membrane. After six months, a nonresorptive membrane will be removed and a bone sample will be taken which will be histologically and immunohistochemically analysed. One month, three months and six months after surgery radiovisiographical methods will be used to asses bone density.

Significance/Expected scientific contribution: In case the hypothesis is confirmed, use of PRGF would have beneficial effects in terms of bleeding control, faster healing, reduction of postoperative complications and increased quality of life in patients with higher risk of complications. and compromised patients after oral surgery.

Keywords: plasma rich wtih growth factors, oral surgery, regeneration, bone healing, imunohistochemistry



Dissertation Proposal Title: Predictors of Poor Outcome and Complications After Surgical Treatment of Hip Fractures in Elderly Population in Croatia

PhD candidate: Tomislav Kokić, MD; Josip Juraj Strossmayer University of Osijek Faculty of Medicine; County General Hospital Vinkovci

Mentor: Professor Roman Pavić, MD, PhD; Josip Juraj Strossmayer University of Osijek Faculty of Medicine; Department of Traumatology, Sestre Milosrdnice University Hospital Center, Zagreb

Introduction: There is a global increase in percentage of elderly population (>65 years old). Hip fracture is very common in this population, it is associated with a high morbidity and mortality, impaired mobility, and poor performance of activities of daily living (ADL) afterwards. Knowledge obtained by this study could improve treatment of these patients, thus giving them better chance of full recovery and reducing health care costs. Also, regarding degree of impairment and related long-term health care cost, it is important to understand why some of the patients survive, but have impairment.

Hypothesis: Main hypothesis is there are specific predictors of poor outcome and complications after surgical treatment of hip fractures in elderly population.

Aims: Our primary aim is to identify poor outcome predictors after surgical treatment of hip fractures in elderly population in Croatia.

Secondary aim is to assess functional and cognitive status of the patients before and after surgical treatment of hip fracture.

Materials/Participants and Methods: Prospective observational longitudinal study including elderly first-time hip fracture patients, surgically treated in County General Hospital Vinkovci. Inclusion criteria will be: age >65 years, X-ray confirmed hip fracture, first-time hip fracture, surgical treatment. Exclusion criteria will be: previous hip fracture(s), periprosthetic fracture(s), other fractures at time of admission, pathologic fracture (metastatic cancer), inability to walk previous to fracture, cognitive impairment compromising communication. Expected sample size is 150.

Statistical analysis will be applied to compare patients' pre- and postoperative variables and outcomes.

Research plan: Enrollment in the study will be on admission to hospital, after giving informed consent. Follow-up time will be 9 months. On enrollment medical history will be noted, as well as cognitive status (Mini-Cog questionnaire), level of physical activity before fracture (IPAQ questionnaire), social situation (living at home or long-term care facility), ADL (Rapid Disability Rating Scale version 2, Barthel Index of Activities of Daily Living), quality of life (Short Form 36), and baseline laboratory values (haemoglobin, urea, creatinine).

Perioperative variables will be noted (type of fracture, timing and type of treatment, postoperative complications, postoperative laboratory values, rehabilitation, length of hospital stay).

On 3rd and 9th month follow-up we will again assess level of physical activity, ADL, and quality of life, as well as measure outcome of hip fracture treatment (Harris Hip Score).

Significance/Expected scientific contribution: To the best of our knowledge, this is the first study of this kind on elderly population in Croatia. The results should further increase our knowledge regarding poor outcome and complications predictors on domestic population, thereby allowing for proper preventive and curative measures to be taken thus improving the outcome of surgical treatment.

Keywords: hip fracture, proximal femur fracture, outcomes, complications, recovery



Dissertation proposal title: Correlation of breast arterial calcification on mammography with peripheral arterial disease grading by color doppler imaging in female patients on chronic hemodialysis in relation with mineral and bone disorder.

PhD candidate: Zdravka Krivdić, MD, Radiologist, Department of Radiology, University Hospital Centre Osijek, Osijek, Croatia

Mentor: Assoc. Prof. Lada Zibar, MD, PhD, Internist - Nephrologist, Department of Nephrology, Internal Clinic, University Hospital Centre Osijek; Department for Pathophysiology, Faculty of Medicine, University J. J. Strossmayer Osijek, Osijek, Croatia

Introduction: Female patients on chronic hemodialysis (CHD) have frequent mineral and bone disorder (MBD). MBD is an additional risk for cardiovascular disease in these patients. Peripheral arterial disease (PAD) is a manifestation of vascular disease. Breast arterial calcification (BAC) is relatively negligible on mammography finding and often not described, although there is an evidence of correlation with other circulatory diseases. Extraosseous calcifications, including BAC and particularly arterial media calcifications, are accompanying MBD on CHD. It would be established whether BAC verified on mammography were prevalent in that population of patients, did they correlate with PAD degree determined by color doppler imaging (CDI) of the lower extremity arteries (LEA), and whether BAC correlated with degree of MBD.

Hypothesis: Female patients on CHD with pronounced MBD have more frequent and more extensive BAC and BAC correlate with PAD degree determined by CDI of LEA.

Research plan and aims: In female patients on CHD:

- To determine the features of MBD (serum concentrations of parathyroid hormone, calcium and phosphate; treatment for hyperparathyroidism and complications).
- To examine the association of MBD with frequency and extent of BAC on mammography imaging.
- To examine the correlation of BAC on mammography imaging with degree of PAD by CDI of the LEA.
- To examine the association of MBD with degree of PAD by CDI of the LEA.
- To investigate the correlation of BAC on mammography imaging with degree of PAD by CDI of the LEA in relation with MBD.

Patients and Methods: The study will include around 100 female patients aged 50 - 70 years in the Region of Eastern Slavonia and Baranja. Breast imaging will be performed by mammography to detect BAC, and CDI of the LEA for arterial lesions. Medical data of MBD will be collected from patients' medical records.

Expected scientific contribution: To prove whether neglected diagnostic method and neglected significance of BAC on mammography imaging indicate the degree of PAD by CDI of the LEA in female patients on CHD, in relation with MBD, and could it contribute to a faster diagnostic and therapeutic procedure.

Keywords: Chronic hemodialysis (CHD); Breast arterial calcification (BAC); Peripheral arterial disease (PAD); Mineral and bone disorder (MBD); Color doppler imaging (CDI)



Dissertation proposal title: The activity of garlic and ginger extracts to the epithelial damage caused by sodium taurocholate in a cell culture model of ulcer disease

PhD candidate: Lucija Kuna, MSc, Faculty of Dental Medicine and Health, Osijek, Croatia

Mentor: Professor Aleksandar Včev, MD, PhD, Faculty of Dental Medicine and Health and Faculty of Medicine Osijek, Osijek, Croatia

Introduction: Peptic ulcer is the most frequent gastrointestinal disorder affecting 10% of the world population. It is estimated that 15000 deaths occur each year as a consequence of peptic ulcer. Pharmacotherapy of ulcer disease includes several groups of drugs, but proton pump inhibitors (PPI) and suppression of *Helicobacter pylori* infection represent the gold standard. Although conventional regimens are effective, side effects can limit their clinical utility. On the other hand, studies have demonstrated that herbal medicines exhibit therapeutic benefit for gastric ulcer with fewer side effects. In concrete, garlic (*Allium sativum*) extract has been reported to show antioxidant effect by scavenging reactive oxygen species (ROS), and the active phenolic compound of ginger (*Zingiber officinale*), gingerol plays a major role in inhibiting parietal cell H⁺/K⁺-ATPase. Although, their effect in gastroprotection of gastric ulceration has been demonstrated, the study of the effect and mechanism of garlic and ginger in the cell model of ulcer disease are not fully elucidated.

Hypothesis: The use of garlic and ginger extracts has a gastroprotective effect in a cell culture model of ulcer disease.

Aims: The aim of this project is to establish a cell culture model of ulcer disease and to measure the toxic effect of sodium taurocholate (NaT). Further aim is to measure the gastroprotective effect of different concentrations of ginger and garlic extracts in the cell culture model of ulcer disease exposed to NaT in different time periods, and determine molecular mechanism by which ginger and garlic extracts achieve gastroprotective effect.

Materials and Methods: Human gastric cell line (AGS) will be used to develop the ulcer disease model in vitro. The extent of cytotoxicity and apoptosis will be evaluated by MTT assay and determination of effect and mechanisms of action of antioxidants

in ulcer disease will be evaluated by prostaglandin (PGE₂) immunoassay (Cayman Chemical, Ann Arbor, MI, USA) and human reduced glutathione (GSH) colorimetric assay (Thermo Fisher Scientific, Waltham, MA, USA) as well as by RT Profiler PCR Array Human Oxidative Stress Plus (Qiagen, Hilden, Germany).

Research plan: To establish a cell culture of ulcer disease, AGS cells will be incubated in different time period with increasing concentrations of NaT. After incubation with NaT the extent of apoptosis will be evaluated by MTT assay. Further, cells will be treated with different concentrations of ginger and garlic extracts as pretreatment and cotreatment with NaT. The extent of apoptosis will be evaluated by MTT, and expressed as a percentage of untreated cells. Determination of mechanisms of ginger and garlic extracts in gastroprotective effect of ulcer disease will be evaluated by PGE₂ immunoassay, GSH colorimetric assay, and RT Profiler PCR Array Human Oxidative Stress Plus.

Expected scientific contribution: A cell culture model of ulcer disease will be established as a useful tool for assessing the efficacy and mechanism of action of potential pharmacotherapy options. The molecular mechanisms of garlic and ginger modeling systems will be elucidated, as well the cell culture model will be established as a useful tool for assessing the efficacy and mechanism of effect of ulcer pharmacotherapy.

Keywords: gastric ulcer, sodium taurocholate, antioxidant, ginger, garlic, AGS cell line



Dissertation proposal title: Correlation between UGT1A1 genotype and the appearance of early hyperbilirubinemia in neonates – A prospective cohort study

PhD candidate: Ivana Lenz, Department of Pediatrics, University Hospital Center Osijek, Croatia

Mentor: Assist. Prof. Silvija Pušeljić, MD, PhD, Department of Pediatrics, University Hospital Center Osijek

Introduction: A polymorphism in the promoter region of the UGT1A1 gene has been identified in the majority of individuals with Gilbert's syndrome (GS). GS is a chronic, non hemolytic unconjugated hyperbilirubinemia caused by a reduction in the activity of uridine diphosphate glucuronosyltransferase (UGT). It has been proven that 6-12% of the population has GS, and it is the most common inherited disorder of hepatic bilirubin metabolism. Over the thirty years it has been hypothesized that GS could play a role in determining increased levels of bilirubin during neonatal age. Also, the cause of early hyperbilirubinemia cannot be found in about 45% of cases, so the differential diagnosis for hyperbilirubinemia can be vast.

Hypothesis: Correlation between children who have UGT1A1 ((TA)₇TAA) genotype with incidence of early hyperbilirubinemia.

Primary aim: Incidence of UGT1A1 ((TA)₇TAA) genotype.

Specific aims: To separate children with hyperbilirubinemia and to determine the etiology of hyperbilirubinemia with other factors (Pre - eclampsia, way of completing the birth, ABO incompatibility, Rh isoimmunization, prematurity, early sepsis, breastfeeding).

Participants and Methods: The study will be conducted at the Maternity ward and in the Neonatal Intensive Care Unit in the Department of Pediatrics, Clinical Hospital Center, Osijek. It will include premature and full term newborns born between February 2019 and May 2019. Only infants whose mothers sign informed consent will be included in the study. Data that will be collected include: samples for gene analysis for every born child in this three month period with measurements of bilirubin levels on a daily basis and with standard sociodemographic data. In babies with

hyperbilirubinemia (visible jaundice or total serum bilirubin level 7 mg/dL during the first 24 hours of life and total serum bilirubin concentration increasing by more than 5 mg/dL/d) other tests and data will be included, such as complete blood count; C – reactive protein; aminotransferases; mother’s blood type; obstetric risk factors; perinatal complications; breastfeeding or formula after birth; microbiological samples (streptococcus in mother’s cervix, and hemoculture in babies).

Research plan: In every newborn baby blood samples for genetic analysis will be taken. In those newborn babies with hyperbilirubinemia during hospitalization standard clinical protocol for hyperbilirubinemia will be performed. Every baby who returns to hospital within first month period with hyperbilirubinemia, samples for genetic analysis will be taken.

Expected scientific contribution: The results of the study will help to ease the causes of hyperbilirubinemia, and make it easier to treat.

Keywords: Early hyperbilirubinemia, Gilbert’s syndrome (GS), UGT1A1 genotype.



Dissertation proposal title: Association of childhood trauma and personality traits with the duration of untreated psychosis in early-course psychosis

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Mentor: Assist. Prof. Branka Restek-Petrović, M.D., Ph.D., Psychiatric Hospital „Sveti Ivan“, Zagreb, Croatia; Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Introduction: Psychosis describes a syndrome involving mainly positive symptoms which are often accompanied by negative symptoms or mood disturbances. It has been suggested that there is a critical period of 5 years from onset of psychotic disorder during which appropriate interventions can influence long-term outcomes. Duration of untreated psychosis (DUP), or the time between onset of psychosis and treatment initiation, is a prognostic factor of schizophrenia. DUP varies, on average, between 1 and 2 years. Childhood trauma is strongly linked to an increased risk of developing a psychotic disorder. Recent study indicated a history of childhood trauma as a potentially underlying factor behind an increased DUP and a poorer premorbid function, and eventually a more severe chronic illness. Previous studies suggest that specific personality traits influence DUP.

Hypothesis: Childhood trauma and personality traits in patients in early-course psychosis (less than 5 years duration of illness) are associated with longer duration of untreated psychosis.

Aims:

Main aim:

To investigate the association between childhood trauma and personality traits with the duration of untreated psychosis.

Secondary aims:

1. To investigate the association between childhood trauma and the duration of untreated psychosis
2. To investigate the association between childhood trauma and personality traits
3. To investigate the association between specific personality traits and the duration of untreated psychosis

4. To investigate the association between childhood trauma and personality traits with psychotic symptoms
5. To determine the prevalence of childhood trauma in total sample

Participants and Methods: Targeted population will be patients in early-course psychosis (less than 5 years duration of illness) who are hospitalized in Psychiatric Hospital "Sveti Ivan". The research will encompass diagnoses of psychotic disorders (codes F20 to F29 according to ICD-10) made by psychiatrists. A consecutive sample of 105 patients from targeted population will be selected according to the start date of the current hospitalization.

Research plan: After explaining the purpose and objectives of the study and obtaining signed informed consent, all participants will be subjected to a clinical interview and will answer the questions from self-report questionnaires and measurement scales. In the clinical interview, the researcher will focus on exact determination of the duration of untreated psychosis. The measurements will be conducted after the initial stabilization of mental state, meaning after transferring the patient from acute to psychotherapeutic ward.

Significance/Expected scientific contribution: In case of confirming our hypothesis, the scientific contribution of this research will be better understanding the mechanism of psychotic disorders and the interdependence of factors affecting the length of duration of untreated psychosis. Focusing therapeutic interventions on childhood trauma could lead to better outcomes in treating that segment of the population of patients with psychotic disorders.

Keywords: childhood trauma, personality traits, duration of untreated psychosis, early-course psychosis



Disertation proposal title: Connection of health literacy with manifestation of obesity, arterial hypertension and diabetes mellitus type 2.

PhD candidate: Božica Lovrić, General County Hospital Požega

Mentor: Assoc. Prof. Lada Zibar, M.D., Ph.D., University Hospital Centre Osijek, Faculty of Medicine Osijek

Introduction: Health literacy attracts more and more attention because low health literacy is considered an important predictor of harmful health outcomes in many chronic diseases. Obesity is one of greater health problems nowadays, which has assimilated global epidemic proportions. According to World Health Organization data, 1.5 billion people are overweight, out of which more than 500 million people are considered obese, whereas a growth of prevalence is predicted in the years to come. Neither Croatia gets behind this data. Around 25,3% men and 34,1% women in Croatia are considered to be obese. Arterial hypertension is around 6 times more common with obese people than when it comes to normally weighted people. More than 220 million people in the world is affected by diabetes mellitus type 2, whereas obesity is one of risky factors for the development of this disease. This type is the most common form of diabetes. Around 90% of all patients has it. For the people with chronic disease, adequate level of health literacy is crucial for getting and understanding health information and services necessary for conducting and deciding about own health. Level of literacy can have a crucial role in communication between health workers and patients. It is necessary to estimate health literacy and to adjust communication.

Hypothesis: Health literacy is worse with the patients who are obese, who suffer from arterial hypertension and those affected by the diabetes mellitus type 2, for each of these diseases separately when compared with the patients without these diseases.

Aims:

1. To examine health literacy with hospitalized patients.
2. To examine demographic characteristics according to health literacy of the hospitalized patients.
3. To explore prevalence of obesity with the examinees.
4. To examine prevalence of arterial hypertension with the examinees.

5. To examine prevalence of diabetes mellitus type 2 with the examinees.
6. To examine health literacy according to obesity.
7. To examine health literacy according to arterial hypertension.
8. To examine health literacy according to diabetes mellitus type 2.
9. To examine prevalence of obesity according to arterial hypertension.
10. To examine prevalence of obesity according to diabetes mellitus type 2.
11. To examine prevalence of arterial hypertension according to diabetes mellitus type 2.

Materials/Participants and Methods: The research is going to be conducted in General county hospital Požega, through a three-month period. Persons who do not understand Croatian language or are unconscious, are going to be excluded from this research. For the purpose of this research, a sectional view research is going to be conducted and original, primary data, gathered from the patients, as well as data gained from medical records, are going to be used.

Before the very inclusion to the research, patients are going to be introduced with the purpose of the research, both orally and in written forms, whereas the participation in the survey itself is going to be voluntarily. Their own consent to participation in this research, patients are going to confirm with their signature on the form of Informed Consent. Anonymity and confidentiality are going to be ensured. As an instrument of the research, a questionnaire that contains the information about year of birth, gender, education, employment, marital status, body weight, height, place of residence, hospitalization department, reason of hospitalization, medical history of a suffered heart attack or a stroke, is going to be applied. Information that are not going to be available from this survey, the researcher is going to collect from the medical records of the patients. As a second instrument of this research, a valid Croatian translation of the survey questionnaire SAHLSA-50 which consists of fifty different terms (main words), is going to be used. Two terms are attached to each main word and the task of examinees is to choose the attached term that, according to their opinion, better matches the main word. This chosen attached term, examinees will have to mark with the letter "X" in a provided area. If the result of attached terms with the main word is lower than 37 or equal to it, it is going to be considered that the examinee is healthy illiterate.

Statistical methods

Numeral data are going to be described with the basic measures of centrality and dispersion. Normality of allocation of the observed numerical variables is going to be tested with Kolmogorov-Smirnov test. Categorical variables are going to be described with absolute and relative frequencies. For the determination of the differences with the measurement indicators between the two groups, Student T-test is going to be used for the parametric dispensation, whereas Mann-Whitney U-test is going

to be used for nonparametric dispensation. For the determination of the differences between three or more groups, when it comes to parametric dispensation ANOVA is going to be used, whereas Kruskal-Wallis test is going to be used for nonparametric dispensation. For the determination of differences of the proportions between the independent samples, χ^2 - test and Fisher exact test are going to be used. Depending on normality of partition, Pearson or Sperman coefficient of correlation are going to be used for grading the connection of certain indicators. For grading significance of obtained results, level of significance $P < 0,05$ has been chosen. Statistical analysis of the information is going to be conducted with the programme IBM SPSS Statistics (ver. 15.0, SPSS Inc., Chicago, IL, USA).

Research plan:

1. To provide permission from the ethical commission of the General county hospital for the conduction of the research.
2. To appoint questionnaire and survey questions to collect relevant information.
3. To inform executives of the General county hospital Požega about purpose and aims of the research and procedure of gathering information, as well as to collect approvals for the research conduction.
4. To collect necessary information (to conduct research) within certain period, until sufficient number of examinees is achieved (planned period is approximately 3 months).
5. Collected information are to be properly entered simultaneously with the conduction of the research and they should be statistically analysed.

Significance/ Expected scientific contribution: Scientific contributions will manifest in uniqueness of the received information about health literacy of the hospitalized patients in the district of Požega and its surrounding area. Such scientific evidence was not available in the published literature so far, related to this complex casuistry nor Croatian population. This information will enable us to examine prevalence of obesity and its connection with prevalence of arterial hypertension and diabetes mellitus type 2 among hospitalized patients. Obtained information will be useful for the healthcare workers who take care of patients, in order to awake the importance of adjusting communication to the level of health literacy of the patients and to make an effort when it comes to health education of the population.

Keywords: health literacy, obesity, diabetes mellitus type 2, arterial hypertension



Dissertation Proposal Title: The effect of 13-cis retinoic acid and high fat diet on gut microbiome, metabolic syndrome and insulin resistance development in Lewis rats

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Mentor 2: Tatjana Belovari, PhD; Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek

Introduction: The application of 13 – cis retinoic acid may cause numerous clinical and metabolic disorders and lead to diabetes mellitus II, cardiovascular complications, alterations in gut microbiome - known as a metabolic syndrome. Obesity and high fat diet distort the diversity of gut microbiota, including the decrease in Lactobacillus and Bifidobacterium.

Aims: to determine the level of haematologic and biochemical parameters in serum of all rat groups to determine the level of glucose in serum of all rat groups to analyze the histological changes in liver (degree of steatosis, fibrosis and necrosis), small intestine (degree of lymphocyte infiltration in Lamina propria, epithelium and Lieberkühn crypt distribution), ovary and uterus (number of mature/athretic follicles, granulose cell appearance), testis (degree of fibrosis) of all rat groups to analyze the short-term (after 30 days) and long-term (after 60 days) effect of 13 – cis retinoic acid and high fat diet on the organism of all rat groups (male and female)

Materials and Methods: 84 Lewis rats will be included in the study and divided into 6 groups, 6-8 animals in each. The first three groups will be fed with standard laboratory chow diet (STD; 10% fat ; CON-STD, STD+7,5 (13cRA), STD+15 (13cRA)), while the the rest will be fed with high fat diet (HFD; 45% fat ; HFD-CON, HFD+7,5 (13cRA), HFD+15 (13cRA)). 13 – cis retinoic acid will be orally administered in different concentrations (7,5 mg/kg; 15 mg/kg) daily for 30 days. Half of the animals will be sacrificed after 30 days, the rest after 60 days.

Results: 13 cRA treatment increased body mass in HFD rats ($p=0,003$). Animals treated with 7,5 (13 cRA) consumed more food than those treated with 15 (13 cRA) ($p= 0,004$). There was significant sex interaction on body weight. Male rats had significant higher body weight than females after 30 /60 days of study ($p=0,002$, $p=0,005$).

The 13cRA treatment had significant effect on body weight and organ/body ratios of ovary, testis, kidney, spleen, heart and lung. Relative weight of uterus and ovaries decreased compared to control group fed with HFD ($p=0,002$) as well as STD ($p=0,002$). Histological analyses of ovaries showed increased percentage of atretic follicles and increased number of follicles with apoptotic granulosa cells. Relative ratio of uterus was also decreased among experimental group fed HFD and treated with 15 (13 cRA) which can be explained with less estrogen produced from ovaries and decreased proliferative capacity of endometrium. Relative weight of testis was also decreased in experimental group ($p= 0,015$).

Analyses of all organ/body weight ratios (spleen, heart, liver) indicated significant effect of sex in which female ratios were higher, except for femur, which can be explained with protective role of estrogen on bone resorption and degradation.

Glucose levels of males treated with 15 (13 cRA) and 7,5 (13cRA) were significantly lower than the controls fed with STD ($p=0,029$) as well as HFD ($p=0,046$). Male rats treated with 15 (13 cRA) had higher glucose levels than the males treated with 7,5 (13 CRA) ($p=0,007$).

Analysis of haematological parameters indicated significant effect of 13 cRA treatment on number of erythrocytes, leukocytes and trombocytes. Among female rats, the number of lymphocytes increased ($p=0,003$) and the number of neutrophils decreased ($p= 0,007$) in group treated with 15 (13 cRA) for 30 days.

Conclusion: 13 – cis retinoic acid and way of feeding rats affect glycemic response, histological changes in ovary and testis, total body weight and organ/body ratio in Lewis rats.

Keywords:13 – cis retinoic acid; metabolic syndrome; obesity; gut microbiome; histology



Title of abstract: Immunochemical methods for determination of ferritins, MTs and HSP10

Dissertation Proposal Title: Ferritins and chaperonin 10 (CPN10) status in gestational diabetes mellitus (GDM)

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Mentor: Prof. Rajko Fureš, M.D., Ph.D., General Hospital Zabok

Mentor 2: Marija Ljubojević, Ph.D. Institute for Medical Research and Occupational Health, Zagreb, Croatia.

Introduction: Physiological stress in pregnancy might be observed through status of ferritins and CPN10. Even without direct common nominator both proteins are present in plasma and through their status changes in pathology of GDM may be observed. Ferritins light and heavy chains are involved in essential metal keeping (mostly Fe but possible Zn) in cells cytoplasm, while secreted light chain ferritin may be in direct correlation with iron status in organism. CPN10 (HSP10) together with other member of heat shock protein family HSP60 act as a multimer involved in mitochondrial protein folding, and as secreted factor in immunosuppression. The interaction of ferritins and CPN10 in their physiological roles and possible changes in pathology, including GDM, is unknown.

Main hypothesis is that changes in ferritin expression and decreased Zn in blood and placenta samples together with decreased Zn occupancy in ferritins and metallothioneins (MTs) can be directly correlated with CPN10 as indicator of protein misfolding in pregnant women with diagnosed GDM and all that factors can be directly involved in condition pathology. The investigation work will be designed as case-control study.

Aim: The first aim is to establish reliable results of immunochemical methods for detection of proteins that will be used in further investigations with aim to investigate from samples in healthy control compared to GDM mothers:

- a) the association of ferritin light chain and CPN10 levels from placenta and possible blood

- b) the correlation of ferritin light chain and heavy chain levels with Zn and Fe levels in biological samples
- c) changes in expression and distribution of ferritins and CPN10 in placenta

Results: On basis of early, up to 24th week fasting glucose > 5.1 mM and criteria of oral glucose tolerance tests (OGTT) group of GDM mothers were formed. From informed and voluntary involved future mother's samples of blood and urine for biochemical and other analysis were collected in one point late in pregnancy (~36 week) in regular control of glycemic normal and diet regulated women with GDM (at least 10 samples from each group). Placenta, after each childbirth, were collected for measurement of trace elements iron and zinc (ICP-MS) and immunochemical analysis of ferritins, MTs and CPN10 (parts in LN for proteins and metal analysis and piece in fixative for IHC).

Conclusions: Investigation of possible causes of GDM and biomarkers of severity is important, and we are detecting by immune methods both ferritins and CPN10 that can be used for this purpose but for detection of MTs protein isolation is planned as by present method we did not detected MT1 and 2.

Keywords: gestation diabetes mellitus (GDM), metallothioneins (MTs), chaperonin 10 (CPN10), heat shock protein 60 (HSP60), immunohistochemistry (IHC), inductively coupled plasma mass spectrometry (ICP-MS)



Dissertation proposal title: Association of GERD with outcome of antipsychotic therapy and the quality of life; a prospective cohort study

PHD candidate: Katarina Matić, MD, Psychiatric hospital "Sveti Ivan", Zagreb

Mentor: Prof. Igor Filipčić MD, Ph.D., Psychiatric Hospital „Sveti Ivan“, Zagreb

Introduction: Psychosis is a mental disorder in which the primary symptom is the alienation of the patient from reality. It is reflected in a disturbed contact or even terminating contact with reality, deep perceptual disturbances, emotions, opinions, and behaviors. A psychotic person often lacks insight into his own illness, because of which the patient may be quite limited to life in society. There are several types of psychosis, but two are most common: schizophrenia and bipolar affective disorder (BAP). Psychosis that we will follow in this research are schizophrenia, acute psychotic disorders, unspecified psychosis, and somnolent disorder. In Croatia in the period from 1970 to 2012. the age-standardized rate of hospital incidence of schizophrenia and schizoaffective disorders averages 0.26 / 1000 population over 15 years. All psychoses are severe and very often chronic mental disorders requiring serious, disciplined and long-term psychiatric treatment, taking prescribed drug therapy (antipsychotics, mood stabilizers, antidepressants). Schizophrenia and psychotic disorders similar to schizophrenia are equally endangered by women and men, and most people appear between 15 and 25 years of age. The prevalence is around 1% in the world. Psychosis is recognized by the characteristic symptoms such as stained ideas, hallucinations, disorder of thought, and strange behavior. Delusional ideas are misguidance, false beliefs that have no basis in reality. Hallucinations are very common, and the most common and most common hallucinations are hallucinations, while hallucinations and hearing are less common. Disease is also characterized by disorder of thoughts that are divided into formal (signifies the occurrence of unrelated flow of thought, without logic and order) and content (refer to delusional ideas). There is a lack of normal emotional responses or other processes of thought, including indifference or empathy, speech poverty (alogia), inability to experience satisfaction (anhedonia), lack of desire to connect with people (asocialism), and lack of motivation (avolice). Research shows that negative symptoms contribute to low quality of life and functional disability, and are more burdensome than positive symptoms. People with pronounced negative symptoms often have a history of poor adaptation before the onset of the disease, and response to treatment is often limited. In the initial stage of

the illness, the symptom is the loss of emotional heat, causing the emotionally cold. The sufferers are often aware of these changes and are appalled by the feeling of separation from others and lack of feelings towards their neighbors. They lose their joy, their interest in work and everyday activities. These symptoms cause the inability of patients to find their way into everyday life. GERB (Gastro-oesophageal Reflux Disease) is a GIS disease, caused by the return of (reflux) content of the stomach into the esophagus caused by the release of the antirefluxive barrier of the esophagus. Symptoms are the sense of acid in the mouth, typically roasting along the esophagus usually described as heartburn, numbness, cough, pain behind the sternum. Incidence of gastritis and ulcers in psychotic patients is 1.27 times higher than the general population. Numerous patients with schizophrenia suffer from impaired therapeutic response or intolerance to various antipsychotics. Some innovative pharmacotherapeutic approaches to date suggest that the addition of an anti-inflammatory drug to antipsychotics therapy in patients with psychotic disorders who have comorbidity of peptic ulcer leads to a significant deficit of psychotic symptoms. Thus, in one study of schizophrenic patients who were resistant to antipsychotics therapy, when anti-inflammatory drugs were added to therapy with antipsychotics, it was shown that co-therapy has led to faster recovery and symptomatic breakdown of the schizophrenia circle. It has also been shown that in schizophrenic patients the appearance of stomach ulcers is associated with the harmful use of alcohol, with the tendency to develop rare forms of duodenal ulcers and disrupt the motility of upper GIS. Numerous patients who report to a family medicine physician for gastric illness often suffer from psychotic problems in the background. It has also been shown that the symptoms of reflux disease are more common in psychiatric patients compared to healthy populations, and are not related to specific therapy although the perception of symptoms is questionable. The GERD diagnosis itself does not necessarily include a review of gastroenterologists, pH measurement and endoscopy, but a GERD-Q questionnaire may be used. Comorbidities of body and psychiatric disorders are more of a rule than an exception, but often, unfortunately, to the detriment of the patient, remain unidentified. By reviewing many previous research and review articles, there is an unquenchable association between gastrointestinal disorders and psychiatric disorders, as well as the effect of anti-inflammatory drugs on mental disorders and vice versa, through the brain-digestive tract. Most of the previous studies have looked at the effect of antidepressants on the reduction of gastric disorders, especially from the SSRI drugs group. Despite the same, some studies have shown contradictory results, while the area of schizophrenia and other psychosis, and antipsychotic and gastric disorders remains largely unmanageable. Also, numerous studies suggest an increased incidence of GI disease in psychiatric patients, which can be related to pathophysiological mechanisms, but we must also take into account the reduced quality of life of psychiatric patients themselves, their weakened capacity to buy

stress, taking large amounts of various drugs, and increasing Alcohol consumption, mostly for the sake of self-education and anxiety reduction. It is of great importance to timely recognize comorbidity and adequately provide a psychiatric patient with care and treatment to extend their life span and bring their quality of life to a higher level. It is indisputable that further research in the field of pharmacokinetics and pharmacodynamics of polytherapy, ie further investigation in the field of synergistic effect of psychopharmacotherapy and anti-inflammatory drugs, is required.

Hypothesis: The existence and the weight of GERB is associated with the weaker success of treating psychosis and weakening the quality of life of a patient.

Aims:

General aims:

To investigate whether there is a difference in the effect of antipsychotic therapy and the change in the quality of life among patients with different probabilities of GERB, ie different gravity of GERB symptoms.

Specific aims

- 1) Investigate the number of patients with GERB unrecognized.
- 2) Describe patients without and with GERB, ie with varying GERB weight according to different sociodemographic, vital and clinical parameters.
- 2) To investigate whether there is a difference in the effect of psychiatric treatment of psychosis, a distinct difference in the CGI score scale and a CGI-I score among patients with different probabilities of GERB.
- 3) Investigate whether there is a difference in the overall outcome of the EQ-5D-5L analogue-visual scale of self-estimated overall health among patients with a different probability of GERB.
- 4) Investigate whether there is a difference in the composite outcome: a weighted variation inversion index variation on the CGI-S scale, CGI-I scores and the difference in the overall result on the analogue-visual scale of self-estimated overall health EQ-5D-5L between patients with varying probabilities GERD.

Participants and methods: Targeted population will be treated by patients of both sexes aged 18 to 90 years with diagnosed schizophrenia, disorders like schizophrenia or abnormal conditions (MKB-10 F20-F29) (further: psychosis) treated ambulance, daily hospital or hospital in PH „Sveti Ivan „who reported in the European (EU) Health Survey that they have GERB (Gastro-oesophageal Reflux Disease). The control population will be diagnosed with patients with a diagnosed psychosis who did not state the existence of GERB in the EU health survey. The sample from the control population will be aligned with the sample from the trial population according to

sex, age, duration of major psychiatric disease, treatment of antipsychotics and antidepressants, education and the number of somatic and psychiatric comorbidities.

Inclusion Criteria: Diagnosed Schizophrenia, Schizophrenia-like Disorder (MKB-10: F20-F29), 18-90 years, both sexes.

Non-inclusion criteria: current suicidality, inability to independently complete the questionnaire. Exclusion criteria: newly discovered suicidality, hospitalization in another hospital for somatic disease lasting longer than six months.

Sample type: A consecutive sample will be selected according to the order of arrival of the patient for inspection or the order of hospital admission.

Sample size: The expected association of GERB with score on VAS score, standard deviation of these results and determination coefficient of 10 confusing variables with the results on that scale was evaluated on the basis of the study „Somatic Comorbidities of Psychiatric Diseases“ performed on $n = 303$ patients with PBD diagnosed „Sveti Ivan„ during May 2019. In the covariant analysis, a sample size of $n = 48$ patients with $n = 48$ patients without self-administered GERB is finally required to be statistically significant ($p < 0.05$) with a statistical strength of 80% and control of ten covariates whose total coefficient of determination as a result of VAS the rankings are $R^2 = 0.08$, determine the difference of 15 points; between the arithmetic mean of 65 in the group without GERB, or 50 in the GERB group ($SD = 27$) on the VAS scale, which is the minimum difference we hold clinically and theoretically relevant. With the expected maximum of 10% lost for monitoring, the initial size required was set at $n = 54$ in each cohort. Thus, a total of $n = 108$ patients will be included in the study. The required sample size is calculated in the program: PASS 14 Power Analysis and Sample Size Software (2015). NCS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. VARIABLE Variables

Main outcome: The composite index is weighted by inversion variance of three variables:

VARIABLE Variables

Main outcome: The composite index is weighted by inversion variance of three variables:

- a) differences in the CGI-scale for inclusion and after six months of treatment,
- b) Results on the CGI-I scale after 6 months of tracking
- c) Differences in the overall result on the analogue-visual scale of self-assessed general health EQ-5D-5L (VAS). CGI-S (Clinical Global Impression-Improvement Scale) and CGI-I (Clinical Global Impression-Improvement Scales) are well validated in routine long-term use in psychiatric practice. Both will be applied

by an experienced psychiatrist. Each patient will be evaluated on CGI scales by a doctor / physician who will otherwise cure and control the course of treatment. On VAS ranges, the respondents themselves assess their total health at the time of the test by indicating the number on a vertical column similar to a thermometer whose values range from 0 „worst possible health” to 100 „of the best possible health.” The chart was developed by the EuroQoL Group in 1990 and has since been validated in various Croatian populations including the population of patients with diagnosed psychosis. (14)

Independent variable: Different probability of GERB, ie different weight of symptoms of GERB and its impact on everyday life. Different probability of GERB, ie different difficulty of GERB symptom, will be determined on the basis of points in the GERB-Q questionnaire and divided into four categories: a) GERB zero probability, ie lack of GERB symptom (0-2 points), b) GERB probability of 1% -50% and mild and transient symptoms of GERB (3-7 points), c) GERB probability of 51% -79%, or unpleasant GERB without affecting daily life (> 8 points with <3 points on issues affecting daily life; questions 5 and 6); and d) probability of GERB 80-100%, or alarming GERB with great influence on everyday life (> = 8 points with > 3 points on issues affecting daily life, questions 5 and 6).

The GERB symptom self-assessment questionnaire has overall accuracy in setting a diagnosis comparable to a clinical diagnosis set by a gastroenterologist. It consists of six questions about the frequency of bruising (burning), unpleasant gastric (fluid or food) back into the throat or mouth (regurgitation), the feeling of pain in the middle of the upper part of the stomach, a feeling of nausea, a problem with sleepiness caused by symptoms of the disease (heartburn and / or regurgitation), taking medication for heartburn or regurgitation by those prescribed or recommended by a physician. The offered frequency response categories are: 0 days, 1 day, 2-3 days, 4-7 days during the last week.

Potentially confounding variables whose influence we try to control by equilibrating the experimental and control groups and by multivariate statistical analysis: age, duration of major psychiatric disease, treatment of antipsychotics and antidepressants, education, marital status, work status prior to actual hospitalization, number of household members, body mass index (kg / m²), smoking, alcohol consumption, number of somatic and psychiatric comorbidities, major psychiatric illness at time of diagnosis, inclusion depression measured by Beck's scale, and treatment of proton pump inhibitors, H₂ receptor antagonists or antacids for 6 months prior to inclusion in the study

Procedures: The tracking will take 12 months. Three measurements will be made: a) upon inclusion, b) after six months, c) after 12 months. Patient involvement and measurement will be performed by 20 doctors PB „Sveti Ivan”.

Expected scientific contribution: In the case of confirmation of our hypothesis about the linkage of GERB's weight with the success of treating psychosis and the change in quality of life, we would theoretically contribute to the understanding of the pathogenesis of psychosis or parameters important for the success of therapy. Clinical contribution would be in the new awareness of the importance of this somatic comorbidity and for the treatment of psychosis alone and in the promotion of a multidisciplinary, holistic approach to treating psychosis, as opposed to today the exchange of frequent separation of psychic and somatic medicine.

Keywords : psychosis, gastroesophageal reflux disease (GERD), quality of life, antipsychotics, antiulcer drugs



Dissertation Proposal Title: The relationship between health literacy, health-related quality of life and satisfaction with the family physician among chronically ill patients

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Mentor: Prof. Robert Steiner, M.D., Ph.D., University Hospital Center Osijek; Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Introduction: Health-related quality of life (HRQoL) is a multi-dimensional concept that comprises the physical, mental, emotional, and social functioning domains. Health literacy is the capacity of a person to acquire, process and comprehend basic health information so that he or she can make appropriate health decisions. There is relatively little research that focuses on the relationship between health literacy, health-related quality of life and satisfaction with the family physician in Croatia. Also, chronically ill patients, as one of the most common users of primary health care, are not included in most study samples.

Hypothesis: Chronically ill patients have low health literacy, a lower health-related quality of life and are less satisfied with their family physician.

Aims: To determine the level of HRQoL, health literacy and satisfaction with the family physician among chronically ill patients in primary health care. Moreover, to investigate the relationship between health literacy, health-related quality of life and satisfaction with the family physician among chronically ill patients.

Materials/ Participants and Methods: This cross-sectional study will be conducted from December 2018 till June 2019. The questionnaires will be distributed to every family physician in the Osijek-Baranja County. The estimated sample size is a 1000 patients. A validated survey questionnaire SF-36 will be used to evaluate the health-related quality of life and a validated survey questionnaire HLS-EU-Q47 will be used to evaluate the level of health literacy. In order to evaluate the level of satisfaction with the family physician, a validated survey questionnaire EUROPEP will be used. Statistical analysis will be conducted via SPSS software.

Research plan: Every doctor employed in the field of family medicine in Osijek-Baranja County will be informed about the research study. They will be asked to

include chronically ill patients who visit their office in the following period. After the patients give their informed consent, they can complete the questionnaire.

Significance / Expected scientific contribution: This study seeks to recognize new facts about health literacy, health-related quality of life and satisfaction with the family physician among chronically ill patients. Family physicians might feel encouraged to alter their communication skills or motivate their patients to continually improve their health literacy. The results will provide new insight into the health-related quality of life of chronically ill patients as they are the most common users of primary health care.

Keywords: health literacy, quality of life, family physician, patients, Croatia



Dissertation Proposal Title: Association of CYBA and ROCK gene polymorphisms with Respiratory Distress Syndrome in preterm infants gestational age between 32 and 38 weeks

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Mentor: Assist. Prof. Silvija Pušeljić, M.D., PhD., Faculty of Medicine Osijek, University of Osijek, Osijek, Croatia

Introduction: Respiratory distress syndrome is the most common cause of morbidity and mortality among preterm infants. Symptoms of the condition are: shallow breathing, apnea, grunting, inspiratory stridor, nasal flaring, poor feeding and tachypnea. Neonates with respiratory distress (RD) are several times more likely to die than those without RD. The manifestations of the disease are caused by diffuse alveolar atelectasis, edema and cell injury. There are many causes for RD development of which about 20% is still unknown.

Rho-kinase (ROCK) is serin/treonine kinase that is activated by Rho proteins and there are two isoforms that have been described (ROCK1 and ROCK2). It plays important role in a wide range of cellular function including cell morphology, motility, adhesion, migration, proliferation, differentiation and apoptosis. There are some evidence indicating that mechanical stretch is essential for lung growth and development and it is also stimulus for Rho-kinase activation.

Cytochrome B-245 Alpha Chain (CYBA) is the gene encoding subunit of NADPH oxidase. It has been linked to several conditions in which oxidative stress plays a pathogenic role. There are some significant evidence that points out that CYBA polymorphism could play important role in emergence of RD.

Hypothesis: Gene polymorphism of ROCK or CYBA gene is associated with RDS development among preterm infants of gestational age 32-37 weeks.

Aims:

1. Determine the link between Rho-kinase gene polymorphisms in RDS development
2. Determine the link between CYBA gene polymorphisms in RDS development

3. Determine the association of genetic polymorphism in development of other preterm conditions (retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage)
4. Formation of certain high risk groups based on infant weight, sex and age and their risk factors

Participants and methods: The research will be performed during the current year. The participants will be all children accepted for treatment at the Department of neonatology, KBC Osijek at a gestational age between 32 and 38 weeks, weighing <2500 g. Venous blood sample will be obtained from all study participants into EDTA-containing tubes. Immediately after collection, blood will be frozen and stored at -20°C until the time of analysis. Genomic DNA will be extracted from whole blood using the salting-out method and will be stored at -20°C. The genotype will be determined in all patients and controls using dynamic array system.

RDS will be diagnosed according to the following criteria: respiratory distress beginning in the first hours of life and lasting at least 24h, need for mechanical ventilation including continuous positive airway pressure, presence of typical radiological findings in chest X-ray, and abnormal arterial blood gas results.

Expected scientific contribution: Finding certain gene polymorphisms of ROCK and CYBA gene that are highly associated with RDS development in preterm neonates GD between 32-38 weeks.

Early detection of certain risk groups through prenatal diagnostics that would be diagnosed and treated on time in the appropriate neonatal center.

Keywords: preterm infants; polymorphism; respiratory distress syndrome; ROCK gene; CYBA gene; NADPH oxidase; oxidative stress;



Dissertation Proposal Title: Prognostic factors for vulvar cancer

PhD candidate: Ivana Miljanović-Špika, MD, Clinic of Gynecology and Obstetrics, University Hospital Center Osijek

Mentor: Prof. Zlatko Topolovec, MD, Ph.D., Clinic of Gynecology and Obstetrics, University Hospital Center Osijek

Introduction: Vulvar cancer is a rare malignant disease of the female sexual system. If diagnosed at an early stage it is curable. Survival is largely due to the absence of lymphatic metastases. According to recent data, survival significantly depends on the number of affected lymph nodes, the size of the primary lesion, the depth of the invasion and the involvement of the lymphovascular space.

Hypothesis: Significant prognostic factors for survival of vulvar cancer in univariate should show the status of lymph nodes, adjuvant and radiotherapy, chemotherapy and clinical stage of the disease.

Aims: To show the influence of clinical, pathological, cytological and therapeutic prognostic factors on the outcome of treatment and survival of patients suffering from vulvar cancer and to determine the prognostic significance of each of the individual factors and their mutual significance and impact on survival.

Participants and methods: The study will include patients treated with vulvar cancer in the period from 2007 to 2017 at the Clinic for Gynecology and Obstetrics, University Hospital Centre Osijek. Retrospective analysis of data from disease history, operational protocols, pathohistological and cytological findings and oncologist findings will be performed.

Statistical analysis will be performed using SPSS statistical software package. The statistical level of significance will be set to $p < 0.05$. The normality of distribution of the used variables will be checked by the Kolmogorov Smirnov test. To show the influence of certain factors on mortality, Kaplan-Meier's curves and Cox's regression test will be used. Also, the hi-hydration test will be used to check the differences between the individual factors and mortality.

Research plan: The following prognostic factors will be analyzed:

I Clinical factors

1. Clinical stage (divided into four groups)
2. Age (determined by age and graphically depicted throughout the five year period)

II Pathological and citological factors

1. histological type of tumor
2. histological gradus (divided into three stages)
3. tumor distance from the surgical edge of the preparation (shown in millimeters and divided into groups of 0-5 mm, 6-10 mm, 11-15 mm, 16-20 mm and > 20 mm)
4. depth of invasion (shown in millimeters and divided into groups <5 mm, 1-5 mm, > 5 mm)
5. tumor size (shown in centimeters and divided into groups of 0-1 cm, 1.1-2 cm, 2.1-3 cm, 3.1-4 cm, 4.1-5 cm and > 5 cm)
6. status of lymph nodes (shown by the number of removed lymph nodes and the number of lymph nodes affected by the tumor)

III Therapy factors

1. Surgical treatment
2. Adjuvant chemotherapy (performed / unperformed)

Expected scientific contribution: To help determine the prognostic significance of clinical and pathohistological factors for survival of the participants.

Keywords: vulvar cancer, prognostic factors



Dissertation Proposal Title: Molecular mechanisms of renoprotective effect of empagliflozin and liraglutide on cellular model of proximal tubular cells.

PhD candidate: Vjera Ninčević, M.D., Department of Pharmacology, Faculty of Medicine Osijek, Faculty of Dental Medicine and Health Osijek, Osijek, Croatia.

Mentor: Assist. Prof. Ines Bilić Ćurčić, M.D., Ph.D., Department of Pharmacology, Faculty of Medicine Osijek, University of Osijek, Osijek, Croatia.

Introduction: Diabetic nephropathy (DN) is one of the most perilous side effects of diabetes mellitus and there are significant changes in the sense of interpapillary glomerulosclerosis, tubulointerstitial fibrosis, and tubule atrophy. Majority of the DN research is focused on glomeruli, however, most recent studies show important role of tubules in the progression of the disease. Key extracellular conditions that contribute to proximal tubular damage in DN include hyperglycemia, proteinuria, hypoxia, and inflammation, and they act by changing the hormone-induced release of cytokines (TGF- β), the renin-angiotensin system, dysregulation of pathways such as polyol pathways. It is known that some antihyperglycemic agents such as liraglutide and empagliflozin have renoprotective effects, however, it is not yet fully elucidated whether they have a direct effect on the proximal tubules.

Hypothesis: Liraglutide and empagliflozin will downregulate expression of genes involved in signaling pathways of tubular damage that are dominant in diabetic nephropathy thus reducing tubular fibrosis, tubular atrophy and apoptosis of proximal tubular cells caused by oxidative stress and hyperglycemia.

Aim: to determine the expression of major genes involved in signal transduction pathways of tubule damage in in vitro model of DN and to assess the influence of hypoglycemic drugs on gene expression involved in signal pathways of tubular damage.

Material and Methods: Immortalized cell line isolated from epithelial cells of proximal tubule of healthy human kidney (HK2) cells will be exposed to pathophysiological mediators that mimic DN: high glucose and oxidative stress. Cells will be grown in cell incubator at 37 °C with 5% CO₂ (v/v), 10-30 mM glucose will be added to induce hyperglycemia and 0.5-1.0 mM H₂O₂ will be added to induce oxidative stress.

The extent of damage will be determined by gene expression involved in signal transduction pathways of tubule damage. Furthermore, cells will be treated with liraglutide and empagliflozin as posttreatment in in vitro model of DN. Additionally, the effect of liraglutide and empagliflozin on gene expression involved in signal pathways of tubular damage will be assessed by RT2 PCR Array Profiler Technology.

Research plan: HK2 cell line from normal adult human kidney will be used to develop characteristics of DN in vitro. The extent of tubule damage and gene expression involved in signal pathways of tubular damage before and after the addition of medicaments will be evaluated by measuring total glutathione (tGSH) concentration spectrophotometrically and profiling of 84 key genes involved in nephrotoxicity mechanisms using RT2 PCR Array Profiler Technology.

Expected scientific contribution: Recent studies point to the leading role of tubules in DN and this renoprotective effect of certain antidiabetic drugs is probably mediated through tubular damage, but the mechanisms are still obscure. Therefore, in vitro studies should first be made to clarify the molecular mechanisms of these drugs on renoprotection, which would potentiate the development of new specific therapeutic options for DN prevention and development.

Keywords: diabetic nephropathy, proximal tubule, GLP-1 analogue, SGLT2, HK2



Dissertation Proposal Title: The trend of antibodies on influenza type A and type B during influenza season

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Mentor: Assoc. Prof. Josip Milas, M.D., PhD., Faculty of Medicine Osijek, University of Osijek, Osijek, Croatia

Introduction: The influenza is an infectious disease which can be entirely asymptomatic or subclinical, but can also manifest in symptoms such as the cough, fever, and myalgia, all the way up to the forms presenting as a severe pneumonia demanding hospitalization that even causes death in the infected. A large portion of the population is infected during influenza season, but despite some individuals not presenting with symptoms, they still spread the virus in the population and mostly undergo serological changes which are a sign that an infection occurred. Our understanding of the characteristics of an immunological response after a natural infection with a virus or a vaccination against influenza is still poor. The number of people who come into contact with the influenza virus during influenza season is unknown, as well as the number of people who truly get sick out of those who come into contact with the virus. Also, the nature of prevalence of antibodies on the influenza is unknown, as well as the concentrations of antibodies in certain age groups and how the concentrations of antibodies change during influenza season.

Hypothesis: Almost the entire population comes into contact with the influenza virus during the winter months and they have an increase in concentration of antibodies for the influenza virus.

Aims: To determine the concentrations of the IgG antibodies for the type A and type B influenza, as well as the changes in antibody concentrations during influenza season. To determine the portion of the population that came into contact with influenza during influenza season. To determine the prevalence of the IgG antibodies against influenza type A and type B in the general population. To determine the prevalence of antibodies, antibody concentrations as well as the changes in concentrations of antibodies during influenza season according to individual age groups of patients, as well as gender.

Participants and methods: The material will be made up of serum samples which will undergo ELISA measurement of IgG antibodies specific to influenza type A and type B.

Research plan: A series of cross-sections will be made on serums taken in one month intervals in order to gain a trend of antibodies throughout influenza season. These will be the serums taken in the period between October and April. The prevalence of antibodies IgG of influenza type A and type B will be analyzed from the serum, as well as the concentrations of antibodies depending on the age and gender of the examined. The trend of antibody concentration during influenza season will be analyzed.

Expected scientific contribution: This research will provide information on the prevalence of antibodies against influenza type A and type B in certain age groups depending on the gender and the concentrations of antibodies and their changes during influenza season. A contribution will also be made in the form of an answer to the question of which portion of the population comes into contact with influenza during influenza season.

Keywords: influenza, asymptomatic, antibodies, prevalence, concentration



Title of abstract: The Effect of Amiodarone and Tamoxifen on Hepatocyte Steatosis Development *in vitro*

Dissertation Proposal Title: The molecular mechanisms involved in development of Drug-Induced Fatty Liver Disease (DIFLD) models and the use of Glucagon-like peptide-1 (GLP-1) analogues in the therapy of DIFLD *in vitro*

PhD candidate: Tea Omanović Kolarić, MD, Faculty of Medicine Osijek, Faculty of Dental Medicine and Health

Mentor: Assoc. Prof. Martina Smolić, MD, PhD, Faculty of Medicine Osijek, Faculty of Dental Medicine and Health

Introduction: Drug-induced liver disease (DILI) represents emerging public health problem, with unknown true incidence because of lack of a simple objective test for diagnosis, unknown denominator of individuals receiving a drug and lack of systematic reporting. Various histological findings can be seen with different types of DILI, such as hepatitis, nodular regenerative hyperplasia, cholestasis, steatohepatitis, fibrosis etc. Accordingly, numerous drugs are capable of inducing the fatty liver disease (DIFLD), a condition with a broad spectrum of appearance, from simple hepatic steatosis, to steatohepatitis, an advanced form of steatosis, followed by progression to fibrosis and cirrhosis. DIFLD is strongly associated with duration and dose of medication. Number of drugs have been involved in the development of chronic DIFLD, however, the exact type of steatosis and molecular mechanisms of DIFLD are not yet fully enlightened.

Aims: The aim of our study was to evaluate the effect of amiodarone and tamoxifen on cell survival and on formation of lipid droplets in HuH7 cell line.

Materials and Methods: HuH7, a cell line derived from differentiated hepatocellular carcinoma, was used as a model of DIFLD *in vitro*. Two known hepatotoxic drugs were used to induce DIFLD, amiodarone (Amiodarone hydrochloride 98%, Sigma Aldrich) and tamoxifen (Tamoxifen citrate 98%, Acros Organics). Cells were exposed to 5 μ M and 10 μ M solution of each drug, respectively. After 48 hours, the extent of steatosis was evaluated by Oil-Red-O and DAPI staining. Afterwards the changes were observed by fluorescent microscopy. MTT assay was used for evaluation of cell viability after 48h exposure to above mentioned drugs.

Results: Massive increase in the number and size of lipid droplets into the cytosol of drug- treated cells compared to controls was demonstrated, with peripheral accumulation of droplets on the inner side of cell membrane without displacement of the nucleus. Oil-Red-O staining was used to stain lipid droplets, which are shown as multiple red changes, with blue nuclei due to DAPI counterstaining, being present in the center of the cell. The number of lipid droplets increased with increasing concentration of each drug. MTT assay demonstrated the decrease in cell survival with increasing concentrations of drugs. The greatest difference in cell viability occurred with 15 μ M amiodarone treatment where only 36,4% of cells were viable.

Conclusion: Amiodarone and tamoxifen induced lipid droplet formation and occurrence of hepatic steatosis, followed by decrease in cell viability. These results are in accordance with previous studies, thus confirming the hepatosteototic effect of listed drugs. Nevertheless, further research is necessary in order to better understand molecular mechanisms underlying DIFLD development and progression of simple steatosis to advanced steatohepatitis.

Keywords: DILI, DIFLD, amiodarone, tamoxifen, HuH7



Dissertation Proposal Title: The anti-inflammatory effect of intravenous anesthetics in abdominal surgery

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Mentor: Stjepan Barišin, M.D., Ph.D, Department of Anesthesiology, Reanimatology and Intensive Care Medicine, University Hospital Dubrava, Zagreb. Faculty of Medicine, J. J. Strossmayer Osijek

Introduction: Clinical studies have shown that IV administration of anesthetics, lidocaine and ketamine with their anti-inflammatory properties, modulates the acute immune response associated with surgical tissue injury, and in this manner they are able to reduce postoperative pain. Lidocaine has anti-inflammatory effects on polymorphonuclear granulocytes, IL-6 and IL-8 cytokines, complement component C3a and IL-1ra in serum. Ketamine produces its anti-inflammatory effects by reducing CRP and IL-6 in serum and by inhibiting NF- κ B, which regulates gene transcription responsible for the production of proinflammatory factors.

Hypothesis: Perioperative combinend IV administration of lidocaine and ketamine could have a more favorable anti-inflammatory effect compared to anesthetic given alone or with placebo.

Aims: To investigate the effects of lidocaine and ketamine in patients undergoing abdominal surgery on:

- 1) Acute immune response following the level of proinflammatory factors in serum (CRP, IL-6, IL-8)
- 2) Postoperative pain management
- 3) Recovery of bowel function
- 4) Length of stay in the ICU and length of hospitalization
- 5) Reduced administration of opioids
- 6) Reduction of total treatment costs
- 7) Recovery time between patients undergoing conventional and laparoscopic resection of the colon

Materials/Participants and Methods: A double-blind, placebo-controlled study will include 120 patients: 60 undergoing conventional and 60 undergoing laparoscopic resection of the colon. Patients will be randomly assigned to one of four groups: lidocaine, ketamine, lidocaine-ketamine, and placebo. Lidocaine will be administered at a dose of 1.5 mg/kg prior to surgical incision followed by an infusion at a rate of 1.5–2 mg/kg/hr until the end of surgery. Ketamine will be administered at a dose of 0.5 mg/kg in a bolus prior to surgical incision followed by an infusion at a rate of 0.1–0.2 mg/kg/hr until the end of surgery. Bolus and continuous placebo infusion (0.9% NaCl) will be equally administered at the same dose as the aforementioned anesthetics until the end of the surgery.

Research plan: The intensity of pain will be measured using the VAS score 2 hours and 4 hours following surgery and every 12 hours the following days. We will measure the consumption of opioids during and after surgery, the length of stay in the ICU, where pain control and analgesics use will be measured, as well as recovery of bowel function. Proinflammatory markers in serum (CRP, IL-6, IL-8) will be measured before induction of anesthesia, then 2 hours and 48 hours following the completion of surgery.

Significance/Expected scientific contribution: The modulation of the acute immune response to surgical stress following the administration of IV anesthetics during colorectal surgery results in faster recovery of patients, reduced time of hospitalization along with reduced treatment costs.

Keywords: anti-inflammatory effect, surgical stress, lidocaine, ketamine, abdominal surgery



Dissertation Proposal Title: The effect of age, cigarette smoking and oral L-arginine supplementation on hepatic blood flow in healthy subjects

PhD candidate: Tijana Pandurović, Department of Radiology, General Hospital Vukovar

Mentor: Assoc. Prof. Lada Zibar, M.D., Ph.D., Faculty of Medicine, Josip Juraj Strossmayer University of Osijek; Department of Dialysis, Clinic of Internal Medicine, University Hospital Centre Osijek

Introduction: Arterial system is a blood distribution system adaptable to variations in blood flow in certain body parts, especially in muscles. One of the main causes of vascular dysfunction by arterial damage is atherosclerosis. Less attention is paid to blood flow disorders that occur distally from regional arteries (arterioles, capillary plexuses), to elasticity and to adaptability of parenchymal organs. There is not much research that observes several levels of circulatory system concurrently within a subject. There's a possibility of identifying three subgroups of disorders: dominantly arteriosclerosis, capillary dysfunction caused by parenchymal organ fibrosis and mixed forms. It is important to point out that a tissue with an inadequate perfusion often depends on local synthesis of nitric oxide (NO). Since an increased synthesis of NO occurs in such patients, a relative deficit of L-arginine as a crucial precursor is possible.

Hypothesis: Older age and nicotinism attribute to vascular dysfunction in subjects that do not suffer from circulatory or liver diseases and peroral L-arginine administration affects blood flows in tissues, including liver.

Aims:

- To determine liver circulatory and microcirculatory system within healthy subjects before and after L-arginine administration
- To determine the effect of age and nicotine on vascular function
- To determine the effect of L-arginine on vascular function

Materials and Methods: Four groups of subjects are formed, defined by their age and nicotine consumption. Each group consists of at least 30 subjects. The first two groups are made of people aged 30 or younger, defined as younger adults; one group

is comprised of smokers, while the other of non-smokers. The next two groups are made of people older than 30, defined as older adults, and are also divided into a smoker and a non-smoker group. A smoker is defined as a person who has, in the last year, smoked at least 10 cigarettes per day.

A Color Doppler on a Philips Affinity 70 ultrasound device will be used to observe arteries and to measure blood flow velocity through its lumen; also, a Biopac Student Lab device will be used for multichannel recording of different signals (infrared plethysmography and electrocardiography).

Research plan: Two groups of subjects, without any evident clinical data on circulatory or liver diseases, are formed. Two consecutive recordings are planned for each subject in the morning for two consecutive days. Every subject will, at the same time, have a blood flow velocity in the abdominal aorta, superior mesenteric artery, renal arteries and portal vein by Doppler ultrasound recorded, as well as plethysmography of capillary flow in little fingers of fists along with an ECG. After the first recording, the subject will receive two 500 mg L-arginine capsules (NO precursor) which they should take in the evening after a lighter meal not containing high amounts of protein, for the intention of periphery tissues to synthesize NO by tomorrow measurement.

Expected scientific contribution:

- Types of circulatory dysfunction according to age and cigarette smoking
- Understanding regulation of blood flow through large regional arteries including liver arteries and through capillary network
- Clinical peroral administration of L-arginine as a precursor of NO



Disertation Proposal Title: Influence of omega-3 fatty acid supplementation during pregnancy and lactation on the components of the humoral immunity in mature human breast milk

PhD candidate: Dragica Pavlović, MSN, RN, Faculty of Dental Medicine and Health University of Osijek, Health Centre Osijek, Osijek, Croatia

Mentor: Assist. Prof. Martina Mihalj, MD, PhD, Faculty of Medicine University of Osijek, University Hospital Centre Osijek, Osijek, Croatia

Introduction: Supplementation of omega-3 fatty acids, particularly docosahexaenoic acid (DHA), in lactating women increases breast milk and plasma DHA levels and changes infants omega 6:3 fatty acid ratio in favour of n-3 fatty acids (Sherry et al., 2015). During the infection of the mother and/or infant, there is an increase in the number of leukocytes secreting cytokines appropriate for the immune response against the specific pathogen (Pacheco et al., 2015). In addition, the levels of omega-3 polyunsaturated fatty acids positively correlate with soluble IgA and CD14 levels in human milk, suggesting a close relation of fatty acid status and function of the mother's immune system (Dunstan et al., 2004). Recent pre-clinical studies on blood lymphocytes showed that omega-3 PUFAs induced B-cell mediated humoral immune responses (Teaqua et al., 2013, Whelan et al., 2016); however, data on their effect on the humoral immune components in mature human milk are scarce.

Hypothesis: Omega-3 fatty acids affect immune properties of the mature human breast milk by increasing humoral immune response capacity and promoting antiinflammatory environment.

Aims: The aim of this study is to investigate the effect of omega-3 fatty acids supplementation during pregnancy and lactation on the cellular and soluble components of the humoral immunity in mature breast milk.

Materials/Participants and Methods: The study will include 60 women from the Osijek-Baranja County who gave a term birth of their second or any of the next children, had a normal, regularly controlled pregnancy and uncomplicated postpartal period. Experimental group will include 30 women who will receive omega-3 fatty acids supplements during their second or any of the subsequent pregnancies and

postpartal periods (minimum 12 weeks before and 30 days after the birth). Given the known and significant variations in the composition of the breast milk depending on the time passed since the birth (colostrum, transient and mature milk), and during each breastfeeding (first milk is acellular in order to quench baby's thirst), a standardized collection of the sample will be arranged. Mothers will receive detailed instructions and, if necessary, education on how to raise milk. The sample will be taken from mature milk - which is produced a month after a term birth and so called. „The last“ milk which is released at the end of the each breastfeeding session. The samples will be processed for immunophenotypization by flow cytometry, determination of the fatty acid composition, immunoglobulin content via immunoelectrophoresis and cytokine determination by ELISA or Luminex method.

Work plan: The proposed study duration is 12±4 months. The FIRST PHASE of 4-6 months will include issuing of the Ethics Committee of the Faculty of Medicine in Osijek approval, procurement of necessary reagents, optimization and introduction of protocols for isolation and enrichment of milk lymphocytes, setting up primary cell cultures and in vitro stimulation of breast milk lymphocytes, followed by implementation of immunophenotyping protocols and recruitment of participants. At the same stage, women in the experimental group are going to starting the omega-3 fatty acid supplementation during the last 12 weeks of pregnancy and continue with the supplementation for a period of minimum 30 days or until the enrollment into the study protocol. In the SECOND PHASE (6-8 months), the milk samples will be collected and processed for planned analyses, while the THIRD PHASE (4 months) will be utilized for data analysis and preparation of the publication.

Significance/ Expected scientific contribution: The results of this study could help to elucidate the mechanisms underlining the beneficial effects of omega-3 fatty acids on the immune system of the breast milk, and to help in the process of creating recommendations for the mothers diet protocol during breast-feeding period.

Keywords: humoral immunity, B lymphocytes, follicular T-helper cells, breast milk, omega-3 fatty acids



Title of abstract: Bile duct diameter changes after laparoscopic cholecystectomy: magnetic resonance cholangiopancreatography prospective study

Dissertation Proposal Title: Bile duct diameter changes after laparoscopic cholecystectomy: magnetic resonance cholangiopancreatography prospective study

PhD candidate: Tomislav Pavlović, M.D., Department of Radiology, University Hospital "Sveti Duh" Zagreb

Mentor: Prof. Zvonimir Sučić, M.D., Ph.D., Department of Radiology, University Hospital "Sveti Duh" Zagreb, Faculty of Medicine Josip Juraj Strossmayer University of Osijek

Introduction: The bile duct diameter can be changed because of different factors. Obstructive changes, stones and previous surgical procedures can cause bile duct dilatation. As an additional factor that can cause bile duct dilatation, age and cholecystectomy are mentioned. Previous studies have contradictory results about the dilatation of bile ducts after cholecystectomy. With this research we want to help resolve the controversy, the advantage of this prospective study compared to earlier studies is based on the sample and methods and the accuracy because of sensitivity and specificity of the MRCP review.

Aims: To determine the influence of laparoscopic cholecystectomy on the diameter of the bile duct measured by MRCP. Investigate changes in intrahepatic and extrahepatic bile ducts before and after laparoscopic cholecystectomy (3 months and 6 months after surgery), investigate changes intrahepatic and extrahepatic bile duct diameters with age and the possible association of diameter changes with biochemical parameters.

Materials/Participants and Methods: The examinees are the patients older than 18 years who are referred to elective laparoscopic cholecystectomy due to gallstones or gallbladder cholesterol. It will be screened for 50 patients. The control group will consist of 50 people without liver disease, gallbladder disease, bile duct disease and pancreas and with normal laboratory findings. Patients will be screened after for at least 8 hours fasting, within 7 days before cholecystectomy, then after 3 months and 6 months after cholecystectomy. The standard MRCP protocol will be used for examination. The diameter of the intrahepatic and extrahepatic bile duct will be

measurement at multiple points in the frontal and sagittal plane perpendicular to the bile duct os from the mucosal to mucosal surface.

Results: Fifteen patients (12 female and 3 male) were analyzed, mean age 53 ± 14 years. The results were analyzed by Repeated measures ANOVA test. The diameter of the right intrahepatic bile duct was statistically significantly higher for 3 months and 6 months after cholecystectomy ($p=0.0002$, $p<0.0001$) as well as 6 months after cholecystectomy in comparison with 3 months of cholecystectomy ($p=0.0003$). At the same measurement intervals the diameter of the left intrahepatic bile duct was also statistically significantly higher ($p=0.004$, $p<0.0001$, $p=0.001$). Statistically significant difference was found at the level of right hepatic bile duct in the laterolateral direction for 3 months and 6 months after cholecystectomy ($p=0.04$, $p=0.04$) and at the level of proximal common bile duct in the laterolateral direction 6 months after cholecystectomy ($p=0.03$).

Conclusion: Preliminary results indicate a statistically significant change in the diameter of intrahepatic bile ducts after cholecystectomy as well as some segments of extrahepatic bile ducts.

Keywords: bile duct, cholecystectomy, magnetic resonance, diameter, dilatation, cholangiopancreatography



Dissertation proposal title: The use of an injectable bone substitute based on biphasic calcium phosphate in a two-stage maxillary sinus floor augmentation: radiological and histological evaluation

Ph.D. candidate: Marija Pejakić, D.M.D., Faculty of Dental Medicine and Health Osijek

Mentor: Assist. Prof. Marko Matijević, D.M.D., Ph.D., Faculty of Dental Medicine and Health Osijek

Introduction: Maxillary sinus floor augmentation (MSFA) is indicated prior to dental implant placement when the height of the residual alveolar crest is insufficient. When choosing bone graft material, autologous bone is the gold standard. However, because there are limitations while using it, regarding availability and morbidity at the donor site, different alternatives have been developed. One of these is biphasic calcium phosphate (BCP), consisting of 60% hydroxyapatite and 40% β -tricalcium phosphate, known for its osteoconductive and osteoinductive properties. The injectable form of this material allows easy handling and application. Currently, there are no clinical studies on the use of an injectable biphasic calcium phosphate (I-BCP) in two-stage MSFA.

Hypotheses:

1. The use of I-BCP in two-stage MSFA leads to bone regeneration.
2. I-BCP undergoes nearly complete degradation.

Aims:

1. To examine the bone regenerative potential of an I-BCP by assessing histological results of bone biopsy harvested from maxillary sinus.
2. To analyze radiological changes of the augmented area.
3. To assess degradation of I-BCP 6 months after augmentation.
4. To register wound healing complications.

Participants and methods: Twenty healthy patients, who require two-stage MSFA prior to implant placement and with a residual bone height of 5mm or less, will be selected. Unilateral MSFA according to Tatum will be performed with I-BCP. Implant placement will be performed after 6 months of healing. Simultaneously with implant placement, bone biopsy for histologic analysis will be harvested using trephine burr

and fixed in 4% formaldehyde. The sections will be examined under a light microscope. Cone beam CT will be done immediately after the first stage of MSFA and 6 months after, prior to the re-entry procedure. During the study detailed photographic documentation of all clinical procedures and healing process will be done. Data will be analyzed using the Statistical Package for the Social Sciences (SPSS).

Research plan: This prospective, single-arm study will be performed in the period between October 2018 and December 2019. Patients will be recruited in a Community Health Center in Osijek. To enter the study, patients need to provide written consent. All surgeries will be performed by one experienced oral surgeon.

Expected scientific contribution: This study will provide a valuable clinical, histological, and radiological results that can simplify bone augmentation procedures.

Keywords: maxillary sinus floor augmentation, CBCT, histology, biphasic calcium phosphate



Title of abstract: Correlation of Cerebrovascular Risk Factors and Carotid Plaque Score: a pilot study

Dissertation Proposal Title: Correlation of Cerebrovascular Risk Factors and Carotid Plaque Score

PhD candidate: Romana Perković, MD, Department of Neurology, University Hospital Osijek

Mentor: Prof. Silva Butković Soldo, MD, PhD, Department of Neurology, University Hospital Osijek

Introduction: In order to identify asymptomatic patients with latent vascular risk, we need to upgrade and extend the methods for identifying such patients. There is a shared opinion that simple, inexpensive and non-invasive methods for recognizing subclinical atherosclerosis should be used, such as measurement of plaque in carotid arteries.

Aims: The primary objective of this study is to investigate whether we can estimate the percentage of risk for cerebrovascular disease based on the sum of atherosclerotic plaques of carotid arteries or known as plaque score.

Participants and Methods: The research included 160 subjects, male and female, from eastern Croatia between 60 and 69 years of age. The main group of subjects, 60 male and 60 female, had one or more of the four major risk factors for atherosclerosis - hypertension, diabetes, hypercholesterolemia, smoking. The controls, 20 male and 20 female, were free from examined risk factors. Ultrasound scanning was performed by a single expert sonographer using a 7 MHz linear transducer. Maximal height (thickness) is measured in every plaque. Sum of all heights is plaque score.

Results: There is a statistically significant difference in the total plaque depending on gender, with women having a statistically lower overall plaque value. There is a statistically significant difference in total plaque height depending on the number of risk factors where subjects with no risk factors have a statistically lower total plaque value than subjects with one or more risk factors. A subject with one risk factor has a higher average plaque score of 19.50% in relation to a subject who has no risk factor.

A subject with two risk factors has a higher average score of 55.42% in relation to a subject who has no risk factor. A subject with three risk factors has a higher average score of 137.77% compared to a subject who has no risk factor.

Conclusion: We have shown that the subjects who do not have any risk factors have a statistically lower overall plaque score than subjects with one or more risk factors and that the height of the plaque score increases with the number of risk factors. There is a possibility of calculating the percentage of plaque score from risk factors, in relation to healthy subjects. Plaque scores can identify asymptomatic people who will benefit from aggressive preventive measures which will consequently lower number of atherosclerotic cerebrovascular incidents.

Keywords: carotid artery, atherosclerosis, plaque score, risk factors, stroke



Title: Macular thickness changes in diabetic patients after uncomplicated phacoemulsification cataract surgery

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Introduction: Pseudophakic macular edema is the most common cause of visual impairment after uncomplicated phacoemulsification cataract surgery. Cataract surgery is a risk factor for incidence or worsening of macular edema in diabetic patients. The etiology of cystoid macular edema is not completely understood. The incidence of clinical pseudophakic cystoid macular edema in early postoperative period is 0.1-2.35%.

Aim: To analyse macular thickness changes after uncomplicated phacoemulsification cataract surgery in early postoperative period in diabetic patients using optical coherence tomography (SD-OCT).

Participants And Methods: This prospective study included 55 patients divided in two groups. The first group consisted of 25 diabetes mellitus patients, of whom 7 men (12,73%) and 18 women (32,73%). The control group consisted of 30 patients, 11 men (20,00%) and 19 women (34,55%) with no history of diabetes, nor any other ophthalmic disease. All patients underwent uncomplicated phacoemulsification cataract surgery at the Department of Ophthalmology, University Hospital Centre Osijek in the period from October 2017. to January 2018. and were followed up 1 month after surgical procedure. Exclusion criteria were: previous intraocular surgery of any type, history of previous uveitis, non diabetic retinal disease, earlier macular edema or thickening of any etiology, previous laser photocoagulation treatment within 3 months before cataract surgery, choroidal disorders, proliferative diabetic retinopathy or impossibility to perform OCT due to mature cataract, pupil seclusion or progressive corneal degenerations. Patients were followed up 1 month after cataract surgery. Preoperatively, all patients passed through full ophthalmological examination, the

best corrected visual acuity (BCVA) using Snellen chart was measured, they all passed slit lamp grading of lens opacification according to the Lens Opacities Classification System III (LOCS III) and all underwent SD-OCT macular thickness measuring of eye planned for surgery. The first control was performed one week after surgical procedure and the second control one month after cataract surgery. At each control, BCVA was determined, a complete ophthalmological examination was performed and SD-OCT measuring macular thickness of operated eye was recorded. Cumulative dissipated energy (CDE) and estimated fluid used (ccm^3) were measured as the most important parameters during surgical procedure, which may be related to macular thickness changes in the early postoperative period.

Results: With this prospective study, we wanted to investigate the effect of uncomplicated phacoemulsification cataract surgery on macular thickness changes in diabetic and control group of patients in the early postoperative period. We proved that there was statistically significant difference in macular thickness changes in diabetic group of patients before surgery and on the second control ($p = 0.0045137$) as well as between the first and the second control ($p = 0.0069024$). There was also a statistically significant difference in macular thickness changes in the control group of patients before surgery and on the second control ($p = 0.052657$) and between the first and the second control ($p = 0.01285$). By comparing the macular thickness changes between the diabetic patients and control group, we proved that there was not statistically significant difference in macular thickness changes neither on the first ($p = 0.6848$) nor on the second control ($p = 1$). The effect of CDE on macular thickness changes was investigated using Spearman's correlation coefficient for all measurements. We proved that the correlation between CDE and macular thickness changes was not statistically significant in diabetic group of patients neither on the first ($p = 0.25858$), nor on the second postsurgical control ($p = 0.38402$). Also, it was proved that the correlation between CDE and macular thickness changes was not statistically significant prior to surgery and on the second control ($p = 0.40211$), as well as between the first and the second control ($p = 0.8416$) in the control group of patients. The influence of estimated fluid used (ccm^3) on macular thickness changes was investigated using Spearman's correlation coefficient for all measurements. The correlation between estimated fluid used and macular thickness was not statistically significant on the first ($p = 0.6241$), as well as on the second control ($p = 0.74875$) in the diabetic group, also within the control group on the first ($p = 0.90735$) and on the second control ($p = 0.69987$). Intraocular pressure curve was followed in both group of patients in preoperative period as well as on the first and on the second control. We proved that there was no statistically significant difference in the intraocular pressure in the diabetic group of patients prior to surgery and on the first control ($p = 0.23304$), as well as before surgery and the on second control ($p = 0.77922$). The difference in

intraocular pressure was no statistically significant before the surgery and on the first control ($p = 0.27146$), as well as before surgery and on the second control ($p = 0.69968$) in the control group of patients.

Conclusion: Uncomplicated phacoemulsification cataract surgery causes macular thickness changes in the early postoperative period in both groups of patients. Statistically significant differences in macular thickness were observed one month after the surgery compared to preoperative macular thickness and compared to macular thickness seven days after the surgery in both groups of patients. The effect of cumulative dissipated energy (CDE) and estimated fluid used during cataract surgery was not statistically significant on macular thickness changes in early postoperative period. Although phacoemulsification cataract surgery significantly reduced the proportion of early postoperative complications, this study has been shown that surgery per se has effect on macular thickness changes in the early postoperative period, which is proved using SD-OCT. In this prospective study, macular thickness changes did not present with clinically significant macular edema as well as with decreased visual acuity in early postoperative period. In both groups of patients, there was a statistically significant difference in visual acuity before surgery and on the second control, as well as between the first and the second control.

Keywords: macular edema, phacoemulsification, diabetes, OCT, early postoperative period



Dissertation Proposal Title: Impact of Defence Mechanisms and Alexithymia on the Level of Sleep Disorder and Co-Operability in Patients on Chronic Haemodialysis Program

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Mentor: Assoc. Prof. Dunja Degmečić, M.D., Ph.D., Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Introduction: Patients with end-stage renal failure are included in the haemodialysis treatment program, i.e. renal replacement therapy program, at various stages, depending on comorbidities. Patients on the haemodialysis treatment program are faced with health limitations caused by their primary disease and obligations to comply with a dietary restriction program and undergo the prescribed treatment. In addition to the above-mentioned factors, a person's inclusion in haemodialysis treatment, in and of itself, imposes certain limitations through an obligation to respect specific treatment protocols. All of the above represents stressors that patients deal with more or less successfully. Whether a patient will be successful in coping with stressors largely depends on his defence mechanisms against stress developed by the person's ego. Defence mechanisms protect a person from anxiety caused by external and internal stressors that may threaten personality integration. Depending on the structure of their ego, an individual may use the following types of defence mechanisms: neurotic (reaction formation, somatization), psychotic (denial), immature (passive-aggressive behaviour, projection), or mature defence mechanisms (sublimation, identification) - which are the most acceptable. Patients on the haemodialysis treatment program more often use neurotic and immature defence mechanisms (reaction formation, projection and denial), which is directly linked to lower quality of life and negatively affects their co-operability. The use of denial, which falls under psychotic defence mechanisms, may be linked to higher levels of secondary alexithymia, because in order to alleviate intrapsychic instability, patients avoid becoming conscious of or showing negative feelings evoked by haemodialysis treatment. Alexithymia – inability to identify and express emotions, connect emotions with physical manifestations or express them – is highly prevalent among patients with chronic renal failure. It is linked to their depression symptoms, as well as high levels of sleep disorders and sleepiness in these patients. There is not enough research that examines the relationship between the type of defence mechanisms against

stress and the levels of alexithymia, sleep disorders and daytime sleepiness, as well as serum levels of phosphorus, calcium, parathyroid hormone, haemoglobin, albumin, total proteins, total cholesterol, triglycerides, CRP, which represent factors used in nephrology to monitor patients with chronic renal failure and related to treatment outcome.

Given that no questionnaires for assessment of ego defence mechanisms have been translated and validated into Croatian, with prior permission of the authors, as part of this study, we will translate and validate the DSQ-40 self-report questionnaire (Defence Style Questionnaire-40), which uses 40 items to evaluate 20 defence mechanisms. The questionnaire was originally designed as a 63-item scale by Bond et al.; however, in 1993, the questionnaire was updated as a self-report instrument that includes 40 items. So far, DSQ-40 has been successfully translated and validated into several different languages. The translated versions evaluate similar results, so, therefore, as authors, we hold that DSQ-40, as an instrument for indirect assessment of unconscious defence mechanisms, may be highly useful in similar research studies dealing with the same or related topic.

Hypotheses:

1. Patients on the haemodialysis treatment program use immature and psychotic defence mechanisms against stress, have higher levels of alexithymia and suffer more from sleep disorders what has negative influence on compliance in therapy process.
2. Higher levels of mature defence mechanisms against stress in patients on haemodialysis correlate with lower levels of parathyroid hormone, phosphorus, creatinine and potassium.
3. For the Croatian translation of the DSQ-40, coefficients of Cronbach's alpha reveal good reliability and validity for examining subjects' defence mechanisms, whereas the factor analysis confirms the correlation between variables grouped under three subscales of this questionnaire.

Goals:

1. Measure the levels of psychotic, mature, immature and neurotic defence mechanisms against stress, levels of alexithymia and sleeping disorders in patients on the chronic haemodialysis program.
2. Determine the relationship between levels of defence mechanisms, alexithymia and sleep disorders and blood biochemical parameters in patients on haemodialysis what will explain the levels of compliance.
3. Examine the reliability (Cronbach's alpha) and correlation of variables in the Croatian translation of DSQ-40.

Participants and methods: Prior to conducting the research, all participants will be given an informed consent form by virtue of which they consent to participate in the research. Only the patients who give their consent will be included in the research.

The proposed cross-sectional study will be carried out with patients on the haemodialysis treatment program at the Department for Haemodialysis of the General County Hospital Vinkovci and Department for Nephrology of the Clinical Hospital Centre Osijek. The research includes participants aged 30 to 80, regardless of sex, educational profile or marital status. Etiology of the chronic renal failure in the above-mentioned participants varies, so the study includes patients diagnosed with type 1 and type 2 diabetes, hypertension, glomerular and interstitial kidney disease, as well as cystic kidney disease. Patients receive haemodialysis two or three times per week. Exclusion criteria for participation in the study include psychiatric disorders, psychoorganic syndrome, recorded alcohol consumption in the past 6 months, occurrence of psychotic episodes and severe emergency somatic conditions (heart failure, pneumonia, sepsis-associated conditions, etc.).

Patients will be asked to fill out a questionnaire on their socio-demographic characteristics, which will assess their age, sex, marital status, educational profile and financial status.

To measure alexithymia, we plan to use the validated Croatian version of the Toronto Alexithymia Scale (TAS 20). TAS 20 is a self-report instrument consisting of 20 items organized in three subscales used to assess alexithymia factors. The factors measure difficulties identifying feelings, difficulties describing feelings and externally oriented thinking.

To measure defence mechanisms, DSQ (Defence 40 Questionnaire) will be used, which is a self-report scale featuring 40 questions and measuring twenty ego defence mechanisms classified into mature, immature and neurotic defences. With the permission of the authors, DSQ will be translated into Croatian. Translation of the questionnaire will be entrusted to two experienced bilingual psychiatrists, who use English in everyday professional communication. After translation has been completed, a qualified proof-reader with experience in proofreading both Croatian and English will be recruited to check the questionnaires. The Croatian and English versions of the questionnaire will be simultaneously distributed per a set of 20 bilingual participants respectively, the sample being composed of students with no access to the other version of the questionnaire. Defence mechanisms being permanent character traits relatively resistant to change, participants will be distributed the other version of the questionnaire after two weeks, which will prevent participants from memorizing the questions. Collection of filled-out questionnaires will be followed by reliability assessment (Cronbach's alpha) and factor analysis of the above-described questionnaire.

To determine the level of dullness, we will use the Epworth Sleepiness Scale (EES), a questionnaire with eight questions that assess subjects' daytime sleepiness in different situations. The questionnaire has been validated for use in Croatian-speaking context. Each question is rated from 0 to 3, according to the extent to which subjects agree or disagree with the provided statement, with the maximum score being 24.

Participants will also be presented with the Pittsburgh Sleep Quality Index (PSQ), a questionnaire, previously validated for use in Croatian, which consists of 18 items creating 7 components that assess subjective sleep quality. The maximum score for each component is 3, whereas the overall component score is 21. PSQ score above 5 indicates that a person suffers from a sleep disorder.

Statistical methods: Categorical data will be presented via absolute and relative frequencies. Numerical data will be described by arithmetic mean and standard deviation in cases that follow normal distribution, whereas in all other cases by median and interquartile range limits. Numerical variables will be tested for distribution normality using the Kolmogorov-Smirnov test. Differences between normally distributed numerical variables in two independent groups will be tested by the Student's t-test, whereas in case of deviation, Mann-Whitney U test will be used. Correlation of normally distributed variables will be measured by the Pearson correlation coefficient r , whereas in case of normal distribution deviations, we will use Spearman's rank correlation coefficient ρ (rho). All P-values will be presented as two-sided P-values. In order to evaluate reliability of the translated measurement scales (DSQ), we will use Cronbach's alpha, a measure used to assess internal consistency of the sum for both scales as well as their subscales. Factor analysis will be conducted in order to assess the consistency of items grouped under subscales and scales of the questionnaire. Level of significance will be set at $\alpha = 0.05$. As a statistical analysis tool, we will use SPSS software package for Windows 8 (version 21, SPSS inc., Chicago, IL, USA).

Research plan: Researchers will firstly collect data on the socio-demographic characteristics of participants and then apply the following self-report scales: Toronto Alexithymia Scale (TAS 20), Epworth Sleepiness Scale (EES), which have been validated for use by Croatian-speaking subjects, and Defence Style Questionnaire-40. As part of laboratory tests for routine check-up of patients on the haemodialysis treatment program, we will measure the serum levels of urea, creatinine, potassium, phosphorus, calcium, parathyroid hormone, haemoglobin, albumin, total proteins, total cholesterol, triglycerides, CRP and vitamin D. We will also record information on average duration of a haemodialysis session, haemodialysis adequacy (Kt/V index), systolic pressure and diastolic pressure values, interdialytic weight gain, number of haemodialysis sessions per week, vascular access (arteriovenous fistula or intravenous catheter).

Research will start only after approvals have been obtained from all competent ethics committees.

Expected scientific contribution of the research: This research is expected to contribute to the scientific community by determining the prevalence of alexithymia among participants on haemodialysis, defining the ego defence mechanisms that participants use to deal with everyday stressors and by establishing any possible correlations between the said defence mechanisms, alexithymia and sleepiness levels and laboratory tests of patients' blood levels of electrolytes, haemoglobin and parathyroid hormone as key parameters for determining a patient's clinical condition. According to the published research data available, no research has so far been conducted on correlation between defence mechanisms and sleepiness in patients on haemodialysis, for which reason scientific contribution will consist in better understanding – regardless of multiple etiology of patients – of the relationship between defence mechanisms and sleepiness. By linking defence mechanisms, alexithymia, sleepiness and haemodialysis quality parameters, the research aims to emphasize the role and importance of providing psychotherapeutic support as part of treatment programs for patients on haemodialysis, considering its impact on patients' overall health.

Key words: alexithymia, haemodialysis, sleep disorder, defence mechanisms, parathyroid hormone



Dissertation Proposal title: “Serum concentrations of folic acid, vitamin B12 and homocysteine in patients with treatment-resistant and non-treatment resistant depression”.

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Mentor: Assist. Prof. Bjanka Vuksan-Ćusa, Department of Psychiatry University Hospital Center Zagreb

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Introduction: Major depressive disorder (MDD) is the second leading cause of disability worldwide and it affects about 350 million people. In spite of the huge progress in the treatment of depression, at least 15% of patients do not sufficiently respond to first-line treatment: pharmacotherapy or psychotherapy. Regarding pharmacotherapy, an antidepressant trial lasting at least 4 weeks with the optimal dose of antidepressant (within the approved dosing range) was considered as an adequate treatment. Treatment resistance was defined as a failure to decrease the HAM-D-17 score to ≤ 17 , at least 2 adequate consecutive antidepressant trials were administered during the index episode. Treatment response was defined as the presence of HAM-D-17 score of < 17 ; either after the first or the second antidepressant trial.

In addition to functional disability, MDD increases the risk of severe physical disorders such as cancer, diabetes, stroke, inflammation and acute coronary syndrome through multiple molecular mechanisms. It is often related to stressful conditions and unhealthy lifestyle, such as smoking, low physical activity, sleep disturbances, less social activities and poor nutrition. Several potential biomarkers are relevant for different facets of depressive disorders. And differentially regulated by antidepressant treatment. Those parameters include metabolic, inflammatory, cardiovascular and apoptotic factors, i.e., adiponectin, apolipoprotein-B, B-type natriuretic peptide, cortisol, C-reactive protein, cysteine, homocysteine, fibrinogen, growth-differentiation factor-15, glycated hemoglobin A1c, leptin, high-density lipoprotein, interleukin-6, insulin-like growth factor-1, low-density lipoprotein, myeloperoxidase, osteoprotegerin, tumor necrosis factor- α , troponins and triglycerides. In addition, folic acid, vitamin B12 and homocysteine have been increasingly recognized as important players in the development and treatment of MDD.

Folic acid, also referred to as vitamin B9, is a pteroylglutamic acid consisting of

three components: 2-amino-4-hydroxypteridine nucleus, p-aminobenzoic acid and glutamic acid. It is important for DNA synthesis and conversion of some amino acids. Vitamin B12, also called cobalamin, is a water-soluble vitamin that is involved in the metabolism of every cell in the human body: it is a cofactor in DNA synthesis, and in both fatty acid and amino acid metabolism methylation and mitochondrial metabolism. It is particularly important in the normal functioning of the nervous system via its role in the synthesis of myelin, and in the maturation of developing red blood cells in the bone marrow. Subclinical deficiency affects between 2.5% and 26% of the general population.

Amino acid homocysteine is formed in the metabolism of methionine, which is introduced into the body food as a product of numerous S-adenosyl-methionine-dependent transmitting reactions. An important role in the homocysteine-methionine metabolism is the creation of a donor of S-adenosyl-methionine (SAM) methyl groups in a number of biological reactions. Homocysteine can be recycled into methionine or converted into cysteine with the aid of certain vitamins B. It is proven that brain neurons create homocysteine and circulate over the blood-brain barrier in both directions. Plasma homocysteine concentrations are 20 to 10 times higher than in cerebrospinal fluid, but there is a positive correlation between these two concentrations. In conditions of experimentally induced deficiency of folate neurons produce more homocysteine than neurons in folate rich media. The role of folate in the metabolism of homocysteine in the brain is confirmed and in vivo. Namely, in the cerebrospinal fluid of patients receiving antifolate therapy / methotrexate / lower folate and SAM values were found and elevated homocysteine concentrations.

Low levels of both folate and vitamin B12 have been repeatedly observed in patients with MDD, as well as in those with recurrent mood disorders treated by lithium. A relationship between depression and low folate has also been found in patients with alcoholism.

Folate and vitamin B12 are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAM) is formed. SAM donates methyl groups that are crucial for neurological function. Increased plasma homocysteine is a functional marker of both folate and vitamin B12 deficiency, and elevated homocysteine levels have been reported in depressive patients. In a large population study from Norway increased plasma homocysteine was associated with increased risk of depression but not anxiety

Hypothesis:

1. Serum folic acid concentration is lower in patients with treatment-resistant depression (TRD) than in participants with non-treatment-resistant depression (non-TRD)
2. Serum vitamin B 12 concentration is lower in patients with TRD than in patients with non-TRD

3. Serum homocysteine concentration is higher in patients with TRD than in patients with non-TRD

Aims: The aim of the present study is to compare serum concentrations of folic acid, vitamin B12 and homocysteine between patients with TRD and non-TRD.

Materials/Participants and Methods: In this cross-sectional study, we will include patients diagnosed with MDD, with the different levels of response to treatment with antidepressants. The diagnosis of MDD would be confirmed using ICD-10 and DSM-5. Sociodemographic data would be collected by semi-structured questionnaire. Symptoms of depression would be assessed by Hamilton Rating Scale for Depression, (HAM-D-17) and Montgomery-Åsberg's Depression Scale, (MADRS). Cognitive function would be tested by Test Test Series Verbal Fluency Test, Numerical Memory Test from Wechsler's Intelligence Test and Subtest encoding (psychomotor speed), derived from Wechsler. Sampling would be done by venepuncture of the forearm, in the morning, after an overnight fasting. Overall, 116 patients would be enrolled. Sample size is calculated for the purpose of verifying the three above mentioned hypotheses. Expected values in the non-TRS group were estimated based on Assies et al. 2015: arithmetic mean (standard deviation) of folic acid 3,12 (0,15), vitamin B12 314 (53,0), homocysteine 2,23 (0,15). (1) The lowest difference considered to be theoretically and clinically relevant is +/- 10%. Targeted statistical strength is determined at 0.80, and the level of statistical significance at $p < 0.05$. We will check the hypothesis using the three univariate Mann-Whitney-Wilcoxon two-way test of the statistical significance of the difference. Under these preconditions, $n = 17$ for folic acid, $n = 49$ for vitamin B12 and $n = 10$ for homocysteine is required for each group. Therefore, the largest sample is required to test the hypothesis of the difference in the homocysteine level between the two patient groups. Expecting $\leq 15\%$ of incorrectly collected data, the initial sample size was estimated at $n = 58$ in each group. This sample size was calculated using 2000 Monte Carlo samples in the program: PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. The investigation will take place in the University Hospital Centre Zagreb, Department of Psychiatry.

Research plan: In this cross-sectional study, we will plan include equal number of patients with TRD and non-TRD, i.e., 58 in each group, which makes 116 participants in total.

Patients with TRD would be recruited predominantly from inpatient population, while patients with non-TRD are expected to be mostly outpatients.

Each patient would be provided with sufficient information regarding the research process and will be offered to sign informed consent document for participation. The

patients would be checked for the following criteria:

Inclusion criteria: Women diagnosed with MDD, aged 18-70 years, who signed an ICD, approved by the local Ethics Committee

Exclusion criteria: Men and children diagnosed with MDD . Women diagnosed with MDD who have antipsychotic therapy.

The subjects will continue to take antidepressant therapy.

The examiner will conduct a psychiatric interview, confirm the diagnosis in accordance with the existing classification systems as provided above, and also collect the sociodemographic data (expected duration is 40 minutes).

After this procedure, HAMD-17, MADRS and cognitive test battery would be performed (expected 45 minutes).

Blood sample (5 to 10 ml) will then be taken to measure folic acid, vitamin B 12 and homocysteine concentrations in both patient groups. Within the aforementioned research, we will ask patients to complete the questionnaire on religious coping (about 15 minutes) and the Fagerstrom Test for Nicotine Dependence (FTND) (about 10 minutes).

Significance /Expected scientific contribution: There is now substantial evidence of a decrease in serum/red blood cell folate, serum vitamin B12 and an increase in plasma homocysteine in depression. Low folate levels are linked to a poor response to antidepressants, and treatment with folic acid is shown to improve response to antidepressants. It has also recently been suggested that high vitamin B12 status may be associated with better treatment outcome. While decreased levels of folic acid and B12 vitamin, and an increased homocysteine level are related to depression, and decreased folic acid and B12 levels to poor treatment response, there is currently no data on the association between the levels of folic acid, B12 vitamin and homocysteine serum concentration and TRD. Our results would expand the current knowledge on the TRD, and, in case of the confirmation of one or more of hypotheses, the aforementioned easy-to-obtain potential biological markers of TRD might be used in clinical practice in order to recognize the development of TRD as soon as possible. Namely, the application of B12 and folic acid might overcome their deficit, while the introduction of more healthy eating habits might decrease homocysteine levels. Eventually, those results are expected to improve the diagnosis and treatment of patients with TRD.

Keywords: Non – treatment-resistant depression; Treatment-resistant depression; Folic acid; Vitamin B12; Homocysteine



Dissertation Proposal Title: Risk Factors for Allergy Development in the First Year of Life – a Prospective Study

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Introduction: There is an increase in incidence and prevalence of allergic diseases in the world and numerous risk factors have been linked to this increase including the type of childbirth, antibiotic use in the first few days of life, the type of diet, environmental factors and domestic animals in the family. However, in the last few years, neonatal jaundice has been investigated as one of the possible co-factors. The pathomechanisms of this association include antioxidant effect and direct effect on the immune system.

There is some evidence showing increase in allergic asthma and rhinitis in children who had neonatal jaundice and/or phototherapy. However, there is a lack of well-designed prospective studies which will further analyse this association taking into account other factors.

Hypothesis: The neonatal jaundice significantly reduces the incidence of early atopic diseases in healthy-born infants.

Primary aim: To determine the role of neonatal jaundice on the occurrence of atopic diseases in children in the first year of life.

Specific aims: To determine the role of the childbirth type, early antibiotic use, early feeding (breast milk or infant formula) and introducing food supplements on the occurrence of atopic diseases in children in the first year of life.

Participants, Methods and a Research plan: The study will be conducted at the Maternity ward of the Clinical Medical Center Osijek, and it will include full-term infants born between December 2017 and October 2018 through four months (December, March, June and September). Only infants whose mothers sign informed consent will be included in the study. Data that will be collected include: sex of the child; the number

of the pregnancy; mother's and father's age; birth at gestational age; the Apgar score; birth weight and length; type of childbirth; complications during childbirth; highest bilirubin level; phototherapy; mother's blood type; perinatal complications; early infections; early antibiotic use; streptococcus in mother's cervix; stay in the NICU; breastfeeding or formula after birth; mother's diet during pregnancy and lactation; family history of allergic diseases; household; smoking; household animals; vaccination.

The children will be monitored throughout the first year of life via direct contact with the parents, as well as collecting data from primary paediatricians. Data on the atopic disease (atopic dermatitis and food allergies) will be collected at the age of 4, 8 and 12 months and occurrence of obstructive bronchitis will be determined at the end of the first year.

Expected scientific contribution: The results of the study will help determine, for the first time, the influence of early-stage factors of neonatal jaundice and other co-factors on allergy occurrence in the first year of life.

Keywords: neonatal jaundice, atopic diseases, food allergies, children



Dissertation Proposal Title: The effects of GLP-1 receptor agonist on testosterone levels in obese men with type 2 diabetes

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Mentor 2: Prof. Aleksandar Včev, MD, PhD, Faculty of Dental Medicine and Health Osijek, Faculty of Medicine Osijek, Croatia.

Introduction: The prevalence of type 2 diabetes (T2D) is increasing worldwide and it has reached global epidemic proportion. It is estimated that over 425 million adult have diabetes and one in two remains undiagnosed. Fifty percent of obese men with T2D have low serum testosterone levels (2). A meta-analysis has shown that body weight loss, either by diet or surgery, leads to a testosterone rise in diabetic patients. Sulfonylurea increases total testosterone (TT) levels and TSI values. Metformin and low calorie diet decreasing TT levels. A clinical study of rosiglitazone in T2D men with hypogonadism resulted in increased serum testosterone levels. Pioglitazone therapy significantly decreases total, free and bioavailable testosterone in eugonadal men with T2D. Insulin therapy increases SHBG in newly diagnosed type 2 diabetic patients. Considering that the levels of testosterone in men with T2D are differently depending of various application of antihyperglycemic therapy, its indicates that the levels of testosterone and plasma glucose changes are not directly related. Treatment with GLP-1 receptor agonists (GLP-1 RAs) reduces body weight in obese patients with T2D and body weight loss should increase levels of testosterone.

Hypothesis: Men with T2D who were on oral antihyperglycemic therapy and with BMI equal or higher than 35 kg/m² should have decreased testosterone levels in a high percentage. Treatment with GLP-1 receptor agonist (GLP-1 RA) should increase testosterone levels in such patients.

Aims: the main aim of this study will be to investigate the effects of GLP-1 receptor agonist (GLP-1 RA) on testosterone serum levels in men with T2D who were on oral antihyperglycemic therapy and with BMI equal to or higher than 35 kg/m². The

additional aims will be to investigate the impacts of treatment with GLP-1 RA on other biochemical and anthropological parameters.

Materials/Participants and Methods: A group of fifty male patients with T2D, aged 18 -75 years, who were on oral antihyperglycemic therapy and with BMI equal or higher than 35 kg/m² and fifty otherwise men, comparable in age, BMI and previous oral antihyperglycemic therapy will be enrolled in the prospective study which will be conducted at Department of Endocrinology, diabetes and clinical pharmacology, Dubrava University Hospital. Exclusion criteria will be: female patients, aged <18, patients with presence of severe heart, liver, kidney, pancreas disease, chronic obstructive pulmonary disease, cancer, autoimmune disease, allergy to GLP-1 RA, use of exogenous hormones, gastrointestinal motility drugs, glucocorticoids, thyroid hormone or other disorders. All blood samples will be obtained and analyzed in Central laboratory of Dubrava University Hospital. Statistical analysis will be carried out using SPSS version 17.0. Normality of distribution of numerical variables will be tested using the Shapiro-Wilk test. Numerical variables will be presented as mean ±-standard deviation or median and interquartile range and compared between the groups using the Student's t test or the Mann Whitney U test depending on normality of data distribution. Categorical variables will be presented as proportions and percentages and compared between the groups using the Fisher's test or Chi squared test where appropriate. Correlation between numerical variables will be tested using the Spearman's rank correlation. P values <0.05 will be considered statistically significant.

Research plan: One hundred subjects will be randomly grouped and treat with GLP-1 RA plus other oral antihyperglycemic therapy and other group will be comparable in age, BMI and previous oral antihyperglycemic therapy but without GLP-1 RA. They will receive liraglutide, Novo Nordisk, Bagsværd, Denmark. Height, weight, waist circumference, BMI, blood pressure, fasting sample, HbA1c, LH, FSH, SHBG, testosterone levels, lipid profile, liver enzymes and other biochemical parameters will be measure before and 6 months after treatment.

Significance/Expected scientific contribution: There was no study that compares effects of GLP-1 receptor agonist on serum testosterone levels in obese men with T2D who were on oral antihyperglycemic therapy. The main contribution of this study will be to predict if the GLP-1 receptor agonists should be a therapeutic approach to treatment of lowered testosterone levels in men with type 2 diabetes.

Keywords: GLP-1 receptor agonist, testosterone, male, obese, type 2 diabetes.



Disertation Proposal Title: The role of vitamin C in the treatment of acute myeloid leukemia

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Mentor: Assoc. Prof. Lada Zibar, PhD, MD, Department of Nephrology, Clinic of Internal Medicine, University Hospital Center Osijek, Faculty of Medicine, University Josip Juraj Strossmayer Osijek, Osijek, Croatia

Introduction: Acute myeloid leukemia (AML) is malignant clonal disorder of myleoid cells. Some AML is caused by mutation in the Tet Methylcytosine Dixoygenase 2 (TET2) gene which helps stem cells to mature into specialized white blood cells. TET2 deletion increases hematopoetic stem cells (HSC) frequency and function and promotes AML in mice and humans. Ascorbate stimulates TET activity in pluripotent and leukemia cells culture. Many healthy people carry TET2 heterozygous mutations in HSC which cause clonal hematopoiesis (CH). CH is associated with increased risk of leukemia. Many leukemia patients are severely ascorbate deficient.

Hypothesis: Ascorbate supplementation renders benefit in ascorbate deficient AML patients.

Aim: To evaluate prognostic significance of ascorbate supplementation in patients with AML and TET2 mutation.

Participants and Methods: Around 30 AML patients who will be treated at University Hospital Center Osijek, Croatia, from 2018 to 2023, will be analyzed. Included will be those with fluorescent in-situ hybridization, cytogenetic characteristics and ascorbate serum concentration (ASC) at diagnosis. ASC will be measured by high performance liquid cromatography at the beginning at the time of reevaluation of initial therapy. Univariate and Cox regression analysis will be performed by SPSS.

Research plan: The AML patients will be randomized into group that will be treated with high dose of vitamin C with conventional chemotherapy or only chemotherapy treated group. We will evaluate overall survival and event-free survival.

Significance/Expected scientific contribution: Early recognition of lower ASC in AML patients with TET2 mutation can help to select them for an early treatment with vitamin C supplementation used along with chemotherapy. It was found that using high doses of vitamin C intravenously did suppress the growth of leukemia cancer stem cells in mice implanted with cell lines from human patients with leukemia.
DORDE

Keywords: Acute myeloid leukemia, vitamin C, TET2, chemotherapy, survival



Dissertation Proposal Title: Combined use of conventional pharmaceutical medications and herbal remedies among patients within primary health care system in Osijek-Baranja County

PhD candidate: Sabina Steiner Srdarević, MPharm., Faculty of Dental Medicine and Health Osijek

Mentor: Assoc. Prof. Ana-Marija Domijan, Ph.D., Faculty of Pharmacy and Biochemistry Zagreb

Introduction: The co-use of conventional drugs and herbal remedies has increased and became very common over the last two decades amongst patients. Pharmacodynamics and pharmacokinetics of conventional drugs may be affected by herbal remedies in combined use. This is significant with patients suffering from chronic diseases that are often accompanied with polypharmacy. There are not many studies conducted on patients awareness about possible adverse interactions and their communication on this matter with general practice physicians.

Hypothesis:

1. Co-use of conventional drugs and herbal remedies are widely spread amongst patients in Osijek-Baranja County despite their lack of knowledge about possible adverse interactions.
2. Patients mostly do not communicate with their general practice physicians about possible adverse interactions between conventional drugs and herbal remedies.

Aims:

1. To investigate on how many patients combine herbal remedies with their prescribed conventional drugs.
2. To investigate patient awareness of possible adverse interactions in co-use of herbal remedies with conventional drugs.
3. To investigate patient reasons for combining conventional drugs with herbal remedies.
4. To investigate on how many patients inform their general practice physicians about co-use of prescribed conventional drugs with herbal remedies.

Materials/Participants and Methods: This cross-sectional study will be conducted in period between December, 2018 and June, 2019. The anonymous questionnaire will be distributed to patients through general practice offices. Estimated sample size will be 1500 patients. Questionnaire will have several types of questions such as general information about age, gender, education, rural or urban place of residence. Other types of question will include general information about their conventional drug therapies, their herbal remedies use (if any), reasons for their combined use and patient awareness of possible adverse interactions in such cases. Last part of questionnaire will ask about patient communication with their general practice physicians about their co-use of conventional drugs with herbal remedies.

Research plan: Every general practice office in Osijek-Baranja County will receive questionnaires to distribute them to their patients.

Significance/Expected scientific contribution: This study will possibly increase patient awareness about adverse interactions in combined therapy. Also it aims to improve on communication on this matter between patients and their general practice physicians since this is still considered as a marginal subject in healthcare.

Keywords: Herb-drug interaction, General practice, Adverse interactions, Herbal remedies, Polypharmacy



Dissertation Proposal Title: Diagnostic accuracy of serum calprotectin for early diagnosis of sepsis in patients presenting to the emergency department with suspected sepsis.

PhD candidate: Anika Stepić, M.D., Clinical Hospital „Sv. Duh“, Zagreb

Mentor: Assist. Prof. Višnja Neseak Adam, Ph.D., Clinical Hospital „Sv. Duh“, Zagreb

Introduction: Sepsis is a potentially life-threatening complication of an infection. It occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses throughout the body. This inflammation can trigger a cascade of changes that can damage multiple organ systems, causing them to fail. Sepsis still has high mortality despite available diagnostic tests and therapeutic methods. Numerous studies have shown that administration of antibiotic therapy within the first hour of documented hypotension is associated with a survival rate of 79.9%. However, the early diagnosis of patients with sepsis remains a challenge for clinicians in the emergency department. Biomarkers that have been assessed clinically such as C-reactive protein (CRP) and procalcitonin (PTC) do not have 100% specificity for sepsis. Mentioned above indicates the need to find and introduce new diagnostic and laboratory procedures at the very early stages of the disease. Acute phase protein calprotectin is a new biomarker that has been proposed for the diagnosis of many inflammatory conditions. Calprotectin is an antimicrobial peptide that protects cells against invasive microorganisms and regulates adhesion of leukocytes to the endothelium and extracellular matrix during the inflammatory process. It is released by innate immunity cells immediately after hostpathogen interaction and is detectable in body fluids by means of a simple ELISA technique. The aim of this study would be to investigate the diagnostic accuracy of serum calprotectin for early diagnosis of sepsis in patients presenting to the emergency department with suspected sepsis.

Hypothesis: Serum calprotectin is a more reliable biochemical marker for early diagnosis of sepsis compared to the previous laboratory parameters (CRP, PTC).

Aims: The main aim would be to determine the diagnostic accuracy of serum calprotectin for early diagnosis of sepsis in patients presenting to the emergency department with suspected sepsis.

Specific objectives would be:

- to identify demographic characteristics (age and gender) and associated diseases (cardiovascular diseases, chronic renal insufficiency, liver lesions, diabetes, cerebrovascular disease).
- to determine clinical status, vital signs, multiple organ dysfunction.
- calculate the initial Sequential Organ Failure Assessment (SOFA) score and determine its correlation with the serum calprotectin levels.
- to determine measures of diagnostic accuracy for serum calprotectin: sensitivity, specificity, predictive values, likelihood ratios and the area under the curve (AUC).
- to determine relationship between calprotectin levels and clinical stages of sepsis (uncomplicated sepsis, severe sepsis, septic shock).
- to determine differences in diagnostic accuracy of serum calprotectin compared with diagnostic accuracy of previous laboratory parameters (CRP, PTC).
- to determine prognostic value of serum calprotectin in predicting an outcome (mortality, duration of hospitalization) compared with current indicators (albumin, lactate and sodium concentration, SOFA score).

Materials/Participants and Methods: We would preforme a cross-sectional study of patients presenting to the Emergency Department of Clinical Hospital Sveti Duh with suspected sepsis. The group, 'with suspected sepsis', would consists of patients who have suspected infection + two or more criteria for systemic inflammatory response syndrome (SIRS): body temperature $> 38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; heart rate $> 90/\text{min}$; respiratory rate $> 20/\text{min}$ or $\text{SpO}_2 < 90\%$ in room air or $<94\%$ with O_2 ; leukocytes $> 12 \times 10^9$ or $<4 \times 10^9$. We would take informed consent to conduct the study. Excluding criteria would be age <18 years, pregnant women, patients who do not want to participate in the study.

Research plan: In all patients with suspected sepsis during stay in the Emergency Department we would monitor the clinical status and vital signs (noninvasive blood pressure, body temperature, heart rate, respiratory rate, oxygen saturation levels), level of consciousness, acute phase proteins (CRP, PTC), multiple organ dysfunction (partial pressure of oxygen in arterial blood (pO_2), creatinine level, platelet count, bilirubin level) and serum calprotectin. A blood samples would be taken by properly qualified and authorized persons immediately upon arrival to the Emergency Department. We would calculate the initial SOFA score by using clinical findings and laboratory test results (pO_2 , creatinine level, bilirubin level and abnormally low blood pressure). The final diagnosis would be based on bacteriological analysis (hemoculture, urine culture, sputum and stool culture, cerebrospinal fluid culture and other microbiological cultures depending on the clinical findings). Patients would be divided into two groups according to final diagnosis : patients without sepsis and

those with diagnosed sepsis. Group of patients with sepsis would be divided into three groups: those with uncomplicated sepsis, severe sepsis and septic shock.

Significance/Expected scientific contribution: The results obtained in this study would provide us with new information on diagnostic accuracy of serum calprotectin for early diagnosis of sepsis in patients presenting to the emergency department. Considering the mentioned difficulties in diagnosing sepsis, the availability of accurate sepsis biomarker to facilitate diagnosis could be of use to enable timely appropriate treatment to be started, thus optimizing a patient's chances of survival.

Keywords: serum calprotectin, sepsis, emergency department, sepsis biomarkers, early diagnosis.



Title of abstract: Evaluation of left ventricular diastolic function in primary prevention of cardiovascular disease in adults with positive family history of early cardiovascular disease

Dissertation Proposal Title: Evaluation of left ventricular diastolic function in primary prevention of cardiovascular disease in adults with positive family history of early cardiovascular disease

PhD candidate: Livija Sušić, M.D., Health Centre Osijek, Osijek, Croatia

Mentor: Prof. Josip Vincelj, M.D., PhD, FESC, University Hospital Dubrava, Zagreb, Croatia

Introduction: Cardiovascular diseases (CVD) are the leading cause of mortality worldwide. Although the recommended charts for cardiovascular (CV) risk evaluation are used, it is a great challenge to identify apparently healthy people < 50 years of age who have a high relative CV risk. The European Society of Cardiology (ESC) recognizes those with a positive family history of early CVD as the most important group in that population.

Aim: To evaluate the DF of the left ventricle in adult < 50 years of age with a positive family history of early CVD and compare it to the DF of a person with a negative family history.

Materials/Participants and Methods: Diastolic function (DF) is first cardiac function to be impaired in ischemic heart disease. Age, hypertension, obesity and diabetes are established risk factors for development diastolic dysfunction (DD) which is often associated with subclinical coronary artery disease.

Our study will include about 160 respondents, both sexes, aged between 20 and 50 who are coming to an examination at the Internist ambulance of the Health Center Osijek and did not get over any of CVD so far. They will be equally divided into 2 groups (positive and negative family history of early CVD). DF of left ventricle will be evaluated by transthoracic echocardiography. Ten parameters will be measured: E/A ratio, Valsalva E/A ratio, DT, E' velocity, E/E' ratio, IVRT, PVS/PVD, PVA, adur-Adur and LA volume. Based on the obtained values, the respondents will be divided into 3 groups: normal DF (< 50% of measured values are pathological), indeterminate

(50% of measured values are pathological) and DD (> 50% of measured values are pathological).

Results: We have done preliminary research on 57 respondents (33 with positive and 24 with negative family history of early CVD) of which 51% men and 49% women. The median age of the respondent is 36 years, ranging from 21 to 49 years. In the group with positive family history 8 subjects had impaired DF, unlike the control group in which impaired DF was found in 2 subjects.

Conclusion: Note that the preliminary research we conducted did not meet the minimum sample size needed to adequately interpret the obtained results. So, even we did not get it significant, we can see that positive respondents have more impaired DF than those with negative family history. Further research should check the difference in the occurrence of impaired DF with the age, sex and other risk factors for CVD development.

Keywords: left ventricular diastolic function, primary prevention, family history of premature cardiovascular disease, adults, echocardiography



Dissertation proposal title: Alexithymia and anxiety sensitivity in panic disorder

PhD candidate: Daniela Šago, M.D., Psychiatric Hospital “Sveti Ivan”, Zagreb, Croatia

Mentor: Prof. Igor Filipčić, M.D., Ph.D., Psychiatric Hospital “Sveti Ivan”, Zagreb Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Introduction: Panic disorder differs among anxiety disorders mainly presenting with physical symptoms such as palpitations, chest pain, dizziness, trembling, nausea, sweating. The current prevalence of panic disorder in the general population is about 2%. Life prevalence in the general population is 3% to 4%. Panic disorder has high rates of relapse (25% -50% of patients within six months of therapy discontinuation), a significant negative impact on the quality of life, and is associated with high total treatment costs. Alexithymia and anxiety sensitivity (AS) are dimensional personality constructs, although they share common features that potentially act as diathesis for translating emotional distress into a somatic experience. A small number of empirical studies have highlighted that the percentage of alexithymia in individuals with panic disorder is high and ranges up to 46.7%. Many studies have found large associations between AS and panic disorder. AS is a fear of anxiety symptoms and anxiety-related physical symptoms. The most commonly used instrument for measuring AS is the Anxiety Sensitivity Index.

Hypothesis: Patients with AS and more prominent alexithymia have a more severe panic disorder than patients with AS and less prominent alexithymia, regardless of the sociodemographic characteristics of the patient.

Aims: The aim of the current study is to examine the influence of both of these personality traits on panic disorder.

Materials/Participants and Methods: A cross-sectional study will be carried out over a period of six months at Psychiatric Hospital „Sveti Ivan“. Targeted population will be outpatients of both sexes with diagnosed panic disorder ages 18 to 50 years without somatic or psychiatric comorbidity. A consecutive sample of 69 patients will be collected.

Research plan: The psychiatrist will conduct a clinical interview during which the panic disorder will be diagnosed. After that the psychiatrist will explain to the patient the aim and objectives of the study and ask the patient to participate in the research. Upon obtaining signed informed consent, the psychiatrist will assess the severity of panic disorder according to Panic disorder severity scale. After that the patient will be given sociodemographic questionnaire, and Toronto alexithymia scale (TAS-20) and Anxiety sensitivity index (ASI). The total expected clinical interview duration and questionnaires would be 60 minutes.

Significance/Expected scientific contribution: The proposed study presents a unique analysis of the effects of alexithymia and AO on panic disorder which is a significant public health problem. The scientific contribution of the research will be better understanding of the pathogenesis of panic disorder. If our hypothesis will be confirmed it will be possible to set new clinical hypotheses on the improvement of panic disorder treatment and prognosis by focusing therapy on AS and alexithymia.

Keywords: panic disorder, alexithymia, anxiety sensitivity



Title of abstract: Poincaré plot analysis and neonatal pain

Dissertation proposal title: Poincaré plot dynamics in neonatal pain

Phd candidate: Matej Šapina, MD, Faculty of Medicine Osijek, Cara Hadrijana 10/E, Osijek, Croatia, University Hospital Osijek, J. Huttlera 4, Osijek, Croatia

Mentor: Assist. Prof. Silvija Pušeljić, MD, PhD, Faculty of Medicine Osijek, Cara Hadrijana 10/E, Osijek, Croatia, University Hospital Osijek, J. Huttlera 4, Osijek, Croatia

Introduction: Traditional examination of newborn stress is mostly based on utilizing various pain scales. Due to the limited knowledge of neonatal pain response, subjective or inconsistent pain assessment, and the lack of a “gold standard” scale, estimating newborn pain or stress may suffer from lack of objectivity. The analysis of the heart rate variability is a valuable physiological response measure, of which the Poincaré plot analysis is both a qualitative and quantitative way for presenting the autocorrelation of heart rate variability. A Poincaré plot is a first difference phase space scatter plot where the successive RR intervals are plotted as a function of the previous. Further, utilizing an ellipse fitting method, two standard descriptors are obtained, representing short and long term correlation, but also provide a measure of the autonomic nervous system tone.

Aims: To study the changes in the standard Poincaré plot descriptors in a neonatal stress framework, as well as the asymmetry of the obtained Poincaré plots.

Methods: Only full term infants APGAR score >9/9, without congenital malformations, were included in the study, 72 hours old, were included in the study. Inc. The serialized nature of the protocol is decomposed into two separate baseline phases, each followed by a stress phase, differing both in magnitude and duration. While the protocol is conducted, RR intervals are obtained, and further used in the analysis.

Results: In the pilot study, significant changes were observed in both in the linear and nonlinear heart rate variability measurements. Stress stimuli decreased the values of the standard descriptors. The results showed positive correlations between the descriptors and linear measurements, as well as a significant positive correlation between the long axis descriptor and total heart rate variability.

Conclusion: The Poincaré plot analysis in the neonatal stress framework provides a useful, objective way in the discrimination of neonatal pain and stress. This novel approach may not only be useful in basic scientific research, but also in real life clinical situations, where neonatal stress is inevitable.

Keywords: autonomic nervous system, Poincare plot, recurrence plot, pain



Dissertation Proposal Title: Cognitive impairment in patients with obstructive sleep apnea

PhD candidate: Jelena Šarić Sučić, University Hospital Center Osijek, Department of Neurology

Mentor: Prof. Silva Butković Soldo, University Hospital Center Osijek, Department of Neurology

Introduction: Obstructive sleep apnea (OSA) is a sleep disorder that involves cessation or significant decrease in airflow in the presence of breathing effort. It is characterized by recurrent episodes of upper airway collapse during sleep. Signs and symptoms of obstructive sleep apnea include excessive daytime sleepiness, loud snoring, observed episodes of breathing cessation during sleep, abrupt awakenings accompanied by gasping or choking, morning headache, difficulty concentrating during the day, high blood pressure and cognitive impairment. Many studies have reported a wide range of neurocognitive impairments in obstructive sleep apnea hypopnea syndrome patients, including selective and sustained attention, information processing speed, short-term memory including working memory and executive functioning.

Hypothesis: Patients with obstructive sleep apnea have cognitive impairment in comparison with healthy population.

Aims: The primary aim of this prospective study is to examine whether there are certain cognitive changes in patients with obstructive sleep apnea that can be proven by capturing and analyzing cognitive evoked potentials P300, or determining whether there are differences in the cognitive potential evoked values compared to the results obtained in a healthy population.

Secondary aim is determine which part of cognition is most damaged in patients with obstructive sleep apnea.

Materials/Participants and Methods: In preliminary testing we include 27 patients with obstructive sleep apnea and a control group of 27 healthy subjects. The study covers subjects of both sexes, in the age range of 18-65 years. All patient with symptoms of obstructive sleep apnea was recorded with computerized polysomnography to get diagnose of obstructive sleep apnea. We exclude all patients with other severe

organic and psychiatric impairment and patient. Cognitive evoked potentials P300 was recorded in all patients with obstructive sleep apnea and to a healthy individuals using sound paradigm and neuropsychological testing to determine which part of cognition is most damaged.

Results: Patients with obstructive sleep apnea have prolonged latency of N2 i P300, as a reduced amplitude of P300 wave in comparison with healthy subjects. Neurophysiological testing demonstrates deficits in concentration, attention and personality.

Conclusion: Patients with obstructive sleep apnea have cognitive impairment detectable with cognitive evoked potentials and neuropsychological testing.

Keywords: sleep apnea, obstructive sleep apnea, cognitive impairment, cognitive evoked potentials, neuropsychological testing



Dissertation proposal title: The relationship between urinary iodine concentration, anthropological characteristics and physical activity of children aged 6-12 years

PHD candidate: Valentina Vidranski, University Hospital Center "Sestre milosrdnice", Zagreb

Mentor 1: Assist. Prof. Maja Franceschi, University Hospital Center "Sestre milosrdnice", Zagreb

Mentor 2: Prof. Ivan Mihaljević, University Hospital Center Osijek

Introduction: Inadequate iodine intake causes functional and developmental disorders of which is the most important psychomotor development of children. Term psychomotor encompasses the relationship between physical activity and cognitive abilities. Significant number of literature shows link between iodine deficiency and lower intelligence quotient, all based on the initial part of the word-"psycho" (cognitive function). Correlation of iodine deficiency influences the "motoric" development of children as well as different levels iodine saturation is not well examine and literary data is insufficient or none.

Hypothesis: Hypotheses of this work are that there is relationship between urinary iodine concentration (UIC) and anthropological characteristics (AC), that there is relationship between UIC and physical activity (PA) and that there is no relationship by sex and age between UIC, AC and PA among children aged 6-12 years.

Aims: The aim of this study is to determine relationship between UIC and AC, between UIC and PA and between UIC, AC and PA, by sex and age, among children aged 6-12 years.

Materials, Participants and Methods: The survey will include a minimum of 384 children aged 6-12 years randomly select (morning shift) in schools of Osijek and Zagreb. For each child it will be included Form for consent, urine sample and Physical Activity Questionnaire (PAQ). Samples will be collect in sterile vacuum tubes (4 aliquots) and frozen at -20°C. It will be measure height (cm) and weight (kg) and on the special diagnostic instrument-body composition: body mass index (kg/m²), basal metabolism (kcal), % of muscle and body fat. Children will have ultrasonic examination of thyroid and measuring of motor skills (Crofit norm). UIC in µg/L will be determined

on automatic analyzer using colorimetry. It will used MedCalc program for statistical data processing.

Research plan:

- distribution of Form for consent and PAQ
- collecting of first morning urine sample and ultrasonic measuring
- Anthropological characteristics and motor skills measuring
- storing aliquots of urine in the freezer until determination on analyzer

This study is cross-sectional.

Significance/Expected scientific contribution: Expected scientific contribution of this research are new findings of UIC in accordance with AC and PA within children aged 6-12 years. Iodine intake is in direct relation with risk for thyroid diseases. Its shape is like "U", which means impact of insufficiency and sufficiency so this thesis will have direct influence on clinical practice.

Keywords: iodine compounds, urine, thyroid gland, physical activity, antropometric

Acknowledgement: I am grateful to my mentor and co-mentor, to Academician Kusić and to colleges from my Department who helped me with this work. I have no conflicts of interest.



Dissertation proposal title: Frequency of loss of CDX2 protein expression in patients with colorectal cancer depends on the type of DNA mismatch repair gene mutation

PhD candidate: Ivan Vlahović, MD, General Hospital Našice

Mentor: Assist. Prof. Dražen Švagelj, MD, PhD, University Josip Juraj Strossmayer Osijek, pathologist, General County Hospital Vinkovci

Introduction: Increased incidence of malignant diseases, especially colorectal cancer in Slavonia, is one of the leading public health problems. Although the development of new drugs such as monoclonal antibodies improves the fight against malignant diseases, it also raises the cost of treatment which demands responsible, rational and targeted spending of limited financial resources intended for healthcare. This research is based on cancer genetics since the postoperative treatment of colorectal cancer mostly depends on genetical disorders of cancer cells. Colorectal cancer in 20-30 % of cases has some form of DNA mismatch repair genes mutations (MLH1, MSH2, MSH6, PMS2) which is the reason for routine determination of such mutations in each detected colorectal cancer. Some forms of this mutations are associated with bad response to oncological therapy and bad survival rates. In addition, loss of CDX2 protein expression (CDX2 physiologically stimulates cell differentiation and proliferation inhibition) is also associated with worse response to oncological therapy. So far, there has been no scientific research in the Republic of Croatia that would justify the use of these tests as routine, nor did it determine the incidence of these proven mutations in colorectal cancer patients.

Hypothesis: The frequency of various mutations of DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2), as well as loss of CDX2 protein expression depends on gender and age of patients with colorectal cancer. Loss of CDX2 protein expression in colorectal carcinoma depends on the type of mutation of DNA mismatch repair genes.

Aims:

1. Determine the frequency of mutations of DNA mismatch repair genes in patients with colorectal cancer and determine whether there is a correlation between a specific mutation and age and gender of patients with colorectal cancer.
2. Determine the frequency of loss of CDX2 protein expression in patients with colorectal cancer and its correlation with patients age and gender

3. Investigate whether there is a link between increased or decreased frequency of loss of expression of CDX2 protein with one or more mutation of DNA mismatch repair genes.

Material and Methods: The materials are paraffin-embedded tumor tissue samples taken from the surgically removed tumor specimen. Diagnosis of colorectal cancer will be confirmed histologically on a tissue samples stain with standard hematoxylin and eosin method. The representative paraffin-embedded tumor tissue samples will then be immunohistochemically stained on CDX2, MLH1, MSH2, MSH6 and PMS2. Immunohistochemical expression of these proteins will be classified as 0 (negative nucleus of tumor cells) and + (positive nucleus of tumor cells.). Data such as age, gender, localization, pathohistological diagnosis, lymph node involvement, tumor diameter, vascular, lymphatic and perineural invasion will be gather in for every patient.

Research plan: The research will be designed as a retrospective study. It will last for three years (2016.-2018.) and it will include 150-200 paraffin-embedded tissue samples of representative colorectal cancer. The research will be done at the Patology and cytology department of General county hospital Vinkovci. The specified data will be collected in the MS Excel computer program and processed in R program. The sample will be described by descriptive statistics methods. Shapiro test will be used to test the normal distribution of numeric variables. A comparison of the nominal variables will be performed using the Pearson χ^2 test and, if necessary, Fisher's exact test. The differences between normally distributed numeric variables between the two independent groups will be tested by the Student t test, and in the case of a deviation from the normal distribution by Mann-Whitney's U test. The differences between normally distributed numeric variables between three and more independent groups will be tested by variance analysis (ANOVA), and in the case of a deviation from the normal distribution by the Kruskal-Wallis test, and depending on the obtained results with the appropriate post-hoc analysis. The level of statistical significance for all comparative tests is $\alpha = 0.05$. All p values are two-sided.

Expected scientific contribution: Confirmation or rejection of the hypotheses investigated in this paper will examine the justification for the use of certain routine immunohistochemical tests (DNA mismatch repair proteins) and the introduction of new immunohistochemical tests in routine usage (CDX2). This will contribute to minimizing the costs involved in detecting accurate genetic backgrounds in colorectal cancer patients. In addition, the possible determination of certain regularities of the

occurrence of different genetic changes is a prerequisite for the creation of criteria for the introduction of new tests that would most easily detect the most common genetic mutations in newly diagnosed colorectal carcinomas.

Keywords: mismatch repair genes, CDX2, colorectal cancer, immunohistochemistry



Dissertation Proposal Title: The Development of Dental Medicine in Osijek

PhD candidate: Nikola Volarić, MD, Faculty of Dental Medicine and Health Osijek

Mentor: Prof. Aleksandar Včev, MD, PhD, Faculty of Dental Medicine and Health Osijek

Introduction: History of dentistry is as old as the history of medicine. At its beginnings, dentistry was closely related to surgery. Pierre Fauchard (1678-1761), father of modern odontology, established scientific foundations for the development of dental medicine. Gerard Van Swieten (1700-1772), with the help of Empress Maria Theresa, became a successful reformer of medicine at the University of Vienna and established cooperation with Pierre Fauchard, sending the best dental practitioners from the Austro-Hungarian Monarchy to further education. The Austro-Hungarian Monarchy which included Croatia at that time, adopted in 1787 a legal provision that all dental practitioners must pass the examination and receive a valid certificate. The development of practical dentistry in Croatia was slower than European due to political and economic reasons, the lack of adequate education and literature. The dental care service was performed by shavers, barbers, and lower surgeons until the second half of the 19th century. A key event for the development of modern dentistry in Croatia is the establishment of the Faculty of Medicine in Zagreb in 1917.

Hypothesis: Dentistry as a specific health profession in the Osijek area has solid foundations and in some periods very intense development.

Aims: To study the development of dentistry in Osijek and highlight the most important determinants that have influenced the expansion and development of dentistry, to study the development of health care institutions, analyze their work and determine their role in the development of dental profession, and present the role of individuals who are responsible for dental development in Osijek.

Materials and Methods: The archival material of the relevant institutions, such as the Croatia State Archives in Osijek and the legacy of the former Osijek Polyclinic for the protection of the mouth and teeth, as well as materials collected from other similar institutions in Slavonia region, will serve as sources of data. Materials and verified data from dental symposiums, various researches about dental development in Croatia and Osijek, journals and independent publications will be used. During the research, the methods of deduction, description, analysis, synthesis and comparison will be used.

Research plan: During 2018, it is planned to conduct research in the Croatia State Archives in Osijek and to collect publications written by persons of significant importance for the development of dentistry in Osijek. During 2019 the research will be carried out at the Natural History Museum Vienna and the Hungarian National Museum in Budapest.

Expected scientific contribution: This research represents a major contribution to the understanding of dentistry development in Osijek. The most significant persons and the key determinants that have influenced the development of dentistry will be shown. The results and conclusions will have significant implications for further development plans in our area and in particular on the foundation of the new Faculty of Dental Medicine in Osijek, which will be the cornerstone of academic and scientific development of this health profession.

Keywords: Dental medicine, Osijek, Dental polyclinic, Faculty of dental medicine, Dental care service, History



Dissertation Proposal Title: Prevalence of traumatic dental injuries and associated factors among schoolchildren in Eastern Croatia

PhD candidate: Martina Vrdoljak, D.M.D., Faculty of Dental Medicine and Health Osijek

PhD Student Advisor: Assist. Prof. Marko Matijević, D.M.D., Ph.D., Faculty of Dental Medicine and Health Osijek

Introduction: A traumatic dental injury (TDI) is a public dental health problem because of its frequency, occurrence at a young age, costs and that treatment may continue for the rest of the patient's life. They are frequently met to schoolchildren ; therefore, the prevention and inter-ception of traumatic pathology within parents, teachers and children is more than necessary. There has been little research on the prevalence of dental trauma in comparison with the prevalence of dental caries, and even less on the provided treatments after these injuries. There are no epidemiological studies available on the traumatic dental injuries in schoolchildren in Eastern Croatia.

Hypothesis: Prevalence of TDIs in Eastern Croatia is high among schoolchildren.

Aims:

1. To assess the prevalence and types of TDIs in 9- and 14-year-old schoolchildren in Eastern Croatia
2. To determine whether TDIs were related to gender and socio-economic indicators
3. To assess the prevalence of treated and untreated TDIs.
4. To determine the type of treatments provided after the occurred TDI.

Materials/ Participants and Methods: This cross-sectional study will be conducted from January 2019. till December 2019. on a sample of children enrolled at public schools in 5 counties of Eastern Croatia (Virovitičko-podravska, Osječko-baranjska, Požeško-slavonska, Brodsko-posavska, Vukovarsko-srijemska). Estimated sample size is 2000 children. The epidemiological classification adopted by WHO and modified by Andreasen et al. will be used to classify TDIs. All clinical examinations will be carried out on patients by a trained dentist. Dental examination will be conducted in a seated position, in a room with good lightning using sterilized or disposable dental mirrors, probes and gauzes. The universal infection control precautions will be followed during examination. Data will be processed and analyzed using the Statistical Package for Social Sciences(SPSS).

Research plan: Schools will be contacted via e-mail about their interest in participating in the study. When the schools send their agreement, information letters will be sent to all caretakers of the children explaining the objectives of the study. The letter will also contain an anonymous socio-economic questionnaire, as well as a questionnaire about childrens general dental practioner information. In case of a found dental trauma, childrens general practioners will be contacted so that their medical records could be retrieved. In them, we hope to find information about dental treatments provided after dental trauma. The clinical examination will be conducted only on children whose parents signed the consent and filled the questionnaire.

Significance / Expected scientific contribution: This research will show patterns of TDI occurence and treatment possibilites which may induce some public health prevention programs of TDIs itself, and all of their possible consequences.

Keywords: prevalence, traumatic dental injuries, schoolchildren, treatment of traumatic dental injuries



Dissertation Proposal Title: Diabetes type 2 as a prognostic factor for schizophrenia remission quality

PhD candidate: Antonia Vuk, Psychiatric Hospital "Sv. Ivan", Zagreb

Mentor: Prof. Igor Filipčić, Psychiatric Hospital "Sv. Ivan", Zagreb

Introduction: Diabetes mellitus (DM) is a global pandemic disease. It is a heterogeneous group of metabolic diseases characterized by hyperglycemia, leading to harmful and costly micro and macro vascular complications, physical disability and functional impairment.

Schizophrenia is a complex mental illness characterized by psychotic symptoms, cognitive impairment, functional decline and usually a chronic course. It affects about 1% of the population and is associated with 2-2.5-fold higher risk for premature death related to somatic comorbidities.

It has been reported that people with schizophrenia have 2-5-fold increased risk of diabetes type 2 (DMT2) than the general population but the reasons why individuals with schizophrenia are more prone to developing DM are not entirely defined. Recent studies have demonstrated an association of etiopathology of schizophrenia and DM, particularly poorly controlled, with elevated concentrations of inflammatory mediators. Specifically: IL-6 (Interleukin 6), TGF β (Transforming growth factor beta) and TNF α (Tumor necrosis factor alpha).

Although there are indications of shared vulnerability factors, some recent studies suggest that hyperglycemia itself is an inducer of oxidative stress and through several different mechanisms lead to elevated levels of various inflammatory mediators.

Hypothesis: DMT2 comorbidity at patient's hospital discharge is associated with a lower quality of schizophrenia remission determined after six months, regardless of other clinical, vital and sociodemographic parameters.

Aims: To estimate prognostic value of DMT2/hyperglycemia for impairment of schizophrenia remission quality.

Materials/participants and methods: The targeted population will be patients diagnosed with schizophrenia (MKB-10: F20) and DMT2, diagnosed at least three months before the start of the study. Participants will be of both sexes, aged 25-65 and treated in a specialized psychiatric hospital.

Research plan: A prospective cohort study will be conducted at the Psychiatric Hospital "Sveti Ivan" in Zagreb. The recruitment period will last for four months and follow-up after hospital discharge will last for six months.

Significance/expected scientific contribution: Contribution to the understanding of etiopathology and the remission of schizophrenia.

Keywords: schizophrenia, remission, diabetes, hyperglycemia, cytokines



Dissertation Proposal Title: Pathophysiological Consequences of Glycolipid Biosynthesis Inhibition on Lipid Rafts Composition, Insulin and Leptin Signalling and Amyloid Precursor Protein Cleavage in SHSY-5Y Human Neuroblastoma Cell Line.

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Mentor: Prof. Marija Heffer, MD, PhD, Faculty of Medicine Osijek

Introduction: Gangliosides (GG) are glycosphingolipids (GSL) expressed on membranes of all vertebrate cells, most abundant in neurons of central nervous system (CNS). GG play role in maturation, synaptogenesis, myelination and plasticity of neurons. Frequently, signalling takes place on lipid rafts (LR) - segments of cell membrane enrich in cholesterol and GSL. Correct positioning in or out of lipid rafts affects receptor activity. Changes in lipid raft composition are previously reported in Alzheimer disease (AD) and type 2 diabetes (T2D). Also, development of insulin resistance was connected to amyloid precursor protein (APP) cleavage. We propose that changes in lipid raft composition connect both diseases and provide new target for treatment.

Hypothesis: Manipulation of lipid raft composition in SHSY-5Y human neuroblastoma cell line affects insulin and leptin downstream signalling and APP cleavage.

Aims:

1. Establish such differentiation protocol for SHSY-5Y cell line that supports expression of IR, ObR, APP and the major GG.
2. Establish protocol for lipid raft isolation from cells without and with detergent.
3. Measure LC50 for inhibitors of glycolipid synthesis CDP 71 and P4 and verify effectiveness of each inhibitor.
4. Verify effectiveness of transient siRNA knockout for ST3GAL3, ST3GAL2, B4GALT1, ST8SIA1
5. Verify potential of added purified GG as treatment for repositioning targeted molecules.
6. Verify activity of IR and ObR downstream signalling after each treatment and find the one causing IR/ObR resistance and the highest production of A β .

Materials and Methods: Cell line SHSY-5Y will be cultivated in DMEM:F12. Inhibitors LC50 will be determined by cell viability count and MTT test. Transient knockout for targeted genes will be performed by manufacturer guidelines. Ganglioside expression will be determined by immunocytochemistry (ICC). Protocol for lipid raft isolation will be modified from existing protocols for tissue and cells with detergents Triton 100x and Brij 020, and without detergent. Molecular changes of cell membrane and lipid rafts will be observed with Western blot technique using antibodies against epitopes of interest.

Research plan: Grow and differentiate cells, find effective inhibitors concentrations, determine expression and positioning of epitopes by using ICC and Western blot analysis. Knockout genes for GG synthesis, perform ICC, lipid raft isolation and Western blot analysis. Add purified gangliosides GD1a and GM1 and determine afterward positioning in lipid rafts.

Expected Scientific contribution: Inhibitors of GSL biosynthesis and catabolism will effectively change amount of GG and cause shift of IR and ObR in and out of LR of SHSY-5Y In the sense of alleviating/correcting hormone resistance. Results will be basis for preclinical studies on animals.

Keywords: Gangliosides, Inhibitor, Lipid rafts, Alzheimer, Diabetes

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