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September 4-7, 2019

University of Medicine, Pharmacy, Science and Technology „George Emil Palade" of Târgu Mureș

BOOK OF ABSTRACTS

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NATURAL BLEACHING GELS USED IN DENTISTRY – BIOCOMPATIBILITY STUDY

Mărioara Moldovan[1], Alexandra Dreancă[2], Mihai Blidaru[3], Orsolya Sarpataki[2], Ioan Marcus[2], Bogdan Sevastre[2]

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[2] University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca;
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The main purpose of this research is to evaluate the biocompatibility of the bleaching gel made from natural agents, compared to comercial products by assessing cytotoxicity, acute oral toxicity and skin iritability. Tooth whitening is not a new practice, but current aesthetic trends make it more demanding on the market, being a symbol of oral health. Firsltly, the cytotoxicity assay was performed on dermal fibroblast cultures. No toxicity was recorded for the experimental gel, but the cell viablity comercial products was lower than 40% after 24h. *In vivo* studies, for acute toxicity were done using the fixed dosed procedure according to OECD gudeliness;b while skin irritability test was done according to ISO 10993-10. According to the acute toxicity, the 500 mg/rat dose of the testing gel does not show acute systemic toxicity. According to the skin irritability test, both gels, the testing gel and the commercial one, were found in the negligible irritability response category, and are not considered toxic. However teh study showed that applying compressive bandages, as the standart requred, generated major stress on the animals causing weight loss over 24 hours.

Keywords: biocompatibility, bleaching gell, toxicity, iritability

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ATYPICAL ONSET OF ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute lymphoblastic leukemia (ALL) is common in children but can have interesting features. The aim of this work is to present a case of ALL with atypical onset.

Case presentation: This is the case of a 7 y.o. boy, who first presented seizures, considered to be epilepsy related and for which he received specific treatment. Despite the treatment, the seizures continued and he had a cerebral trauma as a consequence. CT was performed and showed hematoma. In this phase the child developed fever and a urinary tract infection was suspected (urine culture was negative). He received antibiotics, but the fever did not cease. The child was referred to the Pediatrics Department. The complete blood count (CBC) was normal. One month later the CBC sowed anemia (Hb 7g/dl) and leuko-eritroblastic picture on the peripheral blood smear. The bone marrow (BM) showed blastic infiltration (44%). Immunophenotyping was performed and CD19 (96%), CD10 (99%), CD22 (98%), HLA-DR (90%) were positive. The diagnosis established was ALL. The boy was transferred to the neurosurgery department and during the surgery brain metastasis was discovered. Biopsies were taken, and the morphopathological result confirmed the diagnosis of ALL and specific treatment was initiated. The question is if the ALL onset was in the CNS or in the BM? Because in the beginning the seizures were the first manifestation and the CBC was normal, we assume that the disease had cerebral onset.

Conclusion: ALL can have atypical onset and because of that the diagnosis can be delayed.

Keywords: ALL, seizures, immunophenotyping

LIFESTYLE AND RISKY BEHAVIORS AT ADOLESCENTS

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Objective: The study aims to analyze obesogenic behavioral patterns of adolescents living in Târgu Mureş, Romania, as well as to establish a relationship between these behaviors and their Body Mass Index (BMI), in an attempt to provide effective prevention strategies for obesity.

Material and Methods: Were included in the study 153 students between 9th to 12th grade, aged between 14 and 19 years old, from the Vocational and Art Highschool of Târgu Mureş. All the candidates filled out an evaluation questionnaire of lifestyle and risky behaviors. Target parameters: sex, age, residence, BMI and risky eating behavior defined as the consumption of carbohydrates (bread, potatoes, sweets), sodas, junk food, alcohol (wine, distilled beverages, beer), beer separately, level of physical activity (school and extra-school sports activities), sedentary behaviors (≥2 hours/day in front of a screen: personal computer-PC and television-TV), and spending ≥2 hours/day separately on the PC and on the TV.

Results: A statistically significant association was observed between BMI and consumption of fast-food, tobacco, beer, sedentary behavior and spending ≥2 hours/day in front of the PC. Also, there was a statistically significant difference between the BMI values of adolescents presenting all studied risk behaviors compared to those who did not.

Conclusions: Fast-food, tobacco, beer, sedentary behavior and spending ≥2 hours/day in front of the PC highly influence obesity in adolescence.

Keywords: BMI, adolescents, risk behavior

REPOLARIZATION STUDIES IN NIGHT SHIFT WORKERS – PRELIMINARY RESULTS OF THE ECGNOCT STUDY

Marina Ruxandra Oțelea[1*], Anca Streinu-Cercel[1,2], Daniela Manolache[2], Andreea Mutu[1], Lavinia Călugăreanu[2,3], Dana Mateș[3], Oana Săndulescu[1,2]

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Objectives: The ECGnoct study intends to evaluate the modifications of the ST segment and of the T wave in nurses working night shifts.

Methods: ECGnoct is enrolling female nurses. Up to now, 38 nurses completed the baseline examination protocol. The medical history, the number of years of night shift work and the average of night shifts/month are documented and anthropometric parameters, blood pressure, fasting glucose, tryglicerides and HDL-cholesterol are measured. For this analysis, the ECG recorded in the morning was evaluated. QT was corrected by the Framingham formula (QTcFr). The Tpeak to Tend (in V5) was adjusted to the QT duration. Regression (Backward method) was used to find the best correlation between the independent variables (age, waist circumference, a previous diagnosis of cardiovascular disease, glycemia, serum triglycerides and HDL-cholesterol) and the TpTe/QT and the QTc.

Results: The average age was 42.10 years (± 8.03). The nurses had worked, on average, 10.55 years (± 10.39) years of night shift; the mean number of shifts/months was 3.86 (±2.84). High level of triglycerides was recorded in 10 cases, while 8 participants had low HDL-cholesterol and 8 had high glycemia. The best regression model for the TpTe/QT included the number of night shifts/month and the waist circumference as predictors (R squared=0.217, p=0.017). In what concerns the QtcFr, the best model maintained only the age as independent factor (R squared=0.234, p=0.002).

Conclusion: These preliminary data support the assumption that both occupational and non-occupational risk factors interact to influence the transmural dispersion of the left ventricle repolarization.

DETECTING HELICOBACTER PYLORI ON GASTRIC PINCH BIOPSIES AND WHY ISN'T THIS SO SIMPLE

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Introduction: Helicobacter pylori infection is the most common cause of chronic inflammation of the stomach, it is known to cause intestinal metaplasia and gastric gland atrophy which are the first steps in the development of intestinal type gastric cancer, and it also plays a role in the development of gastric MALT lymphoma. A crucial step for the treatment of this condition is the detection of the microorganism. The gold standard of diagnosis is considered to be the histopathologic detection on gastric endoscopic pinch biopsies.

Material and Methods: We examined 1149 endoscopic gastric biopsy specimens with histologic evidence of gastritis, diagnosed between 2015 and 2019 in the Pathology department of the Mures County Clinical Hospital. We analysed the characteristics of the inflammatory infiltrate (density, lymphoid follicles with germinal centres, neutrophils) and the distribution of H. pylori in different regions of the stomach to ascertain which area of the stomach is a preferential site for obtaining biopsies and to correlate the histologic characteristics of inflammation with the presence of the organism in the same biopsy specimen. The presence of H. pylori was demonstrated with modified Giemsa stain and immunohistochemistry with Ventana anti-Helicobacter pylori (SP48) Rabbit Monoclonal primary antibody.

Results: We found that in multiple cases the microorganisms were not detectable on all biopsies taken from one patient at the same time, from different areas of the stomach. Pattern of inflammation correlates well with the presence of microorganisms (dens superficial mixed or acute inflammatory infiltrate, lymphoid follicles with germinal centres), but in a few cases microorganisms were present without dense inflammation.

Conclusions: We recommend that a minimal number of two biopsies should be taken from two different areas of the stomach (corpus and antrum) to increase the sensitivity for detecting H. pylori. Routine modified Giemsa stain is advised and mandatory for gastric endoscopic biopsies. Immunohistochemistry should be used as complementary tool in cases like: assessment of equivocal cases on Giemsa, in the identification of scanty bacteria and in the identification of coccoid forms which are difficult to recognize on Giemsa.

BONE MARKERS ASSESSEMENT REGARDING A NOVELTY BONE CEMENT TREATMENT

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Introduction: The healing of bone defects is a multiple process of reconstruction and bone remodeling (Li, 2015). Bone cement is a material used to fix implants and orthopaedic prostheses, to fill cavities with defects following traumatic surgical procedures (Vaishya et al, 2013).

Aims: The purpose of this study was to test bone cement, based on polylactic acid, by evaluating some systemic and tissue specific bone markers response.

Materials and Methods: The effectiveness of the treatment has been investigated using an experimental non critical femoral bone defect protocol (Hoerth et al, 2015). The study was carried out on 35 Wistar rats, divided into 7 equal groups (n=5), negative and positive controls and experimentally treated groups. Blood and bone tissue samples were collected at 30, 60 and 90 days postsurgical intervention. Serum bone regeneration markers (PHA and osteocalcin), oxidative stress markers and local bone markers (TNFα and osteocalcin) were evaluated.

Results: There was a positive correlation between serum alkaline phosphatase and serum concentrations of osteocalcin, based on their growth throughout the study. Bone cement treatment had a protective role by maintaining higher glutathione and glutathione peroxidase levels, thus decreasing cellular damage and bone resorption. The moderate increase in tissue necrosis factor does not prevent the expression of osteocalcin, both promoting the bone remodeling process.

Conclusion: According to systemic and local bone markers evaluation, the treatment with polylactic acid, hydroxyapatite and calcium phosphate based bone cement is bone inductive.

Keywords: bone defects, Wistar rats, bone cement, biochemical bone markers, osteoinductive

References: Li, Y. (2015). Bone defect animal models for testing efficacy of bone substitute biomaterials, Journal of Orthopaedic Translation, 3: 95-104. Vaishya R., Chauhan M., Vaish A. (2013). Bone cement, Jounal of Clinical Orthopedics and Trauma, 4(4): 157-163. Hoerth R., Seidt B., Duda G., Wagermaier M. (2014). Mechanical and structural properties of bone in non-critical and critical healing in rats, Acta Biomaterialia, 10: 4009-40019.

ANTIOXIDATIVE EFFECTS OF CURCUMIN ON EXPERIMENTAL INDUCED MYOCARDIAL INFARCTION IN RATS

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Objective: This study aimed to investigate the effects of pre-treatment with curcumin nanoparticles compared to conventional curcumin on oxidative stress parameters on isoproterenol(ISO)-induced myocardial infarction (MI) in rats.

Methods: Fifty six Wistar-Bratislava white female rats were randomly divided into 8 groups of 7 rats/group. Curcumin (CC) and curcumin nanoparticles (CCNP) were given by gavage in three different doses (100 mg/kg body weight (bw), 150 mg/kg bw, and 200 mg/kg bw) for 15 days. The MI was induced starting from 13th day, using 100 mg/kg of ISO administrated twice, with the second dose at 24h after the initial dose. The blood samples were taken 24 hours after the last dose of ISO, and five oxidative stress parameters were measured: malondialdehyde (MDA), thiol, the indirect assessment of NO synthesis (NOx), total oxidative status (TOS), and total antioxidative capacity (TAC).

Results: The induction of MI resulted in an elevation of all oxidative stress markers, up to 2.7 times, and a significant decrease in both thiol and TAC values up to 0.4 times. Doses of 150 and 200 mg/kg bw CC proved more efficient in preventing the increase in MDA and TOS ($p \leq 0.0152$). Higher doses of CCNP had same effect on MDA, TOS, and NOx levels ($p > 0.05$). Pretreatment with any CC or CCNP dose prevented the reduction in thiol levels. Higher levels of thiol and TAC were obtained after CCNP administration than after CC ($p \leq 0.0152$).

Conclusion: Curcumin nanoparticles exert better antioxidative effects compared to conventional curcumin, in case of acute myocardial infarction induced by isoproterenol.

Keywords: myocardial infarction, isoproterenol, rats, oxidative stress

THE ANTI-INFLAMMATORY EFFECTS OF CURCUMIN NANOPARTICLES IN EXPERIMENTAL INDUCED MYOCARDIAL INFARCTION

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Objective: This study aimed to evaluate the anti-inflammatory effects of pre-treatment with curcumin nano-particles (CN) compared to conventional curcumin (CC) in isoproterenol(ISO)-induced myocardial infarction (MI).

Methods: Seven groups containing eight adult female Wistar Bratislava rats/group assigned randomly were investigated. The first two groups were pre-treated with saline. Groups 3-5 were pre-treated with CC in doses of 100, 150, and 200 mg/kg bw and groups 6-8 were treated with CN in the same doses as CC, for 15 days. MI was induced in the 13th day with ISO in a dose of 100 mg/kg bw, which was subcutaneously injected at 24 h intervals for two days. The serum levels of six inflammatory cytokines, namely tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1α, IL-1β and IL-6, Monocyte Chemoattractant Protein-1 (MCP1), and Regulated upon Activation, Normal T cell Expressed, and Secreted (RANTES) were evaluated.

Results: The serum levels of all studied cytokines were increased, up to 5.6 times, after the induction of MI. All CC and CN doses prevented elevation of TNF-α, IL-1α, IL-1β, and RANTES, with better results observed for CN as compared to CC ($p \leq 0.0409$). All doses of CN had a similar effect regarding the prevention of IL-6 elevation ($p > 0.05$) with a significantly better effect than CC ($p \leq 0.0409$). MCP-1 levels were reduced by CN in the highest doses but were not influenced by CC ($p > 0.05$).

Conclusion: Curcumin nanoparticles possess increased antiinflamatory effect due to their ability to reduce serum levels of pro-inflammatory cytokines, in ISO-induced myocardial infarction.

Keywords: myocardial infarction, isoproterenol, rats, inflammation, cytokines

EFFECTS OF HYPERLIPIDEMIC DIET ON SALIVARY, BLOOD AND URINE NITRO-OXIDATIVE STRESS

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Hyperlipidemic diet has systemic effects. The aim of the study was to find if the prolonged hyperlipidemic diet is associated with significant nitro-oxidative stress and if saliva and urine are the proper biological product for its evaluation.

The study was conducted on C57Bl / 6j mice 12 weeks old randomized into the following groups (n = 10): female with norm caloric standard diet, male with norm caloric standard diet (10% lipid calories), female with hyperlipidemic diet, males with hyperlipidemic diet (45% of lipid calories). During the experiment the animals had free access to food and water; they had a 12:12 hour light: dark regime and the temperature was maintained at 22oC. For five months daily food and water consumption were monitored. Weekly body weight was monitored. The following nitro-oxidative stress markers were evaluated from plasma, urine and saliva: nitric oxide level (NO), total oxidation status (TOS), total antioxidant reactivity (TAR), oxidative stress index (OSI), malondialdehyde (MDA) and total thiols (SH).

The hyperlipidemic diet caused an important reduction of TAR and SH, associated with an elevation of TOS, OSI, NO and MDA in blood, saliva and urine. The most severe changes developed in the 5th month of the experiment. If comparing the biological products, nitro-oxidative stress parameters were more significantly changed in saliva and urine.

In conclusion, the prolonged hyperlipidemic diet induces systemic nitro-oxidative stress, and saliva and urine can be good biological products for nitro-oxidative stress evaluation.

Keywords: hyperlipidemic diet, nitro- oxidative stress, saliva, urine

EFFECTS OF ARTEMISIA ABSINTHIUM ON NITRO-OXIDATIVE STRESS IN EXPERIMENTAL INFLAMMATION

Dalina Diana Zugravu[1], Uifălean Ana[1], Mihai Blidaru[1], Adriana Bulboacă[1], Florinela Cătoi[1], Carmen Sfrângeu[1], Manuela Mîrza[1], Ramona Jurcău[1], Meda Orăsan[1], Andreicuţ Andra[1], Iulia Pfingstgraf[1], Iulia Morar[1], Teodora Bonci[1], Paul Boarescu[1], Alina Elena Parvu[1]

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Previous studies identified the positive effect of the *Arthemisia absinthium* in infections, wounds healing and rheumatic pain. Therefore we tested the *A. absinthium* total extract for its effect in acute experimental inflammation, especially focused on the nitro-oxidative stress.

A. absinthium was extracted with 70% ethanol by a modified Squibb repercolation method. The anti-inflammatory activity of the tincture from *A. absinthium* was tested in acute inflammation induced with turpentine oil (i.m. 0.6 ml/100 g b.w.) in male Wistar rats. The animals were divided into six groups (n=6). The tinctures were tested in three dilutions (100%, 50%, 25%). The results were compared with those from a negative control group, a positive inflammation group, and a group treated with diclofenac (30 mg/100 g b.w.). The effects were evaluated by measuring the malondialdehyde (MDA), the nitric oxide (NO), the total antioxidant reactivity (TAR), oxidative Stress Index (OSI) and total thiols (SH).

A. absinthium 100%, 50% and 25% extract dilutions reduced significantly OSI, TOS and NO. The 50% extract had a better inhibitory effect than diclofenac. Only *A. Absinthium* 50% reduced MDA. The *A. Absinthium* extract had no significant effect upon TAR. A. Absinthium increased significantly SH in a dilution independent way.

In conclusion, *A. Absinthium* extract had a significant inhibitory effect on the nitro-oxidative stress induced by acute inflammation through OSI, TOS and NO reduction and SH increase. The effect on the nitro-oxidative stress was better than that of Diclofenac for *A. Absinthium* 50%.

Keywords: *Artemisia absinthium*, acute experimental inflammation, nitro- oxidative stress.

HEART RATE AND PULSE WAVE ANALYSIS IN PATIENTS WITH HYPERTENSION AND HIGH NORMAL BLOOD PRESSURE

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Objective: Heart rate and pulse wave analysis provide useful information in cardiovascular risk assessment. It was the aim of the present study to assess the relationship between heart rate and hemodynamic and pulse wave variables respectively, in patients with hypertension and high normal blood pressure.

Methods: A total of 56 patients with hypertension and high normal blood pressure underwent pulse wave analysis using a Mobil-O-Graph and standard 12-lead ECG. Resting heart rate (HR), intrinsic heart rate (IHR) and the difference between IHR and resting heart rate (DHR) were additionally calculated for each patient.

Results: HR, IHR, DHR, pulse wave velocity (PWV), systolic blood pressure (SBP) and mean arterial pressure (MAP) were, as follows: 69±11 beats/minute, 91±3 beats/minute, 22±11 beats/minute, 7.27±0.69 /s, 136±14 mmHg and 111±11 mmHg, respectively. Significant negative correlations were obtained between PWV and IHR and DHR, respectively in all study participants, and between HR and PWV just in female patients. Linear regression analysis revealed significant associations between PWV and IHR, DHR, SBP and MAP, respectively, and between early vascular ageing (EVA) and IHR, central and peripheral blood pressure variables, respectively. Multiple regression analysis revealed just IHR as an independent predictor of PWV (beta = -0.623, $p<0.001$, R square =0.476), but not of EVA.

Conclusions: There are gender differences in the relationship between heart rate variables and pulse wave analysis in patients with elevated blood pressure. IHR is an independent predictor of pulse wave velocity, but not of EVA in patients with hypertension and high normal blood pressure.

Acknowledgment: The present study was funded by the Bioclinica grant 9/2743/9.03.2016.

THE FRONTAL PLANE QRS-T ANGLE IN PATIENTS WITH HYPERTENSION AND HIGH NORMAL BLOOD PRESSURE

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Objective: A large frontal QRS-T angle (fQRST) was shown to carry prognostic value related to cardiac death. The objective of the present study was to explore the relationship between fQRST and other electrocardiographic, hemodynamic and pulse wave variables in patients with hypertension and high normal blood pressure.

Methods: A total of 23 middle-aged patients with hypertension and high normal blood pressure underwent standard 12-lead ECG and pulse wave analysis. Pearson (rP), Kendall (rK) and Spearman (rS) correlations were used as statistical methods.

Results: QRS and QT interval duration and fQRST, respectively, were, as follows: 96±19ms, 408±60 ms, -7.86±35.3º. Significant negative correlations were obtained between QRS axis and QRS duration (rP=-0.46,p=0.027), T axis and QT interval (rP=-0.515,p=0.012) and heart rate corrected QT interval (rP=-0.428, p=0.041), as well as between fQRSTand QRS duration (rS=-0.429, p=0.041). No significant correlations were obtained between fQRST and the other assessed electrocardiographic, hemodynamic and pulse wave variables.

Conclusions: The frontal QRS-T angle is related to QRS duration in middle-aged patients with hypertension and high normal blood pressure.

Acknowledgment: The present study was funded by the Bioclinica grant 9/2743/9.03.2016.

CLINICAL AND EPIDEMIOLOGICAL FEATURES OF INFECTIVE ENDOCARDITIS: AN OBSERVATIONAL RETROSPECTIVE STUDY

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Introduction: Infective endocarditis (IE) represents a severe pathology with a high mortality and morbidity. Rheumatic heart disease, congenital heart defects or the presence of prosthetic valves are risk factors for IE. The microorganisms commonly associated with IE are *Staphylococcus aureus* and *Streptococcus spp*. *Viridans* streptococci group, which are present in healthy oral ecosystems, can cause transient bacteriemia during surgical dental procedures, being associated with high risk of development of IE, especially in presence of underling conditions.

Objectives: The aim of the study was to estimate the prevalence and clinical and epidemiological characteristics of IE with presumed oral bacterial sources.

Materials and Methods: Our study enrolled 128 patients with IE, admitted to the National Institute of Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, from January to December 2017. We assessed the etiology of IE, the type of valvular infection (native or prosthetic, the site of valvular infection), the associated comorbidities and the mortality rate.

Results and discussions: The mean age of our cohort was 58.815.3 years; the most affected age group was 60-69 years (34 patients; 25.56%). IE bacterial etiology was identified in more than half of the patients (75 patients; 58.59%): *S. aureus* – 25 cases (19.53%), *E. faecalis* – 16 cases (12.50%), *S. Gallolyticus* – 11 cases (8.59%), *Coxiella burnetii* – 3 cases (2.34%). IE with oral origin included: *S. mitis* – 6.67%, *S. mutans* – 2.67% and *S. salivarius* group – 2.67%, leading to a total of 12.00%. The aortic valve was the most frequent site of endocardial infection (47 patients; 36.72%) followed by mitral valve (41 patients; 32.03%). The most common associated comorbidities were: hypertension – 38 patients (29.69%), anemia – 47 patients (36.72%), thrombocytopenia – 13 cases (10.16%), diabetes mellitus type 2 – 16.41%; hepatitis C – 14 patients (10.94%). The case fatality rate was 5.46%.

Conclusions: Dental surgical procedures can be associated with high risk of transient bacteriemia, leading to IE. Consequently, the dentist should identify the patients with high risk of developing IE and to prevent its occurrence by strictly applying the latest AHA/ADA protocols.

Keywords: infectious endocarditis, oral microorganisms, AHA/ADA guidelines

EXTENT OF PERIODONTAL IMPAIRMENT IN PATIENTS WITH LOW BONE MINERAL DENSITY

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Introduction: Osteoporosis is a systemic metabolic disorder defined by the impairment of the balance between the two fundamental processes that concern the bone: resorption and apposition. Periodontal disease brings together all the settings in which the periodontal tissue – comprised of the structures that maintain the teeth in the alveolar bone – is damaged.

Objectives: The aim of the study was to determin the extent of periodontal impairment in a group of patients with low bone mineral density.

Materials and Methods: 50 patients diagnosed with low bone mineral density by means of bone densitometry (DXA scan) were clinically examined and a complete periodontal examination was performed. The following indices were determined: the plaque index, the calculus index, the bleeding on probing index and the CPITN index (Community Periodontal *Index* of Treatment Needs).

Results: The mean values of the indices for the osteoporotic patients were: plaque index 33.2%, calculus index 22%, bleeding on probing index 26.8% and CPITN index 2,45 per sextant. For the patients with osteopaenia, the mean values of the same indices were 27.8%, 34.6%, 11.2%, 2.07, respectively. The prevalence of periodontal disease was 88% across the whole group and similar between the osteoporotic and osteopaenic groups.

Conclusions: Age is a non-modifiable risk factor for osteoporosis itself as well as for periodontal disease, both in healthy population and

osteoporotic patients. Oral hygiene, evaluated by plaque index, calculus index and bleeding on probing index, was poor in both categories of patients. According to the CPITN index, it is necessary for both categories of patients to perform routine hygiene treatment consisting of supra- and subgingival scaling and professional tooth brushing, associated with local and general antimicrobial treatment. Patients with osteoporosis had a higher number of absent teeth compared to the patients with osteopaenia.

Keywords: periodontal disease, osteoporosis, DXA scan, periodontal index

TYPE 1 DIABETES AND THE IMPLICATIONS OF INTESTINAL MICROBIOTA ALTERATION IN ITS ETIOPATHOLOGY

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Introduction: The type 1 diabetes frequency has increased by 2-5% worldwide and one out of three hundred eighteen-year-olds suffers from this disease. There has been identified a range of factors involved in the development of type 1 diabetes, among which, in the last couple of years, the intestinal flora alteration (dysbiosis) has been suggested to be one of the main ones. The dysbiosis phenomenon increases intestinal permeability and sets off pro-inflammatory reactions which stimulate the autoimmunity process of pancreatic beta cells for the prone subjects.

Material and Methods: I have picked 25 bibliographical sources from the PubMed and Science Direct databases, which I have analyzed and also compared the results.

Results: The most common alteration was the reduction of the *Firmicutes/Bacteroides* ratio, especially in human related studies. Moreover, there has been noticed a significant growth of *Clostridium, Bacteroides* and *Veilonella,* and an important reduction of *Lactobacillus, Bifidobacterium, Balutiacoccoides/Eubacterium* rectal groups and *Prevotella* to children diagnosed with type 1 diabetes. There has also been recorded in studies conducted on humans a growth of *Bacteroides genus,* especially B, dorei and vulgatus. The abundant growth of *Bacteroides dorei* determines the emerging of specific antibodies before the age of 8 months.

Conclusions: The area of intestinal microbiota research and the connection with the etiopathology of the autoimmune diseases is a relevant and an important subject for the XXIst century medicine as in the following years can be developed new methods for early diagnosis, options for treatment focused on the etiologic mechanism of autoimmune disease and even prevented the evolution of type 1 diabetes from its incipient stages.

CHRONIC INFLAMMATION – OXIDATIVE STRESS – ANEMIA INTERRELATION IN OBESITY

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Objectives: Obesity is a pathological state characterized by increased numbers of structurally modified and functionally active macrophages in the adipose tissue which secrete pro-inflammatory cytokines (IL-6, IL-1β, TNF-α). Pro-inflammatory cytokines lead to chronic inflammation which is associated with increased reactive oxygen species (ROS) levels and stimulate the hepcidin synthesis by hepatocytes leading to reduced intestinal iron absorption by directly blocking ferroportin and causing iron sequestration in enterocytes, and also reducing erythropoiesis by blocking iron in macrophages. We aimed to evaluate serum ferritin, ROS levels and the total antioxidant capacity (TAC) in obese anemic *versus* obese non-anemic patients.

Methods: We enrolled 85 patients diagnosed with obesity based on body mass index (BMI) according to the WHO criteria (informed consent obtained). Patients were stratified based on age, sex, area of residence, obesity class, presence/absence of anemia. Complete blood count, serum ferritin, ROS levels *via* the Free Oxygen Radical Testing (FORT) and TAC *via* the Free Oxigen Radical Defense (FORD) assays were evaluated.

Results: The mean age of the patients was 61.85 ± 10.60 years, women/men ration 4/1; 54.12% resided in rural areas, 45.88% in urban areas. Distribution on obesity classes: I=44.70%, II=36.47%, III=18.33%. 47 patients had anemia (39 normochromic normocytic and 8 hypochromic microcytic anemia). Serum ferritin was high in patients with normochromic normocytic anemia *versus* low in patients with hypochromic microcytic anemia. FORT levels were high and FORD levels were low in obese anemic *versus* obese non-anemic patients (3.18 ± 0.33 mmol/L vs. 2.16 ± 0.38 mmol/L; 0.66 ± 0.13mmol/L vs. 1.41 ± 0.44 mmol/L).

Conclusions: In obesity, chronic inflammation induces an increase in oxidative stress levels and contributes to the development of inflammatory anemia via reduced intestinal iron absorption and blocking iron in macrophages.

Keywords: obesity, inflammation, oxidative stress, anemia.

CORRELATIONS BETWEEN SERUM FERRITIN, OXIDATIVE STRESS AND JAK2V617F MUTATION IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA

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Objectives: Essential thrombocythemia (ET) is a chronic BCR-ABL-negative myeloproliferative neoplasm associated with low-grade chronic inflammation, increased levels of oxidative stress and, in approximately 50-60% of cases, the JAK2V617F mutation. We aimed to evaluate serum ferritin and oxidative stress in ET patients based on the homozygous/heterozygous JAK2V617F genotype.

Methods: We recruited 62 ET patients (informed consent obtained), diagnosed according to the 2016 revised WHO criteria, and a control group. ET patients were stratified based on age, sex, JAK2V617F status. The complete blood count was evaluated using a BM-800 analyzer, serum ferritin was evaluated by chemiluminescence, oxidative stress by determining reactive oxygen species (ROS) levels and the total antioxidant capacity (TAC), evaluated by flow-cytometry (CyFlow Space Sysmex, reagents from Abcam) and using a microplate reader (FLUOstar Omega, reagents from Sigma Aldrich), respectively.

Results: The mean age of ET patients was at diagnosis 59.5 years and the sex distribution was women:men=4:3. The JAK2V617F mutation was positive in 36 ET patients (58.06%) patients (heterozygous genotype in 30 patients and homozygous genotype in 6 patients) and negative in 26 ET patients (41.94%). We registered increased ROS and serum ferritin levels and decreased TAC in ET patients vs. controls. We found positive weak correlations between ROS – serum ferritin $r_s = 0.16646$, p (2-tailed) = 0.19598, and between TAC – serum ferritin $r_s = 0.05653$, p (2-tailed) = 0.66253, without statistical significance between JAK2V617F-heterozygous and JAK2V617F- homozygous cases.

Conclusions: ET patients depict increased oxidative stress and serum ferritin levels, with no significant differences between JAK2V617F-heterozygous and JAK2V617F-homozygous cases. Serum ferritin can be used as a marker of chronic inflammation in ET patients.

Keywords: essential thrombocythemia, oxidative stress, serum ferritin, JAK2V617F mutation

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THE ROLE OF AIR DISPLACEMENT PLETHYSMOGRAPHY AND ABDOMINAL ULTRASOUND IN ASSESSING BODY FAT: A PILOT STUDY OF CORRELATION WITH BODY MASS INDEX

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Obesity is a pathological condition with an alarming increase in prevalence worldwide that contribute to the global burden of chronic diseases. Body mass index (BMI), albeit currently used in clinical practice to diagnose obesity in adults, is a simple, age and sex-independent weight-for-height index, but it does not provide information on fatness. Measurement of body fat is nowadays mandatory since adiposity (as opposed to BMI) determines the cardiometabolic risk. The present study was double aimed: i) to assess the body fat percentage (BF%) via the air displacement plethysmography (ADP) and the abdominal subcutaneous adipose tissue (SAT) via the A-mode ultrasound (US) and ii) to assess their correlations with the BMI. For each patient, three ADP tests and three US measurements of the SAT layer thickness were taken. The median of the recorded values as the result of a triplicate assessment was used for computation. A number of 43 obese patients were included in our study (19 men and 24 women). BMI was 35.2±4.5 kg/m^2 (mean±SD), ranging from 30.4 to 47.9 kg/m^2, whereas BF% was 42.4±6.8 %, ranging from 28.4 to 56.4 %. The coefficient of determination (R^2) for BF% vs. BMI was 0.52 for men and 0.39 for women. As for abdominal SAT thickness vs. BMI, R^2 was 0.67 for men and 0.27 for women. In conclusion, especially in women, BMI is a poor indicator of body adiposity assessed by two independent methods.

Keywords: body fat, obesity, air displacement plethysmography, ultrasound

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PLATELET RESPIRATION IS IMPAIRED IN PREECLAMPTIC PREGNANCIES: A PILOT STUDY

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Background: Preeclampsia is a potential life-threatening condition of partially elucidated pathophysiology, with both endothelial and mitochondrial dysfunction being incriminated. Assessment of mitochondrial respiration in circulating platelets has been increasingly recognized as peripheral biomarker of mitochondrial dysfunction in metabolically active tissues.

Objective: The aim of the present study was to assess mitochondrial respiration in circulating platelets in the setting of preeclampsia.

Methods: Blood samples were collected from participants in this pilot study that were included in 3 groups: preeclamptic pregnancies, healthy pregnancies, and controls (age-matched non-pregnant women). All pregnant women were evaluated in the third trimester of pregnancy. A two-step centrifugation protocol was used to obtain platelet-rich plasma and platelet pellet, respectively. Respiration of isolated platelets was assessed at 37ºC, by means of high-resolution respirometry using the Oxygraph-2k (Oroboros Ltd.), according to the Substrate-Uncoupler-Inhibitor-Titration protocol adapted to measure complex I and complex II-dependent respiration. The main respiratory parameters were as follows: basal respiration, active respiration and the maximal respiration (in the presence of an uncoupler).

Results: A significant decrease in basal and active respiration was found in platelets collected from preeclamptic vs. healthy pregnancies and controls, respectively. Also, the maximal uncoupled respiration was significantly lower in preeclampsia as compared to the control group.

Conclusion: Respiratory function is significantly decreased in platelets harvested from patients with preeclamptic pregnancies. Further studies are required to determine whether this observation correlates with the placental mitochondrial dysfunction.

Keywords: preeclampsia, platelets, mitochondrial respiration

ASSESSMENT OF OXIDATIVE STRESS (OS) IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML) IN TREATMENT WITH TYROSINE KINASE INHIBITORS (TKI)

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Introduction: CML is a chronic myeloproliferative neoplasm, following the oncoprotein bcr-abl; standard treatment in CML are TKIs; optimal response to the therapy involves BCR-ABL < 0.1% - major molecular response (MMR) one year after the start, while therapeutic resistance – the absence of MMR (primary resistance - PR) or its loss (secondary resistance - SR); there is evidence that OS is involved in the response to TKI therapy.

The **aim** of the study is to determine the level of OS in patients with CML, in treatment with TKI I / II and to correlate the values with the response to the treatment - MMR, therapy failure (BCR-ABL decrease > 75% , without MMR), PR or SR.

Materials and Methods: We analyzed 75 patients (35 M, 40 F, mean age 60.57 years) with CML (ELN criteria, informed consent), treated with TKI I / II / I + II, whom were obtained MMR / therapy failure / PR / SR; reactive oxigen species (ROS) were determined with a CyFlow-Space flow cytometer and total antioxidant capacity (TAC) with a FluoStar Omega microplate reader.

Results and discussions: Statistically, we observed: male predominance among patients with therapy failure and TKI resistance; the minimum TAC value and the minimum ROS value were registered in the patients with therapy failure; the maximum ROS value was recorded in patients with TKI therapeutic resistance (subgroup PR) and the maximum TAC value was obtained in patients with MMR (subgroup ITK I).

Conclusions: The PR predominance to TKI I therapy, as well as the unfavorable prognosis of the male were observed. A better correlation of TAC level with the response to TKI therapy was found. The minimum TAC value concomitantly with the maximum ROS value were registered in the subgroup with TKI II resistance.

Keywords: CML, OS, TKI

FUNCTIONAL EVALUATION IN PSORIASIS

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Introduction: Psoriasis is an auto-immune papulo-squamos disease characterized by cutaneous and musculo-skeletal manifestations.

The **aim** of the study was represented by the functional evaluation of 38 patients with psoriasis.

Material and method: The including criteria were based on the next parameters: mean age, gender, duration of the disease, clinical signs and functional parameters.

Results: The patients presented itching, pain and intertrigo. Psoriatic arthropathy was presented in 18% of cases but was not correlated with the severity of cutaneous manifestations. The lesions had a simmetrically distribution, on upper and inferior part of the body. These lesions are evaluated with PAS index: 62% of the patients had a mild chronic form with the index between 10-50. In a high percent of patients, the

anemia and the positive parameters for the inflammatory syndrome were present: leukocytosis, high CRP, ESR and fibrinogen. In 52% of the patients subcondral erosions and periostal reaction were present. EMG aspect revealed the myogenic type characterized by low amplitude and duration of motor unit potential, determinated by the damage of muscular fibers induced by autoreactive cells and by immune response in acute phase, increased the recruitment pattern of the muscular recording.

Conclusion: Evolution of the disease is correlated with the skin manifestations, lab parameters and EMG aspect. The specific topical and systemic treatment, the decrease of risk factors and a medical education will keep under control the acute phases progression.

Keywords: psoriasis, electromiography, inflammatory syndrome

KIDNEY SONOELASTOGRAPHY - A USEFUL INVESTIGATION IN HYPERTENSIVE NEPHROSCLEROSIS

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Objective: Hypertensive nephrosclerosis represents the second most common cause of end-stage renal disease. But its evolution may be slowed, if it is diagnosed early. Besides serum and urinary biomarkers, ultrasonographic investigations (B-mode and Doppler) play an important role in the early diagnosis of hypertensive nephrosclerosis. Kidney lesions secondary to essential hypertension can cause elastic compliance changes, determined by a new ultrasonographic method, known as Acoustic Radiation Force Impulse Elastography (ARFI), as shear wave velocity (SWV).

The **aim** of this study is to investigate the kidney SWV in patients with hypertensive nephrosclerosis, and to establish the correlations between SWV and urinary albumin/creatinine ratio, creatinine clearance, and intrarenal resistive index.

Material and Methods: The study was done on a group of 15 patients with hypertensive nephrosclerosis and 15 healthy, sex and age-matched, as controls. Urinary albumin/creatinine ratio (ACR) (urinary immunoturbidimetry), creatinine clearance (Cr Cl) (Jaffe method), intrarenal resistive index (RRI), and renal SWV (Siemens Acuson 2000) were determined in all patients and controls. Data were expressed as mean ± standard deviation. Statistical analysis was done by means Pearson's test and t-Student test, p values of less than 0.05 were considered statistically significant.

Results: ACR, Cr Cl, RRI and SWV showed statistically significant differences between the patients and controls ($p < 0.0001$). In the hypertensive patients group, statistically significant correlations were observed between the SWV and ACR ($r = -0.7980$, $p = 0.0003$), Cr Cl ($r = 0.6401$, $p = 0.01$), and RRI ($r = -0.7448$, $p = 0.0014$).

Conclusion: Kidney sonoelastography characterizes imagistically the existence of intrarenal lesions associated with essential hypertension, offering a new diagnosis method for these patients.

Keywords: hipertension, sonoelastography, nephrosclerosis

ARE THROMBOPHILIA COMBINED MUTATIONS A TRUE CAUSE OF ITERATIVE VENOUS THROMBOTIC EVENTS?

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Introduction: Hypercoagulable states such as inherited thrombophilia are known factors for venous thrombotic accidents.

Case presentation: A female patient with a personal and family history of iterative venous thrombotic events was admitted to our surgical clinic at the age of 59. At presentation, the patient exhibits classic symptoms and signs for deep vein thrombosis of the left lower limb, confirmed at the time by Duplex venous Ultrasonography. This presentation represented the third episode of a venous thrombotic event. The first episode was represented by a left calf superficial venous thrombosis at age 43, and the second one manifested as a left calf deep vein thrombosis at age 57. During the evoked admission, the evolution was satisfactory under anticoagulant treatment (low molecular weight heparin and Vitamin K antagonists). Due to the fact that the most common risk factors for thromboembolism excluded, she was advised to test for genetic thrombophilia mutations. Four years later, using DNA thrombophilia tests, five of the most frequent mutations found in inherited thrombophilia were found in our patient. In the same year she experienced a fourth episode of thrombosis (superficial left upper limb venous thrombosis) with a good resolution under anticoagulant treatment.

Conclusions: Patients with iterative venous thrombotic events and positive family history of thrombotic accidents should be screened for inherited thrombophilia.

Keywords: Iterative thrombosis, inherited thrombophilia, genetic tests.

PHYSIOPATHOLOGICAL INSIGHTS IN PSORIASIS

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Objective: To assess the physiopathological mechanisms involved in psoriasis.

Methods: A review has been performed in order to identifiy key concepts regarding the pathogenesis of psoriasis. The most important theories and aspects are to be discussed in this paper.

Results: Concerning the pathogenesis of psoriasis, different theories were formulated during the years. Nowadays, psoriasis is considered to be a chronic autoimmune disease, with genetic determinism. Nevertheless, the hidden antigen theory has also been accepted regarding this disease, as well as direct activation of the keratynocites. All these theories have all found a support in the therapeutic approach, clinical aspects and molecular studies. Increased neuronal density and neuromodulation is recently discussed as being involved in the development of inflammatory skin diseases, such as psoriasis. Cholinergic stimulation may have an anti-inflammatory effect on such diseases, both systemic and skin limited.

Conclusions: The most important concept regarding the pathogenesis of psoriasis might not be related to “how” is the disease induced, but as to “why” does it appear. Understanding and elucidating the complex pathogenesis of psoriasis is the key to finding a cure for this debilitating disease.

Keywords: psoriasis, pathogenesis, keratynocite, autoimmune.

HIGH-RESOLUTION RESPIROMETRY IN HUMAN PLATELETS: ASSESSMENT OF MITOCHONDRIAL DYSFUNCTION IN BLOOD MALIGNANCIES

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Objective: Recent studies revealed that mitochondrial dysfunction is the central pathomechanism in several acute and chronic pathologies, including blood malignancies. In particular, the impairment of mitochondrial respiration in circulating platelets has emerged as potential biomarker of organ mitochondrial dysfunction. The present study was double-aimed: i) to characterise mitochondrial respiration in patients with leukemias and lymphomas and ii) to assess the effect of plasma isolated from these patients on platelets obtained from healthy volunteers.

Material and Methods: Peripheral blood samples were obtained from patients (adults and children) with newly diagnosed blood malignancies and healthy volunteers, respectively. A two-step centrifugation technique was applied to obtain isolated platelets that were further used for high-resolution respirometry studies at 37°C by means of the Oxygraph-2k (Oroboros Instruments, Austria). Platelets were resuspended in plasma and respiratory function was assessed after membrane permeabilization with digitonin according to a classic Substrate-Uncoupler-Inhibitor-Titration protocol adapted to measure basal, active and maximal respiratory rates. In a different set of experiments, platelets harvested from healthy donors were resuspended in plasma from patients with blood malignancies and further subjected to the Substrate-Uncoupler-Inhibitor-Titration protocol.

Results: A significant decrease in all respiratory rates, mainly the active respiration and the maximal capacity of electron transport chain, was found in all patients at the moment of diagnostic. Moreover, plasma isolated from patients with blood malignancies elicited an acute respiratory depression in healthy platelets.

Conclusion: Mitochondrial respiratory dysfunction is present at the onset of blood malignancies. Whether chemotherapy may interfere with cancer-induced mitochondrial dysfunction remains to be elucidated.

Keywords: mitochondrial dysfunction, respirometry, lymphoma, leukemia

METFORMIN ELICITS VASCULOPROTECTION AGAINST MONOAMINE OXIDASE-RELATED ENDOTHELIAL DYSFUNCTION

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Objective: Metformin, the mainstay therapy of type 2 diabetes mellitus, has been reported to elicit beneficial effects on vascular function that might be responsible for a decrease in cardiovascular complications via partially elucidated pathomechanisms. We have previously demonstrated that monoamine oxidases (MAOs) are major contributors to vascular oxidative stress in the presence of angiotensin II (AII), lipopolysaccharide (LPS) and high glucose. The present study was aimed at assessing the effects of metformin on vascular reactivity, oxidative stress and MAO expression in isolate rat aortic rings acutely exposed to AII, LPS and glucose.

Materials and Methods: To this aim, measurements of ROS production (by spectophotometry and immunofluorescence), vascular reactivity (myograph studies), and MAO expression (immunohistochemistry and quantitative PCR) were performed in isolated rat aortas treated or not with metformin (10 μM, incubation for 12 hours, organ culture) with or without AII (100 nM), LPS (1 mg/dl) or glucose (400 mg/dl).

Results: MAO expression is upregulated in vascular preparations after exposure to AII, LPS and glucose. Metformin reduced contractility, improved the endothelium-dependent relaxation, and decreased oxidative stress in all treated rings.

Conclusion: Incubation with metformin significantly improved vascular function and reduced oxidative stress in aortic rings in conditions associated with high MAO expression and oxidative stress.

Keywords: metformin, endothelial dysfunction, monoamine oxidase, oxidative stress

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STIMULATION OF PURINERGIC RECEPTOR P_2Y_{11} ALLEVIATES ANGIOTENSIN II-RELATED ENDOTHELIAL DYSFUNCTION IN RAT AORTAS

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Objective: The involvement of purinergic signaling in the modulation of vascular dysfunction is an emerging field of research. The aim of the present study was to investigate the role of the purinergic receptor P_2Y_{11} in the modification of vascular reactivity and reactive oxygen species (ROS) production induced by angiotensin II (Ang II) stimulation.

Materials and Methods: To this aim, rat aortic rings were incubated with Ang II (100 nM, 30 min) in the presence vs. absence of the P_2Y_{11} receptor activator (NF_{546}, 10 μmol/L) with or without the P_2Y_{11} inhibitor (NF_{340}, 10 μmol/L). Aortic rings were used for vasomotor studies (DMT myograph) and the assessment of hydrogen peroxide (H_2O_2) production by means of Ferrous iron xylenol orange OXidation (FOX assay).

Results: Activation of P_2Y_{11} receptor with NF_{546} reduced the contractility to phenylephrine, improved the endothelial-dependent relaxation to acethylcholine, reduced contractility to L-NAME, and decreased H_2O_2 production in aortic rings exposed to Ang II. These effects were blocked in the presence of the P_2Y_{11} receptor inhibitor (NF_{340}).

Conclusion: Activation of P_2Y_{11} purinergic receptor alleviated endothelial dysfunction and mitigated oxidative stress elicited by acute ex vivo exposure to Ang II. Further investigations are required in order to elucidate the signal transduction mechanisms of the purinergic-mediated vasculoprotection.

Keywords: endothelial dysfunction, purinergic receptor P_2Y_{11}, angiotensin II

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PROTECTIVE EFFECTS OF TWO CHEMOTYPES OF THYMUS MARSHALLIANUS ON EXPERIMENTAL-INDUCED HYPERGLYCAEMIA

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Introduction: Diabetes mellitus (DM) is a chronic metabolic disorder that can associate with oxidative stress and behavioral dysfunction. We aimed to evaluate the comparative effects of two chemotypes of *Thymus Marshallianus* (TM), wild flora (TMW) and culture (TMC) on both *in vitro* and *in vivo* models.

Materials and Methods: *In vitro* studies were performed on HUVEC cell line, using TMW and TMC in two different dilutions (1/10000, 1/100000), under normoglycemic and hyperglycemic conditions. NF-kB, activated pNF-kB, HIF 1α and γH2AX were assessed by western blot and MDA levels by spectrofluorimetry. 36 Wistar rats were used for the *in vivo* study. The animals were divided in 4 groups (n=9/group): Control (Carboxymethylcellulose, CMC), DM, STZ + TMW, STZ+ TMC. TMW and TMC (200 mg/kg b.w.) were orally administered for 14 days. On the 15th day, one dose of Streptozotocin (STZ, 30 mg/kg b.w.) was intraperitoneally administered to induce hyperglycemia. Subsequently, natural compounds were administrated for the next 14 days. On the 33rd day, Open Field Test (OFT) and Elevated Plus Maze (EPM) were conducted. Oxidative stress biomarkers in hippocampus and frontal lobe homogenates (MDA, GSH/GSSG) and NF-kB levels in hippocampus and frontal lobe samples were also assessed. Methyl CpG binding protein (MECP) 2 and histone deacetylase 1 (HDAC1) expressions in rats `brain were analyzed by western blot.

Results: *In vitro*, TMW and TMC diminished MDA, NF-kB and γH2AX levels and increased pNF-kB and HIF 1α expressions. *In vivo*, TMW and TMC administration reduced blood glucose levels. TMW improved central locomotion of the rats, both in OFT and EPM. In frontal lobe, both extract diminished lipid peroxidation, HDAC1 expression. and enhanced the antioxidant capacity. TMW administration increased NF-kB level and diminished MECP2 expression in hippocampus.

Conclusions: Our findings indicate that TM administration might represent a good option in diabetes – related complications. Both compounds exerted beneficial effect by increasing the antioxidant defence and improving the anxiety-like behaviour.

Keywords: Thymus Marshallianus, diabetes, oxidative stress, signaling pathways

REDUCED EJECTION FRACTION, WALL MOTION ABNORMALITIES AND THE D ALLELE- A NEW PATHOPHYSIOLOGICAL TRIANGLE OF THE CORONARY ARTERY DISEASE

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Background: Coronary artery disease (CAD) is the leading cause of cardiovascular death around the world. The classic risk factors have been widely studied, but recent trials focused on revealing the importance of angiotensin converting enzyme (ACE) gene polymorphism in the determinism of this pathology, since this enzyme is a key factor in the pathophysiology of cardiovascular diseases and the cardiovascular hemodynamics.

Purpose: Our purpose was to investigate the genetic predisposition of the patients with D allele genotype to a more severe coronary artery disease, with reduced ejection fraction and left ventricle wall motion abnormalities (akinesia, hypokinesia) in the north-eastern part of Romania.

Methods: The study included 154 patients (mean age 64.56+/-10.85 years) with acute coronary syndrome (unstable angina pectoris or myocardial infarction) who underwent coronary angiography at the Institute for Cardiovascular Disease "Prof. Dr. George I.M. Georgescu" from Iasi,Romania. The patients were divided in four groups, depending on the severity of the lesions: no/one/two/three vessel disease. We collected 200 ml venous blood from each patient and extracted the DNA, which was then amplified using the polymerase chain reaction. With the help of gel-agarose electrophoresis and UV light, we determined three possible mutations of the ACE gene, according to the length of the fragments and established three possible mutant genotypes: II,ID,DD. We measured the left ventricular ejection fraction and recorded the presence of akinesia or hypokinesia for each patient.

Results: In the no-vessel disease group, 87.5% had II genotype, 12.5 % ID genotype,while in the three-vessel disease group, 82.4% had the DD genotype and 14.3% ID genotype. The mean value of the EF was significantly more reduced in the patients with DD genotype (p=0.001). 54% of the akinetic patients were DD carriers, 39.7% ID and only 6.3% had II genotype (p=0.001). By contrast, hypokinetic patients were mainly ID (75.7%) and only a small number were DD carriers (2.9%) (p=0.001).

Conclusions: Not only are patients with DD genotype more predisposed to developing acute coronary disease, but they are also likely to develop a mutivessel disease with reduced ejection fraction and severe wall motion abnormalities. This points out the need for a more intensive prevention for this group of patients.

THE EFFECTS OF EUGENOL ON THE BIOENERGETIC PROFILE OF HACAT HUMAN KERATINOCYTES

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Objective: Modulation of cellular bioenergetics has emerged as a potential therapeutic strategy since mitochondrial dysfunction is currently accepted as the central pathomechanism of most chronic non-communicable diseases. Eugenol (EU) is a phenolic component of essential oils with antioxidant, antimicrobial, anticancer, and anti-inflammatory properties, but with less characterized effects on cellular bioenergetics. The present study was purported to assess the effects of eugenol on the bioenergetic profile of HaCaT human keratinocytes.

Material and Methods: To this aim, oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured at 24, 48, and 72 h of treatment of HaCaT cells with 50 μM free EU or EU encapsulated in polyurethane structures using the extracellular flux analyzer Seahorse XF^{e}24 (Agilent Technologies Inc.). The cytotoxic activity of the tested compounds on HaCaT cells was evaluated by means of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay while the migratory effect was tested with the scratch assay.

Results: Our data demonstrated that OCR and ECAR were not modified after 24 h treatment with EU; on contrary, both bioenergetic parameters were inhibited after 48 and 72 h treatment with EU in both types of administration. We also found that EU incorporated in polyurethane structures represents a safe formulation, showing no cytotoxic effect on HaCaT cells and stimulating cell migration.

Conclusion: We showed here that eugenol in different formulations modulates mitochondrial bioenergetics and cellular metabolism of HaCaT human keratinocytes in prolonged administration. Whether these effects can be recapitulated in malignant cells deserves further investigations.

Keywords: eugenol, HaCaT human kerationcytes, bioenergetic profile

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A CLINICAL AND PATHOPHYSIOLOGICAL APPROACH TO ACCELERATED CORONARY ATHEROSCLEROSIS

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Introduction: Atherosclerosis is the most common underlying cause of ischaemic heart disease and stroke. Two types of atherosclerosis were described, spontaneous and accelerated. Although the general mechanisms of native atherosclerosis are well established, the pathophysiology of accelerated atherosclerosis is unclear. Because of the rarity of the condition no management guidelines exist.

Case presentation: We present the case of a 56-year-old man who was admitted with an acute coronary syndrome (ACS) - unstable angina (UA) and underwent a PCI of the left anterior descending coronary artery (LAD). There were also two non-significant lesions, estimated at 30% located in proximal segment of the first obtuse marginal artery (OM) and in the third segment of the right coronary artery (RCA). Six months after discharge the patient suffered another ACS-UA. The coronary angiography showed a 80-90% lesion of the RCA. After 3 months the patient presented another ACS-UA and the coronary angiography surprisingly revealed a new stenosis of 80-90% distal to the stent implanted 3 months earlier.

Conclusions: ACS should be understood as a panvascular disease with a high risk for recurrent ischemic events, both in culprit and nonculprit coronary sites. Finding the cause of the accelerated kinetics is key for prevention of post-interventional atherosclerosis.

MONOAMINE OXIDASE IN CARDIOMETABOLIC DISEASES: AN ENZYME WHOSE TIME HAS COME

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Obesity and the related cardio-metabolic complications are reaching epidemic proportions worldwide. Excess visceral adipose tissue is hypothesized to contribute to a state of local and systemic chronic inflammation. Monoamine oxidase (MAO) with two isoforms (A and B) are flavoenzymes located at the outer mitochondrial membrane that are responsible for the oxidative deamination of neurotransmitters and biogenic amines. MAO expression increases with age and unequivocally contributes to oxidative stress in cardiovascular system. We here report that inflammation in obese patients is responsible for an increase in MAO expression in both vascular system and visceral adipose tissue in line with the novel concepts of "inflammageing" and adipageing". MAO-A related oxidative stress is responsible for endothelial dysfunction in

the setting of obesity while the MAO-B isoform is mainly increased in the vascular bed in patients with coronary heart disease regardless the presence of diabetes. MAO inhibition with the new generation of reversible and selective drugs (devoid of the well-known "cheese-effect") has recently emerged as pharmacological strategy aimed at mitigating oxidative stress and inflammation.

Keywords: monoamine oxidase, obesity, inflammation, oxidative stress

CORRELATIONS BETWEEN THE BIOCHEMICAL PROFILE, THE INFLAMMATION PATTERNS AND THE THROMBOTIC STATUS IN THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS: A PROTEOMIC STUDY

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Background: Diabetes mellitus has become one of the most costly chronic pathology worldwide with a continuous rising incidence. There is a close link between diabetes and cardiovascular events. Diabetes mellitus is associated with vascular events, especially when the glycated hemoglobin has elevated values. Diabetic patients seem to develop abnormalities of the haemostatic process, such as alterations of the thrombocytic function, modifications of the coagulation and of the fibrinolysis that lead to a thrombophillic status.

Purpose: We wanted to evaluate if the acquired thrombophilia present is diabetic patients with acute coronary syndromes may be due to the non-enzymatic glycosilation of clotting inhibitors such as antithrombine. Antithrombin III has both an anticoagulant and an antiinflammatory effect. The anticoagulant effect appears after acting upon endothelial heparan sulfate or on the molecule of heparine, thus leading to an inhibition of thrombin. A decrease in antithrombin III levels may lead to a diminished neutralisation of thrombin and a lower activity of proteins C and S, thus inducing procoagulant consequences and increasing the susceptibility for thrombotic events. Our research tried to establish whether the levels of antithrombin III in type 2 diabetic patiens are modified, thus creating a predisposition for thrombotic events and acute coronary syndromes.

Methods: Therefore we conducted an observational study on a sample composed of 60 patients having a diagnostic of type 2 diabetes associated with coronary artery disease and we evaluated the levels of antithrombin III in function of the metabolic, inflammatory and coronarographic parameters. In order to assess the haemostasic process we measured the levels of fibrinogen, the thrombocytes count and their morphology and the antithrombin III plasmatic activity. The antithrombin III levels were measured through the chromogen method (which is an activity test) that is based on the inhibition of clotting factor IIa (thrombin), by forming a complex between antithrombin and heparin, while the remaining free clotting factor IIa will fragment a chromogen substrate, which will induce a color change; the absorbance measured at 405 nm is inversely correlated with the plasmatic antithrombin activity. In order to assess the severity of coronary artery disease all patients underwent a coronarographic examination.

Results and conclusion: Our research showed that even though all patients were characterized by the diabetic dyslipidemia, there was no statistic relationship between antithrombin III and the lipidic fractions. As a result we cannot say that the adverse cardiac events seen in type 2 diabetic patients are influenced by the levels of antithrombin III, as a marker of an increased clotting activity.

ROLE OF MAST CELLS IN MELANOMA ANGIOGENESIS

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Objective: Mast cells' role in normal angiogenesis is supported by the release of a variety of factors and cytokines, such as heparin and tryptase, transforming growth factor β, tumor necrosis factor α and vascular endothelial growth factor. An adequate vascular supply is essential for tumor survival and progression. Our aim was to determine whether mast cells contribute to tumor angiogenesis in invasive cutaneous melanomas.

Methods: Fourteen excision biopsy tissue samples from patients with advanced primary cutaneous malignant melanoma were sectioned and double immunostained with monoclonal murin anti-CD34 antibody for endothelial cells and mast cell tryptase monoclonal murin antibody to visualize mast cells. We used hot spot method to assess microvessel density and mast cells count in normal tissue, peritumoral and intratumoral areas. Pearson correlation test and paired samples T-test were used for statistical analysis.

Results: The highest statistically significant correlation between microvessel density and mast cells count was found in peritumoral areas (76.9%, $p<0.01$), followed by normal tissue (76.5%, $p<0.01$). Intratumoral mast cells count was lower and the correlation with microvessel density did not reach statistical significance (66.4%, $p=0.01$). In tumoral areas, however, mast cells were larger and predominantly found in intensely pigmented sections. In areas with immature vessels mast cells were in contact with endothelial cells.

Conclusion: The significant correlation between mast cells' count and microvessel density around tumor edges and their proximity to immature microvessels advocate for mast cells' role in invasive cutaneous malignant melanoma angiogenesis.

Keywords: mast cells, microvessel density, malignant melanoma, tumor angiogenesis

EFFECT OF THREE ADAPOGENIC PLANTS, ON FATIGUE AND GLYCEMIA, IN HUMAN PHYSICAL EFFORT - A ROMANIAN EXPERIENCE

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Background: This paper presents a plant recognized as an adaptogen, *Panax Ginseng* (PG), and another two with adaptive role, sometimes called "Ginseng", namely *Lepidium meyenii* (LM), also called Peruvian ginseng or Maca, and *Angelica sinensis* (AS), also called female ginseng or Dong Quai.

Objectives: The objective was to highlight the effect of PG, LM and AS, on muscle fatigue (MF) and glycemia (GL), in human physical effort.

Methods: 40 healthy men were voluntarily enrolled in 4 groups: placebo (P=10), PG (=10), LM (=10), AS (=10). P, PG, LM, AS were administered for 21 days before an intense short duration exercise, the same for all groups: running on a treadmill, until the appearance of the MF sensation. Evaluation: MF with VAS scale; GL with a glucometer. Evaluation moments: before administration of P, PG, LM, AS (T1) and after the effort at 15 min (T1) and 4 hours (T3).

Results: MF and GL were significantly increased for P, at T2 and T3 compared to T1. At T2 and T3, MF and GL were significantly increased at P compared to PG, LM and AS. There were no significant differences for MF and GL, between LM and AS at T2 and T3. There were moderate significant differences for ML and GL, between PG and LM and AS respectively, both at T2 and T3. The highest impact on MF and GL has PG, compared to LM and AS. The highest impact of all, PG, LM and AS, was on MF and on T2.

Conclusions: (1) PG was more efficient for both MF and GL, compared to LM and AS. (2) MF and GL, were significantly reduced after PG, LM and AS administration. (3) PG, LM and AS acted more efficiently on MF than on GL, especially immediately after the effort. 4) We consider PG, LM and AS may be useful in modulating MF and GL, in intense short duration physical effort, but further research is needed to deepen the mechanisms and application details.

Keywords: *Panax Ginseng*, *Lepidium meyenii, Angelica sinensis*, muscle fatigue, glycemia, physical effort

VARIATIONS OF INFLAMMATORY BIOMARKERS ACCORDING TO THE PRIMARY SITE OF INFECTION IN SEPSIS

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Objective: To analyze the differences between baseline levels of inflammatory biomarkers in septic patients, according to the primary infectious focus.

Methods: We performed a prospective study which included randomly-selected patients diagnosed with sepsis in "Matei Balș" Institute. According to the primary septic focus, patients were divided in three groups: patients with respiratory, urinary and digestive sepsis. The levels of biomarkers including neutrophil/lymphocyte count ratio (NLCR), red cell distribution width (RDW), fibrinogen (FIB), C-reactive protein (CRP) and procalcitonin (PCT) were comparatively analyzed between groups. Statistical analysis was performed using SPSS, version 21.

Results: Ninety-three patients were enrolled. In the first group, the median values of biomarkers were: NLCR – 12.4 (4.12; 24.3), RDW – 13.2 (12.7; 14), FIB - 696 (474; 770) mg/dl, CRP – 150 (68.1; 197) mg/l, PCT 0.83 (0.13; 8.08) ng/dl. The second group had the following median values: NLCR – 16.24 (10.42; 23.5), RDW – 13.8 (13; 14.67), FIB – 618 (495; 836) mg/dl; CRP 170 (111; 229.5) mg/l, PCT – 1.09 (0.44; 17.99) ng/dl. In the third group, the median values were: NLCR – 14.26 (5.66; 25.4), RDW – 14.55 (13.4; 16.1), FIB - 478.5 (330; 696) mg/dl, CRP – 145.5 (65.6; 190) mg/l, PCT – 4.57 (1.47; 24.9) ng/dl. The differences were statistically significant for RDW (p=0.009) and PCT (p=0.04). For NLCR, FIB and CRP, the differences were insignificant (p=0.239, p=0.06 and p=0.323, respectively).

Conclusions: RDW and PCT had significantly higher levels in digestive sepsis, compared with other locations. Initial values of NLCR, FIB and CRP did not significantly vary according to the primary septic focus.

Keywords: sepsis, inflammatory biomarkers, respiratory sepsis, urinary sepsis, digestive sepsis.

BIOACTIVE PEPTIDES FROM ANIMAL SOURCES AS A NOVEL THERAPY AGAINST CANCER

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Cancer is the most common cause of human death worldwide. Anticancer therapies, like chemotherapy and radiation, are associated with severe side effects and toxicities. A growing number of studies have shown that some of the cationic peptides, exhibit a broad spectrum of cytotoxic activity against cancer cells. According to the literature, in this in vitro study, we evaluated the tumoricid potential of magainine II, cecropine A and B, dermaseptin, defensins and cathelicidins on tumor cell lines: MDA-MB-231 (breast adenocarcinoma) and M14K (human mesothelioma). We analyzed the effects of these cationic peptides on cell viability, cytotoxicity and proliferation cells from the tumor cell lines. The viability study was performed using Annexin and 7-AAD (7-amino-actinomycin D). These test was used to detect and measure apoptosis by flow cytometry technique. They act on many locations of membrane ion channels, transporters, receptors, enzymes and other systems that are involved in cellular signaling pathways. Most of the these peptides are cytolytic and can destroy membrane integrity with loss of cellular content to cell destruction. The experimental results of our study revealed that the cytotoxic effects of the peptides depend on their concentration. Their efficiency is significant at 120μM concentrations and it persists even at 60μM concentrations. The effects were insignificant at 30μM concentrations. On the other hand, the cytotoxic potential was not significantly dependant on the type of peptide but more on the type of tumour cell line used.

MEDIATED CARCINOGENESIS AND STEPS MODULATED BY CHEMOPREVENTIVE POLYPHENOLS

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Uncontrolled cell proliferation is a major feature of cancer cells and consequently any molecule capable of inhibiting cancer cell proliferation may be considered as a potential chemo-preventive agent. At cell level, there is clear evidence that polyphenols influence tumor carcinogenesis and development, in the sense that they can interact with reactive intermediates, activated carcinogens and mutagens, they can modulate the activity of key proteins involved in cell cycle evolution control, and they can influence the expression of many genes associated with cancerous disease.

The anticarcinogenic effects of polyphenols rely on the following mechanisms: reduction of oxidative stress involved in multistage carcinogenesis, suppression of NF-kB activity and ILBα degradation, inhibition of angiogenesis, stimulation of cytotoxic T lymphocyte activation, telomerase blocking, inhibition of matrix metalloproteases and inhibition of intracellular tyrosine kinase signaling pathways. Polyphenols (epigallocatechin gallate, epicatechin, quercetin, myricetin and naringenin), under neutral or alkaline pH conditions, undergo structural degradation which results in a remarkable increase in telomerase inhibition. Using both in vitro cell cultures and in vivo pattern tumors, researchers have confirmed the effect of polyphenols mediated by telomerase inhibition on cancer.

Their administration has strong anti-angiogenic effects, as they may control tumor growth or cause tumor regression. Natural polyphenols, or their molecular scaffolds, may also be the starting point for the development of new medicines designed specifically to control chronic inflammatory conditions and carcinogenesis. Future multidisciplinary studies will focus on the possibility of using these natural compounds as an alternative to the prevention/local or systemic treatment of tumor lesions.

MULTIDISCIPLINARY TREATMENT AND ORAL CAVITY TOXICITY IN A PAROTID CANCER SYNCHRONOUS WITH TYROIDIAN CANCER

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The presence of two synchronous cancers in the head and neck region is so much a rare case. Cystic adenoid carcinoma is a rare tumor accounting for less than 1% of all malignant tumors of the head and neck, being the most common malignant tumor in minor salivary glands and second malignant tumor as frequent frequencies in major salivary glands. We present the case of a patient diagnosed with locally advanced neoplasm of the right parotid gland with invasion in the mandible for which surgical treatment was performed. Evidence of a resection margin in contact with tumor of the parotid gland tumor made it necessary a multidisciplinary approach including adjuvant radiotherapy. During the

post-surgical hospitalization, the patient presented respiratory disfunction caused by a bulky tumor of the thyroid gland, for which the pathology proved a micro-papillary carcinoma. The patient will also be consulted in a nuclear medicine department for metabolic radiation therapy for thyroid cancer. Radiation therapy is part of the adjuvant treatment of head and neck cancers, the risk of associated toxicity being increased with implications for morbidity of the oral mucosa, mandible and teeth, severely affecting the quality of life of patients.

Keywords: cystic adenoid carcinoma, mandible, synchronous cancers, radiotherapy, toxicity, oral cavity

ORAL TOXICITY INDUCED BY RADIOTHERAPY FOR OROPHARYNGEAL CANCER: IMPLICATIONS FOR ORAL HEALTH

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In the group of head and neck cancers, oropharyngeal cancer presents an increased incidence especially in the young population. Unlike head and neck cancers related to smoking cancers that usually occur in the 6th decade of life, oropharyngeal cancers with viral etiology associated with HPV infection have a favorable prognosis. Long time survivals and the curable potential of this entity have led to the necessity of toxicity reduction strategies to improve the quality of life of these patients. Radiotherapy is most often used for the treatment of head and neck tumors as an independent method or in combination with surgery and chemotherapy, the multidisciplinary approach being the therapeutically standard in locally advanced cancers. Although modern radiotherapy techniques IMRT and VMAT have greatly reduced the dose received by the radiosensitive organs, the oral mucosa is close to the target volumes or even partially included in these volumes irradiated with high doses leading to acute and late toxicities: oral inflammation, loss of taste, dry mouth syndrome caused by xerostomia and secondary infections. Most commons late effects are dental caries, trismus and osteoradionecrosis. The aim of the study is to evaluate the doses received by organs at risk (the oral cavity, the parotid glands and the mandible) for 20 cases of multimodal treated oropharyngeal cancers and to discuss these data in relation to treatment toxicity.

Keywords: head and neck cancers, radiotherapy, oral cavity, toxicity

PREDICTORS OF LEFT VENTRICULAR REMODELING AFTER ACUTE CORONARY SYNDROME – THE ROLE OF RENAL FUNCTION

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Background: Cardiac remodeling after myocardial infarction represents a consequence of loss of viable myocardium that leads to left ventricular dilatation. This complex process involves the cardiomyocytes, the blood vessels and the extracellular matrix. Once the viability of the myocytes is compromised, the end-diastolic volume (EDV) increases as a response to a larger preload. The activation of biochemical intracellular signaling reactions will promote dilatation, hypertrophy and the synthesis of a collagen scar tissue.

Material and Methods: Our study included 274 subjects admitted in the Cardiology Department of the Emergency Clinical County Hospital with acute coronary syndrome who underwent interventional and surgical myocardial revascularization. The patients were equally divided into two groups depending on whether they had chronic kidney disease (CKD) and several markers were investigated whether they correlate with the incidence of the cardiac remodeling, defined as a decrease of the EDV with more than 20%. The compared groups were matched by age, sex, anthropometric data, and treatment.

Results: The LV remodeling signs on the echocardiography were reported in 41 subjects from the CKD group, whereas 25 subjects with normal kidney function had a decrease of the EDV with more than 20%. Anterior myocardial infarction was positively associated with LV remodeling due to the important extension of the territory irrigated by the anterior interventricular branch of the left coronary artery. Cardiac necrosis markers were positively associated with the infarct dimensions and their role in predicting an increase in the ventricular volume and LVEF reduction was significant. The ST segment resolution less than 70% after myocardial revascularization and a low myocardial blush or a decrease perfusion revealed on the angiography are other elements suitable for identifying the subjects with high risk of ventricular remodeling. Serum creatinine represented a marker of rapidly progressive LV remodeling.

Conclusions: LV remodeling represents a serious condition and the prevention of the pathological process should be achieved through early myocardial revascularization. The markers used to assess the risk of the LV remodeling occurrence should be identified in every patient diagnosed with acute coronary syndrome.

PATHOPHYSIOLOGICAL MECHANISMS OF MYOCARDIAL ISCHEMIA IN AORTIC STENOSIS AND THE ROLE OF IF CHANNELS INHIBITORS ON THE IMPROVEMENT OF MYOCARDIAL PERFUSION

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As the aortic valve sclerosis progresses to aortic stenosis, the afterload increases, which leads to the concentric hypertrophy of the left ventricle.

Although left ventricular hypertrophy is a compensatory mechanism, the consequences can be detrimental. Effects include diastolic dysfunction of the left ventricle, decreased coronary blood flow, increased oxygen consumption, and cardiovascular mortality.

In patients with aortic stenosis, myocardial ischemia occurs as a result of multiple mechanisms. On the one hand, the decrease of the cardiac flow and the consequent hypoperfusion of the mechanical obstruction of the aortic valve, determine the reduction of the coronary flow. Coronary atherosclerosis, commonly identified in patients with aortic stenosis, is another common etiology. Another mechanism is secondary to left ventricular hypertrophy. With increasing of left ventricular muscle mass, capillary density decreases, and coronary flow reserve is reduced, resulting in increased myocardial ischemia, even in the absence of coronary atherosclerotic lesions.

As a result of the detrimental effects associated with left ventricular hypertrophy, the integrity of atrial contraction is extremely important for maintaining cardiac output. Sinus tachycardia as a compensatory mechanism, secondary to decreased cardiac output, can precipitate pulmonary congestion, arterial hypotension and lead to the appearance of angina pectoris.

Ivabradine (an inhibitor of If channels) decreases the sinus node automatism, with no effect on blood pressure (therefore does not exacerbate coronary hypoperfusion secondary to mechanical obstruction at the aortic valve level). The effect would be beneficial on reducing oxygen consumption of ventricular myocardium already deprived of optimal blood perfusion, improving myocardial ischemia in patients with aortic stenosis.

PROFILE AND PATHOPHYSIOLOGICAL CORRELATIONS FOR DIABETIC AND DERMATOLOGIC PATIENTS- A 5 YEAR RETROSPECTIVE STUDY OF PATIENTS ADMITTED FOR THESE CONDITIONS IN ARAD CLINICAL COUNTY HOSPITAL

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Introduction: Diabetes mellitus represents a major healthcare problem and it is known to complicate other diseases as well. Skin lesions are also a very common pathology and their association with diabetes is rather under diagnosed, although diabetes can generate a poorer evolution for dermatological patients as well as the skin complications can aggravate the condition of a known diabetic patient.

Material and method: 10520 electronic registries of patients admitted in the period 2014-2018 in the Arad Clinical County Hospital with diagnosis of diabetes or dermatological conditions were statistically retrospectively analyzed in order to determine patterns of patients presenting both conditions and to describe a profile of such a patient.

Results: 6439 patients with diabetes and 4101 dermatological patients were found, 1188 presenting both conditions. Gender distribution revealed a female predominance (53.14% for diabetes and 51.21% for dermatology). The profile we obtained suggested for diabetes female, retired, with low to medium education, in her sixties coming from an urban environment, while for dermatological lesions the profile was very similar, except most where belonging to a rural environment.

Conclusions: Lifestyle and poor medical education correlates with higher incidence of both diabetes and dermatological lesions. The common features revealed by profiling patients with both conditions can be used by healthcare providers to target specific population for prevention and early recognize and treatment of these conditions.

Keywords: diabetes, dermatologic lesions, patient profile

MULTIDISPLINARY APPROACH IN COLORECTAL CANCER

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Introduction: Colorectal cancer is the 3rd most frequent cancer after lung and breast cancer according to GLOBOCAN data and the 4th cause of cancer related death with more than 7 million deaths per year and at least 1.3 million new cases diagnosed per year and by al these it constitutes a major healthcare problem.

Materials and method: Our team analyzed the data of the patients admitted for this pathology in the Arad County Clinical Hospital putting an accent on genetic factors, family history, aging, unhealthy lifestyle, smoking, physical activity, obesity, diabetes and intestinal inflammatory disease.

Results: We found that at least 70% of the colorectal cases have at least one of these features, most of them having multiple association of risk factors, but also that there was a lack of continuity in the management of these cases as they were admitted on different departments of our clinical hospital, a high number of cases being diagnosed in advanced stages. Results were better since last year, when a European project was implemented in order to have a better management of these patients in a multidisciplinary team.

Conclusions: Insufficient medical education and lack of knowledge or interest in health programs aimed at reducing, preventing or treating malignant disease in the early stages contributes to increasing the burden of the disease and its impacts on society, while implementing a multidisciplinary approach for this pathology reveals better outcome.

Keywords: colorectal cancer, multidisciplinary approach

PREVALENCE OF HIGH-RISK HPV GENOTYPES INFECTION IN ARAD COUNTY

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Introduction: HPV infection is considered the most common sexually transmitted disease worldwide and affects both sexes, but women are more prone to the occurrence of symptomatology or dysplasic or neoplastic lesions especially in the uterine cervix. The study pursued high-risk HPV prevalence, as single or associated genotypes and the chance of infection in Arad County.

Material and method: 180 samples were analyzed, tested HPV on automatic platform Cobas 4800 (Roche Diagnostics), real-time PCR method, taken from January 2016 to December 2017, with samples being positive HPV high risk 3.07% o for women between 18-58 Years.

Results: The HPV frequency and high risk associations reach 29.44% (P = 0.0001) of the samples, the 25-29 age group presenting this infection with a 1% prevalence for genotypes 16, 18, 31, 33, 35, 51 , 58, 59, 16 + 33, 16 + 45, 16 + 56, 18 + 68, 51 + 52 + 59, Odds ratio 5.4106 (95% CI 1.2438 to 23.5363, P = 0.0244) . HPV and low-risk associations reach 6.66% of samples, and other 19.44% HPV genotypes. Positive patients come from 58 (77, 44%) of the 75 administrative units of the county, with no statistically significant differences in the living environment.

Conclusions: Cobas HPV testing can intercept patients with cervical cancer, knowing that one of ten positive HPV 16 and 18 women already have a precancerous lesion even if the Pap test is normal.

Keywords: HPV, Odds ratio, prevalence

THE BURDEN OF THE DISEASE OF CERVICAL CANCER IN ARAD COUNTY

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Introduction: In the 21st century, cancer is considered the main obstacle to increasing life expectancy worldwide and represents the most important cause of death before the age of 70. Romania ranks second in terms of the incidence of cervical cancer at the European level and the first place in mortality due to this pathology. DALY (the burden of disease) is a measurement that combines the problem of disease and death by disease in a single number, being a method of determining the overall burden of the disease to which the World Health Organization calls.

Materials and method: The cases were collected unrandomized from the statistical data, registers and protocols of the oncology section and supplemented with the data from the patient's observation sheets.

Results: The 2616 cases of cervical cancer diagnosed between 1957 and 2017 were followed by 1570 deaths. The mean age to diagnose cervical cancer is 52.42 years, and the death occurs at the average age of 60.9 years. Total life years lost (YLL) by premature death due to cervical cancer are 264.6 per thousand, and years of cervical cancer disability (YLD) represent 30.6 years for every one thousand women.

Conclusions: Insufficient medical education and lack of knowledge or interest in health programs aimed at reducing, preventing or treating malignant disease in the early stages contributes to increasing the burden of the disease.

Keywords: cervical cancer, DALY, YLL, YLD

GRAVES' THYROID DISEASE AND RHEUMATOID ARTHRITIS - CASE SERIES

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Background: Graves' disease (GD) is one of main clinical presentations of AITD (autoimmune thyroid disease), featuring thyrotoxicosis, goiter, ophthalmopathy (GO), and in rare cases pretibial myxedema. As GD is an autoimmune disorder, in which the body produces antibodies to the receptor for thyroid-stimulating hormone (TRAb), it can be associated with other organ specific, or systemic autoimmune diseases in the same patient.

Case report: A 45 female patient attended the endocrinology department for a relapse of GD, presenting anxiety, tachyarrhythmia, hypotension, diaphoresis and flapping tremor. Other complaints were: weight loss, insomnia, arthralgia with insidious onset during the last two month. Lab tests came out positive for thyrotoxicosis, but negative for nonspecific inflammatory syndrome. The patient was examined by a cardiologist and an ophthalmologist - diagnosed with cardiothyreosis and inactive Graves ophthalmopathy (no corticoid therapy was applied). The treatment was initiated with anti thyroid drugs, antiarrhythmics, diuretics. General condition has improved over the next 40 days, but polyarthralgia with local edema were amplified, especially in wrist, elbow and shoulder joints. New tests revealed positive antibody panel for rheumatoid arthritis.

Conclusions: GD patients with nonspecific clinical signs or symptoms for the primary thyroid disease, should be appropriately screened for the presence of other autoimmune disorders. Early diagnosis and proper therapy greatly improved the outcome.

Keywords: autoimmune, Graves' disease, rheumatoid arthritis.

NANOCONJUGATES FOR PERSONALIZED MEDICINE

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Engineered nanoconjugates have attracted a lot of attention for their potential multiple benefits in the recent era of precision medicine. Gold nanoparticles are considered excellent drug delivery vehicles and are promising tools as imaging agents. Nanoparticle surface coating with cell penetrating peptides is one of the most efficient ways to increase the cellular delivery and uptake of nanoconjugates. This presentation will focus on personal results showing synthesis and evaluation of gold nanoparticles with improved stability and conjugated with drugs and cell penetrating peptides.

Keywords: Nanoparticles, Nanoconjugates, Precision Medicine

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SUN INDUCED CARCINOGENESIS IN A BATCH OF BASAL CELL CARCINOMA

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Introduction: Basal cell carcinoma (BCC) is for sure the most common malignant skin cancer and the most common human malignancy. Its incidence increases continuously, ultraviolet (UV) radiation being the most important risk factor. As the BCCs appears on the exposed skin years or decades after UV exposure in a cumulative way, the changes of the skin histology of the perilesional skin may link sun exposure to the tumour emergence, as well as the age and anatomical site of the tumour

Material and Methods: A transversal descriptive study was performed on a batch of 49 patients presenting 52 BCCs. The cases belong to the Dermatology Department in Colentina clinical Hospital. Besides the age of the patients and tumour localisation, histological features as solar elastosis, actinic degeneration, desmoplastic reaction and severity and type of inflammatory infiltrate was assessed in order to demonstrate the link between BCCs and sun exposure.

Results: The batch consists in 29 men and 20 women, with a mean age of 63 years, most of the BCCs being on head (especially on cheeks), followed by other sun exposed body areas as arms and trunk. Solar elastosis was present in 11/52 lesions. Desmoplastic reaction was present in 23/52 lesions. Actinic degeneration was found in 3/52 lessions. Most of the lesions (32/52) had moderate-severe lympho-plasmocytic infiltrate.

Conclusions: As results suggest a strong relation between UV exposure and BCCs formation, it is important to keep in mind other risk factors for BCCs development as arsenic exposure, genetic and molecular alterations, immunosuppression, to better explain the mechanisms that lead to malignancy. Sun protection remains the most avoidable risk factor.

ASSOCIATED RISK IN HEART FAILURE

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Objective: The study aims to monitor who the risk factors influence heart failure (HF), establishing correlation between the evolution of HF and lifestyle, cardiac and noncardiac hystory.

Material and method: The study included 50 patients with HF who were analyzed for clinical, demographic and biological variables, especially the parameters that represent risk factors ("classics", but also those related to the lifestyle) for HF. Odds ratio (used MedCalc software) was calculated to highlight how risk factors influence symptomatology, clinical examination and ultrasound aspects. $p < 0.05$ was considered statistically significant.

Results: The main reason for admission is dyspnoea, and most patients are in NYHA Class III and IV. The most important and frequent triggering factor of HF is ischemic heart disease (76%), and 32% suffered a myocardial infarction (32%). Most patients are obese, dyslipidemic, hypertensive and diabetic, and chronic kidney disease is the most common associated disease. Although obesity is correlated with increased cardiovascular risk, only 20% of patients studied had grade II or III obesity. Patients with uncontrolled blood pressure and unbalanced diabetes had an earlier onset of HF. The precipitating factor of HF in smokers is hypertension, however only a small number of smokers develop HF by early onset of chronic bronchopneumopathy. Pulmonary manifestations of HF appear earlier in smokers in the group. Of the patients who can do physical exertion, the only effort they can make is walking about once a week, and those who do exercise have a higher ejection fraction and a slower progression of the disease. Sedentary and normoponderous patients show more frequent manifestations of HF. Alcohol has a protective role in the studied group with regard to the appearance of cardiac pathological breaths, but the ejection fraction is significantly lower in patients who consume alcohol.

Conclusions: In order to prevent the HF or to slow its evolution, it is very important to look at the factors that underlie its triggering, as well as the comorbidities that may influence its progression.

EFFECTS OF A COUMESTAN DERIVATIVE AND CUCURBITACIN B ON APOPTOSIS OF PRE-B CELLS

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One of the suggested pharmacologic mechanisms for antitumoral effects of coumestan and cucurbitacin B derivatives might be represented by the modulation of apoptosis through mitochondrial and cytosolic calcium fluxes. Thus, the goal of our studies (each in triplicate) was represented by the characterization of the effects of 7-methoxy-5,11,12-trihydroxy-coumestan, an inhibitor of NF-kappa B-mediated transcription, and of cucurbitacin B hydrate, an inhibitor of signaling mediated by JAK, on pre-B cells apoptosis, using contrast microscopy. Cyclosporine A (1 μM) alone did not induce statistical significant apoptotic effects on murine pre-B cells (8.12±1.97%). For some experiments, pre-B lymphocytes were treated with 5 μM 7-methoxy-5,11,12-trihydroxy-coumestan in culture medium for 48 hours. As proven, 91.39±7.47% of the pre-B cells are not going apoptotic after 48 h (statistically not significant results, $p>0.05$) in the presence of cyclosporine A (1 μM). On the other hand, 5 μM cucurbitacin B hydrate induced a statistically significant apoptosis (62.95±5.99, $p<0.05$) in pre-B lymphocytes after 48 h of treatment in the presence of cyclosporine A (1 μM). The fine mechanisms need deeper exploration starting from the point that cyclosporine A concomitant administration did not block the effects of cucurbitacin B hydrate, a very similar structural compound to cucurbitacin I.

Keywords: pre-B cells, apoptosis, 7-methoxy-5,11,12-trihydroxy-coumestan, cucurbitacin B, cyclosporine A

PREVALENCE OF SARCOPENIA AND FACTORS ASSOCIATED WITH IT IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

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Objective: We investigated the prevalence of sarcopenia in elderly patients with chronic kidney disease and its relationship with various markers of nutrition, cognitive function, depression and activities of daily living.

Methods: A cross-sectional study was conducted with 80 patients having chronic kidney disease aged over 65 years. Sarcopenia was defined as a decline in muscle mass, strength and physical activity.

Results: The mean age was 76.74 ± 5.9 years; 22.4% were men and 65% had diabetes. Sarcopenia was highly prevalent in elderly patients (66.2% - 57.1% in men and 71.1% in women). Malnutrition was significantly associated with sarcopenia (p=0.005). Most of the diabetic patients (68.9%) had sarcopenia. Additionally, patients with depressive symptoms showed a higher risk of sarcopenia. The mean score in the Geriatric Depression Scale was significantly higher in cases with sarcopenia (7.75) compared to the cases with presarcopenia (5.26, p = 0.03). The activities of daily living were also influenced by the presence of sarcopenia (p=0.036).

Conclusions: Sarcopenia is highly prevalent in elderly patients with chronic kidney disease and is closely associated with malnutrition, depression and physical dysfunction.

Keywords: elderly, sarcopenia, malnutrition, depression, chronic kidney disease.

THE EFFECT OF ASSERTIVENESS TRAINING ON THE SELF-ESTEEM, VIOLENCE AND STRESS RESPONSE IN ADOLESCENTS

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Objective: This study investigates the effect of assertiveness training on assertiveness, self-esteem, violence, and stress response among adolescents.

Methods: In this study, 40 students aged 15 to17 years were selected. In the frame of the European project, *Lights camera and action: against dating violence*, students were trained in 10 sessions (50 minutes each) through practical activities and in 5 other sessions do produce video-capsules. Psychological tests were administrated before and after training: Maudsley violence scale, assertiveness schedule (interpersonal reactivity index), Rosenberg self-esteem, and perceived stress scale.

Results: The results of the study showed a significant improvement in the students' level of assertiveness and self-esteem after the intervention. The findings also confirmed that assertiveness training was effective in violence prevention and stress reduction in adolescents, especially in female students.

Conclusions: Assertiveness training in schools is effective to improve the self-esteem among adolescents and as a consequence to diminish violence and stress level in adolescence. This project has received funding from the European Commission Directorate, General Justice and Consumers Rights, Equality and Citizen Violence Against Women Programme 2016, under grant agreement No. 776905.

Keywords: assertiveness training, self-esteem, violence, experimental stress

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PARTICULARITIES OF STRESS RESPONSE IN ADOLESCENTS: EXPERIMENTAL RESEARCH

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Objective: Acute stress has been defined as stress lasting from a few minutes to several hours, and chronic stress as a stress that persists for several hours a day for weeks or months. Activation of the stress system leads to a series of psychic and physical changes defined as the stress syndrome. These changes are normally limited in time because they are designed to maximize an individual's chances of survival by mobilizing his or her physical and mental reserves. We assessed the slaivary cortisol changes during an experimentally-induced acute stress.

Methods: The experimental study group included 17 adolescents aged 15-17 years. We have induced an acute stress in all participants using three different digital tasks. We measured salivary cortisol before the induction (T0), during the stress test (T1, T2, T3) and 25 minutes after the stress test (T5). We applied psychological tests for assessing the perceived stress level before and after the stress test.

Results: Statistical analysis revealed significant differences between the participants in terms of gender. Mean salivary cortisol at each point during the stress test significantly varied ($p < 0.01$, ranging between minimum 3.68 pmol/l and maximum 53.38 pmol/l). The girls have higher salivary cortisol levels at T0, T1, T3, T4, and T5 as compared the boys. Also, the repeated measurement analysis, which was performed to evidence the individual reaction to the induced stress, we found that girls had a higher level of stress than boys in all samples.

Conclusions: Our results revealed different cortisol response during experimental depending on gender and type of stress stimulation.

Keywords: experimental stress, salivary cortisol, Trier test

THE IMMUNOHISTOCHEMISTRY AND MORPHOMETRY STUDY OF THE EPICARDIAL ADIPOSE TISSUE CHANGES IN CORONARY ARTERY DISEASE PATIENTS ON RIGHT ATRIAL APPENDAGES BIOPSIES

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Objective: Epicardial fat is a measurable and modifiable risk factor that can serve as a novel and additional tool for cardiovascular risk stratification. Alterations in epicardial adipose tissue (EAT) biology, including increased fat thickness, inflammation and angiogenesis, have been described in (CAD) patients. Here, we proposed to measure EAT thickness and characterize inflammatory infiltrate and angiogenesis in epicardial adipose tissue in coronary artery disease (CAD) patients with and without chronic heart failure (CHF). We attempted also to identify clinical factors that may predict the development of CAD/cardiac ischemia.

Methods: The paper studies the association between the cardiovascular risk factors (CVRFs) and morphological EAT hallmarks (EAT thickness, inflammation and angiogenesis) in patients with CAD. EAT thickness was done by using morphometry based on usual histological stains. Inflammatory cell infiltration and angiogenesis was investigated by immunohistochemical staining, using antibodies against CD68 and CD34 markers, and morphometry was done in 5 random 200+ power fields of EAT on right atrial appendages (RAA) samples subsequently obtained during cardiac surgery.

Results: All CAD patients showed CVRFs such as age >50 years, arterial hypertension, smoking, DM, obesity and hyperlipidemia. EAT thickness, macrophage infiltration and angiogenesis of the EAT in the CAD patients (patients) with CHF was greater than that in CAD patients without CHF.

Conclusion: EAT thickness, inflammation and angiogenesis is related by age, HTA, HL, obesity and diabetes in patients with CAD and CHF, suggesting that these CV RFs factors may have a role in promoting cardiac ischemia.

Keywords: epicardial adipose tissue, epicardial inflammation, angiogenesis, coronary artery disease, chronic heart failure.

NUTRITIONAL STATUS IN ELDERLY PATIENTS WITH END-STAGE RENAL DISEASE

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Objective: The value of Mini Nutritional Assessment as nutritional assessor of protein-energy wasting in elderly is well known. However, its value on patients diagnosed with end-stage chronic kidney disease have, with some exceptions, been less investigated.

Methods: In 77 elderly hemodialyzed patients, Mini Nutritional Assessment, body mass index, lean tissue index and fat tissue index, handgrip strength and serum albumin were examined at baseline and after a six-month follow-up period.

Results: Protein-energy wasting was found in 20.7% (n=16) patients, and 58.4% (n=45) were at risk of malnutrition. Patients with protein-energy wasting had lower body mass index, lean tissue index and fat tissue index, handgrip strength and serum albumin. Among 57 hemodialyzed patients who were re-assessed after 6 months, 13 (22.8%) remained well-nourished, 34 (59.7%) were at risk of malnutrition and 10 (17.5%) were with protein-energy wasting. Among those who died, 17 out of 20 had nutritional problems. From the deceased patients, there were significantly more cases with low lean tissue (80% compared to 28.1% of the survivors, p = 0.0001). The risk of death was 41.11% higher than in patients with normal levels.

Conclusions: Mini Nutritional Assessment, a valid assessor of nutritional status is a robust prognosticator of clinical outcome. Although our results are significant, the group sample size during follow-up was small, which may affect the association of MNA and other nutritional parameters with clinical outcome.

Keywords: malnutrition, elderly, hemodialysis.

SUBCUTANEOUS WHITE ADIPOCYTES AREA CORRELATION WITH METABOLIC SYNDROME BIOMARKERS IN OBESE BARIATRIC PATIENTS

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Objective: White adipose tissue cellularity is a highly versatile and precocious marker for metabolic status. Fat morphology can be estimated by comparing body fat mass with an average fat cell size. Recent studies have shown that adipocyte hypertrophy is negatively correlated with dyslipidemia and insulin resistance, independent of body composition.

Methods: The study group includes 18 obese patients, with a mean age of 38.76 ± 8.89 years and a mean BMI of 46.06 ± 6.48 kg/m2 for which subcutaneous abdominal fat tissue (1–2 g) was harvested during the laparoscopic sleeve gastrectomy. Histological sections were analyzed using Tissue Gnostic FACS Histo software and Adiposoft for automatic cell size measurement. Metabolic syndrome criteria as established by IDF were evaluated for the patients in the study, leptin, adiponectin, C peptide, and HOMA-IR measurements were performed.

Results: Mean subcutaneous adipocyte area was higher in obese patients with associated metabolic syndrome criteria compared with those without metabolic syndrome (3200 vs 1289 μm2; p=0,001). For HOMA-IR and C peptide levels a positive correlation (r= +0,493; p=0,017) respectively (r= +0,622; p=0,002) was found with mean adipocyte area. Also adipocyte area was correlated with BMI values (r= + 0,575; p=0,004) and increased Leptin/Adiponectin ratio (r= +0,602; p=0,002).

Conclusions: Measuring fat cell size might have important implications. Impaired adipogenesis leads to disfunctional, hypertrofic adipocytes, local inflammation and peripheric insulin resistance. As recently discussed, other parameters are needed to better classify subtypes of obesity that have different impacts on the risk of developing type 2 diabetes and other obesity complications.

Keywords: subcutaneous adipocyte size, laparoscopic sleeve gastrectomy, insulin resistance, leptin, adiponectin

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EXPRESSION OF GROWTH HORMONE SECRETAGOGUE RECEPTOR (GHS-R) 1A ASSESSED BY IMMUNOCHEMISTRY AND RT-PCR IN SEVERELY OBESE PATIENTS

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Objective: Ghrelin induced increase adiposity, hepatic steatosis, increasing lipid droplet number and triacylglycerol content by a GHS-R(1a)-dependent mechanism. We evaluated the expression of GHS-R(1a) in adipose tissue samples from obese and normal weight patients.

Methods: The adipose tissue was obtained from normal weight subjects undergoing unrelated surgical procedures (N=4) and from morbidly obese patients (N=6) who underwent laparoscopic sleeve gastrectomy (LSG). The GHS-R(1a) expression was analyzed by immunohistochemistry staining and RT-PCR mesurement of GHS-R(1a) mRNA expression.

Results: In obese patients, the GHS-R(1a) immunohistochemistry staining in adipose tissue was diminished as compare to normal weight patients. We found significantly higher PPAR γ expression in the subcutaneous adipose tissue and a positive correlation between PPAR γ expression and body mass index (BMI). The ghrelin receptor mARN expression was lower in obese patients as compared to control.

Conclusions: Our data could suggest that exposure to ghrelin may limit adipose tissue expression of GHS-R(1a) in relationship with lipid retention in adipocyte.

Keywords: ghrelin receptor, GHS-R(1a), obesity, adipocyte differentiation.

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IMMUNOHISTOCHEMICAL ASSESSMENT OF GHRELIN RECEPTOR EXPRESSION ON GASTRIC TISSUE IN ANIMAL MODELS AND HUMANS

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Ghrelin is a 28-amino-acid endogenous ligand of the growth hormone secretagogue receptor (GHS-R) and is primarily secreted from gastric endocrine cells. Ghrelin is known to have a strong orexigenic effect and has been reported to enhance gastrointestinal motility. In vitro, ghrelin contracts muscle strips of rat forestomach and antrum. Treatment with ghrelin and agonist of ghrelin receptors induces contractions in the antrum and increases the motility index in rodents and humans, improving delayed gastric emptying. These effects of ghrelin are believed to act on the central nervous system via the afferent vagus nerve and promote gastrointestinal motility through an efferent pathway. The unique identified ghrelin receptor is the growth hormone secretagogue receptor, GHSR1a. We overviewed literature evidence for effects of GHR receptor ligands with actions at GHSR1a at stomach level.

Keywords: ghrelin, GHSR1a, stomach

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DEVELOPING AND TAILORING PROTOCOLS FOR TRANSDIFFERENTIATION OF MUSCLE SATELLITE CELLS TO ADIPOCYTES IN RODENT EXPERIMENTS

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In our studies, we focused on pathogenic mechanism involved in transdifferentiating myoblasts (satellite cells) in adipocytes. Transdifferentiation of skeletal muscle into adipocytes could lead to sarcopenia or insulin resistance. Adipocyte differentiation of muscle precursors could be used as an *in vitro* cell culture model for studying the various interventions that could inhibit this transformation. We present our experience and protocol to collect, extract, characterize, proliferate and transdifferentiate the satellite cells in adipocytes in rodents experiments. The knowledge could be translated on human satellite cells studies in older adults with frailty.

Keywords: adipocytes, myoblasts, sattelite cells, transdifferentiation, rodent

METAINFLAMMATION IN OBESE PREGNANT WOMEN LEAD TO METABOLIC DISEASE AND FETAL DISTRESS

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The perception of adipose tissue has shifted from being regarded as a passive organ with a storage role to a metabolically active organ. As we all know, the concept of metainflammation describe the chronic low-grade inflammatory response to obesity. Pregnancy similar to obesity also represent chronic low grade of inflammation with the expression of proinflammatory cytokine from the placenta. In obese pregnant women the balance between proinflammatory and anti-inflammatory cytokine is modified and this may lead to maternal insulin resistance and metabolic syndrome in offspring by influencing placental function. Also, obese women are at greater risk for developing pregnancy complications such

as preeclampsia, thromboembolism, and gestational diabetes mellitus. This review also discuss how inflammation can lead to other aspects of metabolic syndrome in obese pregnant women including hyperphagia β cell dysfunction.

Keywords: obesity, chronic inflammation, metabolic desease, pregnancy

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IMMUNOHISTOCHEMICALLY APPROACH OF SUBCUTANEOUS ADIPOSE TISSUE IN NORMAL WEIGHT AND OBESE PATIENTS UNDERGOING BARIATRIC SURGERY

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Objective: The study aims to study inflammatory markers and their relations with ghrelin axis in adipose tissues from normal weight and severely obese patients.

Methods: The subcutaneous adipose tissues samples were collected via the laparoscopic technique of gastric sleeve (obese patients) and laparoscopic cholecystectomy (normal weight controls). Tissue samples were fixed with PFA and paraffin-embedded in blocks for IHC techniques tailored in our laboratory. Procedures involved slices on microtome being assessed via IHC using various antibodies for ghrelin receptor (GHSR-1A), adipogenic proliferation marker (CD10), and inflammatory markers (CD3, CD20, CD68, TNFα).

Results: For analysis, digital photomicrographs of the entire adipose tissue sections were used to quantify the immunohistochemical staining in three different regions to assess the regional heterogeneity in tissue samples. Using software, the color and intensity thresholds were established to detect immunostaining as positive and background staining as negative pixels. Once the conditions were established, all slides were analyzed using the same parameters. The adipose tissue samples from obese patients were positive for inflammation markers. The normal weight samples were positive for adipogenic proliferation marker and ghrelin receptor (GHSR-1A).

Keywords: obesity, ghrelin receptor (GHSR-1a), inflammatory markers, immunohistochemistry, bariatric surgery

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PATHOPHYSIOLOGY OF PARANEOPLASTIC PLEURAL EFFUSION

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Background: The space between the two pleura accumulates physiologically a daily amount of 500-600 ml of liquid. The paraneoplastic pleural effusions are characterized by heterogenity with a minor portion of fluids reaching values typical for para-inflammatory effusions. Pleural effusion may be exudate or transudate, with multiple etiological causes. Paraneoplastic pleural effusions are usually exudates, but there are cytological and biochemical differences depending on the histopathologic type of the primary tumor. Paraneoplastic pleural effusion is accompanied by an intense inflammatory process, demonstrated by increased levels of inflammatory biomarkers. The differentiation between paraneoplastic and para-inflammatory exudates must be regarded with prudence, due to the presence of a high-expressive paraneoplastic sub-population, including effusions associated with metastatic tumors.

Case report: We present the case of a 71-year-old woman with a history of chronic ischemic disease for several years, with stent implantation, with episodes of pulmonary thromboembolism, hospitalized and monitored in Pulmonology Department for recurrent hemorrhagic pleural effusion. The clinical and paraclinical examinations performed excluded the cardiac or thromboembolic etiology of pleural effusion. Biochemical investigations revealed high concentrations of rheumatoid factor in the serum and pleural fluid without a clear evidence of an autoimmune disease. The suspicion of pleural mesothelioma or secondary pleural effusions arises. The diagnosis of certainty, established post-mortem, revealed a pulmonary adenocarcinoma with multiple secondary determinations.

Conclusions: Etiology of recurrent pleural effusion sometimes remains difficult to establish, due to the many etiologies involved. Despite all the investigations carried out, physio pathological mechanisms implied are multiple and the cause cannot be revealed.

Keywords: pleural effusion, paraneoplastic, pleural mesothelioma

NEUROLEPTIC MALIGNANT SYNDROME COULD MIMIC EARLY PHASE OF SEPSIS - CASE SERIES

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Background: Neuroleptic Malignant Syndrome (NMS) is a potentially lethal process related to the use of neuroleptic agents (eg, butyrophenones, phenothiazines, thioxantenes), that produce dopaminergic blockade. It is characterized by several cardinal features: autonomic dysfunction, altered mental status, muscular rigidity, and hyperthermia.

Case report: We present two male cases referred to ICU department as septic shock without specified entry point presenting high fever, tachycardia, hypotension and diaphoresis occurred after haloperidol administration for extreme agitation. New onset fever without a definitive etiology, but under neuroleptic treatment had raised the suspicion for NMS and elevated CK level was a useful diagnostic tool. Once NMS diagnostic was established, aggressive supportive therapeutic measures were performed and renal replacement therapy was mandatory, with rapid improving of clinical condition.

Conclusions: The risk factors that increase the likelihood of developing NMS are pharmacological, environmental (high ambient temperature, dehydration), demographic (age, comorbidities) and genetic liability. Rapid loading with potent neuroleptics (haloperidol) is considered a major contributing factor. In all cases of septic shock suspicion, in patients undergoing neuroleptic treatment, NMS should be considered as a differential diagnostic. Early diagnosis and aggressive therapy greatly improved the prognosis.

Keywords: NMS, septic shock, neuroleptics, CK

INFERTILITY TREATED WITH LOW MOLECULAR WEIGHT HEPARIN AND THROMBOPHILIA

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Background: Thrombophilia is a pathology with embolic risk in pregnancy, but also an infertility factor.

Objectives: The use of anticoagulants has increased fertility and requires consideration of the low molecular weight heparins in the treatment of infertility associated with thrombophilia.

Material and Methods: In this study, we have followed the evolution of 42 patients with thrombophilia and infertility without any other cause to whom Fraxiparine in prophylactic dose has been administered and in whom the resistive index) of the uterine artery as a predictor factor of the increase of endometrial vascularization, compared with the same group before the administration of the anticoagulant.

Results: 40 patients got pregnant, finding a decrease of the uterine artery resistance and so the resistive index can be used successfully in monitoring the vascularization of the endometrium, which is essential in the implantation of the embryo.

Discussions: In implantation, the vascularization of the endometrium plays an important role along with a series of proteins, enzymes, and immunological factors. These low molecular weight heparins seem to be involved not only in the haemostasis, but also in the local vascularization and according to some literature data even in the angiogenesis and mediation of embryo implantation.

Conclusions: Fraxiparine has proven essential in the treatment of patients with idiopathic infertility associated with inherited thrombophilia.

Keywords: Infertility, fraxiparine, thrombophilia, resistive index

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ENTHESITIS: A UNIFYING COCEPT IN THE PATHOGENESIS OF SPONDYLOARTHRITIS

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Enthesitis represents the most specific manifestation in Spondyloarthritis and it is included in all the diagnostic criteria. Enthesitis is an early SpA occurrence. Enthesis is localized extra-articular (localized outside the joint), a fibrocartilage structure that transducts mechanical forces from muscles to bones. It can be localized outside the joint, or distant from any sinovial joint. Enthesis has several precise function: it is responsable for the mobility of the skeletal system - providing stability, transduce mechanical forces from the muscles to the bones, being essential for locomotion and also reduces to minimum the lesions at the insertion site. The "enthesis organ" is comprised of enthesis insertion and adjacent tissues including the tendon, bone, fat layer, bursa and synovial. The synovial-enthesis complex is an anatomic and functional

interdependency of the two structures (the synovial membrane and the enthesis). The mechanical stress is the factor that lead to enthesis micro-lesions, which are the cause of the entire inflammatory process that occurs at the enthesis level. Entheses are exposed to repeated biomechanical stress during movement. The IL-23/IL-17 axis plays a key role in the pathogenesis of spondyloarthritis. Enthesitis is determined by mechanical stress which leads to immune activation phase (activation of prostaglandin E2 and IL-23), followed by innate inflammatory response (release of TNF and IL-17). Mesenchymal proliferation elicited by IL-17 and IL-22 will precede new bone formation at entheseal site. IL-17 is a key cytokine for enthesitis induction and it is known to have a bond role between innanate immune system and the adaptative one. Mechanical stress is the factor that determines microdamage of the enthesis which becomes responsable of the inflammatory process at the entheseal site. Interestingly is also the enthesitis localized at distance from any synovial joint, the most frequently sites being Achille tendon, plantar fascia, lateral epicondyl or annulus fibrosus insertion at the vertebral bodies. IL-23/IL-17 pathway activation presents a central role in spondilartropathies pathogenesis. Enthesitis is associated with pain and functional damage and also has an important value in diagnostic and prognostic.

ABORTION- STILL A PATHOLOGICAL CONTRACEPTIVE METHOD FOR ROMANIAN PEOPLE

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Introduction: Contraception is largely used worldwide to prevent unwanted pregnancies. Romania has had a negative history related to unsafe abortion and prohibition of the contraceptive methods during the communist regime. Although Romania is a member of the European Union and now contraceptive methods are available on a large scale, there are still a great number of unwanted pregnancies for which abortion is demanded by the female population.

Material and method: Statistical analysis of the data regarding abortion performed in state hospital or private medical facilities was performed for the period 2013-2016. Age groups, place of living, way of performing the procedure were investigated.

Results: For the period 2013-2016, there were 3068 abortions performed, out of which 2749 were performed on the patients request. 16 abortions were performed in unsafe conditions and the rest were represented by incomplete abortions. 35-38% of the TOP performed on the patients request were done in private medical facilities. Persons with more than 5 abortions were registered frequently; most of these procedures being asked for by the age group 30-34 and 35-39 years old. Majority of TOP were performed by dilation and curettage technique.

Conclusions: The rates of abortion in Romania are one of the highest in Europe and the way of performing it can generate a lot of complication (D&C method). Official data is scarce regarding abortions as not all private facilities need to declare this procedure. As persons appeal several times for TOP, we conclude there is a poor contraceptive education and abortion is still considered a contraceptive method.

Keywords: abortion, contraception, termination of pregnancy (TOP)

QUALITY OF LIFE FOR PERSONS HAVING DIABETES MELLITUS AND ASSOCIATED DERMATOLOGICAL LESIONS

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Introduction: The quality of life requires a state of well referring to physical, mental and social status and not only the absence of disease. Diabetes mellitus, being a chronic condition that affects 425 million people worldwide, determines by its complications such as degradation of sight, kidney failure, aggravation of vascular disorders, diabetic leg, nerve impairment which all can contribute to a lowering of the self esteem, depression and social depravation.

Materials and method: We used the EPICES score and Beck Depresion Inventory (BDI) to investigate the socio-economic and mental health perspectives and analyzed statistically the outcomes, focusing on socio-demographic data like: age, gender, residence, level of education, occupation, marital status in BDI, chronic illness if present.

Results: 1081 subjects replied to both EPICES and BDI questionnaires between January-June 2019. The mean age was 42.27 (SD 14.666) and 56.8% were female. The BDI score mean value was 16.31, Standard deviation SD (SD 12.925), with extreme values 0-56.The EPICES score mean value was 50.12 (SD 17.09273) with extreme values 7.10-100.DM was present in 11.47% (n=124) and HTN in 26.27% (n=284) of the responders. Depression was prevalent in 40.76% (n=505) of our sample, which is worrying; chronic illness was prevalent in 37.74% (n=408) and 64.95% of them were depressed (n=265) compared to 35.66% (n=240) of non chronically ill subjects.

Conclusions: Diabetes and deprivation is, no doubt, a twin problem in Arad County, for the DM patients being worse than for general population. A large part of the subjects having both diabetes and associated dermatological lesions present a mild to moderate form of depression.

Keywords: diabetes mellitus (DM), quality of life, depression, burden of disease

CHANGES OF GHRELIN AND GHRELIN RECEPTORS IN REPONSE TO STRESS

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Ghrelin, an orexigenic hormone, plays an important role in the motility of the stomach and duodenum. Ghrelin binds to the growth hormone secretagogue receptor, which is widely expressed in the hypothalamus and brainstem. Expression of ghrelin receptors in the hypothalamus shows marked increase in prolonged fasting or chronic dietary restriction. On the other hand, circulating ghrelin levels are reduced with overeating, high fat diets, after excessive glucocorticoid administration, and following successful treatment of celiac disease or anorexia nervosa. All types of stress, whether mental or physical, increase the plasma level of acyl ghrelin, ghrelin mRNA and the number of cells that produce ghrelin from the stomach. In addition, intraperitoneal acyl-ghrelin administration results in a significant dose-dependent increase in serum corticosterone level one hour after administration. Stress-induced changes in ghrelin secretion could be the biological basis of overeating and one of the contributing factors to obesity development.

Keywords: ghrelin, ghrelin receptor, cortisol, stress

THE ROLE OF GHRELIN RECEPTOR IN THE PROLIFERATION AND DIFFERENTIATION OF ADIPOCYTES

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Ghrelin is a 28-amino-acid peptide and an endogenous ligand for growth hormone secretagogue-receptor 1a (GHS-R1a). GHS-R1a is a G-protein-coupled receptor with seven transmembrane regions. There is an increasing interest in therapeutic potential of antagonism of ghrelin signaling concerning its use for the treatment of obesity and metabolic syndrome. The results of several different GHS-R1a antagonists were reported, which induced 10–15% weight loss in experimental obesity. The GHS-R1a inverse agonists and GHSR fusion proteins were also used for the treatement of obesity but the results were modest. An additional phenomena associated with ghrelin signaling blockade is the ghrelin resistance which has been demonstrated in animals and confirmed in clinical studies using an anti-ghrelin vaccine whith induction of anti-ghrelinantibodies.

Keywords: ghrelin, growth hormone secretagogue-receptor 1a (GHSR1a), adipocyte

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CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY WITH GOOD THERAPEUTIC RESPONSE TO PERIPHERAL PLASMAPHERESIS

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Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated disorder of the peripheral nervous system in which the primary pathogenic mechanism is presumed to be mediated by both cellular and humoral immune reactions against myelin and the peripheral nerve axon causing motor deficits, sensory dysfunction, peripheral loss of reflexes. CIDP has a progressive evolution during at least 8 weeks or has episodes of relapses.

Case report: We present the case of a young male of 21 years old with CIDP. He had six episodes of acute relapses which were treated either with corticotherapy or with intravenous immunoglobulins (IG Iv) administration with good response initially at corticotherapy, lately only at IG Iv. At the last two admissions in hospital he did not show improvement after IV Ig administration and required plasmapheresis as a therapeutic procedure with subsequent improvement. At the last hospitalization, the therapeutic solution chosen was plasmapheresis by peripheral approach performed by the neurologist.

Conclusions: In the treatment of CIDP neurologists have a number of therapeutic options, including administration of corticosteroids, IV Ig and therapeutic procedures such as plasmapheresis. The advantage of plasma exchange is the procedural removal of pathogenic auto-antibodies and circulating immune complexes followed by the rapid installation of the therapeutic effect. Plasmapheresis is generally reserved for severe cases in which other therapies have failed, being a treatment given on the short term until obtaining the remission and followed by immunosuppression. There are also situations in which the long-term use with the individualized and careful analysis of the risk-benefit ratio is necessary. Peripheral veins access is preferred and is easy to be achieved by the neurologist because it is associated with fewer infections, thrombotic complications and pneumothorax compared to central veins and additionally relieves the intensive care clinic from a neurological therapeutic procedure that can be performed in these conditions safely in the neurology clinic.

Keywords: plasmapheresis, CIDP , IV Ig, peripheral nervous system

ASPECTS OF PATIENTS BEING DIAGNOSED WITH PERIPHERAL ARTERY DISEASE AND PRESENTING LEUKOCYTOSIS

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Introduction: Peripheral artery disease of the lower extremity is one of the main causes of morbidity when it comes to atherosclerotic cardiovascular disease. For many years atherosclerosis was considered to be a passive process of lipid deposition in the vascular wall, today it is considered to be a chronic inflammatory disease caused by lipids and leukocytes. Increased levels of leukocytes influence atherosclerosis and its complications.

Objective: The aim of the study is to evaluate the condition of the patients suffering from obliterative arterial disease of the lower limbs and having increased leukocyte values, upon admission.

Material and Methods: We performed a retrospective, observational study on 30 patients admitted in the Vascular Surgery Department of the Mures County Emergency Hospital, being diagnosed with peripheral artery disease of the lower limbs and having elevated leukocyte values. Medical data such as: disease characteristics and demographic data were extracted from patient records.

Results: Most of the patients were male (70%), with a mean age of69 years. Leukocytes recorded an average value of14.65±4.76 10^3/μL, with a maximum value of27.6 10^3/μL. Upon admission, all patients presented lower limb pain, 66% fall in stage III and IV of the Leriche-Fontaine classification, 30% presenting trophic skin lesions. The symptoms have occurred for most in more than 1 year from the admission (43%). The lesion was located at all patients at the femural-popliteal axis. Following the risk factors for the onset of atherosclerosis 76.6% reported smoking tabacco actively or in the past. From the personal pathological background we noticed a procent of 76% being hypertensive, and 30% suffering from dyslipidemia. 60% of the cases required more than 7 days of hospitalization.

Conclusion: Observing that most patients present an advanced stage of the disease we can affirm that the increased levels of leukocyte values can be considered both a marker of atherosclerosis exacerbation and a risk factor for it.

Keywords: peripheral artery disease, atherosclerosis, leukocytosis

EPIDEMIOLOGICAL, CLINICAL AND EVOLUTIVE ASPECTS IN PATIENTS WITH OBESITY, TYPE 2 DIABETES AND INFECTIONS IN BRASOV, ROMANIA

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Introduction: The increase of obesity and type 2 diabetes prevalence worldwide has drawn attention to this major health problem in our century. It is also known that both obesity and type 2 diabetes are increasing the susceptibility for infections and chronic diseases.

Objective: The objective the study was to evaluate some epidemiological, clinical and evolutive aspects of patients diagnosed with obesity, type 2 diabetes and admitted with an acute infection.

Material and method: We have analyzed the epidemiological, clinical and evolutive aspects on 69 patients diagnosed with obesity and type 2 diabetes, admitted for investigations and treatment of different acute infections in the Infectious Diseases Clinical Hospital of Brasov in 2017-2018, in a retrospective, transversal and descriptive study.

Results: 49.28% patients out of 140 obese patients admitted had type 2 diabetes, from which 60.86% were female patients, most patients from the urban area (73.91%) and over 83% of the patients being over 45 years old. As in terms of hospitalization period, most patients were admitted for more than 3 days (82.60%). Acute infections were various, as well as respiratory – 28.98% (pneumonia – 60%), cutaneous-33.33% (cellulitis – 82.60%), digestive - 34.78% (acute diarrhea disease – 54.16%), urinary - 18.84% and others - 21.73%. Associated chronic diseases were found in 94.20% of patients – cardiovascular (66.66% cases), liver disease (37.68% cases), respiratory (7.24% cases) and renal

and neurological (28.98% cases). Cephalosporine was the most used antibiotic (36.92% of antibiotics used), and over 43.37% cases were admitted for 2 or more acute infections. Evolution of the patients was favorable in 95.65% cases.

Conclusion: Patients were admitted for various infectious diseases, with favorable evolution in most of the cases. Obese patients with type 2 diabetes and acute infections require concomitant therapy for acute and chronic diseases and adequate medical supervision, with favorable evolution in most of the cases.

BRAF MUTATION DETECTION IN MELANOMA: LITERATURE REVIEW

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Background: Metastatic melanoma is a fatal disease with a poor prognosis. Recent progress in understanding its physiopathology leads to the necessity of developing more precise and affordable molecular testing techniques.

Objective: Our objective was to review the advantages and disadvantages of the molecular techniques employed in the pathology laboratories.

Material and Methods: We have analysed 20 articles using PubMed Central published in the last seven years, mainly focusing on BRAF mutation detection.

Results: The identification of BRAF mutations through DNA sequencing 20 years ago lead to a revolution in the treatment of melanoma, correct identification of mutation status being mandatory. Two types of analysis are described: DNA-based represented by Sanger bidirectional sequencing, pyrosequencing, Droplet Digital PCR, Idylla BRAF Mutation Test, next-generation sequencing (NGS) and protein-based test- immunohistochemistry (IHC). Currently, the gold standard is represented by DNA-based test, but IHC could be used as a reliable tool. The advantages of IHC are: short turn-around time, short hands-on time, available in almost all pathology laboratories, few material used for diagnosis but it is limited by the only detection of the V600E clone which means that additional tests should be performed to identify the V600-nonE clones which benefit also from targeted-therapy. Idylla is a fully automatic technique with short turnaround and hands-on time, identifying all V600 mutations but it is more expensive than IHC. The cheapest option is ddPCR but it is restricted to V600E detection and it is more laborious. NGS is the most laborious, expensive, with the longest turn-around time and requires sophisticated bioinformatics systems, fast data processing and large data storage capabilities, but it allows the detection of all BRAF-V600 and non V600 mutations.

Conclusion: Fast testing for BRAF mutation is mandatory. Therefore, Idylla or IHC could be used as first step approach, but they cannot replace NGS which provides a broader molecular profile.

MERKELL CELL CARCINOMA OF THE SKIN –CASE REPORT

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Background: Merkell cell carcinoma known as trabecular carcinoma of the skin was first described by Toker in 1972. It is a rare neuroendocrin cancer with a low incidence rate and high rate of aggressive biological behavior. The objective of the paper was to present a particular case of a tumor of the gluteal region.

Material and Methods: A 77 year-old woman was hospitalized for surgically removal of a slowly-growing nodule of the skin of the gluteal region. The histopathological analysis revealed a tumor proliferation that interests the dermis and the hypodermis with the invasion of the striated muscles from this level. Tumoral cells present scant eosinophilic cytoplasm and round nuclei with finely granular and dusty chromatin. Immunohistochemically tumor cells were positive for chromogranin, synaptophysin and CD56 but also for the epithelial markers keratin AE1/AE3, keratin 20 and EMA. Immunolabelling with S100, TTF1 and CTK7 was negative. Based on the immunoprofile, the focally dots-like expression of Keratin 20 and clinical information, the possibility of occurrence of a metastasis from a carcinoma with other location was excluded and the diagnosis of Merkell cell carcinoma was established.

Conclusion: Correct diagnosis of a neuroendocrine skin tumor should be based on clinicopathological information and a possible metastasis should be firstly excluded.

Keywords: neuroendocrine tumor, Merkell cell carcinoma, skin, immunoprofile

LIVER METASTASES – A CHALLENGING DIAGNOSIS

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Background: Chromophobe Renal Cell Carcinoma is the 3rd most common subtype of RCC. It is most frequently sporadic however, several familial cases, associated with Birt-Hogg Dubé syndrome, have been described.

Material and Methods: A 68 year-old male which on CT examination, presents in the left hepatic lobe a focal lesion of 93 mm, well delimited with contrast socket. Liver biopsy is performed. Microscopic examination shows a tumor proliferation with a pseudoglandular- pseudo-accinar pattern with the delimitation of numerous vascular spaces. Immunohistochemical tumor cells are positive for CTK7 and CTK8 / 18 and negative for CEA, CTK19, CTK20 and CDX2 immunolabeling. Based on the immunohistochemical profile and morphological aspect, the diagnosis was malignant hepatic tumor possible hepatocellular carcinoma but a gastric metastasis of a carcinom with hepatoid pattern cannot be excluded. One week later it was found that the patient had a history of renal tumor, whose histopathological diagnosis was of chromophobe renal cell carcinoma. The immunohistochemical panel was supplemented with the reaction to CD117 in which the tumor cells were diffused positive and thus the definitive diagnosis of hepatic metastasis of renal carcinoma with chromophobic cells was established.

Conclusion: In order to establish the primary origin of a liver metastasis, all the clinical information and all the pathological history of the patient are required.

Keywords: chromophobe renal cell carcinoma, metastasis, liver biopsy, hepatoid pattern

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A RARE CASE OF VERRUCOUS SQUAMOUS CELL CARCINOMA-CASE REPORT

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Introduction: Veruccous carcinoma is a rare and well differentiated variant of the cutaneous scquamous cell carcinoma and it was described first by Ackerman (also called Ackerman tumour). It can appear on both skin -especially palm and soles- and oral cavity and it's more common in older men (>60 years old). This type of carcinoma is characterised by slow growth, minimal local invasion and rare metastases, on a long term having a better prognosis than the other types of squamous carcinoma.

Case report: We present a case of veruccous carcinoma located on the sacral region in a 54 year old female patient with no medical background.

Results: The H&E stains revealed a lesion characterized by endophytic and exophytic architecture with proeminent hyperkeratosis. The microscopy of the carcinoma showed the "rete ridges" which are bulbous, with "bulldozing" pattern that invade in the depth of the skin. The epidermis is also interested by papillomatosis, hypergranulosis and acanthosis of the squamous layer. The cytologic changes were minimal, these tumors don't usually show significant anaplasia. A chronic inflammatory cell dermal infiltrate was also present, but due to the fact that the lesion was fragmented during excision we couldn't evaluate the edges of the tumor.

Conclusion: Verrucous carcinoma is more common in the oral cavity,soles and palms,it can rarely appear in any other skin area. It has a better prognosis than the classic type of squamous carcinoma.

Keywords: verrucous carcinoma, immunoprofile, squamous cell carcinoma

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PRIMARY OVARIAN ENDOMETRIOID CARCINOMA ASSOCIATED WITH SIMPLE ENDOMETRIAL HYPERPLASIA-CASE REPORT

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Introduction: The endometriod carcinoma of the ovary is a rare ovarian tumor which represents 10-25% of the primary ovarian carcinomas and can be associated in around 30% of the cases with endometrial, benign or even malignant, lesions. It can occur in patients with a wide range of ages, from 26 to 87 years old, but it is more common in the 50-70 range.

Case report: we report the case of ovarian endometrioid carcinoma in a 44 year old female patient who underwent surgery for a left ovarian tumor.

Results: In the ovary, H&E stains revealed a proliferation of glandular structures with different sizes and aspects, some of them presenting cystic dilatations and villoglandular pattern. The glands were surrounded by a reduced stroma and their epithelium was columnar and displayed moderate cytological atypia: proeminent nucleoli, typical and atypical mitotic figures and pleomorphism. Squamous metaplasia, areas of necrosis and inflammation were present in the tumoral area. The pathological stage was pT1c2NxMx. Immunohistochemistry exhibits diffuse positivity for CK7, and focal positivity for WT1 and CDX2.

The examination of the endometrium showed features of simple endometrial hyperplasia without atypia of the glandular epithelium.

Conclusion: Our case captures the coexistence of these two lesions: primary ovarian endometrioid carcinoma and simple endometrial hyperplasia, both favored by hyperestrogenism.

Keywords: ovarian endometrioid carcinoma, endometrial hyperplasia, immunoprofile.

B-LINES AND LEFT ATRIAL STRAIN IN PATIENTS WITH SUSPECTED HEART FAILURE AND PRESERVED EJECTION FRACTION

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Background: The prevalence of heart failure with preserved ejection fraction (HFpEF), continues to increase likely because of common risk factors, including older age, female sex, hypertension, metabolic syndrome. Lung ultrasound and left atrial strain are promising screening tools to assess pulmonary congestion and left atrial dysfunction in patients with suspected HFpEF.

Objective: The objective of the research was to evaluate the correlation of lung ultrasound with left atrial strain in patients with HFpEF.

Method: We enrolled thirty-six patients, 24 of them women, the mean age 70±6 years with clinical signs of heart failure. Exclusion criteria were: ejection fraction <55%, more than mild mitral and/or aortic valve disease, pulmonary disease, pulmonary atrial hypertension. Patients underwent comprehensive echocardiographic evaluation including left atrial strain analysis (peak atrial longitudinal strain-PALS), lung ultrasound assessment of B-lines on the antero-lateral and posterior chest wall, and NT-proBNP levels.

Results: The mean ejection fraction was 65,5 ±8,6%. In 28 patients (85%) a significant number of B-lines (≥15) was observed. We found a positive correlation between the number of B-lines and NT-proBNP levels (p<0,0001, r:0,76), left atrial volume (p<0,05, r:0,45) and PALS (p<0,05, r:0,5). We didn't found any correlation between the number of B-lines and E/e' ratio (p=0,1 r:0,28), or between E/e' ratio and NT-proBNP level (p=0,2 r:0,2).

Conclusion: Lung ultrasound is a simple and accessible device to detect pulmonary congestion in HFpEF. B-lines correlate well with NT-proBNP values and with parameters of left atrial dysfunction. PALS is a promising reflection of pulmonary congestion and elevated NT-proBNP values than the conventional echocardiographic parameter E/e'.

Keywords: HFpEF, lung ultrasound, b-lines, echocardiography, strain rate imaging

METATARSAL AMPUTATION AS A RESULT OF PARANEOPLASTIC VASCULITIS: A CASE REPORT

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Introduction: Amongst the large spectrum of neoplasia-associated syndromes are counted vasculitis, usually systemic, but sometimes with only one site evidently involved. With pancreatic and gastric cancers being the most well known type of tumors that could associate paraneoplastic syndromes, gallbladder adenocarcinoma can also represent the etiologic factor of these kind of clinical systemic manifestations.

Objective: We aimed to emphasize the direct relation between the tumor and focal ischemic changes, as a paraneoplastic syndrome.

Methods and materials: We reported a case of an otherwise healthy, non-smoker male, with no evidence of diabetes mellitus, diagnosed with gallbladder adenocarcinoma, who developed acute left leg ischemia after 7 days post-cholecystectomy. For both diagnoses, it were used standard histological techniques: light microscopy and standard hematoxylin-eosin staining.

Results: The tumor consisted of a proliferation of atypical glandular structures with a micropapillar component, which infiltrated diffusely the colecystic wall on both hepatic and free, peritoneal sides. Metastases were present in all 4 surgically removed lymph nodes. Perineural and angio-lymphatic invasion were also present. Both of the resection margins, of cystic duct and hepatic surface, were infiltrated by tumor cells. At the level of the forefoot amputation, changes were observed in the medium and small caliber arteries, these presenting a very thick wall, a decreased diameter of the lumen and a rich inflammatory intramural and periarterial infiltrate. There was no evidence of vascular tumor emboli.

Conclusion: Given the relatively short period between the diagnosis of cholecystic tumor and the occurrence of perfusion disorders in the forefoot, with absence of classic risk factors for obstructive arterial pathology of the patient, there is most likely a direct causal relationship between the tumor and the acute ischemia of the lower limb.

SMALL BOWEL METASTASES: REPORT OF 4 CASES

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Introduction: With primary small bowel tumors being relatively rare, the vast majority of them being neuroendocrine tumors, metastases at this site are relatively uncommon. The most frequent primary tumor with metastatic affinity for this location is considered to be cutaneous melanoma.

Objective: We aimed to report a series of 4 cases of small bowel metastases with different locations for the primary tumor, emphasizing the heterogeneity of origin for those tumors.

Materials and Methods: A series of 4 patients undergoing segmental enterectomy for small bowel tumors were diagnosed with metastatic disease, primary tumor being either lung adenocarcinoma, cutaneous melanoma, or cervical and laryngeal squamous carcinomas. For all 4 diagnoses, it was used standard histological techniques: light microscopy and standard hematoxylin-eosin staining, and to establish the origin of the metastasis, we used tumor specific immune markers. Regarding the pulmonary tumor, metastases in small bowel were incidentally discovered at the autopsy.

Results: First small bowel metastasis reported is from cutaneous melanoma. Secondary tumor was diagnosed 4 years after the primary diagnosis. The microscopic aspect revealed diffusely infiltrated intestinal wall by a proliferation of epithelioid cells, with marked citonuclear atypia and frequent mitoses. Metastases were present in 3 out of 12 mesenteric lymph nodes. The melanoma-origin was confirmed by the positivity for S100 and Melan A markers.

The second case origin was a squamous cell cervical carcinoma. The primary, cervical tumor was diagnosed 2 years before the detection of intestinal involvment. Microscopic assessment of the matastasis revealed numerous small tumor cells, organized in clusters with different shapes and sizes, with pronounced atypia and frequent mitoses. The immune profile was identical to that of the primary tumor, respectively positive for pancitokeratin and p63.

The third case represented a metastasis from a laryngeal squamous cell carcinoma. The primary tumor was diagnosed 1 year before the metastasis. Also, the microscopic assessment and the immune profile were identical between those two. The origin from the laryngeal carcinoma was demonstrated by the positivity of p63 and pancitokeratin, respectively negativity for CD117, DOG1, Synaptophysin and Chromogranin.

The last case was and incidental autopsy finding in case of a patient diagnosed with pulmonary adenocarcinoma 3 months before death. The microscopic aspect of the intestinal tumor showed similarities with that from the pulmonary site, and also shared the same immune panel: positivity for pancitokeratin, cytokeratin 7, respectively negativity for cytokeratin 5/6, S100, CD3, CD20 and CD138.

Conclusions: Even though the literature report cutaneous melanoma as being the most frequent tumor which metastasize to small intestine, there was demonstrated a heterogeneity of this aspect, all 4 consecutive metastatic small bowel tumors having 4 different origins.

PREVALENCE AND HISTOPATHOLOGICAL CHARACTERISTICS OF CERVICAL CANCER AND PRECURSOR LESIONS IN MUREȘ COUNTY: A RETROSPECTIVE, COHORT STUDY

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Introduction: Cervical cancer is the fourth most commonly type of cancer among women, especially in developing countries.

Material and Methods: We performed a retrospective, cohort study and evaluated all cases of cervical cancer and precursor lesions registered at the Department of Pathology, Târgu-Mureș County Hospital between 2014-2018. Only cone excision and hysterectomy specimens were included in the study. Demographic (age at diagnosis, year of diagnosis) and histopathological data were collected from database registries and original pathological reports.

Results and discussions: Our study included 136 patients with age ranging between 16 and 81 years-old. Among the 136 cases 91(66.9%) were cone excision and 45(33%) hysterectomy specimens. Cone excisions were performed predominantly at women aged between 26-40 years-old; 82 (90.1%) cases were consistent with a diagnosis of cervical intraepithelial neoplasia (CIN I, II or III), 3 (3.3%) cases were keratinizing squamous cell carcinomas and 6 (6.6%) cases were non-keratinized squamous cell carcinomas. Hysterectomies were performed predominantly at women aged between 45-55 years old-women with 28 cases of CIN (62.3%), 6 (13.3%) cases of keratinizing squamous cell carcinoma, 9 (20%) cases of non-keratinized squamous cell carcinoma, one lymphoepitelioma –like carcinoma (2.2%) and one case of serous carcinoma. No association between cervical cancer and other diseases in the gynecological sphere were demonstrated by our data

Conclusions: Cervical cancer remains a central problem, common in most developing countries, including Romania. Squamous cell carcinoma was the most common type of cervical cancer in our study group. Most of the cases occurred in patients older than 45 years-old, with two peaks of incidence (46-50 and 61-65 years-old, respectively).

Keywords: cervical cancer, squamous cell carcinoma, cervical intraepithelial neoplasia

PLASMACYTOID UROTHELIAL CARCINOMA. A CASE REPORT

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Background: Plasmacytoid urothelial carcinoma (UC) is a rare and agressive variant of UC, accounting for 1% to 3% of invasive UCs, characterised by dischoesive individual cells that resemble plasma cells.

Material and Methods: We present the case of a 66-year-old female admitted to the Urology Department for a bladder cancer suspicion. A transurethral resection was performed and the morphological features suggested a malignant tumor infiltrating the bladder wall, composed of discohesive cells with eccentrically placed nuclei and abundant cytoplasm, resembling plasma cells. Carcinoma in situ was observed in some limited areas. Reviewing the medical history, we found that the patient was diagnosed in 2005 with gastric lymphoma. Considering the morphology, unusual for a conventional UC, in order to exclude a lymphoma or a secondary involvement of the bladder from other organs, immunohistochemistry was performed.

Results: Tumor cells expressed GATA3, CK7, CK20, p63 and CD138, and were negative for LCA, ER and PR. The morphological features, the presence of carcinoma in situ and the immunohistochemical profile confirmed the urothelial origin of the tumor cells and led to a diagnosis of plasmacytoid UC.

Conclusion: Although very rare, plasmacytoid UC in the bladder should be kept in mind when facing a bladder tumor with unusual morphology. It is important to differentiate it from other plasmacytoid neoplasms in the bladder, as they have different prognoses and therapeutic implications. In our case, the presence of carcinoma in situ and the immunohistochemical profile facilitated the correct diagnosis.

MULTIPLE MYELOMA. DISEASE RELETAD COMPLICATIONS, PATHOLOGIC MECHANISMS AND THE SUCCESSFUL TREATMENT OF PATIENTS

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Background: Multiple myeloma (Kahler disease) is a protein reletad hematological malignancy. The genetical mechanisms of maturation of Progenitor – B cells are affected and resulting non – normal, genetically affected plasma cells, myeloma cells. The malign plasma cells are producing Bence – Jones proteins (urine) and M – proteins (blood), named together paraproteins. The multiplication and infiltration by the malignant plasma cells is resulting the MGUS. At this situation the symptoms are absent, but when these cells are affecting the body systems by different pathological mechanisms, the symptoms are appearing and resulting the multiple myeloma stage. In this malignant stage is affected the skeletal system, immune system, urinary system, nervous and the hematopoietic system.

Objective: The aim of this retrospective study is to investigate the treatment success rate of multiple myeloma. This study is investigating the gender, age, laboratory analysis of patients, the Durie – Salmon staging, the presence of CRAB symptoms, the complications of the disease.

Materials and methods: This is a retrospective study about the 20 investigated patients between 2018 - 2019 from II. Hematological and stem cell transplant hospital Târgu – Mures. The study makes possible to evaluate the conditions of the patients after using adecvate treatment algorithm (Alkeran and autologic stem cell transplant), and to evaluate how successful is the stem cell transplant. The disease related complications are mostly bacterial infections, osteolytic lesions, anemia, hypercalcemia and pathological fractures.

Results: After investigating 20 patients, the study showing that this malignancy is appearing in younger ages, this is a significantly big change to the last years. Every investigated pacient is developed thrombocytopenia. In 79% of the cases was present leukocytosis, in 60% of the cases infections. The osteolytic lesions and the CRAB symptoms were developed in 69% of the cases. 72% of pacients was anemic. The prognostics after the stem cell transplants was in 80% favorable, and only in 20% was infavorable.

Conclusions: The study confirms the apparition of disease at younger ages, more frequent for male gender. This disease is showing complex mechanisms, affecting different systems of the organism, showing complications and severe simptomathology. Most frequently are appearing opportunistic infections caused by immunodeficiency. 70% of patients is presenting kidney, skeletal, hematological diseases related to the multiple myeloma. The autologic stem cell transplant (unic or double) is making a favorable evolution for patients.

Keywords: Multiple myeloma, Bence – Jones proteins, M – Proteins, immunodeficiency, CRAB symptoms, autologic stem cell transplant, Durie – Salmon staging.

SPONTANEOUS CORONARY ARTERY DISSECTION IN A YOUNG PREGNANT PATIENT COMPLICATED WITH BOTH FETAL AND MOTHER DEATH

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Spontaneous coronary artery dissection (SCAD) is a rare, elusive cardiac disease, which affects women in 90% of cases, with a mean age of 44 years old. Vascular pathology consists in sudden disruption of the coronary artery wall, resulting in separation of the inner intimal lining from the outer vessel wall. Depending on the extention of the dissection, clinical features range from acute coronary syndrome to sudden death. It is known to be the most common cause of myocardial infarction in pregnant woman with high rates of maternal morbidity and mortality and also causing fetal complications and death as well. Diagnosis of SCAD in pregnant women presentng with chest pain is based on ECG abnormalities, troponine levels and is confirmed on invasive coronary angiography (ICA).

We report a case of a young pregnant woman (19 years old) who underwent a cesarean section for a stillbirth (at 28 weeks gestational age) and died two days post surgery. Complete authopsies were performed on both mother and fetus, with extended organ sampling and Haematoxilin and Eosin (H&E) staining.

The fetus had cerebral and lung diffuse sanguine stasis with edema and no malformations. Microscopic sections of the mother coronary arteries with H&E stain showed coronary dissection of the subepicardial artery between the media and adventitia, creating a false lumen, together with thick intimal fibrous proliferation. Cerebral sections revealed diffuse signs of acute infarction.

Pregnancy-related SCAD accounts for a small proportion (less than 5%) of all SCAD. Hormonal changes during pregnancy with high progesterone levels can result in weakening of the vessel wall. Although SCAD are usually complicated with myocardial infarction, in our case cerebral infarction was reported. An early diagnosis and management of SCAD is mandatory in preventing mortality and morbidity in both mother and fetus, ICA beeing the imaging method of choice to confirm the diagnosis and in selected cases also for therapeutic revascularization.

LUNG BIOPSIES EVALUATION IN MOLECULAR ERA

Ovidiu Pop

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Lung cancer is not only the most common cancer worldwide and remain on second position after skin cancer world-wide.

In most of the cases the diagnosis is done on small tissue biopsies. Diagnosis should be based upon the criteria from the 2015 WHO classification. These samples frequently have limited number of cancer cells and for this reason should be handled differently like normally we are used to do. According with the necessity for molecular profile achievement the cutting of paraffin blocks is done in a single step process and not in multiple steps process.

In the era of personalized medicine and target therapies the immunohistochemistry plays an double role; on the one hand are use for assessing the histological subtype of lung cancers and one the other hand plays the role of predictive biomarkers used in the accurate therapeutic decision-making.

The presence of oncogenic alterations, such as activating mutations and chromosomal rearrangements, predicts responsiveness to selective targeted therapies, for EGFR, ALK, ROS1, BRAF are mandatory to be evaluated by stand-alone tests or by next-generation sequencing (NGS)

The immunotherapy is another toll in la cancer field and the PD-L1 status shoud be evaluate by IHC according with protocols.

As pathologists is important to take in account that more and more test should be perform from a limited tissue material.

PATHOPHYSIOLOGICAL CONSIDERATIONS AND MANAGEMENT PRINCIPLES IN POST-INFARCTION LEFT VENTRICULAR PSEUDOANEURYSM – A CASE PRESENTATION

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The incidence of acute myocardial infarction related left ventricular free wall rupture has been consistently reduced due to modern reperfusion therapies. However, in non-diagnosed or late presenting myocardial infarctions the risk could be high and is responsible for the increased mortality in these cases. A peculiar structure resulted from myocardial rupture is the so called post-infarction pseudoaneurysm (PP), when the development of hemopericardium and cardiac tamponade is precluded by the formation of a barrier formed by clot and surrounding, mostly pericardial, tissue. PP has a complex pathophysiology which involves left ventricular volume overload, mitral regurgitation, enhanced arrhythmogenesis and – finally – the development/acceleration of heart failure. These major pathophysiological aspects and the main management issues related to PP will be presented and illustrated in detail in the frame of a case presentation. Interestingly, in our patient, a 69 years old man with severe pulmonary pathology, PP was an accidental finding during a routine echocardiographic examination.

”SURGICAL” HYPERCALCEMIA - CLINICAL FEATURES AND MULTIDISCIPLINARITY

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Objectives: We present 3 cases of primary hyperparathyroidism with surgical indication in which the clinical aspects posed certain diagnostic problems, therefor interdisciplinary collaboration was needed.

Material and method: Case 1: A 33-year-old patient, known with hypercalcemia since childhood, without any etiological diagnosis, with recurrent urinary lithiasis and multiple extarcorporeal shock wave lithotripsy therapies. She addresses the orthopedic doctor for a tumoral mass at the level of left tibia, for which biopsy results showed a brown tumor in the context of primary hyperparathyroidism.

Case 2: A 69 year-old patient, who presented at the emergency room with severe neuro-psychiatric symptoms that required admission to psychiatry department with neurodepressive syndrome. During the hospitalization, he developed an acute psychotic episode that does not improved under specific treatment. After repeating laboratory investigations hypercalcemia and primary hyperparathyroidism with surgical indication was proven.

Case 3: A 16-year-old patient, who presented with symptoms of hypercalcemic crisis, the values of calcium being 14.9 mg / dl and iPTH level was 184 pg / ml. She is admitted to the endocrinology department for hypercalcemia treatment; further investigations revealed a right inferior parathyroid adenoma.

Conclusions: Hypercalcemia in hyperparathyroidism with surgical indication involves extremely varied clinical aspects that require interdisciplinary collaborative diagnosis.

Keywords: hyperparatyroidism, surgery, hypercalcemia

THE ACTION MECHANISM OF BOTULINUM TOXIN IN REDUCING MUSCLE SPASTICITY

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The Botulinum toxin (BTX) is a neurotoxins family, produced by anaerob Gram + bacterium, ,,Clostridium botulinum”. Seven serotypes (from A to G) are part of the family, sharing similar structure, but immunologically distinct. Most clinically used are A serotype (Botox, Dysport, Xeomin) and B serotype (Neurobloc, Myobloc). BTX, injected in high dilutions has a great influence in pharmacological management of spasticity of cerebral or spinal origin. This involuntary hyperactivity of muscles appears as consequence of motor neuron lesions due to spinal cord and traumatic brain injury, stroke, multiple sclerosis. The Botulinum toxin blocks the release of acetylcholine neurotransmitter from the level of neuromuscular junction to several muscular grups generating the so-called ,,chemical denervation”. By BTX injection under electromyograph guidance is obtained the reduction of: muscular spasticity, the abnormal postures and also the associate pain.

The management of spasticity and mobility improvement have been tried in the 3rd Clinic of The National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest. The subject of the trial was a patient with spastic tetraplegia, predominantly crural after a spinal

cord injury (C_5- $C_{6)}$, due to car crash. The pharmacological therapy with BTX, associated with rehabilitation program (physiotherapy and kinetotherapy) led to an improvement in the functional status of the patient.

Concluding, BTX administration has to be considered as an important part in a multidisciplinary approach of a patient with spasticity having a purpose the decrese of disability.

BREAKING NEWS FROM THE FIELD OF COMPLEMENTARY ONCOLOGY, AN EXISTING PRESENTATION OF NEW INTEGRATIVE THERAPIES IN BREAST CANCER PATIENTS

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The aims of the integrative and complementary oncology is to minimalize the side effects of the classic oncologic therapy including such as chemotherapy or anti endocrine therapy and above all to enhance life quality of patients. There is a great interest among patients worldwide in complementary oncological approaches.

The incidence of breast cancer continues to increase in Europe. The prognosis in the metastasing stage is unfortunately still poor: only one in four patients survives the following five years. All the big university hospitals in Germany recognized the increasing needs of the patients and are therefore collecting scientific data and establishing departments of complementary oncology.

Curcumin is a plant-based substance known for thousands of years that is seen as a promising substance in numerous preclinical studies, studies of carcinoma cell lines and in animal research. It has been reported to have a synergistic effect with a number of chemotherapeutic substances.

The aim of our randomised, double-blind, placebo-controlled study was to demonstrate the efficacy of curcumin in combination with taxane in the treatment of advanced breast cancer for the first time. (Study registration: Unique Protocol ID at the U.S. National Institute of Health: 5592-17-02.23 ClinicalTrials.gov Identifier: NCT03072992). Official study name: “Study of Efficacy of Curcumin in Combination with Chemotherapy in Patients with advanced Breast Cancer: Randomized, Double Blind, Placebo Controlled Clinical Trial.”

150 patients with advanced breast cancer were randomly divided into two groups of 75 each. Group A were given paclitaxel (80 mg/ BSA) q1w with an intravenous placebo for a total of 12 weeks Group B received curcumin 300 mg intravenously + paclitaxel q1w also for 12 weeks.

The aim of the study was to demonstrate the potential benefits of curcumin administered intravenously in combination with paclitaxel compared with the placebo and paclitaxel for patients with advanced breast cancer. The primary objectives were the efficacy of the combined treatment with regard to the objective response rate (ORR), progression-free survival (PFS), time-to-tumour progression (TTP), quality of life (QoL) as well as the influence of tumour markers (CEA and CA 15-3). The secondary objectives were treatment safety and the observation of possible side effects and disease progression during the 12 weeks of treatment and an additional period of 12 weeks following the study.

The exact design of the study and the differentiated results were presented and discussed for the first time anywhere in the world at the 2019 German Senology Congress in Berlin. This lecture was awarded high-ranking and will be published soon.

Different exciting aspects of the complementary oncology will be presented in this key note lecture at the THE 11TH NATIONAL CONFERENCE WITH INTERNATIONAL PARTICIPATION OF THE ROMANIAN SOCIETY OF PATHOPHYSIOLOGY, SEPT 4th to 7th, 2019.

APPLYING 5S TOOL IN HEALTHCARE. A CASE STUDY

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Worldwide managers use Lean tools as a business strategy to achieve the proposed objectives. In healthcare the implementation of Lean concept continues to prove incredible results. 5S Method, as a Lean instrument, is a Japanese methodology for the workplace organization, which includes the principles of order, organization, cleanliness and standardization.

As a Premiere in Romania, we introduced 5S Method in a medical laboratory during an 11-weeks project. We reduced unnecessary objects, introduced clarity and orderliness, established specific standards and team’s results showed increased productivity.

This presentation shows the taken steps and the concrete improvements achieved as a result.

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