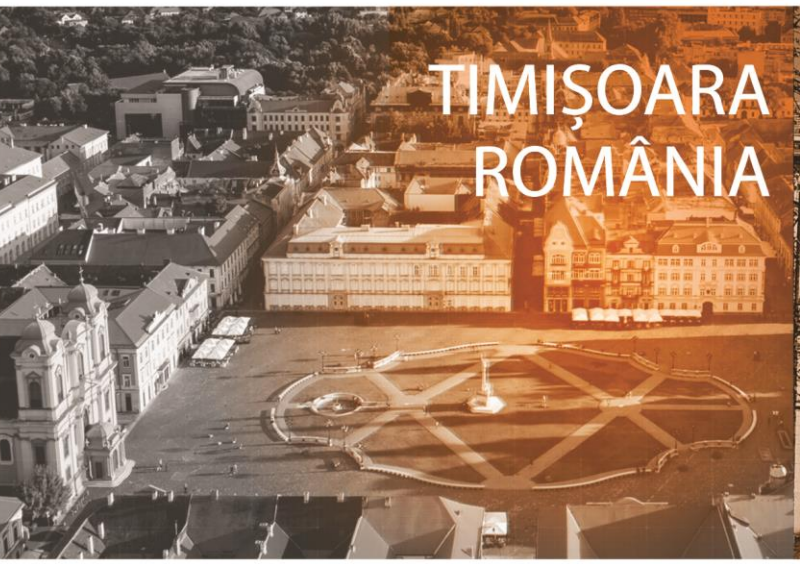
UNIVERSITATEA
DE MEDICINĂ ȘI FARMACIE
„VICTOR BABEȘ" DIN TIMIȘOARA

SOCIETATEA ROMÂNĂ DE FIZIOPATOLOGIE
SRFP

FUNDAȚIA UNIVERSITĂȚII
DE MEDICINĂ ȘI FARMACIE
TIMIȘOARA

NATIONAL CONGRESS OF THE ROMANIAN SOCIETY OF PATHOPHYSIOLOGY

with international participation



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PROGRAMME & ABSTRACTS

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Timișoara, 2024

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PROGRAMME & ABSTRACT BOOK

Editors: Danina M. Muntean, Adrian Sturza, Ovidiu Burta

WELCOME ADDRESS

Dear Colleagues,

On behalf of the Romanian Society of Pathophysiology and the Organizing Committee, we are delighted to invite you to attend the **National Congress of the Romanian Society of Pathophysiology *"Tradition in Education and Collaboration in Interdisciplinary Research"*** scheduled to take place in Timișoara, between October 2-5, 2024, with the support of the "Victor Babeș" University of Medicine and Pharmacy from Timișoara, by means of the Centre for Translational Research and Systems Medicine and the Foundation of University of Medicine and Pharmacy from Timișoara.

The Congress will be held under the patronage of Prof. Daniel Florin Lighezan, Vice-Rector for Education of the university and will have the scientific endorsement of the International Society of Pathophysiology, view the participation of Prof. Vladimir Jakovljevic, the Acting President and Prof. Olga Pechanova, the Past President of the International Society of Pathophysiology, both Visiting Professors of our university.

Pathophysiology is a biomedical science, which is the typical example of interdisciplinarity, being situated at the interface between basic disciplines and clinical medicine, and at the forefront of the progress of knowledge of the mechanisms of disease and the rational basis of therapy.

The event will serve as an academic platform for the dissemination of the latest pathophysiological concepts and pathogenetic therapies of chronic diseases, will bring together doctors and pharmacists, leading specialists and reputed international researchers, will allow the establishment/reinforcement of collaborations with research groups from home and abroad, and will provide an excellent educational opportunity for young people.

The 4-day scientific program includes state-of-the-art lectures, plenary conferences and oral communications held by pathophysiologists and invited lecturers from home and abroad (12 invited speakers from 7 countries) organized in workshops

dedicated to medical and pharmaceutical specialties. We will provide the opportunity for young investigators to present their latest research results and compete in oral (Young Investigator Award Competition) and poster sessions.

We also strongly encourage both participation and free-of-charge attendance of the undergraduate students.

Through the topics of the lectures followed by debates, through the direct interactions with renowned specialists and through the presence of the International Society of Pathophysiology leaders, we hope that the meeting from Timisoara will mark an important moment in the development of national and international Pathophysiology and provide a venue that will ensure communication in the broadest meaning of the word.

We cordially invite you to join us, renew old friendships, and make new ones!

With best regards,

Ovidiu Burta, MD, PhD
Danina M. Muntean, MD, PhD

Invited Speakers (alphabetical order):

Prof. Ludovico Abenavoli – Catanzaro, Italy
Prof. István Baczkó – Szeged, Hungary
Prof. Fabio Di Lisa – Padova, Italy
Assoc. Prof. Ludovic Gomez – Lyon, France
Prof. Vladimir Jakovljevic – Kragujevac, Serbia
Prof. Norbert Jost – Szeged, Hungary
Assoc. Prof. Melanie Paillard – Lyon, France
Prof. Olga Pechanova – Bratislava, Slovakia
Prof. Bruno Podesser – Vienna, Austria
Prof. Mariana Roșca – Michigan, USA
Prof. Zoltan Papp – Debrecen, Hungary
Prof. Attila Toth – Debrecen, Hungary

Honorary President of the Congress:

Prof. Daniel Lighezan – Vice-Rector for Education

Organizing Committee

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Danina M. MUNTEAN – Vice-President of the Romanian Society of Pathophysiology

Vice-President:

Assoc. Prof. Adrian STURZA

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Assist. Prof. Silvia GIUCHICI

Assist. Prof. Darius BURIMAN

PhD student Bogdan LOLESCU

PhD student Karla Andrea POP

PhD student Alina BĂTRÎN

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Prof. Cristian FURĂU – Western University "Vasile Goldiș" Arad

Assoc. Prof. Loredana PAZARA – University „Ovidius" from Constanța

Assoc. Prof. Cristiana BUȘTEA – University from Oradea

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Pre-Congress ADVANCED RESEARCH WORKSHOP

"Education Through Research – Meet the Experts"

October 2nd, 2024

Aula Magna Hall	
9:00 - 9:30	**WELCOME MESSAGES / PRESENTATION OF SPEAKERS** **Daniel F. Lighezan (Vice-Rector for Education)** **Vladimir Jakovljevic (President of International Society for Pathophysiology)** **Danina M. Muntean (Vice-President of the Romanian Society of Pathophysiology)**
9:30-13:00	**PLENARY LECTURES**
Chairs:	**Vladimir Jakovljevic (Serbia), Danina Muntean (Romania)**
9:30 - 10:00	**Vladimir Jakovljevic (Kragujevac, Serbia)** *Pathophysiology as the Best Bridge Between Basic & Clinical Research and Education*
10:00 - 10:30	**Bruno Podesser (Vienna, Austria)** *The Future of Animals in Cardiovascular Research*
10:30 - 11:00	**Fabio Di Lisa (Padova, Italy)** *Some Aspects of Mitochondrial Relevance in Cardiac Injury and Protection*
11:00 - 11:30	**Coffee Break**
Chairs:	**Fabio Di Lisa (Italy), Bruno Podesser (Austria)**
11:30 - 12:00	**Zoltán Papp (Debrecen, Hungary)** *Cardiomyocyte Contractility During Health and Disease: Calcium Sensitivity vs. Calcium Availability*
12:00 - 12:30	**Attila Tóth (Debrecen, Hungary)** *Personalized Medicine – Biomarker Based Approaches*

PROGRAMME

National Congress of the Romanian Society of Pathophysiology

with international participation

"Tradition in Education and Collaboration in Interdisciplinary Research"

October 2-5, 2024, Timișoara

DAY 1 - October 2, 2024 *Aula Magna Hall*	
13:00 -	**Registration – Central Lobby of the University**
15:00 -15:20	**OPENING CEREMONY / WELCOME MESSAGES** **Vladimir Jakovljevic (President of the International Society of Pathophysiology)** **Olga Pechanova (Past-President of the International Society of Pathophysiology)** **Ovidiu Burta (President of the Romanian Society of Pathophysiology)** **Danina Muntean (Vice-President of the Romanian Society of Pathophysiology)**
15:20 -16:35	**PLENARY LECTURES**
Chairs:	**Vladimir Jakovljevic (Serbia),** **Ovidiu Burta (Romania)**
15:20 - 15:45	**Fabio Di Lisa (Italy)** *Monoamine Oxidases in Cardiac Pathophysiology*
15:45 - 16:10	**Mariana G. Roșca (USA)** *Nicotinamide Nucleotide Transhydrogenase in Metabolic Syndrome*
16:10 - 16:35	**Bruno Podesser (Austria)** *Remodelling of the Left ventricle in Pressure Overload - Translational Aspects* **University Recognition: Presentation of the Award "*Excellence in Translational Research*"**

16:35 -17:00	**Coffee Break**
17:00 -18:30	**UNIVERSITY RECOGNITIONS: Visiting Professor Awards** **Presentation by Claudia Borza (Vice-Rector for International Affairs)**
Chairs:	**Olga Pechanova (Slovakia),** **Danina Muntean (Romania)**
17:00 - 17:25	**István Baczkó (Hungary)** *The Potential Role of Transgenic Rabbit Models with Impaired Repolarization Reserve in Preclinical Cardiac Safety Electrophysiology Studies*
17:25 - 17:30	*Presentation of the Visiting Professor Award*
17:30 - 17:55	**Norbert Jost (Hungary)** *Investigation of the Antiarrhythmic Effects of Novel Proarrhythmia Free Amiodarone-Like Mexiletine Analogue Compounds*
17:55 - 18:00	*Presentation of the Visiting Professor Award*
18:00 - 18:25	**Ludovico Abenavoli (Italy)** *The Gut-Liver Axis*
18:25 - 18:30	*Presentation of the Visiting Professor Award*
19:00 -	**Welcome Ceremony (University building)**
DAY 2 - October 3, 2024 ***Parallel sessions in Aula Magna Hall, Senate Hall***	
08:30-10:00	**Session 1: NOVEL INSIGHTS INTO PATHOPHYSIOLOGY, DIAGNOSTIC & THERAPY OF CARDIOMETABOLIC DISEASES I** ***Aula Magna Hall***
Chairs:	**Ioana Mozoș (Timișoara), Viviana Ivan (Timișoara)**
	SERVIER SYMPOSIUM: PATHOPHYSIOLOGY OF ENDOTHELIAL DYSFUNCTION: *What is Old and What Is New?*
08:30-08:50	**Adrian Sturza (Timișoara)** *Mechanisms and Therapeutic Targets of Endothelial Dysfunction*

08:50-09:10	**Viviana Ivan (Timișoara)** *Pharmacological Approaches to Alleviate Endothelial Dysfunction in Cardiometabolic Diseases*
09:10-09:30	**Mihai Iacob (Timișoara)** *Vascular Ultrasound Multiparametric Screening of Subclinical Arteriosclerosis & Assessing Plaque Vulnerability for Risk of Evolution Towards Thromboembolic Complications Through Strain-Elastography*
09:30-09:50	**Ioana Mozoș (Timișoara)** *Vascular Ageing: From Bench to Bedside*
09:50-10:00	**Dana Emilia Man (Timișoara)** *Arterial Stiffness and Insulin Resistance in Long COVID*
10:00-10:30	**Coffee Break**
10:30-12:45	**Session 2: NOVEL INSIGHTS INTO PATHOPHYSIOLOGY, DIAGNOSTIC & THERAPY OF CARDIOMETABOLIC DISEASES II** ***Aula Magna Hall***
Chairs:	**Istvan Baczkó (Szeged), Zoltán Papp (Debrecen)**
10:30-10:55	**Zoltán Papp (Debrecen)** *From Myosin Activation to Myosin Inhibition for the Treatment of Cardiac Disease*
10:55-11:20	**Ludovic Gomez (Lyon)** *The Phosphorylation of SERCA2 at the Heart of Cardioprotection*
11:20-11:45	**Mélanie Paillard (Lyon)** *Sarcoplasmic Reticulum-Mitochondria Communication in Diabetic HFpEF*
11:45-12:10	**Alina Scridon (Târgu Mureș)** *Atrial Fibrillation: Pathophysiology and Novel Therapeutic* Targets
12:10-12:35	**Attila Tóth (Debrecen)** *Towards Personalized Medicine in Cardiovascular Diseases: Biochemical Efficacy of Cardiovascular Drugs*
12:35-12:45	**Mirela Baba (Timișoara)** *Serum Lipids and Pulse Wave Analysis Variables in Patients with Normal and Early Vascular Ageing*

12:50 -13:00	**GROUP PHOTO IN FRONT OF THE UNIVERSITY**
13:00-14:00	**Lunch Break** *(lunch boxes provided)*
14:00-15:30	**Session 3: MECHANISMS OF NATURAL COMPOUNDS AND NANOFORMULATIONS AS POTENTIAL TARGETED THERAPY** ***Aula Magna Hall***
Chairs:	**Manuela Ciocoiu (Iași),** **Ovidiu Cotoi (Târgu Mureș)**
14:00-14:20	**Vladimir Jakovljević (Kragujevac)** *The Use of Different Plant Extracts in Cardiovascular Pathophysiology*
14:20-14:40	**Manuela Ciocoiu (Iași)** *Flavonoids: Mechanisms of Action and Future Trends*
14:40-15:00	**Alina Pârvu (Cluj)** *The Therapeutic Potential of Honey*
15:00-15:20	**Olga Pechanova (Bratislava)** *Renin Inhibition: Beyond Blood Pressure Lowering Effect*
15:20-15:30	**Raoul Lupușoru (Iași)** *Personalized Medicine for Osteosarcoma*
15:30-16:00	**Coffee break**
16:00-17:40	**Session 4: NOVEL INSIGHTS INTO THE PATHOPHYSIOLOGY AND DIAGNOSTIC BIOMARKERS OF METABOLIC AND RENAL DISEASES** ***Aula Magna Hall***
Chairs:	**Ligia Petrica (Timișoara),** **Alexandra Sima (Timișoara)**
16:00-16:20	**Ligia Petrica (Timișoara)** *Metabolomics Biomarkers in Diabetic Kidney Disease*
16:20-16:40	**Alexandra Sima (Timișoara)** *Uric Acid – Consequence or Risk Factor in the Cardio-Reno-Metabolic Syndrome*
16:40-17:00	**Florica Gădălean (Timișoara)** *Assessment and Risk Prediction of Chronic Kidney Disease Among Solitary Kidney Patients Using Non-Invasive Biomarkers*

17:00-17:20	**Laura Gaiță (Timișoara)** *Pathophysiology of Lipid Disorders – What Do We Know in 2024?*
17:20-17:40	**Vlad Avram (Timișoara)** *Mitochondrial Dysfunction in the Pathogenesis of Diabetes Mellitus*
17:40-18:10	**TERAPIA SYMPOSIUM –** **Roxana Buzaș (Timișoara)** *Primary Prevention of the Dyslipidemic Patient*
15:30-16:00	**Coffee break**
16:00-17:45	**Session 5: CLINICAL PATHOPHYSIOLOGY & CASE MANAGEMENT – SELECTED CASES** ***Senate Hall***
Chairs:	**Cristiana Bușteа (Oradea), Ana Lascu (Timișoara)**
16:00-16:15	**Cristiana Bușteа (Oradea)** *A Complicated STEMI Case: Challenges in Management and Outcome*
16:15-16:30	**Nicoleta Bertici (Timișoara)** *The Effectiveness of Eosinophil-Depleting Therapy with Benralizumab in a Patient with Multiple Chronic Respiratory Diseases, Toxocariasis and Hypereosinophilic Syndrome*
16:30-16:45	**Laura Ghenciu (Timișoara)** *Cytomegalovirus Retinitis in the Context of SARS-CoV2 Infection – A Case Presentation*
16:45-17:00	**Silvia Giuchici (Timișoara)** *A Complex Case of Imune-Mediated Endocrine Toxicity in a Patient With Non-Small Cell Lung Cancer*
17:00-17:15	**Darius Buriman (Timișoara)** *Cannula-Associated Deep Vein Thrombosis After Veno-Venous Extracorporeal Membrane Oxygenation in Cardiac Surgery – A Case Report*
17:15-17:30	**Bogdan Lolescu (Timișoara)** *The Benefits of Empagliflozin in Cardiovascular Prevention in Heart Failure with Preserved Ejection Fraction in Elderly – A Case Report*
17:30-17:40	**Q & A**

18:00-19:00	**Poster Session (Sport Hall)** **Chairs: Adrian Sturza (Timișoara), Norbert Jost (Szeged)** **& Get Together**
DAY 3 - October 4, 2024 ***Parallel sessions in Aula Magna Hall, Senate Hall, Iagnov Hall***	
08:30-10:25	**Session 6: UPDATES ON THE PATHO-PHYSIOLOGY & THERAPY OF CHRONIC INFLAMMATION ASSOCIATED WITH CARDIOVASCULAR DISEASES** ***Aula Magna Hall***
Chairs:	**Roxana Buzaș, Simina Crișan (Timișoara)**
08:30-08:50	**Simina Crișan (Timișoara)** *The Role of Low-Grade Chronic Inflammation in the Pathogenesis of Atherosclerosis*
08:50-09:10	**Ioana Cîtu (Timișoara)** *Mechanisms and Inflammatory Mediators in Heart Failure Progression*
09:10-09:30	**Cristian Sarău (Timișoara)** *Anti-Inflammatory Therapeutic Strategies in Heart Failure*
09:30-9:50	**Roxana Buzaș (Timișoara)** *Inflammatory Biomarkers and Cardiovascular Risk Assessment*
9:50-10:00	**Q & A**
10:00 - 10:30	**Coffee Break**
10:30-12:15	**Session 7: THE GUT MICROBIOME AS KEY PLAYER IN HEALTH & DISEASE.** **LIVING IN THE TIME OF COVID & ITS COMPLICATIONS** ***Aula Magna Hall***
Chairs:	**Florinela Cătoi (Cluj-Napoca), Sorin Aramă (București)**
10:30-10:50	**Sorin Aramă (București)** *Gut Microbiota: Facts and Hopes*

10:50-11:10	**Ovidiu Burta (Oradea)** *Microbiota Dysregulation in Irritable Bowel Syndrome*
11:10-11:30	**Florinela Cătoi (Cluj-Napoca)** *Weight Loss and Weight Regain After Bariatric Surgery*
11:30-11:50	**Loredana Pazara (Constanța)** *SARS CoV2 - Induced Alterations in Blood Rheology*
11:50-12:10	**Cătălin Tilișcan (București)** *COVID-19: An Overview of Pathogenic Mechanisms and Current Real-Life Treatment Options*
12:10-12:30	**Anca Bacârea (Târgu Mureș)** *Lymphogram in the Evaluation of Septic Patients*
12:30-12:50	**Rodica Lighezan (Timișoara)** *Platelet Dysfunction - An Overview*
13:00-14:00	**Lunch Break** *(lunch boxes provided)*
14:00-15:00	**GENERAL ASSEMBLY OF SRFP – AULA MAGNA HALL**
15:00-16:00	**Session 8: NOVEL INSIGHTS INTO THE BLOOD PATHOPHYSIOLOGY. MITOCHONDRIA IN FOCUS.** ***Aula Magna Hall***
Chairs:	**Amelia Găman (Craiova), Ludovic Gomez (Lyon)**
15:00-15:20	**Emilia G. Vânturiș (Craiova)** *Involvement of Oxidative Stress in the Evolution of Patients with Chronic Myeloid Leukemia*
15:20-15:40	**Oana M. Aburel (Timișoara)** *Platelet Mitochondrial Dysfunction in Disease as Peripheral Bioenergetic Marker*
15:40-16:00	**Gheorghe I. Mihalaș (Timișoara)** *Sonic Representation of Cellular Processes*
16:00-16:30	**Coffee Break**
14:00 - 16:00	**YOUNG INVESTIGATOR AWARD COMPETITION** ***Iagnov Hall***
Chairs:	**Claudia Borza (Timișoara),** **Olga Pechanova (Bratislava)**

14:00-14:15	**Cozma Elena-Codruța (Craiova)** *Correlations Between Gut Microbiota, Oxidative Stress and Inflammation in Patients with Psoriasis*
14:15-14:30	**Dănilă Maria-Daniela (Timișoara)** *Assessment of Imeglimin Effects on Platelet Mitochondrial Respiration & Oxidative Stress: A Pilot Study in Diabetic Patients*
14:30-14:45	**Glăvan Mihaela-Roxana (Timișoara)** *Mitochondrial Platelet Bioenergetic Profile in Chronic Kidney Disease Patients With and Without Diabetes*
14:45-15:00	**Kosovski Irina-Bianca (Târgu Mures)** *The Influence of Adiposity on Peripheral Blood Immune Cells in Young Adults*
15:00- 15:15	**Ticolea Mădălina (Cluj-Napoca)** *Phytochemical Composition Antioxidant and Anti-Inflammatory Activity of Artemisia dracunculus and Artemisia abrotanum*
15:15- 15:30	**Trușculescu Ana-Adriana (Timișoara)** *Time, Space, and Asthma: An Interdisciplinary Study in Timiș County*
15:30- 15:45	**Usatiuc Lia-Oxana (Cluj-Napoca)** *Assessment of Phytochemical Content and Antidiabetic, Antioxidant, and Anti-inflammatory Activities of Gypsophila paniculata in Rats with Streptozotocin-Induced Diabetes*
15:45- 16:00	**Vornic Ioana (Arad)** *Antioxidant Defenses, Oxidative Stress Responses, and Apoptosis Modulation in Spontaneous Abortion: An Immunohistochemistry Analysis of First-Trimester Chorionic Villi*
16:00-16:30	**Coffee Break**
16:30 - 17:45	**Session 9: NOVEL INSIGHTS INTO THE PATHOPHYSIOLOGY AND DIAGNOSTIC OF RESPIRATORY DISEASES** ***Aula Magna Hall***
Chairs:	**Ovidiu Fira-Mlădinescu (Timișoara),** **Adrian Trifa (Timișoara)**
16:30-16:50	**Ovidiu Fira-Mlădinescu (Timișoara)**

	Epithelial Era in Asthma Pathophysiology
16:50-17:10	**Ștefan Frenț (Timișoara)** *Neuro-Immune Pathways in Inflammation and Airway Remodeling in Asthma*
17:10-17:30	**Adrian Trifa (Timișoara)** *Genetics of Asthma*
17:30-17:50	**Emanuela Vaștag (Timișoara)** *Current Concepts Regarding the Role of the Lung Microbiome in Respiratory Diseases*
17:50-18:00	**Corina Budin (Târgu Mures)** *Novel Biomarkers in Lung Cancer. The Inolung Study*
16:30-18:00	**Session 10 – NOVEL INSIGHTS INTO THE PATHOPHYSIOLOGY AND THERAPEUTIC APPROACHES OF GYNECOLOGICAL AND RHEUMATOLOGICAL CONDITIONS** ***Senate Hall***
Chairs:	**Cristian Furău (Arad), Loredana Pazara (Constanța)**
16:30-16:50	**Cristian Furău (Arad)** *Human Papilomavirus Infection in Pathology: From Genital to Head & Neck Cancers*
16:50-17:10	**Federico Villani (Arad)** *Prenatal Perineal Training to Prevent Dysfunctions of the Perineal Floor*
17:10-17:30	**Anamaria Ardelean (Arad)** *A MetaAnalysis of the Risks of Symptoms Affecting Life Quality in Natural Menopause vs Premature Menopause*
17:30-17:40	**Victoria Ciobanu (Arad)** *Cervical Dysplasia – Management Options*
17:40-17:50	**Damiano Rigano (Arad)** *The Benefits of Vaginal Cone Training in Pelvic Floor Dysfunctions*
17:50-18:00	**Daniela Dușa (Constanța)** *Low Back Pain: Risk Factors for Chronicity*
19:30 -	**CLOSING & AWARDS CEREMONY**

DAY 4 (October 5, 2023)	
08:30-10:30	**Session 11: NOVEL INSIGHTS INTO THE PATHOPHYSIOLOGY OF OXIDATIVE STRESS AND MALIGNANCY** ***Aula Magna Hall***
Chairs:	**Maris Mihaela (Timișoara),** **Dorina Coricovac (Timișoara)**
08:30-08:50	**Mihaela Mariș (Timișoara)** *An Overview of the Impaired Antioxidant Defence System in the Pathogenesis of Chronic Venous Disease*
08:50-09:10	**Raluca Soșdean (Timișoara)** *Monoamine Oxidase Contribution to Valvular Oxidative Stress: A Novel Pathomechanism in Severe Mitral Regurgitation*
09:10-09:30	**Dorina Coricovac (Timișoara)** *Malignant Melanoma-Mitochondria - An Intriguing Relationship: Betulinic Acid as A Potent Antimelanoma Agent*
09:30-09:50	**Alexandra Mioc (Timișoara)** *Targeting Cancer Cells with Triterpene-Based Natural and Novel Semisynthetic Compounds*
09:50-10:10	**Maria Suciu (Timișoara)** *Potential Molecular Mechanisms Proposed to Be Involved in the Diabetogenic Effect of Statins*
10:10-10:30	**Ramona Jurcău (Cluj-Napoca)** *Auriculotherapy Effectiveness in Modulating Oxidative Stress and Inflammation in Third Molar Extraction*
10:30 -11:00	**Coffee Break**
11:00-12:30	**Session 12:TOWARDS PATHOPHYSIOLOGICAL APPROACHES IN CLINICAL PHARMACY**
Chairs:	**Valentina Buda (Timișoara),** **Ligia Hui (Cluj-Napoca)**
11:00-11:20	**Ligia Hui (Cluj-Napoca)** *Augmented Renal Clearance in Critically Ill Patients and Vancomycin Therapeutic Drug Monitoring*
11:20-11:40	**Valentina Buda (Timișoara)** *Black Chokeberry Juice Effect in Pre-Hypertensive and*

	First Grade Hypertensive Patients: A Prospective Study
11:40-12:00	**Aura Blendea (Cluj-Napoca)** *A Clinical Pharmacist Intervention in Vancomycin Infusion Reaction Case Management*
12:00-12:20	**Elena Cucerdean (Târnăveni)** *The Importance of Interdisciplinary Collaboration in Handling, Preparation and Administration of Parenteral Preparations*
12:20-12:30	**Q & A**
12:30	**Closing Remarks**

ADVANCED RESEARCH SYMPOSIUM FOR PhD STUDENTS

"Trends in Cardiovascular Research: *Where Do We Stand in 2024?*"

October 5th, 2024

Iagnov Hall	
9:00 - 9:30	**WELCOME MESSAGES / PRESENTATION OF SPEAKERS** **Cristina A. Dehelean (Head of the Doctoral Schools)** **Danina M. Muntean (Vice-President of the Romanian Society of Pathophysiology)**
9:30-12:30	**PLENARY LECTURES**
Chairs:	**Danina Muntean (Romania), Mélanie Paillard (France)**
9:30 - 10:00	**Mélanie Paillard (Lyon, France)** *Mitochondrial Ca^{2+} Regulation: Players, Tools and Pathophysiological Roles*
10:00 - 10:30	**Ludovic Gomez (Lyon, France)** *Can We Still Protect Our Heart?*
10:30 - 11:00	**Olga Pechanova (Bratislava, Slovakia)** *Effect of Natural Polyphenolic Substances on Nitric Oxide/ROS Balance in Cardiometabolic Disorders*
11:00 - 11:30	**Coffee Break**
Chairs:	**Claudia Borza (Romania), Mariana Roșca (USA)**
11:30 - 12:00	**Mariana Roșca (Michigan, USA)** *The Division of Work in the Heart's Bioenergetics*
12:00 - 12:30	**Norbert Jost (Szeged, Hungary)** *An Overview of the Arrhythmia Mechanisms*

LIST OF POSTERS

1. **Cărpinișan Liliana (Timișoara, Romania)**
   Clinical Aspects and Therapeutic Management in Acute Pancreatitis in Dogs in A Veterinary Clinic

2. **Hâncu Iasmina-Maria (Timișoara, Romania)**
   Evaluation of Empagliflozin-Monoamine Oxidase Interaction in a HFmEF Model Induced in Wild-Type and SGLT2 KO Mice

3. **Stanciu-Lelcu Theia (Timișoara, Romania)**
   Modulation of the Bioenergetic Profile of a Human Cell Line by Anticancer Phytochemicals

4. **Szilárd Nagy (Debrecen, Hungary)**
   Post-COVID Syndrome: Long-Lasting Immunological Alterations Drive Auto-Immune Responses in Cardiac Tissue

5. **Ottó Tatai (Debrecen, Szeged)**
   A Hidden Aftermath: Autoimmunity's Potential Role in Post-Covid Syndrome Regarding Lung Tissue

6. **Sandu Oana (Timișoara, Romania)**
   New-Onset Atrial Fibrillation in Young Patients Following COVID-19 Infection

7. **Haj Ali Lina (Timișoara, Romania)**
   Pathophysiological Mechanisms of Arrhythmias in Patients Diagnosed With COVID-19

8. **Adamescu Aida (București, Romania)**
   Associations Between Inflammatory Markers and Severe Forms of SARS-CoV-2 Infection – A Retrospective Study

9. **Mîțu Diana-Alexandra (Timișoara, Romania)**

COVID-19 and the Battle of the Blood Clots: A Pulmonary Perspective

10. **Pecingină Radu-Mihai (Timișoara, Romania)**
    Pathophysiological Mechanisms of Atrial Fibrillation in Dialysis Pacients: Therapeutic Implications

11. **Ionică Loredana-Nicoleta (Timișoara, Romania)**
    Empagliflozin-Monoamine Oxidase Interaction in Human Cardiac and Vascular Tissues – A Pilot Study in Overweight Patients With Heart Failure

12. **Ciortea Ioana (Timișoara, Romania)**
    Subclinical Carotid Atherosclerosis is Present from Early COPD Stages Being in Closer Relationship with Systemic Inflammation Than with the Airflow Obstruction

13. **Vînturiș Emilia-Georgiana (Craiova, Romania)**
    The Interrelationship Between Oxidative Stress Levels and Metabolic Parameters in Obese Patients

14. **Simon-Szabo Zsuzsanna (Târgu Mureș, Romania)**
    Interdisciplinary Approach of a Complex Case With Multiple Congenital Malformations

15. **Furdui-Lința Adina (Timișoara, Romania)**
    Cardiac Toxicity of Endocrine Disruptors: Unraveling the Mitochondrial Effects of Bisphenols and Phthalates

16. **Cismaș Cristina (Constanța, Romania)**
    Hematological and Hemorheological Profile in Patients Newly Diagnosed With Tuberculosis – Study Design

17. **Bătrîn Alina Doruța (Timișoara, Romania)**

Common MicroRNAs in the Regulation of Liver and Cardiac Fibrosis

18. **Pop Andrea Karla (Timișoara, Romania)**
    Targeting the Epicardial Adipose Tissue with Glucagon-like Peptide 1 Receptor Agonists (GLP1-RA) in Humans

19. **Jianu Narcisa (Timișoara, Romania)**
    Osteoporosis Level of Comprehension of Romanian General Population: Results of An In-Person Survey

20. **Tolan Gloria Alexandra (Arad, Romania)**
    Pathophysiological Aspects and Advanced Surgical Treatments in Anterior Cruciate Ligament Pathology

21. **Merlan Elena-Cristina (Timișoara, Romania)**
    Misuse of Drugs in The Western Romanian Elderly Population Based on Stopp/Start V.2 Criteria

22. **Gruin Silvia (Timișoara, Romania)**
    Synthesis, Antiproliferative Evaluation, and *In Silico* Analysis of a Betulinic Acid-Benzotriazole Ester

23. **Ofițeru Narcis (Timișoara, Romania)**
    Heart Rate Variation in Coronary Revascularized Patients

24. **Ionescu Patricia (Timișoara, Romania)**
    The Relationship Between Estimated Pulse Wave Velocity and Anthropometric Indices

25. **Mozoș Costin (Timișoara, Romania)**
    The Effect of Physical Exercise on Arterial Stiffness and Vascular Age

26. **Păcurar Andra (Timișoara, Romania)**

Prescribing Differences Between Rural and Urban Areas of Western Romania Using Stopp V.2 Criteria

27. Mareș Anita (Timișoara, Romania)

Inappropriate Management of Constipation Among Romanian Population: Results of An Online Study Survey

28. Dimcea Karina (Timișoara, Romania)

From Pilot Project to Core Curriculum: Introducing Medical Communication With Standardized Patients — Insights from a Romanian Medical University

29. Croitoru Alexandru (București, Romania)

Innovative Applications of Aerogels in Combating Antimicrobial Resistance

30. Moroz Simina (Timișoara, Romania)

Gender Disparities in the Impact of Transcatheter Aortic Valve Replacement on Left Ventricular Ejection Fraction in Caucasian Patients

31. Mareș Răzvan (Târgu Mureș, Romania)

Acute-Phase Inhibition of Pro-Inflammatory Alarmin S100a8/A9 Attenuates Cardiac Fibrosis After Myocardial Infarction

32. Cozac-Szoke Andreea (Târgu Mureș, Romania)

Diagnostic Challenges in The Diagnosis of Primary Gastrointestinal Mastocytosis

33. Hârșan Sofia (Târgu Mureș, Romania)

Pulmonary Carcinoid Tumour - A Rare Neuroendocrine Malignancy: A Case Report

34. Maksimovic T. (Timișoara, Romania)

Evaluation of Cytotoxic Effects of Cymbopogon Flexuosus Essential Oil on Human Colorectal Adenocarcinoma and Malignant Melanoma Cell Lines

35. **Mardale G. (Timișoara, Romania)**
    In Vitro Evaluation of Origanum Vulgare L. Essential Oil Effect on Human Cancer Cells

36. **Antal G. (Timișoara, Romania)**
    The *In Vitro* Characterization of Syzygium Aromaticum L. Essential Oil Cytotoxic Effect on Colorectal Adenocarcinoma and Malignant Melanoma Cells

ABSTRACTS OF THE LECTURES

MONOAMINE OXIDASES IN CARDIAC PATHOPHYSIOLOGY

Fabio Di Lisa

Department of Biomedical Sciences, University of Padova, Padova, Italy

Numerous physiological and pathological roles have been attributed to the formation of mitochondrial reactive oxygen species (ROS). However, the individual contribution of different mitochondrial processes independently of bioenergetics remains elusive and clinical treatments unavailable. A notable exception to this complexity is found in the case of monoamine oxidases (MAOs). Unlike other ROS-producing enzymes, especially within mitochondria, MAOs possess a distinct combination of defined molecular structure, substrate specificity, and clinically accessible inhibitors. Another significant aspect of MAO activity is the simultaneous generation of hydrogen peroxide alongside highly reactive aldehydes and ammonia. These three products synergistically impair mitochondrial function at various levels, ultimately jeopardizing cellular metabolic integrity and viability. This pathological condition arises from exacerbated MAO activity, observed in many cardiovascular diseases, thus justifying the exploration of MAO inhibitors as effective cardioprotective strategy. In this context, we not only summarize the deleterious roles of MAOs in cardiac pathologies and the positive effects resulting from genetic or pharmacological MAO inhibition, but also discuss recent findings that expand our understanding on the role of MAO in gene expression and cardiac development.

REMODELING OF THE LEFT VENTRICLE IN PRESSURE OVERLOAD- TRANSLATIONAL ASPECTS

Bruno K. Podesser

Center for Biomedical Research and Translational Surgery, Medical University of Vienna, Austria

Prevalence of aortic valve stenosis is increasing with age. At the age of 65 and older, 2-4% of the population show a highly calcified valve. The consequence of aortic valve stenosis is left ventricular hypertrophy and, if untreated, progressive valvular heart disease, leading to heart failure. The only therapeutic measurement is replacement of the valve either surgically or interventionally. Available prostheses are either mechanical or biological solutions. The decision for operation is based on symptoms and the remaining orifice area of the stenotic valve (>1cm^2). However, whether this very subjective timepoint is really the optimal time point of surgery or intervention remains unclear.

Structural, pressure overload leads to hypertrophy of the cellular compartment and interstitial fibrosis. Functional, hypertrophy is characterized by an increasing stiffness of the left ventricle with reduced diastolic function but initially preserved ejection fraction and later leading to a reduction in ejection fraction- a process that is called remodeling. After aortic valve replacement, the heart undergoes reverse remodeling and function should improve again- however, the degree, to what extend hypertrophy and fibrosis are reversal, is poorly understood.

In a translational animal model of pressure overload in mice we have studied both, the consequences of pressure overload and of unloading at a functional and molecular level. After identifying the extracellular matrix as mayor area of interest, we focused on tenascin-C (TNC) as a key-player in fibrosis. Using a KO-mouse model of TNC, we were able to show the importance of this matricellular protein, using magnetic resonance imaging to describe the reverse remodeling in vivo. Finally, we went back to humans and set up a clinical study, were we follow patients, undergoing aortic valve replacement over a period of 3 years and monitor function by echocardiography and quality of life. In parallel, we have established a human bio-bank from liquid biopsies and left ventricular myocardium from all timepoints. This allows us to correlate the functional data with transcriptomics and proteomics.

With this translational approach we hope to get new insights in the underlying processes of pressure overload and unloading, that will allow us in the future to better determine the optimal time point for surgery or intervention for our patients.

THE USE OF DIFFERENT PLANT EXTRACTS IN CARDIOVASCULAR PATHOPHYSIOLOGY

Vladimir Jakovljevic

Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
Center of Excellence for Redox Balance Research in Cardiovascular and Metabolic Disorders, Kragujevac, Serbia
Department of Human Pathology, First Moscow State Medical University IM Sechenov, Moscow, Russia

This study summarizes our recent animal investigations regarding the research of the effects of *Galium verum* extract (GVE) on different pathophysiological processes linked with the cardiovascular system. We aimed to assess the influence of GVE on cardiac function using an isolated rat heart model and showed that GVE may have a beneficial effect on the intact myocardium and coronary circulation. Firstly, we assessed the effects of methanol GVE on myocardial ischemia/reperfusion injury in healthy *Wistar albino* rats as well as in spontaneously hypertensive rats. The study involved rats divided randomly into control group and group of rats treated with 500 mg/kg of methanol GVE for 28 days *per os*. Our results demonstrated that GVE preserved cardiac contractility, systolic, and diastolic function as well as structural damage of the heart after ischemia. Furthermore, GVE led to a drop in the generation of most of the measured prooxidants, thus mitigating cardiac oxidative damage. In the other investigation, we estimated the impact of 14-day treatment with GVE on doxorubicin-induced cardiotoxicity through functional, biochemical and histological examinations. A total of 24 rats *Wistar albino* rats were divided into the following groups: control (CTRL), doxorubicin (DOX), and DOX + GVE. GVE was administered orally at a dose of 50 mg/kg/day for 14 days, while a single dose of doxorubicin was injected into the DOX groups. We showed that the consumption of GVE effectively suppressed the disturbed response of the heart to changes in perfusion pressures caused by the administration of DOX. GVE pretreatment seems to be able to prevent the pathological injuries caused by DOX injection via decrease in oxidative stress and apoptosis. In light of these findings, our research paves the way towards clinical studies on GVE as a promising phytochemical in alleviation myocardial injury.

THE ROLE OF NITRIC OXIDE IN METABOLIC SYNDROME: EFFECTS OF POLYPHENOLIC SUBSTANCES

Olga Pechanova

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Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Bratislava, Slovakia

Nitric oxide (NO) plays a crucial role in the pathogeneses of metabolic syndrome components and is involved in blood pressure control, insulin production, or lipid profile regulation. We aimed to determine NO synthase (NOS) activity under conditions of different lipid profiles. In our studies, normotensive Wistar Kyoto rats (WKY), spontaneously hypertensive rats (SHR), obese SHR (SHR/cp), lean and obese Zucker rats have been used. In 12-week-old male rats, the lipid profile in plasma and NOS activity in the left ventricle and aorta have been determined. Simultaneously, we studied the effects of different polyphenolic substances. We demonstrated that WKY and SHR have the same level of total cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL). In SHR/cp, however, the level of total cholesterol, triglycerides, LDL, but also HDL increased significantly. Lean Zucker rats have a similar lipid profile to WKY. However, obese Zucker rats have all investigated lipid parameters significantly higher than SHR/cp. NOS activity was significantly higher in the left ventricle and aorta of SHR compared to WKY. In SHR/cp, however, NOS activity was comparable to that in WKY. This indicates that obesity reduces NOS activity in spontaneous hypertension. Lean and obese Zucker rats had comparable NOS activity in the heart, but it was significantly reduced in the aorta of obese Zucker rats. In accordance with these findings, polyphenol rich natural compounds like Lonicera caerulea L. and cornelian cherry varieties, Koralovij Marka and Wilde Type, increased NOS activity in the aorta, while not affecting the activity in the left ventricle. Likewise, the polyphenol rich wine extract had a moderate effect on NOS depending on the level of NOS activity in the studied models of metabolic syndrome. In conclusion, deteriorated lipid profile may reduce NOS activity, while natural polyphenolic substances can moderate it through different signaling pathways.

This study was supported by the national grant agency VEGA 2/0025/23 and 1/0048/23.

NICOTINAMIDE NUCLEOTIDE TRANSHYDROGENASE IN METABOLIC SYNDROME

Mariana G. Roșca

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Nicotinamide nucleotide transhydrogenase (NNT) is a mitochondrial inner membrane enzyme that transfers electrons from mitochondrial NADH to NADPH by using the inner membrane proton motive force to boost the peroxide antioxidant defense. Chronic conditions (heart failure, diabetes, aging) cause mitochondrial bioenergetic alterations and cardiac disease. Mitochondrial cardiomyopathy is also a frequent, fatal but rather late manifestation of inherited mitochondrial defects, suggesting that the heart has a protective mechanism to overcome the bioenergetic defects. When this protective mechanism fails, mitochondrial cardiomyopathies are severe, and manifest as heart failure, arrhythmias, and death. More than half of inherited mitochondrial diseases are caused by defects within the electron transport chain (ETC). Specific mechanisms by which these deficiencies affect the heart include energy deficit, oxidative stress, and an increased [NADH]. In the heart, NADH originates mostly from fatty acid (FA) β-oxidation and is oxidized to NAD+ by complex I (C I) in the ETC adding to the inner membrane proton gradient used to drive ATP synthesis (oxidative phosphorylation, OXPHOS). Because OXPHOS is an energy demand-driven process and the heart continuously consumes ATP, NADH is constantly oxidized back to NAD+ to maintain a low mitochondrial NADH/NAD redox ratio. ETC defects limit NADH oxidation, and lead to NADH accumulation to the detriment of the oxidized form, NAD+ (reductive stress) that causes oxidative stress. Conceptually, an increase in NADH concentration should also limit FA β-oxidation. Strikingly, we observed that cardiac FA β-oxidation continues despite an increased NADH concentration suggesting that C I defective cardiac mitochondria can convert excessive NADH to NAD via NNT and allow FA oxidation to continue generating FADH2 that bypasses the inhibited C I, feeding into Q-complex III and providing maintenance of ATP synthesis. Therefore, preventing the inhibition or pharmacological activation of this alternate pathway may delay or alleviate cardiac disease induced by ETC defects, conditions that currently have no cure. We recently reported that normalizing [NADH] alleviated retinal photoreceptor damage and cardiac dysfunction in two models of mitochondrial complex I defect. We are now unfolding the role of NNT in alleviating the NADH/NAD ratio during metabolic syndrome.

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FROM MYOSIN ACTIVATION TO MYOSIN INHIBITION FOR THE TREATMENT OF CARDIAC DISEASE

Zoltán Papp & Attila Tóth

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Conformation changes of the myosin molecule during the actin-myosin cross-bridge cycle are closely related to cardiac systolic and diastolic performances. In the absence of side-effect-free inotropic drugs, the development of direct myosin activators and direct myosin inhibitors evolves with considerable professional interest. Omecamtiv mecarbil is the most studied representative of direct myosin activators and has recently been shown to be effective in the GALACTIC-HF large randomized clinical trial in heart failure patients with reduced ejection fraction (HFrEF). However, accumulating knowledge on less favourable effects of the agent - and the similar behaviour of the second-generation myosin activator, danicamtiv - implies that rapid clinical introduction of direct myosin activators cannot be attained. As a result of the action of direct myosin activators, systolic duration increases - and consequently diastolic duration decreases - the rates of ventricular contractions and relaxations are slowed, which together may precipitate left ventricular (LV) diastolic dysfunction. Mutations in genes encoding certain myocardial proteins result in hypercontractility of the LV and are thought to drive pro-hypertrophic signalling in hypertrophic obstructive cardiomyopathy (HOCM). Accordingly, targeting the myosin heavy chain-β by small molecules to partially inhibit its function appears to be an attractive approach to prevent the development HOCM. Indeed, clinical evidence now supports that negative modulation of the myosin motor can be an effective treatment option to well-defined HOCM patient groups. Moreover, the potential benefit of myosin inhibitors has been also implicated for heart failure patients with preserved ejection fraction (HFpEF) in the absence of known genetic alterations. Thus, direct myosin inhibitors (mavacamten and aficamten) may have a role in the treatment of hypertrophic cardiomyopathy, due to their negative inotropic effects. As far as we know, the reduction of hypercontractility in HOCM can indeed slow down the hypertrophic transformation of the heart, which may prevent invasive treatments of hypertrophic cardiomyopathy (septal myectomy, septal ablation, heart transplantation). Nevertheless, many questions remain to be answered regarding the development and use of myosin inhibitor drugs.

Taken together, data so far suggest that myosin inhibition, in a well-chosen HOCM patient population, may become part of everyday practice sooner than a positive inotropic treatment based on myosin activation in HFrEF patients.

This work was supported by a grant from the National Research, Development, and Innovation Office (K147173 to ZP). Project no. K147173 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the K_23 „OTKA" funding scheme.

TOWARDS PERSONALIZED MEDICINE IN CARDIOVASCULAR DISEASES: BIOCHEMICAL EFFICACY OF CARDIOVASCULAR DRUGS

Attila Tóth & Zoltán Papp

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In the realm of cardiovascular medicine, adherence to therapeutic regimens is crucial for achieving desired clinical outcomes. However, suboptimal adherence remains a persistent challenge, often impeding the effectiveness of evidence-based guidelines. This study advances the field of personalized medicine by introducing innovative biochemical assays that offer enhanced precision in drug efficacy measurement and adherence monitoring.

We developed a novel biochemical assay for evaluating the efficacy of angiotensin converting enzyme (ACE) inhibitors. Our assay revealed a significant correlation between circulating ACE activity and the presence of ACE inhibitory drugs, thereby providing a reliable metric for assessing patient adherence. Additionally, the assay demonstrated a robust correlation between the level of ACE inhibition and the therapeutic target of blood pressure reduction, facilitating individualized dosage optimization based on objective biochemical data. Furthermore, we addressed the limitations in monitoring Factor X inhibitors, a class of anticoagulants lacking sufficiently sensitive assays. Our newly developed method quantified the range of inhibition achieved by these drugs, enabling precise identification of non-adherent patients and evaluation of treatment efficacy across a broad dosage spectrum. This real-time biochemical monitoring allows for dynamic assessment of drug efficacy and identification of patients experiencing insufficient therapeutic effects.

In summary, our findings underscore the potential of biochemical assays to revolutionize personalized medicine in cardiovascular disease management. By integrating these assays into clinical practice, we can enhance adherence monitoring, optimize drug dosing, and ultimately improve patient outcomes in cardiovascular therapy.

This work was supported by a grant from the National Research, Development, and Innovation Office (K132623 to ZP). Conference travel costs were supported by the University of Debrecen Program for Scientific Publication.

THE POTENTIAL ROLE OF TRANSGENIC RABBIT MODELS WITH IMPAIRED REPOLARIZATION RESERVE IN PRECLINICAL CARDIAC SAFETY ELECTROPHYSIOLOGY STUDIES

Istvan Baczko

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Drug-induced proarrhythmia represents a potentially lethal side effect of various compounds. Proarrhythmia is often mechanistically linked to the drug's potential to interact with repolarizing cardiac ion channels causing a prolongation of the QT interval on the ECG. Despite sophisticated screening approaches during drug development, reliable prediction of proarrhythmia in novel drug candidates remains a major challenge. Drug-induced pro-arrhythmia occurs primarily in patients with pre-existing repolarisation disturbances, however, healthy animals, tissues, and cells isolated from healthy animals are used in pro-arrhythmia screening. To improve current safety screening, transgenic long QT (LQTS) rabbit models with impaired repolarisation reserve are useful tools not only to assess I_{Kr}-blocking but also I_{Ks}- and I_{K1}-blocking properties of drugs. In this presentation, the currently available transgenic LQTS rabbit models are discussed, which carry pathogenic variants in KCNQ1 (LQT1, loss of I_{Ks}), KCNH2 (LQT2, loss of I_{Kr}), KCNE1 (LQT5, reduction of I_{Ks}), or KCNH2+KCNE1 (double-transgenic LQT2-5, loss of I_{Kr} and reduction of I_{Ks}) and the pharmacological proof-of-principle studies that have been performed with these models-highlighting the advantages and disadvantages of LQTS models for proarrhythmia research. In summary, LQTS models represent patients with reduced repolarisation reserve due to different pathomechanisms. Since they demonstrate increased sensitivity to different specific ion channel blockers (I_{Kr} blockade in LQT1 and LQT5 and I_{K1} and I_{Ks} blockade in LQT2 and LQT2-5), their combined use could provide more reliable and more thorough prediction of (multichannel-based) pro-arrhythmic potential of novel drug candidates.

INVESTIGATION OF THE ANTIARRHYTHMIC EFFECTS OF NOVEL PROARRHYTHMIC FREE AMIODARONE-LIKE MEXILETINE ANALOGUE COMPOUNDS

Norbert Jost

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HUN-REN SZTE Research Group for Cardiovascular Pharmacology, Hungarian Research Network, Szeged, Hungary

Cardiovascular diseases, and in particular cardiac arrhythmias such as ventricular fibrillation, play a leading role in mortality statistics in developed countries. Accordingly, cardiac arrhythmias have become a major area of cardiovascular research. Drug therapy has traditionally been the main treatment for ventricular and supraventricular arrhythmias. It is therefore important to understand the mechanism of action of antiarrhythmic drugs at the organ, tissue, cellular and subcellular levels in order to develop new, more effective, less proarrhythmic agents. One such potential development direction is the development of a series of amiodarone-like antiarrhythmic agents in which repolarisation-inducing (class III) activity is combined with other pharmacological properties (combined class III+I/B, II and/or IV activity) that are considered to be beneficial. These compounds are also excellent tools for pathophysiological investigation of pathophysiology of the antiarrhythmic and proarrhythmic effects. Therefore, we investigated the antiarrhythmic and cardiac electrophysiological effects of a novel antiarrhythmic compound (SZV-2649), similar to amiodarone but lacking the benzofuran chemical structure, in rat and canine cardiac cell line cardiac preparations. SZV-2649 exerted antiarrhythmic effects on coronary occlusion reperfusion-induced ventricular fibrillation in rats and acetylcholine and burst stimulation-induced atrial fibrillation in dogs.
SZV-2649 inhibited hERG/IKr and GIRK/IK,ACh currents in expressed HEK293 cell lines and in vitro in canine atrial muscle preparations. Based on these observations, it was concluded that SZV-2649 has antiarrhythmic effects similar to amiodarone, with multiple ion channel blocking properties.
However, as its chemical structure is substantially different from that of amiodarone, it is expected to have less severe side effects than amiodarone, making it a promising tool for investigation at cellular level the pathophysiology of the antiarrhythmic and proarrhythmic effects.

SARCOPLASMIC RETICULUM-MITOCHONDRIA COMMUNICATION IN DIABETIC HEAR FAILURE WITH PRESERVED EJECTION FRACTION

Mélanie Paillard

Cardiovascular Diseases, Metabolism, Nutrition (CarMeN) Laboratory, University Claude Bernard Lyon 1, Lyon, France

Type 2 diabetes (T2D) and obesity strongly lead to heart failure with preserved ejection fraction (HFpEF). In front of the rising prevalence of obesity and T2D, deciphering the underlying mechanisms of metabolic HFpEF remains crucial to develop new therapeutic strategies.
Within the cardiomyocyte, mitochondria and sarcoplasmic reticulum (SR) interact at contact points to form microdomains known as mitochondria-associated reticular membranes (MAMs). MAMs are recognized as a signaling hub in the cell, notably through the SR-mitochondrial Ca^{2+} coupling which contributes to the cardiac excitation-energetics coupling. Mitochondrial dysfunction has been reported in metabolic HFpEF; but a role for the SR-mitochondria Ca^{2+} coupling remained to be explored.
Here, I will discuss how the SR-mitochondria Ca^{2+} coupling is altered during metabolic HFpEF both in a murine model and in T2D patients. Finally, I will suggest new therapeutic strategies targeting the mitochondrial Ca^{2+} signaling to improve HFpEF outcome.

THE PHOSPHORYLATION OF SERCA2 AT THE HEART OF CARDIOPROTECTION

Fabrice Gonnot[1], Laura Boulogne[1*], Camille Brun[1*], Maya Dia[1], Yves Gouriou[1], Gabriel Bidaux[1], Christophe Chouabe[1], Claire Crola Da Silva[1], Sylvie Ducreux[1], Bruno Pillot[1], Andrea Kaczmarczyk[1], Christelle Leon[1], Stephanie Chanon[1], Coralie Perret[1], Franck Sciandra[1], Tanushri Dargar[2], Vincent Gache[2], Fadi Farhat[3], Laurent Sebbag[3], Thomas Bochaton[3], Helene Thibault[3], Michel Ovize, Melanie Paillard[1] & **Ludovic Gomez[1]**

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Despite advances in cardioprotection, new therapeutic strategies capable of preventing acute myocardial ischemia-reperfusion injury and reducing secondary event of patients are still needed. Here, we discovered that the phosphorylation of SERCA2 at serine 663 is a clinical and pathophysiological event of cardiac function. We demonstrated that the phosphorylation level of SERCA2 at serine 663 is increased with heart damage in both patient and mouse ischemic hearts. Mechanistically, we demonstrated that preventing serine 663 phosphorylation significantly increased SERCA2 Ca^{2+} pumping activity into the reticulum and protected against hypoxia/reoxygenation-induced cell death, by counteracting the cytosolic and mitochondrial Ca^{2+} overload in several human cell types, notably hiPSC-CM. To link this specific residue event to a physiological role of SERCA2 in heart, we demonstrated that gene therapy for the phosphoresistant form of SERCA2 at serine 663 improved the excitation/contraction coupling of cardiomyocytes and significantly reduced infarct size in an *in vivo* myocardial infarction model, whereas mice expressing a phosphomimetic form of SERCA2 developed a larger infarct size. Together, these findings establish the pathophysiological role and the therapeutic potential of SERCA2 modulation in acute myocardial infarction, based on the hotspot phosphorylation level of SERCA2 on its serine 663 residue.

THE GUT-LIVER AXIS

Ludovico Abenavoli

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The gut-liver axis represents a complex bidirectional communication system, between the gastrointestinal tract and the liver, mediated by several molecular, cellular and anatomic pathways. This intricate relationship is pivotal to maintaining homeostasis and is involved in various physiological and pathological processes. The gut microbiota plays a central role in this axis, influencing liver function through metabolic, immunological, and direct microbial translocation mechanisms. Dysbiosis, the imbalance in the gut microbiota equilibrium, has been involved in the onset and evolution of liver disease, including liver steatosis, alcoholic liver disease, and liver fibrosis. Microbial metabolites such as short-chain fatty acids (SCFAs), bile acids, and lipopolysaccharides (LPS) significantly impact liver metabolism and immune responses. SCFAs, products of dietary fiber fermentation, exert anti-inflammatory effects and modulate lipid and glucose metabolism, thus influencing hepatic steatosis. Conversely, LPS, a component of the outer membrane of Gram-negative bacteria, can translocate from the gut to the liver, triggering inflammatory pathways via toll-like receptor 4 and contributing to liver inflammation and fibrosis. Furthermore, bile acids, synthesized in the liver from cholesterol and modified by gut microbiota, act as signalling molecules regulating lipid, glucose, and energy homeostasis through nuclear receptors such as farnesoid X receptor and G protein-coupled bile acid receptor 1. Dysregulated bile acid metabolism can lead to cholestatic liver diseases and influence systemic metabolic disorders. Emerging therapeutic strategies targeting the gut-liver axis, including probiotics, prebiotics, and fecal microbiota transplantation, aim to restore microbial balance and mitigate liver disease progression. Additionally, modulation of dietary components and lifestyle interventions play a significant role in managing gut-liver axis-related disorders. In conclusion, the gut-liver axis represent a new area of interest in digestive diseases domain. Understanding its mechanisms offers potential therapeutic approaches to treat liver diseases, by targeting gut microbiota and their metabolic products. Further research is essential to elucidate the complex interactions of this axis, to develop effective therapeutic strategies and finally, to define guidelines.

CARDIOMYOCYTE CONTRACTILITY DURING HEALTH AND DISEASE: CA^{2+} SENSITIVITY VS. CA^{2+} AVAILABILITY

Zoltán Papp & Attila Tóth

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Cardiac contractions are brought about by highly differentiated muscle cells called cardiomyocytes. Cardiomyocytes are excitable, i.e. they respond to an appropriate electrical stimulus with a beat, depending on the interplay between their intracellular Ca^{2+} concentration changes (Ca^{2+} availability) and the Ca^{2+} sensitivity of their contractile protein apparatus. The electrical and mechanical components of the excitation-contraction coupling have been studied for a relatively long time. Pathologic signals may adversely affect the responsiveness of the heart, and thus they can lead to weakened cardiac contractions. Additionally, pathologic epigenetic regulation often evokes structural/functional changes in the myocardium, in other words "remodelling".

Cardiac pump function declines: in chronic heart failure; in ischaemic/reperfusion syndromes (e.g. angina pectoris, myocardial infarction, but also after cardiac surgery and cardiac catheterisation); in parallel with certain inflammatory processes (e.g. septic and autoimmune myocarditis, transplant rejection); and as a side effect of certain drugs (e.g. doxorubicin). In all of these conditions, complex processes are activated that may damage the extra- and/or intracellular structures of the myocardium, and can be accompanied by functional changes, some reversible and some irreversible. In certain cases, myocardial remodelling is clearly linked to inherited mutations in genes encoding myocardial proteins (e.g. hypertrophic cardiomyopathy). In other cases, the links between the genetic background and alterations in myocardial cell signalling are only partially established (e.g. dilated cardiomyopathy).

The causal links responsible for myocardial dysfunction still harbour many uncertainties due to the complex system of mediators and complementary molecular interactions involved in cardiac pathologies. Nevertheless, the effector mechanisms directly responsible for the loss of cardiomyocyte function share common elements in several acquired or genetically determined cardiac diseases, despite their different pathological origins. Mapping of common pathological processes at the molecular level may bring us closer to the development of therapeutic approaches to ensure the intact morphological and functional state of the myocardium during different cardiac diseases.

In this presentation, two major factors of cardiomyocyte contractility: Ca^{2+} sensitivity and Ca^{2+} availability will be addressed in the above contexts to illustrate their significances during physiological and pathological conditions.

PHARMACOLOGICAL APPROACHES TO ALLEVIATE ENDOTHELIAL DYSFUNCTION IN CARDIOMETABOLIC DISEASES

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There is plethora of experimental and clinical evidence for the crucial role of endothelial dysfunction as cornerstone of cardiovascular diseases, responsible for the appearance, evolution and prognosis of the diseases. Several therapeutic strategies aimed at improving hemodynamic conditions, also alleviated endothelial dysfunction. Several randomized trials addressed its pathophysiological background. EUROPA and PERTINENT studies showed that perindopril reduced MACE – myocardial infarction fatal or nonfatal, heart failure decompensation, hospitalization and death, and, these effects are not the class effects for all ACE inhibitors. Perindopril improved endothelial dysfunction, pulse wave velocity and central aortic pressure beyond its beneficial effect on blood pressure, and also reduced left ventricle negative remodeling. Metabolic therapeutic approaches in coronary artery disease is extremely important in controlling angina, improving the quality of life by means of complex pathophysiological mechanisms, such increased ATP production, decreased oxidative stress and maintenance of the intracellular homeostasis. Although, fewer studies reported composite hard endpoints on trimetazidine, its recent labelling as forbidden for sportsmen, rise the compelling question whether the well-known beneficial effects on heart failure are not regarding reduction of symptoms but also improvement of cardiac performance. Last but not least, endothelial dysfunction is alleviated via the pleiotropic, endothelial-mediated effects of statins, all randomized studies showing their tremendous benefits on MACE.

VASCULAR AGEING: FROM BENCH TO BEDSIDE

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Vascular aging, characterized by structural and functional alterations of the vascular wall, comprises the cumulative effect of all cardiovascular risk factors on the arterial wall and may help identify patients at elevated cardiovascular risk, early in disease development. The present paper discusses the role of the most important molecular pathways in vascular aging, recent guidelines mentioning pulse wave velocity, and several biomarkers associated with pulse wave analysis, including serum lipids, inflammatory tests, oxidative stress, and dietary products, emphasizing the pathophysiological mechanisms of the mentioned associations.

Vascular aging and pulse wave analysis provide valuable data in several disorders and should be considered a reliable tool in managing cardiovascular risk, combined with other biomarkers in patients with chronic disorders.

MECHANISMS AND NOVEL THERAPEUTIC TARGETS OF ENDOTHELIAL DYSFUNCTION

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Endothelial dysfunction is a central pathophysiological mechanism in all cardiovascular and metabolic diseases, mainly in hypertension, atherosclerosis, diabetes, and heart failure. The impaired function of the endothelial cells is the result of an imbalance between vasodilatory and vasoconstrictive factors, as well as of the release of a plethora of pro-inflammatory molecules. Understanding the signal transduction elicited by these mediators is mandatory in order to identify therapeutic targets that will be used for the development of effective treatments. According to the current understanding, endothelial cell damage from cardiometabolic diseases is caused by the combination of low-grade inflammation and chronic oxidative stress. However, the individual contribution of the various sources of reactive oxygen species (ROS) and the way they that potentiate and/or allow the persistence of the systemic inflammatory status are still poorly understood. Over the past two decades, ROS-mediated endothelial dysfunction, cardiac injury, and, more recently, dysfunctional visceral adipose tissue have all been linked to the increased expression/activity of monoamine oxidase (MAO), a flavoenzyme with two isoforms, MAO-A and MAO-B, located at the outer mitochondrial membrane in almost all mammalian cells, being responsible for the neurotransmitters and catecholamines' degradation. In this presentation, we provide an overview of the contribution of MAO-related oxidative stress to the endothelial dysfunction in the setting of cardiometabolic pathologies and the beneficial effects of MAO inhibitors as viable candidates of drug repurposing in these diseases.

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VASCULAR ULTRASOUND MULTIPARAMETRIC SCREENING OF SUBCLINICAL ARTERIOSCLEROSIS & ASSESSING PLAQUE VULNERABILITY FOR THE RISK OF EVOLUTION TOWARDS THROMBOEMBOLIC COMPLICATIONS THROUGH STRAIN-ELASTOGRAPHY

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Atherosclerosis is a chronic inflammatory disease of the arterial wall induced from endothelial injury followed finally by the complications of plaque and its obstruction. It is the leading cause of morbidity and mortality from heart attacks and strokes in Romania. In order to assess the vulnerability of atherosclerosis plaque we conducted a randomized clinical trial, controlled, on 500 Caucasian patients, aged 40-80 years, with a sex ratio 1:1. Inclusion criteria were asymptomatic patients with high-risk lipid profile (LDL>160mg%) with or without statins and antiplatelet therapy in the past two years. Exclusion criteria were target organ damage. We formed two groups: first under treatment with statins and antiplatelet agents and second as a control group with untreated patients. All patients were examined with Doppler ultrasound and SE in three regions: carotid, abdominal aorta, and femoral arteries. We monitored the following: IMT, velocity, RI, PI, and stenosis. We have established some criteria of elastography, for the classification of atherosclerotic plaque in "stable-uniform elasticity" or „unstable–mosaic stiffness", and designed an ultrasound risk score to diagnose the vulnerable plaque. Results: Increase of carotid IMT between 0.9-1.5 mm had meant: mild and moderate atherosclerosis in 42% of patients in the first and 33% in the control group. IMT over 1.5 mm had meant severe atherosclerosis in 58% of the first and 67% in the second group. Cut-off value of the aorta and femoral IMT>0.5 cm. Sensitivity:96.2%, specificity:88%, 95%CI:79.97% to 93.64%, prevalence: 83%. The relative risk was:0.86 with 95%CI: 0.75 to 1, Odds Ratio:0.68, $p<0.05$.
Conclusions: Ultrasound measurement of IMT in three regions, when assessing subclinical atherosclerosis and atheroma plaque stiffness as a predictive factor in unstable vulnerable atherosclerotic plaque, were important for the primary prevention of cardiovascular events.

ATRIAL FIBRILLATION: PATHOPHYSIOLOGY AND NOVEL THERAPEUTIC TARGETS

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia found in clinical practice and a major cause of morbidity and mortality. Yet, currently used antiarrhythmic drugs for AF prevention and therapy have major efficacy and safety limitations. This is at least partly due to the complex pathophysiology of AF, which varies widely from one patient to the other and encompasses various combinations of three distinct atrial diseases: an electrical myopathy, a structural myopathy, and an autonomic neuropathy. Traditionally, antiarrhythmic strategies have focused almost exclusively on atrial electrical myopathy, mainly by blocking cardiac ion channels. Unfortunately, these interventions have been shown to provide very limited success over the long-term. Different atrial-specific and non-conventional ion channel blockers are being studied and several other agents are underway. Meanwhile, increasing knowledge regarding the major role of atrial structural and autonomic remodelling in AF onset and persistence has clarified, at least partially, the failure of conventional antiarrhythmic drugs, and has opened the way for a different therapeutic approach, upstream of AF. Strategies whose main effects are not exerted at ion channel level have thus emerged as approaches that carry the potential to prevent, delay, or even reverse AF-related atrial structural or autonomic remodelling. By modifying the structural and/or autonomic substrate upstream of AF, these strategies could prevent new-onset AF, delay AF transition to more persistent forms, and/or prevent recurrent AF, while lacking the undesirable effects of ion channel blockers. Such strategies include agents with anti-inflammatory, antioxidant, and/or antifibrotic properties, neuromodulation techniques, as well as more novel, molecular approaches, including transcription factor or microRNA targeting. If proved efficient, such approaches could prevent or at least postpone the need for conventional antiarrhythmic drugs and would considerably lower the adverse effects.

FLAVONOIDS – MECHANISMS OF ACTION AND FUTURE TRENDS

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The major subclasses of flavonoids with health-promotional properties are the flavanols or catechins (e.g., epigallocatechin 3-gallate (EGCG) from green tea), the flavones (e.g., apigenin), the flavonols (e.g., quercetin glycosides from apples, berries), the flavanones (e.g., naringenin from citrus), the anthocyanins (e.g., cyanidin-3-O-glucoside from berries), and the isoflavones (e.g., genistein). There is no relationship between the amount of polyphenols in food and their bioavailability in the human body. In general, aglycones can be absorbed from the small intestine, but polyphenols present as esters, glycosides or polymers cannot be absorbed in their native form. They are hydrolyzed by intestinal enzymes, such as -glucosidases and lactase-hydrolase, or by colonic microflora, and then later adsorbed. Polyphenols play a role in decreasing several inflammatory markers: tromboxane A2 (TXA2), leucotriene B4, ICAM-1 and VCAM-1, IL-1ß, IL-6, NF-κB and its activators, high sensitivity CRP. Flavonoids inhibit platelet adhesion, thromboxanesTXA2 secretion and block GPIIbIIIa with a role in platelet aggregation. Many polyphenols from plants (e.g., EGCG, catechin, epicatechin) exhibit inhibitory activity against collagenases and elastases, thus facilitating maintenance of proper skin structure. The determination of advanced glycosylation end products (AGEs): Nε-carboxymethyl-lysine and arg-pyrimidine, in several human tumors highlighted their involvement in the progression of cancer. Certain polyphenols counteract the formation of AGE both in vivo and in vitro, thus limiting their impact on the carcinogenesis process. Furthermore, AGEs receptors such as RAGE have been found to play an important role in regulating cancer cell invasion and metastasis, and flavanols, for example EGCG, can inhibit cancer cell proliferation by blocking RAGE signaling. In order to increase polyphenol solubility and bioavailability and provide site-specific drug administration with improved pharmacokinetic properties, the development of nanoengineered polyphenol delivery systems is urgently required: liposomes, micelles, nanosphere, gold nanoparticles, nanoemulsion, solid lipid nanoparticles.

Additional multidisciplinary research is needed on the specific mechanisms of action of different flavonoids and how they can be optimized as an alternative to local or systemic prevention/treatment of lesions in different pathologies. This could involve exploring the use of combination therapies, personalized medicine approaches and developing new drug delivery systems to enhance the bioavailability and efficacy of different flavonoids.

THE THERAPEUTIC POTENTIAL OF HONEY

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Since ancient times, honey has been used for nutritional and therapeutic purposes. Lately, honey has gained significant consideration because of the beneficial biological activities that have been widely studied. Honey is a hepatoprotective, cardioprotective, neuroprotective, anti-inflammatory, anticancer, immunomodulatory, antidiabetic, and hypolipidemic agent. Furthermore, honey has a positive effect against gastroinitestinal diseases and thyroid dysfunctions. The antibacterian effect was demonstrated on some gram-negative bacteria, like Escherichia coli, Salmonella sp., Shigella sp., and Helicobacter pylori, on some multidrug resistant pathogens. Honey is also among the best natural wound healers available, and it is effective in the treatment of a broad range of wound types, including burns, scratches, diabetic boils, malignancies, leprosy, fistulas, leg ulcers, traumatic boils, cervical and varicose ulcers, amputation, burst abdominal wounds, septic and surgical wounds, cracked nipples, and wounds in the abdominal wall.

Honey is one of the most complex natural foods as it contains about 200 substances, such as carbohydrates, proteins and amino acids, lipids, vitamins, phenolic compounds, minerals, and organic acids. Bee species, floral origins, geographical origin, climatic conditions or beekeeper strategies are factors that directly affect its composition and quality. Honey has gained significant consideration because of the beneficial role of its antioxidant compounds, such as enzymes, proteins, amino and organic acids, polyphenols, vitamin C, vitamin E, trace elements and carotenoids, but mainly due to flavonoids and phenolic acids. It has been proven that phenolic compounds are responsible for honey's biological activity and that its physicochemical properties, antioxidants, and antimicrobial potential are significant for human health.

In honey the antioxidants have diverse mechanism of action including reducing the negative properties of the reactive oxygen and nitrogen species, inhibiting the activity of enzymes responsible for the production of superoxide anions and chelating metal ions, as well as disrupting the radical chain reactions. Moreover, further investigations are still needed in order to elucidate the genome-wide influences of honey and patterns of global gene expression, protein expression, intracellular signaling pathways, and metabolite production in response to particular compounds. However, the molecular mechanisms honey effects are not fully understood and therefore further studies are necessary.

RENIN INHIBITION: BEYOND BLOOD PRESSURE LOWERING EFFECT

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Aliskiren, a direct renin inhibitor is well tolerated and has a dose-dependent effect on blood pressure. Nevertheless, high doses (300 mg) of aliskiren are required to achieve similar blood pressure reduction comparable with that of losartan or angiotensin-converting enzyme (ACE) inhibitors. The limiting factor might be the relatively low bioavailability of aliskiren (2–7%). Therefore, we aimed to determine effects of aliskiren loaded onto polymeric nanoparticles and focusing on potency other than lowering blood pressure, mainly affecting reactive oxygen species (ROS) production in the heart.

Twelve-week-old male SHRs were divided into an untreated group and groups treated with powdered aliskiren or aliskiren-loaded nanoparticles (25 mg/kg/day). After three weeks, the accumulation of aliskiren, distribution of polymeric nanoparticles, gene expression of (pro)renin receptor (*Atp6ap2)*, angiotensin II type 1 receptor (*Agtr1)* and *ACE*, and protein expression of NADPH oxidase along with the conjugated diene (CD) concentration were analyzed.

The accumulation of aliskiren in the heart was higher in the aliskiren-loaded nanoparticle group than in the powdered group. The fluorescent signals of nanoparticles were visible in cardiomyocytes, vessel walls, and erythrocytes. Aliskiren-loaded nanoparticles decreased the gene expression of *Atp6ap2* and *ACE*, while not affecting *Agtr1*. Both forms of aliskiren decreased the protein expression of NADPH oxidase, with a more pronounced effect observed in the aliskiren-loaded nanoparticle group. CD concentration was decreased only in the aliskiren-loaded nanoparticle group.

We hypothesize that aliskiren-loaded nanoparticle-mediated downregulation of *Atp6ap2* and *ACE* may contribute to a decrease in ROS generation with beneficial effects on the heart. Moreover, polymeric nanoparticles may represent a promising tool for targeted delivery of aliskiren.

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METABOLOMICS BIOMARKERS IN DIABETIC KIDNEY DISEASE

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Diabetic kidney disease (DKD), as a major microvascular complication of both type 1 and type 2 diabetes mellitus (DM), accounts for over 40% of patients which reach end-stage renal disease and are referred to renal replacement therapies worldwide. Metabolomics represents a new field of interest and a systematic approach to biomarker discovery, such as small molecules (less than 5000 Da), as metabolites are, which allows the understanding of certain metabolic pathways. Metabolomics includes two types of approaches, such as the untargeted profiling and the targeted analysis of certain metabolites. The untargeted profiling of metabolites allows the simultaneous separation and identification of many metabolites using mostly the advanced liquid chromatography/mass spectrometry (LC/MS)-based techniques and provides their general fingerprint, based on retention time and mass/charge ratios, unlike the targeted metabolomics, where a defined set of metabolites is analyzed and quantified. Since the DKD incidence is continuously rising, the metabolomic techniques are promising tools for discovering specific biomarkers in tissues, plasma, serum, and urine samples of incipient DKD. Metabolites obtained from these samples are expressed in molecular mass/retention times, are confronted with information from the human metabolome database for their specific identification.
The metabolites biomarkers for DKD are markers of tubular and glomerular function, mitochondrial function, and markers of alteration in amino acid metabolism or urea cycle. Implementation of biomarkers assessment in DKD is highly expected in the future to provide information on the mechanisms of kidney disease improve clinical practice are able to forecast both cardiovascular and renal endpoints, which represent the most frequent events in DKD patients.

URIC ACID: CONSEQUENCE OR RISK FACTOR FOR THE CARDIO-RENO-METABOLIC SYNDROME?

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The association between the metabolic syndrome and an increased level of serum uric acid is a topic of interest approached by Kylin, in 1923, and Reaven, in 1993, but at the time being hyperuricemia is still not considered to be part of the metabolic syndrome although there is evidence regarding the strong association between hyperuricemia, cardiovascular disease and the metabolic syndrome

Hyperuricemia induces inflammation, endothelial dysfunction, decreased production of nitric oxide, and oxidative stress.

Hyperuricemia increases the risk of diabetes mellitus and prediabetes, dyslipidemia, hypertension, cardiovascular disease, events and mortality, stroke, chronic kidney disease, metabolic syndrome, and dysfunction of the vascular smooth muscles.

The mechanism of the relation between hyperuricemia, type 2 diabetes mellitus and insulin resistance is still unclear. On one hand, a high insulinemia decreases the renal excretion of uric acid, on the other hand, insulin regulated glucose uptake is possible only if nitric oxide is available, but an increased uric acid decreases nitric oxide, thereby accentuating insulin resistance. But also, the different components of the metabolic syndrome may cause hyperuricemia. Obesity leads to hyperuricemia through different pathways (interference with urate synthesis and excretion, glomerular dysfunction, renine-angiotensin-aldosterone system dysfunction) and uric acid decreases after bariatric surgery. More than 25% of the patients with hypertension have an increased serum uric acid, generated by different mechanisms: urate reabsorption stimulated by a decreased renal blood flow, alterations of the small vessels that lead to local ischemia and increased lactate production, thereby inhibiting the secretion of urate in the proximal tubules, ischemia-induced increased production of xanthine oxidase, etc. Finally, uric acid acts like a component of the metabolic syndrome, because fructose, one of the main causes of the metabolic syndrome, leads also to an increase in uric acid because it induces production of uric acid in the hepatocytes and because hyperuricemia represents an independent risk factor for atherosclerosis and its consequences and correlates with fatty liver disease. All these facts justify the recommendation renewed by Nejatinamini, in 2015, to consider uric acid as a component of the metabolic syndrome.

ASSESSMENT AND RISK PREDICTION OF CHRONIC KIDNEY DISEASE AMONG SOLITARY KIDNEY PATIENTS USING NON-INVASIVE BIOMARKERS

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A solitary kidney (SK) can be congenital or acquired after unilateral nephrectomy. Among SK individuals, the 50% reduced renal mass is followed by adaptive compensatory hyperfiltration and hypertrophy of both the glomeruli and the tubules to preserve kidney function. The compensatory changes reduce the functional renal reserve, leading to an increase in risk of chronic kidney disease (CKD). In clinical practice, estimated glomerular filtration rate (eGFR) and albuminuria are generally used for the diagnosis of CKD and for the assessment of prognosis. These biomarkers currently used in clinical practice become relevant only when there is already significant kidney damage limiting the early use of successful nephroprotective measures. Therefore, highly sensitive and specific novel biomarkers of early kidney damage improve SK patients' outcome and allow for efficacious management of CKD. Among SK patients, compensatory changes are more expressed in the tubulo-interstitial compartment and, therefore these structures become more vulnerable to injury. The progression of CKD is strongly correlated with tubulo-interstitial lesions and markers of tubular damage in SK population are considered early risk biomarkers of subsequent loss of kidney function. Urinary markers of proximal tubular (PT) injury such as N-acetyl-b-hexosaminidase, N-acetyl-beta-D-glucosaminidase, Beta-2 microglobulin, and epidermal growth factor are elevated in SK patients. There is a significant relationship between tubular markers and eGFR, suggesting a valuable role for these biomarkers in predicting renal function impairment. In addition, in SK individuals, urinary PT biomarkers are a reliable non-invasive tool for the early detection of drug-induced kidney toxicity, before an increase in serum creatinine.

Another promising panel of biomarkers of the subclinical SK damage is represented by markers of renal inflammation and fibrosis. The urinary monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), regulated on

activation, normal T cell expressed and secreted chemokine (RANTES), urinary procollagen III aminoterminal propeptide and Galectin-3 may detect early tubulointerstitial injury in SK individuals. Hyperfiltration-mediated injury can be accurate assessed by urinary prostaglandin-E which is significantly increased in SK population, even in the normoalbuminuric individuals. Recently, it was demonstrated that microRNAs deregulation is linked to the risk of developing CKD in the general population. In the case of SK, miR-193b-3p upregulation is associated with morphological features of inflammation, fibrosis and atrophy. MiR-193b-3p could be a reliable tool for estimating the risk of CKD among SK patients.

To conclude, there are validated biomarkers which could accurately monitor the kidney function and the risk of CKD progression among SK patients. Biomarkers that distinguish subjects at an elevated risk of kidney injury as opposed to subjects with a lower risk, before overt kidney damage occur, can improve the clinical management and prognosis of this specific population.

PATHOPHYSIOLOGY OF LIPID DISORDERS – WHAT DO WE KNOW IN 2024?

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Dyslipidemia is a modifiable risk factor with a major impact on the early development of atherosclerotic cardiovascular disease. In the past few decades, since this association has been proven in 1961 in the Framingham Study, important research aimed to identify the key mechanisms involved in the pathophysiology of dyslipidaemia, the most important treatment targets, their optimal values, and the most efficient, yet safe therapeutic agents that would improve lipid levels and reduce cardiovascular mortality and morbidity. The therapeutic approach should be individualised according to patients' CV risk and comorbidities and usually comprises of a combination between lifestyle and pharmacologic interventions, while monitoring the LDLc values - the primary target – non-HDLc and apoB as secondary (or co-primary) targets, alongside TG, HDLc and, if available, Lp(a). Current guidelines' recommendations for LDLc lowering include a high-intensity statin therapy, wherever possible, with multiple options of intensification or alternatives such as ezetimibe, bempedoic acid, monoclonal antibodies that inhibit PCSK9 or siRNA such as inclisiran. Other recent drugs inhibit the synthesis of lipoproteins that contain apoB, with effects in reducing LDLc (lomitapid which inhibits the microsomal triglyceride transfer protein, approved by the EMA and FDA for homozygous familial hypercholesterolemia cases or mipomersen, an antisense oligonucleotide which inhibits the messenger RNA of apoB100, only approved by the FDA for homozygous familial hypercholesterolemia cases), in reducing LDLc, Lp(a) and TG (evinacumab, an angiopoietin-like protein 3 - ANGPTL3 - antibody) in reducing TG levels (volanesorsen, pradigastat) or in increasing the HDLc levels, although multiple studies suggest that low HDLc levels are not a cause of ASCVD (such as the inhibitors of the cholesteryl ester transfer protein – CETP – dalcetrapib, evacetrapib, anacetrapib, obicetrapib). Other research is focused in reducing ASCVD through reducing inflammation with interleukin-6 inhibitors such as ziltivekimab, while also genetic targets are being explored. Nevertheless, recent ongoing state-of-art research describing the complex intracellular mechanisms opens new perspectives on the pathogenesis of lipid disorders.

THE ROLE OF LOW-GRADE CHRONIC INFLAMMATION IN THE PATHOGENESIS OF ATHEROSCLEROSIS

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Coronary artery disease (CAD) refers to a broad spectrum of clinical entities, from chronic to acute coronary syndromes (ACS). The major pathophysiologic mechanism underlying the development of CAD involves atherosclerotic coronary plaque disruption, with successive platelet aggregation and thrombosis. In atherosclerotic lesions, vascular inflammation involves both proatherogenic and antiatherogenic immune networks, which contribute to plaque destabilization and the progression of acute coronary events. Also, regarding the pathogenesis of atherosclerosis, endothelial dysfunction plays a critical role by facilitating the uptake of low-density lipoprotein (LDL) particularly in plaques that are prone to disruption. The endothelial inflammatory response amplifies the activation of both innate and adaptative immunity. Moreover, inflammatory signaling provides the release of cytokines with a significant role in the process of plaque rupture. Various inflammatory biomarkers, such as C-reactive protein and interleukins, have been demonstrated to be predictors of prognosis in patients with ACS. Most patients with ACS have a high level of high-sensitivity C-reactive protein, a biomarker of systemic inflammation and a predictive factor for high cardiovascular mortality.

In conclusion, there is constant new growing evidence regarding the involvement of the inflammatory process in the development and prognosis of CAD, due to its major contribution to the thrombus formation process. Both innate and adaptative systems play critical roles in atherosclerosis and thrombotic complications by mediating the interactions between immune and vascular cells. In this context, emerging new anti-inflammatory therapies might be of great interest in the treatment of different forms of coronary artery disease.

MECHANISMS AND INFLAMMATORY MEDIATORS IN HEART FAILURE PROGRESSION

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Heart Failure (HF) is the final common pathway of various cardiac and non-cardiac condition. The implacable progression of this multifaceted and debilitating syndrome remains a significant clinical and therapeutic challenge. Understanding the pathophysiology of heart failure progression is crucial for effective management. This review navigates the intricate landscape of conceptual models and pathophysiological mechanisms underlying HF progression with insights into the role of inflammation mediated by the innate and adaptive immune system. Inflammation contributes to the pathogenesis and progression of HF across the spectrum of HF with reduced ejection fraction (HFrEF), HF with midrange EF, and HF with preserved EF (HFpEF) subtypes. The relationship between inflammation and HF is bidirectional and they are strongly interconnected and mutually reinforcing each other. Long-term persistence of increased levels of pro-inflammatory cytokines determines the alteration of myocyte structure and the interstitial matrix, inducing increased oxidative stress, myocyte hypertrophy, apoptosis and necrosis, decrease in contractile force, fibrosis. Recent standpoints focus attention on the importance of chronic low-grade systemic pro-inflammatory state in HFpEF induced by aging and highly prevalent comorbidities. We discuss the putative roles of inflammatory mediators with relevance for HF pathophysiology including tumor necrosis factor-alpha; interleukin 1, 6, 8, 10, 18, 33, myeloperoxidase, nitric oxide synthase inhibitors and C-reactive protein, to which experimental and clinical efforts have been made to target or regulate them. In the next years we should focus on how to personalize anti-inflammatory therapies by targeting specific pathways, patients and phenotypes.

INFLAMMATORY BIOMARKERS AND CARDIOVASCULAR RISK ASSESSMENT

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Chronic inflammation plays a critical role in the development and progression of atherosclerosis, a primary contributor to cardiovascular disease. Inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and fibrinogen provide valuable insights into systemic and vascular inflammation, offering predictive value for cardiovascular events, including myocardial infarction and stroke. Emerging markers like pentraxin-3 and soluble CD40 ligand further enhance the precision of risk assessment and open new avenues for therapeutic monitoring.

Integrative cardiovascular risk evaluation, combining inflammatory biomarkers with traditional risk scores (e.g., Framingham or SCORE), improves individualized risk stratification. These markers also guide therapeutic interventions, particularly the use of anti-inflammatory treatments such as statins or targeted therapies like canakinumab or ziltivekimab which have shown promise in reducing cardiovascular events by modulating inflammatory pathways.

Despite their clinical potential, challenges such as biomarker standardization, assay accuracy, and guideline development remain critical to ensuring effective implementation. Advancing the understanding and application of inflammatory biomarkers is essential for improving cardiovascular risk prediction, prevention, and personalized treatment strategies.

ANTI-INFLAMMATORY THERAPEUTIC STRATEGIES IN HEART FAILURE

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The knowledge on inflammation in patients at risk for heart failure or with established HF is more limited, the most established notions being that several comorbidities elicit systemic inflammation, and this may contribute to the development of HF with preserved ejection fraction (HFpEF), although it is not completely known whether inflammation plays a key role in HFpEF or is just a by-product of various comorbidities. The cause–effect relationship between inflammation and the development or progression of HF may require further investigation. Taken together, current research evidences suggests that high levels of fibrinogen, interleukin-6, C-reactive protein are risk factors for cardiovascular disease and can be used as biomarkers to predict the development of cardiovascular disease to some extent.

IL-6 levels are commonly elevated in HFpEF, and patients with elevated IL-6 display greater body fat accumulation, more severe exercise intolerance, greater evidence of cardiac congestion manifest by natriuretic peptide elevation, and more severe cardiometabolic disease, renal dysfunction, and anemia. These findings suggest that therapies to inhibit IL-6 in this subgroup of patients with HFpEF may be helpful for improving clinical status.

Targeted anti-inflammatory therapy in HF have been studied over the last 30 years, starting from colchicine and urate lowering therapy, nitric oxide synthases inhibitors and other drugs that have been put through Phase III clinical trials: anti-cytokine therapies, anti-inflammatory therapies, immunomodulation.

Several small studies have demonstrated the benefits of exercise on systemic inflammation and larger population studies have shown an inverse relationship between physical activity and biomarker levels of systemic inflammation. Diet is another potential intervention that has been proposed to favourably alter gut microbiota in HF patients.

GUT MICROBIOTA – FACTS AND HOPES

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The intestinal mucosa is one of the main areas of contact with pathogens; it has an estimated area of 250 m2, comparable to that of a tennis court. The mechanisms of non-specific immunity at the level of the intestinal mucosa represent the first line of defense against pathogens that reach the level of the digestive tract. The efficiency of these mechanisms is indirectly demonstrated by the finding that there are patients with total IgAs deficiency who had a perfectly normal bowel function throughout their lives. The commensal gut microbiota (especially lactobacilli and bifidobacteria) is involved in non-specific immunity through numerous mechanisms, among which we mention: Inhibits colonization with pathogenic microorganisms, through: production of bacteriostatic/bactericidal substances, lactic acid, competition on adhesion sites, direct competition for nutrients; Stimulates the immune system of the whole body. In germ-free laboratory animals the immune system is underdeveloped; Anti-inflammatory effect – inhibits TNFα synthesis; The main indications of probiotic therapy or prophylaxis are: Acute infectious diarrhea, Post-antibiotic diarrhea and diarrhea with *Cl. Difficile,* Hepatic encephalopathy, Ulcerative colitis, Irritable bowel syndrome. Considering the development of bacterial resistance to antibiotics, probably in the future probiotics will have a special value as a means of prophylaxis or therapy of digestive infections. The studies have still to generate clear indications regarding the adaptation of the probiotic according to the existing pathology, duration of administration etc. We will have to abandon the generic terms of probiotic or prebiotic, and refer precisely to the effective strain or combination. Students and young doctors will have to be taught to stop looking at microbes as invariable enemies, but to consider some of them as allies in maintaining health.

MICROBIOTA DYSREGULATION IN IRRITABLE BOWEL SYNDROME

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Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, affecting 10-15% of the population globally. It presents with symptoms like abdominal pain, bloating, and altered bowel habits, and is classified into subtypes: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and mixed-type (IBS-M). The precise pathophysiology remains unclear, but recent research suggests that gut microbiota dysregulation, or dysbiosis, plays a central role in symptom development. Dysbiosis in IBS is marked by reduced microbial diversity, with an increase in pro-inflammatory bacterial species, particularly in IBS-D.

Gut microbiota dysregulation leads to several pathological changes, including increased gut permeability, immune activation, and altered communication between the gut and brain (microbiota-gut-brain axis). Additionally, changes in the production of microbial metabolites like short-chain fatty acids (SCFAs) and gases contribute to symptoms such as bloating and altered bowel function. Certain beneficial bacterial strains, such as *Lactobacillus reuteri* and *Bifidobacterium brevis*, have demonstrated potential in alleviating these symptoms by enhancing gut barrier integrity and modulating the immune response.

Therapeutic approaches targeting the gut microbiota in IBS include the use of probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary interventions like the Low-FODMAP diet. Probiotics containing *Lactobacillus reuteri* and *Bifidobacterium brevis* have shown efficacy in reducing symptoms such as abdominal pain, bloating, and altered bowel habits by restoring gut microbial balance. While FMT offers another potential treatment avenue, its success has been inconsistent, with varying responses depending on the IBS subtype.

Ongoing research into microbiota-targeted therapies, including precision probiotics and personalized interventions, holds promise for improving the management of IBS. Future treatments will likely focus on restoring microbial balance and addressing individual patient needs through tailored therapeutic strategies.

WEIGHT LOSS AND WEIGHT REGAIN AFTER BARIATRIC SURGERY

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Obesity is a chronic, relapsing disease that is increasing worldwide at an alarming rate. Beyond caloric intake and physical exercise, complex physiological mechanisms are involved in maintaining a normal body weight. Weight loss is a challenging process and data from the literature show that there are some biological pathways such as altered gut hormone secretion that predispose to weight regain after diet induced weight loss. For patients with severe obesity, bariatric surgery is the most efficient method to obtain and sustain weight loss. Changes in food selection, increased energy expenditure, elevation of anorectic gut peptides secretion as well as modifications of gut microbiota profile are some mechanisms involved in bariatric surgery induced weight loss. However, it has been reported that some patients submitted to bariatric surgery fail to reach their goals in terms of weight loss while others face, within time, weight regain. These patients may benefit form new anti-obesity medication in aiming for weight optimization after bariatric surgery.

SARS –COV2 – ALTERATIONS IN BLOOD RHEOLOGY

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Even if COVID – 19 remains primarily a respiratory illness, more organs and systems in the body can be affected. Many studies have observed an increased tendency to complicate with complications as stroke, deep vein thrombosis, pulmonary embolism. The inflammatory response in the body results into an increased release of pro-inflammatory cytokines and mediators that can alter the properties of RBCs, including aggregability and deformability and subsequent disturbances in microcirculation. We have analysed 31 patients recently diagnosed with COVID-19 disease in acute phase, compared with 29 healthy controls. Fresh samples have been rheologically analysed (deformability and aggregability indexes) and correlations with inflammatory status and chest CT imaging, adjusted for previous co-morbidities. EDTA and serum samples were obtained from all participants as per study protocol (COVID-19 patients and controls).
Blood samples revealed a high percentage of RBCs with altered shape with reduction in their deformability, but with unaffected RBCs aggregation index. These changes were observed in both, female and male COVID-19 patients although certain haematological parameters and morphological changes seemed to be more pronounced in female patients. Our results may represent pioneers into observations of rheological changes in various inflammatory diseases, a tool into disease severity evaluation and, maybe, a prognosis instrument for monitoring complications.

COVID-19: AN OVERVIEW OF PATHOGENIC MECHANISMS AND CURRENT REAL-LIFE TREATMENT OPTIONS

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COVID-19 is a highly contagious viral infection that has caused significant mortality and morbidity over the past four years since the pandemic began. With over 775 million confirmed cases and 7 million deaths attributed to SARS-CoV-2, the pandemic has posed a major challenge to global human health. SARS-CoV-2 affects the respiratory system by entering the body through angiotensin-converting enzyme 2 receptors found on respiratory epithelial cells. If the host can generate a strong interferon-mediated response, as observed in children and adults, it may control viral replication and reduce the severity of the disease at this early stage. Respiratory symptoms represent the most common clinical presentation, but the virus affects various organ systems, resulting in a range of extrapulmonary manifestations such as neurological, cardiovascular, hepatobiliary, renal, gastrointestinal, dermatological, and endocrinological complications. The systemic inflammatory response syndrome triggeredin persons that can not control viremic spread in the early stage can lead to a cytokine storm, characterized by the excessive release of pro-inflammatory cytokines like interleukin-6, interleukin-1β, and tumor necrosis factor-alpha. This cytokine storm can increase vascular permeability and cause capillary leakage. Additionally, COVID-19-related coagulopathy, marked by elevated D-dimer levels and other indicators of thrombosis, can lead to effusion formation through microvascular thrombosis and impaired lymphatic drainage. Treatment for COVID-19 includes antiviral medications that inhibit SARS-CoV-2 replication, such as remdesivir, along with immunosuppressive and immunomodulatory drugs to reduce systemic inflammation. Corticosteroids and targeted cytokine-blocking agents, such as IL-6R antagonists and IL-1 inhibitors, are used. This report examines the current knowledge regarding the distinct phases of COVID-19 pathogenesis (interactions and entry of the SARS-CoV-2 into the cell, acute or pneumonia phase, viremia phase, and lethal/recovery phase) and presents real-world data from a non-ICU department in Romania during the second and third waves of the SARS-CoV-2 pandemic, focusing on the use of anakinra (an IL-1 antagonist) and tocilizumab (an anti-IL-6 receptor monoclonal antibody used to treat various inflammatory disorders) compared to standard care. Despite major advances, COVID-19 remains one of the foremost healthcare challenges, with continuous emergence of novel strains, virus evolution leading to immune evasion and antiviral resistance.

LYMPHOGRAM IN THE EVALUATION OF SEPTIC PATIENTS

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Lymphogram allows the evaluation of lymphocyte subcategories: T helper (CD3+CD4+), T cytotoxic (CD3+CD8+), B (CD19+), NK lymphocytes (CD16+56+/CD3-) by flow cytometry. There is little information in the literature regarding the changes of lymphocyte subcategories in sepsis. Due to this lack of knowledge related to the dynamics of lymphocytes in sepsis, we propose a study which aims to assess the changes of lymphocyte subcategories in septic patients.
We included in this study 102 patients with sepsis, who were admitted in the Intensive Care Unit (ICU) of the County Emergency Clinical Hospital from Târgu Mureș (Mureș, Romania), between 2021 and 2023. The lymphocyte subcategories were evaluated on day 1 versus day 5 after admission to the ICU, in sepsis versus septic shock, and in survivors versus non-survivors. We did not obtain a significant difference between day 1 and day 5 and nor between survivors and non-survivors. The cytotoxic T lymphocytes (%) were significantly decreased and the NK lymphocytes (%) were significantly increased in patients with septic shock versus sepsis. The small cohort of patients included in our study is an important limitation and larger studies are needed for the evaluation of lymphocyte subcategories in sepsis and the dynamic changes they suffer according to the pathogenesis of sepsis.

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PLATELET DYSFUNCTION - AN OVERVIEW

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Platelets are small, anucleate blood cells that play a pivotal role in hemostasis, preventing blood loss by forming blood clots. Platelet dysfunction refers to conditions where platelets fail to function properly, leading to either excessive bleeding or, in some cases, to thrombosis.
Platelet dysfunction can be inherited or acquired and encompass a diverse range of disorders, that have distinct genetic, systemic, or pharmacological causes. While in inherited disorders like Glanzmann's thrombasthenia and Bernard-Soulier syndrome, genetic mutations affect proteins that are essential for platelet adhesion, activation, or aggregation, in systemic conditions such as liver cirrhosis or kidney failure, dysfunctional platelets result due to the altered circulating environment. In other cases, medications such as aspirin or anticoagulants impair platelet function to prevent clotting complications and may inadvertently lead to an incresed risk of bleeding. Therefore, accurate diagnosis is essential, as the treatment varies widely depending on the etiology of the dysfunction. Diagnostic workup of platelet dysfunction includes both a thorough clinical examination, laboratory tests, and/or genetic testing. Recent advances in gene therapies and diagnostic tools hold promise for better management and outcomes in the future. Therefore, further research tackling the pathophysiological mechanisms of platelet dysfunction is required in order to develop novel therapies for these complex disorders.

INVOLVEMENT OF OXIDATIVE STRESS IN THE EVOLUTION OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Oxidative stress (OS) is defined by an imbalance in the cellular redox status characterized by overproduction of reactive oxygen species (ROS) and/or the deficiency of antioxidant systems. OS is involved in the pathogenesis of several pathologies, including chronic myeloid leukemia (CML), a chronic myeloproliferative neoplasm, treated by tyrosine kinase inhibitors (TKIs).
The aim of the study was to analyze the involvement of OS in the pathogenesis of CML, progression to advanced phases of disease (accelerated/blastic) and in the resistance to TKIs.
This research was an analytical, observational, case-control study (2018-2022, aproval no.74/23.02.2017), associating an experimental research, by determining ROS, total antioxidant capacity (TAC), 8hydroxy-2deoxyguanosine (8OH-2dG) in 75 CML patients hospitalized in the Hematology Clinic of Filantropia City Hospital, versus 20 healthy subjects.
Lower mean TAC values and higher mean ROS values were recorded in CML patients versus the control group, suggesting the involvement of OS in the pathogenesis of CML. OS can play a dual role in CML progression: it can promote genomic instability and accelerate the progression of CML to advanced phases or it can contribute to leukemic cell apoptosis by providing a favorable environment for TKIs action. Increased values of 8OH-2dG in CML patients with disease progression suggest that OS promotes clonal instability and progression to an advanced disease stage. In these patients, an imbalance of the redox status was found long before hematological changes. There is a fragile balance between the proapoptotic and antiapoptotic effects of the OS reported at the leukemic clone in CML, but it seems that TKIs therapy induces, in most cases, an optimal OS level, adequate to determine apoptosis in the leukemic clone. CML patients who required repeated therapeutic switches presented a more important deterioration of the redox status as compared to other patients. There have been cases of TKIs resistance uncorrelated with altered oxidative status, thus suggesting there are also redox-independent mechanisms involved in the resistance to TKIs therapy. Lower ROS values and higher TAC values were found in CML patients with associated comorbidities and specific treatments for them (possible modulatory effect on the oxidative status).

PLATELET MITOCHONDRIAL DYSFUNCTION IN DISEASE AS PERIPHERAL BIOENERGETIC MARKER

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One of the most recent theories regarding the pathogenic mechanism of chronic diseases states that "failure to remove damaged mitochondria by mitophagy and replace them with healthy organelles can result in a progressive deterioration in bioenergetic function which precedes the onset of more severe clinical systems". Accordingly, evaluation of cellular bioenergetic profile represents a modern concept of the 21st century, yet no clinical tests being available at present. Assessment of platelet respiration by high-resolution respirometry has emerged as a peripheral biomarker of mitochondrial dysfunction with potential use in early diagnostic, disease progression and/or therapeutic response assessment in both acute and chronic pathologies. Accordingly, we have demonstrated the occurrence of platelet mitochondrial dysfunction at the onset of pediatric acute lymphoblastic leukemia and also, in adults newly diagnosed with hematological malignancies, prior to the initiation of anti-neoplastic treatment. We also showed that platelets from preeclamptic pregnancies showed a decreased coupled and uncoupled respiration as compared to healthy pregnancies. Platelet mitochondrial respiratory function is globally depressed in patients with sepsis, whereas in COVID-19 infection, mitochondrial respiration was influenced by the severity of the disease. As such, the severe forms of COVID-19 infection expressed a significant decrease in platelet active respiration for both respiratory complexes I and II of the electron transport system, while the moderate forms of disease elicited a significant decrease in the active respiration, particularly for complex I. We have also reported that mitochondrial respiratory dysfunction that can be rescued by a novel compound, a cell-permeable succinate. All these studies unequivocally demonstrated that monitorization of oxygen consumption in peripheral platelets provides a reliable assessment of the cellular bioenergetic profile in a variety of diseases and a putative contribution to the early diagnostic or evaluation of therapeutic response.

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SONIC REPRESENTATION OF CELLULAR PROCESSES

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Sonification, the process of transforming data into sound, provides an innovative approach for interpreting complex biological processes by engaging the auditory senses. This method is particularly useful in medical informatics, where large and multidimensional datasets can be difficult to grasp visually. By converting biological data into sound, sonification enhances pattern recognition and the understanding of dynamic processes, offering new perspectives for both research and education. The most common approach to sonification is parameter mapping, where data points - such as values from biological signals like ECG or molecular sequences - are translated into sound properties like pitch, volume, or rhythm. However, this straightforward technique can oversimplify complex biological processes, making it less effective for representing intricate systems. To address these limitations, a higher level correspondence was called structure mapping. This approach captures the relationships and sequences within biological data, allowing for a richer and more accurate auditory representation of cellular processes. As an application we selected the Electron Transport Chain (ETC) within mitochondria as an exemplary system for sonic representation. The ETC, a fundamental biochemical pathway in cellular respiration, involves a sequence of electron transfers across several protein complexes (I-IV) and culminates in ATP synthesis. By mapping the elementary steps of the ETC to corresponding musical structures - such as motives, harmonic progressions, and rhythmic patterns - it becomes possible to create a sound-based narrative of energy production within cells. Thus, the electron transfer across the complexes is expressed through arpeggios and rising melodic sequences, symbolizing the increasing energy states of the process. The formation of the proton gradient across the inner mitochondrial membrane is represented by tension-building harmonic structures, while the final step - ATP synthesis - depicted as a resolving cadence, signalling the conclusion of the energy conversion process. Additionally, variations in rhythm and dynamics reflect the flow of energy and the efficiency of the ETC, providing an intuitive understanding of cellular bioenergetics. By combining biological insights with musical structures, this method offers an intuitive and innovative way to represent cellular bioenergetics, enhancing both data analysis and educational communication of complex biological systems.

HUMAN PAPILLOMA VIRUS INFECTION IN PATHOLOGY: FROM GENITAL TO HEAD AND NECK CANCERS

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Human papilloma virus (HPV) infection is a very common infection affecting ~ 85% of population. Although in more than 90% it will cause no further complication, in a small percentage it can evolve to severe forms of cancer. It is more than 99% involved in cervical cancer, but recent studies have proven a tight connection with other genital and anal cancers and also with head and neck cancers. The presentation will cover aspects from epidemiology and pathophysiology to clinical features and management options. Despite the many complications that HPV infection can cause, efficient screening and testing can reduce significantly the mortality and morbidity caused by it. Educational programs for patients and doctors are needed, along with better vaccination campaigns.

PRENATAL PERINEAL TRAINING TO PREVENT DYSFUNCTIONS OF THE PERINEAL FLOOR

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Pelvic floor disorders have a worldwide prevalence ranging and it is now recognized that pregnancy and childbirth are the primary risk factors for the development of pelvic floor pathologies. The growth of the fetus during pregnancy involves a postural reorganization of the woman due to the direct effect of the pelvic organs, abdominal muscles, and due to the volumetric increase of the uterus. The vaginal birth can cause fascial, muscular, vascular/ischemic and/or neurogenic damage to the pelvic floor. The talk presents a retrospective study aimed at investigating the impact of pelvic floor preparation for childbirth – by means of stretching balloons and perineal massage – namely, to assess whether perineal training techniques reduce the prevalence and severity of perineal injuries during childbirth and improve postpartum maternal health outcomes.
A study group of 150 primiparous women who accessed private clinics in Padua (Italy) in the period 2019–2023 were evaluated regarding the rate of perineal trauma and postpartum dysfunction across three subgroups: the balloon stretching group (BSG, n = 50), the perineal massage group (PMG, n = 39), and the control group (CG, n = 61).
Prenatal perineal training had a significant impact on reducing the rate of perineal injury and episiotomy and the duration of the second stage of labor (BSG and PMG had a shorter duration compared to the CG). Patients who carry out the preparation with the stretching balloon are less likely to develop urinary and anal incontinence and pain during intercourse. Dyspareunia in BSG was detected in less than half of the cases compared to the PMG. Symptomatology inherent to the posterior compartment was reported in less than 10% of cases in BSG vs. more than 20% in PMG and 30% in CG, respectively. In conclusion, stretching balloons and perineal massage can be chosen as tools to prevent and reduce the rates of obstetric trauma during childbirth and to reduce the use of episiotomies as well as protect against the development of dysfunctions of the pelvic floor.

A META-ANALYSIS OVER THE RISKS OF SYMPTOMS AFFECTING QUALITY OF LIFE IN NATURAL MENOPAUSE VS PREMATURE MENOPAUSE

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Menopause inflicts many consequences over a woman's health especially regarding to weight, cardiovascular risk, and osteoporosis. It can be defined as very early (<40 years), premature (40-44 years), natural (45-51), relatively late (52-54), late (>55 years). Adding to these the consequences of losing the function of sex hormones, the lower quality of sexual life, the impact on the socio-professional life and the risk of psychological problems, it is presumable that the earlier the onset of menopause, the more symptoms affecting quality of life will occur. We present here a study aimed establishing the risk for specific symptoms associated with menopause depending on the age of onset. We used a network meta-analysis to simultaneous compare more studies on the topic and to assess the frequency of symptoms affecting quality of life in natural menopause vs premature menopause.

The main symptoms identified for the 987 women identified from 3 eligible studies were: insomnia (675), asthenia (68%), irritability (66.66%), flushes (47.11%), dyspareunia (27.05%). These studies showed that insomnia, flushes and asthenia have 2 times higher chances to affect a women in natural menopause, irritability has similar figures for both groups, while dyspareunia will affect more the younger women. Correlations between these were further analyzed.

The symptoms inflicted by menopause will affect all women and the perception will depend mainly on the cultural and geographical particularities of the population. Some symptoms will affect more women entering menopause at a normal age (insomnia, asthenia, irritability, flushes), while dyspareunia will affect more the younger ones. The strong associations of several symptoms in the same woman, explain the life quality decrease.

EPITELIAL ERA IN ASTHMA PATHOPHYSIOLOGY

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The etiopathogenic concepts of asthma have evolved over time. While in antiquity it was considered a neuropsychological disorder, in the second half of the 20th century, it was viewed as a disease of the bronchial smooth muscle. By the end of the last century and the beginning of the current one, asthma came to be defined as a chronic inflammatory disease of the bronchial mucosa. According to the latest hypotheses, this inflammation is triggered and sustained by a dysfunction of the bronchial epithelium, which is responsible for both the local inflammatory process and airway remodelling.

Exposure to environmental factors (inhaled noxious agents, aeroallergens, pathogenic microorganisms) triggers, in the context of specific genotypes, a targeted injury to the airway epithelium, which not only loses its protective barrier function with a sensory role but also becomes responsible for altering the local immune response, both innate and adaptive. Dysfunctional bronchial epithelium becomes a continuous source of alarmins, pro-inflammatory cytokines that can potentially induce also structural changes locally, particularly in the smooth muscle. As a result, inflammation, hyperreactivity, and bronchial remodelling, which constitute the principal interconnected pathophysiological mechanisms of asthma, are direct consequences of this self-sustaining process.

The inflammatory pathways potentially triggered are multiple (eosinophilic allergic inflammation, non-allergic eosinophilic inflammation, mast cell infiltration of smooth muscle fibers) and have diverse consequences, which explains the complexity and heterogeneity of asthma, both in terms of clinical and inflammatory phenotypes, but especially in terms of endotypes, specifically high T2 vs. low T2 asthma. Furthermore, several clinical features of asthma with persistent airflow limitation are also associated with airway remodeling processes (goblet cell hyperplasia, mucus hypersecretion, smooth muscle hypertrophy, thickening of the basement membrane, subepithelial fibrosis, etc.), primarily driven by epithelial cytokines (TSLP, IL-25, IL-33) alongside T2-type cytokines (IL-13, IL-4, IL-5).

NEURO-IMMUNE PATHWAYS IN INFLAMMATION AND AIRWAY REMODELLING IN ASTHMA

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Asthma is a common airways disease characterized by chronic inflammation, eventually leading to remodeling of the airways. Based on the predominance of certain cell types, asthma is currently classified as Type 2-high and Type 2-low asthma. In type 2-high asthma, the airways are infiltrated with large numbers of Th2 and ILC2 cells. By secreting type 2 cytokines, these two types of cells can initiate a series of signaling cascades, further activating effector cells such as B cells, basophils and eosinophils, and thus initiate the pulmonary inflammatory response. Although immune response plays a vital role in the occurrence and development of asthma, in recent years, the role of neuro-regulation in the occurrence of asthma has gradually attracted investigators' attention. The lung is a highly innerved organ. Nerves in the lung can be divided into sensory or afferent nervous system and motor or efferent nervous system according to the signal direction travelling within the nerve. Recent research reveals the role of neuro-immune regulation in the development of asthma, by the complex interplay between nervous and immune cells of the innate immunity on one side (dendritic cells, mast cells, eosinophils, ILC2) and between nervous and immune cells of the adaptive immunity on the other side (Th2 and B cells). Neural regulation also plays a vital role in airway remodeling process, which is one of the most characteristic pathological features of persistent asthma and main reason for hospital care. Finally, pulmonary neuroendocrine cells may serve as a center of neuro-immune regulation in the asthmatic lung by activating and stimulating ILC2 cells to produce IL5 and IL13, thus triggering a Th2 response.

GENETICS OF ASTHMA

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Asthma is a common multifactorial and polygenic disease, arising from complex interactions between multiple genetic/epigenetic and environmental factors. Before the genomics era, twin studies have shown that up to 70-80% of the susceptibility to asthma could be attributed to genetic factors. Moreover, classical approaches in genetics, such as linkage analysis and candidate-gene studies have linked numerous genetic loci to asthma. The GWAS (genome wide association studies), which gained momentum in the last two decades, added important new data to these findings. There are about 100-150 genetic loci identified so far in susceptibility to asthma. They fall in three large categories, namely: immune system function, mucosal biology and function, and lung function and disease expression. Although these new approaches greatly contributed to our knowledge in the field of genetic susceptibility to asthma, they still explain only a part of asthma's heritability. Also, epigenetic modifications, such as changes in DNA methylation, likely play an important role in the molecular pathophysiology of asthma. As such, genetic testing for asthma susceptibility has not yet been implemented in the clinical practice, given the complex genetic and epigenetic factors involved in this disease. Genetic testing should be used only to exclude monogenic obstructive lung diseases that can be misdiagnosed as asthma, including mucoviscidosis, and other primary ciliary dyskinesia, or alpha-1 antitrypsin deficiency.
In conclusion, genetic susceptibility to asthma still remains incompletely characterized, despite the tremendous progress made in the last decades. Future research should bring more insight not only in the genetic and epigenetic factors involved in asthma, but in their interaction with environmental factors, as well. This would pave the way for personalized treatments. Also, a genetic test for asthma predisposition would be welcome in the future.

CURRENT CONCEPTS REGARDING THE ROLE OF THE LUNG MICROBIOME IN RESPIRATORY DISEASES

Emanuela Vaștag, Monica Marc, Ovidiu Fira-Mladinescu

For a long time the lungs were considered to be sterile, however in the last decades the technological processes identified the presence of a pulmonary microbial community. In 2010, the composition of the lung microbiome, especially the bacteriome, was discovered, showing that the lung has its own microbiota. The relationship between the lung microbiome and lung diseases has been discovered. For example, in 2011 and 2012, diseases such as COPD, cystic fibrosis, pneumonia, and bronchial diseases were found to be closely associated with the lung microbiome. With the lung transplant study, immunity and the lung microbiome were shown to have a strong relationship. From the end of 2019 until now, researchers have found important links with COVID-19 and lung cancer.

It is worth noting is the fact that the movement of air, mucus and microbes in the lung are bidirectional, without having a physical barrier between the larynx and the most distal alveolus, a fact that determines a much more dynamic and transient aspect of its composition, than in the case of the gut microbiome.

The composition and size of the pulmonary microbiome changes dynamically, under the influence of certain diseases. For example, in patients with asthma and COPD, pathogenic Proteobacteria, especially Haemophilus, were predominantly found, while in patients with cystic fibrosis, Candida albicans was predominantly found, so this can be considered an indicator of disease and diagnosis.

In conclusion, the lung microbiome of a healthy organism plays an important role in maintaining lung homeostasis, by regulating the lung environment and modulating the immune response. In recent years, researchers have discovered a link between the lung microbiome and a variety of lung diseases, with the microbiome of respiratory patients being significantly impaired as compared with healthy subjects, and the number and abundance of dominant bacteria varying fom one disease to another. In turn, lung microbiome disturbances contribute to diseases onset and exacerbation. The association microbiome - lung cancer has emerged as a novel research avenue.

AN OVERVIEW OF THE IMPAIRED ANTIOXIDANT DEFENSE SYSTEM IN THE PATHOGENESIS OF CHRONIC VENOUS DISEASE

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Oxidative stress is defined as the imbalance between excessive reactive oxygen species (ROS) generation and/or deficient antioxidant defense systems. An increasing number of studies have addressed over the past decades the role of oxidative stress in the pathogenesis of chronic venous disease (CrVeD), particularly the pathomechanisms underlying the varicose veins (Vv) formation. Impairment of the antioxidant defense systems occurs in most cardiovascular diseases and worsens with ageing. The major antioxidant systems in the venous vascular bed are similar to those in arteries. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) are the main enzymatic components, and glutathione (GSH) is the primary non-enzymatic component. SOD is a major enzymatic antioxidant, being critical for protecting cells from oxidative damage caused by the superoxide radicals. Half of the studies demonstrated statistically significant lower SOD activity in either Vv tissue or plasma from CrVD patients vs control subjects. In over 70% of the studies, CAT activity was also significantly reduced in CrVD patients. GPx activity showed inconsistent results, being higher, lower or not significant in patients vs controls. Similarly, in most of the studies GSH, the most abundant antioxidant in the human body, showed no significant differences between the study and control groups. In conclusion, a decreased antioxidative defense might contribute to the pathogenesis of CrVeD venous pathology, yet larger studies are needed to assess the stage of disease where this occur in order to allow for early therapeutic intervention.

MONOAMINE OXIDASE CONTRIBUTION TO VALVULAR OXIDATIVE STRESS: A NOVEL PATHOMECHANISM IN SEVERE MITRAL VALVE REGURGITATION

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Mitral regurgitation, the second most common worldwide, is a debilitating disease, with a slow progression, partly due to the mechanical stress induced by the regurgitant jet on the valvular tissue. This shear stress activates several signalling pathways resulting in overproduction of reactive oxygen species. Monoamine oxidases (MAOs) A and B are mitochondrial enzymes that catalyse the oxidative deamination of neurotransmitters and dietary amines and have emerged in the past two decades as important contributors to the cardiovascular oxidative stress. Their increased activity/expression occurs with the age and results in overproduction of hydrogen peroxide as reaction by-product. Oxidative stress in both the heart and vessels is further enhanced via the activation of local and classic renin-angiotensin-aldosterone systems (RAAS). We conducted a pilot study aimed at assessing MAOs expression and oxidative stress in mitral tissue samples harvested from patients with severe mitral regurgitation that underwent replacement and/or repair surgery. We found that both MAO isoforms are expressed in the explanted valvular tissue regardless the disease etiology and/or presence of the cardiovascular risk factors; the expression was further increased after acute incubation with angiotensin II. Both MAO expression and oxidative stress were mitigated by *ex vivo* exposure to either MAO inhibitors or an angiotensin receptor blocker (ARB). The level of valvular oxidative stress was negatively correlated with left ventricular ejection fraction. Further research on the relationship between long-term RAAS suppression with either ARB or ACE inhibitors and MAO-dependent oxidative stress in other valvular disorders is warranted in order to clarify a novel pathomechanism that may be therapeutically exploited to prevent/delay the progression of the disease.

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MALIGNANT MELANOMA-MITOCHONDRIA – AN INTRIGUING RELATIONSHIP: BETULINIC ACID AS A POTENT ANTIMELANOMA AGENT

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Melanoma has gained the title of the most aggressive type of skin cancer in consequence of several specific features as heterogeneity in cellular populations (cancerous and non-cancerous cells), rapid growth, long phases of quiescence, broad metastases, late recurrence, tumour resistance, and a high mortality rate in late stages. Recent research revealed the “hybrid” glycolysis/OXPHOS metabolic phenotype of melanoma cells, a characteristic known as metabolic plasticity having mitochondria as central piece. A liaison between the role played by the metabolism in melanoma’s refractory character was implied, but further research is needed to better comprehend the pathophysiology of the intriguing relationship between mitochondrial metabolism and melanoma progression and resistance to treatment, a potential target for novel therapeutical compounds.
Betulinic acid (BA), a compound of natural origin, a pentacyclic triterpenoid, with a myriad of pharmacological effects, including antibacterial, antiangiogenic, anti-HIV, anti-inflammatory, hepatoprotective, antimetastatic, and others, proved a potent anticancer effect in melanoma both *in vitro* and *in vivo* conditions. Even though the mitochondrial-dependent proapoptotic effect of BA has been described, its impact on mitochondrial bioenergetics is rather unexplored. So, we investigated the BA effects on mitochondrial bioenergetics and cellular behaviour in A375 human melanoma cells. We showed that BA inhibited in a dose-dependent manner both mitochondrial respiration and glycolysis in melanoma cells, and also induced cytoskeleton reorganization, modifications in mitochondrial morphology, and a reduction of mitochondrial potential. These findings together with the ability of BA to interfere with other key signalling pathways in cancer, make this compound a viable therapeutic alternative for the treatment of melanoma or to antagonize the resistance to standard treatment.

TARGETING CANCER CELLS WITH TRITERPENE-BASED NATURAL AND NOVEL SEMISYNTHETIC COMPOUNDS

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Cancer, in all its types and manifestations, remains a leading cause of death worldwide and hence, drives the need for innovative and effective therapeutic strategies. Numerous potentially effective anticancer drugs derived from plants have been reported in the scientific literature; these substances include natural molecules as well as several of their later modified derivatives that displayed improved pharmacological and pharmacokinetic properties. Herein, we share our research findings, mainly involving the development, chemical derivatization, and biological evaluation of novel triterpene-based semisynthetic derivatives that retained the natural compound's basic scaffold. The heterocyclic triterpene derivatives investigated include pyridinylidene-lupane and ursane derivatives, ursonic and oleanonic pyperazinyl amides, hollongdione arylidene derivatives, betulin as well as betulinic acid-1,2,4-triazole derivatives and betulinic acid benzotriazole and fatty acid esters. Moreover, we have also developed gold nanoparticles and liposomal-based formulations of some of these above-mentioned compounds to increase the biological activity, stability, and drug delivery and to overcome certain limitations, such as the low bioavailability reported in many natural compounds. Another key element of this work has been to decipher the underlying mechanisms of action of these novel agents, with an emphasis on their effect on mitochondrial function. Currently, agents that preferentially target cancer cell mitochondria, called mitocans, are actively explored in cancer treatment research, as mitochondria play crucial roles in regulating cancer cell metabolism, apoptosis, and ROS production. Our results show that the natural compound we studied and many of our novel developed semisynthetic and synthetic agents inhibit the proliferation, trigger apoptosis, and induce mitochondrial dysfunction of various cancer cells. By developing and testing advanced drug delivery systems, our work also offers new insights into the potential of these compounds as targeted anticancer therapies.

POTENTIAL MOLECULAR MECHANISMS PROPOSED TO BE INVOLVED IN THE DIABETOGENIC EFFECT OF STATINS

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Despite advances and current therapeutic strategies, cardiovascular diseases (CVD) continue to be the principal cause of mortality worldwide, and hypercholesterolemia, a major risk factor for CVD, has thus become a significant therapeutic target. Clinical evidence recognizes and supports the therapeutic benefits of statins, lipid-lowering medication, in the primary and secondary prevention of CVD, making them the gold standard for lipid-lowering therapy[1]. Statins also possess a series of pleiotropic effects that increase their cardioprotective potential, such as improving endothelial dysfunction, stabilizing atheroma plaques with strong antioxidant potential and anti-inflammatory properties. Their multiple benefits have increased the prescription rate among patients, which has also led to the identification of new adverse effects. Initially, elevated liver transaminases and myopathy were most identified, and more recently, special attention has been paid to their potential for inducing new-onset type 2 diabetes (NODM). The results of various studies estimate that the magnitude of the risk of statin-induced NODM is 10-22% compared to non-users. This risk increases depending on the statin molecule used and the intensity of the therapeutic regimes, but also on the type of patient[3], such as age, associated comorbidities, etc. The pathophysiological mechanisms proposed to underlie the statin-NODM relationship are centered in two directions: i).*a pancreatic β-cell dysfunction*[4] translated by a decrease in insulin secretion, following a direct action on voltage-dependent Ca^{2+} channels, but also indirect, intracellular actions, by disrupting the coupling of metabolic and electrophysiological events; ii).*a decrease in insulin sensitivity of peripheral tissues*[5], following the disruption of intracellular signaling pathways responsible for the distribution and cellular expression levels of glucose-transporter 4. Other possible mechanisms underlying the link between statins and NODM include inhibition of adipocyte differentiation and a decrease in levels of leptin (an inhibitor of β-cell proliferation) and adiponectin. According to recent studies, statins' benefits in reducing cardiovascular risk remain clearly superior to the risk of NODM's occurrence. Collins and his collaborators[6], in the 2016 meta-analysis, state that the possibility of NODM's occurrence is 1:10 major vascular events prevented. This paper aims to present the most relevant and up-to-date data from the literature regarding the possible mechanisms proposed to underlie the diabetogenic effect of statins.

AURICULOTHERAPY EFFECTIVENESS IN MODULATING OXIDATIVE STRESS AND INFLAMMATION IN THIRD MOLAR EXTRACTION

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Background. Third molar extraction (TME) is a frequent surgical intervention in dentistry, associated with physical, biochemical and psychological implications. Auriculotherapy (AT) is a treatment performed by stimulating the acupuncture points located on the ear.
Objectives. Evaluation of the AT effectiveness in modulating oxidative stress and inflammation in TME.
Materials and methods. 30 patients who required TME were randomly divided into 3 groups: control, without AT (C, no=13); with AT only pre-TME (AT1, no=13); with AT both pre- and post-TME (AT2, no=13). Evaluated parameters: malondialdehyde (MDA), pain (P), C-reactive protein (CRP), leukocytes (L), fibrinogen (F), local edema (LE).
Results. For all groups, it was found post-TME: reduction of MDA; in the first 7 days, P, PCR, F and L-PMN increased moderately and LE was present. At AT1 and AT2 compared to C, post-TME, the reduction of MDA was significantly higher, and the post-TME increase of P, PCR, F, L-PMN and LE was significantly lower. Differences were more important at AT2 for all the parameters, so the effect of reducing oxidative stress and the anti-inflammatory one are more intense when AT is applied pre- and post-TME
Conclusion. TME causes a reduction in oxidative stress associated with the pathology and a moderate inflammatory response. AT additionally contributes to the post-TME reduction of MDA and reduced the post-TME inflammation. AT can be an accessible and efficient way of modulating oxidative stress and inflammatory response associated with TME.

AUGMENTED RENAL CLEARANCE IN CRITICALLY ILL PATIENTS AND VANCOMYCIN THERAPEUTIC DRUG MONITORING

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Background: Patients with critical illnesses represent a distinct category of patients undergoing significant pathophysiological alterations that may fluctuate from day to day. These specific patient characteristics lead to alterations in drug pharmacokinetics and pharmacodynamics. One such particularity is augmented renal clearance (ARC), which results in variability in vancomycin plasma concentration (PC). The present paper's first objective was to do literature research and identify the characteristics of the critically ill, including ARC characteristics. The second objective was to identify critically ill patients with ARC in the Intensive Care Unit and prescribed vancomycin in whom the plasma concentration was determined to adjust their vancomycin dose.
Material and method: Literature research used the following keywords: “critically ill”, “augmented creatinine clearance”, and “vancomycin therapeutic drug monitoring”. Systematic literature research, including ARC, was selected to describe critically ill patients' particularities. Two critically ill patients with similar characteristics were analyzed, including ARC, in whom vancomycin PC was determined.
Results: First, several authors were found to describe the characteristics of critically ill patients, the ARC signs, and their consequences. Second, following the determination of vancomycin PC, both patients required significant dose increases to achieve therapeutic targets.
Conclusions: Our research underscores the significant impact of augmented renal clearance on vancomycin therapy in critically ill patients. It highlights the importance of a clinical pharmacist in the medical team, the need for daily evaluation of ARC, and the importance of adjusting vancomycin doses to counterbalance the accelerated drug clearance. These findings are significant and practical and should be considered in the clinical management of critically ill patients.

BLACK CHOKEBERRY JUICE EFFECT IN PRE-HYPERTENSIVE AND FIRST GRADE HYPERTENSIVE PATIENTS: A PROSPECTIVE STUDY

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Background. Black chokeberry (BCK) fruits are among the richest fruits in polyphenols, phytochemicals responsible for the antioxidant and anti-inflammatory effect. We have previously demonstrated the alleviation of oxidative stress in an experimental model of mice for several extracts of BCK. Since hypertension (HTN) is associated with oxidative stress and low-grade inflammation, supplementation with BCK may positively impact blood pressure levels.
Objective. The aim of the present study was to assess the effect of black chokeberry juice (BCKJ) on lowering blood pressure (BP) levels and reversing endothelial damage in patients with high-normal or 1st-grade HTN (BP values: 130 – 159/85 – 99 mmHg) and low-moderate cardiovascular (CV) risk.
Methods. A prospective, comparative study was conducted in the Cardiology Clinic ASCAR of Timișoara City Hospital from March 2022 to February 2023. Patients for whom the 24-hs monitorization device confirmed the previously mentioned BP values, had a low-moderate CV risk, and were under no previous medication were recommended a non-pharmacological approach to lowering BP levels consisting of lifestyle changes and 100 mL/day BCKJ for a period of 3 months. The complete list of investigations was performed at the beginning (T0) and after 3 months of treatment (T3).
Results. Seventy patients completed the 3 months of treatment. The control group (n=30) is represented by patients for whom the 24-hour monitorization device did not confirm the diagnosis, both groups being matched by age and sex. The mean age of the study group was 49.2 ± 12.02 versus (vs) 46.73 ± 12.29 (control group). 54.29% of the included patients were female vs 46.67% (control group). After 3 months of non-pharmacological treatment, the SBP decreased from 143.33 ± 10.21 (T0) to 132.2 ± 9.61 (T3), with $p<0.001$, vs 113.2 ± 12.02 (control group). DBP decreased from 92.243 ± 5.539 (T0) to 82.40 ± 6.382 (T3), with $p<0.001$, vs 78.9 ± 8.543 (control group). Endothelial damage was assessed by ADMA (asymmetric

dimethylarginine) and PTX-3 (pentraxin-3), which decreased and increased after treatment.

Conclusion. BCKJ supplementation, in conjunction with lifestyle changes, can be a more natural, well-tolerated alternative for the initial stages of high BP levels in patients with low-moderate CV risk.

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THE IMPORTANCE OF INTERDISCIPLINARY COLLABORATION IN HANDLING, PREPARATION AND ADMINISTRATION OF PARENTERAL PREPARATIONS

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Introduction: The clinical pharmacist has an essential role in verifying the compliance of parenteral preparations with quality standards and in ensuring that all handling, preparation and administration (HPA) processes are carried out in optimal conditions. Parenteral preparations being administered directly into the bloodstream, have an increased potential to produce adverse reactions if they are not handled, prepared and administered properly. Thus, physiological disorders and associated complications may occur.
Objectives: The objective of the study is to analyse how the interdisciplinary collaboration was influenced by the implementation of a working procedure that regulates the involvement of the clinical pharmacist in the medical team. The aim of this collaboration is to reduce the risk of adverse reactions, which may be generated by the HPA of parenteral preparations.
Materials and methods: In this analysis was used the database and working procedures of the Municipal Hospital „Dr. Gheorghe Marinescu" from Târnăveni, as well as the data from the Nomenclature of Medicines for Human Use, developed by the National Agency for Medicines and Medical Devices în Romania. A procedure was drawn up that regulates the mode of HPA of parenteral preparations, as well as the duties of the medical personnel involved.
Results: Analysing the number of records that referred to parenteral preparations, it results in an increase in the number of recommendations of the clinical pharmacist to the medical staff, after the implementation of the procedure. Thus, the average number of recommendations before the implementation of the procedure was 2.57/month, and post-implementation was 5.89/month. This means an increase of 129.18% in the average number of recommendations per month. There has been an increase in awareness of the importance of complying with official regulations regarding the HPA activities of

parenteral preparations. This can prevent the risk of medication errors, which can generate adverse reactions.
Conclusions: The direct involvement of the clinical pharmacist in regulating the way parenteral preparations are handled, prepared and administered can prevent medication errors. This could reduce the risk of adverse reactions in patients receiving parenteral preparations. The clear regulation of the specific duties of each medical staff involved in the handling, preparation and administration of parenteral preparations has improved the interdisciplinary collaboration.

CLINICAL PHARMACIST INTERVENTION IN VANCOMYCIN INFUSION REACTION CASE MANAGEMENT

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Background: Vancomycin infusion reaction (VIR), previously known as red man syndrome, is a hypersensitivity reaction involving mast cells and basophils, likely to appear during parenteral administration of vancomycin. Its clinical symptoms range from flushing, erythematous rash, pruritus, and in some instances hypotension and angioedema.
Case presentation: A 31-year-old female diagnosed with MRSA proximal tibial osteitis received vancomycin postoperatively. At the end of the first 1-hour infusion she developed a rash on the face (more accentuated on the lower cheeks), neck and periumbilical area, also complaining of pruritus on the neck and arms. Her blood pressure was 130/70 mmHg, heart rate 85 bpm, 98% oxygen saturation on ambient air and normal renal function. The manifestation was interpreted by the orthopedic surgeon as allergy to vancomycin. The infusion was stopped, the patient received iv hydrocortisone and was switched on iv linezolid. After 10 days of iv linezolid treatment the blood cell count revealed thrombocytopenia and, based on the clinical pharmacist's interventions, switching back on iv vancomycin was considered. The patient resumed vancomycin treatment with a body weight calculated dose, accordingly diluted, and infused over 2 hours. She also received premedication with oral clorfeniramine, 1 hour before the vancomycin infusion. During the next 2 doses of vancomycin the patient still developed a mild erythema on the lower cheeks at the end of the infusion, without other clinical manifestations of VIR. Consequently, famotidine was added to the oral premedication, the patient being able to tolerate the 2-hour vancomycin infusions without any symptoms and complete 6 weeks of iv vancomycin treatment, with weekly monitoring of blood cell count and renal function at every 3-4 days.
Conclusion: As VIR is caused by non-IgE mediated mast cell degranulation with histamine release, antihistaminic medication targeting H1 and even H2 receptors is useful to reduce its manifestations, as well as slowing the infusion rate of vancomycin. It is important to correctly identify VIR and not label it as an "allergy", as the alternatives to vancomycin can be broader spectrum, more expensive and sometimes less well tolerated antibiotics.

ABSTRACTS OF ORAL COMMUNICATIONS

ARTERIAL STIFFNESS AND INSULIN RESISTANCE IN LONG COVID

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Background: The COVID-19 pandemic has led to widespread health complications and substantial economic losses globally. Among the key comorbidities that heighten the risk of severe COVID-19 and increase mortality are cardio-metabolic conditions, including type 1 and type 2 diabetes mellitus, atherosclerotic cardiovascular disease, chronic kidney disease, hypertension, heart failure, and obesity. The persistence of symptoms beyond the acute phase of infection is referred to as long-COVID-19 syndrome. The arterial stiffness is a reliable indicator of vascular system age and overall cardiovascular health. It serves as an integrated biomarker that reflects the cumulative harmful effects of genetic and environmental factors, along with the impact of established cardiovascular risk factors, on the arteries. Pulse wave velocity is essential in assessing vascular age, is noninvasive and reproductible and now is regarded as the gold standard in assessing arterial stiffness.
Objectives: This study aimed to evaluate the relationship between long-COVID-19 syndrome and the development of insulin resistance in previously non-diabetic individuals, as well as the impact on vascular stiffness, measured by pulse wave velocity.
Materials and methods: A prospective observational study was conducted on 143 non-diabetic patients who tested positive for SARS-CoV-2 via PCR between January 2020 and December 2022. Clinical and paraclinical data were collected at 0, 4, and 12 months post-infection. Blood glucose, insulin, and C-peptide levels were measured at baseline and at 2, 5, 10, and 30 minutes after the intravenous arginine stimulation test. Additionally, BMI, high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and pulse wave velocity were recorded. The results were then subjected to statistical analysis.
Results: Over one-third (30.07%) of the patients developed long-COVID-19 syndrome. Among those hospitalized with long-COVID-19,

75% developed diabetes within a year of their acute COVID-19 infection, highlighting long-COVID-19 as a major risk factor for metabolic disturbances, including diabetes. Additionally, nearly 62% of patients with a BMI over 30 kg/m² exhibited elevated blood glucose levels at the one-year mark, along with evidence of insulin resistance. A negative correlation was observed between long-COVID-19 and inflammatory markers, with hsCRP and ESR showing correlations of -0.40 and -0.38, respectively, compared to the acute phase of COVID-19. The inflammatory markers and PWV of subjects were higher among patients with high cardiovascular risk.
Conclusions: The link between long-COVID-19 and insulin resistance underscores the broad and diverse effects of SARS-CoV-2 infection. Managing long-COVID-19 requires a comprehensive approach that addresses not only respiratory issues but also metabolic health, which is essential for improving the quality of life for individuals experiencing this chronic condition. Vascular injury is a hallmark of acute COVID-19, playing a significant role in the development of thrombotic, myocardial, and pulmonary complications. Endothelial dysfunction, arterial stiffening, and inflammation are key characteristics of acute COVID-19. Endothelial-derived inflammatory biomarkers serve as predictors of disease severity and outcomes in hospitalized COVID-19 patients. Given the increasing number of long COVID patients experiencing persistent cardiovascular symptoms and exercise limitations, future research on vascular health in COVID-19 survivors is essential. Comprehensive physiological studies are a crucial first step toward developing strategies for cardiovascular risk assessment, treatment, and prevention for millions of individuals recovering from COVID-19. PWV has a high prognostic value since it may help identify individuals who are at a higher risk for future cardiovascular events and even for all-cause mortality.

SERUM LIPIDS AND PULSE WAVE ANALYSIS VARIABLES IN PATIENTS WITH NORMAL AND EARLY VASCULAR AGING

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Background: Pulse wave analysis and serum lipids are two important concepts in cardiovascular health assessment.
Objective: To assess the relationship between pulse wave analysis variables and serum lipids in normal and early vascular aging patients.
Material and methods: A total of 48 patients with normal vascular aging (NVA), aged 64±9 and 28 with early vascular aging (EVA), aged 61±12 years, with cardiovascular risk factors, were included in the study, matched for age, blood lipid levels, pulse wave velocity (PWV) and augmentation index (AI). They underwent pulse wave analysis using a Mobil-O-Graph. Serum lipids were assessed, including total cholesterol, LDL-cholesterol (LDL) and triglycerides (TG). Several other lipid biomarkers were calculated, such as Atherogenic Index of Plasma (AIP), Castelli Risk Index I (CRI) and Remnant Cholesterol (RC).
Results: PWV was: 9.15±1.24 vs. 9.56±1.78 (p=0.24) and AI: 22.89±16.59 vs. 27.82±15.3 (p=0.2). Significant higher blood pressure levels were obtained in the EVA compared to the NVA group. Significant correlations were obtained in the NVA group between AI and LDL (r=0.31, p=0.03), diastolic blood pressure (DBP) and TG (r=0.29, p=0.045), AIP (r=0.3, p=0.039), and CRI (r=0.29, p=0.049), and between pulse pressure (PP) and RC (r=-0.37, p=0.009). No significant correlations were obtained in the EVA group between pulse wave analysis variables and serum lipids.
Conclusion: Serum lipids impair pulse wave analysis variables only in patients with NVA, and not in patients with EVA.

PERSONALIZED MEDICINE FOR OSTEOSARCOMA

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Osteosarcoma is the most common primary malignant tumor of the bone and 20 % of the patients already have metastatic disease on admission. Osteosarcoma is typically treated with surgery and adjuvant chemotherapy. However, the clinical outcome is usually limited because of multiple side effects and development of multidrug resistance. New therapeutic strategies try to overcome these challenges in order to develop precision medicine and eventually improve patient survival. This presentation summarizes recent advances in personalized medicine for osteosarcoma including personal experience with gold nanoparticles conjugates on human osteosarcoma cells.

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MITOCHONDRIAL DYSFUNCTION IN DIABETES MELLITUS

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Diabetes mellitus (DM) is a metabolic disorder whose prevalence is ever on the rise. The burden of this disease and its numerous complications pose a great problem today from medical and social standpoints. Studying its pathophysiology continues to be addressed by the scientific community in order to identify novel therapeutic targets. Mitochondrial dysfunction has emerged in the past decades as a central pathomechanism in both pathogenesis and progression of DM. Mitochondrial dysfunction manifested as decreased ATP generation due to defective oxidative metabolism provides a link between obesity and the development of types 2 DM. Hypercaloric diets generate an excess of substrates which need to be metabolized at mitochondrial level. The excessive substrate metabolization will invariably end up in increased oxidative stress. The pancreatic β-cell is particularly susceptible to oxidative stress that will contribute to a decrease in insulin synthesis. Impairment of ATP generation further decreases insulin production in the remaining β-cells. Moreover, the insulin receptor is a tyrosine-kinase receptor and depends on cellular ATP for its function; a decreased ATP availability will translate in impaired insulin signaling, and ultimately to insulin resistance. Mitochondrial dysfunction and oxidative stress are the central pathomechanisms of the vast majority diabetes complications.
Targeting mitochondrial dysfunction for the treatment of diabetes is currently an active field of research. Lifestyle changes, such as diet and exercise, reduce oxidative stress and increase the number of mitochondria. Metformin is also reported to increase the mitochondrial biogenesis. The novel antidiabetics, such as the SGLT2 inhibitors increase the availability of ketones as energetic substrate, while the GLP-1 receptor agonists improve mitochondrial function and limit lipotoxicity. Several studies are ongoing with novel molecules, such as imeglimin, which targets mitochondrial bioenergetics besides enhancing insulin secretion, further emphasizing the importance of mitigating mitochondrial dysfunction in the therapy of diabetes.

A COMPLICATED STEMI CASE: CHALLENGES IN MANAGEMENT AND OUTCOMES

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ST-elevation myocardial infarction (STEMI) is a life-threatening condition caused by the occlusion of a coronary artery, leading to the death of myocardial tissue. It is a medical emergency that requires immediate intervention to restore blood flow to the affected area of the heart. While timely reperfusion therapy, such percutaneous coronary intervention (PCI), has significantly improved outcomes for STEMI patients, the condition can still be associated with various complications. In this case report, we present a STEMI patient with multiple complications, highlighting challenges faced in diagnosis, treatment, and management. The case emphasizes the importance of early recognition, appropriate interventions, and comprehensive care to address the complexities and potential complications associated with STEMI. The occurrence of ventricular septal rupture following acute myocardial infarction is a rare but severe complication associated with high mortality rates. Coagulation necrosis is the primary pathological observation in an infarcted septum. Ventricular septum rupture is primarily caused by the application of physical shear stress, particularly at the boundary between the infarcted region and the adjacent healthy myocardium. Surgical repair remains challenging, and delayed intervention may not significantly improve survival outcomes.

THE EFFECTIVENESS OF EOSINOPHIL-DEPLETING THERAPY WITH BENRALIZUMAB IN A PATIENT WITH MULTIPLE CHRONIC RESPIRATORY DISEASES, TOXOCARIASIS AND HYPEREOSINOPHILIC SYNDROME

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Background: Toxocariasis is a parasitic disease, rarely diagnosed, with manifestations often attributed to asthma, COPD, pneumonia. Helminth infections usually trigger a Th2 immune response in the host, with an increased number of specific and non-specific IgG antibodies, eosinophilia, eosinophil degranulation products, Th2 cytokines, including interleukins 4, 5, 10 and 13 and IFN-gamma. Eosinophilia lead to thickening of the basal membrane of the bronchial epithelium, with inflammation, fibrosis and increased risk of exacerbation.

Clinical case: A 55-year-old male, heavy smoker, with COPD under dual bronchodilator treatment. The patient presented in December 2023 in emergency, with resting dyspnea, wheezing, severe cough, asthenia, weight loss. Lung CT showed nodular lesions on bilateral upper lobs, bacteriological sputum tests for tuberculosis were negative, but genetic GenExpert test was positive. At that time, it was diagnosed as active tuberculosis, and standard treatment was initiated for six months. Additionally, the blood count revealed eosinophilia (2050/mmc), which steadily persist and increased (up to 14150/mmc). Subsequent tests were negative for HIV, fungal infection, intestinal parasites, lung cancer, vasculitis, collagenosis. Tryptase was slightly elevated, and molecular cytogenetic analysis for PDGFRA, PDGFRB, FIP1L1 was negative for blood cancer Total IgE levels were high (2268.1 IU/mL, normal ≤ 158) and, anti-Toxocara canis IgG antibodies were found with huge values (of 3892 index, normal value under 0.900), confirming the parasitic infestation. Three successive cures with Albendazole, Metronidazol and four cures with oral corticoids were performed in the next 6 months. Inhaled high-dose corticosteroid

was also associated. Although radiologically the evolution was good, the hypereosinophilic syndrome and symptoms persisted, with three moderate exacerbations COPD assigned. But surprisingly, spirometry revealed moderate obstructive dysfunction with great reversibility at Ventolin. Finaly, a severe asthma was also diagnosed, such that it was decided to add Benralizumab (anti-IL5Rα) at treatment. The response was very good, with the reduction of eosinophils (from 9410/mmc to 450/mmc in 48 hours) and clinical improvement.
Conclusions: In a rare overlap of respiratory diseases (asthma, COPD, tuberculosis, toxocarosis) associated with hypereosinophilic syndrom, Benralizumab proved to be safe and efficient, with rapid and sustained decrease of eosinophilia, improvement of clinical and respiratory function.

CYTOMEGALOVIRUS RETINITIS IN THE CONTEXT OF SARS-COV-2 INFECTION

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Background: Cytomegalovirus (CMV) retinitis is a serious opportunistic infection, particularly in individuals with compromised immune systems, such as those with untreated Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS). Coinfection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) may exacerbate immune dysregulation, leading to the reactivation of latent CMV. This case highlights the intersection of these viral infections in a severely immunocompromised patient.
Case Report: A 32-year-old male with a history of HIV/AIDS presented with rapidly worsening visual acuity and ocular pain. Ophthalmological examination revealed bilateral anterior uveitis and retinitis, with significant findings of hemorrhagic necrosis and retinal edema in the left eye. The patient tested positive for both CMV and SARS-CoV-2, with extremely low CD4 counts (<50 cells/μL). Despite mild COVID-19 symptoms, the patient developed severe CMV retinitis. He was treated with systemic Valganciclovir and topical corticosteroids. Although the inflammation in the right eye stabilized, the left eye progressed to complete vision loss (no light perception).CMV retinitis primarily affects patients with severe immunosuppression, particularly when CD4+ T-cell counts fall below 50 cells/μL. The connection between CMV and SARS-CoV-2 infections is likely driven by immune dysregulation. SARS-CoV-2 is known to induce a cytokine storm, with elevated interleukin-6 (IL-6) levels, further impairing immune function and potentially triggering CMV reactivation. This patient exhibited markedly elevated IL-6, suggesting a compounded inflammatory response. Additionally, both viruses manipulate the immune system by upregulating pathways like IL-6 and cyclooxygenase-2 (COX-2), leading to severe tissue damage. SARS-CoV-2 infection may accelerate the reactivation of latent CMV, further complicating the clinical course of CMV retinitis. Understanding these interactions is critical for managing co-infections in immunocompromised patients.
Conclusion: This case highlights the complex interaction between CMV and SARS-CoV-2 in immunosuppressed patients. The reactivation of CMV following SARS-CoV-2 infection can lead to rapid and severe retinal damage, emphasizing the need for early diagnosis and treatment in co-infected individuals. Further research is required to elucidate the exact mechanisms behind viral interactions and improve clinical outcomes for such vulnerable populations.

A COMPLEX CASE OF IMUNE-MEDIATED ENDOCRINE TOXICITY IN A PATIENT WITH NON-SMALL CELL LUNG CANCER

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Lung cancer is the leading cause of cancer related deaths worldwide, and recent years have led to significant improvements in terms of treatment and survivorship with the availability of new treatments like immunotherapy. However, these novel drugs come along with a plethora of side effects that have become a real challenge in patient management for clinicians.
Endocrine toxicities are among the most prevalent side effects of immunotherapy in the case of anti PD1/ PD-L1 (programmed cell death protein / programmed death-ligand 1) therapies with hypophysitis and thyroiditis being the most common compared to adrenal insufficiency or diabetes. Symptoms can range from sever fatigue, headache, dizziness, nausea/emesis, fevers, anorexia, visual field cuts, and palpitations.
We present a case of 55 year-old patient with stage IV B non-small cel lung cancer (adenocarcinoma) upon diagnosis, which was undergoing maintenance immunotherapy with Nivolumab after a completion of induction chemotherapy, and after progression of the disease on maintenance chemotherapy. The patient also underwent initial palliative radiotherapy for a 4th rib metastasis. Initial administration of the drug went smoothly until the 13th administration when the patient presented with sever altered state, intense fatigue, sleepiness, daytime drowsiness, loss of appetite, balance and memory disorders.
The suspicion of immune-mediated thyroiditis and hypophysitis was confirmed after obtaining a low serum cortisol level, elevated TSH, low fT4 levels and low levels of sodium were detected. Given the young age of the patient, early diagnosis elicited the administration of substitutive hormonal therapy together with corticoid administration so that the patient was able to continue their course of immunotherapy.
A good clinical assessment of this patient endorsed the first stage of establishing an early diagnosis, so that the toxicities can be managed and the course of immunotherapy rechallenged as soon as possible. Due to the fact that many symptoms of endocrine toxicity could be related to other acute illnesses or underlying malignancy, diagnosis remains challenging.

CANNULA-ASSOCIATED DEEP VEIN THROMBOSIS AFTER VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION IN CARDIAC SURGERY – CASE REPORT

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Extracorporeal membrane oxygenation (ECMO) is a form of prolonged mechanical cardiopulmonary supportive therapy implemented for the survival of patients with refractory cardiac and respiratory dysfunction. A common complication of extracorporeal membrane oxygenation (ECMO) is circuit and patient thrombosis, even when systemic anticoagulation is utilized. A 64-year-old patient was referred to our clinic with a diagnosis of acute cardiogenic pulmonary edema, severe mitral regurgitation and severe tricuspid regurgitation. The decision was made to stabilize the patient in preparation for surgical intervention. Mitral valve repair and tricuspid valve repair were performed via an anterolateral minithoracotomy. In the early postoperative period in the intensive care unit, the patient exhibited hemodynamic deterioration, with an increased need for inotropic and vasopressor support, becoming oligo-anuric. The transthoracic echocardiography did not reveal significant changes. Additionally, inadequate ventilation was observed, with increased pulmonary resistance and decreased O_2 saturation. The onset of ARDS was suspected. The decision was made to initiate veno-venous ECMO, resulting in a favorable outcome. At 24 hours after ECMO removal, marked swelling of the right lower limb was observed. Doppler echocardiography and venous angioCT were performed, confirming the diagnosis of deep vein thrombosis. The decision was made to administer continuous infusion heparin therapy and monitor aPTT, resulting in a favorable outcome. It is well known that cannula-related venous thrombosis after VV-ECMO decannulation has a high incidence. This case illustrates the challenges encountered in cardiac surgery, as well as the value of early screening and prompt decision-making, which can have a big impact on how a case turns out.

BENEFITS OF EMPAGLIFLOZIN IN CARDIOVASCULAR PREVENTION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION IN ELDERLY - A CASE REPORT

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Background: Heart failure (HF) is a syndrome associated with poor prognosis and increasing prevalence among the aged population; in particular, it has been estimated that the risk for HF with preserved ejection fraction (HFpEF) will increase in men. SGLT2 inhibitors are the novel class of antidiabetics, with pleiotropic, systemic and local cardioprotective "off-target effects", such as improvement of cardiac metabolism, reduction of cardiac fibrosis/remodelling and enhancement of ventricular function.
Clinical case: An 84-year-old patient, presented in May 2024 with astheniform syndrome, marked fatigability and inspiratory dyspnea on medium-intensity efforts. Blood pressure was 150/85 mmHg and heart rate 70 beats/minute. Risk of developing a cardiovascular event was assessed by the *Smart risk* score and was 71.8%. The resting electrocardiogram showed 2 isolated unifocal ventricular extrasystoles. Laboratory analyses showed: dyslipidemia, elevated NT-pro-BNP values (461.9 pg/mL) and an elevated serum creatinine level with an eGFR = 51 mL/min/1.73 $\sqrt{m^2}$. Twenty-four hours Holter ECG monitoring recorded a sinus rhythm with episodes of asymptomatic junctional rhythm and isolated, multifocal ventricular extrasystoles. Transthoracic echocardiography revealed left ventricle hypertrophy, particularly of the interventricular septum; left ventricle ejection fraction was 51% allowing the diagnostic of HF with preserved ejection fraction (HFpEF), and the global longitudinal strain was -15.2%, associating areas of decreased contractility in the anterior and inferior myocardium. Three-month therapy with SGLT2 inhibitors (empagliflozin) added to the standard treatment with a loop diuretic (furosemide), a calcium channel blocker (amlodipine), statin (atorvastatin) and nitroglycerin, resulted in a reduction of the cardiovascular risk with 34.7%.
Conclusion: SGLT2 are useful in decreasing the cardiovascular risk in non-diabetic elderly patients with HFpEF, besides their well-recognized benefits regarding the reduction in the number of hospitalizations in patients diagnosed with HF.

NOVEL BIOMARKERS IN LUNG CANCER. THE INOLUNG STUDY

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Background. The connection between inflammation and carcinogenesis supports that the determination of inflammatory biomarkers, along with the lymphocyte/neutrophil ratio (NLR) or platelet/lymphocyte (PLR), may represent new directions for estimating the evolution and prognosis of neoplastic disease.
Objectives. The objective of this study was to highlight the correlation of these parameters with the diagnosis of lung cancer and histopathological subtypes.
Material and method. A retrospective study of patients with lung cancer was conducted at the Clinical County Hospital Mureș, Târgu Mureș, from February 2023 to December 2023. The parameters analyzed included: histopathological type (NSCLC - squamous cell carcinoma or adenocarcinoma; SCLC), molecular mutations (EGFR, ALK, PD-L1), parameters from the complete blood count (hemoglobin level, leukocyte count, platelet count, NLR, PLR, lymphocyte count), inflammatory parameters (C-reactive protein), and associated comorbidities. Patients diagnosed with endobronchial biopsy-confimated lung cancer in the mentioned period were included in the lung cancer group. The control group consisted of patients admitted to the Pneumology Clinic in February-December 2023, with non-neoplastic diagnosis.
Results and Conclusions. After the inclusion and exclusion criteria were applied, 380 patients were included in our study: 115 patients in the cancer group and 265 patients in the control group. The NRL and PLR values are significantly higher ($p<0.001$) in cancer patients compared to the control group. The correlation of NLR and PLR with histopathological type was also analyzed, but they did not meet the statistical significance threshold ($p= 0.580$, respectively $p=0.448$). The CRP value was analyzed in the two groups of patients and the PCR correlation with histopathology type was followed. The PCR value does not correlate with histopathological type (p=0,2422) or EGFR mutation presence(p=0,6791). PCR was significantly lower in patients with NSCLC and PD-L1 mutation compared to those without PD-L1 mutation.
In addition to other biometric, clinical, imaging, serological data, the NLR and PLR values constitute new predictive biomarkers of disease progression in patients with lung cancer, especially those with NSCLC.

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CERVICAL DYSPLASIA- MANAGEMENT OPTIONS

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Background: Premalignant cervical lesions are often diagnosed in clinical settings. The management may vary due to a lot of factors. We present the experience of the Emergency Clinical County Hospital of Arad for different types of management.
Objective: This study aims to present a series of clinical cases of cervical dysplasia managed at Arad Clinic, illustrating the diagnostic and treatment process, and highlighting patient outcomes through regular follow-ups.
Materials and methods: We retrospectively analyzed several clinical cases of cervical dysplasia diagnosed at Arad Clinic from January 2020 to December 2022. The diagnostic workflow included initial Pap smears, followed by colposcopy, CINtec testing, and biopsies. Treatment involved LEEP procedures, and outcomes were assessed through margin status and regular follow-ups.
Clinical Cases: The cases included a range of cervical dysplasia severities, from mild to severe. Patients presented with abnormal Pap smears indicative of various degrees of squamous intraepithelial lesions. Diagnostic steps consistently involved colposcopy and CINtec testing, with biopsies confirming the extent of dysplasia. Treatment approaches varied based on the severity of the dysplasia. Mild dysplasia cases were managed conservatively with regular observation and follow-up Pap smears. Moderate and severe dysplasia cases often required LEEP procedures, ensuring margin-free resections.
Conclusion: This series of clinical cases demonstrates the effective management of cervical dysplasia at Arad Clinic, from initial diagnosis to treatment and follow-up. LEEP procedures with margin-free resections have shown excellent outcomes. Regular follow-ups are essential to monitor for recurrence and ensure long-term patient health.

LOW BACK PAIN: RISK FACTORS FOR CHRONICITY

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Background. Chronic low back pain (cLBP) can affect individuals of all genders, ethnicities, and age groups, certain groups are more susceptible than others, indicating that some underlying risk factors are associated with the higher occurrence rate.
Objectives. The present research aimed to analyze the transition from acute to chronic low back pain by identifying and discussing the key risk factors that determine chronicity.
Materials and methods. The study involves a cohort of 63 patients with lumbar pain. An initial evaluation was performed, which included a thorough history, clinical examination, and paraclinical investigations, so that a diagnosis could be established as accurately as possible. Six months after the initial assessment, the patients were re-evaluated, especially to highlight potential risk factors that determined the chronicity of the pain.
Results & Conclusion. The analysis of specific risk factors in our study was as follows: The findings are showing that women are more predisposed to experience cLBP than men; We notice a trend suggesting a direct relationship between aging and cLBP increased incidence, particularly among patients in the 60–70 age group, before declining slightly in those over 70; Obesity emerged as a strong risk factor for cLBP; Smoking had no discernible effect on the persistence of back pain based on the statistics; The findings demonstrate a strong inverse relationship between physical-activity frequency and cLBP; Patients with insidious pain onset showed a higher incidence of cLBP compared to those with sudden onset; it appears to be an indirect association between morning sickness and cLBP; A direct relationship was found between nocturnal pain and cLBP; Statistically, pain radiation had no discernible effect on back pain chronicity; Our study concludes that lower back pain is a multifactorial phenomenon, with several key risk factors influencing the progression from acute to chronic pain persisting beyond three months.

YOUNG INVESTIGATOR AWARD COMPETITION (8 abstracts selected)

CORRELATIONS BETWEEN GUT MICROBIOTA, OXIDATIVE STRESS AND INFLAMMATION IN A GROUP OF PATIENTS WITH PSORIASIS

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Background: Psoriasis is one of the most common dermatological diseases, involving numerous genetic and environmental factors. Even though significant efforts and progress have been made in understanding its pathogenesis, numerous key cytokines being identified, the impact of other factors, such as oxidative stress (OS) or modulation of the skin and gut microbiota, seems to be gaining increasing interest.
Objectives: We introduce the first prospective observational study carried out in Romania that aims to evaluate the interplay between composition of gut microbiota - OS - hematological and biochemical parameters in a group of 10 treatment-naïve patients with moderate-to-severe psoriasis, compared to a control group of 10 matched healthy volunteers.
Materials & Methods: The study was conducted over a period of approximately 7 months, with the approval of the Ethics Committee. The gut microbiota composition was evaluated through a quantitative PCR examination of stool samples, for the six main bacterial groups: *Lactobacillus, Firmicutes, Bacteroides, Bifidobacterium, Enterobacteriaceae, and Actinobacteria*. The oxidative status was assesed using spectrophotometric tests (Free Oxygen Radical Test – FORT, respectively Free Oxygen Radical Defense) from capillary blood. The hematologic, inflammatory, and biochemical parameters were evaluated from venous peripheric blood.
Results: The study group presented a mean age of 47.9 years (+/-12.59), 50% females, while the control group had a mean age of 40 years (+/-14.73), 25% females. Lower levels of *Firmicutes* and *Enterobacteriaceae* were observed in the psoriasis group compared with control group. A positive correlation was identified between FORT levels and *Lactobacillus* (p=0.034, r=0.669). A negative correlation was observed between *Firmicutes* levels and DLQI scores (p=0.02, r=-0.685), but also between *Firmicutes* and inflammatory markers (fibrinogen and C-reactive protein). The level of *Bacteroides* was negative correlated with systemic inflammatory index (p=0.05, r=-0.617) and neutrophils-to-lymphocytes ratio (p=0.02, r=-0.709).
In conclusion, the identified correlations may represent a starting point for explaining how changes in the gut microbiota and oxidative stress may influence the development and evolution of psoriasis as a systemic disease, and hence its cardio-metabolic complications.

ASSESSMENT OF IMEGLIMIN EFFECTS ON PLATELET MITOCHONDRIAL RESPIRATION AND OXIDATIVE STRESS: A PILOT STUDY IN DIABETIC PATIENTS

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Background: Type 2 diabetes mellitus (T2DM) is the most severe chronic metabolic disorder with an alarming rise in global incidence and prevalence. Imeglimin is a novel antidiabetic compound, reported to increase insulin sensitivity, improve mitochondrial function and mitigate oxidative stress. Assessment of mitochondrial respiration in platelets serves as a reliable indicator of the body's bioenergetic status.
Objectives: This pilot study performed in patients with T2DM was aimed at investigating the concentration-dependent effect of imeglimin on mitochondrial respiration and oxidative stress in in peripheral platelets isolated from plasma sampled from patients diagnosed with T2DM.
Material and Methods: Peripheral venous blood was sampled from 15 patients diagnosed with T2DM. Platelet isolation was performed according to a standardized protocol. Mitochondrial respiration was measured by means of high resolution respirometry at 37°C using the oxygraph-2k. Platelets isolated from each patient were incubated with increasing concentrations of imeglimin (1500 µg/mL, 3000 µg/mL, 6000 µg/mL). Platelets were permeabilized with digitonin with the measurement of the following respiratory parameters: maximal active respiration (OXPHOS capacity), non-phosphorylating respiration (LEAK), maximal uncoupled respiration (ET capacity), all corrected for the residual oxygen consumption (ROX). Samples were collected from the oxygraph and oxidative stress was assessed via the Ferrous OXidation – xylenol orange (FOX) assay.
Results: Respiratory parameters OXPHOS capacity, LEAK, ET capacity)were largely unaffected by the presence of imeglimin regardless of concentration. Imeglimim significantly decreased ROX in a concentration-dependent manner, i.e. 3,2±0,1 ($p<0.05$) for 3000 µg/mL imeglimin and 2,9±0,2 ($p<0.01$) for 6000 µg/mL, respectively. Imeglimin also mitigated hydrogen peroxide production (FOX assay), i.e. 3,5±0,1 nM H_2O_2/mL ($p<0.0001$) and 3,2±0,1 nM H_2O_2/mL ($p<0.0001$) for the above mentioned concentrations.
Conclusion: In patients diagnosed with type 2 diabetes, imeglimin did not interfere with platelet mitochondrial respiration and elicited a concentration-dependent decrease in the oxidative stress.

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MITOCHONDRIAL PLATELET BIOENERGETIC PROFILE IN CHRONIC KIDNEY DISEASE PATIENTS WITH AND WITHOUT DIABETES

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Background: Mitochondrial respiration impairment plays a significant role in the onset and progression of chronic kidney disease (CKD), particularly in diabetic kidney disease (DKD). To date, several reports show that ATP production by mitochondria and utilization by the PT are coordinated by the metabolic demands of the kidney in the course of DKD.
Objectives: The present study was aimed at characterizing mitochondrial respiratory (dys)function of circulating platelets in the early stages of DKD in type 2 DM patients and non-diabetic CKD patients, respectively.
Materials and methods: Mitochondrial respiration of platelets isolated from peripheral blood was assessed by high-resolution respirometry in patients with DKD and CKD and compared to healthy individuals. A total number of 30 DKD patients (divided by the urinary albumin/creatinine ratio in 3 subgroupsș 20 normoalbuminuric, 10 microalbuminuric and 10 macroalbuminuric), 29 CKD patients, and 30 healthy subjects were evaluated.
Results: In CKD patients and DKD patients with microalbuminuria and macroalbuminuria all respiratory parameters (basal, coupled, and maximal uncoupled respiration) were significantly lower as compared to the control healthy subjects. Although a decreasing trend in mitochondrial respiration was observed in the DKD subgroup with normoalbuminuria, it did not reach statistical significance.
Conclusion: In peripheral platelets impairment of mitochondrial respiration is observed from the early stages of DKD. Further studies in larger study groups are required to confirm whether assessment of platelet respiration might have potential clinical applicability as biomarker of kidney mitochondrial dysfunction and/or prognostic tool in CKD and DKD.

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THE INFLUENCE OF ADIPOSITY ON PERIPHERAL BLOOD IMMUNE CELLS IN YOUNG ADULTS

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Background: The pathophysiology of obesity is still under investigation, as it plays a significant role in the development of various chronic diseases. This study aims to evaluate the effect of adipose tissue on the distribution of peripheral blood immune cells in the complete blood count (CBC) of healthy young adults.
Material and method: This cross-sectional study enrolled 128 apparently healthy subjects aged 20-35 years, divided into three groups: normal weight (NW), overweight (OW), and obese (OB), according to body mass index (BMI). Health status was assessed through a questionnaire, and subjects reporting acute or chronic inflammatory diseases were excluded. After blood collection, the CBC was analyzed using fluorescent flow cytometry with a semiconductor laser and hydrodynamic focusing methods. Each leukocyte population was expressed as a percentage (%) from total leukocytes and absolute count (#, $x10^3/\mu L$).
Results: Significant increases were observed in the OW and OB groups compared to the NW group for white blood cell count (WBC: 5.92-NW, 6.18-OW, 7.07-OB, $p < 0.0001$), neutrophils # (Ne#: 3.11-NW, 3.14-OW, 4.04-OB, $p = 0.0017$), Ne% (53.30-NW, 51.40-OW, 56.75-OB, $p = 0.0254$), and basophils # (Ba#: 0.03-NW, 0.04-OW and OB, $p = 0.0141$). Additionally, significant differences, though without a consistent linear increase, were found for Ne% (53.30-NW, 51.40-OW, 56.75-OB, $p = 0.0254$), eosinophils # (Eo#: 0.10-NW, 0.14-OW, 0.12-OB, $p = 0.0219$), and Ba% (0.50-NW, 0.70-OW, 0.50-OB, $p = 0.0286$). A similar trend, but without significant differences, was observed for lymphocytes # (Ly#: 2.11-NW, 2.15-OW, 2.33-OB, $p = 0.2025$) and monocytes # (Mo#: 0.53-NW, 0.54-OW, 0.55-OB, $p = 0.4585$). In contrast, significant differences with an inverse distribution were found for monocytes% (Mo%: 8.6-NW, 8.00-OW, 7.70-OB, $p = 0.0317$).
Conclusions: Obesity significantly alters the distribution of immune cells in the CBC of healthy young adults, suggesting that excess adipose tissue may influence immune cell dynamics.

PHYTOCHEMICAL COMPOSITION ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY OF ARTEMISIA DRACUNCULUS AND ARTEMISIA ABROTANUM

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Background: Medicinal plants are relevant sources with anti-inflammatory and antioxidant activities for many therapeutic purposes. In the last few years, Artemisia species have attracted research attention due to the 2015 Nobel Prize award in medicine for the discovery of artemisinin in Artemisia annua, a sesquiterpenoid lactone with an antimalarial effect. The Artemisia genus of the Asteraceae family includes over 500 species worldwide that are used in traditional and contemporary medicine.
Objectives: This study aimed to investigate the antioxidant and anti-inflammatory activities mechanism of Artemisia dracunculus (A. dracunculus) and Artemisia abrotanum (A. abrotanum) ethanol extracts in acute rat inflammation induced in Wistar male rats with turpentine oil.
Materials and methods: The characterization of the polyphenolic compounds in the extracts was conducted using UV–Vis and Fourier-transform infrared spectroscopy and high-performance liquid chromatography coupled with mass spectrometry techniques. The antioxidant activity of the extracts was evaluated in vitro by DPPH, FRAP, H_2O_2, and NO scavenging tests and in vivo by measuring the total oxidative status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI), 8-hydroxy-deoxyguanosine (8-Oxo-dG), advanced oxidation protein products (AOPP), malondialdehyde (MDA), nitric oxide (NO), 3-nitrotyrosine (3NT), and total thiols (SH). Inflammation was evaluated by measuring nuclear factor-kB-p65 (NfkB-p65) and NLRP3 inflammasome activation with IL-1β, IL-18, and gasdermin D. Liver and renal toxicity was determined following transaminases (ALT and AST), creatinine, and urea.
Results and conclusions: The experimental results indicated that A. dracunculus and A. abrotanum ethanol extracts have moderate in vitro antioxidant activity and had in vivo antioxidant activity and an anti-inflammatory effect by NfkB-p65, IL-1b, IL-18, and gasdermin D serum level reduction. The antioxidant activity correlated with the chemical composition of the extracts. These results bring evidence-based use of A. dracunculus and A. abrotanum in traditional and contemporary medicine.

TIME, SPACE, AND ASTHMA: AN INTERDISCIPLINARY STUDY IN TIMIȘ COUNTY

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Background: Asthma, a chronic respiratory disease, significantly impacts public health. Objectives: This study aimed to explore the temporal, spatial, and socio-economic factors associated with asthma prevalence in Timiș County, Romania, over an 11-year period (2013-2023).
Materials and methods: A retrospective analysis was conducted on 13,695 patient records that presented asthma codes as either primary or secondary diagnosis. Interdisciplinary research methods, including epidemiological analysis, seasonal analysis, and spatial modelling, were employed to investigate the influence of various factors on asthma incidence and severity.
Results & Conclusion: Results revealed notable gender disparities in asthma prevalence, with the expected higher incidence among females. However, the COVID-19 pandemic highlighted significant changes to this pattern. Additionally, the study identified a strong correlation between asthma exacerbations and specific patterns. Seasonal analysis provided valuable insights into socio-economic determinants of asthma, revealing disparities between female and male patterns that influence disease course. Furthermore, the study investigated the potential impact of Artemisia vulgaris, a common allergen in the region, using seasonal analysis to rank its influence. Geo-spatial and temporal clustering with or without using Haversine distance and temporal and space weights can provide a more nuanced understanding of patterns related to urban and rural areas, as well as pollution. To evaluate the effectiveness of clustering algorithms and parameter settings, a silhouette score can be employed. These metric measures how similar each data point is to its own cluster compared to other clusters, providing a quantitative assessment of cluster cohesion and separation. By optimizing the silhouette score through varying temporal and space weights, researchers can identify the optimal clustering configuration that best captures the underlying patterns in wind direction and pollution data. While this interdisciplinary approach has yielded significant findings, challenges remain in implementing these methodologies on a larger scale due to data limitations and resource constraints. Future research should focus on expanding data collection efforts and developing more proficient methods for interdisciplinary analysis to inform effective asthma prevention and management strategies.

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ASSESMENT OF PHYTOCHEMICAL CONTENT AND ANTIDIABETIC, ANTIOXIDANT, AND ANTI-INFLAMMATORY ACTIVITIES OF GYPSOPHILA PANICULATA IN RAT STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

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Background: Diabetes mellitus is a complex metabolic disease with a multifactorial etiology, significantly impacting global morbidity and mortality. Previous experimental and clinical studies have established the significant contribution of hyperglycemia-induced oxidative stress and the overactivation of inflammatory pathways in Diabetes Mellitus (DM). Extensive screening for antidiabetic agents has established natural products as one of the major potential sources of drug discovery.
Objectives: The present study aimed to investigate the effects of Gypsophila paniculata ethanol extract (GPEE) on oxidative stress, inflammation, and metabolic markers in a rat model of Streptozotocin-induced diabetes.
Materials and methods: Phytochemical analysis using high-performance liquid chromatography coupled with mass spectrometry was performed to measure the total phenolic and flavonoid contents. In vitro antioxidant activity was evaluated through DPPH, FRAP, H2O2, and NO scavenging tests, and the in vivo effects of GPEE were assessed in Streptozotocin-induced DM rats. Treatments with GPEE, metformin, and trolox were administrated by gavage for 10 days. On day 11, blood was harvested, and serum oxidative stress (total oxidative status, oxidative stress index, malondialdehyde, advanced oxidation protein products, 8-hydroxydeoxyguanosine, nitric oxide, 3-nitrotyrosine, advanced glycation end-products, total antioxidant reactivity, total thiols), inflammatory (IL-1β, NF-κB, IL-18, Gasdermin D), metabolic (fasting glucose, total cholesterol, triglycerides, triglyceride–glucose index), and liver injury (AST, ALT, AST:ALT ratio) markers were measured.
Results: GPEE was found to have a significant content of polyphenols and a moderate in vitro antioxidant effect. In vivo, GPEE lowered oxidants and increased antioxidants, decreased inflammatory markers and blood glucose, and improved lipid profiles and transaminases in a dose-dependent manner, with higher doses having a better effect, comparable to those of metformin and trolox.
In conclusion, the presented experimental results suggested that the GPEE may serve as an adjuvant pathogenetic therapy in T2DM due to its hypoglycemic, lipid-lowering, hepatoprotective, antioxidant and anti-inflammatory effects.

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ANTIOXIDANT DEFENSES, OXIDATIVE STRESS RESPONSES, AND APOPTOSIS MODULATION IN SPONTANEOUS ABORTION: AN IMMUNOHISTOCHEMISTRY ANALYSIS OF FIRST-TRIMESTER CHORIONIC VILLI

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Background: Oxidative stress (OS) and apoptosis are critical factors in placental development and function. Their interplay influences trophoblast proliferation, differentiation, and invasion, as well as vascular development. An imbalance between these processes can lead to pregnancy-related disorders such as preeclampsia, intrauterine growth restriction, and even spontaneous abortion.
Objectives: Our study seeks to elucidate the associations between preventive antioxidant/ protective OS response factors—glutathione (GSH), MutT Homolog 1 (MTH1), and apoptotic regulation modulators—tumor protein p53 and B-cell lymphoma (Bcl-2) transcripts, in the context of spontaneous abortion (30 samples) versus elective termination of pregnancy (20 samples), using immunohistochemistry (IHC) to determine their proteomic expression in chorionic villi within abortive fetal placenta tissue samples.
Materials and methods: We analyzed 50 patients (30 spontaneous abortions with no obvious medical cause and 20 patients with abortion on demand) admitted in our department that had a termination of pregnancy. Histopathological analysis of the fetal tissue and placenta was performed and antioxidant and apoptotic factors were the evaluated for spontaneous abortion compared with abortion on request.
Results: A comparative statistical analyses revealed that both OS response factors, GSH and MTH1, were significantly under-expressed in spontaneous abortion cases as compared to elective. Conversely, for apoptotic regulators, p53 expression was significantly higher in spontaneous abortion cases, whereas Bcl-2 expression was significantly lower in spontaneous abortion cases. These findings suggest that a strong pro-apoptotic signal is prevalent within spontaneous abortion samples, alongside reduced anti-apoptotic protection, depleted antioxidant defenses and compromised oxidative DNA damage prevention/repair, as compared to elective abortion controls. Our hypothesis that OS and apoptosis are closely linked processes contributing to placental dysfunction and spontaneous abortion was thus seemingly corroborated. Our results further highlight the importance of maintaining redox homeostasis and apoptotic regulation for a successful pregnancy. Understanding the mechanisms underlying this interplay is essential for developing potential therapies to manage OS, promote placentation, and avoid unwanted apoptosis, ultimately improving pregnancy outcomes.
Conclusion: Antioxidant supplementation, modulation of p53 activity, and the enhancement of DNA repair mechanisms may represent potential approaches to mitigate OS and apoptosis in the placenta. Further research is needed to explore these strategies and their efficacy in preventing spontaneous abortion.

ABSTRACTS OF THE POSTERS

CLINICAL ASPECTS AND THERAPEUTIC MANAGEMENT IN ACUTE PANCREATITIS IN DOGS IN A VETERINARY CLINIC

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Pancreatitis is an inflammatory condition affecting the pancreas and is the most common disease of the exocrine pancreas in dogs. Acute pancreatitis is characterized by the rapid onset of inflammation, which can range from mild to severe, potentially leading to fatal outcomes. The causes are often varied and unclear, while the symptoms are diverse but non-specific. This makes accurate diagnosis and effective treatment of pancreatitis a significant challenge for veterinarians. The study was conducted on 10 dogs of different breeds, aged between 7 months and 10 years. The patients were presented at the veterinary clinic with apathy and gastrointestinal symptoms: anorexia/lack of appetite, vomiting, and/or diarrhea. In addition to each patient's history, anamnesis showed that six of them had been fed human food rich in sugars, carbohydrates, and additives. Clinical examination revealed various degrees of dehydration, abdominal sensitivity, and changes in body temperature. SNAP-cPL rapid test (ELISA assay for canine pancreas-specific lipase) and biochemical exams (VetTest Chemistry Analyzer) were performed. All the dogs tested positive for SNAP-cPL and showed elevated serum levels of lipase and urea, along with higher creatinine levels. Alterations in serum glucose, alkaline phosphatase, GGT, pancreatic amylase, globulin, calcium, and phosphorus levels were also noted. All 10 dogs were diagnosed with pancreatitis, and six of them were also found to have related conditions such as kidney failure, liver failure, and diabetes. The treatment consisted of administering symptomatic medication (antiemetics, analgesics, anti-inflammatory, antispasmodics, gastric protectants, and fluid resuscitation) and correcting nutritional intake with dietary food for all patients. After treatment initiation, it was observed that dogs under 6 years of age showed rapid improvement (within 5-10 days), and their evolution was better compared to the older ones, whose symptoms partially subsided and required longer treatment. In conclusion, although acute pancreatitis is a severe condition, it can be controlled with appropriate medication and diet. It is recommended that owners avoid human food in dogs' diets, as it is a significant risk factor in acute pancreatitis.

EVALUATION OF EMPAGLIFLOZIN-MONOAMINE OXIDASE INTERACTION IN A HFmrEF MODEL INDUCED IN WILD-TYPE AND SGLT2 K.O. MICE

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Background: The antidiabetic drugs known as the sodium-glucose-cotransporter 2 inhibitors (SGLT2i) protect the cardiovascular system through pleiotropic actions. In previous studies performed in human mammary arteries and atrial tissue, we have systematically shown that SGLT2i reduced the expression of monoamine oxidase (MAO) isoforms, MAO-A and MAO-B, and oxidative stress. While SGLT2i have shown cardiovascular benefits, it remains unclear if these effects on MAO-A and MAO-B expression extend to heart failure with mildly reduced ejection fraction (HFmrEF). Additionally, the impact of SGLT2 gene knockout on MAO regulation in HF is unknown.
Objectives: This study aimed to evaluate the protein and mRNA levels of MAO-A and MAO-B in mice with HFmrEF and to determine whether the administration of Empagliflozin (EMPA) or the knock-out of SGLT2 influences these levels.
Materials and Methods; A *TSlc5a2-* deficient (encoding SGLT2) mouse model with HFmrEF induced by transverse aortic constriction (TAC) plus the placement of DOCA pellet was employed. Six experimental groups were established, classified according to the treatment administered (chow with or without EMPA), the presence of heart failure, and the mouse genotype (wild type or knockout). Western blot analysis was conducted to evaluate MAO-A and MAO-B protein levels in the kidney and left ventricle, while PCR was utilized to assess mRNA levels in kidney and aorta samples. Additionally, RNA sequencing was performed for gene expression analysis of MAO-A and MAO-B in heart ventricular tissue.
Results: In mice with HFmrEF, chronic EMPA treatment did not modify MAO-A or MAO-B protein expression in the kidneys and even showed a tendency to increase them. MAO-A protein levels were significantly reduced in the left ventricle of HF groups, independent of EMPA administration. In the aorta, EMPA administration had no effect on MAO gene expression in heart failure. EMPA treatment lowered MAO-A RNA in the SGLT2 KO hearts ($p=0.02$), with a trend ($p=0.08$) for lowering MAO-A RNA also in WT hearts. No effects of EMPA on ventricular MAO-B RNA were observed.
Conclusions: In the murine model of HFmrEF MAO-A protein levels in the left ventricle of failing hearts were reduced, whereas EMPA decreased MAO-A RNA levels in failing SGLT2 knockout hearts, with a similar trend in failing wild-type hearts. Addressing the relationship between MAO and SGLT2 inhibitors is essential for deciphering the "off-target" pleiotropic effects that mediate cardiovascular protection.

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MODULATION OF THE BIOENERGETIC PROFILE OF A HUMAN CELL LINE BY ANTICANCER PHYTOCHEMICALS

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Background: Mitochondrial dysfunction is a central pathophysiological mechanism in non-communicable diseases, including cancer. Phytochemicals with anti-neoplastic effects have been reported to attenuate chemoresistance and/or exert chemoprotective effects. Eugenol, commonly found in clove oil, exerts beneficial effects by reducing neoplastic proliferation and anti-inflammatory action. Bromelain, derived from the pineapple stem, also presents an important anti-cancer effect.
Objectives: The study was purported to assess the time and concentration-dependent effects of two phytochemicals on the bioenergetic profile (mitochondrial respiration and anaerobic glycolysis) in human keratinocytes (HaCaT cell line) using the extracellular flux analyser (Seahorse Agilent XF24e).
Material and Methods: The extracellular flux analyser allows the simultaneous assessment of oxygen consumption rate (OCR), a parameter of mitochondrial respiration and the extracellular acidification rate (ECAR) as a marker for anaerobic glycolysis. The time-dependent effects of eugenol (50 µM) on mitochondrial bioenergetics were measured in HaCaT cells at 24, 48 and 72 hours. The concentration-dependent effects of bromelain on mitochondrial bioenergetics were assessed at 24 hours for 0,25 µg/mL, 2,5 µg/mL and 25 µg/mL, respectively.
Results & Conclusions: Incubation with eugenol at 48-hours and mainly at 72-hours (but not at 24 hours) resulted in significant decreases in both oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). Bromelain at 24 h caused a steady increase of the OCR (the highest dose elicited the highest OCR) and a corresponding decrease in ECAR, albeit no statistical significance was found in these preliminary experiments. Further research will elucidate the time and dose-dependent effects of these phytochemicals in both normal and malignant cell lines in order to exploit their therapeutic potential.

POST-COVID SYNDROME: LONG-LASTING IMMUNOLOGICAL ALTERATIONS DRIVE AUTOIMMUNE RESPONSES IN CARDIAC TISSUE

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Background: Although many years have passed since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, its negative impact recurs with patients suffering from infection-associated complications and other pathological disorders. In the aspect of long-term effects, it was essential to distinguish an entity that is able to represent all of the infection-linked complications: the post-COVID syndrome. The broad spectrum of these complications has driven the development of a multidisciplinary approach that successfully revealed organ-specific components, but the underlying pathophysiology regarding post-COVID is still unclear.
Objectives: Our study focuses on identifying possible immunological mechanisms in the cardiac tissue that might contribute to the development of post-COVID syndrome.
Materials and methods: 148 COVID-positive sera collected from ambulance tests were analyzed by Western blot technique. After SDS-PAGE electrophoresis and blotting to nitrocellulose membranes were performed on cardiac tissues, we incubated the membranes in patients' COVID-positive sera. Then, both human IgG and IgM in 1:13000 dilution were added. Finally, chemiluminescence was used for detection of suspected autoantibodies.
Results: Within 148 analyzed samples, we detected IgG-type autoantibodies in 33 samples (22%) and, IgM-type autoantibodies in 53 samples (36%). A significant part of the positive samples were present with multiple autoantibodies. To some extent, it was possible to identify certain molecular patterns in connection with the assumed molecular weight of the autoantibodies.
Conclusion: Our results emphasize that the remarkable fraction of the samples containing autoantibodies might contribute to the pathophysiology of post-COVID syndrome, highlighting the fact that it may be associated with autoimmune responses. On the other hand, large number of identified autoantibodies might suggest that post-COVID syndrome can be related to impaired isotype-switching or other immunological dysfunctions, giving rise to theories including hijacking of the immune system or modifying proteins to act as autoantigens.

Funding: University of Debrecen, Department of Cardiology, Division of Clinical Physiology, National Academy of Scientist Education.

A HIDDEN AFTERMATH: AUTOIMMUNITY'S POTENTIAL ROLE IN POST-COVID SYNDROME REGARDING LUNG TISSUE

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Background: As the COVID-19 pandemic fades, another crisis quietly unfolds—post-COVID syndrome. Though the virus may have loosened its grip, millions are still wrestling with persistent symptoms that remain elusive to both explanation and cure, including fatigue, brain fog, and chronic pain.
Objectives: We explored a novel pathomechanism to explain these symptoms: that the virus has triggered an autoimmune process, contributing to the development of post-COVID syndrome.
Materials and methods: We used a Western-blot-based approach to detect autoantibodies in patients' sera recognizing human proteins in lung. It involves several steps: first, proteins in the homogenized human tissue are separated based on size using gel electrophoresis. They are then transferred onto a nitrocellulose membrane. The membrane is incubated with human serum (1:1,000 dilution, potentially containing the antibodies specific to the autoantigen). Finally, a secondary antibody, linked to an enzyme, reveals the presence of the autoantigen-antibody interaction.
Results: Post-COVID serum samples were collected (n=140) at regular visits from patients complaining about a variety of symptoms (considered to be post-COVID syndrome). Out of the 140 patients, 17 of them showed IgG autoantibodies (12,4%), while 19 of them showed IgM autoantibodies (13,6%). Both IgG and IgM were present in two cases, but even here, the molecular masses of the autoantigens were different.
Conclusion: The analysis revealed the presence of specific autoantibodies in lung tissue, indicating a potential autoimmune component in post-COVID syndromes. These findings suggest that autoimmune mechanisms may play a role in the lingering symptoms experienced by post-COVID patients. The study is ongoing, with further analysis needed to fully understand the implications.

Funding: University of Debrecen, Department of Cardiology, Division of Clinical Physiology, National Academy of Scientist Education.

NEW-ONSET ATRIAL FIBRILLATION IN YOUNG PATIENTS FOLLOWING COVID-19 INFECTION

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Introduction: COVID-19 has been associated with a wide range of cardiovascular complications, including atrial fibrillation (AF). While AF is more commonly seen in the old population with pre-existing heart disease, its emergence in young, healthy individuals raises questions about the arrhythmogenic potential of COVID-19. This study aims to evaluate the incidence of new-onset AF in young/adult patients without prior structural or functional heart disease during COVID-19 infection and to explore the effectiveness of early treatment strategies.
Materials and Methods: We conducted a prospective study of 43 patients aged 32 to 51 who developed AF during a confirmed COVID-19 infection. All patients were free from prior structural or functional heart disease. Initial treatment included anticoagulation therapy, beta-blockers, and antiarrhythmic drugs. Comprehensive clinical and biological evaluations were performed on all patients, including blood tests and echocardiograms. Follow-up assessments included a 24-hour Holter ECG at 3 months and further clinical evaluation at 6 months to monitor AF recurrence and other cardiac symptoms.
Results: At the 3-month follow-up, none of the 43 patients exhibited AF on 24-hour Holter ECG monitoring. All patients maintained normal sinus rhythm, leading to the discontinuation of antiarrhythmic therapies in all cases. At the 6-month follow-up, none of the patients experienced AF recurrence, and all remained in sinus rhythm. As a result, anticoagulation therapy was safely discontinued in all patients.
Conclusions: Our study suggests a strong association between COVID-19 infection and new-onset AF in previously healthy young/adult individuals. The findings highlight the importance of early detection and management of AF in COVID-19 patients in order to reduce recurrence rates and improve long-term outcomes. Inflammatory markers such as CRP may play a role in the pathogenesis of AF in the context of COVID-19, warranting further investigation of the mechanisms underlying this arrhythmogenic response.

PATHOPHYSIOLOGICAL MECHANISMS OF ARRHYTHMIAS IN PATIENTS DIAGNOSED WITH COVID-19

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Background: The coronavirus pandemic has affected a significant number of the global population, revealing for the first time on a global scale the cardiovascular effects of both severe respiratory infections in general and specifically those caused by COVID-19. Cardiac arrhythmias occur due to the impact of the virus on the respiratory and cardiovascular systems, as well as the systemic inflammation it cauzes. Additionally, they result from the proarrhythmic effects of COVID-19 pharmacotherapies, other drug interactions, and the associated autonomic imbalance that increases arrhythmogenicity. The most concerning of all arrhythmogenic mechanisms is the QT interval prolongation induced by various anti-COVID pharmacotherapies, which can lead to polymorphic ventricular tachycardia in the form of torsades de pointes and sudden cardiac death.
Inclusion criteria: 161 patients diagnosed with COVID-19 and admitted between 2020-2022 to the Cardiology Clinic of the Timișoara County Emergency Clinical Hospital. Cardiovascular risk factors: coronary artery disease, reduced left ventricular ejection fraction, patients with diabetes, chronic kidney disease, or a history of stroke.
Material and methods:PCR test for the diagnosis of COVID-19. Biological samples: complete blood count, inflammatory markers, cardiac and liver enzymes, creatinine, Na, K, D-dimers, 12-lead ECG,24-hour 3-channel Holter ECG monitoring, transthoracic echocardiography. Two groups of patients with and without cardiovascular risk factors, with inflammatory syndrome present, with or without associated systemic infection.
Results: It is imperative that, in order to better protect ourselves in the future, we both accurately quantify the risk of arrhythmia occurrence during severe infections and develop diagnostic and treatment algorithms for these arrhythmias that enable the fastest and safest possible therapy. Atrial fibrillation was the most common arrhythmia observed in patients with SARS-CoV-2 infection, with 54% of these patients showing elevated levels of CRP and IL-6. Increased D-dimer levels are a negative prognostic factor, significantly raising the risk of death. Diabetic patients and those with chronic kidney disease are more likely to experience electrolyte imbalances, which can consequently lead to ventricular arrhythmias. Disturbances in phosphocalcic metabolism precipitate endomyocardial calcifications, which further impair tissue depolarization and conduction pathways, thereby increasing the risk of arrhythmias through re-entry mechanisms.

ASSOCIATIONS BETWEEN INFLAMMATORY MARKERS AND SEVERE FORMS OF SARS-COV-2 INFECTION – A RETROSPECTIVE STUDY

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Background: The COVID-19 pandemic has influenced the emergence of social, sanitary and economic difficulties and despite the efforts made worldwide, SARS-CoV-2 infection remains a public health problem.
Inflammation in COVID-19 plays a central role in the pathophysiology of the disease and the development of long-term complications. When an imbalance occurs between the release of pro-inflammatory and anti-inflammatory mediators, it can lead to severe disease, coagulation disorders, acute respiratory distress syndrome, or even death.
Objectives: We aimed to determine whether serum levels of TNF-alpha, IL-6 and PAI-1 are associated with an increased risk for progression to severe forms of disease.
Materials and methods: We conducted a retrospective study in the "Prof. Dr. Matei Balș" National Institute of Infectious Diseases, which included 255 patients with confirmed SARS-CoV-2 infection. Clinical, biological and imagistic parameters were analyzed.
Results: The studied group included 113 women (44.3%) and 142 men (55.7%). Median age was 64 (IQR: 50.70-71.96) among women and 53.36 (IQR: 45-68.60) among men. There were 139 patients (54.5%) with severe forms of disease. Medium forms of disease were identified in 108 patients (42.4%), and mild forms in 8 patients (3.1%). Increased values of TNF-alpha were correlated with hepatic cytolysis among men (p=0.009), and the development of complications during hospitalization in women (p=0.005). In women, increased IL-6 values were correlated with the development of acute respiratory failure (p=0.001) and bacterial co-infection (p=0.012). Increases in PAI-1 levels were identified in male patients who developed complications during hospitalization (p=0.032).
Conclusions: Our results suggest that TNF-alpha, PAI-1 and IL-6 are key elements in the pathophysiology of the disease. Early identification and monitoring of patients at risk of developing cytokine storm are essential to prevent complications and progression to severe forms of the disease. In the future we intent to identify if there are correlations between these inflammatory markers and development of the long-COVID syndrome, and if the use of immunomodulatory therapies can decrease the impact that the cytokine storm has on tissues and organs.

COVID-19 AND THE BATTLE OF THE BLOOD CLOTS: A PULMONARY PERSPECTIVE

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Pulmonary thromboembolism (PTE) is a frequent and life-threatening complication in patients with SARS-CoV-2 infection. The pathogenesis of PTE in COVID-19 is distinct, driven by virus-induced endothelial injury, hypercoagulability and profound inflammatory responses, differentiating it from classic thromboembolic disorders.
We present the case of a 70-year-old female patient who presented to the emergency department complaining of marked dyspnea, chest pain, pain and enlargement of the right lower extremity, symptoms onset 2 weeks after diagnosis with SARS COV 2 infection. Imaging confirmed the presence of pulmonary embolism as well as complete thrombosis in the common femoral vein, popliteal vein and small saphenous vein, and laboratory tests showed significantly elevated levels of D-dimer -3500 ng/mL as well as inflammatory (C-reactive protein-170 mg/L, hsV-115 mm/h). The main driver of thrombosis in SARS-CoV-2 infection is endothelial dysfunction induced by direct viral invasion via the ACE2 receptor, abundantly expressed in the pulmonary vascular endothelium. This endothelial damage triggers local inflammation, with increased production of proinflammatory cytokines, such as IL-6, IL-1β and TNF-α, leading to systemic hyperinflammation, often referred to as cytokine storm. In parallel, activation of the coagulation cascade via the tissue factor pathway promotes a prothrombotic state, resulting in both microvascular thrombosis and macrovascular pulmonary embolism. Increased D-dimer and fibrinogen levels reflect enhanced fibrinolysis and continued thrombus formation. In addition, hypoxemia - a feature of severe COVID-19 - exacerbates this prothrombotic environment by further inducing platelet activation and altering coagulation dynamics. The systemic inflammatory response, along with venous stasis due to immobilization and hypoxia-induced coagulation abnormalities, complete Virchow's triad, placing patients at high risk for PTE. This distinctive coagulopathy in COVID-19, which sometimes resembles disseminated intravascular coagulation (DIC), differs in that patients often have normal platelet counts despite the presence of extensive thrombosis. The patient received therapeutic anticoagulation with low-molecular-weight heparin (LMWH) according to current recommendations for COVID-19-related thrombosis, with a slowly favorable course. This case illustrates the complex pathophysiology of PTE in the context of SARS-CoV-2 infection. The combination of systemic inflammation, endothelial dysfunction, and coagulation dysregulation increases the risk of thrombotic events in elderly patients, and early recognition and aggressive anticoagulation are essential to improve prognosis in these high-risk populations.

EMPAGLIFLOZIN - MONOAMINE OXIDASE INTERACTION IN HUMAN CARDIAC AND VASCULAR TISSUES: A PILOT STUDY IN OVERWEIGHT PATIENTS WITH HEART FAILURE

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Background: The SGLT2 inhibitor class has demonstrated cardioprotective beneficial effects in heart failure (HF) and obesity through multiple mechanisms, one of the most extensively researched being the antioxidant one. Monoamine oxidases (MAOs) are mitochondrial enzymes with 2 isoforms, MAO-A and MAO-B, responsible for the biogenic amines degradation with the constant generation of hydrogen peroxide as ancillary product. Recently, the contribution of MAOs to the obesity-related oxidative stress has been revealed.
Objective: The aim of the current study was to assess the interaction of MAO with empagliflozin (EMPA) in vascular (mammary arteries rings) and cardiac (atrial appendages) samples harvested from non-diabetic, overweight patients with all types of HF. The samples were acutely incubated *ex vivo* with angiotensin II (AII) or high glucose (GLUC) to mimic the activation of RAA or uncompensated diabetes mellitus.
Material and methods: Internal mammary arteries were isolated from patients with indication of CABG. All patients were overweight (BMI = 26.89 ± 1.26 kg/m^2) and had heart failure with mildly-reduced EF (HFmrEF) (EF = 46.87 ± 2.82%). Right atrial appendages were isolated from patients subjected to elective open-heart surgery. All patients were overweight (BMI = 28.98±0.31 kg/m2) and diagnosed with all types of HF (EF = 43.47±11). MAO A and B expression was assessed at gene level (by RT-PCR) and at protein level (by immune-fluorescence).
Results: Both MAO isoforms are present in human cardiac and vascular tissues and the (gene and protein) expression was significantly upregulated following acute *ex vivo* stimulation with AII or high GLUC. Interestingly, MAO expression was reduced by acute incubation (12 h) with EMPA not only in GLUC and A2-treated but also in control samples.
Conclusion: In non-diabetic, overweight patients with HF, MAO contributes to vascular and cardiac oxidative stress that can be acutely targeted by EMPA, as a novel "off target" effect of SGLT2i.

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SUBCLINICAL CAROTID ATHEROSCLEROSIS IS PRESENT FROM EARLY COPD STAGES BEING IN A CLOSER RELATIONSHIP WITH SYSTEMIC INFLAMMATION THAN AIRFLOW OBSTRUCTION

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Background: It is already demonstrated by several cohort studies that there is a link between subclinical atherosclerosis and obstructive chronic airflow limitation. These conditions share common risk factors related to unhealthy lifestyle but also similar pathophysiological mechanism.
Objective: To investigate the involvement of various biomarkers related to airflow limitation, dyslipidemia, muscle dysfunction parameters and systemic inflammation in subclinical carotid atherosclerosis in COPD patients.
Materials and methods: This is a cross-sectional study which involved 109 COPD patients with stable disease. All the patients were evaluated by spirometry, carotid ultrasound, chest x ray, lipidogram, inflammatory biomarkers, six minute walking test, dynamometry, bioelectrical impedance for body composition and COPD assessment test, anxiety and depression questionnaires. Possible links between carotid subclinical atherosclerosis and the evaluated biomarkers were analysed. We also defined as COPD inflammatory phenotype the group of patients with at least two positive biomarkers of inflammation and differences between inflammatory and non-inflammatory groups were analysed.
Results**:** Significant statistical differences were found in carotid intima-media thickness (c-IMT) values related to the severity of airflow limitation (1.03 mm in COPD stage 1-2 GOLD, *vs.* 1.07 mm in COPD GOLD 3, and 0.96 mm in GOLD 4 stage; (p=0.04), but not a direct correlation with FEV1. The post-hoc analysis demonstrated a significant increase in carotid wall thickness in early COPD stages. C-IMT significantly correlated with parameters of muscle dysfunction, body composition, lipid profile and inflammation. Comparison of inflammatory with non-inflammatory phenotype also showed significant differences between groups regarding age, c-IMT, exercise tolerance, COPD symptoms and anxiety.
Conclusions: Subclinical carotid atherosclerosis is present form early stages of obstructive airflow limitation. Carotid intima media thickness is significantly higher in the COPD inflammatory phenotype patients and closely correlated with body composition parameters and muscle dysfunction.

THE INTERRELATIONSHIP BETWEEN OXIDATIVE STRESS LEVELS AND METABOLIC PARAMETERS IN OBESE PATIENTS

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Background: Obesity is a public health problem and its prevalence is increasing both in adults and children over the world. It is associated with an increase level of oxidative stress and a low-grade chronic inflammatory status which are both involved in the pathogenesis of the disease and the cardio-metabolic complications associated obesity.
Objective: The objective of the study was to evaluate oxidative stress levels in patients stratified by different classes of obesity and to establish possible correlations between oxidative stress and metabolic parameters in these patients.
Materials and methods: The study was conducted over a period of three years, with the approval of the Ethics Committee of University of Medicine and Pharmacy of Craiova (no. 40/27.03.2018) and included 105 patients with different classes of obesity according to WHO criteria, and a control group. The evaluation of metabolic parameters: blood glucose, lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), serum uric acid, was based on the normal values established using a KONELAB 601 analyzer and oxidative stress levels were evaluated using a Calegary 3000 analyzer by FORT (Free Oxygen Radical Test, normal range ≤ 2,3 mmol/L H_2O_2) and FORD (Free Oxygen Radical Defense, normal range 1.07-1.53 mmol/L Trolox).
Results & Conclusion: Obese patients presented higher serum concentrations of LDL-cholesterol, total cholesterol, triglycerides, fasting plasma glucose and uric acid, and lower concentrations of HDL-cholesterol versus control group, the value of metabolic markers changing significantly with increasing degree of obesity. Patients with obesity showed significantly higher values of FORT ($p<0.0001$) and lower values of FORD versus control group ($p< 0001$). Univariable linear regression analysis established that dyslipidemia, type 2 diabetes mellitus and hyperuricemia were positive predictors of FORT values. Multivariable analysis confirmed a positive association between the absence of dyslipidemia and FORD levels, and a negative association between serum uric acid and FORD levels.

INNOVATIVE APPLICATIONS OF AEROGELS IN COMBATING ANTIMICROBIAL RESISTANCE

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Background: Antimicrobial resistance (AMR) poses a significant threat to global health, necessitating the development of innovative therapeutic strategies. Aerogels, with their unique properties such as high porosity and large surface area, have gained attention as potential materials for enhancing antimicrobial therapies.
Objectives: This study aims to explore the recent advancements in aerogel technology and evaluate their efficacy in antimicrobial applications, particularly in improving drug delivery systems and reducing the impact of AMR.
Materials and Methods: The research reviews various types of aerogels, focusing on their synthesis, functionalization with agents like APTES, and application in biomedical fields. The study examines both in vitro and in vivo data to assess the antimicrobial effectiveness and stability of aerogels when integrated into therapeutic regimes.
Results and Conclusion: Findings indicate that aerogels not only serve as effective antimicrobial agents but also enhance the controlled release and stability of incorporated drugs. Their multifunctional capabilities suggest a promising role in addressing the challenges posed by AMR. Continued research and development in this area could lead to significant improvements in patient outcomes and the effectiveness of antimicrobial therapies.

ACUTE-PHASE INHIBITION OF PRO-INFLAMMATORY ALARMIN S100A8/A9 ATTENUATES CARDIAC FIBROSIS AFTER MYOCARDIAL INFARCTION

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Background: Myocardial infarction (MI) is a disease associated with high mortality and morbidity and represents the first cause of heart failure (HF) worldwide. We have previously identified S100A8/A9, an alarmin abundantly stored in neutrophils, as a dual promoter of inflammation and repair after MI.
Objectives: In this study, we investigated the effects of short-term S100A8/A9 blockade on myocardial inflammation and post-ischemic myocardial fibrosis in a mouse model of permanent coronary artery ligation.
Materials and methods: After MI induction, the mice were randomly assigned into three groups: sham-operated mice (sham group), MI-operated mice that received phosphate-buffered saline (PBS) treatment (MI group) and MI-operated mice treated with 30 mg/kg S100A8/A9 blocker ABR-238901 (MI+ABR group). Mice sacrificed on day 1 received one intraperitoneal (i.p.) dose of PBS or ABR immediately after MI. All other mice received a total of three i.p. injections of either PBS or ABR administered at the time of the MI, and repeated after 24 and 48 h. The presence of lymphocyte antigen 6 family member G6D (Ly6G), a marker specifically expressed on the surface of mouse neutrophils, and the extent of fibrotic tissue area revealed by the Masson's trichrome staining were histologically assessed at 1, 3, and 7 days after MI.
Results: ABR-treatment significantly decreased the infiltration of Ly6G-positive neutrophils on day 1 post-MI in the border zone of the infarction, and the effect was even more pronounced on day 3, at the end of the treatment. Three doses of ABR significantly reduced the extent of myocardial fibrosis at 3 and 7 days after MI, both in the infarct border zone and in the left ventricle as a whole. Importantly, the effects were also observed in the remote myocardium, demonstrating beneficial effects of the treatment in this area as well.
Conclusion: In the current work, we show that ABR-treatment administered in the early acute inflammatory period post-MI lowers neutrophil infiltration and attenuates post-ischemic myocardial fibrosis. Our findings promote S100A8/A9 blockade as a promising therapy in the acute-phase of MI, to modulate neutrophil recruitment, reduce cardiac fibrosis, and prevent long-term HF.

INTERDISCIPLINARY APPROACH OF A COMPLEX CASE WITH MULTIPLE CONGENITAL MALFORMATIONS

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Background: The identification of a broad spectrum of developmental disorders, ranging from mild to severe, is becoming a challenge due to the diversity of genetic and environmental factors that have a multiple and significant impact on embryonic development.
Objectives: This case report aims to present the identification process of a complex developmental disorder, based on morphological and clinical data, supplemented by molecular biology assays. It underlines the importance of interdisciplinary collaboration integrating insights from embryology, genetics, molecular biology, and pathology.
Materials and methods: The authors present the case of a female preterm, born at 34 weeks of gestation in June 2022 as the second child of consanguineous parents, from a 17-year-old mother, with no perinatal controls, in a secondary level hospital in Romania.
Results and Conclusion: At birth several severe anomalies were present, among prematurity, complete cheilo-gnato-palato-schisis, with the total absence of the nose, nostrils and the presence of proboscis lateralis. Orbital hypertelorism, associated with right eyelid ptosis, and unilateral right mandibular ramus hypoplasia was also present. A frontal meningoencephalocele with the herniation of the brain and meninges, brachycephaly, and vertical talus were observed. The newborn passed away after 17 hours. Through the autopsy and the analysis of the obtained morphometric data, complex craniofacial abnormalities were described, and molecular biology tests offered a better understanding of the possible etiology leading to the development of malformations that were incompatible with life. The case highlights the challenges of neonatal care and the crucial importance of early diagnosis. The case will contribute valuable perspectives to the debate on effective strategies for detection and treatment, expanding our understanding of the multifaceted and multifactorial nature of these disorders.

DIAGNOSTIC CHALLENGES IN THE DIAGNOSIS OF PRIMARY GASTROINTESTINAL MASTOCYTOSIS

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Background: Mast cells (MCs) are immune cells that play a crucial role in the gastrointestinal (GI) tract. Their primary function is to mediate allergic reactions and inflammation. Primary GI mastocytosis is a rare condition characterized by the abnormal proliferation of mast cells in the GI tract and presents a diagnostic challenge due to the heterogeneity of clinical presentations and frequently non-specific endoscopic findings.
Objectives: To conduct a review of the existing literature on primary GI mastocytosis, focusing on the clinical manifestations, endoscopic findings, and histological aspects of primary GI mastocytosis, while critically evaluating the diagnostic complexities associated with this condition.
Material and methods: The literature search was performed using PubMed, Google Scholar, and Scopus to identify case reports/case series reporting primary GI mastocytosis diagnosed by endoscopy and GI tract biopsy. The search strategy employed a combination of keywords encompassing various anatomical locations within the GI tract, including "gastrointestinal mastocytosis", "esophageal mastocytosis", "gastric mastocytosis", "small bowel mastocytosis", "large bowel mastocytosis", and "colonic mastocytosis."
Results: Our literature search identified 11 papers describing cases of primary GI mastocytosis established on biopsy specimens, following endoscopy. These studies included a total of 16 patients. We identified abdominal pain and diarrhea (n=10; 62.5%) as the most frequent presenting symptoms, followed by nausea/vomiting (n=5; 31.2%). Only 6.2% (n=1) of the patients presented with hematochezia (bloody stools), and 18.7% (n=3) were asymptomatic. The most common endoscopic findings were diffuse nodularity/pseudopolypoid lesions/polyps (n=9; 56.2%), followed by mucosal inflammatory changes – erythema friability/erosions (n=5; 31.2%). Also, 31% (n=5) of patients presented normal mucosa at endoscopy. Among the immunohistochemical markers evaluated in the reviewed studies, CD177 was identified as the most frequently employed marker, followed by CD25. Mast cell tryptase was performed in 50% of the cases. For the KIT p.D816V mutation, 18.7% (3 out of 5 patients) were tested.
Conclusion: Primary GI mastocytosis can present diagnostic challenges due to potential subtle endoscopic findings and inconspicuous histological involvement. Confirmation of MCs requires dedicated immunohistochemical analysis for specific markers, while molecular profiling may be employed for further characterization.

PULMONARY CARCINOID TUMOUR- A RARE NEUROENDOCRINE MALIGNANCY: A CASE REPORT

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Background: Neuroendocrine neoplasms (NENs) are heterogeneous tumours that originate from cells of the neuroendocrine system and can arise from any organ, the gastrointestinal tract being the most common place with more than >60% of total cases and secondly, the lung with more than 20% of neuroendocrine primary located. Pulmonary carcinoid tumours are very rare neuroendocrine malignancies that occur in less than 1% of patients with lung cancer and are divided in typical and atypical carcinoid tumours, with a survival rate at five years of 90%, respectively 60%.
Objectives: The mechanisms underlying the development and progression of carcinoid tumours are not fully understood and remain uncertain. They are recently linked to air pollution, but have no connection to smoking, and it appears that this type of tumours affect more women than men, especially individuals of white ethnicity.
Materials and methods: We present the case of a 39 years old woman, non-smoker, with exposure to dust and humidity for 4 years, with a surgically removed uterine leiomyoma, endometriosis and chronic infection with hepatitis B virus, who incidentally discovers a right pulmonary mass during a breast MRI investigation. Further imaging testing is done and her thoracic CT scan describes an inhomogeneous right perihilar process, of 42/37/38 mm, which almost completely compressed the right lower lobar bronchus. The fibrobronchoscopy describes an endoluminal, round, glossy mass with very thin walls, very well vascularized and easily bleeding at minimal touches, with a highly suggestive appearance of a carcinoid tumour, from which biopsy cannot be performed due to the high risk of significant bleeding. She is then admitted in the thoracic surgery department for a right lower lobectomy, along with biopsy of the right hilar and interlobar nodes. The histopathological result of the tumour shows a typical endobronchial carcinoid without lymph node metastases.
Results & Conclusion: Although the diagnosis of a lung tumour has a negative impact on the life and health of patients, in most cases receiving the diagnosis of non-small cell or small cell lung cancer, these being among the most aggressive forms of cancer, there are also rare cases of neuroendocrine tumours (<1%) with a more favourable prognosis for the patient and a greater life expectancy.

GENDER DISPARITIES IN THE IMPACT OF TRANSCATHETER AORTIC VALVE REPLACEMENT ON LEFT VENTRICULAR EJECTION FRACTION IN CAUCASIAN PATIENTS

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Background and objective: Transcatheter Aortic Valve Replacement (TAVR) has revolutionized the management of severe aortic stenosis, offering a minimally invasive alternative to conventional surgical approaches. While TAVR has demonstrated efficacy in improving clinical outcomes, including symptom relief and survival rates, the interplay between TAVR and specific cardiac parameters, such as Left Ventricular Ejection Fraction (LVEF), remains an area of ongoing research.While TAVR primarily targets aortic valve pathology, its effects on LVEF are of considerable interest due to their implications for overall cardiac function and clinical outcomes. Moreover, understanding potential gender differences in the response to TAVR is crucial for optimizing patient care and outcomes. The present study aims to investigate the impact of TAVR on LVEF and examines gender disparities in its effects among Caucasian patients.
Design and method: A retrospective analysis was conducted on a cohort of 100 patients (52 men and 48 women), who underwent TAVR between 2020-2023 in our Institute of Cardiovascular diseases. Statistical analysis was performed using MedCalc Statistical Software version 20.015 (MedCalc Software Ltd, Ostend. Belgium).The left ventricular ejection fraction was evaluated before and post-procedural with the modified Simpson formula.Patients were stratified according to their gender and post-procedural LVEF.
Results: Before undergoing the procedure, patients had an average LVEF of approximately 44.89%, (95% C.I 43.06 to 46.71) versus post-procedural 46.70%, (95% C.I 45.12 to 48.27), the difference between pre-procedural and

post-procedural LVEF was calculated to be 1.81 (95% C.I 0.8271 to 2.7929), p=0.0004.Mean pre-procedural LVEF in female participants was 47.1458 % (95% C.I. 45.0804 to 49.2112), post-procedural LVEF in female was 48.6458 (95% C.I. 46.9062 to 50.3855), the difference between pre-procedural and post-procedural LVEF was calculated to be 1.5000% (95% C.I 0.07245 to 2.9276), p=0.0399.Mean pre-procedural LVEF in men participants was 42.8077% (95% C.I. 39.9066 to 45.7088), post-procedural LVEF in men was 44.9038 (95% C.I. 42.3700 to 47.4377), the difference between pre-procedural and post-procedural LVEF was calculated to be 2.0962% (95% C.I 0.6990 to 3.4933), p=0.0040.

Conclusions: Transcatheter Aortic Valve Replacement represents a paradigm shift in the management of severe aortic stenosis, offering a less invasive treatment option with favorable clinical outcomes. However, the impact of TAVR on specific cardiac parameters, such as LVEF, and potential gender disparities in its effects need further investigation. Understanding the nuanced relationship between TAVR, LVEF, and gender in Caucasian patients is essential for refining patient selection criteria, optimizing treatment strategies, and ultimately improving clinical outcomes.

PATHOPHYSIOLOGICAL MECHANISMS OF ATRIAL FIBRILLATION IN DIALYSIS PACIENTS: THERAPEUTIC IMPLICATIONS

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Objective: This study aims to highlight the pathophysiological mechanisms most frequently involved in atrial fibrillation in dialysis patients and their response to treatment by analyzing a cohort of 46 individuals undergoing hemodialysis.
Methods: We performed a retrospective analysis on a cohort of 46 patients to investigate pathophysiologic mechanisms involved to the high prevalence of atrial fibrillation in dialysis patients. They were clinically evaluated, laboratory tests and imaging investigations were performed and dialysis parameters were analyzed. The main variables investigated were left atrial enlargement, fluid overload, electrolyte imbalances and systemic inflammation. We utilized multivariate analysis to identify the primary pathophysiological contributors to atrial fibrillation in this population.
Results: The study revealed that left atrial enlargement indicated by wave abnormalities on ECG, increased left atrial size or volume on echocardiography and clinical conditions was the main factor leading to atrial fibrillation in 67% of cases. Volume overload evidenced by pitting edema, increased weight and dyspnea, was present in 57% of the cohort and was strongly associated with atrial fibrillation episodes. Systemic inflammation, documented by elevated C-reactive protein levels, was present in 50% of the cohort and correlated with atrial fibrillation severity. Electrolyte imbalances, were found in 47% of patients and were significantly related to the frequency of atrial fibrillation but its impact on atrial fibrillations was less pronounced compared to fluid overload and left atrial enlargement.
Conclusions: Left atrial enlargement was the main factor precipitating atrial fibrillation in hemodialysis patients along with volume overload. Atrial fibrillation and systemic inflammation are closely related by the mechanisms that can influence both the onset and persistence of arrhythmia. Electrolyte imbalances has a significant contribution in the mechanism of atrial fibrillation, but with a lesser extent. These results underscore the importance for special attention to volume control, electrolyte balance, and inflammation in the treatment of atrial fibrillation in dialysis patients.

INAPPROPRIATE MANAGEMENT OF CONSTIPATION AMONG ROMANIAN POPULATION: RESULTS OF AN ONLINE STUDY SURVEY

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Background: Constipation, one of the most common gastrointestinal tract disorders, is a debilitating condition that is still underappreciated and is investigated only in severe cases, affecting mainly the elderly. Studies show a continuous increase in its prevalence, with self-medication practices representing the primary treatment modality among the general population, leading to potentially serious long-term health complications.
Aim: Thus, we aimed to identify possible issues related to the Romanian population's deficiency in the appropriate management of this pathology by collecting information on lifestyle and the extent to which patients resort to self-medication practices. We also aimed to assess the respondents' level of knowledge regarding the possible adverse effects and drug interactions induced by laxative administration.
Material and methods: This cross-sectional study consisted of distributing a questionnaire among patients suffering from constipation. The questionnaire was developed after consulting the literature in 2020, and due to the establishment of a nationwide state of emergency on March 15, 2020 (due to the spread of SARS-Cov-2 infection, which led to restrictions on in-person interactions and healthcare services), we decided to distribute it online through the Google Form platform.
Results: As a consequence, the questionnaire was distributed to a total of 117 respondents; 54% were in the age category 18-30, followed by 28% persons between 31 and 50 years old, 12% were between 51 and 65 years old, and a small proportion, 6%, of elderly persons (over 65 years old). 47.4% of participants stated that they experience constipation quite frequently. Regarding preventive measures, only 13.9% of respondents reported drinking 2 liters of fluids daily, 47.8% reported not having a high-fiber diet, and 47.4% declared not being physically active. The preferred laxative for self-medication was bisacodyl, a common over-the-counter stimulant and irritant laxative, with the majority of respondents (49.57%) being unaware of possible drug interactions.
Conclusion: In order to decrease the incidence of constipation and also to reduce laxative abuse (especially of stimulant laxatives such as senna or bisacodyl), better patient therapeutic education is needed through health campaigns and information brochures emphasizing non-pharmacological preventive as well as safer and better-tolerated options of treatment (such as macrogols or lactulose).

OSTEOPOROSIS LEVEL OF COMPREHENSION OF ROMANIAN GENERAL POPULATION: RESULTS OF AN IN-PERSON SURVEY

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Background: Osteoporosis, a severe, chronic metabolic bone disease, represents a significant public health problem that leads to a high rate of fractures, morbidity, and mortality. Certain studies carried out in Romania have highlighted a trend of underdiagnosis of this pathology and a significant proportion of people at high risk of fractures who do not receive suitable treatment.
Aim: To better understand the possible causes of underdiagnosis of this disease, we aimed to assess the level of knowledge and awareness of osteoporosis and its risk factors, as well as the preventive measures and lifestyle adopted by the Romanian population.
Material and methods: The research was based on a validated questionnaire, aimed to provide information on socio-demographic data, level of knowledge about osteoporosis and its risk factors, sources of information, co-existing pathologies, and also the presence or absence of an osteoporosis diagnosis.
Results: 189 questionnaires were collected, 78.8% of the survey respondents being female (21.2% male), the participants having an overall mean age of 58.89 ±10.24 years. The educational level of the study participants was predominantly medium (high school - 40.2%), followed by higher education (university - 34.9%). Surprisingly, a total of 60.8% participants did not received any information on the risk of developing osteoporosis from their general practitioner. Regarding the level of knowledge, there were differences in the knowledge level scores between men and women (7.83 men vs. 9.19 women) and also in patients with a family history of osteoporosis compared to those without a family history of osteoporosis (8.76 vs. 9.59). Another important finding is related to the presence of comorbidities (diabetes mellitus, hypo/hyperthyroidism, kidney problems, rheumatoid arthritis) in the study participants, who experienced more recent falls and a higher rate of osteoporosis diagnosis than those without other pathologies.
Conclusion: In light of the results obtained in this research, we can state that to increase the rate of diagnosis of osteoporosis and decrease the socio-economic burden, it is necessary, first of all, to have a much better understanding of the pathophysiological mechanisms of this disease among healthcare providers (clinicians and pharmacists) and the Romanian general population.

MISUSE OF DRUGS IN THE WESTERN ROMANIAN ELDERLY POPULATION BASED ON STOPP/START V.2 CRITERIA

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Background: Romania is today facing rapid population ageing. Elderly people are often suffering from multiple chronic pathologies and their treatment plan involves polymedication. Medication review is currently not routinely practiced in the Romanian healthcare system, although it can prevent medication-related harm, thus lowering hospitalization and preventable mortality rates.
Objectives: Our study aimed to assess chronic electronic medical prescriptions of patients aged over 65 years old using STOPP/START v. 2, 2015 criteria.
Materials and methods: We conducted a cross-sectional study encompassing 1498 chronic electronic medical prescriptions gathered from community pharmacies. The prescriptions were analyzed by a multi-disciplinary team of physicians and pharmacists during weekly encounters. Resulting data were then processed using the Statistical Package for Social Sciences software.
Results: More than half of collected prescriptions (57 %) were issued for female patients, while 43% were for male patients. Most of the prescriptions (89%) were issued by a general practitioner rather than a specialist (11%). Regarding prescription duration, 78% were prescribed for 30 days and 20 % for 90 days of treatment. The analysis of included chronic electronic prescriptions revealed that almost 19 % of them contained potentially inappropriate medications, while 49 % had potentially prescription omissions. A significant proportion of prescriptions (24%) contained medications exceeding the recommended treatment duration. Two of the most encountered STOPP criteria were the prescription of central nervous system drugs: neuroleptics (15%) and zopiclone (14%). Moreover, we found that around 12 % of the prescriptions contained medication without evidence base for clinical indication and 9 % contained duplicated drug class or medication prescription, with an increased risk of adverse events.
Conclusion: We found multiple drug-related problems in the chronically ill elderly population. Considering that natality rates are declining [4], healthcare policies should focus more on reducing preventable mortality rates and increasing the quality of life of elderly people. Comprehension of the pathophysiologic mechanisms of diseases is extremely important in establishing proper treatment regimens for elderly patients and in preventing medication-related harm. Medication review services should be implemented by clinical pharmacists in order to assess the appropriateness of medication prescribing and optimizing patient care.

PATHOPHYSIOLOGICAL ASPECTS AND ADVANCED SURGICAL TREATMENTS IN ANTERIOR CRUCIATE LIGAMENT PATHOLOGY

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Introduction: Anterior cruciate ligament (ACL) injuries are a common issue in sports traumatology and can lead to joint instability and long-term complications, such as osteoarthritis. This study aims to analyze both modern surgical treatment options for ACL reconstruction and the outcomes of conservative treatment, comparing recovery periods and the effectiveness in preventing complications.
Objectives: The study aims to evaluate the pathophysiological impact of anterior cruciate ligament (ACL) injuries and to analyze modern surgical treatment options, focusing on restoring knee functionality. The primary objective is to compare patients treated surgically and those treated conservatively for ACL injuries, as well as their recovery period and the prevention of complications such as joint instability and osteoarthritis.
Materials and Methods: The study included 50 patients with ACL injuries, diagnosed through clinical and imaging examinations (MRI), aged between 18 and 50 years. The patients were divided into two groups: one group treated through ACL reconstruction surgery using the bone-tendon-bone (BTB) method. Pathophysiological parameters (inflammation, edema, joint laxity) and functional recovery were monitored using clinical scores (IKDC and Lysholm) and biomechanical evaluations preoperatively and at 6 and 12 months postoperatively.
Results: Patients in both groups showed significant improvements in knee stability and pain reduction. The BTB autograft group had a faster functional recovery, with a lower incidence of graft rejection and early osteoarthritis, as well as a relatively quick return to daily and sports activities. In contrast, the conservative treatment group experienced a longer recovery period, although there were no major differences in biomechanical performance compared to the surgically treated group at 12 months postoperatively.
Conclusions: ACL injuries have a significant pathophysiological impact on knee function, causing joint instability and an increased risk of osteoarthritis. Modern surgical interventions, especially those based on autograft reconstruction, offer superior clinical outcomes, with faster functional recovery and minimal complications. The choice of treatment should be personalized based on the patient's needs and associated risks, and long-term pathophysiological monitoring is essential for preventing recurrence and late complications.

HEMATOLOGICAL AND HEMOREOLOGICAL PROFILE IN THE PATIENT NEWLY DIAGNOSED WITH TUBERCULOSIS – STUDY DESIGN

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Tuberculosis (TB) remains a major public health problem, with a global incidence reported by the World Health Organization (WHO) of approximately 10 million new cases in 2022. Recent studies have highlighted various hematologic and hemorologic changes associated with TB, including anemia, leukocytosis, and changes in blood viscosity. However, there are still significant gaps in understanding the mechanisms and impact of these changes. In the context of tuberculosis, hemorheological studies reveal critical changes that may influence patient management and prognosis. Detailed understanding of these changes in TB patients may provide new insights into disease pathogenesis and identify useful biomarkers for prognosis and monitoring.

This research could guide new therapeutic strategies to reduce the impact of TB, bringing potential benefits to public health and public health policies at national and international levels. Tuberculosis can induce pathological changes in these properties of erythrocytes, which may contribute to vascular complications and microcirculation impairment.

We propose a proof-of-concept study aimed at understanding the impact of tuberculosis on the blood cells. The study will explore the direct relationship between Mycobacterium tuberculosis infection and the mechanical properties of erythrocytes, a relatively unexplored field in the context of tuberculosis. The working hypothesis is that TB infection will decrease in the deformability of erythrocytes and will interfere with their This could be caused by systemic inflammation and oxidative stress induced by TB infection. An increase in erythrocyte aggregation is also expected, which may contribute to compromising microcirculation and aggravating clinical symptoms. It is also anticipated to identify a consistent hypercoagulability profile in newly diagnosed TB patients, reflected by parameters such as increased fibrinogen, decreased prothrombin time, and other altered coagulation markers. Detailed understanding of these aspects will allow faster and more effective interventions to prevent thrombotic complications.

CARDIAC TOXICITY OF ENDOCRINE DISRUPTORS: UNRAVELING THE MITOCHONDRIAL EFFECTS OF BISPHENOLS AND PHTHALATES

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Cardiovascular diseases (CVD) remain a leading cause of death worldwide, with significant mortality and morbidity rates. A growing body of evidence suggests that endocrine disruptors (ED), among which bisphenols and phthalates, may also significantly contribute to the development/progression of CVD.
We summarized the data literature on the ED effects on cardiac health, particularly examining the mitochondrial toxicity linked to bisphenols and phthalates. Given the widespread presence of these chemicals, understanding their pathophysiological effects on cardiac function is crucial for the identification pharmacological approaches to counteract it.
A relevant number of experimental studies in animal models and cell lines unequivocally demonstrated the mitochondrial toxicity elicited by ED. Exposure to BP A in rats resulted in a significant reduction in ATP production, disruption of mitochondrial function, and elevated oxidative stress. Similarly, in human stem cell-derived cardiomyocytes, exposure to bisphenol A induced an increase in hypertrophic markers alongside with diminished ATP levels. BP S exposure was found to trigger oxidative stress and reduce the antioxidant systems in murine myocardial cells. Bisphenol AF exposure led to structural alterations and promoted abnormal mitochondrial fission through specific signalling pathways. Additionally, di(2-ethylhexyl) phthalate (DEHP) exposure increased impaired oxygen consumption in neonatal rat cardiomyocytes. Collectively, these findings underscore the cardiotoxic potential of these endocrine disruptors.
The evidence indicates that exposure to bisphenols and phthalates poses a significant threat to cardiovascular health and mitochondrial dysfunction has emerged as a major pathomechanism. Investigating their deleterious effects and identifying the molecular targets of these ED in human samples is essential for the discovery of therapeutic/preventive pharmacological strategies.

TARGETING THE EPICARDIAL ADIPOSE TISSUE WITH GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS IN HUMANS

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Cardiovascular disease (CVD) remains the most prevalent cause of death worldwide. Increased epicardial adipose tissue (EAT) has been identified as a risk factor for several CVD, such as coronary heart disease, heart failure, and sudden cardiac death. The glucagon-like peptide-1 receptor agonists (GLP-1 RA) is a novel family of antidiabetic drugs, with pleiotropic beneficial effects in CVD. The discovery of GLP-1 receptors in the EAT lead to an increased interest of the scientific community for assessing the direct effects of GLP-1 RA on the cardiac adipose tissue.
A literature study was conducted regarding the GLP-1 RA impact on the reduction of EAT. Statistically significant improvements in various cardiometabolic parameters have been demonstrated in animal models when GLP-1 RAs are administered. Also, reduction of EAT volume has been demonstrated in diabetic patients treated with GLP1-RA. Activation of EAT GLP-1 receptors is associated with promoting fat browning, a process which improves cardiac insulin sensitivity, which ultimately results in an increase in myocardial metabolic rate. Also, cardioprotection against ischemia-related injury has been reported.
Current evidence suggests that reducing EAT may have beneficial effects on cardiovascular health and disease risk. The reduction in EAT thickness reported with GLP-1 RA is an encouraging discovery that may contribute to the cardiovascular advantages of these drugs. However, additional research is required to decipher the signal transduction underlying their beneficial effects on the cardiac adipose tissue in patients with and without diabetes.

COMMON MICRORNAS IN THE REGULATION OF LIVER AND CARDIAC FIBROSIS

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Fibrosis occurs due to excessive accumulation of extracellular matrix. In critical organs such as the liver and heart, fibrosis contributes to the progression of chronic diseases, significantly impacting organ function and overall health. Increasing evidence suggests that microRNAs (miRNAs), have a crucial role in the development of fibrogenesis and tissue remodelling, in both liver and heart.
We summarized the literature addressing the miRNAs involved in the regulation of fibrotic pathways in liver and cardiac tissues, in order to assess their role as biomarkers for early diagnosis and monitoring of fibrosis progression. The expression of the pro-fibrotic miRNAs: miR-21, mir-34, mir-155 was upregulated in serum and tissues in mouse models of experimental liver and cardiac fibrosis. Inhibition, downregulation, or using K.O. animals for these miRNAs decreased the profibrotic gene expression and interstitial fibrosis, alleviating both hepatic and cardiac dysfunction. On the other hand, the expression of anti-fibrotic miRNAs exhibited significant downregulation in heart and liver affected by fibrosis. miRNAs are crucial regulators of liver and cardiac fibrosis, affecting essential processes such as cell activation and extracellular matrix synthesis. In liver fibrosis, miRNAs modulate the activation of hepatic cells, while in the heart, they influence fibroblast activity and cardiac remodeling. Targeting specific miRNAs to mitigate fibrosis in both organs in human samples and exploring their potential role as biomarkers offers a promising approach for therapeutic interventions.

THE IN VITRO CHARACTERIZATION OF SYZYGIUM AROMATICUM L. ESSENTIAL OIL CYTOTOXIC EFFECT ON COLORECTAL ADENO-CARCINOMA AND MALIGNANT MELANOMA CELLS

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Background: Cancer is the second worldwide cause of death, after cardiovascular diseases. In the last decades, despite the scientific efforts that led to significant improvement in anticancer therapy, the use of traditional anticancer therapy, such as chemotherapy and radiotherapy, is limited by serious side effects, resistance, metastasis, or relapse. To mitigate these disadvantages, current research focuses on natural products with anticancer properties that will enhance the effectiveness of conventional anticancer therapy with fewer side effects.
Objectives: The present study aimed to investigate the effects of clove essential oil, *Syzygium aromaticum* L. Myrtaceae, on human keratinocytes HaCaT, human malignant melanoma A375, and human colorectal adenocarcinoma HT-29 cells.
Materials and methods: Using the Alamar blue colorimetric assay, cell viability was determined after 24h stimulation with clove essential oil diluted in cell culture media (Clo 0.5% and 1%), with clove essential oil dispersed in PEG-4000 and with clove essential oil dispersed in Tween 20 (Clo-PEG and Clo-TW 100 µg/ml and 200 µg/ml).
Results & Conclusion: The results showed that clove essential oil did not decrease the cell viability of normal HaCaT cells at any of the concentrations tested. On the contrary, on A375 cells, the clove essential oil proved cytotoxic at all concentrations, with the strongest effect observed for 200 µg/ml Clo-TW. Against colorectal carcinoma HT-29 cells, the highest concentration of simple Clo (1%) was the most efficient in decreasing the cell viability. Moreover, it was determined that the bare PEG-400 and Tween-20 did not exert any cytotoxic effects against the tested cell lines. These results suggest that clove essential oil has a strong cytotoxic effect on human cancerous cell lines A375 and HT-29 without exerting any cytotoxic effect on normal HaCaT cell lines at the concentrations tested. Further experiments are needed to elucidate the underlying mechanism of action and to explore in detail the anticancer effect of the compound of this essential oil.

EVALUATION OF CYTOTOXIC EFFECTS OF CYMBOPOGON FLEXUOSUS ESSENTIAL OIL ON HUMAN COLORECTAL ADENOCARCINOMA AND MALIGNANT MELANOMA CELL LINES

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Background: Cancer represents one of the main causes of death worldwide, alongside cardiovascular diseases. Conventional cancer treatments, like radiation and chemotherapy, have shown many side effects; hence the need for continuous search of new drugs with antitumor properties. One of the substances that has shown great anticancer potential is Lemongrass essential oil (*Cymbopogon flexuosus),* a natural, plant-derived product that contains a significant number of pharmacologically active molecules.
Objectives: This study aimed to test the effects of lemongrass essential oil (LEO) on human keratinocytes (HaCaT), human melanoma cells (A375), and human colorectal adenocarcinoma cells (HT-29).
Materials and methods: The cells were stimulated for 24h, using three different methods: 1) the classical method - 0.5% and1% LEO mixed with culture media, 2) the PEG method - LEO (100µg/ml and 200µg/ml) mixed with PEG-400 (LEO-PEG) and 3) the Tween method, where LEO (100µg/ml and 200µg/ml) was mixed with Tween 20 (LEO-TW). Subsequently, cell viability was determined using the Alamar blue assay.
Results & Conclusion: Even at the highest concentrations (1% and 200µg/ml), LEO did not significantly affect the viability of the HaCaT cell line. Meanwhile, LEO showed a dose-dependent cytotoxic effect against cancer cells. The viability of A375 melanoma cells decreased to 9.2%- 32.3% depending on the LEO concentration and method used. The HT-29 colorectal cancer cells presented a significantly reduced viability ranging from 43.7% to 16.4% after treatment with LEO, LEO-PEG, and LEO-TW. The lack of toxic activity on healthy keratinocytes is a promising hallmark, indicating selectivity for cancer cells. Reduced viability of melanoma and colorectal cancer cells implies that LEO has a promising antitumor effect.

IN VITRO EVALUATION OF ORIGANUM VULGARE L. ESSENTIAL OIL EFFECT ON HUMAN CANCER CELLS

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Background: Even though cancer chemotherapy has evolved significantly, transforming cancer from terminal to treatable, the severe side effects encountered have led the scientific community to search for gentler yet effective alternatives. Throughout human history, plant-derived natural products have played a central role in traditional medicine, but recently, the bioactive compounds from plants have been recognized for their potential anticancer properties. *Origanum vulgare* L. (oregano) has shown anticancer potential demonstrating the ability to inhibit cancer cell growth and induce apoptosis, making it a promising, less toxic option for cancer treatment.
Objectives: The present study aimed to investigate the effects of *Origanum vulgare* L. essential oil (OEO) on human keratinocytes HaCaT, human malignant melanoma A375, and human colorectal adenocarcinoma HT-29 cells.
Materials and methods: To increase the dispersion and solubility of OEO in the aqueous cell culture media, PEG-400 (OEO-PEG), and Tween-20 (OEO-TW) were used as solubilizing agents. The Alamar Blue colorimetric assay was used to assess the cell viability of HaCaT, A375, and HT-29 cell lines after 24h stimulation with OEO (0.5% and 1%), OEO-PEG (100 µg/ml, 200 µg/ml) and OEO-TW (100 µg/ml, 200 µg/ml).
Results & Conclusion: The results showed that PEG-400 and Tween-20 alone did not induce any cytotoxic effect on the cell lines used. The various formulations of OEO did not influence the cell viability of normal HaCaT cells at any of the concentrations tested. When tested on A375 cells, OEO (0.5% and 1%), OEO-PEG, and OEO-TW (100 µg/ml and 200 µg/ml) were able to significantly decrease cell viability *vs*. control. On the HT-29 cell line, the smaller concentrations tested of OEO (0.5%), OEO-PEG, and OEO-TW (100 µg/ml) were not able to decrease cell viability in a statistically significant manner. However, at the highest concentrations tested, all OEO formulations decreased HT-29 cell viability. These results suggest that OEO has highly active phytocompounds that exhibit anti-cancer properties against human cancerous cell lines A375 and HT-29 without producing any cytotoxic effect on normal HaCaT cell lines.

SYNTHESIS, ANTIPROLIFERATIVE EVALUATION, AND IN SILICO ANALYSIS OF A BETULINIC ACID-BENZOTRIAZOLE ESTER

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Background: Betulinic acid (BA), a pentacyclic triterpene, has been established as an effective and selective anticancer agent. Chemical modifications of BA (C3, C28, ring A) resulted in several derivatives that demonstrated enhanced antitumor efficacy compared to both the parent compound and commercially available drugs, used as positive controls. Of these compounds, triazole derivatives exhibited enhanced cytotoxic effects against several cancer cell lines. Hydroxybenzotriazole is a commonly employed coupling reagent, alongside carbodiimides, mostly utilized in the synthesis of amides and esters. Several research studies reported the biological evaluation of various hydroxybenzotriazole-triterpene esters, some of which demonstrated enhanced biological effects compared to the unmodified triterpenes.
Objectives: The current study, reports the synthesis and antiproliferative biological assessment of a BA - benzotriazole ester against melanoma. Moreover, this work also tries to elucidate the mechanism of action of the novel synthesized compound correlated with their antiproliferative effect using *in vitro* and *in silico* methods.
Materials and methods: BA-HoBT was obtained using the N,N′-Dicyclohexylcarbodiimide (DCC) coupled esterification reaction of BA, using 1-hydroxybenzotriazole (HOBt). The Alamar Blue colorimetric assay was used to assess the cell viability of HaCaT and A375 cell lines after a 24h stimulation with the obtained compound. Quantitative RT-PCR was employed to determine gene expression variations of the anti-apoptotic Bcl-2 and pro-apoptotic Bax, within the A375 cell line. Molecular docking was used to analyze the binding affinity and interaction mode of the obtained compound against Bcl-2 and to comparatively assess if there is an increase in the theoretical affinity towards Bcl-2 due to the employed structural changes.
Results & Conclusion: BA-HoBT showed increased cytotoxic activity against A375 (69.8% at 50 μM) melanoma cells compared to the parent compound BA (75% at 50 μM). Furthermore, the compound showed negligible cytotoxicity against healthy cells (HaCaT). RT-PCR results show a drop in antiapoptotic Bcl-2 expression while upregulating pro-apoptotic Bax. Molecular docking revealed that the ester hasve a higher affinity for Bcl-2 compared to its triterpenic acid precursor. Therefore, HoBT esterification is a promising approach for increasing the pro-apoptotic effect of triterpenic acids such as BA, in melanoma.

THE EFFECT OF PHYSICAL EXERCISE ON ARTERIAL STIFFNESS AND VASCULAR AGE

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Background: Arterial stiffness refers to the reduced ability of the arteries to dilate and contract in response to blood pressure changes, due to arteriosclerosis, atherosclerosis, and vascular calcifications. Early vascular aging is due to premature vascular structural and functional changes, involves vascular stiffening, affects target organs, and predicts cardiovascular events. Regular physical activity has a positive impact on cardiovascular function through multiple mechanisms.
Objectives: The study aimed to evaluate the relationship between physical activity and pulse wave analysis variables, especially arterial stiffness and vascular age.
Materials and methods: A total of 90 volunteers were included in the study, divided into 3 groups: A: leisure time physical activity, B: daily occupational physical work, and C: sedentary lifestyle. Pulse wave analysis was carried out with an oscillometric device.
Results: Significantly lower values were obtained for pulse wave velocity (PWV) and vascular age in the groups of physically active patients (A+B) compared to the sedentary ones (7.51±1 m/s vs. 8.4± 0.98 m/s, p=0.0004 and 33±10 years vs. 37±10 years, p=0.002, respectively). No statistically significant differences were obtained between the pulse wave analysis variables in groups A and B. Considering the gender of the participants in groups A and B, statistically significant differences were obtained only for some of the blood pressure variables, but not for PWV. Significant correlations of PWV were obtained with central and peripheral blood pressure variables in groups A and B. In sedentary participants, the correlations were significant with central blood pressure variables and body mass index. The independent determinants identified for vascular age were chronological age, systolic blood pressure, PWV, and aortic pulse pressure.
Conclusion: Vascular aging can be delayed or mitigated by adopting positive lifestyle choices, including regular physical activity, as physical work or recreational sports, with no gender differences in pulse wave variables.

THE RELATIONSHIP BETWEEN ESTIMATED PULSE WAVE VELOCITY AND ANTHROPOMETRIC INDICES

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Background: Arterial stiffness and pulse wave velocity are predictors of cardiovascular events, and obesity is a known cardiovascular risk factor.
Objectives: In the context of increased cardiovascular mortality and a true epidemic of overweight and obesity, the study aimed to assess the relationship between estimated pulse wave velocity (ePWV) and several anthropometric indices.
Materials and methods: A total of 25 volunteers, aged 32±17 years, 20% male, were included in the study. Blood pressure variables were assessed and anthropometric indices, such as body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHR), and body shape index (ABSI) were calculated. Estimated pulse wave velocity was calculated using age and mean arterial pressure (MAP).
Results: MAP, ePWV, BMI, WC, WHR, and ABSI were, as follows: 86±10 mmHg, 7.013± 1.936 m/s, 22.27±5.16 kg/m^2, 77.36±16.58 cm, 0.451± 0.089 and 0.0746± 0.005, respectively. Significant correlations were obtained for ePWV with BMI ($r=0.76$, $p<0.001$), WC ($r=0.81$, $p<0.001$), WHR ($r=0.77$, $p<0.001$) and ABSI ($r=0.62$, $p=0.001$).
Conclusion: Estimated pulse wave velocity is increased in overweight and obese, especially in patients with abdominal obesity. BMI, WC, WHR, and ABSI can provide information about arterial stiffness.

PRESCRIBING DIFFERENCES BETWEEN RURAL AND URBAN AREAS OF WESTERN ROMANIA USING STOPP V.2 CRITERIA

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Background: In Romania, preventable and treatable mortality rates are higher than the European average, and many people report unmet medical care needs. The leading causes of death include cardiovascular and cerebrovascular diseases.
Objectives: Our study was designed to compare prescribing practices in rural and urban areas and determine the most frequently inappropriately prescribed medicines using STOPP/START version 2 criteria. This objective has significant implications for improving healthcare practices and patient outcomes.
Materials and methods: Our cross-sectional study involved analyzing chronic electronic prescriptions issued for elderly people. We collected 982 prescriptions from rural community pharmacies [2] and 1498 from urban community pharmacies. An interdisciplinary team of doctors and pharmacists then analyzed the collected medical prescriptions based on STOPP v.2 criteria. SPSS v.17 software was used to process the results.
Results: Over half of the analyzed prescriptions belonged to female patients in both rural (60%) and urban (57%) areas. The vast majority of prescriptions were issued by a general physician (97 % in rural and 89% in urban environments), while only 4 % of rural and 11% of urban collected prescriptions were issued by specialists. We found that 26% of rural chronic prescriptions and 19 % of urban chronic prescriptions contained potentially inappropriate medications. In urban areas, more medical prescriptions contained medication with exceeded treatment duration (24%) compared to those collected from rural pharmacies (6.7 %). Regarding prescribing errors, 12 % of urban and 5 % of rural medical prescriptions contained medications without valid indications and, to a somewhat lesser extent, drug duplications (9% in urban and 3 % in rural areas). In rural areas, we observed inappropriate prescribing of theophylline (6%) and renin-angiotensin-aldosterone system inhibitors (3 %), while in urban areas, the most common problems involved central nervous system medication (15 % for neuroleptics and 14 % for zopiclone).
Conclusions: Facilitating access to specialized treatment for chronically ill patients in rural and urban Romanian areas can improve patients' health outcomes and lower hospitalization rates. Clinical pharmacists have a crucial role in medication review and optimization, especially in rural areas, considering the hindered access to specialists and healthcare services.

HEART RATE VARIATION IN CORONARY REVASCULARIZED PATIENTS

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Background: In Romania, the number one cause of mortality is still represented by the cardiovascular diseases. Given this fact, the heart rate variation (HRVa), which is the parameter that represents the difference between the highest and the lowest heart rate reported by the Holter monitor, could become a significant prognostic marker for coronary revascularized patients as it reflects the heart's autonomic regulation.
Objectives: The main objective was to assess the relationship between HRVa and the occurrence of complications in coronary patients following revascularization (ventricular extrasystoles and rhythm disturbances). The secondary objectives aimed to note if there were any major differences in HRVa as a consequence of the revascularization technique that was performed or due to the artery that has been involved.
Materials and methods: A retrospective study was conducted on 46 patients who underwent revascularization for acute coronary syndrome and their reports. At first, patients were grouped based on their HRVa as low variability (≤ 52 beats per minute) or high variability (> 52 beats per minute) and the odds ratio (OR) for complications was calculated. Secondly, the patients's mean HRVa of those who had the endovascular approach was compared to the one that resulted from the bypass intervention (CABG).
Results: The patients with a lower HRVa have been associated with a 1.24 higher chance of developing conduction disorders and a 3.82 higher chance for ventricular extrasystoles. The patients who have been subjected to surgery (CABG) had a mean HRVa of 50.88 BPM which was significantly lower (p=0.044) than the one of the patients that have been given a stent (mean HRVa = 63.95 BPM). No significant HRVa changes have been noted between the different occluded arteries that led to the coronary disease.
Conclusion: A HRVa ≤ 52 BPM was significantly associated with an increased risk of post-revascularization complications. HRVa assessment could be essential for risk stratification, patient management and vital prognosis, emphasizing the need for continuous monitoring, potential therapeutic adjustments and further research.

FROM PILOT PROJECT TO CORE CURRICULUM: INTRODUCING MEDICAL COMMUNICATION WITH STANDARDIZED PATIENTS — INSIGHTS FROM A ROMANIAN MEDICAL UNIVERSITY

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Background: "Medical Interview with Standardized Patients (SP)" was launched in Timișoara from October to December 2022 to address the lack of standardization in teaching medical interviews in Romania. Medical students were trained in the Cambridge-Calgary communication model and the ICE (Ideas, Concerns, Expectations) concept through workshops, followed by practical SP interviews using predefined role cards. Students received feedback from both SPs and peers. A qualitative analysis was conducted post-project to evaluate its effectiveness.
Objectives: The main objective was to explore the current need to introduce the SP exercise as a learning method at the University of Medicine in Timișoara from the perspective of the medical students participating in the project. Other objectives included: gathering suggestions regarding the ideal form of implementation and developing the multilingual aspect of the project. Essentially, the aim was to outline an honest and comprehensive vision of the medical students.
Materials and methods: This qualitative study involved 17 out of the 34 medical students participating in the project. All seventeen students were interviewed using a semi-structured interview format. The interviews were recorded and transcribed into Word documents. The data were coded and analyzed thematically using MAXQDA software, resulting in four main themes.
Results: Students reported significant improvement of their communication skills and appreciated the structured feedback from peers and SPs in this supportive educational environment. They described the training as crucial for transitioning into real patient care and supported maintaining multilingual options to reflect the global context of medical practice. Suggestions for implementation in the core curriculum proved the strong support for institutionalizing this educational approach.
Conclusion: The project underscored the value of an SP program in medical education by highlighting essential communication skills, advocating for its broader integration into medical training curricula. We plan to expand this program, incorporating specific curriculum enhancements suggested by students to further refine clinical communication training.

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