PROGRAM & ABSTRACTS

(*hybrid meeting*)

Under the Auspices of

UNICAMILLUS
International Medical University in Rome

LOCAL SCIENTIFIC COMMITTEE

Francisco Rios (*Glasgow, **UK***)
Rhian Touyz (*Glasgow, **UK** – Montreal, **Canada***)

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2009: **Mihai Nechifor** (Iasi, ***Romania***)
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2019: **Federica I. Wolf & Michael Lenardo** (Bethesda, MD, ***USA***)

IMS 2022 Organizer

Nathalie SPINELLI

sdrmsociety@gmail.com
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CONGRESS VENUE

1599 @ The Royal College of Physicians and Surgeons
Peter Lowe Lecture Theatre

232 - 242 St Vincent Street, Glasgow

SDRM

International Society for the Development of the Research on Magnesium
www.sdrmsociety.org

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SDRM Official Journal:
Magnesium Research

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SUMMARY

Dear Colleagues,

it is a pleasure for us to welcoming you to the **XVI INTERNATIONAL MAGNESIUM SYMPOSIUM "Magnesium in Health and Disease"**, which will be held on **23th -24th June 2022**.

After the success of the latest XV International Magnesium Symposium held in Bethesda – NIH, USA, March 2019, we will have our meeting in Glasgow (Scotland-UK).

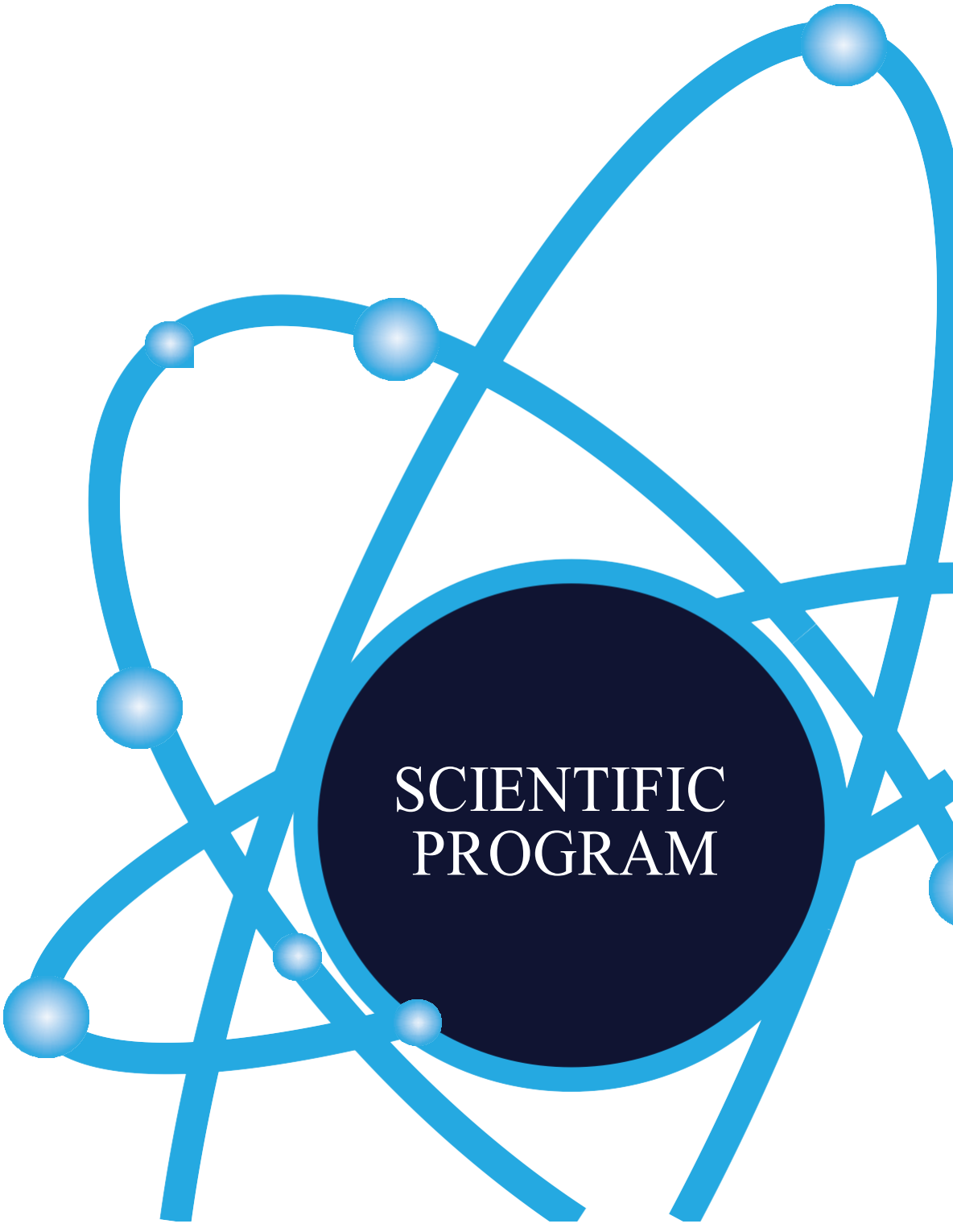
As usual, we collected the latest scientific data on Magnesium Research spanning from molecular mechanisms to epidemiology and clinical data. Indeed this time we bring together the forefront of molecular biology of magnesium transport and analysis and crucial nutritional aspects, as well as biological and clinical research on magnesium in diseases.

We hope that the contributions will stimulate questions, inspire discussions, hypotheses and trigger new projects and collaborations.

We invite you to share your experience, participate to discussions, bring new ideas or suggestions in a heterogeneous, multifaceted, informal atmosphere surrounded by the inspiring environment of Glasgow and attractive area of Scotland.

Join us!

Federica I Wolf & Rhian Touyz



SCIENTIFIC PROGRAM

Glasgow Local Time

Thursday, June 23rd

09:00 – 09:15 **Connection**

09:15 - 09:30 **Welcome Remarks**

Rhian Touyz (*Glasgow, **UK** – Montreal, **Canada***)
Federica I Wolf (*Roma,, **Italy***)

09.30 - 11:40 SESSION 1 Magnesium: Environment, Nutrition and Health

Chairmen: Andrzej Mazur (*Clermont-Ferrand, **France***)
Rhian Touyz (*Glasgow, **UK** – Montreal, **Canada***)

09:30 - 09:50 **Hypomagnesaemia: biomarker, relevance, clinical implications**
Andrea Rosanoff
*CMER Center for Magnesium Education and Research, Pahoa, **USA***

09:50 - 10:10 **Magnesium in soil and consequences in the food chain**
Roberta Cazzola
*Department of Biomedical and Clinical Sciences, University of Milano, **Italy***

10:10 - 10:30 **Magnesium: one of the building block of life**
Stefano Iotti
*Department of Pharmacy and Biotechnology, University of Bologna, **Italy***

10:30 - 10:45 *Coffee / Tea Break*

10:45 - 11:05 **Cyclin M4 silencing and magnesium accumulation in NASH**
Maria Luz Martinez-Chantar
*Laboratory of Head, Liver Disease, Spanish Carlos III Health Institute, Derio, **Spain***

11:05 - 11:25 **Magnesium and Thiamine in Alcohol Withdrawal Syndrome**
Donogh Maguire
Glasgow Royal Infirmary, University of Glasgow, **UK**

11:25 - 11:40 General Discussion

11:40 - 12:25 ***Oral Communications***

11:40 - 11:55 ***OC01***
Mg quantification and distribution as potential biomarkers in Colorectal Cancer
Agnese Razzoli
*Department of Transfusion Medicine, University of Reggio Emilia, **Italy***

11:55 - 12:10 ***OC02***
Magnesium alleviates moderate stress in fibromyalgia
Nicolas Macian
*Department of Clinical Investigation, INSERM Clermont-Ferrand, **France***

12:10 - 12:25 ***OC03***
Decreased ionized magnesium and an increased ionized calcium/magnesium ratio in elderly hypertensives — relationship to artheriosclerosis
Klaus Kisters
*Department of Med. Klinik, St. Anna Hospital & ESH Excellence Centre, Herne, Ruhr University Bochum, **Germany***

12:25 - 13:30 *Lunch Break*

13:30 - 14:20 ## Keynote Lectures

13:30 - 13:50 **Lactate Elicits ER-Mitochondrial Mg2+ Dynamics to Integrate Cellular Metabolism**
Muniswamy Madesh
Department of Medicine, University of Texas Health, San Antonio, ***USA***

13:50 - 13:55 Discussion

13:55 - 14:15 **Magnesium, immunity and infectious diseases an updated overview**
Michael Lenardo
Laboratory of Immune System Biology, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Besthesda, ***USA***

14:15 - 14:20 Discussion

14:20 - 15:50 ## SESSION 2 Magnesium through the lifespan

Chairmen: **Ka Kahe** (*New York,* ***USA)***
Federica I Wolf (*Roma****, Italy***)

14:20 - 14:40 **Mg and development**
Loren Runnels
Department of Pharmacology Rutgers, Robert Wood Johnson Medical School Piscataway, NJ, ***USA***

14:40 - 15:00 **Mg and aging**
Ligia Dominguez
Department of Medicine and Surgery, Kore University of Enna, ***Italy***

15:00 - 15:20 **Magnesium and Progeria**
Ricardo Villa-Bellosta
Department of Biochemistry and Molecular Biology, University of Santiago de Compostela, ***Spain***

15:20 - 15:40 **Magnesium, an invisible deficiency that could be harming your muscle health**
Sara Castiglioni
Department of Clinical and Biomedical Sciences "Luigi Sacco", University of Milano, ***Italy***

15:40 - 15:50 General Discussion

15:50 - 16:00 *Coffee / Tea Break*

16:00 - 17:00 ***Oral Communications***

16:00 - 16:15 ***OC04***

Can a Qualified Health Claim for Magnesium and High Blood Pressure Advance Public Health?

Rebecca Costello

CMER Center for Magnesium Education and Research, Pahoa, ***USA***

16:15 - 16:30 ***OC05***

Fluorescent Indicators for Detection of Cellular Mg2+ with High Selectivity

Daniela Buccella

Department of Chemistry, New York University, New York, ***USA***

16:30 - 16:45 ***OC06***

Magnesium effect on the cardiovascular-muscle-bone triad

Marie-Eva Pickering

Department of Rheumatology, University Hospital Clermont-Ferrand, ***France***

16:45 - 17:00 ***OC07***

Lactobacillus fermentum supplementation normalizes magnesium fecal excretion and delays and reduces high blood pressure and Na, Na/K ATPase activities in salt dependent hypertension

Ruben Biomon

Department of Biophysics and Biochemistry, Venezuelan Institute of Scientific Research, Miranda State, ***Venezuela***

Friday, June 24th

09:00 - 11:00 **SESSION 3**

Molecular Mechanisms of Magnesium Homeostasis

Chairmen: Francisco J. Rios (*Glasgow,* ***UK***)
Jeroen de Baaji (*Nijmegen,* ***The Netherlands***)

09:00 - 09:20 **The molecular appearance and regulatory mechanisms of TRPM7 channel complexes**

Vladimir Chubanov

Department of Pharmacology and Toxicology, Walther-Straub Institute, LMU Munich, ***Germany***

09:20 - 09:40 **Genetic causes of hypomagnesemia**

Jeroen De Baaij

Department of Physiology Radboud institute for Molecular Life Sciences, Radboud University Medical Center Nijmegen, ***the Netherlands***

09:40 - 10:00 **Structural and functional properties of a magnesium transporter of the SLC11/NRAMP family**

Cristina Manatschal

Department of Biochemistry, University of Zurich, ***Switzerland***

10:00 - 10:10 *Coffee / Tea Break*

10:10 - 10:30 **Chanzyme TRPM7 protects against cardiovascular inflammation and fibrosis**
Francisco Rios
Department of Cardiovascular and Medical Sciences, University of Glasgow, ***UK***

10:30 - 10:50 **Severe magnesium wasting in Kenny Caffey Syndrome- searching for molecular causes**
Heidi Schigt
Department of Molecular Life Sciences, Radboud Institute, Nijmegen, ***the Netherlands***
Francisco Rios
Department of Cardiovascular and Medical Sciences, University of Glasgow, ***UK***

10:50 - 11:00 General Discussion

11:00 - 12:00 ***Oral Communications***

11:00 - 11:15 ***OC08***
Palmitoylation regulates cellular distribution of and transmembrane Calcium flux through TrpM7
Xing Gao
Department of Cardiovascular & Medical Sciences, University of Glasgow, ***UK***

11:15 - 11:30 ***OC09***
TRPM7 Modulates Human Pancreatic Stellate Cell Activation
Julie Auwercx
Department of Sciences, University of Picardie Jules Verne, Amiens, **France**

11:30 - 11:45 ***OC10***
TRPM7 channel-kinase, magnesium and pH in immune cells
J. Ashot Kozak
Department of Neuroscience, Cell Biology and Physiology, Boonshoft School of Medicine, Wright State University, Dayton, ***USA***

11:45 - 12:00 ***OC11***
TRPM7 kinase mediates hypomagnesemia-associated seizure and death
Samuel Dudley
Department of Medicine, Division of Cardiology, the Lillehei Heart Institute, University of Minnesota at Twin Cities, Minneapolis, ***USA***

12:00 - 13:00 *Lunch Break*

13:00 - 15:00 **SESSION 4**

Magnesium in communicable diseases

Chairmen: **Federica I Wolf** (*Roma, **Italy***)
Jeanette AM Maier (*Milano**, Italy***)

13:00 - 13:20 **How Pathogens Feel and Overcome Magnesium Limitation**
Eduardo A. Groisman
Department of Microbial Pathogenesis, Yale School of Medicine
*New Haven, **USA***

13:20 - 13:40 **Counteract bacterial infections: factor SLC11A1 restricts *Salmonella* growth through magnesium deprivation**
Olivier Cunrath
*Department of Metals and Microorganisms, University of Strasbourg, Illkirch**, France***

13:40 - 14:00 **Magnesium therapy improves outcome in Streptococcus pneumoniae meningitis by altering pneumolysin pore formation**
Asparouh Iliev
*Department of Molecular Neuroinfectiology, University of Bern, **Switzerland***

14:00 - 14:20 **Interaction of Adenovirus Type 5 E4orf4 with the PRL-CNNM Complex Enhances Magnesium Transport and Viral Replication**
Michel L. Tremblay
*Department of Biochemistry and Goodman Cancer Institute. McGill University, Montreal, **Canada***

14:20 - 14:40 **Mg in Sars-Cov-2**
Fernando Guerrero-Romero
*Biomedical Research Unit of the Mexican Social Security Institute at Durango, Research Group on Diabetes and Chronic Illnesses at Durango, **Mexico***

14:40 - 15:00 **Increased Mortality Associated with Hypermagnesemia in Severe COVID-19 Illness**
Jacob Stevens
*Department of Nephrology**,** Columbia University Irving Medical Center New York, **USA***

15:00 - 15:10 General Discussion

15:10 - 15:25 ***Oral Communication***
OC12
Use of Magnesium for Preventing Cardiac Damages by SARS-CoV-2
Jin O-Uchi
*Department of Medicine, University of Minnesota, **USA***

15:25 - 15:30 *Coffee / Tea Break*

15:30 - 16:40 **SESSION 5**

Magnesium in noncommunicable diseases

Chairmen: **Oliver Micke** (*Bielefeld, **Germany***)
Rhian Touyz (*Glasgow, **UK** – Montreal, **Canada***)

15:30 - 15:50 **Serum magnesium concentration and incident cognitive impairment: findings from the REGARDS study**
Ka Kahe
*Columbia University Irving Medical Center, New York, **USA***

15:50 - 16:10 **Magnesium in oncology an update**
Oliver Micke
*Department of Radiotherapy and Radiation Oncology, Franziskus Hospital Bielefeld, **Germany***

16:10 - 16:30 **News on Magnesium and the Vascular system**
Jeanette AM Maier
Department of Biomedical and Clinical Sciences L. Sacco, University of Milan, **Italy**

16:30 - 16:40 General Discussion

16:40 - 17:25 ***Oral Communications***

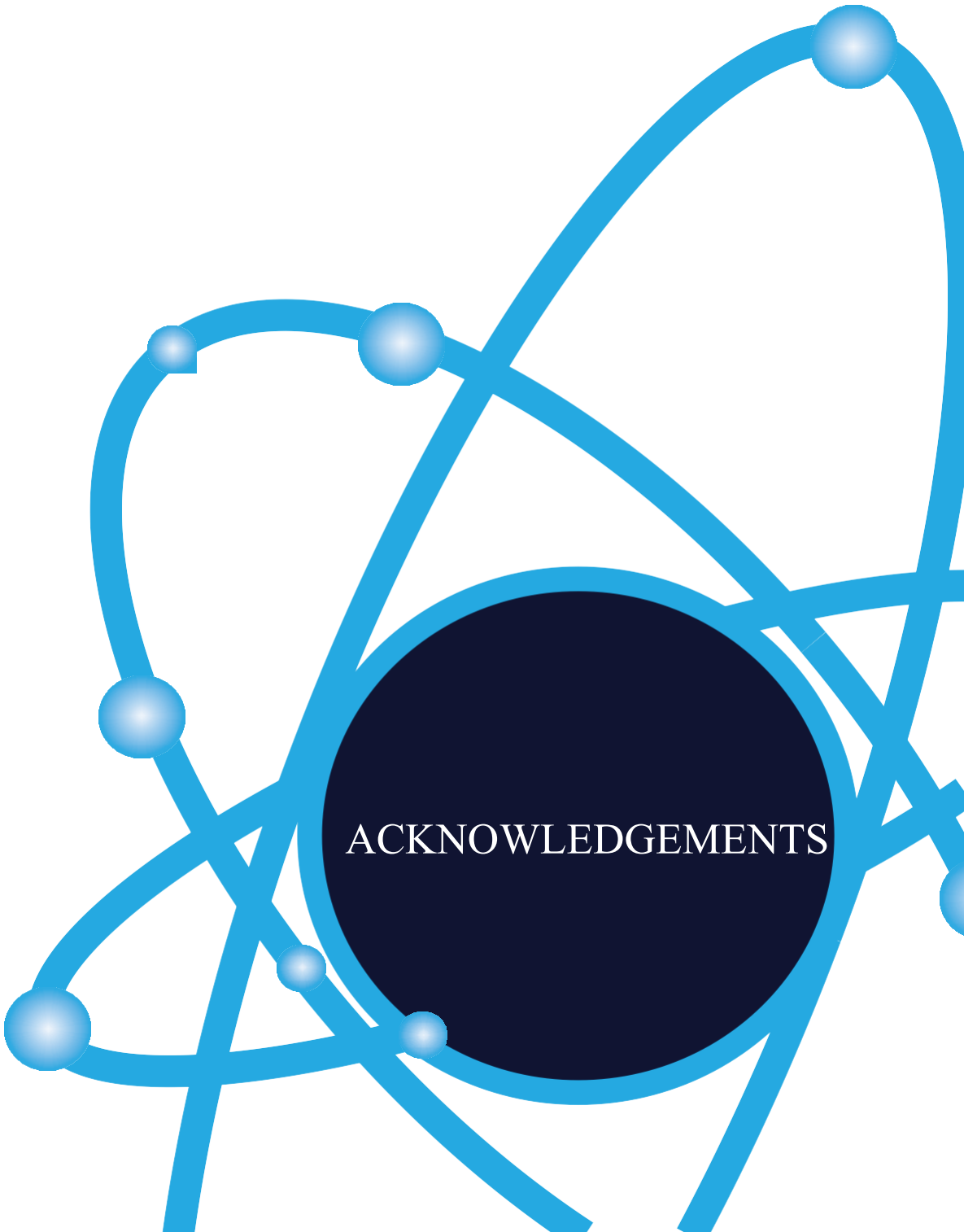
16:40 - 16:55 ***OC13***
Hypomagnesaemia in patients with cardiovascular disease and morbid obesity exacerbates dyslipidaemia and inflammatory syndrome
Ioan A. Gutiu
*Department of Medical Emergencies,"Carol Davila" University of Medicine and Pharmacy, Bucharest, **Romania***

16:55 - 17:10 ***OC14***
Magnesium supplementation improves metabolic syndrome parameters
Kseniia Afitska
*Protina Pharmazeutische GmbH, Ismaning, **Germany***

17:10 - 17:25 ***OC15***
Utility of magnesium sulfate in the treatment of rapid atrial fibrillation in the emergency department: a systematic review and meta-analysis
Megan Hoffer
*Department of Emergency Medicine, George Washington University Washington, DC, **USA***

17:25 - 17:40 **Award Nomination and Closing Ceremony**

Chairmen: **Andrzej Mazur** (*Clermont-Ferrand, **France***)
Rhian Touyz (*Glasgow, **UK** – Montreal, **Canada***)
Federica I Wolf (*Roma, **Italy***)



ACKNOWLEDGEMENTS

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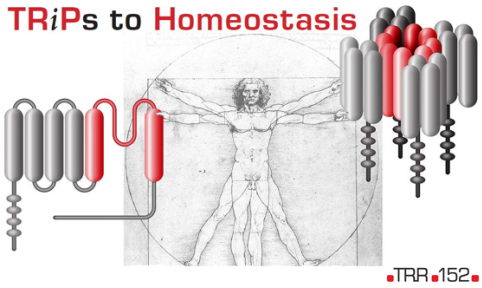

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ABSTRACTS
Invited Speakers

Hypomagnesemia: biomarker, relevance, clinical implications

Andrea Rosanoff
CMER Center for Magnesium Education and Research, Pahoa, ***USA***

Serum Mg is the most frequently used laboratory test for evaluating clinical magnesium status. Hypomagnesemia has been associated with many chronic diseases, but currently no consensus for a normal magnesemia range exists, nationally or internationally. In addition, reports as early as 1983 showed that means of serum Mg are similar in both hospitalized and healthy subjects, but the variance of those hospitalized is wider than the healthy group. A recent review and many hospital laboratories and researchers use symptomatic hypomagnesemia to define the lower range marking hypomagnesemia, but there is a large range of serum Mg above these values which are asymptomatic and yet do not denote a fully "healthy" magnesium status. Two independent groups have recently designated 0.85 – 0.95 mmol/L as a reliable serum Mg reference range, but only the lower boundary marker, i.e. 0.85 mmol/L is evidence based. A reliable, evidence-based upper limit of a health serum Mg has yet to be ascertained, and it is possible that serum Mg alone may not be adequate to designate a compromised magnesium status that is asymptomatic yet portending future development of chronic disease. The potential and recent research of serum Mg:Ca ratio as a potentially more precise marker of a compromised magnesium status will be discussed.

Bio-sketch:

Andrea Rosanoff is Director of CMER Center for Magnesium Education & Research in Pahoa, Hawaii, USA. Dr. Rosanoff earned a Ph.D. degree in Nutrition from the University of California at Berkeley in 1982, and since 1985 has devoted her research to nutritional magnesium and the health impacts of its growing global human deficit. Her main current research interests include the impact of growing global body weights on Mg requirements and the proper use of serum Mg as a Mg status marker.
Contact: ***www.MagnesiumEducation.com - ARosanoff@gmail.com***

Presentation Short Sentence:
Interpretation of serum Mg as a Mg status marker is in flux; this is an update on the research behind those interpretations and a discussion of its potential.

UNIVERSITÀ DEGLI STUDI DI MILANO

Magnesium in soil and consequences in the food chain

Roberta Cazzola
Department of Biomedical and Clinical Sciences, University of Milano, ***Italy***

The chemical properties of the soil are a set of characteristics dependent on physico-chemical phenomena, in close relationship with the climate and especially with living organisms, which influence the production potential and the nutritional value of the plants. Although most cultivated lands are rich in magnesium (Mg), only a small fraction of this mineral is available for plant nutrition. In addition, Mg^{2+}competition with other ions -such as Ca^{2+}, NH_4^+, and especially K^+- for the binding to mineral transporters located on the roots can further reduce its availability. Plants are at the base of the human food chain, and Mg^{2+} is their second most abundant cation; therefore, Mg^{2+}deficiency in plants results in a decreased availability of this nutrient throughout this chain. Cereal seeds are one of the main nutritional sources of Mg^{2+} for the world population. The Mg^{2+} content of historic cereal seeds has declined significantly in recent decades, especially in developed countries, raising concerns about its repercussions on food and human health. One of the causes of this depletion is the so-called green revolution. Since the second half of the last century, this evolution of agriculture has determined intensive crop cultivation sustained by large amounts of N, P, and K fertilization, without paying the opportune attention to Mg^{2+}. Recently, as the progressive depletion of Mg^{2+} of the soil has hurt crop yield, fertilization of Mg^{2+} has been given more consideration. However, even due to other factors, most fertile soils are so degraded that restoring soil health has become a priority to ensure food security and safeguard human health and the environment. For these reasons, soil health is considered a key factor in achieving the objectives of national and supranational strategic plans aimed at protecting the environment and human health.

Bio-sketch:

Roberta Cazzola serves as Associated Professor of Biochemistry as well as coordinator of advanced courses in “Food sciences and applied nutrition” at the University of Milan. Prof. Cazzola has degrees in Agricultural Sciences and has eventually earned her Ph.D. in Experimental and Clinical Nutrition from the University of Milan. Prof Cazzola's research activity is mainly aimed at the study of the interactions between nutrition and risk factors for non-communicable diseases.

Contact: roberta.cazzola@unimi.it

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DEPARTMENT OF PHARMACY AND BIOTECHNOLOGY

Magnesium: one of the building block of life

Stefano Iotti
Department of Pharmacy and Biotechnology, University of Bologna, ***Italy***

Phosphate is a component of numerous biological building blocks, such as nucleotides and phospholipids, therefore it is thought that much higher levels of phosphate and magnesium were required to enable the non-enzymatic (prebiotic) formation of certain biological components, such as nucleotides. However, levels of available phosphate on the early Earth are believed to have been hampered by the limited solubility of a calcium phosphate mineral (hydroxyapatite), a conundrum known as the 'phosphate problem'. Here is, where the magnesium chemical properties played a determinat role in the formation of the first building blocks of life. Mg^{2+} salts are highly soluble in water, therefore Mg^{2+} is immediately available for the formation of the building block of life, differently from salts of Ca^{2+} and of several transition metals, which precipitate at much lower concentrations than corresponding Mg^{2+} salts. The special role that Magnesium plays in biochemistry is primarly due to its ability to coordinate six oxygen atoms efficiently in its first coordination shell. This property of Mg2+ helps the stabilization of diphosphate and triphosphate groups of nucleotides, as well as promoting the condensation of orthophosphate to oligophosphates. The central role of Mg2+ in the function of ribozymes and its 'archaic' position in ribosomes, and the fact that magnesium generally has coordination properties different fromother cations, suggests that the inorganic chemistry of magnesium had a key position in the first chemical processes leading to the origin and early evolution of life. Indeed, of the many metal cations that form complexes with nucleotides, nucleic acids and enzymes, perhaps none is more essential than Mg^{2+}. According to the 'RNA World' hypothesis, the first enzymes – the ribozymes – consisted of ribonucleic acid (RNA), which depended on Mg^{2+} for its self-cleavage. All these circumstances point to a central role for Mg in the geochemistry that presumably led to the first life-like processes. Therefore, it is not surprising the ubiquitous role of magnesium in cellular and tissue metabolism in all living systems. There are a number of evidences suggesting that magnesium acts primarily as a key signaling element and metabolite in cell physiology. In particular, Magnesium is involved in all metabolic and biochemical pathways and is required in a wide range of vital functions, such as bone formation, neuromuscular activity, signaling pathways, bioenergetics, glucose, lipid and protein metabolism, DNA and RNA stability, and cell proliferation. The enzymatic databases list more than 600 enzymes with magnesium indicated as cofactor, and additional 200 are reported in which magnesium acts as an activator . However, since Mg2+ binds to the phosphate moieties of metabolites, the phosphorylated molecules (i.e. ATP, phosphocreatine, as well as all the other phosphometabolites including those related to carbohydrate metabolism and cellular bioenergetics) form a complex with magnesium. This implies that the actual substrates of the biochemical reactions involving these metabolites are magnesium complexes. This is the reason why magnesium should be regarded as a metabolite and not as a cofactor acting in ancillary fashion in biochemical reactions.

The total (bound + free) intracellular magnesium concentrations range from 10 to 30 mM. However, since most magnesium is bound to polynucleotides, ATP, phosphorylated metabolites and proteins, the concentration of its intracellular ionic (free) form falls in the range of 0.5-1.2 mM. The little amount of intracellular [Mg2+], as compared to the intracellular [Na+] and [K+], which are in the order of 50 and 150 mM respectively, strengthens the evidence that the contribution of magnesium to the electric charge of the cell is almost negligible. Therefore, it is time to revise the concept that magnesium is an electrolyte.

It is concluded that Magnesium is an essential element for any living organism and has, no doubt, been so through life's entire history on Earth. The fact that the biogeochemistry of magnesium is intimately coupled to that of phosphorus and nucleotides indicates that it also had a key position in the prebiotic processes leading to the origin of life.

Bio-sketch:

Prof. Stefano Iotti, currently works at Department of Pharmacy and Biotechnology of the University of Bologna coordinating the research group of Molecular Imaging, Biosensors and Cell Biology. He has co-authored more than 120 publications which garnered > 4000 citations (H-index=34) and more than 500 impact points. He is also co-inventor of 6 patents. He has contributed to the development of *in vivo* NMR spectroscopy in basic research and in diagnostic applications. His scientific activity ranged from organic and physical chemistry to biochemical thermodynamics. He contributed to the development of a novel approach to simplify the treatment of the thermodynamics of complex systems. At present the research activity is devoted to the study of magnesium homeostasis in cell culture combining synchrotron X-ray fluorescence and the use of a novel class of fluorescent chemo-sensors (DCHQs).

Contact: stefano.iotti@unibo.it

Cyclin M4 silencing and magnesium accumulation in NASH

Maria Luz Martinez-Chantar
Laboratory of Head, Liver Disease, *Spanish Carlos III Health Institute, Derio,* ***Spain***

A randomised controlled trial of the effect of intravenous thiamine and/or magnesium sulphate administration on erythrocyte transketolase activity, plasma lactate concentrations and alcohol withdrawal scores in patients attending the Emergency Department with alcohol withdrawal syndrome

Donogh Maguire

Glasgow Royal Infirmary, University of Glasgow, ***UK***

Background
Alcohol withdrawal syndrome (AWS) occurs in 2% of patients admitted to U.K. hospitals. Routine treatment includes thiamine and benzodiazepines. Laboratory studies indicate that thiamine requires magnesium for optimal activity, however this has not translated into clinical practice.
Methods
Patients experiencing AWS were randomized to three groups: (group 1) thiamine, (group 2) thiamine plus $MgSO_4$ or (group 3) $MgSO_4$. Pre- and two-hours post-treatment blood samples were taken. AWS severity was recorded using the Glasgow Modified Alcohol Withdrawal Score (GMAWS). The primary outcome measure was 15% change in erythrocyte transketolase activity (ETKA) in group 3. Secondary outcome measures were change in plasma lactate concentrations and time to GMAWS=0.
Results
127 patients were recruited, 115 patients were included in the intention-to-treat analysis. Pre-treatment, the majority of patients had normal or high erythrocyte thiamine diphosphate (TDP) concentrations ($\geq$275 – 675/ > 675 ng/gHb respectively) (99%), low serum magnesium concentrations (<0.75 mmol/L) (59%), and high plasma lactate concentrations (>2 mmol/L) (67%). Basal ETKA increased in groups 1 ($p<0.001$), but not in groups 2 and 3. Magnesium deficient patients (< 0.75 mmol/L) demonstrated less correlation between pre-treatment basal ETKA and TDP concentrations than normomagnesemic patients (R^2=0.053 and R^2=0.236). Median plasma lactate concentrations normalized ($\leq$2.0 mmol/L) across all three groups ($p<0.001$ for all groups), but not among magnesium deficient patients in group 1 (n=22). The median time to achieve GMAWS=0 for groups 1, 2 and 3 was 10, 5.5 and 6 hours respectively ($p<0.001$).
Conclusion
No significant difference was found between groups for the primary endpoint of change in ETKA. Co-administration of thiamine and magnesium resulted in more consistent normalization of plasma lactate concentrations and reduced duration to achieve initial resolution of AWS symptoms.

Bio-sketch:Dr Maguire works as an Emergency Medicine Consultant and Clinical Researcher at Glasgow Royal Infirmary and University of Glasgow Academic Unit of Surgery. He works in close collaboration with the Scottish Trace Elements and Micronutrient Reference Laboratory (STEMRL) and the Academic Unit of Surgery. Our work is focused on magnesium dependent cellular energy metabolism in relation to alcoholic related disease presentations, systemic inflammatory response syndrome and COVID19.

Contact: Donogh.Maguire@glasgow.ac.uk

Lactate Elicits ER-Mitochondrial Mg2+ Dynamics to Integrate Cellular Metabolism

Muniswamy Madesh

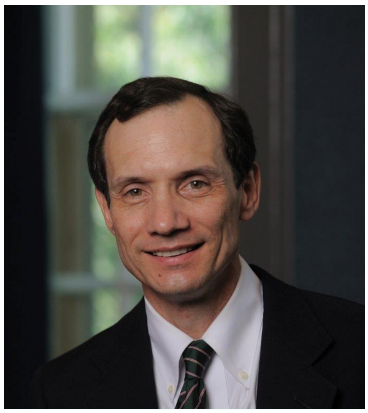
Department of Medicine, University of Texas Health, San Antonio, ***USA***

Bio-sketch:

My research over the years has leveraged my strengths in mitochondrial biology and ion channels in particular Ca^{2+} and Mg^{2+} to answer important questions both cellular and in vivo settings. As an upshot of our scientific fortes, my laboratory identified the *Stromal Interaction Molecule 1 (STIM1) as an ER ROS sensor* apart from its canonical ER Ca^{2+} sensing role (J Cell Biol, 2010; Nat Chem Biol 2012, Nat Rev Mol Cell Biol, 2012, JCI 2013). We recently unveiled a novel regulatory mechanism by which the *upstream Ca^{2+} signaling cascades affect the activity, abundance of the MCU* channel, and bioenergetics (Cell 2012, Cell 2020, Nature 2017, Molecular Cell 2009, 2015 & 2017, Nature Cell Biology 2005, 2006, 2012, Sci Transla Medicine 2013, JCI 2009, 2013, JAMA 2018, Nature Chem Biology 2011, JACC 2015, Immunity 2007, PNAS 2020, EMBO J 2020, Blood 2011, 2017, Circulation Research 2013, 2014, 2016, 2013, Cell Reports 2013, 2015, 2016, 2018, 2019, JCB 2001, 2005, 2010, Science Signaling 2013, 2015, 2019, 2020, Nature Communs 2018, 2020). In depth analysis of the human MCU N-terminal domain uncover a *conserved Cys-97 thiol group* to be surface exposed and primed for an oxidative post-translational modification (PTM) explaining the modification of MCU activity by oxidative milieu. Remarkably, this was the first study of its kind that reveals the *bifunctional role for MCU* as an ion channel and mitochondrial ROS sensor (Molecular Cell, 2017). Having observed that the MCU is a nodal point for mitochondrial bioenergetics in metazoans, our investigation revealed that blockade of the channel perturbs lipid metabolism potentially contributing to the etiology of metabolic disorders (Cell Reports 2019). My laboratory currently explores cutting-edge optical imaging-based methods to address major questions pertaining to explore the phenomenon referred as mitochondrial shape transition (MIST), a process that is independent of fission or fusion (Cell Reports 2018). With these observations, we currently are employing new pharmacologic tools to probe organellar communication and cell function. Our hope is to offer deeper insights behind inter-organellar communication that might be exploited to precisely treat various forms of disease. Our new discovery identified lactate as a ligand for ER-mitochondrial Mg^{2+} dynamics that integrates human cellular metabolism (***CELL 2020***). It is thrilling to define the molecular link between cellular Mg^{2+} homeostasis and physiological function. Our identification and characterization of the Mg^{2+} flux components will further investigate how, and if, these signaling routes impinge on the pathophysiology of a growing number of Mg^{2+} deficiency diseases in humankind.

Contact: muniswamy@uthscsa.edu

Scientific presentation: Intracellular Mg^{2+} mobilizing ligands, channels, and pathways



Regulatory role of Mg2+ in immune cells

Michael Lenardo
Laboratory of Immune System Biology, National Institutes of Allergy and Infectious Diseases, National Institute of Health, Besthesda, ***USA***

Mg2+ is required at micromolar concentrations as a co-factor for ATP, enzymatic reactions, and other biological processes. We show that decreased extracellular Mg2+ reduced intracellular Mg2+ levels, impaired the Ca2+ flux, activation markers, and proliferation after T cell receptor (TCR) stimulation. Reduced Mg2+ specifically impairs TCR signal transduction by IL-2-inducible T cell kinase (ITK) due to a requirement for a regulatory Mg2+ in the catalytic pocket of ITK. We also show that altered catalytic efficiency by millimolar changes in free basal Mg2+ is an unrecognized but conserved feature of other serine/threonine and tyrosine kinases suggesting a Mg2+ regulatory paradigm of kinase function. Finally, reduced serum Mg2+ concentration in mice causes an impaired CD8+ T cell response to Influenza A virus infection and exacerbates morbidity. Thus, Mg2+ directly regulates the active site of specific kinases during T cell responses and maintaining high serum Mg2+ concentration is important for anti-viral immunity in otherwise healthy animals. This research was supported [in part] by the Intramural Research Program of the NIH.

Bio-sketch:

Michael J. Lenardo is a trained geneticist, molecular biologist, and immunologist. He is internationally recognized for discovering the genetic basis, pathogenesis, and treatment of several inborn errors of the immune system. He graduated from The Johns Hopkins University with a B.A. in Natural Sciences. He obtained his MD from Washington University-St. Louis, and postdoctoral research training at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology under the mentorship of Nobel laureates David Baltimore and Philip Sharp. In 1989, he became an investigator in the intramural program of National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health, and later founded and currently directs the NIAID Clinical Genomics Program. He is credited with the discovery of several inborn errors of immunity resulting from mutations of genes encoding for Fas, caspases 8 and 10, PI-3 kinase p110, CTLA-4 and its regulator LRBA, CD55, and the MagT1 magnesium transporter. Dr. Lenardo is a member of the U.S. National Academies of Science and Medicine.

Scientific presentation:
Dr. Lenardo will discuss the impact of magnesium levels on immune functioning and new approaches to measure intracellular magnesium.

Contact: mlenardo@niaid.nih.gov

Mg and development

Loren Runnels
Department of Pharmacology Rutgers, Robert Wood Johnson Medical School
Piscataway, NJ, ***USA***

It has been over fifty years since pioneering studies in rats fed a magnesium-deficient diet demonstrated an essential role for the Mg^{2+} during development. Pregnant females fed a Mg^{2+} deficient diet between days 6 and 14 of gestation showed a high incidence of resorptions and gross malformation in the full-term fetuses. Epidemiological studies in humans point to a similar dependence in that Mg^{2+} deficiency is associated with a negative impact on human fetal growth and development. However, molecular mechanism by which Mg^{2+} influences development is poorly understood. Many of the signaling molecules that regulate early embryogenesis were originally identified in *Xenopus laevis,* whose embryos mature ex vivo, facilitating direct observation and manipulation of the developing embryos. *Xenopus laevis* embryos reared in media with micromolar Mg^{2+} concentrations frequently exhibit edema and gastrulate poorly, showing a curved axis and reduced rates of tail expansion, as well as other phenotypes. Studies of *Xenopus* embryos depleted of TRPM7, TRPM6, and SLC41A1, macromolecules involved in the cellular homeostasis of Mg^{2+}, develop similar but more severe developmental abnormalities, suggesting that cellular Mg^{2+} levels in cells undergoing morphogenesis must be exquisitely regulated for successful completion of embryogenesis.

Biosketch: Professor, Department of Pharmacology**,** Rutgers, Robert Wood Johnson Medical School

Loren Runnels received his B.S. in Engineering Physics from the Colorado School of Mines, an engineering school in Golden, Colorado, U.S.A. Upon graduation he joined the Biophysics program in the Department of Physiology at Stony Brook University (Stony Brook, New York, USA), where he worked with Dr. Suzanne Scarlata, on the study and regulation of phospholipase C (PLC) enzymes by G proteins. Loren Runnels did his postdoctoral studies with Dr. David Clapham (Harvard Medical School). While in his lab, Loren Runnels continued research on PLC by performing a yeast two-hybrid (Y2H) screen using the COOH-terminal of PLC-□1 as bait and discovered the TRPM7 ion channel as the first ion channels with its own kinase domain. Loren Runnels began his career as an independent investigator at Rutgers-Robert Wood Johnson Medical School in 2002. The focus of his lab is to understanding the biological functions and regulation of the channel-kinases TRPM7 and TRPM6.

Contact: runnellw@rwjms.rutgers.edu

Summary of Talk: In this presentation we summarize what is known regarding the role Mg^{2+} in early embryonic development and present research findings regarding the function of the TRPM6 and TRPM7 ion channels during embryogenesis in model organisms.

UNIVERSITÀ DEGLI STUDI DI ENNA "KORE"

Magnesium and Aging

Ligia Dominguez, Mario Barbagallo

Department of Medicine and Surgery, Kore University of Enna, ***Italy***

Aging is often associated with a total body magnesium (Mg) deficit. While serum Mg levels seem to remain constant with age, several changes of Mg metabolism have been reported with aging, including diminished Mg intake, impaired intestinal Mg absorption and renal Mg wasting. Mild Mg deficits are generally asymptomatic and clinical signs are usually non-specific or absent. Asthenia, sleep disorders, hyperemotionality, and cognitive disorders are common in older adults with mild Mg deficit, and may be often confused with age-related symptoms. Chronic Mg deficits increase the production of free radicals, which have been implicated in the development of several chronic age-related disorders. Numerous human diseases have been associated with Mg deficits, including cardiovascular diseases, hypertension and stroke, cardio-metabolic syndrome and type 2 diabetes mellitus, airways constrictive syndromes and asthma, depression, stress-related conditions and psychiatric disorders, Alzheimer's disease (AD) and other dementia syndromes, muscular diseases (muscle pain, chronic fatigue, and fibromyalgia), bone fragility, and cancer. Dietary Mg and/or Mg consumed in drinking water (generally more bioavailable than Mg contained in food) or in alternative Mg supplements should be taken into consideration in the correction of Mg deficits. Maintaining an optimal Mg balance all through life may help in the prevention of oxidative stress and chronic conditions associated with aging. This needs to be demonstrated by future studies.

Bio-sketch:

Dr. Ligia J. Dominguez was born in Colombia where she graduated in medicine and completed her residency in Internal Medicine at the "Universidad del Rosario" in Bogota. She then joined the Division of Endocrinology, Metabolism and Hypertension at Wayne State University (Detroit, MI) carrying out basic and clinical research, and completing the specialization in Endocrinology. She moved to Italy in 1996, continuing her clinical and research interests in the fields of diabetes and its complications, nutrition, and bone and mineral metabolism, in relation to aging.

Dr. Dominguez is currently a full professor at the Kore University of Enna (Italy), where she teaches in the Faculty of Medicine and Surgery and in the Postgraduate School of Geriatrics at the University of Palermo (Italy). She has authored over 300 publications in peer reviewed national and international scientific journals and has been invited as speaker at national and international meetings.
Contact: ligia.dominguez@unipa.it

Mg and aging:

Mg deficiency, aside from having a negative impact on the energy production pathway required by mitochondria to generate ATP, also reduces the threshold antioxidant capacity of the aging organism and its resistance to free-radical damage. Chronic inflammation and oxidative stress have both been identified as pathogenic factors in aging and in several age-related diseases, while aging is very often associated with Mg inadequacy.

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Magnesium and Progeria

Ricardo Villa-Bellosta

Department of Biochemistry and Molecular Biology, University of Santiago de Compostela, ***Spain***

Aging is associated with redox imbalance according to the redox theory of aging. Consistently, a mouse model of premature aging (LmnaG609G/+) showed an increased level of mitochondrial reactive oxygen species (ROS) and a reduced basal antioxidant capacity, including loss of the NADPH-coupled glutathione redox system. LmnaG609G/+ mice also exhibited reduced mitochondrial ATP synthesis secondary to ROS-induced mitochondrial dysfunction. Treatment of LmnaG609G/+ vascular smooth muscle cells with magnesium-enriched medium improved the intracellular ATP level, enhanced the antioxidant capacity, and thereby reduced mitochondrial ROS production. Moreover, treatment of LmnaG609G/+ mice with dietary magnesium improved the proton pumps (complexes I, III, and IV), stimulated extramitochondrial NADH oxidation and enhanced the coupled mitochondrial membrane potential, and thereby increased H+-coupled mitochondrial NADPH and ATP synthesis, which is necessary for cellular energy supply and survival. Consistently, magnesium treatment reduced calcification of vascular smooth muscle cells in vitro and in vivo and improved the longevity of mice. This antioxidant property of magnesium may be beneficial in children with HGPS.

Bio-sketch:

Ricardo Villa-Bellosta holds a PhD (2010) by the University of Zaragoza, Spain. His doctoral thesis got the Spanish Royal Academy of Doctors Award and Extraordinary doctoral Award. He joined (2021) the Center for Research in Molecular Medicine and Chronic Disease (CiMUS) in Santiago de Compostela University, as group leader of the “Metabolic Homeostasis and Vascular Calcifcation” laboratory. His laboratory is focused on the role of phosphate and pyrophosphate homeostasis in vascular calcifcation in progeria, aging, diabetes, chronic kidney disease and several genetic disorders.

Contact: ricardo.villa@usc.es

Magnesium, an invisible deficiency that could be harming your muscle health

Sara Castiglioni
Department of Clinical and Biomedical Sciences "Luigi Sacco", University of Milano, ***Italy***

Purpose:
Magnesium (Mg) deficiency is the most underestimated electrolyte imbalance in Western countries and is related to many dysfunctions. 25% of body Mg is located in skeletal muscle, where it is crucial for fibers relaxation. Hypomagnesemia is associated to muscle weakness and cramps and can contribute to oxidative stress, inflammation and age-related sarcopenia. In a murine model, a mild Mg deficiency is enough to alter the expression of genes important for muscle energy metabolism, regeneration, mitochondria dynamics and muscle proteostasis. We deeper investigated how Mg deficiency impacts on skeletal muscle myogenesis, physiology, and metabolism *in vitro*.

Materials and methods:
We used C2C12 murine myoblasts that, under serum depletion, differentiate to multinucleated myotubes with contractile capacity. Both myoblasts and myotubes were exposed to physiological and low Mg concentrations. Protein expression was evaluated by western blot and immunofluorescence. Oxidative stress and metabolic parameters were studied with colorimetric and fluorescent assays.

Results:
Mg deficiency affects myogenesis through a ROS-dependent impairment of myoblasts membrane fusion. Differentiated myotubes exposed to low Mg show a strong downregulation of myosin heavy chain and myogenin and a reduced thickness compared to controls cultured in physiological Mg. We demonstrated that low Mg impairs the autophagic flux, which is essential for muscle physiology, probably through the overproduction of nitric oxide. In myotubes cultured in Mg deprivation, we also observed a reduction of neutral lipids content and an increase of beta-oxidation rate compared to control cells maintained in physiological Mg. Preliminary data showed that the increase of nitric oxide that occurs in low Mg condition could be responsible for the lipid metabolism remodelling too.

Conclusions:
Our data show that low Mg induces a significant stress response both in myoblasts and myotubes thus impairing essential processes for muscle homeostasis maintenance.

Bio-sketch:

Sara Castiglioni is Associate Professor of General Pathology at the Department of Biomedical and Clinical Sciences of University of Milan, Italy. With a degree in Biological Science (2003) and PhD in Molecular Medicine (2008), she has a strong expertise in cellular and molecular biology. Her areas of research include osteogenic and myogenic differentiation, magnesium homeostasis and cell microgravity.

Contact: sara.castiglioni@unimi.it

Short sentence on my scientific presentation:

In her speech, she will talk about the effects of magnesium deficiency on myogenesis, skeletal muscle physiology and metabolism in an *in vitro* model of murine myoblasts.

The molecular appearance and regulatory mechanisms of TRPM7 channel complexes

Vladimir Chubanov

Department of Pharmacology and Toxicology, Walther-Straub Institute, LMU Munich, ***Germany***

The transient receptor potential cation channel, subfamily M, members 6 and 7 (TRPM6 and TRPM7) are homologous membrane proteins encompassing cation channel units fused to cytosolic serine/threonine-protein kinase domains. An emerging paradigm is that the organismal balance of Mg^{2+} predominantly depends on TRPM6 and TRPM7. Despite extensive electrophysiological studies and recent cryo-EM analysis, an open question is how the channel activity of TRPM6/M7 is regulated. Clinical studies and experiments with animal disease models suggested that selective inhibition of TRPM6 and TRPM7 currents might be beneficial for subjects with immune and cardiovascular disorders, tumours and other pathologies, but the suitable pharmacological toolkit remains underdeveloped. Here, we report the structural underpinnings through which the TRPM7 channel is controlled by cytosolic Mg^{2+}. In addition, we outline our recent progress in the identification and functional characterisation of accessory subunits of native TRPM7. Finally, we present newly identified small synthetic molecules acting as selective inhibitors of the channel and kinase units of TRPM6 and TRPM7. Overall, our study offers new mechanistic insights into the functions of TRPM6 and TRPM7.

Bio-sketch:
Studies of my group are focused on TRPM6 and TRPM7, bifunctional proteins comprising a channel segment linked to an α-type protein kinase. Loss-of-function mutations in the human *TRPM6* gene cause an autosomal recessive disorder, hypomagnesemia 1, intestinal (HOMG1) also called hypomagnesemia with secondary hypocalcemia (HSH). Clinical studies and experiments with animal disease models suggested that *TRPM7* is implicated in immune and cardiovascular disorders, tumours and other pathologies. The major goal of our studies is to attain mechanistic knowledge about the physiological and pathophysiological roles of kinase-coupled channels using TRPM6- and TRPM7-deficient mice and preclinical *in vitro* models of human diseases.
Contact: vladimir.chubanov@lrz.uni-muenchen.de

Short sentence on my scientific presentation:
In his speech, he will talk about the role of intracellular Mg^{2+}, newly identified interaction partners and pharmacological agents in the regulation of TRPM6 and TRPM7.

Genetic causes of hypomagnesemia

Jeroen De Baaij
Department of Physiology Radboud institute for Molecular Life Sciences, Radboud University Medical Center Nijmegen, ***the Netherlands***

Introduction and objective: Over the last decade, advances in genetic techniques have resulted in the identification of rare hereditary disorders of renal magnesium and salt handling. Nevertheless, approximately 20% of all patients with hypomagnesemia lack a genetic diagnosis. In this oral presentation, I'll provide an overview of the two recently identified novel causes of hypomagnesemia.

Results: In eight children from unrelated families with a tubulopathy characterized by hypomagnesemia, hypokalemia, salt wasting, and nephrocalcinosis, we identified heterozygous missense variants in *RRAGD* that mostly occurred *de novo*. Six of these patients also had dilated cardiomyopathy and three underwent heart transplantation. We identified a heterozygous variant in *RRAGD* that segregated with the phenotype in eight members of a large family with similar kidney manifestations.
In a cohort of patients with suspected Gitelman syndrome, we identified four mtDNA variants in 13 families: m.591C>T (n=7), m.616T>C (n=1), m.643A>G (n=1) (all in MT-TF), and m.4291T>C (n=4, in MT-TI). Variants were near homoplasmic in affected individuals. All variants were classified as pathogenic, except for m.643A>G, which was classified as a variant of uncertain significance. Importantly, affected members of six families with an MT-TF variant additionally suffered from progressive chronic kidney disease. Dysfunction of oxidative phosphorylation complex IV and reduced maximal mitochondrial respiratory capacity were found in patient fibroblasts.

Conclusion: Our identification of hypomagnesemia-causing mutations in the mTOR pathway and the mitochondrial DNA demonstrate the central role of cell metabolism in renal magnesium transport.

Bio-sketch:

Jeroen de Baaij (1987) is a physiologist interested in the molecular and genetic origin of renal electrolyte disorders, including hypomagnesemia. He works as associate professor at the Radboud University Medical Centre in Nijmegen, the Netherlands. His research focusses on the identification and characterisation of new genes involved in renal magnesium reabsorption. Using a wide range of molecular, cellular and physiological techniques, he examines new genes or new regulatory pathways in magnesium (re)absorption in the kidney. Supported by ERC Starting, NWO Rubicon and Veni Grants and a Dutch Kidney Foundation Kolff Grant, his team is also examining the role of magnesium in the prevention of cardiovascular complications and in the development of the type 2 diabetes mellitus.
Contact: Jeroen.deBaaij@radboudumc.nl

Universität Zürich[UZH]

Structural and functional properties of a magnesium transporter of the SLC11/NRAMP family

Cristina Manatschal
Department of Biochemistry, University of Zurich, ***Switzerland***

Members of the ubiquitous SLC11/NRAMP family catalyze the uptake of divalent transition metal ions into cells. They have evolved to efficiently select these trace elements from a large pool of Ca^{2+} and Mg^{2+}, which are both orders of magnitude more abundant, and to concentrate them in the cytoplasm aided by the cotransport of H^+ serving as energy source. In the present study, we have characterized a member of a distant clade of the family found in prokaryotes, termed NRMTs, that were proposed to function as transporters of Mg^{2+}. The protein transports Mg^{2+} and Mn^{2+} but not Ca^{2+} by a mechanism that is not coupled to H^+. Structures determined by cryo-EM and X-ray crystallography revealed a generally similar protein architecture compared to classical NRAMPs, with a restructured ion binding site whose increased volume provides suitable interactions with ions that likely have retained much of their hydration shell.

Bio-sketch:
Cristina Manatschal studied Biochemistry at the ETH Zürich (Switzerland) and then moved to the Paul Scherrer Institute (PSI, Villigen, Switzerland) to conduct her PhD thesis in biophysical and structural aspects of microtubule binding proteins. Since 2014 she is working in the group of Prof. Raimund Dutzler at the biochemistry Institute of University of Zurich (Switzerland) to work on structure and function of iron transport proteins of the SLC11/NRAMP family of prokaryotic and eukaryotic origin.

short sentence on my scientific presentation:

We have functionally and structurally characterized a bacterial member of a distant clade of the SLC11/NRAMP family, that was proposed to function as transporter of Mg2+, instead of Fe2+ and Mn2+, and thereby we have shed light on the factors responsible for selectivity of transition and alkali metal ions in this transporter family.

Contact: c.manatschal@bioc.uzh.ch

TRPM7 is protective against cardiovascular damage induced by aldosterone and salt

Francisco Rios
Department of Cardiovascular and Medical Sciences, University of Glasgow, ***UK***

Francisco J Rios, PhD[1]; Zhi-Guo Zou, PhD[1]; Adam P. Harvey, PhD[1]; Katie Y. Harvey, PhD[1]; Livia L. Camargo, PhD[1]; Karla B Neves, PhD[1]; Sarah E.F. Nichol, Hons[1]; Rheure A. Lopes, PhD[1], Thomas Gudermann, MD, PhD[2]; Vladimir Chubanov, PhD[2]; Augusto C. Montezano, PhD[1], Rhian M. Touyz, MD, PhD[1,3]

[1] Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom.
[2]Walther-Straub Institute of Pharmacology and Toxicology, Ludwig-Maximilians-Universität München, Munich, Germany.
[3]Research Institute of McGill University Health Centre, McGill University, Montreal, Canada.

Objective: The channel-kinase Transient receptor potential melastatin-7 (TRPM7) is permeable to Mg^{2+}, Ca^{2+} and Zn^{2+} and regulates cellular signaling homeostasis. We demonstrated that TRPM7 is protective against cardiac inflammation and dysfunction. Since hyperaldosteronism causes hypertension and Mg^{2+} wasting, we questioned whether TRPM7 plays a role in aldosterone-induced hypertension and cardiovascular fibrosis.

Methods: Wild-type (WT) and TRPM7-deficient (M7+/Δ) mice were treated with aldosterone (600µg/Kg/day) and/or 1% NaCl (drinking water) (aldo, salt or aldo/salt) for 4 weeks. Blood pressure (BP) was evaluated by tail-cuff. Vascular function was investigated by wire myography. Molecular mechanisms of fibrosis and inflammation were investigated in cardiac fibroblasts (CF) isolated from WT and M7+/Δ mice. Protein expression was assessed by western-blot and histology.

Results: Aldo/salt reduced renal TRPM7 expression (30%) and kinase phosphorylation (62%) in WT, similarly to levels observed in M7+/Δ-veh tissues. M7+/Δ exhibited increased BP by aldo (140mmHg), salt (135mmHg) and aldo/salt (137mmHg) vs M7+/Δ-veh (117mmHg) ($p<0.05$), whereas in WT, BP was increased only by aldo/salt (134mmHg). All treatments induced endothelial dysfunction small vessels from M7+/Δ as observed in acetylcholine-relaxation curves [Emax% M7+/Δ: aldo (81±4), salt (69±4) and aldo/salt (75±3.0), $p<0.05$], whereas in WT, Emax% was reduced after aldo (68±4) and aldo/salt (80±3). Phenylephrine-contraction and SNP-relaxation curves were similar among groups.

Aldo/salt induced higher collagen deposition in hearts (68%) and kidneys (126%) from M7+/Δ vs WT. Collagen deposition in aortas was increased only in M7+/Δ-aldo (31%) and M7+/Δ-aldo/salt (45%). Hearts from M7+/Δ exhibited increased p-Smad3 (45%), p-Stat1 (51%), TGFβ (125%), IL-11 (72%) and IL-6 (93%) vs WT ($p<0.05$). CF from M7+/Δ exhibit increased p-Smad3 (48%), p-p-Stat1 (32%), TGFβ (43%), IL-11 (38%), IL-6 (48%) and reduced proliferation (33%) vs WT. All these effects were ameliorated by Mg^{2+} supplementation ($p<0.05$).

Conclusions: We define a novel protective role of TRPM7 in aldosterone-salt induced cardiovascular damage, which when downregulated, promotes hypertension, vascular remodeling and cardiac fibrosis through Mg^{2+}-dependent mechanisms.

Bio-sketch:

Research Fellow at the Institute of Cardiovascular and Medical Sciences, University of Glasgow (UK). His research is focused on magnesium transporters in immune/inflammatory mechanisms associated with cardiovascular diseases, including hypertension and organ damage.
In his speech, he will talk about the effects of TRPM7 in cardiovascular fibrosis
Contact: Francisco.Rios@glasgow.ac.uk
Twitter: @fjorios

Radboud umc
university medical center

Severe magnesium wasting in Kenny Caffey Syndrome- searching for molecular causes

Heidi Schigt
*Department of Molecular Life Sciences, Radboud Institute, Nijmegen, **the Netherlands***
Francisco Rios
*Department of Cardiovascular and Medical Sciences, University of Glasgow, **UK***

FAM111A may affect magnesium homeostasis through cytoskeletal disruption and STAT1 signaling

Abstract body:

Introduction and objective: Kenny-Caffey syndrome type 2 is a rare disorder characterized by hypoparathyroidism and electrolyte disturbances, including hypocalcemia and hypomagnesemia. It is caused by mutation in family with sequence similarity 111A (*FAM111A*) that encodes a protein about which little is known. The objective of this study was to elucidate the molecular mechanisms by which FAM111A is involved in magnesium homeostasis.

Materials and methods: A case series and systematic literature review were performed to obtain more insight into the phenotype of KCS2. A FAM111A pull-down on the cytoplasmic and nuclear fractions of HeLa cells was done to identify protein interactors. Immunocytochemistry and a scratch assay were used to study effects on the cytoskeletal integrity and cell migration. The effect of FAM111A on STAT1 transcriptional activity was investigated using a luciferase assay for a gamma-interferon-activation site promoter and quantitative PCR. STAT1 knockout mice were kept on a normal diet and serum and urine were collected to measure magnesium.

Results: The case study and literature review show that hypomagnesemia is a common feature of KCS2 and that patients may be at risk for chronic kidney disease. A pull-down identified cytoskeletal proteins and signal transducer and activator of transcription 1 (STAT1) as interactors of FAM111A. Tubulin repolymerization and cell migration were delayed by FAM111A mutation. Mutations in FAM111A also reduce STAT1-regulated transcription. In turn, STAT1 positively regulates transient receptor potential cation channel 6 (TRPM6). STAT1 knockout mice display hypomagnesemia and renal magnesium wasting.

Conclusion: The cytoskeleton as well as STAT1 signalling may play a role in disturbing magnesium homeostasis in Kenny-Caffey syndrome.

Bio-sketch

Heidi Schigt is a 3rd year PhD student at the Department of Molecular Physiology of the Radboud University Medical Center in Nijmegen, the Netherlands. Previously, she studied Molecular Life Sciences and performed internships in the fields of embryology, ciliopathies and 3D engineered bone tissue. Her current work focuses on the protein FAM111A that is implicated in a rare disorder called Kenny-Caffey syndrome type 2. The phenotype is heterogeneous, but affected patients generally have low parathormone, hypocalcemia and hypomagnesemia and display growth retardation. The relationship between FAM111A and these symptoms is unclear, however, as this protein has received little attention in literature. In her talk, Heidi will discuss recent advances in uncovering this process.

Contact: Heidi.Schigt@radboudumc.nl

Yale University

How Pathogens Feel and Overcome Magnesium Limitation

Eduardo A. Groisman
Department of Microbial Pathogenesis, Yale School of Medicine
*New Haven, **USA***

Salmonella enterica serovar Typhimurium (*S.* Typhimurium) is a facultative intracellular pathogen responsible for gastroenteritis in humans and a typhoid fever-like disease in mice used as a model for the disease that the human-specific serovar Typhi causes in humans. The master regulator of *S.* Typhimurium virulence PhoP/PhoQ is activated by multiple signals including low extracytoplasmic Mg^{2+}. Expression of some PhoP-activated virulence genes is induced in response to an increase in the concentration of adenosine triphosphate (ATP). The negatively charged ATP is normally neutralized by Mg^{2+} and constitutes the energy currency of all living cells. The PhoP-activated MgtC protein reduces the bacterial ATP concentration, which decreases protein synthesis, slows down bacterial growth, and enhances resistance to antibacterial agents. The decrease in ATP concentration decreases proteolysis of functional by ATP-dependent proteases, which speeds the return to a growth state. The PhoP-activated Mg^{2+} transporter MgtB is a necessary for survival in both mammalian hosts harboring a wild-type copy of the macrophage phagosomal protein SLC11A1 and low Mg^{2+} laboratory media, suggesting *S.* Typhimurium experiences Mg^{2+} starvation inside SLC11A1 macrophages. The PhoP-activated MgtU membrane peptide protects MgtB, but not the related Mg^{2+} transporter MgtA, from degradation by the protease FtsH. The inability to protect MgtB from proteolysis renders *S.* Typhimurium hypersusceptible to killing by oxidative stress. Plague agent *Yersinia pestis* requires both MgtB and MgtC for virulence. Disruption of bacterial Mg^{2+} homeostasis emerges as a possible anti-bacterial strategy.

Bio-sketch

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Buenos Aires, Argentina	M.S.	1980	Biochemistry
University of Chicago, Chicago, IL	Ph.D.	1986	Molecular Genetics & Cell Biology
Institut Pasteur, Paris, France	Postdoctoral	1987	Bacterial Pathogenesis
The Scripps Research Institute	Postdoctoral	1987-1989	Bacterial Pathogenesis
University of California San Diego, CA	Postdoctoral	1989-1990	Bacterial Gene Control

Scientific Appointments

1990-1996 Assistant Professor, Department of Molecular Microbiology, Washington University

1996-2000 Associate Professor, Department of Molecular Microbiology, Washington University1997-2016 Investigator, Howard Hughes Medical Institute
2000-2010 Professor, Department of Molecular Microbiology, Washington University 2010-2018 Professor, Department of Microbial Pathogenesis, Yale School of Medicine2010-present Member, Microbial Sciences Institute, Yale University

2018-present Waldemar Von Zedtwitz Professor of Microbial Pathogenesis, Yale School of Medicine

Honors

1987 Philippe Foundation

1987 Association pour Développement de l'Institut Pasteur
1987-1990 The Jane Coffin Childs Memorial Fund for Medical Research1994-1996 American Cancer Society Junior Faculty Research Award
1995-2000 Research Career Development Award, National Institutes of Health2003 Elected to Fellowship in the American Academy of Microbiology
2008 Elected to Fellowship in the American Association for the Advancement of Science2019 Yale Postdoctoral Mentoring Award
2022 Elected to Fellowship in the American Academy of Arts and Sciences

Short sentence on my presentation:

I will discuss how bacterial pathogens detect changes in the magnesium concentrationin their surroundings and in their cytoplasm, and the physiological response they mount to overcome magnesium limitation.

Contact: eduardo.groisman@yale.edu

Counteract bacterial infections: factor SLC11A1 restricts *Salmonella* growth through magnesium deprivation

Olivier Cunrath

*Department of Metals and Microorganisms, University of Strasbourg, Illkirch**, France***

inflammation.

Abstract:

Solute carrier family 11, member 1 (SLC11A1; also called natural resistance-associated macrophage protein 1, NRAMP1) is a major host-resistance factor that controls susceptibility to intracellular pathogens such as *Salmonella*, *Mycobacteria*, and *Leishmania* in mice, cattle, and humans. SLC11A1 is a major host factor with pleiotropic impact on diverse aspects of physiology. Its main resistance mechanism against intracellular pathogens has remained enigmatic for several decades. Here, I will present our study that shows that SLC11A1 reduces *Salmonella* proliferation without enhancing *Salmonella* killing, triggers a divalent metal starvation response but no other stress responses, imposes a specific requirement for high-affinity transport of Mg^{2+} but no other metals, and provokes single-cell properties equivalent to *Salmonella* with poor access to magnesium. Together, these data identify growth-limiting magnesium starvation as the main resistance mechanism of SLC11A1.

Bio-sketch:

Olivier Cunrath is an independent CNRS researcher at the research institute Irebs, Strasbourg, France. He obtained his PhD in microbiology at the University of Strasbourg, France, in 2015 where he studied the implication of siderophores in the general metal homeostasis of the bacterial pathogen *Pseudomonas aeruginosa*. Afterwards, he joined for three years the Biozentrum in Basel, Switzerland, to study the metal homeostasis in *Salmonella enterica* during systemic infection and how the hosts inhibit bacterial pathogens through nutritional immunity. In 2018, he joined the Department of Zoology and Biochemistry at the University of Oxford, UK, to study how the gut microbiome can inhibit enteric pathogens from invading the intestine and causing disease. In 2021, he became a CNRS associate professor at the research institute Irebs, France, where he now studies the metal homeostasis in complex microbial communities.

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Magnesium therapy improves outcome in Streptococcus pneumoniae meningitis by altering pneumolysin pore formation

Asparouh Iliev
Department of Molecular Neuroinfectiology, *University of Bern,* ***Switzerland***

Interaction of Adenovirus Type 5 E4orf4 with the PRL-CNNM Complex Enhances Magnesium Transport and Viral Replication

Michel L. Tremblay
Department of Biochemistry and Goodman Cancer Institute. McGill University, Montreal, ***Canada***

The Adenovirus type 5 E4orf4 protein (E4orf4) is a multifunctional protein that regulates viral and host gene expression and splicing. E4orf4 interacts directly with the cellular phosphatase PP2A and recruits target phosphoproteins into complexes, resulting in dephosphorylation of host factors, such as SR splicing factors and the AP1 transcription factor. A recent proteomic study showed that E4orf4 interacts with a protein complex called PRL/CNNM, which is known to regulate magnesium (Mg2+) homeostasis in mammalian cells. Magnesium is essential for all life as it is bound to nucleotides and is a required co-factor for hundreds of enzymes, thus bearing crucial functions for both cellular and viral activities. Using immunoprecipitation, we demonstrated that E4orf4 forms a complex with PP2A and PRL/CNNM. Furthermore, PRL/CNNM becomes dephosphorylated in the presence of E4orf4. Our results show that E4orf4 binds PRL/CNNM and mediates the PP2A-dependent dephosphorylation of the complex in a similar mechanism previously shown for SR splicing factors and AP1. We then tested the role of the E4orf4-PRL/CNNM interaction for adenovirus replication. We observed that knockout of CNNM3 expression by CRISPR/Cas9 resulted in reduced viral replication. Furthermore, viral mutants that do not express E4orf4 maintained lower intracellular concentrations of magnesium relative to wild-type virus. Our results demonstrate for the first time a viral mechanism to enhance magnesium transport during infection. Current evidence suggests that a wide range of viruses and other intracellular parasites may modulate the PRL/CNNM complex in order to enhance infection.

Bio-sketch

Distinguished James McGill Professor in the Department of Biochemistry at McGill University in Montreal, Canada.
He funded and directed the Rosalind and Morris Goodman Cancer Research Centre from 2000 to 2012. A fellow of the Royal Society of Canada, Dr. Tremblay's laboratory focuses on characterizing the function and regulation of several members of the Protein Tyrosine Phosphatase (PTP) gene family using both biochemical and genetic approaches. He has several translational research programs towards clinical applications of PTP inhibitors in the fields of immunotherapy and cancer. Within international collaborations, he has published key findings on the interaction of the CNNMs and PTP4As gene sub-families and their relationships between magnesium and cancer.
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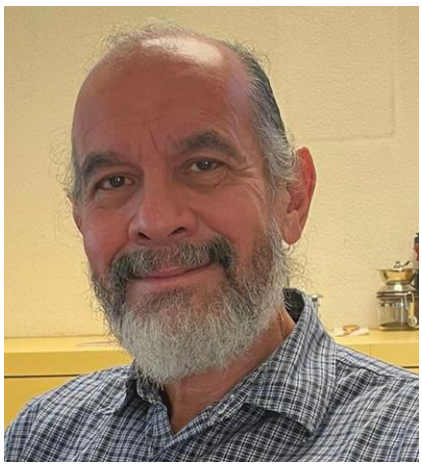

Mg in Sars-Cov-2

Fernando Guerrero-Romero
Biomedical Research Unit of the Mexican Social Security Institute at Durango, Research Group on Diabetes and Chronic Illnesses at Durango, ***Mexico***

Hypomagnesemia is a risk factor for developing of type 2 diabetes, arterial hypertension, decreased immune response, triggering of the cytokine storm, endothelial dysfunction, arrhythmias, depression, fatigue, sleep disturbances, and thromboembolism. Disorders that are common clinical manifestations of COVID-19 and/or the post-COVID syndrome; therefore, it is plausible to assume that magnesium deficiency might play an important role in the SARS-Cov-2 infection.
Current evidence suggests that magnesium plays an important role in the immune response, and in the regulation of NF-κB activation, the cytokine production, and in the proliferation and development of lymphocytes.
We will present novelty results of cross-sectional studies and randomized clinical trials conducted to evaluate the role of hypomagnesemia as a risk factor for both the COVID-19 disease and post-COVID syndrome.

Bio-sketch:

Dr. Fernando Guerrero Romero is a Level III National Researcher of the National Mexican System of Scientists and a Senior Researcher of the Mexican Institute of Social Security. He is currently the Head of the Biomedical Research Unit from Durango, Mexico.
Dr. Guerrero is an Internist, Fellow of the American College of Physicians and the American Society of Internal Medicine, and has a PhD in medicine.
To date, he has published 222 articles in indexed journals and 35 book chapters. As of December 2020 he has 5,700 third party citations.
He has graduated 38 Bachelor's students, 12 Specialty students, 16 Master's students, and 10 Doctorate students.
He is, or has been, Member of the Editorial Committee in 7 international journals and reviewer in 151 scientific journals; currently, is an Academic Editor of Plos One.
His career has been recognized with 30 awards and 15 National and International distinctions.

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Increased Mortality Associated with Hypermagnesemia in Severe COVID-19 Illness

Jacob Stevens
Department of Nephrology, Columbia University Irving Medical Center New York, ***USA***

Background: Although electrolyte abnormalities are common among patients with COVID-19, very little has been reported on magnesium homeostasis in these patients. Here we report the incidence of hypermagnesemia, and its association with outcomes among patients admitted with COVID-19.

Methods: We retrospectively identified all patients with a positive test result for SARS-CoV-2 who were admitted to a large quaternary care center in New York City in spring 2020. Details of the patients' demographics and hospital course were obtained retrospectively from medical records. Patients were defined as having hypermagnesemia if their median magnesium over the course of their hospitalization was >2.4 mg/dl.

Results: A total of 1685 patients hospitalized with COVID-19 had their magnesium levels checked during their hospitalization, and were included in the final study cohort, among whom 355 (21%) had hypermagnesemia. Patients who were hypermagnesemic had a higher incidence of shock requiring pressors (35% vs 27%, $P<0.01$), respiratory failure requiring mechanical ventilation (28% vs 21%, $P=0.01$), AKI (65% vs 50%, $P<0.001$), and AKI severe enough to require renal replacement therapy (18% vs 5%, $P<0.001$). In an adjusted multivariable model, hypermagnesemia was observed more commonly with increasing age, male sex, AKI requiring RRT, hyperkalemia, and higher CPK. Survival probability at 30 days was 34% for the patients with hypermagnesemia, compared with 65% for patients without hypermagnesemia. An adjusted multivariable time to event analysis identified an increased risk of mortality with older age, need for vasopressors, higher C-reactive protein levels, and hypermagnesemia (HR, 2.03; 95% CI, 1.63 to 2.54, $P<0.001$).

Conclusions: In conclusion, we identified an association between hypermagnesemia among patients hospitalized with COVID-19 and increased mortality. Although the exact mechanism of this relationship remains unclear, hypermagnesemia potentially represents increased cell turnover and higher severity of illness, which is frequently associated with more severe forms of AKI."

Biographical Sketch:
Dr. Stevens is an Assistant Professor of Medicine in the Division of Nephrology at Columbia University Medical Center in New York City. His fascination for physiology began at Bowdoin College where he majored in Neuroscience and Neurophysiology. He then completed his medical degree at Dartmouth Medical School and trained at Massachusetts General Hospital for internship and residency before moving to New York City to complete his nephrology fellowship at Columbia University Medical Center where he remains on faculty. His clinical and research interests include critical care nephrology and improving the care provided to patients with acute kidney injury and he is the Medical Director of Acute Care Nephrology at Columbia University Irving Medical Center.

Scientific Presentation:
Although electrolyte abnormalities are common among patients with COVID-19, very little has been reported on magnesium homeostasis in such patients. I will report the incidence of hypermagnesemia and its association with outcomes among patients with COVID-19 illness.

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Serum magnesium concentration and incident cognitive impairment: findings from the REGARDS study

Ka Kahe
*Columbia University Irving Medical Center, New York, **USA***

Purpose: To examine the prospective association between serum Mg level and the incidence of cognitive impairment.

Methods: A random sub-cohort (n = 2063) from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort was included in this study. Baseline serum Mg concentration was measured using inductively coupled plasma mass spectrometry. According to the current reference interval of serum magnesium (0.75-0.95 mmol/L), we classified participants below the interval as Level 1 and used it as the referent. The rest of the study population were equally divided into three groups, named Level 2 to 4. Incident cognitive impairment was identified using the Six-Item Screener. Multivariable-adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using logistic regression models.

Results: After adjustment for potential confounders, an inverse threshold association between serum Mg level and incident cognitive impairment was observed. Compared to those with hypomagnesemia (Level 1: < 0.75 mmol/L), the relative odds of incident cognitive impairment was reduced by 41% in the second level [OR (95% CI) = 0.59 (0.37, 0.94)]; higher serum Mg level did not provide further benefits [Level 3 and 4 versus Level 1: OR (95% CI) = 0.54 (0.34, 0.88) and 0.59 (0.36, 0.96), P for linear trend = 0.08].

Conclusions: Findings from this prospective study suggest that sufficient Mg status within the normal range may be beneficial to cognitive health in the US general population.

Bio-sketch:

Dr. Kahe is Tilden-Weger-Bieler Professor of Preventive Medicine at Columbia University Irving Medical Center, New York, USA. His research is primarily in nutritional and environmental epidemiology, focusing on lifestyle, dietary and environmental factors in relation to chronic diseases, including secondary data analysis and studies collecting new data with multidisciplinary approach.

A short sentence on your scientific presentation:
Serum magnesium concentration and incident cognitive impairment: findings from the reasons for geographic and racial differences in stroke (REGARDS) study

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150 JAHRE FRANZISKUS HOSPITAL Bielefeld

Akademisches Lehrkrankenhaus der Medizinischen Hochschule Hannover

Magnesium in oncology an update

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Purpose: Oncology had not paid much attention to magnesium so far. However, it plays an important role in numerous physiological and pathophysiological processes, e.g. in anticancerogenesis, regulation DNA- and RNA synthesis, mitosis, metastasis, nuclear repair mechanisms, and apoptosis.

Materials and methods: A literature search of “magnesium” and the search terms “oncology”, “cancer”, “tumor”, “neoplasm”, “radiotherapy”, was performed in the PubMed database. Furthermore, quotations in the publications found were used.

Results: Oncological therapies negatively influencing renal function can cause severe hypomagnesaemias, as shown by own studies. The introduction of the epidermal growth factor receptor (EGFR) antibodies to oncology, particularly in colorectal cancers lead to a clinical hypomagnesaemia and in up to 10% to 36% of cases to severe Grad III/IV hypomagnesaemias. Thereby, interestingly it appeared that there is a significant positive correlation between hypomagnesaemia clinical response to the antibody therapy as well was to a significantly better survival. The underlying mechanism is nearly unknown, but maybe for example the inhibition of DNA repair in tumor cells. Therefore, under special circumstances a low magnesium level may be more useful for tumor patients.
Another interesting aspect of magnesium is the treatment of hot flashes due to hormonal deprivation therapy. Magnesium is known for its neuro- and vasoactive effects. So far, there are only some small clinical studies and few case reports on this topic.
Recent studies on the use of magnesium in nephrotoxic chemotherapies like cisplatinum clearly showed, that a pretreatment with magnesium has a special nephroprotection effect.
In addition, several epidemiological studies suggested, that a higher magnesium serum level is accociated with a lower cancer incidence.

Conclusion: In the light of the study data, magnesium remains a highly interesting ion for oncology, whose different facets should be more and more enlightened.

Bio-sketch:
Head of the department of radiotherapy and radiation oncology, and clinical director of the Franziskus Hospital Bielefeld, Germany, teaching hospital of the Hannover Medical School (MHH).
Associate editor of “Trace Elements and Electrolytes”- Official Organ of the – "Society of Magnesium Research", Germany, and – German Working Group “Trace Elements and Electrolytes in Radiation Oncology” AKTE, Germany. He is president of the German Magnesium Society and chairman of the German Working Group “Trace Elements and Electrolytes in Radiation Oncology” AKTE.
One main focus of his scientific interest is complementary and alternative medicine, micronutrients, traditional medicine, and trace elements and electrolytes.
His research on magnesium focused on its importance in oncology and nephrology.

In his speech he will give an update on manifold roles of magnesium in oncology.

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News on Magnesium and the Vascular system

Laura Locatelli and Jeanette AM Maier
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Based on preclinical and clinical evidence demonstrating the beneficial effects of magnesium on the vasculature, sirolimus-eluting magnesium-based scaffolds were introduced in clinical practice to treat coronary artery disease, one of the leading causes of morbidity and mortality worldwide. Magnesium alloys, which are biocompatible, gradually dissolve, thus increasing the concentrations of magnesium in the local microenvironment. We investigated the effects of sirolimus and high extracellular magnesium (1-3 mM, similar to the concentration measured in the coronary arteries after stenting) on coronary artery endothelial and smooth muscle cells (CAEC and SMC, respectively). Sirolimus inhibits CAEC proliferation only in physiological concentrations of magnesium, while high concentrations prevent this effect. On the contrary, high extracellular magnesium does not rescue SMC growth arrest by sirolimus and accentuates the inhibitory effect of the drug on cell migration. Importantly, sirolimus and magnesium do not impair SMC response to nitric oxide. If translated into a clinical setting, these results suggest that, in the presence of sirolimus, local increases of magnesium concentration maintain normal endothelial proliferative capacity and function without affecting rSMC growth inhibition and response to vasodilators.

Bio-sketch
MD, Professor of General Pathology at the University of Milan. She was trained in the USA on the pathophysiology of the endothelium, with a focus on aging and senescence. In the last 15 years she investigated the response of vascular, bone and muscle cells to magnesium and to the silencing of its transporters.
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ABSTRACTS
Oral
Communications

OC01

Mg quantification and distribution as potential biomarkers in Colorectal Cancer

Agnese Razzoli[1,2], Gaia Gavioli[1], Chiara Marraccini[1], Davide Schiroli[1], Eleonora Zanetti[3], Moira Ragazzi[3], Elisa Gasparini[4], Alessandra Gianoncelli[5], Valentina Bonanni[5], Stefano Iotti[6], Roberto Baricchi[1], Lucia Merolle[1]

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[4]Oncology Unit, Azienda USL-IRCCS di Reggio Emilia, Italy;
[5]Elettra - Sincrotrone Trieste, Basovizza, Italy;
[6]Department of Pharmacy and Biotechnology, University of Bologna, Italy;

Introduction and Objective: Magnesium (Mg) involvement in cancer has long been debated, with many studies that produced conflicting results. Alteration of Mg transporters expression is a frequent finding in cancer tissues. This study aims at assessing Mg content and distribution in colorectal cancer (CRC) tissues and evaluating the expression of Mg transporters.

Materials and Methods: From the Biobank of the AUSL-IRCCS of Reggio Emilia, we retrieved 4 CRC samples of tumor and adjacent non-tumoral tissues from patients who underwent colon surgical resection and previously diagnosed with CRC (T3N0 stage). They were formalin fixed and paraffin embedded, sectioned and transferred onto a glass slide for a preliminary histological evaluation with ematoxylin and eosin staining. We exploited synchrotron radiation in order to evaluate tissue morphology (STXM), Mg content and distribution (LEXRF). TRPM6 and TRPM7 expression was assessed by immunofluorescence (IF) microscopy. Finally, the relevant literature and databases were consulted for Mg transporter expression in the colon.

Results: Histological inspection on CRC tissue showed crowded glands with a cribriform pattern. We observed higher overall Mg levels in cancer tissues compared to their healthy counterparts. Furthermore, while Mg was mainly localized in the nuclear and perinuclear regions (high mitochondrion density) in control samples, CRC ones showed disordered Mg distribution across the cell. IF revealed a positive staining only detected for TRPM6 in non-tumoral tissue with main localization in the perinuclei and in the large cytoplasm of epithelial cells facing the gland lumen; we did not detect positive staining in CRC tissues analyzed. Database and literature screening revealed controversial information about Mg transporters in CRC.

Conclusions: Our data represent a proof-of-concept towards the quantification of Mg imbalance as a biomarker in CRC. However, further investigations are needed to shed light on Mg homeostasis mechanisms, the role of its transporters and its biological activity.

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OC02

Magnesium alleviates moderate stress in patients with fibromyalgia: a randomized double-blind clinical trial

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1. Introduction and Objective : Patients suffering from fibromyalgia often report stress and pain, both often refractory to usual drug treatment. Magnesium supplementation has been reported to improve fibromyalgia symptoms but the level of evidence is still poor.

2. Materials and methods: This is a randomized, controlled, double-blind trial in fibromyalgia patients comparing once a day oral magnesium 100 mg (Chronomag®, magnesium chloride technology formula) to placebo, for one month. The primary endpoint was the level of stress on the DASS-42 scale, and secondary endpoints were pain, sleep, quality of life, fatigue, catastrophism, social vulnerability, and magnesium blood concentrations.

3. Results: Magnesium supplementation significantly reduced mild/moderate stress subgroup (DASS-42 stress score: 22.1±2.8 to 12.3±7.0 in magnesium vs 21.9±11.9 to 22.9±11.9 in placebo, p=0.003). Pain severity diminished significantly (p=0.029) with magnesium while other parameters were not significantly different between both groups.

4. Conclusions : Findings show for the first time that magnesium improves mild/moderate stress and reduces the pain experience in fibromyalgia patients. This suggests that daily magnesium could be a useful treatment to improve the burden of disease of fibromyalgia patients and calls for a larger clinical trial.

Biographical sketch: Nicolas Macian is a third year PhD student at Clermont Auvergne University. His PhD explores fibromyalgia in University hospital of Clermont-Ferrand under the direction of Pr PICKERING Gisèle (MD, PhD, DPharm). He received a Master degree in Biology and Health from the Pharmacy faculty of Montpellier (France). He has been working as a health engineer for more than ten years in pain clinical research.

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OC03

Decreased ionized magnesium and an increased ionized calcium/magnesium ratio in elderly hypertensives — relationship to artheriosclerosis

Klaus Kisters [1,2,3,4] Lukas Kisters [1], Oliver Micke[2] Ralph Miicke[2], Sepp Porta[2,3], Thomas Noack[2,4] ,Uwe Gröber[2,5]
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Objective: Alterations in the metabolism of calcium and magnesium are involved in the pathogenesis of essential hypertension. The calcium and magnesium flux across the external membrane is regulated by a calcium pump (calcium-magnesium-ATPase), calcium and magnesium (TRPM 6 and 7) channels and a sodium magnesium antiport. An increased calcium/ magnesium ratio is known to be involved in the development of atherosclerosis. Early onset of this disorders are known in hypertension. In earlier animal studies this phenomenon was described.
Design and methods: We now present a study in18 hypertensive elderly concerning ionized magnesium concentrations and ionized calcium/magnesium ratio in blood measured by a Prime Plus apparatus by Nova Medical, Rödermark, Germany.
Results: In 18 elderly hypertensives (9 male/9 female with normal renal function) ionized magnesium was measured 0.55+/-0.04 mmol/L, normal range 0.54 — 0.80 mmol/L).
The ionized calcium/ionized magnesium ratio was 2.33+/-0.18 (normal range below 2.40). About 40% of elderly hypertensives had an increased ratio of ionized calcium and magnesium, which is known to be a marker for the development of artheriosclerosis. Conclusions: As described earlier, a magnesium deficiency can be involved in the pathogenesis of hypertension and in elderly. Further studies have to be performed in this context. The increased calcium/magnesium ratio is also a pathogenetic factor for artheriosclerosis often found in elderly hypertensives with vascular complications, e.g. stroke or heart disease.
Keywords
Hypertension — Ionized calcium — ionized magnesium — arteriosclerosis - geriatrics

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OC04

Can a Qualified Health Claim for Magnesium and High Blood Pressure Advance Public Health?

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Introduction: The Food and Drug Administration (FDA) monitors health claims on foods and dietary supplements (DS) in the United States. By FDA definition, a health claim recognizes the relationship between a substance and a disease or health-related condition, particularly the relationship between that substance and a reduction in the risk of contracting that particular disease or health-related condition.

Methods: In 2016, CMER spearheaded the effort, which culminated in the August 16, 2016 submission of a 156-page Petition for the Authorization of a Qualified Health Claim (QHC) for Magnesium and Reduced Risk of High Blood Pressure (HBP) application to FDA .

Results: FDA approved a QHC for the Consumption of Magnesium and Reduced Risk of High Blood Pressure (Hypertension) on January 10, 2022. Magnesium now has its first health claim issued by FDA and is one of only three QHC for HBP. Manufacturers of foods and/or DS may now use one of three proposed QHC statements on their products each stating the qualifier that the evidence is inconsistent and not conclusive.

Discussion: The QHC on DS labels permits use of the claim for products with serving sizes less than 350 mg/day. Food products using the QHC must contain at least 85 mg magnesium per serving or 20% of the Daily Value [DV]) for magnesium, which is 420 mg. Foods must also meet the FDA's disqualifier levels for health claims of <480 mg sodium, <13 g total fat, <4 g saturated fat, and <60 mg total cholesterol as well as include one or more of the following nutrients at ≥10% DV per serving: fiber, protein, iron, calcium, potassium, or vitamin D.

Conclusion: We hope the FDA issuance of the Magnesium for Blood Pressure Qualified Health Claim will be a first step in the long and pressing need to update requirements as well as serum magnesium reference ranges and other needs for the improvement of public health. It is yet to be determined if such a QHC will benefit food and/or DS manufactures.

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OC05

Fluorescent Indicators for Detection of Cellular Mg^{2+} with High Selectivity

Michael D. Brady[1] and Daniela Buccella[1]*

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Abstract Body:

Purpose: To develop fluorescent indicators for visualization and quantification of cellular Mg^{2+} with high selectivity against other divalent cations

Materials and Methods: Quinoline-based fluorescent indicators was chemically synthesized and characterized by a combination of NMR, MS and UV-Vis absorption and fluorescence emission techniques. Metal binding profile in vitro was studied in aqueous buffer at pH 7. Magnesium(II) detection in various cells lines was demonstrated by widefield and confocal fluorescence microscopy, as well as flow cytometry techniques.

Results: A new series of fluorescent indicators, the MagZet family, were synthesized and characterized by various spectroscopic techniques. The indicators display high brightness and a wavelength shift upon binding Mg^{2+} that makes them suitable for ratiometric fluorescence detection of the cation. Their dissociation constants were determined to be in the low millimolar range, appropriate for detection of physiological intracellular free Mg^{2+}. The affinity for Ca^{2+} is ten-fold lower than for Mg^{2+}, which enables detection of the latter with virtually no interference from the former cation. Computational studies were employed to model the metal binding mode of the indicators and the origin of the selectivity. MagZet1 displays no pH interference in the physiological range and was applied for detection of changes in intracellular free Mg^{2+} by both fluorescence microscopy and flow cytometry techniques. MagZet2 displays an enhanced dynamic range over MagZet1, but a different subcellular localization pattern that can be controlled through the cellular staining temperature. Overall, the new indicators display general applicability, and Mg^{2+} changes in various cellular processes could be monitored.

Conclusions: New small-molecule fluorescent indicators for the detection of Mg^{2+} with high selectivity over Ca^{2+} were developed. The new indicators and staining methodologies enable imaging of the free Mg^{2+} by microscopy and flow cytometry techniques, crucial for the study of basic mechanisms that support cellular magnesium homeostasis and their disruption in disease states.

Biographical Sketch: Daniela Buccella is an Associate Professor in the Department of Chemistry at New York University. Born and raised in Venezuela, she received her BS in Chemistry in 2002 from Simón Bolívar University in Caracas, and started research as an undergraduate in the Venezuelan Institute for Scientific Research under the supervision of Prof. Roberto Sánchez-Delgado. She moved to New York to pursue a PhD in Chemistry at Columbia University working with Prof. Ged Parkin in the area of inorganic synthesis and catalysis. Following an NIH postdoctoral fellowship at the Massachusetts Institute of Technology, where she worked with Prof. Stephen Lippard, she returned to New York City in the fall of 2011 to start her independent career studying problems at the interface of inorganic chemistry and biology. Work in her research group focuses on the development of new molecular probes and imaging strategies for the study of cellular metal homeostasis.

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OC06

Magnesium effect on the cardiovascular-muscle-bone triad

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1. Introduction and Objective. Magnesium (Mg) is a pivotal component in the cardiovascular-muscle-bone triad. Lower Mg level and intake are associated with poorer outcomes in vascular calcification, endothelial dysfunction, osteoporosis, and muscle dysfunction/sarcopenia. Magnesium supplementation appears to benefit the triad, but randomized clinical trials (RCT) are needed. There are also suggestions in the literature that Mg could have an additive effect with biphosphonates (a main treatment of osteoporosis) on bone turn-over.
2. Material and Methods. We present the protocol of an ongoing RCT, MAGELLAN®, in 40 postmenopausal osteoporosis patients requiring bisphosphonate therapy, at University Hospital Clermont-Fd, France. The trial has obtained autorisation from the French Drug Agency and from the National Ethics Committee in early 2022. The trial has 2 arms, biphosphonates or biphosphonates + oral Mg. Patients are screened at baseline and after 3 months of Mg treatment. Primary outcomes are bone markers concentrations. Secondary outcomes are flow -mediated arterial dilatation, and other cardiovascular parameters, sarcopenia tests, and pain intensity changes.
3. Results. The study is ongoing.
4. Discussion. This trial will explore for the first time how oral Mg may influence each component of the cardiovascular-muscle-bone triad and identify if Mg could be a useful polyvalent tool in slowing down concomitant pathological processes and comorbidities in normal aging of the cardiovascular, muscle, and bone systems.

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OC07

Lactobacillus fermentum supplementation normalizes magnesium fecal excretion and delays and reduces high blood pressure and Na, Na/K ATPase activities in salt dependent hypertension

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Purpose: Essential arterial hypertension (EHT) comprises 95% of diagnosed cases of hypertension worldwide. The pharmacological therapy is often associated with many side effects. Alternative methods such as probiotic bacteria supplementation have been sought. This later known to be associated with increased Magnesium status, inflammation and hypertension. Taking these studies into consideration, we evaluated the effect of continuous administration of *Lactobacillus fermentum* CVCM 1469 on the development of EHT and Magnesium and other mineral excretion in Dahl salt-sensitive rat model.

Materials and methods: For this purpose, six-week-old male Dahl-rats were divided into four groups: 1. Dahl-rats fed a normal-Na-diet (Dahl-standard); 2. Dahl-rats fed a high-sodium-diet (Dahl-NaCl); 3. Losartan, Dahl-rats fed a high-sodium-diet plus Losartan (Dahl-NaCl-Losartan) and; 4. *L. fermentum* CVCM 1469, Dahl-rats fed a high-sodium-diet plus *Lactobacillus* (Dahl-NaCl-Lactobacillus). Biological, physiological, biochemical and immunohistochemical parameters were evaluated at the end of the assay

Results: In Dahl-NaCl-Lactobacillus group when compared to controls: at the biological level, water intake was normalized and urine excretion was mildly increased. Body weight gain was significantly reduced. At physiological level, blood pressure was significantly lower when compared to the Dahl-NaCl group. At the biochemical level, mineral analyses revealed that among the Dahl-NaCl-Lactobacillus group, despite Na^+ ingestion, loss of Mg^{2+} in feces was normalized, indicating a possible mechanism to maintain the homeostasis levels of this ion at intestinal level. Moreover, a normalization of Na^+/K^+ and Na^+ ATPase activity was also observed in this group. Immunohistochemical analyses showed a reduction of proinflammatory-cytokines in the kidney.

Conclusion: Daily administration of $2x10^7$ CFU of *L. fermentum* to Dahl S/S rats was able to delay and reduce the onset of EHT accompanied by normalization of Magnesium excretion, Na^+/K^+ and Na^+ ATPase activity and reduction of proinflammatory-cytokines in the kidney by, among other mechanisms, modulating renal inflammation.

Biosketch:

Lollo, P. C. B., Morato, P. N., Moura, C. S., Almada, C. N., Felicio, T. L., Esmerino, E. A., Barros, E. M., Amaya-Farfana, J., Sant'Ana, A. S., Raices, R. R. S., Silva, M. C. y Cruz, A. G. (2015). Hypertension parameters are attenuated by the continuous consumption of probiotic Minas cheese. Food Research International, Vol 76, pp. 611–617.

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OC08

Palmitoylation regulates cellular distribution of and transmembrane Calcium flux through TrpM7

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Abstract Body:
Magnesium regulates numerous cellular functions and enzymatic reactions, and abnormal magnesium homeostasis contributes to vascular dysfunction and the development of hypertension. The transient receptor potential melastatin 7 (TrpM7) is ubiquitously expressed and regulates embryonic development and pathogenesis of several common diseases, which currently has been discovered as a key player in cardiovascular magnesium homeostasis, cardiac fibrosis, angiotensin II-induced hypertension. The TrpM7 integral membrane ion channel domain regulates transmembrane movement of divalent cations, primarily Ca^{2+}, Mg^{2+} and Zn^{2+}, and its kinase domain controls gene expression via histone phosphorylation. Mechanisms regulating TrpM7 are elusive. TrpM7 not only localizes on the cell surface where it controls divalent cation fluxes but also exists in intracellular vesicles where it controls zinc uptake and release. Palmitoylation is a dynamic reversible posttranslational modification, which regulates ion channel activity, stability, and subcellular localization. We found TrpM7 is palmitoylated at a cluster of cysteines at C terminal end of its TRP domain in multiple cell types. Palmitoylation controls the exit of TrpM7 from the endoplasmic reticulum and the distribution of TrpM7 between cell surface and intracellular pools. Using the Retention Using Selective Hooks (RUSH) system, we discovered that palmitoylated TrpM7 traffics from the Golgi to the surface membrane whereas non-palmitoylated TrpM7 is sequestered in intracellular vesicles. We identified the Golgi-resident enzyme zDHHC17 as responsible for palmitoylating TrpM7 and find that TrpM7 mediated transmembrane calcium uptake is significantly reduced when TrpM7 is not palmitoylated. The close homologue TrpM6 is also palmitoylated on C-terminal side of TRP domain. Our findings illustrate palmitoylation controls ion channel activity of TrpM7 and that TrpM7 trafficking is dependent on its palmitoylation. We defined palmitoylation as a new mechanism for post translational modification and regulation of Trpm7 and other Trps.

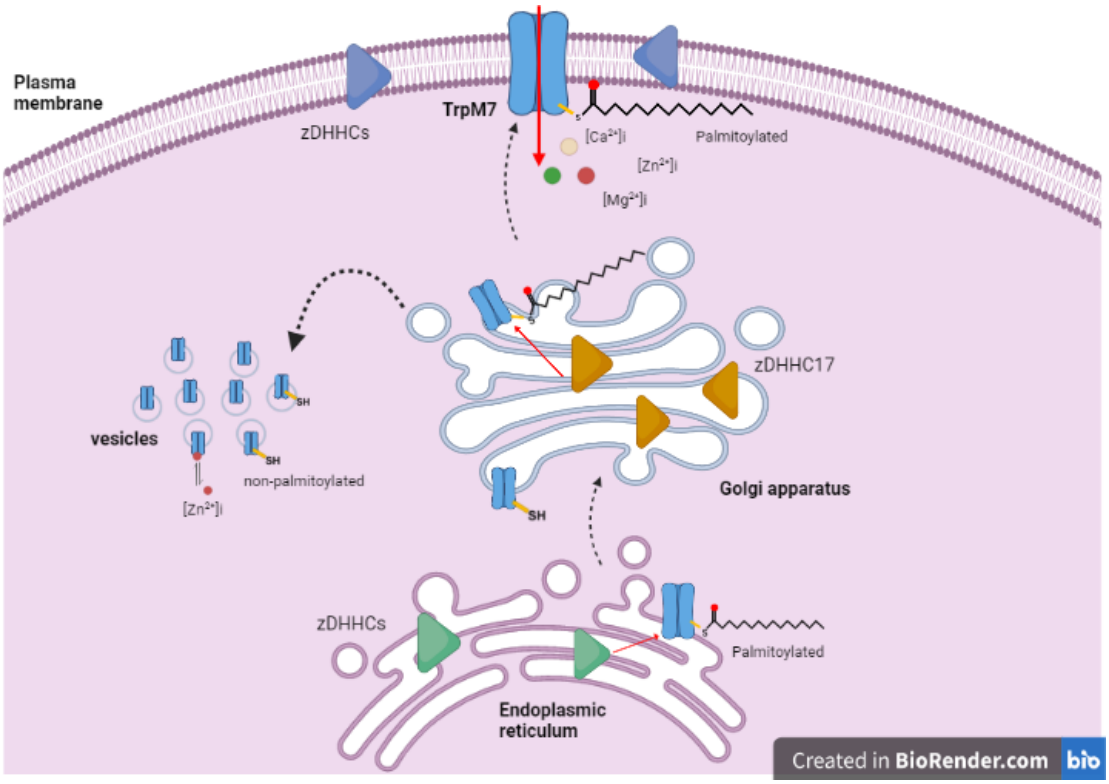
Purpose:
Transient receptor potential melastatin 7 (TrpM7) is a unique member of Trp superfamily, composed of both ion channel and kinase domains, which conducts divalent cations across the surface membrane and in intracellular compartments. TrpM7 controls organism electrolyte balance and is implicated in numerous pathologies. We are aiming to investigate the impacts of palmitoylation on TrpM7 ion channel activity and kinase domain function, thereby accomplishing the regulation of TrpM7 and its underlying mechanisms of signaling transduction. Furthermore, palmitoylation might be a new mechanism for TrpM7-related clinical diseases.

Materials and Methods:
Materials:
1. Plasmids and mutagenesis
A plasmid expressing murine TrpM7 with a C terminal yellow fluorescent protein fusion was kindly provided by Dr Vladimir Chubanov, Walther-Straub-Institut für Pharmakologie und Toxikologie. All mutagenesis utilised either Quikchange II site directed mutagenesis kit (Agilent) or InFusion cloning (Takara) and oligonucleotide primers designed according to the kit manufacturer's instructions
2. Antibodies of TrpM7
The antibodies raised against TrpM7(Abcam ab109438, Alomone Laboratories ACC-047), Flotillin 2 (BD Biosciences), GAPDH (Sigma), GFP (Abcam), HA tag (Roche), Na/K ATPase α1 subunit ((Developmental Studies Hybridoma Bank, clone α6f)
3. Primary cells of VSMCs
4. Stable cells of the ER and Golgi-retention system
5. Stable cells of WT-TrpM7-YFP and non-palmitoylated-TrpM7-YFP
Methods:
1. Purification of Palmitoylated Proteins by Resin Assisted Capture (acyl-RAC)
2. Purification Biotin Labelled Cell Surface Proteins Via Streptavidin Affinity Capture

3. Confocal imaging
4. Generation of stable cell lines
5. Proteomics with Mass spectrometry for protein interaction with WT-TrpM7/non-palmitoylated TrpM7
6. Calcium uptake

Results:
TrpM7 is palmitoylated in a variety of cell types and the palmitoylated sites are in a cluster of cysteines (C1143, C1144 and C1146) at its C terminal end of Trp box. Palmitoylation regulates the intracellular trafficking of TrpM7 and inhibition of palmitoylation would induce reduced abundance on surface membrane. TrpM7 is palmitoylated by Golgi-resident zDHHC17 and inhibiting its palmitoylation would lead to significant decrease in TrpM7-mediated cellular Ca uptake.

Conclusion:
Palmitoylation regulates TrpM7 ion channel activity, and it regulates TrpM7 trafficking during secretory pathway. Its closely related channel/kinase TrpM6 is also palmitoylated at highly conserved Trp domain at its C-termini. Palmitoylation might be a new mechanism for post translational modification and regulation of TrpM7 and other Trps.



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OC09

TRPM7 Modulates Human Pancreatic Stellate Cell Activation

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Purpose: Pancreatic diseases, such as pancreatitis or pancreatic ductal adenocarcinoma, are characterized by the presence of activated pancreatic stellate cells (PSCs). These cells represent key actors in the tumor stroma, as they actively participate to disease development and progression: reprograming these PSCs into a quiescent phenotype has even been proposed as a promising strategy for restoring hallmarks of healthy pancreas. Since TRPM7 channels have been shown to regulate hepatic stellate cells proliferation and survival, we aimed to study the role of these magnesium channels in PSCs activation and proliferation. **Materials and methods:** PS-1 cells (isolated from a healthy pancreas) were used as a model of healthy PSCs: quiescence or activation were induced using all-trans retinoic acid or conditioned media of pancreatic cancer cells, respectively. The role of TRPM7 was studied by RNA silencing or by pharmacological inhibition. **Results:** TRPM7 expression was found to be correlated to the activation status of PS-1 cells. TRPM7 expression was able to regulate proliferation through modulation of cell cycle regulators and most importantly p53, via the PI3K/Akt pathway, in a magnesium-dependent manner. Finally, the analysis of pancreatic cancer sample databases showed the overexpression of TRPM7 in cancer-associated fibroblasts. **Conclusion:** Taken together, we provide strong evidences that TRPM7 can be considered as a marker of activated PSCs.

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OC10

TRPM7 channel-kinase, magnesium and pH in immune cells

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TRPM7 is a dual function ion channel/protein kinase. Mg^{2+} and other divalent metal cations permeate and, at the same time, regulate TRPM7 channels. TRPM7 C-terminal kinase, belonging to the eEF-2 kinase family, is independently regulated by metal cations. The relationship between the kinase and channel activities of this protein and their individual roles in immune cells have been the focus of our studies. TRPM7 can autophosphorylate at serine/threonine residues without noticeably altering channel function. Inactivation of phosphotransferase activity by site-directed mutagenesis does not abolish channel activity. We investigated the consequences of kinase inactivation in a mouse model where K1646R kinase-dead (KD) variant replaced wildtype TRPM7. In macrophages isolated from KD mice, the basal TRPM7 channel activity was increased compared to WT. We showed previously that TRPM7 channels are inhibited by cytosolic acidic pH, therefore we hypothesized that increased activity may result from increased pH. Direct single-cell measurements of pH demonstrated that mean pH was shifted to more alkaline pH in KD mouse peritoneal and splenic macrophage cytoplasm. The phagocytic activity of KD splenic macrophages was substantially higher than in WT. Pharmacological inhibition of sodium-hydrogen exchanger 1 (NHE1) resulted in the reversal of alkalization and decreased phagocytosis. Manipulation of extracellular Mg2+ did not significantly affect phagocytic activity. From these experiments we conclude that TRPM7 kinase appears to maintain macrophage cytosol near normal pH, which suppresses their phagocytic activity and TRPM7 channel activity. The precise mechanisms of alkalinization caused by TRPM7 kinase inactivation remain to be discovered. We investigated the consequences of long-term reduction of external Mg2+, as occurs in hypomagnesemia, on TRPM7 channel activity in intact T lymphocytes. Removal of Mg2+ for 6 hours or longer resulted in complete activation of TRPM7 channels by intracellular Mg2+ depletion. Mg2+ depletion but not loading was sensitive to amiloride. We are currently exploring the effects of Mg2+ depletion on TRPM7 kinase in intact cells.

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OC11

TRPM7 kinase mediates hypomagnesemia-associated seizure and death

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Introduction: Our previous study has shown that hypomagnesemia (HypoMg) induces mitochondrial dysfunction, cardiac diastolic dysfunction, and seizure-related death. Transient receptor potential cation channel subfamily M 7 (TRPM7) is a Mg transporter with both channel and kinase function located in the plasma membrane. We investigated the role of TRPM7 in HypoMg-associated brain changes.
Materials and Methods: Wild type (WT) C57BL/6J mice and transgenic mice with a homozygous K1646R mutation in the TRPM7 kinase domain ($TRPM7^{K1646R}$, with no kinase function) were fed with a low-Mg diet (HypoMg mice, 15-30 mg/kg Mg) or a normal Mg diet (control mice, 2000 mg/kg Mg) for 6 weeks starting at 10 weeks old.
Results: HypoMg caused seizure-associated death in 17 of 48 WT male (35.4%) and 40 of 40 WT female (100%) mice, whereas $TRPM7^{K1646R}$ mice all survived. WT HypoMg mice showed increased TRPM7 protein level in brains (2.4±0.4-fold increase of WT control, $P<0.05$) and decreased serum Mg (0.38±0.03 mM vs. 1.14±0.03 mM of WT control, $P<0.001$). Compared with WT control brains, WT HypoMg brains showed inflammation (increased NLRP3, Asc, and IL-1β: 1.5- to 2.0-fold increase), oxidative stress (nitro-Tyr: 1.4±0.1-fold increase), and apoptosis (Bax: 1.3±0.1-fold increase) ($P<0.05$ for all). $TRPM7^{K1646R}$ HypoMg mice showed decreased inflammation, oxidative stress, and apoptosis vs WT HypoMg ($P<0.05$).
Conclusion: TRPM7 was upregulated in hypomagnesemia in brain tissues and its kinase function contributed to hypomagnesemia-induced inflammation, oxidative stress, apoptosis, and seizure-induced death.

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OC12

Use of Magnesium for Preventing Cardiac Damages by SARS-CoV-2

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Introduction: The impact of COVID-19 on cardiovascular health, especially cardiac tissue damage by COVID-19 and the direct infection of SARS-CoV-2 to the heart, have been well documented in populations with preexisting cardiovascular disease including hypertension. In addition, the development of specific strategies for cardiovascular protection against COVID-19 have been discussed since the beginning of the pandemic, but the detailed molecular mechanisms underlying how SARS-CoV-2 infection damages cardiac function are still unclear. Previous reports from SARS-CoV-1 showed that expression of several SARS-CoV-1 genes including open reading frame (ORF) 3a can damage the host cells. In addition, SARS-CoV-1 patients are found to possess antibodies against ORF3a, indicating that this protein was likely expressed at the surface of the host cells.

Objective: To test 1) whether SARS-CoV-2 genes, including ORF3a, can be expressed in the cardiomyocytes (CMs) of the heart after SARS-CoV-2 infection, and subsequently dysregulate cardiac functions and damage CMs, and 2) whether magnesium supplementation can prevent the CM damages.

Material and Methods: We expressed SARS-CoV-2-ORF3a in human cell lines and human induced pluripotent stem cell (iPSC)-derived CMs, and assessed the impacts on cardiac electrophysiology and cell signaling using a combination of mathematical modeling, genetic, biochemical and physiological assays.

Results: We found that 1) SARS-CoV-2-ORF3a proteins are capable of forming additional K^+-permeable channels at the cell membrane, which dysregulate action potential formation and cellular Ca^{2+} handling; 2) ORF3a can be also expressed at the outer mitochondrial membrane, leading to increased mitochondrial reactive oxygen species and apoptotic signaling; and 3) application of magnesium has the potential to inhibit these detrimental changes in the CMs by ORF3a.

Conclusion: SARS-CoV-2 ORF3a expression in the CMs causes cardiac damage. Magnesium supplementation may be a promising therapeutic strategy for reducing the risk of lethal cardiac arrhythmia and damage by COVID-19.

Biographical Sketch:

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OC13

Hypomagnesaemia in patients with cardiovascular disease and morbid obesity exacerbates dyslipidaemia and inflammatory syndrome

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Purpose: Some studies imply hypomagnesaemia (HMg) in promoting inflammation from atherosclerosis by distinct mechanisms: leukocytes and macrophages activation, freeing of cytokines, increased oxidation of LDL, etc. In obesity the incidence of atherosclerosis and CVD increase, especially in metabolic syndrome. The role of HMg is more little known. In this work we aimed to study the role of HMg in patients with morbid obesity and cardiovascular disease (CVD). For that, we analyzed the relationships between HMg and atherosclerosis risk factors (dyslipidaemia, arterial hypertension, etc), and the level of no specific inflammation implied in atherogenesis (fibrinogenaemia (F), CRP, and missing teeth (MT) number (the consequence of (MO) chronic gum inflammation such as periodontitis and periodontosis).
Materials and Methods: In a cross-sectional study we analyzed 95 patients with CVD (old myocardial infarction, angina pectoris, stroke, arteritis) and MO (BMI >=40; mean age: 54,3+/-9,6 years; 43 (45%) were men; mean BMI: 44,3+/-4,4 . Mean magnesium level: 2,07+/-0,32 mg%, HMg was considered under <=1,75 mg%. We found HMg in 9 patients (9.5%), mean age 52.3+/-7.0 , 6 patients were men.
Results: We found significant statistical differences between atherosclerosis risk factors in patients with HMg versus no HMg only for HDL-Cholesterol (37,7+/-11.5 versus 48.8+/-12.1, P<0.025), and serum glucose (194.6+/-88.5 versus 105.5+/-26.0 mg^, P<0.001). Concerning inflammation: F (535.5+/-126.2 versus 414.4+/-110,3 mg%, P<0.033), Leukocytes (9820.0+/-2792.2 versus 7405.4+/-2103.4, P<0.006, MT (15.4+/-5.5 versus 10.7+/-6.7, p<0.045), CRP (19.3+/-11.5 versus 4.08+/-2.81, P,0.006)
Conclusions: In patients with CVD and MO, HMg is accompanied by low HDL-Cholesterol and high serum Glucose. But, we found too an exacerbation of inflammation and an increased number of MT. It is a provisory study, but we underline the importance of serum Magnesium determination in these patients. We propose a close check of serum magnesium level in patients with CVD and MO and prevention by magnesium supplementation.

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OC14

Magnesium supplementation improves metabolic syndrome parameters

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Purpose: Metabolic syndrome (MetS) is a pathological condition characterized by insulin resistance, obesity, dyslipidemia and hypertension. Magnesium (Mg) supplementation was shown to improve MetS parameters in hypomagnesemic patients. To dissect the effect of additional Mg supplementation from the improvement of hypomagnesemia, we evaluated the role of Mg in normomagnesemic individuals with MetS.

Materials and methods: Patients with MetS, mean age 66±11, participated in the study. MetS was determined by the presence of at least 3 of following symptoms: obesity (BMI > 25 kg/m2), blood pressure (BP) ≥ 130/85 mmHg, hyperinsulinemia (HbA1c ≥ 5.7%), dyslipidemia (triglycerides (TG) > 150 mg/dL). Patients were randomly assigned to 400 mg Mg as Mg citrate or placebo daily for 12 weeks. BP, HbA1c, plasma concentrations of glucose, Mg and Ca, blood ionized Mg, serum concentrations of cholesterol, TG, vitamin D, creatinine, IL-6, and C-reactive protein were measured at baseline and after 12 weeks. Data were obtained from n=13 in the Mg supplemented and n=11 in the placebo group.

Results: Mg supplementation led to a significant increase in plasma Mg concentration (0.78±0.07 mmol/L to 0.83±0.07 mmol/L, p=0.01). Also Mg supplementation decreased such MetS parameters as hypertension (baseline BP: 145±10/85±3 mmHg; BP at 12 weeks: 121±5/79±3 mmHg, p<0.001) and insulin resistance (HbA1c decreased from 6.43±0.64% to 6.15±0.55%, p<0.01). The difference in change between placebo and Mg group was significant for all abovementioned parameters. Serum vitamin D levels significantly increased only in the Mg group (p<0.01). Placebo group exhibited decrease in TG (p=0.04) with no significant difference to Mg supplemented group at any time point. No other measured parameter was significantly different

Conclusions: In normomagnesemic individuals with MetS, oral Mg citrate supplementation reduced HbA1c and BP. Mg supplementation could be an efficient addition to traditional MetS therapy.

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OC15

Utility of magnesium sulfate in the treatment of rapid atrial fibrillation in the emergency department: a systematic review and meta-analysis

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Introduction and Objective
Atrial fibrillation with rapid ventricular response (Afib/RVR) is a frequent reason for emergency department (ED) visits and can be treated with a variety of pharmacological agents. Magnesium sulfate has been used to prevent and treat postoperative Afib/RVR.

Materials and Methods
We performed a systematic review and meta-analysis to assess the effectiveness of magnesium for treatment of Afib/RVR in the ED. PubMed and Scopus databases were searched up to June 2021 to identify any relevant randomized trials or observational studies. We used Cochrane's Risk-of-Bias tools to assess study qualities and random-effects meta-analysis for the difference of heart rate (HR) before and after treatment.

Results
Our search identified 395 studies; after reviewing 11 full texts, we included five randomized trials in our analysis. There were 815 patients with Afib/RVR; 487 patients (60%) received magnesium treatment, whereas 328 (40%) patients received control treatment. Magnesium treatment was associated with significant reduction in HR [standardized mean difference (SMD), 0.34; 95% CI, 0.21-0.47; $P < 0.001$; $I2 = 4\%$), but not associated with higher rates of sinus conversion (OR, 1.46; 95% CI, 0.726-2.94; $P = 0.29$), nor higher rates of hypotension and bradycardia (OR, 2.2; 95% CI, 0.62-8.09; $P = 0.22$). Meta-regressions demonstrated that higher maintenance dose (corr. coeff, 0.17; $P = 0.01$) was positively correlated with HR reductions, respectively.

Conclusion
We observed that magnesium infusion can be an effective rate control treatment for patients who presented to the ED with Afib/RVR. Further studies with more standardized forms of control and magnesium dosages are necessary to assess the benefit/risk ratio of magnesium treatment, besides to confirm our observations.

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The influence of vanadate and/or magnesium on bone mineral density and biomechanical properties of the femur and tibia in male rats

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Introduction: Vanadium is a well-known environmental and occupational pollutant that may be incorporated into the bone. Magnesium is an important contributor to bone health. The impact of both elements on bone biomechanical integrity remains largely unknown.
Objective: The influence of the 12- and 18-week separate and simultaneous administration of sodium metavanadate (SMV, 0.125 mg V/mL) and magnesium sulfate (MS, 0.06 mg Mg/mL) on the volumetric bone mineral density (VBD), geometry, and biomechanical properties of the rat femur and tibia was investigated.
Materials and Methods: The femur and tibia VBD was estimated with the method based on Archimedes' principle. The biomechanical properties of both long bones were evaluated in a three-point bending test (femoral/tibia diaphysis), fracture test (femoral neck), and compression test (tibia).
Results: The tibia VBD, geometry of the femur and tibia, and biomechanical properties of the femoral diaphysis were not altered in rats receiving SMV and/or MS for 12 and 18 weeks, compared to the control; only the femoral VBD decreased in the SMV-supplied rats at 12 weeks. No differences were noted in the biomechanical properties of the femoral neck between the groups at 12 weeks, but some biomechanical parameters of the neck were changed at 18 weeks, compared to the control. SMV and/or MS also had an impact on some variables describing the biomechanical properties of the tibia, but the tibia stiffness was not affected by the SMV and/or MS treatment.
Conclusion: Our findings provide evidence that the separate 18-week administration of V or Mg enhances the femoral neck fracture resistance and point to the potential use of V in effective therapeutic fracture treatments. On the other hand, they reveal that the combined V+Mg administration may decrease the femoral neck resistance to fracture. Further studies are needed to elucidate the influence of V and Mg on the biomechanical properties of long bones.

Biographical sketch: Agnieszka Ścibior, PhD, DSc. She has been working as Associate Professor since 2019. From 2014 to 2022, she was the Head of the Laboratory of Oxidative Stress in the Centre for Interdisciplinary Research, Lublin, Poland. Now she works in the Department of Biomedicine and Environmental Research at the John Paul II Catholic University of Lublin (Poland). The main fields of interest: toxicity of selected elements, metal interactions, mechanisms of metal toxicity (*in vitro* / *in vivo* model). Guest Editor of a Special Issue for the journal of Biology (MDPI) and Oxidative Medicine and Cellular Longevity (Hindawi). She is a member of the Polish Laboratory Animal Science Association, the Polish Society of Toxicology, and the Polish Magnesiological Society. She has been conferred awards of the Rector of the John Paul II Catholic University of Lublin for original and creative scientific achievements. Her Research ID is orcid.org/0000-0003-1724-520X.

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