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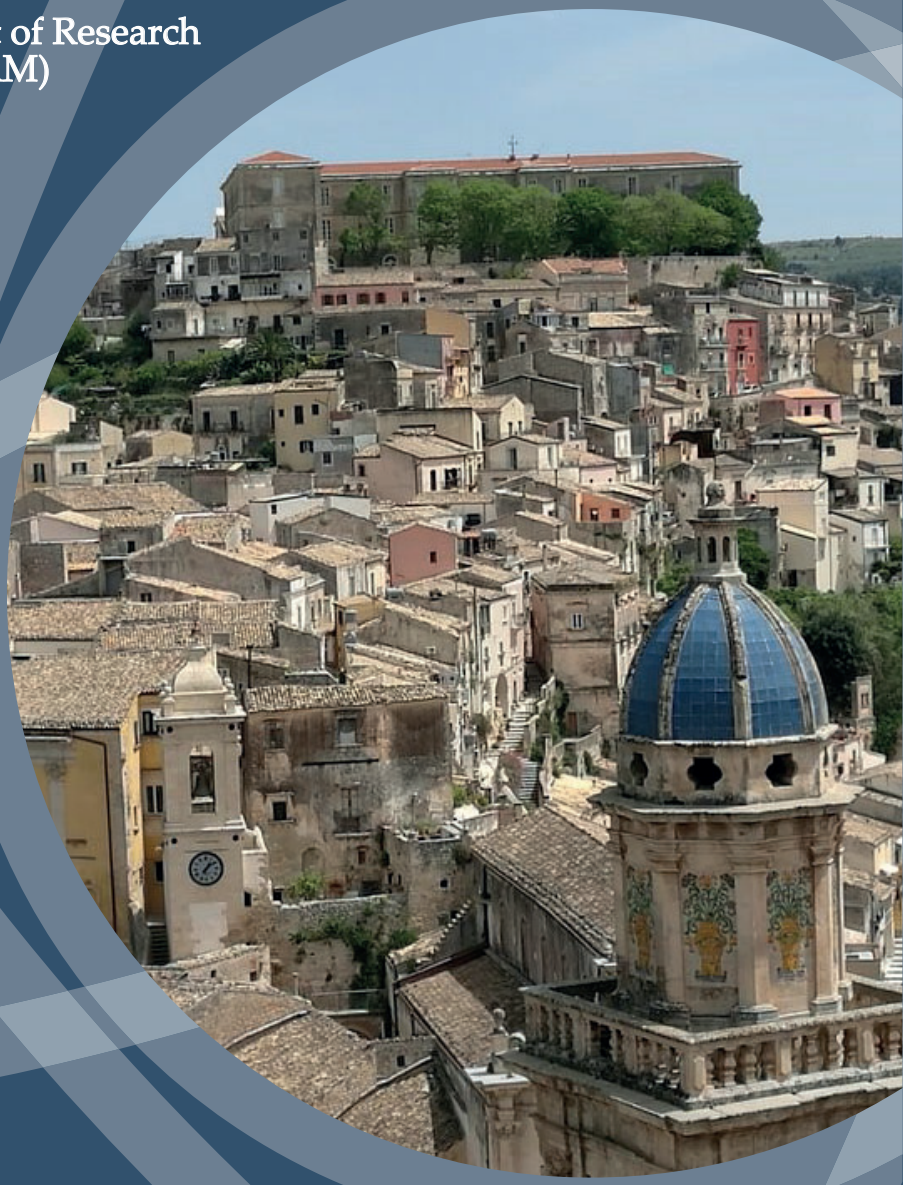

2nd Workshop on Magnesium Neuroscience and Nutrition in current Covid-19 Pandemia

Online Virtual Meeting

MAY 28-29 2021

PROGRAM & ABSTRACTS

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Workshop Organizer
Nathalie SPINELLI

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SDRM Official Journal:
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SUMMARY

Dear Colleagues,

it is a pleasure for us to welcoming you to the **Second Workshop on Magnesium in Neuroscience and Nutrition, in current covid-19 pandemia**, which will be held online on 28th -29th May 2021.

I would have preferred to welcome you personally in Ragusa and share with you the very fascinating environment of the old baroque town of Ibla with its amazing Cathedral, gardens, the Vincenzo Ferreri Auditorium located in a former church and enjoy the delicious Sicilian cuisine, particularly developed in this area (two Michelin star restaurants and several chef academy). To fill this gap, we invite you to watch a short video with a wonderful air view of the area on ***www.magnesiumworkshop2021.com***.

In this workshop we will address two pressing issues: the large variety of neurological disorders (stress, anxiety, depression, sleep disorders) of the current society and the actual health emergency related to Covid-19 pandemia, two somehow related conditions that need innovative intervention approaches.

Is there a role of Magnesium in these complex fields? Can we prevent or improve some of these conditions by an healthier lifestyle?

As usual, our challenge will be to gather the latest scientific data on magnesium in the different aspects of neurosciences and covid-19 infections and discuss potential new avenues to face such diseases.

We hope that lectures by eminent experts in the field and scientific contributions by the delegates will stimulate questions, inspire discussions, hypotheses and hopefully will be the ground for new projects and collaborations.

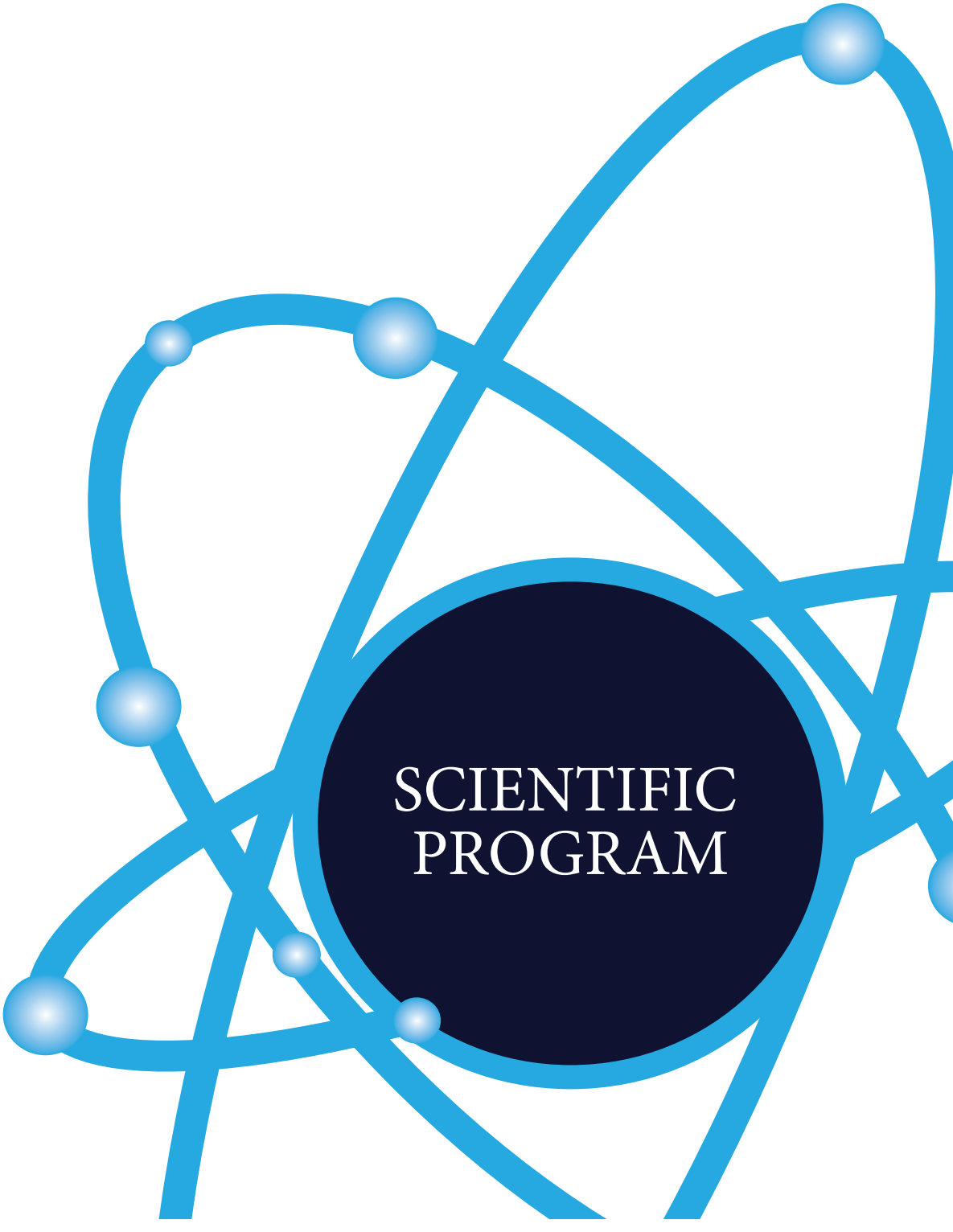
We have invited young researchers to present their work and we will award the best of them to encourage their commitment in a field that needs to be explored and that is potentially very promising.

At this point, we all face an additional challenge which is having our first SDRM meeting online.

We should all engage ourselves to take the best advantage of this experience.

On behalf of the Organizing Committee

Federica I. Wolf, PhD



SCIENTIFIC PROGRAM

FRIDAY, MAY 28th, *MORNING*

08:45 - 09:00 ***Welcome Remark***
Federica I. Wolf (Rome, ***Italy***)

KEYNOTE Lecture
09:00 - 09:45 **Recent advances in magnesium research - from cell biology to human disease**
Rhian Touyz
Institute of Cardiovascular and Medical Sciences, University of Glasgow, ***UK***

SESSION 1 Magnesium Intake and Health

Chairmen **Andrzej Mazur** (Clermont-Ferrand, ***France***)
Federica I. Wolf (Rome, ***Italy***)

09:45 - 10:15 **Global human magnesium status needs re-evaluation and updated reference values**
Andrea Rosanoff
Center for Magnesium Education & Research, Pahoa, ***Hawaii***

10:15 - 10:45 **When Mg is assessed in Clinical setting?**
Yee Ping Teoh
Dept Clinical Biochemistry, Pathology Department, Wrexham Maelor Hospital, ***UK***

10:45 - 11:15 **Serum magnesium assessment needs for standardization**
Oliver Micke
*Klinik für Strahlentherapie und Radioonkologie, Franziskus Hospital Bielefeld,****Germany***

11:15 - 11:30 ***Break***

Oral Communications

11:30 - 11:45 ***OC01***
Systematic review and meta-analysis to determine a reference range for ionized magnesium
Nana Gletsu-Miller
Indiana University, Applied Health Science, Bloomington, ***USA***

11:45 - 12:00 ***OC02***
Magnesium transporters: discovering new potential biomarkers in digestive cancers
Julie Auwercx
Université de Picardie Jules Verne, UFR des Sciences, UR-UPJV 4667, Amiens, ***France***

12:00 - 12:15 ***OC03***
TRPM7 is protective against hypertension, cardiovascular inflammation and fibrosis induced by aldosterone and salt
Francisco J. Rios
Institute of Cardiovascular and Medical Sciences, University of Glasgow, ***UK***

12:15 - 13:30 ***Break***

FRIDAY, MAY 28th, *AFTERNOON*

SESSION 2 Magnesium in Anxiety, Stress, Depression, Sleep and Pain

Chairmen **Louise Dye** (Leeds, ***UK***)
Giséle Pickering (Clermont-Ferrand, ***France***)
Robert Vink (Adelaide, ***Australia***)

13:30 - 14:00 **Dietary magnesium deficiency impairs hippocampus-dependent memories and induces neuroinflammation in mouse**
Satoshi Kida
Graduate School of Agriculture and Life Sciences. The University of Tokyo, ***Japan***

14:00 - 14:30 **The effects of Combination of Green Tea, Rhodiola, Magnesium and B Vitamins on brain activity and the Effects of a Laboratory Social Stressor in Healthy Volunteers**
Louise Dye
Human appetite research unit – School of Psychology University of Leeds, ***UK***

14:30 - 15:00 **Magnesium and Pain comorbidities**
Gisèle Pickering
Clinical pharmacology department, CHU, Université Clermont Auvergne, Clermont-Ferrand, ***France***

15:00 - 15:30 **Magnesium, Vitamin D and Cognitive Function in older adults: results from the US National Health and Nutrition Examination Survey (NHANES) 2011 to 2014**
Menghua Tao
Department of Biostatistics and Epidemiology
University of North Texas, Fort Worth, ***USA***

Oral Communications

15:30 - 15:45 ***OC04***
Magnesium in Bipolar Disorders – a general view
Mihai Nechifor
Department of Pharmacology Gr. T Popa University of Medicine and Pharmacy, Iasi, ***Romania***

15:45 - 16:00 ***OC05***
Can Additional Dietary Magnesium Reduce Stress In Pigs?
Emily V. Bushby
Faculty of Biological Sciences, University of Leeds, ***UK***

16:00 - 16:15 ***OC06***
BDNF and GABA-R expression is modulated in human mini-brain organoids in response to magnesium
Alessandra Cazzaniga
Department of Biomedical and Clinical Sciences L. Sacco, University of Milan, ***Italy***

16:15 - 16:30 ***OC07***
Comparison of the efficiency of different endothelial cells in a model of BBB
Laura Locatelli
Department of Biomedical and Clinical Sciences L. Sacco, University of Milan, ***Italy***

16:30 - 16:45 ***Break***

SESSION 3 Magnesium, Microbiota and gut-brain axis

Chairmen **Valentina Trapani** (Rome, ***Italy***)
Franco Scaldaferri (Rome, ***Italy***)

16:45 - 17:15 **Microbiota and gut-brain axis: nutritional perspectives**
Antonio Gasbarrini
Dipartimento di Medicina e Chirurgia Traslazionale - Fondazione Policlinico Gemelli IRCCS
Facoltà di Medicina - Università Sacro Cuore – Rome, ***Italy***

17:15 - 17:30 **Magnesium for a Healthy Gut Microbiota**
Valentina Trapani
Department of translational medicine and surgery, Faculty of Medicine A.Gemelli, Università Cattolica del Sacro Cuore, Roma, ***Italy***

17:30 - 17:45 **The effect of dietary Magnesium on gut microbiota in mice**
Federica Del Chierico
Multimodal Laboratory Medicine Research Area, Unit of Human Microbiome, Bambino Gesù Children's Hospital, Rome, ***Italy***

17:45 - 18:00 **Supplementation with a magnesium-rich marine mineral blend (MMB) impacts gastrointestinal microbiota, inflammation, and behavior**
Stefanie Grabrucker
Department of Anatomy and Neuroscience, University College Cork, ***Ireland***

Oral Communication

18:00 - 18:15 ***OC08***
Low gut microbiota diversity and dietary magnesium intake are associated with the development of ppi-induced hypomagnesemia
Jeroen H.F. de Baaij
Dept of Physiology, Radboud University Nijmegen, ***NL***

SATURDAY, MAY 29th, *MORNING*

SESSION 4 ROUND TABLE on: Magnesium and Covid

Chairmen **Stefano Iotti** (Bologna, ***Italy***)
Jeanette AM Maier (Milan, ***Italy***)
Andrzej Mazur (Clermont-Ferrand, ***France***)

08:30 - 09:00 **COVID-19 epidemiology and clinics**
Massimo Galli
Department of Medicine and Infectious Disease – Ospedale Sacco, Milan, ***Italy***

09:00 - 09:15 **Magnesium a metabolite that underlies the origin of life**
Stefano Iotti
Department of Pharmacy and Biotechnology, University of Bologna, ***Italy***

What does Magnesium have to do with COVID-19?
Jeanette A.M. Maier
Department of Biomedical and Clinical Sciences L. Sacco, University of Milan, ***Italy***

09:15 - 09:30 **Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors**
Andrzej Mazur
Human Nutrition Unit, INRA and University of Clermont Auvergne, Clermont-Ferrand, ***France***

09:30 - 09:45 **Magnesium and COVID19: Data from the Nationwide US Veterans**
Yan Cheng
Biomedical Informatics Center George Washington University, ***USA***

09:45 - 10:00 **Mg pathophysiology in Covid-19: data from Slovakia**
Martin Kolisek
Divison Neurosciences at Comenius University in Bratislava, ***Slovakia***

10:00 - 10:15 ***Break***

10:15 - 10:30 **Mexican study: the ratio serum Mg/Ca and mortality in patients with severe Covid-19**
Fernando Guerrero-Romero
Biomedical Research Unit, Mexican Social Security Institute, Durango, ***Mexico***

10:30 - 10:45 **Mg pathophysiology in Covid-19: data from Italy**
Lucia Merolle
Laboratory of Biochemistry and Metabolomics (BioMetLab), AUSL-IRCCS di Reggio Emilia, ***Italy***

10:45 - 11:00 **An integrated immunological point of view**
Giuseppe Di Fede
Institute of Biological Medicine-IMBio and of the Institute of Genetic and Preventive Medicine-IMGeP of Milan, ***Italy***

11:00 - 11:15 **Neurocovid and magnesium**
Maria Paola Perini
Department of Pathology, Gruppo Ospedaliero San Donato, Milan, ***Italy***

11:15 - 11:30 **Post-acute COVID-19 syndrome**
Matteo Tosato
Department of Aging Sciences, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCSS, Rome, ***Italy***

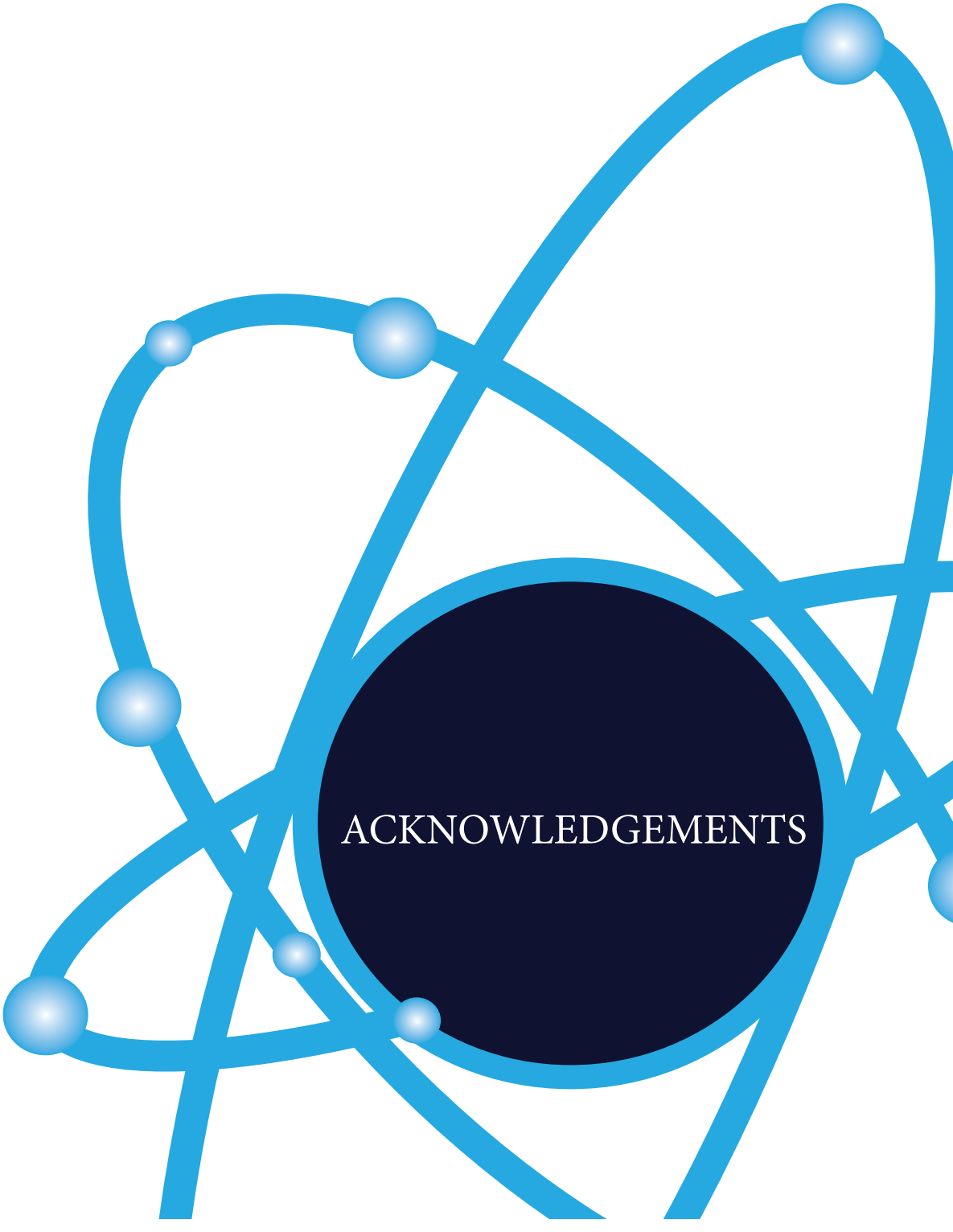
Oral Communication

11:30 - 11:45 ***OC09***
S1 protein of SARS-CoV-2 influences Mg^{2+} transporters and the interferon response in human endothelial cells
Francisco J. Rios
Institute of Cardiovascular and Medical Sciences, University of Glasgow, ***UK***

11:45 - 12:45 ***ROUND TABLE GENERAL DISCUSSION***

12:45 - 13:30 ***AWARD NOMINATION AND CLOSING CEREMONY***

Jury: **Mihai Nechifor** (Iasi, ***Romania***)
Giséle Pickering (Clermont-Ferrand, ***France***)
Federica I. Wolf (Rome, ***Italy***)



ACKNOWLEDGEMENTS

The President of the 2° Workshop on Magnesium, Neuroscience and Nutrition
- in current Covid-19 Pandemia -
would like to thank the following companies for their contribution:

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ABSTRACTS Invited Speakers

Recent advances in magnesium research - from cell biology to human disease

Rhian Touyz

(*Glasgow, **UK***)

*Institute of Cardiovascular and medical Sciences, University of Glasgow, **UK***

The importance of magnesium as an essential cation in the physiological regulation of cell function is well known. This is not surprising considering the critical role of magnesium in enzymatic activity, regulation of ion channels and inhibitory effects on intracellular calcium mobilization. While the biochemical functions of magnesium have been known for over 80 years, it is only more recently with the discovery of magnesium transporters, that molecular mechanisms that control cellular magnesium homeostasis have been unravelled. Intracellular magnesium levels are very tightly regulated and perturbations in magnesium transporters such as TRPM6/7 and MagT1 negatively impact transmembrane magnesium transport leading to intracellular magnesium depletion, impaired magnesium-dependent signaling and altered cell function. These phenomena are associated with various diseases. Despite the pathophysiological importance of magnesium, there are only a few clinical conditions such as Torsades de pointes and eclampsia, where magnesium is the therapeutic agent of choice. This underlies the large gaps in knowledge about magnesium in health and disease. Over the past 10 years there has been enormous progress in magnesium research with identification of new molecular processes, signaling pathways and cellular functions attributed to magnesium. Advances in the field have identified that i) magnesium is an important regulator of clock genes, ii) intracellular magnesium levels have a circadian rhythm, iii) magnesium is critically involved in mitochondrial function and energy regulation, iv) magnesium is a key regulator of chromatin-based biological functions, v) magnesium is linked to redox processes, and vi) magnesium transporters, eg TRMP6/7 cross talk with tyrosine kinases. Dysregulation of these magnesium-dependent processes are linked to inflammation, fibrosis, and apoptosis/proliferation leading to tissue damage important in cardiovascular disease, cancer and other pathologies. Here we will discuss new concepts in magnesium biology and the impact on human disease.

Biographical Sketch

Rhian M Touyz BSc(Hons), MSc(Med), MBBCh, PhD, FRCP, FRSE, FMedSci, FAHA, FESC, FCAHS.
Dr Touyz is Director of the Institute of Cardiovascular & Medical Sciences (ICAMS) and British Heart Foundation (BHF) Chair and Professor of Cardiovascular Medicine, Univ of Glasgow. ICAMS is a research-intensive institute of over 450 staff and students. In August 2021 she will take on the role of Executive Director and Chief Scientific Officer of The Research Institute of the McGill University Health Center, and the Phil Gold Chair in Medicine at McGill University, in Montreal, Canada. She is a clinician- scientist focusing on molecular and vascular mechanisms of hypertension, and is honorary clinical consultant at the Queen Elizabeth University Hospital.
Dr Touyz received her BSc (Hons) (1980), MBBCh (1984), MSc (1986) and PhD (1992) in South Africa. She completed a post-doctoral fellowship at the IRCM, Montreal. She has received numerous awards, including: Dahl Award, Harriet Dustan Award, Hypertension Research Excellence Award (Council on hypertension, AHA), Robert M. Berne Award (American Physiological Society), RD Wright Award (BPRC, Australia), Irvine Page Award (ASH), Joan Mott Award (Physiology Society). She is Editor-in-Chief of Clinical Science and Deputy Editor of Hypertension.
She contributes to best clinical practice and co-chaired the Canadian Hypertension Education Program (CHEP) for clinical guidelines. She is a committee member for Guidelines of the European Society of Cardiology. She played major leadership roles in premier hypertension organisations: President-Canadian Hypertension Society, Chair- Council on hypertension (AHA), President-International Society of Hypertension and President-European Council for Cardiovascular Research.
She has trained over 70 PhD students and fellows and has published over 550 papers [h- index:125 (Google Scholar); 105 (Web of Science)]. Her research has been funded by the CIHR, HSFC, JDRF, BHF, MRC.
Her research focuses on molecular and vascular biology of hypertension and target organ damage, particularly: 1) vascular signaling and redox biology; 2) vascular biology of cations and TRPM channels; 3) cardiovascular toxicity of anti-cancer drugs, 4) the renin angiotensin aldosterone system and pathophysiology of human hypertension. Her research spans molecular biology to clinical studies.
Contact: ***Rhian.Touyz@glasgow.ac.uk***

Global human magnesium status needs re-evaluation and updated reference values

Andrea Rosanoff

(*Pahoa, **Hawaii***)

*Center for Magnesium Education & Research, Pahoa, Hawaii, **USA***

The nutritional magnesium status of humankind has been changing over the last 50 years, bringing a generalized and growing low magnesium status for more and more human beings. In conjunction with this trend we see more and more societies showing rising levels of cardiovascular disease, diabetes, hypertension, and other chronic conditions associated with a low magnesium status. This trend is at least partly driven by agricultural practices of the Green Revolution that focus on high yield cultivars which decrease magnesium concentration of crops, a generalized global rise in human body weight which raises individual Mg requirements, and the transition from traditional high magnesium food diets to low magnesium foods of the commercialized modern processed food diet. This talk will focus on how these lower dietary intakes of magnesium have generally come about, how magnesium requirements, intakes and status have been measured, and how these methods might be improved to better assess human magnesium status both in populations and individuals that more reflects the research of the last 10-20 years.

Biographical Sketch

Dr. Rosanoff will present state of knowledge on magnesium status, focusing on recent and ongoing changes in human nutritional magnesium status, its sources and its impact on human health.
Biography: Andrea Rosanoff, Ph.D. has studied nutritional magnesium in health and disease since 1985. She is Director of CMER Center for Magnesium Education & Research in Hawaii.
Institution: Director, CMER Center for Magnesium Education & Research, 13-1255 Malama St., Pahoa, Hawaii, USA 96778
Contact: ***www.MagnesiumEducation.com - ARosanoff@gmail.com***

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When Mg is assessed in Clinical setting?

Yee-Ping Teoh

(*Wrexham, **UK***)

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Hypomagnesaemia is common but frequently undiagnosed in hospital patients. It is estimated that in an acute hospital setting, 12% of patients will have a degree of hypomagnesaemia. This figure goes up to 60% of all intensive care patients.

Two clinical case studies presenting with symptomatic hypomagnesaemia will be discussed. The clinical manifestation of hypomagnesaemia ranges from mild biochemical impairment to severe neuromuscular and cardiac derangements. As there is no national guidelines available on the treatment of hypomagnesaemia, I will try to provide an overview summary on magnesium replacement options (both oral and intravenous) commonly used in a hospital setting. Ultimately, the identification of hypomagnesaemia requires an increase awareness of at risk patients and most hospitals will benefit from a multidisciplinary approach involving laboratory staff, acute physicians, surgeons, oncologists and pharmacists.

Biographical Sketch

Consultant Chemical Pathologist and Clinical Lead for Biochemistry at the Wrexham Maelor Hospital, North Wales, UK since 2008.
I did my initial undergraduate medical training in Melbourne, Australia before continuing my postgraduate training in UK since 1997. My area of specialist interest includes dyslipidaemia, metabolic stone disease and total parenteral nutrition. I am one of the clinical leads for the regional home parenteral nutritional team and am involved in the management of patients with complex intestinal failure requiring electrolytes, fluids and nutritional replacement.
Contact: ***YeePing.Teoh@wales.nhs.uk***

150 JAHRE FRANZISKUS HOSPITAL Bielefeld
Akademisches Lehrkrankenhaus der Medizinischen Hochschule Hannover

Serum magnesium assessment needs for standardization

Oliver Micke

(*Bielefeld, **Germany***)

Oliver Micke[1], Jürgen Vormann[2], Anton Kraus[3], Klaus Kisters[4]

1 Department of Radiation Therapy and Radiation Oncology, Franziskus Hospital, Bielefeld, DE
2 Institute for Prevention and Nutrition, Ismaning, DE
3 Verla-Pharm Arzneimittel, Tutzing, DE
4 Medical Clinic I, St. Anna Hospital Herne, DE

Purpose: Low magnesium intake or low serum levels are risk factors for e.g., type 2 diabetes and cardiovascular diseases. Despite its scientifically recognized importance, too little attention is paid to magnesium in practice. This may be due to the fact that there is no uniform and evidence-based reference range for serum magnesium. Serum magnesium is also of limited informative value, as it is maintained for a long time by releasing magnesium from body pools. A low serum magnesium is a definite sign of magnesium deficiency; however, values within the reference range do not rule out deficiencies.

Materials and methods: A literature search of “magnesium” in connection with the search terms “reference interval”, “reference range”, “diagnostics”, “status”, “serum”, “plasma”, “hypomagnesemia”, “deficiency” was carried out in the PubMed database. Furthermore, quotations in the publications found were used.

Results: The serum magnesium is the only available parameter for the magnesium status in routine analysis but has only limited informative value. It should therefore be noted in the laboratory results that values within the reference range do not exclude the presence of a magnesium deficiency. To satisfy the high scientific importance of a sufficient supply of magnesium in clinical practice, serum magnesium should be established in routine analysis. In this regard, a uniform and evidence-based reference range is required. The determination of serum magnesium is simple and cost-effective.

Conclusion: •According to current data, an increase in the lower limit value for serum magnesium to 0.85 mmol/L (2.1 mg/dL) is required from a health point of view. The best way to diagnose a magnesium deficiency is based on the clinical symptoms and the presence of risk factors (anamnesis) in combination with the serum magnesium.

Biographical 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 role in oncology and nephrology.
His speech will present data on assessment of serum magnesium and the need for standardization.
Contact: ***strahlenklinik@web***

THE UNIVERSITY OF TOKYO

Dietary magnesium deficiency impairs hippocampus-dependent memories and induces neuroinflammation in mouse

Satoshi Kida

(*Tokyo, **Japan***)

Graduate School of Agriculture and Life Sciences, The University of Tokyo

Magnesium (Mg^{2+}) is an essential mineral for maintaining biological functions. Previous studies have suggested that Mg^{2+} plays critical roles in learning and memory, and synaptic plasticity. However, the effects of dietary Mg^{2+} deficiency (MgD) on learning and memory are unclear. Therefore, we have investigated effects of them in mice and show that MgD impairs hippocampus-dependent memories in mice. Mice fed an MgD diet showed deficits in hippocampus-dependent contextual fear, spatial and social recognition memories, although they showed normal amygdala- and insular cortex-dependent conditioned taste aversion memory, locomotor activity, and emotional behaviors such as anxiety-related and social behaviors. To understand molecular mechanisms underlying MgD-induced memory impairments, we next investigated the molecular signatures in the hippocampus of MgD mice by analyzing the hippocampal transcriptome. We performed RNA-sequencing of the hippocampal transcriptome of MgD mice. We observed that mRNAs for neuroinflammation-related genes were upregulated in the hippocampus and cortex of MgD mice, suggesting that MgD induces neuroinflammation in the mouse brain, including the hippocampus and cortex. Our findings suggest that MgD-induced neuroinflammation triggers the impairments of hippocampus-dependent memory.

Biographical Sketch

Dr. Kida was an undergraduate at the University of Tokyo in 1889 and then received Ph.D from the University of Tokyo in 1994. He worked in the Institute of Molecular and Cellular Biosciences in the University of Tokyo and then moved to Cold Spring Harbor Laboratory as a postdoctoral fellow. In 1997, he joined the Tokyo University of Agriculture as an associate professor and then became a professor in 2008. In 2019, he became a professor at the Graduate School of Agriculture and Life Sciences, the University of Tokyo. He is a president of Molecular and cellular cognition society-Asia. He has focused on understanding the mechanisms of learning and memory and tried to develop methods to improve brain disorders such as PTSD. He also investigated roles of nutrient factors in brain function.

Contact: ***akida@g.ecc.u-tokyo.ac.jp***

UNIVERSITY OF LEEDS

The effects of Combination of Green Tea, Rhodiola, Magnesium and B Vitamins on brain activity and the Effects of a Laboratory Social Stressor in Healthy Volunteers

Louise Dye

(*Leeds, **UK***)

Louise Dye[1], Neil Boyle[1], Jac Billington[1], Clare Lawton[1]

*1 Nutrition & Behaviour Group, School of Psychology, University of Leeds, **UK***

Purpose: The aim of this study was to examine the capacity of Magnesium (Mg, with B vitamins), green tea and rhodiola extracts in combination to moderate the effects of acute stress exposure and to confer protective effects under conditions of acute stress in humans.

Materials and methods: A double blind, randomised, placebo controlled, parallel group design was employed (Clinicaltrials.gov:NCT03262376; 25/0817). One hundred moderately stressed adults received oral supplementation of either (i) Mg + B vitamins + green tea + rhodiola; (ii) Mg+ B vitamins + rhodiola; (iii) Mg + B vitamins + green tea; or (iv) placebo. After supplementation participants were exposed to the Trier Social Stress Test. The effects of the study treatments on electroencephalogram (EEG) resting state alpha and theta, subjective state/mood, blood pressure, and salivary cortisol responses after acute stress exposure were assessed.

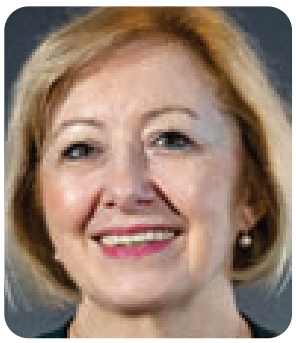
Results: The combined treatment significantly increased EEG resting state theta ($p < .02$) - considered indicative of a relaxed, alert state -, attenuated subjective stress, anxiety and mood disturbance, and heightened subjective and autonomic arousal ($p < .05$). There were no significant effects of treatment on resting state alpha, cortisol or blood pressure. The combined treatment attenuated subjective stress and tension/anxiety and increased subjective energetic arousal.

Conclusion: Mg, B vitamins, rhodiola and green tea extracts are a promising combination of ingredients that may enhance coping capacity and offer protection from the negative effects of stress exposure.

Biographical Sketch

Louise Dye is Professor of Nutrition and Behaviour and leads the Nutrition and Behaviour Group, in the Human Appetite Research Unit in the School of Psychology, University of Leeds. She is a Chartered Health Psychologist and is Associate Editor of Nutritional Neuroscience and the European Journal of Nutrition. Her research interests include functional foods for cognitive performance/decline and the impact of nutrients on stress and wellbeing. She is President of ILSI Europe and chair's their Scientific Advisory Board.

Contact: ***L.Dye@leeds.ac.uk***



CENTRE HOSPITALIER UNIVERSITAIRE CLERMONT FERRAND

Magnesium and Pain comorbidities

Gisèle Pickering

(*Clermont-Ferrand*, ***France***)

Magnesium is commonly used in clinical practice for acute and chronic pain and has been reported to reduce pain intensity and analgesics consumption in a number of studies. Results are however controverted and this presentation will discuss the effectiveness of magnesium treatment on pain and analgesics consumption in situations including postoperative pain, migraine, renal pain, chronic pain, neuropathic pain and fibromyalgia. It will also identify the gaps that need to be addressed in order to achieve a sufficient level of evidence and optimize the use of magnesium in pain and pain comorbidities.

Biographical Sketch

Professor Gisèle Pickering (MD,PhD, DPharm) is Professor of Medicine and Clinical Pharmacology at the University Hospital of Clermont-Ferrand, France. She is the Director of the Inserm CIC 1405 Clinical Research Centre and is a permanent member of the Inserm 1407 Laboratory of Fundamental and Clinical Pharmacology of Pain. Her main topics of research concern the mechanism of action of analgesics, the impact of pain on cognitive-emotional processes and pain management in older persons. She regularly contributes to peer-reviewed publications on Pharmacology and pain, to international meetings and belongs to national and international Pain, Pharmacology and Geriatrics Societies. She is the Chair of the Research Committee at the European Pain Society (EFIC). She is the author of over 150 publications and the editor of several books. Her interest in Magnesium in the context of Pain has been translational for the last 15 years, and her group published on the interest of Mg on NMDA receptors from animal models of pain to patients suffering from chronic neuropathic pain. She presently coordinates clinical trials with Magnesium in cancer patients, neuropathic pain, and in fibromyalgia, with a special focus on pain relief, stress and quality of life. Her presentation at the SDRM Society meeting on May 28-29, 2021 : Magnesium and Pain Comorbidities.

Contact: ***gisele.pickering@uca.fr***

THE UNIVERSITY of NORTH TEXAS HEALTH SCIENCE CENTER at FORT WORTH

Magnesium, Vitamin D and Cognitive Function in older adults: results from the US National Health and Nutrition Examination Survey (NHANES) 2011 to 2014

Menghua Tao

(*Fort Worth, **USA***)

Meng-Hua Tao[1], Jialiang Liu[2]

1 Department of Biostatistics and Epidemiology, University of North Texas Health Science Center, Fort Worth TX, 76116, USA
2 Department of Epidemiology and Biostatistics, College of Public Health, Temple University, Philadelphia, PA, USA 19122

Purpose: Magnesium plays an important role in multiple neurological disorders including cognitive impairment. Magnesium also is linked with the synthesis and metabolism of vitamin D. Studies have linked deficiencies of magnesium and vitamin D with reduced cognitive function. However, very few studies have examined their interactions. This study aimed to examine the associations of magnesium intake, serum vitamin D level with cognitive function, and interactions between these nutrients on cognitive function in a population-based cross-sectional study.

Materials and Methods: Utilizing data from the NHANES 2011 to 2014, 2,512 participants aged 60 years and older who completed the CERAD word learning immediate and delayed recall, and the Animal Fluency (AF) were analyzed. Magnesium intake were determined from 24-hour dietary recalls and supplement interviews. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were used to define vitamin D status. Linear regression models were applied to examine the association between magnesium intake, serum 25(OH)D levels and cognition.

Results: Higher total magnesium intake was associated with higher AF score (p trend=0.04) but not with CERAD scores. Total magnesium intake was associated with increased AF score among those with sufficient vitamin D status (p interaction=0.05). The association of magnesium intake with high AF score was primarily observed among men and non-Hispanic Whites, although the interactions were not significant. There were no linear associations between serum 25(OH)D levels and scores of cognition tests.

Conclusion: Findings suggest that high total magnesium intake may improve cognitive function in older adults. The positive association may be stronger among subjects with sufficient vitamin D status, and be dependent on race/ethnicity.

Biographical Sketch

Dr. Menghua Tao is an Assistant Professor of Epidemiology at the University of North Texas Health Science Center. Her research goals are to identify how lifestyle/behavioral, environmental, and biological factors influence chronic disease risk. She also has particular research interests on investigating nutritional determinant of complex diseases including cognitive impairment, with an emphasis on its interactions with other nutritional and biological factors. She led NIH-funded projects on magnesium, socioeconomic factors and obesity-related disorders and disparities in minority populations. Dr. Tao obtained her medical degree from Fudan University in Shanghai (China). She obtained her Ph.D. from the School of Public Health, University of California, Los Angeles, and completed a postdoctoral fellowship in University at Buffalo.

Title of presentation: Magnesium, vitamin D and cognitive impairment in US adults

Short Sentence on Scientific Presentation

Dr. Tao will talk about her research on magnesium intake, serum vitamin D levels and their interactions on cognitive function based on large national representative sample of the older adults in the United States.

Contact: ***Menghua.Tao@unthsc.edu***

Microbiota and gut-brain axis: nutritional perspectives

Antonio Gasbarrini

(*Rome,* ***Italy***)

The gut and brain are strictly interconnected by multiple molecular pathways including endocrine, neuronal, toll-like receptor, and metabolites-dependent pathways. Alterations in the bidirectional relationship between the gastrointestinal tract and central nervous system (CNS) are linked with the pathogenesis of gastrointestinal and neurological disorders. In this complex network, gut microbiota plays a pivotal role, modulating immune response and synthesizing bioactive compounds including short-chain fatty acids and neurotransmitters. Nutrition has a dramatic influence on gut microbiota composition and functions: many studies have elucidated its impact on gut homeostasis as well as gastrointestinal, metabolic, and neurological diseases. The lecture aims to dissect the influence of nutritional interventions on the gut microbiota and their impact on the development (or possible therapy) of neurological and psychiatric diseases, paving the way to an innovative way of re-thinking the gut-brain axis.

Biographical Sketch

ANTONIO GASBARRINI (male), born in Bologna the October 11th 1963, is Full Professor of Internal Medicine and Director of Postgraduated School in Internal Medicine at the Università Cattolica of Rome, Chairman of Medical and Surgical Sciences Department and Director of Internal Medicine and Gastroenterology Unit at the Fondazione Policlinico Universitario Gemelli IRCCS. He obtained his Medical Degree and specialties in Internal Medicine and Gastroenterology at the University of Bologna. He completed his training in the University of Pittsburgh (USA). His fields of interests are: Gut Microbiome and Metabolome, Irritable Bowel Syndrome, Inflammatory Bowel Disease, Liver insufficiency, viral hepatitis, hepatocellular carcinoma, Liver transplantation, celiac disease and intestinal malabsorption. Author of more than 800 scientific publications (h-index = 85).
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Magnesium for a Healthy Gut Microbiota

Valentina Trapani

(*Rome, **Italy***)

Valentina Trapani[1, 2], Federica I. Wolf[1]

*1 Sezione di Patologia Generale, Dipartimento di Medicina e Chirurgia Traslazionale, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, **Italy***

*2 Alleanza contro il cancro, Rome, **Italy***

Purpose: Diet is undisputably the main driver of gut microbial composition and function. Among nutrients, vitamins and minerals are essential not only for humans, but also for bacteria, that compete with the host to obtain them. Therefore, distribution and concentration of micronutrients may contribute to both host–pathogen communication and commensal bacteria homeostasis. In this context, magnesium may play a crucial role, as suggested by: 1) the absolute requirement for magnesium as a nutrient by all living organisms; 2) the association between disturbances of Mg homeostasis and diverse inflammation-driven chronic conditions; 3) the well-known immunomodulatory properties of magnesium. Here, we review the available evidence that magnesium may shape the gut microbiota composition and modulate its function.

Materials and methods: We performed a literature search of experimental studies exploring the effect of dietary magnesium on microbiota composition, and microbiological evidence supporting mechanistic links between Mg availability and bacterial functions.

Results: In a variety of bacteria there is a connection between Mg homeostasis and virulence. Many bacterial species harbor sensor/DNA binding protein systems that respond to changes in extracellular Mg availability. The pathways activated by low Mg availability lead to increased growth, virulence and survival within macrophages. Although there is no evidence directly linking magnesium to gut microbiota composition in humans, animal studies have showed that Mg deficiency affects bifidobacteria levels, which is associated with altered gut barrier function and systemic inflammation. Alterations in gut microbiota composition induced by Mg deficiency have also been associated to depression and anxiety in mice. Vice versa, Mg supplementation seems to enhance gut microbial diversity and favor gut health.

Conclusion: Alterations in systemic Mg availability may reflect not only in an altered composition of gut microbiota, but also in a significant shift in microbial function. Mg supplementation may be a safe and cost-effective intervention to restore a beneficial intestinal flora, especially on a background of Mg deficiency and/or inflammation.

Biographical Sketch

Adjunct Professor of Pathology at the Catholic University School of Medicine “A. Gemelli” in Rome, and Scientific Officer at Alliance Against Cancer, the largest Italian organization for cancer research. Moving on from a background in biophysics, in her career she has been involved in the preclinical development of several experimental anticancer drugs. Since 2005, her interests have focused on the role of magnesium and magnesium-specific ion channels in diverse pathophysiological processes, including inflammation-driven conditions and colon carcinogenesis.

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Bambino Gesù
OSPEDALE PEDIATRICO

The effect of dietary Magnesium on gut microbiota in mice

Federica Del Chierico

(*Rome, **Italy***)

Federica Del Chierico[1]; Valentina Trapani[2,3], Valentina Petito[4], Sofia Reddel[1], Giuseppe Pietropaolo[2,5], Cristina Graziani[4], Letizia Masi[4], Loris Riccardo Lopetuso[6], Antonio Gasbarrini[7], Lorenza Putignani[8], Federica Wolf[2] and Franco Scaldaferri[6]

1 Multimodal Laboratory Medicine Research Area, Unit of Human Microbiome, Bambino Gesù Children's Hospital, IRCCS, 00147, Rome, Italy
2 Sezione di Patologia Generale, Dipartimento di Medicina e Chirurgia Traslazionale, Fondazione Policlinico Universitario A. Gemelli IRCCS—Università Cattolica del Sacro Cuore, 00168 Rome, Italy
3 Alleanza Contro il Cancro, 00161 Roma
4 Dipartimento di Medicina e Chirurgia Traslazionale, Fondazione Policlinico Universitario A. Gemelli IRCCS—Università Cattolica del Sacro Cuore, 00168 Rome, Italy
5 Dipartimento di Medicina Molecolare, laboratory affiliated to Istituto Pasteur Italia-Fondazione Cenci Bolognetti, Sapienza Università di Roma, 00161 Rome, Italy
6 CEMAD, Unità Operativa Complessa di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS—Università Cattolica del Sacro Cuore, 00168, 00168 Rome, Italy
7 Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; CEMAD - IBD UNIT - Unità Operativa Complessa di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy
8 Department of Diagnostic and Laboratory Medicine, Unit of Parasitology and Multimodal Laboratory Medicine Research Area, Unit of Human Microbiome, Bambino Gesù Children's Hospital, IRCCS, 00165 Rome, Italy

Purpose: In this study, a mouse model was used to assess the role of dietary Magnesium (Mg) content to modulate the intestinal microbiota in presence of DSS-induced colitis.

Materials and methods: Mice were randomly assigned to: CTRL diet (1 g/Kg Mg), hypo-Mg diet (30 mg/Kg) and hyper-Mg diet (4 g/Kg Mg) for 5 days. 2.5% w/v DSS experimental colitis for 5 days was induced in each group. After treatment, fecal samples were collected and analyzed by 16S-rRNA based metagenomics.

Results: In absence of colitis, the CTRL and hypo-Mg groups showed higher microbiota diversity than hyper-Mg group. In DSS induced colitis the trend was inverted, showing high values of alpha diversity indices in the hyper-Mg and CTRL groups.

Beta diversity analysis revealed that, in absence of colitis, there is a clustering of the samples based on the Mg intake. In presence of colitis the separation is evident between hyper- and hypo-Mg groups, while CTRL samples resulted scattered.

Actinobacteria and Verrucomicrobia were incremented in hyper-Mg diet independently of colitis, while Proteobacteria, Firmicutes and Bacteroides were incremented in hypo-Mg group in presence of colitis.

Turicibacter was incremented in hyper-Mg group, while SMB53 was incremented in hypo-Mg group regardless of colitis. *Sutterella* was incremented in hypo-Mg group, only in presence of colitis.

Bacteroides, Lactobacillus and *Sutterella* were the discriminant taxa of gut microbiota in Mg-deficient diet in presence of colitis, while *Bifidobacterium* in Mg-enriched diet, even in presence of colitis.

Conclusion: Dietary magnesium supplementation can affect gut microbiota composition. The Mg-enriched diet in colitis increases beneficial bacteria involved in short-chain fatty acid production, mucin-degradation, intestinal health and glucose homeostasis, and reduces bacteria involved in inflammatory cytokines production and associated with human diseases, such as IBD. Conversely, Mg-deficient diet increases microbial taxa involved in gut inflammation and intestinal permeability.

Biographical Sketch

Institution: Bambino Gesù Children's Hospital and IRCCS
Unit: Human microbiome unit
Position: Researcher
EDUCATION-PROFESSIONAL QUALIFICATION
2004: degree in Biology at University of Rome "Sapienza", Rome, Italy.
2004-2008: post graduate school in Clinical Microbiology and Virology at University of Rome "Sapienza", Rome.
2005-2008: fellow biologist at the Department of Biomedical Sciences, University G. D'Annunzio, Chieti.
2008: biologist at the Istituti Fisioterapici Ospitalieri (IFO) of Rome.
2009-2016: post-doctoral fellow at the Bambino Gesù Children's Hospital of Rome.
2016-to date: researcher at the Bambino Gesù Children's Hospital of Rome.
RESEARCH SKILS and COMPETENCIES
Microbiology, Bacterial genetics , Molecular biology, Cellular biology, Proteomics, Metagenomics based on 16s rRNA NGS, Bioinformatics; Microbiota profile analysis and interpretation.
AWARDS and HONORS
2016 Ricerca Finalizzata project: GR-2016-02364891. Italian Ministry of Health.
2008 Research fellowship at the Department of Biomedical Science, G. D'Annunzio University, Chieti, Italy
2006-2007 Research fellowship at the Department of Biomedical Science, G. D'Annunzio University Chieti, Italy
2005 Research fellowship at the Department of Biomedical Science, G. D'Annunzio University, Chieti, Italy
PUBLICATIONS
2004-2021 Author of 75 scientific peer-reviewed manuscripts
Official H Index: 24
Scopus Author ID: 8976163900
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RESEARCHID Author Code: J-4373-2016

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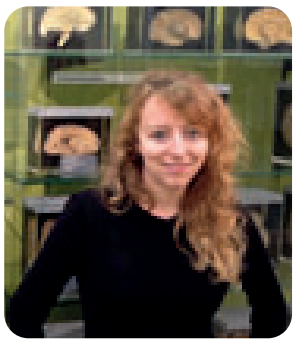

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Supplementation with a magnesium-rich marine mineral blend (MMB) impacts gastrointestinal microbiota, inflammation, and behavior

Stefanie Grabrucker

(*Cork, **Ireland***)

Stefanie Grabrucker[1], Erin K. Crowley[1], Sinead Ryan[1], Amy Murphy, Caitriona M. Long-Smith[1], Alice Stack[2], Denise M. O'Gorman[2], and Yvonne M. Nolan[1,3*]

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Middle age is increasingly accepted as a critical period during which individuals are susceptible to environmental and lifestyle factors. Emerging research indicates that dietary factors play a crucial role in brain health and cognitive function. A diet lacking adequate minerals, in particular magnesium and calcium, is considered a risk factor for cognitive decline and the development of dementia in older age through impairments in activity-dependent neuroplasticity, neurogenesis (a form of brain plasticity), and memory formation. Previous studies indicate that magnesium compounds can act as positive regulators of synaptic plasticity, promote memory function in young and aged rats, and influence gut-brain signaling. The food supplement, Aquamin-FTM is a natural multi-mineral derived from the red algae Lithothamnion corallioides, rich in bioactive calcium and magnesium, as well as 72 other trace minerals.

This study aimed to evaluate how dietary supplementation with a magnesium-rich marine mineral blend (MMB) affects the composition of intestinal gut microbiota and influences middle-age-related cognitive impairment with a focus on a potential anti-inflammatory activity of MMB.

To that end, we performed in vivo assay with two cohorts (young cohort: aged 12 weeks, aging cohort: aged 16 months) of adult male Sprague Dawley rats that were maintained for six weeks on MMB enriched chow. The respective control groups were fed standard rat chow. Rats were tested using several hippocampus-dependent memory tasks (Y-Maze, novel object recognition, modified spontaneous location recognition task). Caecal content was collected after six weeks of MMB dietary supplementation. Microbial diversity was analyzed by 16s rRNA sequencing and SCFA profile in Teagasc Food Research Centre, Cork.

In addition, in vitro assay using glia-enriched primary cultures of rat cortex were performed. Cells were incubated in the presence or absence of LPS and MMB. Twenty-four hours later, the supernatant was removed for analysis of TNF-alpha and IL-1 beta expression by Elisa. Untreated culture media was used as control. The cells were assessed for morphological signs of apoptosis and necrosis before, during, and after 24 h incubation with MMB.

Our results show that supplementation with MMB significantly enhanced gut microbial diversity and led to alteration in the short-chain fatty acid (SCFA) profile in the gut. Supplementation of MMB to middle-aged rats improved cognition, specifically a pattern separation paradigm sensitive to alterations in a type of brain plasticity that involves neurogenesis. In vitro, MMB significantly attenuated the LPS induced increase in inflammatory cytokine secretion.

We conclude that low-grade inflammatory status and changes in intestinal gut microbiota composition are hallmarks of aging, and that modification of dietary factors, for example using MMB, may be beneficial for preventing age-related cognitive decline and increased inflammation.

Biographical Sketch

Dr. Stefanie Grabrucker received her MSc in Neurobiology from Ulm University, Germany, where she continued with her PhD work as student of the international PhD programme in Molecular Medicine, funded by the excellence initiative of the Deutsche Forschungsgemeinschaft (DFG). Her PhD investigated how maternal dietary metal ion deficiency (zinc deficiency) dysregulates glutamatergic synaptic signaling during neurodevelopment and contributes to autism spectrum disorders. In 2019 she joined the Department of Anatomy and Neuroscience at the University of Cork Ireland as a postdoctoral fellow on a Centre of Excellence in Neurodegeneration ("CoEN") funded project. Her research aims to understand how dietary metal ion supplementation and gut microbiota influence the process of aging, inflammation, and cognitive decline and contributes the development of neurodegenerative disorders such as Alzheimer's disease. Since 2014, she has published 11 articles that were cited over 200 times. She is also contributed as author to the book "Biometals in Neurodegenerative diseases".

Short sentence on scientific presentation:

In this presentation, I will present data from a study that builds on accumulating evidence that dietary supplementation with functional food ingredients affects systemic and brain health and promotes healthy aging. Deficiencies in calcium and magnesium due to the increasing prevalence of a high fat/high sugar "Western diet" have been associated with health problems such as obesity, inflammatory bowel diseases, cardiovascular diseases, and metabolic, immune, and psychiatric disorders. In the current study, we show that supplementation with a seaweed and seawater-derived functional food ingredient rich in bioactive calcium and magnesium and 72 other trace elements significantly enhanced the gut microbial diversity, rescued an age-related deficit in cognitive impairment, and reduces pro-inflammatory cytokine secretion in neuronal cell culture.
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UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

COVID-19 epidemiology and clinics

Massimo Galli

(*Milan*, ***Italy***)

Dept. Biomedical and Clinical Sciences Università di Milano and Dept. Infectious Diseases Ospedale Sacco, Milano, Italy

In December 2019, a cluster of patients with unexplained viral pneumonia was reported in Wuhan, China. The causative agent was identified to be a novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although of zoonotic origin, human-to-human transmission rapidly fuelled the spread of SARS-CoV-2 infections globally. Since then, over 155 million confirmed cases of COVID-19 have been reported. Some issues about SARS-CoV-2 infection, including asymptomatic state, transmissibility, different susceptibility and immune responses, are not completely understood. This is further complicated by the emerging new variants which prompt more challenges for epidemiologists and clinicians.

Biographical Sketch

MD, Professor of Infectious Diseases at the University of Milan and head of the department of Infectious Diseases-Sacco Hospital (Milan). Specialized in immunology and allergology, infectious diseases and internal medicine, he has been at the forefront of clinical and translational research against HIV since the 80s. Since February 2020, prof Galli has played a key role in the management of the emergency COVID-19.
In his lecture, Prof Galli will give an overview of the clinical and epidemiological data of the Sars-CoV2 infection.
Contact: ***massimo.galli@unimi.it***

Magnesium a metabolite that underlies the origin of life

Stefano Iotti

(*Bologna, **Italy***)

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 Mg^{2+} helps the stabilization of diphosphate and triphosphate groups of nucleotides, as well as promoting the condensation of orthophosphate to oligophosphates, like pyrophosphate and trimetaphosphate. The central role of Mg^{2+} 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.

Therefore, it is not surprising that the role of magnesium in cell and tissue metabolism is complex and multifactorial. In fact, more and more evidences suggest 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, it should be specified that, since it interacts directly with the substrate, magnesium is itself a substrate rather than a cofactor. Indeed, since Mg^{2+} 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 [Mg^{2+}], 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. The total body magnesium of an adult is approximately 25 g, of which 50-60% is in bone, and the remaining 40-50% is in the soft tissues, with less than 1% present in the blood. Serum magnesium concentration in blood can be efficiently buffered by renal excretion and, in part, by its release from bones. In addition, magnesium is an intracellular cation whose content depends. Therefore, serum magnesium values within the reference range may not rule out a systemic magnesium-depleted state, and the clinical impact of magnesium deficiency may be easily underestimated. Nevertheless, in the absence of a satisfactory and easily measurable biomarker to assess magnesium state, we have to rely on serum magnesium levels, which are found to be altered in many diseases. Unfortunately, serum magnesium levels are still not determined routinely in daily clinical practice.

Worldwide, they are measured primarily in critically ill subjects and sometimes in elderly people at hospital admission. In view of the large variety of pathophysiological conditions associated to a decrease of magnesium availability, we strongly suggest to include Mg in the evaluation of the blood ionogram.

Biographical 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 116 publications which garnered > 3300 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).

The presentation will deal on the possible role of Mg ies on COVID-19. pandemic., since some aspects of the pathogenesis of the disease recall events occurring in Mg deficiency.

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UNIVERSITÀ DEGLI STUDI DI MILANO

What does Magnesium have to do with COVID-19?

Sara Castiglioni and Jeanette A.M. Maier

(*Milan, **Italy***)

When Sars-CoV2 began to spread around the globe, some plausible links emerged between the pathophysiology of the infection and magnesium deficiency, which is a common, but often overlooked, finding in apparently healthy people. Initially, we noted that conditions linked to magnesium deficiency in humans, such as aging, diabetes, obesity, hypertension and cardiovascular diseases, are associated with high odds of COVID-19 mortality. Then we reasoned that Mg deficiency might contribute to crucial events in acute COVID-19, such as viral entry in the cells, endothelial dysfunction and cytokine storm. As the population of patients recovering from COVID-19 grows, a low Mg status might have a role in some symptoms of the so-called post-acute COVID-19 syndrome, i.e. fatigue, brain fog, joint pain, palpitations, which result a decline in the quality of life and increase frailty.It should be recalled that magnesium deficit determines anxiety, insomnia, hyperemotionality, depression, headache, light-headedness symptoms included in the post-acute COVID-19 syndrome.
We conclude that monitoring and restoring magnesium homeostasis through an appropriate nutritional regimen or possibly by supplementation should be regarded as a safe and cost-effective intervention that could contribute to prevent SARS-CoV-2 infection, reduce severity of COVID-19 symptoms and facilitate the recovery after the acute phase.

Biographical 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.
Contact: ***jeanette.maier@unimi.it***
In her speech, she will talk about the possible role of dysregulated magnesium homeostasis in COVID-19.

Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors

Andrzej Mazur

(*Clermont-Ferrand,* ***France***)

Didier Quilliot[1], Olivier Bonsack[1], Roland Jaussaud[2], André Mazur[3]

1 Transversal Nutrition Unit, Nancy University Hospital, University of Lorraine, FR
2 Internal Medicine and Clinical Immunology, Nancy University Hospital, University of Lorraine, FR
3 Université Clermont Auvergne, INRAE, UNH, Unite de Nutrition Humaine, Clermont-Ferrand, FR

Purpose: Hypomagnesemia and hypermagnesemia could have serious implications and possibly lead to progress from a mild form to a severe outcome of Covid-19. Susceptibility of subjects with low magnesium status to develop and enhance this infection is possible. There is little data on the magnesium status of patients with Covid-19 with different degrees of severity. This study was conducted to evaluate prevalence of dysmagnesemia in a prospective Covid-19 cohort study according to the severity of the clinical manifestations and to identify factors associated.

Materials and methods: Serum magnesium was measured in 300 of 549 patients admitted to the hospital due to severe Covid-19. According to the WHO guidelines, patients were classified as moderate, severe, or critical.

Results: 48% patients had a magnesemia below 0.75 mmol/L (defined as magnesium deficiency) including 13% with a marked hypomagnesemia (<0.65 mmol/L). 9.6% had values equal to or higher than 0.95 mmol/L. Serum magnesium concentrations were significantly lower in female than in male (0.73±0.12 vs 0.80±0.13 mmol/L), whereas the sex ratio M/F was higher in severe and critical form ($p<0.001$). In a bivariate analysis, the risk of magnesium deficiency was significantly and negatively associated with infection severity ($p<0.001$), sex ratio (M/F, $p<0.001$), oxygenotherapy ($p<0.001$), stay in critical care unit ($p=0.028$), and positively with nephropathy ($p=0.026$). Logistic regression analysis revealed that the strongest predictors of magnesium deficiency were female sex (OR=2.67, $p<0.001$) and nephropathy (OR=2.12, $p=0.032$) and after exclusion of sex ratio, the severity of infection (OR=0.46, $p=0.04$ and OR=0.39 $p=0.01$), for critical and moderate forms, respectively.

Conclusion: This transversal study reveals a high prevalence of hypomagnesemia in hospitalized patients for Covid-19, while high-level serum magnesium concentration was more prevalent in critical form. For full paper see Magnes Res 2020; 33(4): 114-122.

Biographical Sketch

Research Director at the Human Nutrition Unit, INRAE and University of Clermont Auvergne, Clermont-Ferrand, France, Editor-in-chief of the "Magnesium Research"- Official Journal of the International Society for the Development of Research on Magnesium. His lab is involved in research aimed at providing knowledge of the mechanisms by which nutrients, in particular micronutrients, contribute to the prevention of age-related diseases. His research on magnesium has been focused on its role in inflammation and the CVD risk as well as on magnesium status assessment. His speech will present recent data on the status of magnesium in patients with Covid-19. Contact: ***andre.mazur@inrae.fr***

GW School of Medicine & Health Sciences

Magnesium and COVID19: Data from the Nationwide US Veterans

Yan Cheng

(*Washington, **USA***)

Yan Cheng[1,2], Rebecca B. Costello[3], Ali Ahmed[1], Wen-Chih Wu[4,5], Qing Zeng-TreitleR[1,2]

1 Washington DC VA Medical Center, Washington, DC
2 George Washington University, Washington, DC
3 National Institutes of Health Office of Dietary Supplements, Bethesda, MD
4 Providence VA Medical Center, Providence, RI
5 Brown University, Providence, RI

Background: Low magnesium (Mag) could impair immune function and contribute to cytokine storm and cause worse outcomes in patients with COVID19.

Objective: This study was to examine the relationship of serum Mag with ICU admission, mechanical ventilator (MV) use, total hospitalization LOS, and mortality among the US Veterans with COVID19.

Methods: We used first serum Mag lab within 7 days since the confirmed date of COVID19 as the exposure. The outcomes were measured within 7, 30, and 90 days since the first Mag lab date. We divided Veterans into three groups according to the Mag values: Low (<1.7 mg/dL), Normal (1.7-2.4 mg/dL), and High (>2.4 mg/dL). Multiple logistic and Poisson regression models were conducted for the binary outcomes and count outcomes, respectively, with adjusting for baseline demographics, comorbid conditions, serum potassium, and neutrophil count.

Results: Around 19.5% Veterans with confirmed COVID19 diagnosis had a serum Mag lab. We included a total of 21,697 Veterans in this study: 2,524, 17,919, and 1,254 in Low, Normal, and High Mag group, respectively. The three groups had the mean age of 67-70 years old, with 69-82% inpatients and 93-96% men. Veterans with low Mag were the sickest, however, Veterans with high Mag had the highest prevalence of chronic kidney disease and anemia of chronic disease. There was no significant association between mechanical ventilator use and Mag level. Low Mag level independently and significantly increased the risk of ICU admission. High Mag level independently and significantly prolonged total LOS (within 7 days and 30 days) and mortality risk.

Conclusions: Abnormal serum Mag is associated with a higher risk of adjusted adverse outcomes in patients with COVID-19. Further study needs to further examine these associations and if the outcomes in the subset with low Mag can be improved with Mag supplements.

Biographical Sketch

Dr. Cheng is a research assistant professor at the George Washington University Biomedical Informatics Center. She earned her M.S. in Pharmacoeconomics, Epidemiology, Pharmaceutical Policy and Outcomes Research from the University of New Mexico in 2011 and PhD in Pharmacotherapy Outcomes Research from the University of Utah in 2017. Since 2013, she has been involved in health outcome research on various diseases including HIV, frailty, ADRD, severe mental illnesses, heart failure, and COVID19 in the US Veterans, via analyzing electronic medical record (EMR) data of the nationwide Veterans Health Administration (VHA) databases. Her primary areas of expertise including pharmacoepidemiology, comparative effectiveness research, and biostatical analyses. Her specific research interest is to address health disparities in aging Veterans.

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Mg pathophysiology in Covid-19: data from Slovakia

Martin Kolisek

(*Bratislava, **Slovakia***)

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The pandemic of the coronavirus SARS-CoV2 affected the life of every Man. With almost 159 million positive cases over 15 months worldwide, this is the largest pandemic since the Spanish flu. The symptoms of COVID19, the onset of which is linked to SARS-CoV2 infection, are remarkably variable ranging from respiratory, cardiovascular, gastrointestinal to neurologic complications. Although, most of the infected persons overcome the infection asymptomatically or with only mild, flu-like symptoms, a significant proportion of the COVID19 patients suffer from a severe, respiratory/pulmonary type of the disease (atypical, viral pneumonia), which require intensive care, oxygen therapy, and in the worst cases mechanical pulmonary ventilation. The lethality of the SARS-CoV2 virus ranges from 1.5% to 3.5%, with the percentage of death dramatically increasing with age (60 years old +) and in the group of polymorbid patients.

Slovakia, with a population of 5.45 million people, experienced only a few cases during the first wave of the SARS-CoV2 pandemics. However, it was badly affected by the second wave between October 2020 and May 2021 (the death count on the 25th of September 2020 was 0 / 7-day average was 0, on the 25th of December 2021 it was 68/54, on the 2nd of March 2021 it was 118/102 and on the 10th of May it was 32/35; JHU CSSE). By the 11th of May 386,136 infected were reported with 12,077 fatalities due to the disease in Slovakia.

Magnesium (Mg) is known to be essential for a plethora of biochemical and physiological processes in cells but also at the level of the whole organism. Its role in energy metabolism is fundamental. Noteworthy is also its support of pro-survival and pro-proliferative events in cells.

Mg deficiency was associated with various pathological clusters of human diseases and its supplementation was shown to be beneficial in the treatment of cardiovascular, neurological, immunological, and also respiratory diseases.

Therefore, in our retrospective monocentric data analysis we aim to assess the Mg status of hospitalized COVID19 patients upon their admission to the COVID19 unit of the regional hospital in Cadca and where possible to correlate this parameter with the treatment outcome. Furthermore, we aim to collect data on the status of Na, K, Ca, P, Fe and Cl- in plasma of these patients and also Astrup blood parameters. In this abstract, we do not offer any values or conclusions due to ongoing data collection and analysis.

Biographical Sketch

Assoc. Prof. RNDr. Martin Kolisek Ph.D.
Earned his master degree (MSc.) in Molecular Biology (1999) and RNDr. degree in Biotechnology (2001) at Faculty of Natural Sciences of Comenius University in Bratislava (Slovakia). He further joined PhD. program in Genetics at Max F. Perutz Laboratories at University of Vienna (Austria), which he accomplished in 2002. His junior post-gradual years he spent in Laboratory of Cell and Molecular Signaling at the Queens Medical Center and University of Hawai'i, Honolulu (USA). In 2005 he started his senior postdoc in Molecular Transport Physiology at the Institute of Veterinary-Physiology at Free University of Berlin (Germany). Since 2006 he was leading own research group, "Magnesium Transport AG". In 2016 he relocated to Slovakia where he is conducting his research at Jessenius Faculty of Medicine of Comenius University until present. In 2019, Dr. Dr. Kolisek became an associated professor in clinical, medical, and pharmacological biochemistry after successfully completing the process of habilitation. Prof. Kolisek's research since his early carrier focuses on the various aspects of Mg2+ transport in cells and on the cellular homeostasis of this cation. His research played the pivotal role in functional identification of superconducting mitochondrial Mg^{2+} channel Mrs2, Na+/Mg^{2+} exchanger SLC41A1, mitochondrial Na+-dependent Mg^{2+} carrier SLC41A3 and Mg-homeostatic factor CNNM2. Recently he is exploring the role of Mg homeostasis in pathoetiology of Parkinson disease and rare mitochondrial diseases.
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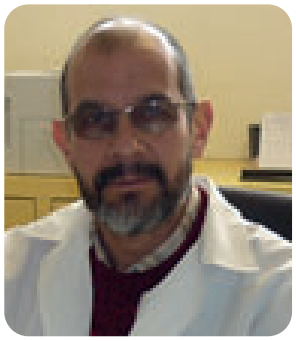

Mexican study: the ratio serum Mg/Ca and mortality in patients with severe Covid-19

Fernando Guerrero-Romero

(*Durango, **Mexico***)

Objective. To evaluate the association between the ratio of serum Magnesium-to-Calcium (Mg/Ca) and mortality in patients with severe COVID-19

Material and Methods. A total of 438 medical records were retrieved and analyzed in a retrospective case-control study. Eligible participants were men and women older than 19 years, with positive polymerase chain reaction test for SARS-CoV2 and diagnosis of severe COVID-19, hospitalized in a Tertiary care Mexican institution during February to December 2020. Missing laboratory data, previous diagnosis of chronic renal disease, history of calcium, magnesium, or glucocorticoids intake over the last month, were exclusion criteria. Patients with hospital discharge per death were allocated in the Case group and compared *versus* Patients with hospital discharge per recover allocated in the Control group.

Results. A total of 289 (66%) and 149 (34%) individuals, with average age of 56.8±15.2 years, were allocated in the case and control groups. 276 (63%) men and 162 (37%) women, of which 179 (40.9%) men and 110 (25.1%) women were in the case group. The proportion of individuals with obesity (44.3% versus 49.7%, p=0.49) was similar, whereas that proportion of diabetes (47.6% versus 36.7, p=0.01) and hypertension (47.0% versus 34.6%, p=0.001) was higher in the case group. Furthermore, individuals in the case group were older and exhibited higher leukocytes, neutrophils, lymphocytes, C reactive protein, and D-dimer, than individuals in the control group. The multivariate regression analysis showed a significant association between the Mg/Ca ratio cutoff ≤3.0 and death by COVID-19 (Odds ratio 2.88; 95%CI 1.4-7.1, p=0.001). Data from gasometry were available for 89 individuals, 57 (19.7%) and 32 (21.5%) in the case and control groups, pNS. There were no significant differences between the groups for pH (p=0.83), pCO2 (p=0.69), P02 (p=0.22), HCO3 (p=0-95), and SatO2 (p=0.71). Also in this subgroup, the multivariate regression analysis showed a significant association between the Mg/Ca ratio cutoff ≤3.0 and death by COVID-19 (Odds ratio 1.62; 95%CI 1.1-12.4, p=0.04).

Conclusion. Our results suggest that the serum Mg/Ca ratio ≤3.0 is among the risk factors associated with mortality by severe COVID-19.

Key words. Magnesium; Calcium; COVID-19; Risk, Death

Biographical Sketch

He is Medical Internist and Doctor in Science.
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RESEARCH SUBJECT
Clinical and Molecular Epidemiology of Complex Diseases with focus in magnesium, obesity, diabetes, and metabolic syndrome.
He has tutored 38 degree, 12 Specialty, 16 Master, and 10 PhD students and published 212 articles in peer-reviewed journals and 33 book chapters, obtained more than 45 national and international awards and distinctions, and is member of several Research and Ethics Committees.
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Mg pathophysiology in Covid-19: data from Italy

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Purpose: The purpose of the present study was to test whether Mg serum levels variations could be considered as a risk factor of Covid-19 disease worsening, considering death as the main outcome.

Materials and methods: We performed a retrospective study including hospitalized patients from March to May 2020 with Covid-19 diagnosis for whom serum Mg levels were available in our archives. A survival proportional hazard Cox model was used to assess the risk of death in patients classified for their pre-diagnosis Mg serum level, adjusting for sex, age and comorbidities (cancer and/or diabetes).

Results: A cohort of 241 Covid-19 patients, 146 male and 95 female, were involved in the study. The median serum levels was 1.99 (inter-quartile range 1.81-2.17), similar in females and males, but lower in older patients. In patients for whom Mg was evaluated before being diagnosed as Covid-19 (149), the hazard ratio (HR), adjusting for sex, age and comorbidities, was 1.09 with a 95% confidence interval (CI) of 0.43 to 2.79.

Conclusion: Based on our data, Mg serum levels variations can not be considered a risk factor of death caused by Covid-19 disease. However, main limitation of this study is that we do not know information about the decision making process leading to prescribe Mg serum anlaysis, neither about administered therapies and oral supplementations. A prospective study, in which the assessment of serum Mg is performed on all Covid-19 patients upon their admission to hospital, could helpt clarify the data herein presented.

Biographical Sketch

Lucia Merolle is senior scientist at the AUSL-IRCCS di Reggio Emilia, where she is currently pursuing her research activity at the Laboratory of Biochemistry and Metabolomics (BioMetLab). Her scientific activity ranges from transfusion medicine to tumour biochemistry with main focus on Mg homeostasis and colon cancer. Starting this year, she is the scientific responsible of the platelet-based therapies research line.

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An integrated immunological point of view

Giuseppe Di Fede

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Spike protein (S protein) is a protein found on the surface of some viruses, and most recently studies have found the Spike protein on the surface of SARS-CoV-2. It is a homotrimeric protein, divided into two domains: S1 and S2. S1 contains an RBD domain and a region that adheres to the host's ACE2 receptor and allows the virus to bind to the target cell, whilst S2 allows the actual entry of the virus into the cell. One can measure the value of the neutralizing antibodies RBD IgG in people who have contracted the infection and in vaccinated subjects. The antibody titer, as it is known, decreases after a few months.
The Immune System (SI) activates the APC cells, stimulated by the viral infection, the CD4 + are activated, producing INFg which activates the APC again, and IL2 which activates the CD8 + cytotoxic T lymphocytes with the possibility of killing and eliminating the virus. Macrophages and IL6 play an important role in this immunological mechanism.
If IL6 levels are high, the viral infection lasts a long time and delays healing with the support of type 2 Macrophages.
The control of the Neutrophils / Lymphocytes ratio is decisive for predicting the antibody response (N / L Ratio) if the N / L Ratio is => 3.13 the prognosis is severe, there will be a reduction in CD8 + T lymphocytes and an increase in levels of IL6, IL10, INFg and IL2. The Mediterranean-type ketogenic diet can help reduce healing times by supporting a good level of antibody response.

Biographical Sketch

Giuseppe Di Fede, Surgeon, has been working in the preventive and genetic field since 2000; he is medical director of the Institute of Biological Medicine-IMBio and of the Institute of Genetic and Preventive Medicine-IMGeP of Milan. He graduated in Medicine and Surgery in 1992 from the University of Milan; he obtained a Master's in Clinical Nutrition and Dietetics at the Polytechnic University of Marche, several diplomas in Natural Medicine and Biotechnology at the University of Milan and a Diploma in Acupuncture and Traditional Chinese Medicine. He is an expert in preventive and genetic medicine, in oncological hyperthermia and in immunological cancer biotherapy.
He currently lectures at the University Master in "Human Nutrition" of the University of Pavia and at the Master on breast cancer in Rome Sacred Heart University Faculty of Medicine and Surgery Gemelli Hospital Rome He is a Founding Member of the Integrated Cancer Therapies Research Association-ARTOI From Rome.
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UNIVERSITÀ DEGLI STUDI DI MILANO

Neurocovid and magnesium

Maria Paola Perini

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Viral infections have detrimental impacts on neurological function and can cause severe neurological damage. SARS-CoV-2 exhibits neurotropic properties and may be an underestimated opportunistic pathogen of the brain. It can enter the nervous system directly through the olfactory nerve, through blood circulation or neuronal pathways, resulting in neurological disorders.
SARS-CoV-2 has been found in the brain or in the cerebrospinal fluid. It can damage the nervous system through the hyperactivation of the immune responses. The high neurosusceptibility of COVID-19 might also be linked to the hypoxic conditions caused by lung injury.
The pathobiology of these neuroinvasive viruses is still incompletely known, and it is therefore important to explore the impact of CoV infections on the nervous system.
We review the research available on the neurological complications in CoV infections and the possible mechanisms of damage to the nervous system.

Biographical Sketch

MD, PhD. Clinical Neurologist at Policlinico San Donato - University of Milan. She was trained in Milan on mitochondrial myopathies and neuromuscular diseases. In the last 20 years she worked as clinician with particular interest in pain treatment and headache.
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In her speech, she will talk about the possible role of magnesium and neuro COVID-19.
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Post-acute COVID-19 syndrome

Matteo Tosato

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As the number of patients recovered from COVID grows, a new syndrome has emerged, that is being referred to as Long Covid, Post COVID or Post-Acute Sequelae of COVID-19 (PASC). This syndrome is characterized by the persistence or the development of new symptoms after months from the acute phase of Covid.
The most commonly complained disorders are fatigue, dyspnea, attention deficit, myalgia, joint pain, tachycardia palpitations. In the present talk the one-year experience of the Day Hospital Post Covid at Policlinico Gemelli In Rome will be described.
On a total number of 1334 patients, only 25% of patients were free from covid-related symptoms after three months post acute phase , while 45% reported 3 or more symptoms. This prevalence of symptoms was not correlated with the severity of the acute phase of COVID and did not vary with age.
As for the quality of life, a significant reduction was observed across
all age groups, with a more relevant decline experienced by people aged between 30 and 55 years. The prevalence of post traumatic stress disorder, (about 30% of patients) was also very high.
About 40% of our patients failed attention tests, while 60% had at least one altered lung function parameter. For what concerns muscle function and nutritional aspects, 38% of our elderly patients met EWGSOP2 criteria for probable sarcopenia, while 30% of the entire sample had a condition of malnutrition identified by Glim criteria (about 45% of older subjects vs 25% of younger subjects).
While there are still no diagnostic criteria to uniquely identify this condition, the accumulating evidence on its clinical relevance has spurred the World Health Organization to add a specific chapter dedicated to the follow-up of post-acute manifestations in its living guidance for covid 19 clinical management.

Biographical Sketch

Matteo Tosato is an Assistant professor at Università Cattolica del Sacro Cuore of Rome and the Leader of Day-Hospital Post Covid at Department of Geriatrics, Neurosciences and Orthopedics, Fondazione Policlinico Universitario Agostino Gemelli. His research activities are focused on sarcopenia, nutrition, physical activity, and frailty. He participated to several large national and international trials, e.g. as Leader of the Central Reading Unit for DXA Analysis in the SPRINTT Project (IMI-JU; grant # 115621), Co-I, Study site coordinator of Frailtools study DG SANCO - Third Health Programme. Founding Health Initiatives (2014-2020), Co-I and Study site coordinator of CRiME study (CRiteria to assess Inappropriate use of Medicines among Elderly patients) funded by the Italian Ministry of Health, Co-I and Study site coordinator of the SHELTER study (Services and Health for Elderly for Elderly in Long TERm care) funded by the EU 7th Framework Programme for Research and Technological Development in the area of Health. He published extensively in peer-reviewed scientific journals on topics related to frailty, sarcopenia, pharmacoepidemiology, and behavioral interventions in older adults.
The presentation will describe the Post-Covid Syndrome, also known as Long Covid or PASC, showing results derived from one-year experience at DH Post Covid at Department of Geriatrics, Neurosciences and Orthopedics, Fondazione Policlinico Universitario Agostino Gemelli.
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ABSTRACTS Oral Communications

OC01

Systematic review and meta-analysis to determine a reference range for ionized magnesium

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Purpose: A lack of consensus exists for the reference range for ionized magnesium (iMg^{+2}) blood concentration. Using a systematic review and meta-analysis, we sought to estimate the reference range of iMg^{+2} for the healthy adult population, and to compare our estimated values with values obtained for populations with diabetes, hypertension, renal, and cardiovascular diseases. As a secondary outcome, we described reference ranges for serum (and plasma) total Mg concentrations in healthy adults.

Materials and methods: We searched OVID MEDLINE®, Cochrane Central Register of Controlled Trials, and EMBASE through 24 July 2020 to identify related articles. We included English peer-reviewed randomized controlled trials (RCT's), prospective and retrospective cohort studies, nested case-controlled studies, case-controlled studies, cross-sectional studies, and mendelian randomization studies that measured iMg^{+2} in blood at baseline. The protocol for this systematic review was registered at PROSPERO (CRD42020216100). Baseline means and standard deviations (SDs) were extracted or calculated from each included study. The reference range for our population-level study was estimated as the 2.5th and 97.5th percentiles of the distribution. Descriptive statistics were used to show medians, minimum and maximum means, and 2.5th and 97.5th percentiles of the distribution for iMg^{+2} and serum Mg concentrations for each health status.

Results: Total 94 articles were included (n= 54, 16, 8, 4, and 12 articles for healthy populations and people living with cardiovascular disease, diabetes, hypertension, and renal diseases, respectively). Results from our healthy population data showed a reference range of 0.47-0.63 mmol/L for iMg^{+2}. All of the ranges for the diseased populations overlapped with our estimated reference range for iMg^{+2}.We obtained a reference range of 0.79-0.94 mmol/L for serum Mg concentrations. Similarly, diseased populations had measures that were within the reference range for serum Mg.

Conclusion: Based on our findings, the reference range for iMg^{+2} captures the means for the diseased population. This harmonized reference range may not be sensitive for diagnosing Mg deficiency. Our findings suggest a research and clinical need for future studies to establish sensitive reference range for blood iMg^{+2} and serum Mg.

Funding: None

Keywords: ionized magnesium, serum magnesium, total magnesium, magnesium, reference range, ion-selective electrodes.

OC02

Magnesium transporters: discovering new potential biomarkers in digestive cancers

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Purpose: Many epidemiological studies suggest that a bad diet and lifestyle could increase the risk of developing digestive cancer [2-4]. Notably, magnesium (Mg^{2+}) intake decreases over the years and could be linked to the incidence of some digestive cancers such as pancreatic cancer [5]. Mg^{2+} is essential for cellular physiology, as it regulates a lot of cellular processes. Its homeostasis is regulated by membrane transporters, such as TRPM6, TRPM7, MAGT1, CNNM4, SLC41A1, and MRS2. However, their distribution in tissues from digestive cancers has not been exhaustively studied.

This work aims to study Mg^{2+} transporter expression in digestive cancers and their impact on patient survival.

Materials and methods: We analyzed the Mg^{2+} transporters *TRPM6, TRPM7, MAGT1, CNNM1-4, SLC41A1*, and *MRS2* mRNA relative expression from the TCGA transcriptomic datasets to investigate their expression pattern, combinatory correlation, and their impact on survival in esophageal carcinoma (ESCA), stomach adenocarcinoma (STAD), pancreatic adenocarcinoma (PAAD) and colorectal adenocarcinoma (COADREAD). Genotype Tissue Expression (GTEx) and Cancer Genome Atlas (TCGA) datasets were analyzed in this study, using GEPIA2 and RStudio tools.

Results: By comparing non-tumoral and tumoral tissues, we observed an alteration of Mg^{2+} transporters expression in most of digestive cancers. *MAGT1* and *CNNM4* are overexpressed in all digestive cancers and are negatively correlated with overall-survival and in disease-free in PAAD patients. High *TRPM6* was correlated with a better outcome in those patients. Interestingly, we identified a gene signature involving *MAGT1, CNNM4* and *TRPM7*. This signature is associated with poor prognosis in some digestive cancers, like PAAD, ESCA or COADREAD.

Conclusion: Our work suggests the importance of Mg^{2+} transporters such as MAGT1, TRPM7, and CNNM4 as potential new biomarkers in digestive cancers. More analyses are required to evaluate the functional interaction among those proteins and their impact on cancer processes such as cell proliferation, migration, or invasion.

Biographical sketch:

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OC03

TRPM7 is protective against hypertension, cardiovascular inflammation and fibrosis induced by aldosterone and salt

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Purpose: TRPM7 is a channel permeable to Mg^{2+}, Ca^{2+} and Zn^{2+} bound to an alpha-kinase domain with essential role in cell homeostasis. Hyperaldosteronism is associated with Mg^{2+} wasting. Here, we investigate the importance of TRPM7 in hypertension and fibrosis induced by aldosterone and salt.

Material and 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. Vessel structure was assessed by pressure myography. Inflammatory infiltrate was investigated by FACS. Molecular mechanisms were investigated in cardiac fibroblasts (CF). Protein expression was assessed by western-blot and histology.

Results: M7+/Δ mice exhibited reduced TRPM7 expression (30%) and phosphorylation (62%), levels that were recapitulated in WT-aldo-salt. M7+/Δ exhibited increased BP by aldo, salt and aldo-salt (135-140mmHg) vs M7+/Δ-veh (117mmHg)($p<0.05$), whereas in WT, BP was increased only in aldo-salt group (134mmHg). Mesenteric arteries from M7+/Δ-aldo-salt exhibited thinner walls by reducing cross-sectional area (35%) vs WT-aldo-salt($p<0.05$). Aldo-salt induced greater collagen deposition in hearts (68%), kidneys (126%) and aortas (45%) from M7+/Δ vs WT. In kidneys from WT mice, aldo-salt increased frequency of macrophages (47% vs 32% WT-veh) and CD4+T cells (33% vs 22% WT-veh)($p<0.05$), effects observed already in M7+/Δ-veh (macrophages: 42%, CD4+T cells: 34%). Hearts from M7+/Δ-veh exhibited increased TGFβ, p-Smad3(1.5-fold). Similar characteristics were found in WT-aldo-salt. Cardiac expression of PPM1A, a Mg2+-dependent phosphatase, was reduced (3-fold) in M7+/Δ mice. CF from M7+/Δ mice showed reduced of proliferation (30%) and PPM1A (4-fold) and increased expression of TGFβ (3-fold), p-Stat1 (2-fold), p-Smad3 (9-fold) and p-ERK1/2 (8-fold) vs WT. Mg2+ supplementation normalized cell proliferation and reduced protein phosphorylation in M7+/Δ CF($p<0.05$).

Conclusion: Our findings identify a protective role of TRPM7 in aldosterone-salt induced cardiovascular injury, which when downregulated, facilitates hypertension, vascular remodeling and cardiac fibrosis through Mg^{2+} -dependent mechanisms.

OC04

Magnesium in Bipolar Disorders – a general view

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The influence of magnesium on human and animal behavior is certain and has been repeatedly demonstrated. However, the data related to the involvement of magnesium in mood disorders in the human clinic are more heterogeneous. The implications of magnesium in bipolar disorders(BP) have been controversial. There are data showing that low levels of magnesium are associated with more severe symptoms of BD, but also data showing that magnesium concentration has no correlation with the of BD severity. The causes for which there is an important heterogeneity in the data regarding the role of magnesium in BD are the following: lack of accurate diagnosis of the type of BP and the phase in which the patients were when the study was initiated; dosing of plasma or cerebrospinal fluid only and lack of determinations of intracellular magnesium, different age of the disease in different patients which makes it difficult to compare the results, omission of the influence of some associated diseases and drugs used to treat them on the concentration of magnesium. In our studies the administration of mood modulators (sodium valproate 900mg/day p.o., carbamazepine 600mg/day p.o. or quetiapine 600mg/day) in BD type I hospitalized adult patients during the maniacal episode has increased magnesium erythrocyte concentration and we consider that this increase is a part of the mechanism of action of some mood modulators. This increase in magnesium concentration was positively correlated with the improvement in the clinical state of the patients. BD is recurrent diseases with repeated relapses. In our study, all patients who had relapses in the first two years after hospital discharge after BD type I treatment had lower intraerythrocyte magnesium than at discharge level and lower compared to non-relapsed patients. Our data showed a really positive involvement of magnesium in BD.

OC05

Can Additional Dietary Magnesium Reduce Stress In Pigs?

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Purpose: Additional dietary magnesium may be an effective way to improve pigs' welfare, health and overall production performance by reducing stress. This study aimed to investigate how additional dietary magnesium may reduce stress before and after a stressful event (regrouping) in pigs.

Materials and methods: 240 pigs were weaned at 28 days of age and assigned to pens of five balanced for sex, origin litter and weaning weight. Two focal pigs per pen were selected based on highest and lowest weight (96 focal pigs). All animals received a standard commercial diet for the first 20 days post-weaning before beginning one of four study diets: (A) control; (B) magnesium phosphate (0.15%); (C) phytase (0.03%); or (D) magnesium phosphate (0.15%) and phytase (0.03%). After two weeks, the pens were combined ('regrouped') within treatment resulting in pens of ten. Pig and feed weights were recorded on the first day of the study diets, the day before regrouping and the end of the study. Saliva from each focal pig and pooled pen faecal samples were collected for two consecutive days before the trial diet began. Following this, samples were collected the week before, day after and week after regrouping. Each focal pig was assessed for skin lesions on a weekly basis. Blood samples were collected from each focal pig at the end of the study.

Results: Pigs receiving the phytase diet (C) had significantly more body lesions than both of the magnesium diets (B - p=0.009; D - p=0.011). There was no significant difference between diets for the number of ear and tail lesions. There was no significant effect of diet on plasma mineral levels, faecal or salivary cortisol.

Conclusion: Overall, magnesium phosphate may have some welfare benefits in terms of the stress response of pigs after regroupin.

OC06

BDNF and GABA-R expression is modulated in human mini-brain organoids in response to magnesium

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Purpose: Mini-brain organoids 3D model represent a unique model to study neurobiology and neuropathology. Since magnesium protects against neuroinflammation and neurodegeneration, we evaluated the effects of different concentration of magnesium (Mg) salts (MgSulphate and MgPidolate) on human mini-brain organoids in the presence or not of an *in vitro* generated blood brain barrier (BBB). Indeed, we have previously shown that the BBB is differently permeable to distinct Mg salts. We focused on BDNF and GABA-receptors, both involved in neurodegeneration and neuroregeneration.

Materials and methods: The brain-organoids were generated from human induced Pluripotent Stem cells and differentiated for 30 days. The organoids, alone or in the presence of BBB, were treated with different concentrations of MgSulphate and MgPidolate for 5 days. The expression of different neurological markers was evaluated by Real Time PCRs. The structure of organoids was evaluated by hematoxylin eosin staining and neurological markers by immunofluorescence.

Results: Our data show that the presence of the BBB influences the expression of BDNF and GABAR in mini-brain. Indeed, high concentration of MgPidolate (5mM) upregulates only the GABAB-r when organoids are cultured without BBB. On the contrary, in the presence of BBB, a significant upregulation of BDNF and GABAR was induced by 5mM MgPidolate. No differences in the structures of organoids were detected by hematoxylin eosin staining and immunofluorescence.

Conclusion: This study demonstrates that the presence of the BBB selectively changes BDNF and GABAR expression in mini-brain exposed to high concentration of MgPidolate. Because BDNF and the GABAergic system are involved in critical CNS functions, ranging from neuronal development and neuronal survival to learning and memory, these results might illuminate novel pathways explaining the neuroprotective effect of Mg.

OC07

Comparison of the efficiency of different endothelial cells in a model of BBB

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Purpose: The blood-brain-barrier (BBB), the tight network of endothelial cells in direct contact with astrocytes, isolate the central nervous system (CNS) from the systemic circulation. The integrity of BBB is fundamental to protect the brain from the diffusion of harmful substances but also to guarantee the passage of molecules necessary for the metabolic function. Modifications of BBB's permeability are associated with several neuropathological disorders. The aim of this study was the evaluation of the capability of different endothelial cells in creating a tight barrier in experimental models of BBB and the evaluation of different magnesium salts in modulating BBB performance.

Materials and methods: To mimic BBB, HUVEC, a widely used model of macrovascular endothelial cells, or HBMEC, microvascular brain endothelial cells, were co-cultured with astrocytes in transwells. The ability of creating a tight barrier was evaluated both measuring the transendothelial electrical resistance and also monitoring the passage of fluorescent molecules from the apical to the basal component of the system. Then the differential expression of the adhesion molecules VE-cadherin and ZO-1 were evaluated in HUVEC and HBMEC. Moreover, the effects of different magnesium salts in modulating these molecules were analyzed.

Results: We show that HBMEC create a better barrier tha HUVEC, showing a reduced passage of molecules and and increased transendothelial electrical resistance. Moreover, the addition of different magnesium salts to the culture medium prevents BBB hyperpermeability induced by LPS and Bradikinin, both known to augment endothelial permeability, by modulating the expression of adhesion molecules.

Conclusion: Our results demonstrate that HBMEC should be used in models mimicking BBB. Moreover, the permeability of the BB and the expression of adhesion molecules is modulated by magnesium salts which are beneficial to counteract the increased permeability induced by LPS and Bradykinin.

OC08

Low gut microbiota diversity and dietary magnesium intake are associated with the development of ppi-induced hypomagnesemia

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Purpose: Proton pump inhibitors (PPIs) are used by millions of patients for the treatment of stomach acid-related diseases. Although PPIs are generally considered safe, about 13% of the users develops hypomagnesemia (serum magnesium (Mg^{2+}) < 0.7 mmol/l). Despite rising attention for this issue, the underlying mechanism is still unknown. Here, we aim to examine whether the gut microbiome is involved in the development of PPI-induced hypomagnesemia.

Materials and methods: To assess the effects of the PPI omeprazole on Mg^{2+} homeostasis and gut microbiota, wild-type C57BL/6J mice were treated daily with 20 mg/kg bodyweight omeprazole for 4 weeks under normal or low dietary Mg^{2+} availability. Subsequently, the effect on Mg^{2+} homeostasis was assessed by means of serum, urine and fecal electrolyte measurements and gut microbiota composition was investigated by 16S rRNA gene sequencing.

Results: Omeprazole significantly reduced serum Mg^{2+} levels in mice on the low Mg^{2+} diet (1.20 ± 0.05 vs. 1.05 ± 0.05 mmol/L) without affecting the mRNA expression of *Trpm6* and *Trpm7* in colon or kidney. Overall, these mice showed a lower gut microbial diversity in response to omeprazole treatment. Redundancy analysis identified a shift in microbial composition in omeprazole-treated mice compared to controls. In particular the abundance of *Lactobacillus* and *Bifidobacterium* was increased with 3-fold and 2-fold, respectively. To examine metabolic consequences of the microbial alterations, the colonic composition of organic acids was further evaluated. Low dietary Mg^{2+} intake, independent of omeprazole treatment, resulted in a 10-fold increase in formate levels.

Conclusion: Our study demonstrated that omeprazole treatment alters the gut microbial composition. Additionally, low dietary Mg^{2+} intake affects the metabolic potential of the gut bacteria. Together, these results imply that both omeprazole treatment and low dietary Mg^{2+} intake disturb the gut internal milieu and may pose a risk for malabsorption of Mg^{2+} in the colon.

Biographical sketch: Jeroen de Baaij is assistant professor in renal physiology at the Radboud university medical center in Nijmegen, the Netherlands. His research group focuses on magnesium (Mg^{2+}) in health and disease. By identification of genes involved in hereditary hypomagnesemia, his team aims to increase our understanding of the molecular mechanisms of Mg^{2+} reabsorption in the kidney. The fundamental insights of Mg^{2+} reabsorption from these rare renal disorders can be applied to common magnesium deficiencies. Jeroen's team has demonstrated that hypomagnesemia is common in type 2 diabetes mellitus and contributes to insulin resistance. Moreover, he demonstrated that magnesium prevents vascular calcification in cell and animal models of chronic kidney disease. These findings have resulted in clinical trials using magnesium supplements to treat these diseases, which are currently running together with clinical.

OC09

S1 protein of SARS-CoV-2 influences Mg^{2+} transporters and the interferon response in human endothelial cells

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Purpose: Reduced Mg^{2+} levels are associated with viral infections, inflammation and endothelial damage. Hypomagnesemia has been reported in some patients with COVID-19. Interferon (IFN) alpha (IFNα) and lambda3 (IFNL3) constitute the first line of immunity against viral infection by increasing expression of interferon-stimulated genes (ISGs). Both are produced in SARS-CoV-2 infection in COVID-19. Here, we questioned whether S1-protein (S1P) of SARS-CoV-2 influence expression of Mg^{2+} transporters and IFN-related inflammatory responses in endothelial cells.

Material and Methods: Cultured human Microvascular Endothelial Cells (MEC) were stimulated with SP1 of SARS-CoV-2 (1µg/10^6 cells), IFNα (100ng/mL) or IFNL3 (100IU/mL). Expression of ISGs (ISG15, IFIT1, and MX1) was investigated by real-time PCR, cytokine production by ELISA and protein expression by immunoblotting.

Results: S1P reduced gene expression for TRPM7 (30%) and increased MagT1 (1.5-fold) and ISGs: ISG15 (2-fold), IFIT1 (5-fold), MX1 (6-fold) ($p<0.05$), indicating activation of the IFN pathway. IFNα and IFNL3 increased protein expression of MagT1 (100%), CNNM2 (40%), SLC41a1 (30%) and phosphorylation of TRPM7 (Ser1511) (100%). IL-6 production was increased in MEC stimulated with IFNα (1230pg/mL) and IFNL3 (1124pg/mL) vs control (591pg/mL). This was associated with increased activation of pro-inflammatory pathways with increased phosphorylation of Stat1 (134%), Stat2 (102%), ERK1/2 (42%). Nitric oxide production and phosphorylation of the eNOS activation motif and Ser1177 was reduced by IFNLα and (40%) and IFNL3 (40%).

Conclusion: In human endothelial cells S1P decreased TRPM7 expression and increased the interferon-stimulated gene response. Together these findings suggest that S1P downregulates TRPM7 while increasing the interferon response in endothelial cells. Increased ISG expression together with IFN-induced upregulation of Mg^{2+} transporters may act as a compensatory mechanism in response to SARS-CoV-2 infection. S1P effects on TRPM7 may contribute to perturbed Mg^{2+} homeostasis and inflammation, which may contribute to endotheliitis in COVID-19.

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