Glasgow Magnesium Symposium 2022: Wrap up and depart

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Despite the challenges of the Covid-19 pandemic - we made it! The XVI International Magnesium Symposium was held on the 22nd-23rd July 2022, in hybrid mode: 15 people including organizers, chairs and selected speakers gathered at the charming location of The Royal College of Physicians and Surgeons of Glasgow, to conduct and animate two full-immersion days on "Magnesium in Health and Disease". Speakers from Europe, USA, Canada, Mexico, Venezuela and many international participants joined virtually, and were enabled to interact by the outstanding IT services of the Royal College staff. With over 100 participants joining the symposium over the 2 days, with interactive questions and discussions, the symposium was truly outstanding.

Following the consolidated tradition of our magnesium (Mg^{2+}) meetings, the scientific program aimed at highlighting the most relevant advances in Mg^{2+} research, from basic science to translational and clinical data. Magnesium 2022 was committed to a scientific meeting of the highest quality with the priority of engaging with new Mg^{2+} researchers and new and exciting scientific discoveries. During a time of a pandemic there are of course challenges: both scientific and organizational. Moreover, we were faced with decreasing industry sponsorship. Nevertheless, despite the challenges, we rose to the occasion and successfully reached our goals, and we are especially proud of the outcomes. We share some of the highlights of Magnesium 2022.

Session 1

The first session was opened by *Andrea Rosanoff (CMER, Hawaii)*, who dealt with a key, long-debated issue: serum Mg^{2+} levels as a clinical biomarker of Mg^{2+} status. Although we are all aware that serum Mg^{2+} levels may not reflect the cation biological availability in Mg-utilizing tissues, nevertheless magnesemia values still are the most widespread, if not the only, available data to assess magnesium in patients. In the absence of more reliable biomarkers, we have to use this parameter cautiously. The normal Mg^{2+} reference range is crucial to assess pathologic hypo- or hyper-magnesemia conditions. Rosanoff, after highlighting the great discrepancy in such reference ranges around the globe, proposed to increase the minimal normal value from 0.75 mM to 0.85 mM (0.85 mmol/L = 2.07 mg/dL or 1.7 mEq/L) total Mg, in order to unmask what has been defined Chronic Latent Magnesium Deficiency (CLMD), which ranges from 0.75 to 0.85 mM Mg. CLMD is an often overlooked condition that has been associated to an increased risk in developing relevant chronic diseases, such as CVD, hypertension, metabolic syndrome, diabetes, chronic inflammation and some neurologic diseases [1, 2].

The next presentations included two basic, fundamental fascinating talks that illustrated the impoverishment of Mg^{2+} in the environment and the essential role of Mg^{2+} in all living

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organisms. *Roberta Cazzola* (*University of Milano, Italy*) underlined that Mg^{2+} has also been considered the forgotten cation in agriculture: the "green revolution" occurred in the second half of the last century promoted intensive crop cultivation by providing large amounts of N, P, and K fertilization, without paying adequate attention to Mg^2, until the progressive depletion of Mg^{2+} has hindered crop yield. Consequently, most fertile soils are so degraded that restoring soil health has become a priority to ensure food security and safeguard both human health and the environment. "Soil health" is now considered a key factor in national and supranational strategic plans aimed at protecting the environment and humans [3, 4]. We were also introduced to the concept of 'precision agriculture'.

Moving from inorganic soil to organic life, *Stefano Iotti (University of Bologna, Italy)* provided evidence to support a catalytic role of Mg^{2+} in the very early (prebiotic) steps leading to the origin of life, before the appearance of more complex, coordinated enzymatic reactions. Phosphate is a component of numerous biological building blocks, and its availability to build molecules such as nucleotides was triggered preferentially by the soluble highly hydrated Mg^{2+} ion. Convincing experimental evidence confirms that that Mg^{2+} took part in the prebiotic environment to the formation and polymerization of nucleotides, the polymerization of peptides and the self-assembly of primitive membrane of protocells. The special role that Mg^{2+} plays in biochemistry is primarily due to its ability to efficiently coordinate six oxygen atoms in its first coordination shell, providing stabilization of diphosphate and triphosphate groups of nucleotides, and promoting the condensation of orthophosphate to oligophosphates. According to the 'RNA World' hypothesis, the first enzymes – the ribozymes – consisted of ribonucleic acid (RNA), which depended on Mg^{2+} for its self-cleavage. The fact that biogeochemistry of Mg^{2+} is intimately coupled to that of phosphorus and nucleotides witnesses its key position in the prebiotic processes leading to the origin of life. Altogether these intriguing observations contribute to explain why Mg^{2+} is an essential element for any living organism and to support its role as a metabolite, rather than an electrolyte, as it has traditionally been regarded [5-7].

The program then progressed from Mg^{2+} paleobiology to steatonecrosis and its sequelae. Steatonecrosis is a condition that is gaining increasing clinical attention due to its dual etiology linked to alcohol and obesity, which are both important causes of serious chronic liver disease worldwide. *Maria Luz Martinez-Chantar (Carlos III Health Institute, Spain*) illustrated her elegant work on the role of CNNM4 in regulating Mg^{2+} content in non-alcoholic steatohepatitis (NASH). The cyclin M family, CNNM, perform key functions in the transport of Mg^{2+} across cell membranes. Cyclin M4 (CNNM4) is overexpressed in NASH and promotes the export of Mg^{2+} from the liver; indeed, NASH patients tend to be hypomagnesemic. *In vivo* and *in vitro* liver-specific silencing of CNNM4 ameliorates NASH by inducing cellular Mg^{2+} accumulation, reducing endoplasmic reticulum stress, and increasing microsomal triglyceride transfer activity, which promotes hepatic lipid clearance by increasing the secretion of VLDLs. These data demonstrate that overexpression of CNNM4 is responsible for dysregulated Mg^{2+} transport in NASH patients, and suggest that hepatic CNNM4 is a promising therapeutic target for the treatment of NASH [8, 9].

Donough Maguire (University of Glasgow, UK) illustrated another aspect of the role of Mg^{2+} in liver pathophysiology, namely alcohol-induced chronic liver disease. He reported results of a RCT on the effect of intravenous thiamine and/or Mg^{2+} sulphate administration on erythrocyte transketolase activity (ETKA), plasma lactate concentrations and alcohol withdrawal scores in patients attending the Royal Glasgow Infirmary Emergency Department with alcohol withdrawal syndrome (AWS). Routine treatment includes thiamine and benzodiazepines. Thiamine requires Mg^{2+} for optimal activity, but apparently no data were available on an intervention including Mg^{2+}. Maguire's data show that while no significant difference was found between groups for changes in ETKA, nevertheless co-administration of thiamine and Mg^{2+} resulted in more consistent normalization of plasma lactate concentrations and reduced duration to achieve initial resolution of AWS symptoms. Maguire's results suggest that thiamine treatment of AWS can be ameliorated when associated to $MgSO_4$ [10, 11].

Further exploring the fascinating role of Mg^{2+} in cell biology, *Muniswamy Madesh (UT Health, San Antonio TX)*, in his keynote lecture, took us on a journey in the cell through mesmerizing live confocal imaging, to study interplay between cell organelles. His work elegantly shows how lactate elicits Mg^{2+} dynamics between the ER and mitochondria to integrate cellular metabolism. Considering that the "metabolic switch", consisting in preferential glycolytic *vs* oxidative pathway, occurs in normal proliferating cells as well as in tumor cells, the role of lactate is crucial to drive cell metabolism in many pathophysiological circumstances. In this context, the observation that lactate induces redistribution of Mg^{2+} for different energetic needs is an important addition to the complex cell Mg^{2+} homeostatic mechanisms [12].

A second keynote lecture was given by *Michael Lenardo (NIAID-NIH, Bethesda, USA),* who reviewed his research on Mg^{2+} as a trigger of cellular immune responses. Starting from the early studies on XMEN (X-linked immunodeficiency with Mg^{2+} defect, EBV infection, and neoplasia) syndrome, his work has shown how a mutation in the MagT1 gene affects Mg^{2+} fluxes inside T lymphocytes and reduces TCR-mediated activation. Similar effects are obtained by reducing extracellular Mg^{2+}: low Mg^{2+} specifically impairs TCR signal transduction by IL-2-inducible T cell kinase (ITK) due to a requirement for a regulatory Mg^{2+} in the catalytic pocket of ITK. In a mice model, low Mg^{2+} causes an impaired $CD8^+$ T cell response to Influenza A virus infection and exacerbates morbidity. Thus, Mg^{2+} directly regulates the active site of specific kinases during T cell responses, and maintaining high serum Mg^{2+} concentration is important for anti-viral immunity in otherwise healthy animals, a key message especially in the current pandemic time [13, 14].

Session 2

Session 2 focused on the role of Mg^{2+} throughout the lifespan, with four talks ranging from embryogenesis to aging.

It is well documented that lack of Mg^{2+} affects development in human and animal models in different ways. *Loren Runnels (Robert Wood Johnson Medical School, NJ, USA)* showed that, following Mg^{2+} deprivation, *Xenopus laevis* frequently exhibits edema and gastrulates poorly, with a curved axis and reduced rates of tail expansion, among other phenotypes. *Xenopus* embryos depleted of TRPM7, TRPM6, and SLC41A1, key transporters involved in the cellular homeostasis of Mg^{2+}, develop similar but more severe abnormalities, which suggests that cellular Mg^{2+} levels in cells undergoing morphogenesis must be exquisitely regulated for successful completion of embryogenesis. Thus, Mg^{2+} is indeed a building block in "early life" as well as in each single embryogenetic process [15, 16].

Ligia Dominguez (Kore University, Enna, Italy) comprehensively reviewed aging-associated diseases highlighting the contribution of decreased Mg^{2+} availability to their pathogenesis. Aging people tend to be hypomagnesemic for several reasons: diet, medications, malabsorption or poor retention. As to the pathophysiologic mechanisms, increased oxidative stress and inflammaging were advocated. This overview underlines how important it is to provide sufficient amounts of Mg^{2+} to aging people to prevent or slow down aging-associated chronic diseases [17].

In the two following talks, the redox theory of aging and the underlying mechanisms were investigated in *in vitro* and *in vivo* experimental models.

Sara Castiglioni (University of Milano, Italy) explored in detail the role of Mg^{2+} on muscle homeostasis. Previous data showed that in mice Mg^{2+} deficiency alters expression of genes critical for muscle Mg^{2+} homeostasis and physiology. Here, C2C12 myoblasts under moderate Mg^{2+} deficiency displayed altered myogenesis and metabolism, including autophagy to control protein and lipid remodeling, associated to nitric oxide overproduction and consequent nitrosative stress. These data show that low Mg induces a significant stress response both in myoblasts and myotubes thus impairing essential processes for muscle homeostasis maintenance [18, 19].

Ricardo Villa-Bellosta (University of Santiago de Compostela, Spain) studied an original, very interesting murine model of progeria (LmnaG609G/+), which is ideal to recapitulate the hallmarks of aging. Villa-Bellosta showed that in these animals, Mg^{2+} supplementation ameliorated the syndrome, reduced calcification of vascular smooth muscle cells and improved the longevity of mice. He suggested that the

antioxidant property of Mg^{2+} may be beneficial in children with HGPS [see 20, 21].

Session 3

Session 3 was devoted to "Molecular mechanisms of magnesium homeostasis" and chaired by Jeroen de Baaij and Vladimir Chubanov, the leading European researchers in the field.

The transient receptor potential cation channel, subfamily M, members 6 and 7 (TRPM6 and TRPM7) are homologous membrane proteins that were named "chanzymes" since their cation channel units are fused to cytosolic serine/threonine protein kinase domains. It is widely accepted that the organismal balance of Mg^{2+} predominantly depends on TRPM6 and TRPM7. *Vladimir Chubanov (LMU Munich, Germany)* pointed out that regulation of the TRPM6/M7 channel activity remains an open question. Experimental evidence suggests that selective inhibition of TRPM6 and TRPM7 currents might be beneficial for subjects with immune, cardiovascular and oncological disorders, among other pathologies, and stressed that regulatory mechanisms of these channels might be crucial to design an effective pharmacological intervention. Chubanov's recent research has added further details in this context. In particular, he has been studying the regulation of TRPM7 channel activity by cytosolic Mg^{2+}, and has contributed to the identification and functional characterization of accessory subunits of native TRPM7, as well as to the identification of small synthetic molecules acting as selective inhibitors of the channel and kinase units of TRPM6 and TRPM7 [22, 23].

Talking about the master Mg^{2+} channel, in a mouse model of hypertension, *Francisco Rios (University of Glasgow, UK*) investigated the role of TRPM7 in aldosterone induced hypertension and fibrosis. Comparing wildtype (WT) vs $M7^{+/-}$ mice, treated with aldosterone, and/or 1% NaCl for 4 weeks, he was able to highlight a novel protective role of TRPM7 in aldosterone-salt induced cardiovascular damage, since TRPM7 downregulation promotes hypertension, vascular remodeling, and cardiac fibrosis through Mg^{2+}-dependent mechanisms [24].

Jeroen de Baaij (University of Nijmegen, NL) is a physiologist interested in the molecular and genetic origin of renal electrolyte disorders, including hypomagnesemia. He has contributed significantly to unraveling the renal regulatory mechanisms of magnesemia, which marked the beginning of the mechanistic deciphering of a complex homeostatic control. The experimental approach by de Baaij's group consists in studying rare genetic diseases associated to hypomagnesemia, to identify new genes involved in the control of Mg^{2+} homeostasis. Here he described two such genes: 1) *RRAGD* is involved in the activation of the mTOR pathway, and its mutation is a causative factor for kidney tubulopathy and cardiomyopathy; and 2) other gene variants in MT-TF and MT-TI have been identified in suspected Gitelman Syndrome which affect mtDNA causing a dysfunction of complex IV of OxPhos, demonstrating the central role of cell metabolism in renal Mg^{2+} transport [25, 26].

Among the ever-growing list of Mg^{2+} transporters, we were introduced to a new member. The ubiquitous SLC11/NRAMP family catalyze the uptake of divalent transition metal ions into cells. They have evolved to efficiently select these trace elements from a large pool of Ca^{2+} and Mg^{2+}. *Cristina Manatschal (University of Zurich, Switzerland)* has functionally and structurally characterized a bacterial member of a distant clade of the SLC11/NRAMP family, that was proposed to function as a transporter of Mg^{2+}, instead of Fe^{2+} and Mn^{2+}. Manatschal also studied the factors responsible for selectivity of transition and alkali metal ions in this transporter family. Interestingly, this transporter exhibits a restructured ion binding site whose increased volume provides suitable interactions with ions that likely have retained much of their hydration shell [27].

Further novel findings on genes involved in Mg^{2+} transport and homeostasis have come from the pioneering project stemmed from the collaboration between *Randboud University of Nijmegen* and *University of Glasgow*. Part of this work was presented by *Heidi Schigt* and *Francisco Rios*, who searched for molecular causes of severe Mg^{2+} wasting in Kenny Caffey Syndrome (KCS). Kenny-Caffey syndrome type 2 is a rare disorder characterized by hypoparathyroidism and electrolyte disturbances, including hypocalcemia and hypomagnesemia. It is caused by mutation in family with sequence similarity 111A (FAM111A) that encodes a poorly characterized protein.

The case study and literature review show that hypomagnesemia is a common feature of KCS2 and that patients may be at risk for chronic kidney disease. A pull-down assay identified cytoskeletal proteins and signal transducer and activator of transcription 1 (STAT1) as interactors of FAM111A. Tubulin repolymerization and cell migration were delayed by FAM111A mutation. Mutations in FAM111A also reduce STAT1-regulated transcription. In turn, STAT1 positively regulates transient receptor potential cation channel 6 (TRPM6). STAT1 knockout mice display hypomagnesemia and renal Mg^{2+} wasting. In conclusion, the cytoskeleton as well as STAT1 signalling may play a role in disturbing Mg^{2+} homeostasis in KCS2 [*unpublished observations*].

Session 4

Session 4 was dedicated to Magnesium in communicable diseases, an important and timely topic in view of current concerns for pandemic infectious diseases. The MagNet group already addressed the issue of how Mg^{2+} can affect Sars-Cov2 infection and disease severity [28]; in this session we gathered the top experts in the importance of divalent cations in microorganisms, together with speakers who could provide an update on Mg^{2+} and Covid-19.

The pivotal role of Mg^{2+} in bacteria has been well known for decades; indeed, it is no coincidence that the first characterization of specific Mg^{2+} transporters was achieved in bacteria [29]. Now that a wide panel of mammalian Mg^{2+} transporters has been discovered, it remains to be deciphered how Mg^{2+} can affect the relationship between microorganisms and their host. This topic is very timely, because it may shed light not only on the mechanisms of emerging infectious diseases, but also on the link between microbiota and Mg^{2+}, and thus may offer a promising alternative intervention in otherwise untreatable chronic diseases [30].

Three enlightening talks on the competition between pathogenic bacteria and their host for Mg^{2+} availability followed. *Eduardo Groisman (Yale School of Medicine, USA)* discussed how bacterial pathogens detect changes in Mg^{2+} concentration in their surroundings and in their cytoplasm and described the physiological response they mount to overcome Mg^{2+} limitation. The master regulator *of S. Typhimurium* virulence PhoP/PhoQ is activated by multiple signals including low extracytoplasmic Mg^{2+}. PhoP/PhoQ regulates ATP concentration and a series of Mg transporters (Mgts) to allow the required hydrolysis of triphosphates. MgtB, MgtC, MgtU, MgtA are differently regulated by PhoP/PhoQ and selectively involved in virulence, bacterial proliferation and survival to macrophage phagocytosis. Groisman's results point out that disruption of bacterial Mg^{2+} homeostasis emerges as a possible anti-bacterial strategy.

Olivier Cunrath (University of Strasbourg, France) continued this fascinating journey of discovery on the bacteria/host relationship by describing the role of SLC11A1/NRAMP1 (natural resistance-associated macrophage protein). He brilliantly showed that SLC11A1 reduces *Salmonella* proliferation, triggers a divalent metal starvation response, imposes a specific requirement for high-affinity transport of Mg^{2+}, and provokes single-cell properties equivalent to *Salmonella* with poor access to Mg^{2+}. Altogether, his data demonstrate that the main SLC11A1 resistance mechanism consist in growth-limiting Mg^{2+} starvation.

Finally, *Asparouh Iliev (University of Bern, Switzerland)* showed how Mg^{2+} therapy improves outcome in *Streptococcus pneumoniae* meningitis. Pneumolysin (PLY), a member of the cholesterol-dependent cytolysin (CDC) group is the major pneumococcal neurotoxin. PLY produces pores and cell lysis at high concentrations and non-lytic changes at lower concentrations. Iliev showed that therapeutic concentrations of Mg^{2+} chloride prevented pneumolysin-induced brain swelling and tissue remodelling both in brain slices and in animal models. Mg^{2+} also prolonged survival and improved clinical condition of mice with pneumococcal meningitis, in the absence of antibiotic treatment. These results identify Mg^{2+} as a promising candidate for effective adjunctive treatment to antibiotic therapy for *pneumococcal meningitis* [31].

Moving to Mg^{2+} in viral infection mechanisms, *Michel Tremblay (McGill University, Canada)* provided novel evidence for a crucial interaction between Adenovirus Type 5 E4orf4 with the PRL-CNNM complex, which leads to enhanced Mg^{2+} transport and viral replication. Adenovirus type 5 E4orf4 protein (E4orf4) is a multifunctional

protein that regulates viral and host gene expression and splicing. A recent proteomic study showed that E4orf4 interacts with a protein complex called PRL/CNNM, which is known to regulate Mg^{2+} homeostasis in mammalian cells. Tremblay demonstrated that E4orf4 forms a complex with PP2A and PRL/CNNM, leading to PRL/CNNM dephosphorylation. He also showed how expression of both E4orf4 and PRL/CNNM are positively associated to virulence. These results demonstrate for the first time a viral mechanism to enhance Mg^{2+} transport during infection. Current evidence suggests that a wide range of viruses and other intracellular parasites may modulate the PRL/CNNM complex to enhance infection [32, 33].

The last two talks of session 4 were dedicated to updated data on the relationship between serum Mg^{2+} and Sars-Cov2 infection and Covid-19 severity. *Fernando Guerrero-Romero (MSSI Durango, Mexico)* conducted a large cross-sectional studies and randomized clinical trials to evaluate the role of hypomagnesemia as a risk factor for both the COVID-19 disease and post-COVID syndrome. Results show that, the Mg^{2+}-to-calcium ratio equal or lower than 0.20 is strongly associated with the risk of mortality among inhospitalized patients (Odds Ratio -OR- 6.93; 95% CI 1.6–29.1); in men (OR 4.93; 95%CI 1.4–19.1) and in women (OR 3.93; 95%CI 1.6–9.3).Furthermore, preliminary results show that oral supplementation with Mg^{2+} chloride (330 mg) plus Vitamin D 4000 U. per day, for 40 days significantly improves clinical manifestations of post-COVID syndrome, such as memory loss, depression, anxiety, attention disorders, weakness, joint and muscle pain, hyperglycemia, high blood pressure, and arrhythmias, all mainly related with Mg^{2+} deficiency[34].

Finally, *Jacob Stevens (Columbia University, USA*) reported a retrospective study on the incidence of hypermagnesemia in COVID-19 illness. A total of 1685 patients hospitalized with COVID-19 were included in the study cohort, among whom 21% had hypermagnesemia. Patients who were hypermagnesemic had a higher incidence of shock requiring pressors, respiratory failure requiring mechanical ventilation, AKI and severe AKI. Survival probability at 30 days was 34% for the patients with hypermagnesemia, compared with 65% for patients without hypermagnesemia. Increased risk of mortality associated also with older age, need for vasopressors, higher CRP levels. Stevens' data show an association between hypermagnesemia and increased mortality among hospitalized COVID-19 patients. Hypermagnesemia potentially represents increased cell turnover as in the case of multiorgan failure, frequently occurring in highly compromised forms of AKI [35].

The results of the last two talks, which included large cohorts, confirmed what had already been observed in smaller studies, namely that dysmagnesemia is an important indicator of death risk in Covid-19. It could be argued that hypomagnesemia might be viewed as an early indicator of disease severity, whereas hypermagnesemia, which seems to be even more strongly associated to death, could be the final outcome not only in acute kidney injury, as already described, but also in a wide variety of severe co-morbidities such as hypertension, hypercoagulation, CVD, metabolic impairments, that might have been all exacerbated by an earlier hypomagnesemic state. Larger clinical studies are needed to better define this "magnesium paradox" [36].

Session 5

The last session, Session 5, was devoted to Mg^{2+} in non-communicable diseases. The field is so wide that we had to select only a few key topics: a quick look to neuroscience, oncology and vascular biology.

Ka Kahe (Columbia University, USA) examined the prospective association between serum Mg level and the incidence of cognitive impairment from a random sub-cohort (n = 2063) of the REGARDS study which aimed at defining geographic and social causes of stroke. Compared to those with hypomagnesemia (<0.75 mmol/L), the relative odds of incident cognitive impairment were reduced by 41% in the normomagnesemic subjects. Altogether, findings from this prospective study suggest that sufficient Mg status within the normal range may be beneficial to cognitive health in the US general population [37].

Oliver Micke (Franziskus Hospital Bielefeld, Germany) thoroughly reviewed the complex interaction between Mg^{2+} and cancer. Hypomagnesemia is often observed in oncologic patients

due to several direct biological reasons or secondary to specific nephrotoxicity-inducing treatments (e.g. cisplatin). The crucial point is whether hypomagnesemia may interfere with radio/chemotherapy. As for radiotherapy, some previous work hypothesized that hypomagnesemia could act as a radiosensitizer for two reasons: first, hypomagnesemia is a pro-oxidant condition thus enhancing indirect radiation damage, and second, low Mg^{2+} should be an unfavourable condition for DNA damage response; experimental evidence, however, is scarce and contradictory. As for chemotherapy, it has been described that EGFR monoclonal antibodies (cetuximab and similar), often used in the treatment of colon cancer and head and neck cancer, induce renal Mg^{2+} wasting by interfering with TRPM6-driven Mg reabsorption. It was proposed that hypomagnesemia could be considered a marker of treatment efficacy, but subsequent work did not confirm these findings. In addition to what Micke described, we showed that in tumor cells Mg^{2+} availability also affects doxorubicin uptake but does not influence cetuximab-mediated cell death. [38-41]

Last, but not least, *Jeanette Maier (University of Milano*) proposed a new perspective for Mg^{2+} and the vascular system. Based on preclinical and clinical evidence on the beneficial effects of Mg^{2+} on the vasculature, sirolimus-eluting Mg^{2+}-based scaffolds were introduced in clinical practice to treat coronary artery disease [42]. Mg^{2+} alloys gradually dissolve, thus increasing the concentrations of Mg^{2+} in the local microenvironment. In vitro, high extracellular Mg^{2+} does not interfere with Sirolimus action in vascular coronary cells. In particular, high extracellular Mg^{2+} does not rescue smooth muscle cell (SMC) growth arrest by sirolimus, accentuates the inhibitory effect of the drug on cell migration and does not impair SMC response to nitric oxide. If translated into a clinical setting, these results suggest that, in the presence of sirolimus, local increase of Mg^{2+} concentration maintains normal endothelial function and smooth muscle cell reactivity to vasodilators [43].

With the growing interest in "Mg^{2+} and disease" as evidenced by the doubling of the numbers of papers in Pubmed with key word 'magnesium, disease' over the past 10 years, it is clear there are many interesting topics that could not be addressed at the Glasgow meeting. Nevertheless, we managed to capture the areas where there are new discoveries and emerging trends in the field and believe this provides an excellent foundation for further advancements and new questions to be answered.

The main take home messages from Magnesium 2022 include:
– Basic biology of Mg^{2+} homeostasis, that has been enriched by new challenging data pointing to a crucial role for Mg in metabolism.
– Novel clues regarding Mg organismal regulation, thanks to a continuously growing list of channels and transport mechanisms, which inspire original approaches for their modulation.
– Discovery of new transporters and regulators of cellular Mg^{2+}.
– The role of Mg^{2+} in pathophysiology, that spans not only upmost chronic diseases, but also communicable diseases, such as bacterial infections and Covid-19.
– Finally, we should embrace the challenge of convincing clinicians to look at Mg^{2+} as a key player for health and, consequently, to consider magnesemia in the assessment and treatment of many diseases.

Our mission is to encourage Mg^{2+} research in order to leverage this "building block of life" to achieve more effective prevention, diagnosis and treatment of many pathological conditions. We are grateful to the brilliant speakers of the Glasgow symposium and look forward to meeting you all in a two years-time to learn more about this fascinating cation.

Disclosure

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