SciForschen
Open HUB for Scientific Research

ISSN 2471-4925

Journal of Clinical Case Studies

Short Communication Volume: 1.2 Open Access

Importance of Ionized Magnesium Measurements in Physiology and Medicine and the Need for Ion-selective Electrodes

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Received date: 30 Jan 2016; **Accepted date:** 18 Mar 2016; **Published date:** 23 Mar 2016.

Citation: Altura BM, Altura BT (2016) Importance of Ionized Magnesium Measurements in Physiology and Medicine and The Need for Ion-selective Electrodes. J Clin Case Stu 1(2): doi http://dx.doi.org/10.16966/2471-4925.111

Abstract

Mg is a co-factor for more than 500 enzyme systems, and is the second most abundant intracellular cation after potassium. It is critical in numerous physiological, cellular and biochemical functions and systems, running the gamut from hormone-receptor binding, transmembrane fluxes of cations and anions, muscle contraction, nerve conduction, cardiac functions and stability, control of vasomotor tone and distribution of blood flows, among many others. Serum total Mg measurements have suggested that it is depleted in numerous types of hospitalized patients. Mg is depleted in normal methods of food preparation (e.g., boiling, frying, etc.) and processing. The daily intake of Mg has been declining since 1900, from where it was about 500-600 mg/day to 150-225 mg/ day. Surprisingly, most mammals, including humans, exhibit similar levels of serum Mg. Overall, this has suggested that total Mg measurements on serum or plasma aren't sensitive blood variables or analytes to reflect what may be going on at the cellular and subcellular levels. Moreover, Mg is known to exist in at least three forms: free or ionized, complexed, and protein-bound. In addition, up until our studies, there were no methods to measure ionized Mg on whole blood specimens needed for rapid analysis in the ER and OR. In this report, we review many of the strides that have been made in utilization of Mg^{2+} ion-selective electrodes, their accuracy, and their uses in numerous human diseases, pathophysiological states, and in animals. It is our contention that the use of Mg^{2+} ion-selective electrodes should prove invaluable in the diagnosis and treatment of numerous diseases. These ISEs should also be very useful, clinically, in determining Mg body homeostasis and whether dietary intakes of Mg are providing enough Mg.

Keywords: Blood magnesium levels; Diabetes; Heart diseases; End-Stage renal diseases; Migraine headaches

Abbreviations: Mg^{2+}: Ionized magnesium; IHD: Ischemic heart disease; ^{31}P-NMR: Phosphorus-31-nuclear magnetic resonance spectroscopy; NIDDM: Non-insulin-dependent diabetes; HEMO: Hemodialysis; CAPD: Continuous ambulatory peritoneal dialysis; ISE: Ion-selective electrode; RBC: Red blood cells.

Introduction

Next to potassium, magnesium (Mg) is the second most abundant intracellular cation and the fourth most abundant cation in the body. Mg is a co-factor for more than 500 cellular enzymes involved in: cellular energy generation(and utilization), membrane functions such as various receptors, hormone- receptor binding, gating of calcium channels, transmembrane fluxes of cations and anions, regulation of adenylate cyclases, regulation of DNA and RNA molecular structure, muscle contraction, and control of intracellular Ca^{2+}-Ca^{2+} release. In addition, Mg^{2+} exhibits numerous structural attributes, it stabilizes cell membranes, regulates cell growth and reproduction, it can function as a natural Ca^{2+} antagonist, thereby regulating muscle contraction, relaxation, and neurotransmitter release. Reduction in this divalent cation can lead to inflammatory conditions, heart attacks, high blood pressure, strokes, asthmatic attacks, sudden cardiac death, angina, leg cramps, migraine headaches, and numerous other disorders. Mg^{2+}, thus, plays major and multiple roles in control of smooth, cardiac, and skeletal muscle activities and functions, cardiac excitability, neuromuscular transmission, nerve conduction pathways in the brain and periphery, vasomotor tone, distribution of blood flows (both in the brain and peripheral circulation). Recently, Mg^{2+} has been shown to be quite important in control of apoptosis (cell death) [1].

Progressive decline in Dietary Mg intake Worldwide over the Past 100 plus Years

Multiple, epidemiologic data from North America, Europe, Africa, Asia, Australia, and South America over the past 100 years indicate a decline of Mg dietary intakes from about 450-600 mg/day to 35-75% of these amounts, resulting in shortfalls of between 100-400 mg/day, depending on geographical region [2-7]. A number of factors increase our needs for a higher, than normal, Mg intake. High dietary intake of calcium, phosphate, vitamin D, or even high protein diets will result in a greater daily Mg requirement in order to maintain a positive Mg balance [6,7]. In addition, environmental stresses, as well as high fat or high carbohydrate diets will increase the need for higher than normal daily intake of Mg [6,7].

Type of Food Preparation can result in Deficiency of Mg

Dietary intake of Mg can alter tissue and blood levels of Mg, particularly if the foods are first cooked before eaten. Boiling most naturally-occurring Mg-rich foods will result in sizeable losses in their Mg contents, which in turn could result in inadequate amounts of tissue and extracellular levels of ionized Mg^{2+}. Refining and/or processing of many foods will result in large losses (e.g., 78-99%) of Mg content and, thus, dietary intake could prove to be inadequate [2,6,7].

Hospitalized Patients exhibit Losses in Serum Mg Levels

Disturbances in Mg balance are now recognized as quite common, when looked for with appropriate testing. Hospitalized patients have been observed to often exhibit between a 7and 65% incidence in hypomagnesemia [2,8,9]. Astute clinicians will often administer, frequently, Mg salts to both hypomagnesemic and normomagnesemic patients for their antiarrhythmic, vasomotor, and neuronal actions, as well as to patients exhibiting preeclampsia, myocardial infarctions, and ischemic heart disease. Since either high or low serum Mg concentrations may be life-threatening, it is important to be able to assess and monitor the exact level of ionized Mg^{2+}, the physiologically-active Mg, at any one instance in whole blood, plasma, or serum in our opinion.

Alcohol-, Drug-, and Chemotherapy-induced reductions in Levels of Mg

The clinician and the ER-people must constantly be on the lookout for alcohol-and drug-induced loss of body Mg stores. Although alcohol is the number-one drug-waster of body Mg [2], cocaine, heroin, PCP, and other abused drugs are also big wasters of body Mg, and are, unfortunately, usually overlooked by clinicians as underlying causal agents. Many cancer chemotherapeutic drugs (e.g., cis-platin) as well as drugs imbibed for heart-burn prevention (e.g., proton-pump inhibitors), diuretics (e.g., thiazides, furosemide), certain well-known cardiac drugs (e.g., digitalis), and certain antibiotics (e.g., azithromycin) are also wasters of body Mg and are usually also overlooked as causal agents of cardiovascular problems, in particular.

Similar Levels of Total Mg in sera of Most Mammals, including Humans

Despite the varying needs of mammals, including humans, for daily intake of Mg, the blood level of total Mg concentration doesn't appear to differ from very small mammals, such as the rat or mouse, to very large mammals such as sheep, cows, gorillas, or elephants(e.g., range from 0.7-1.15 mM/L) [10]. This might suggest that total Mg measurements in sera or plasma aren't sensitive blood variables to reflect what may be going on in the body. Only about 0.3% of the total Mg in the body is found in the extracellular fluid or blood compartment [6,7]. According to most textbooks, and researchers, the blood total Mg is, generally, not thought to be a reflection of body Mg stores. However, up until our studies over the past two decades, no accurate information on what the concentration of free, ionized Mg is in the blood compartment was known. In the ER or operating suite, rapid measurement of ionized Mg is, ideally, essential. A need to accurately measure free, ionized Mg on whole blood has become *a-sine-qua-non.* As Mg appears in the blood in different forms (e.g., total, ionized, and complexed Mg) [2,10-13], the need for whole blood measurements has clearly become essential.

Techniques for Total Mg, Ultra Filterable Mg, and Ion-Selective Electrode Mg Measurements

Current techniques employed in clinical laboratories are generally restricted to measuring total Mg levels. However, it is the free or ionized form of Mg that (as stated above) is the physiologically-active form. Up until about 20 years ago, previous estimates of these levels relied upon tedious total Mg measurements of protein-free ultra filtrates which took several hours to complete [12,13]. In addition, besides the time element, this procedure requires a relatively large sample volume and does not lent itself to automation.

Moreover, estimation of the ionized Mg in serum or plasma by analysis of ultra filtrates is somewhat unsatisfactory and cannot be done on whole blood. Furthermore, these methods do not distinguish the truly ionized form from Mg^{2+} bound to organic and inorganic anions as well as to fatty acids. Since the levels of these moieties, can vary significantly in numerous pathological states, it is highly desirable to directly measure, accurately, the levels of ionized Mg in complex matrices such as whole blood.

Novel ion-selective electrodes (ISEs), employing ionophores and neutral carrier-based membranes have been designed to function in the presence of ionized calcium levels and potential cationic interferences found in the blood of normal and diseased patients and animals [14-17].

Measurements of Ionized Mg^{2+} in Normal and Diseased Human Subjects and Animals with Unique ISEs: Correspondence with Intracellular Free Mg^{2+}

Using novel ISEs for Mg, over the past 25 years, our laboratories have helped to pioneer the utility of these electrodes in both human subjects and diverse animals, including sub-human primates [1,11,14-52]. Using novel ISEs for ionized Mg^{2+}, in our studies, we have demonstrated that analysis of whole blood, plasma, and sera in human subjects clearly shows that there is virtually no difference in ionized Mg^{2+}, irrespective of whether one samples whole blood, plasma or sera [11,14-17]. In addition, and most importantly, our data obtained on more than 750 subjects indicate that the concentration of free ionized Mg in human blood is about 600 micromoles/liter, or about equivalent to that measured intracellularly in a number of mammalian cell types (exclusive of the brain), such as cardiac and vascular smooth muscle cells, endothelial and epithelial cells [1,11,14-17,21,24,27-29], unpublished findings.

Data based on several hundred healthy, human subjects suggest that even though the range for total Mg in blood represents a difference of about 300 micromolar (0.7-1.00 mM/L), the range for normal ionized Mg^{2+} represents a difference of only about 130 micromolar (0.54-0.67 mM/L). In addition, our quantitative measurements demonstrate that between 64-72% of the total Mg in blood is free or biologically-active [11,14-17]. In contrast, data derived by our group for calcium, indicates that the reference range for total and ionized Ca is about 50% larger that for either total or ionized Mg [11,14-17]. We feel strongly the narrower and tighter reference range for ionized Mg^{2+} provides for better discrimination between normal and abnormal patients or analyte changes within a patient with time. This, however, is very dependent on the laboratory carrying out precise measurements under the strictest conditions, and using multiple standards throughout the testing of the blood samples, as we have stated previously [11,14-17].

Mg^{2+} Measurements in Blood and Cells in Different types of Diabetic Patients

Precise, careful measures on blood and intracellular, free Mg^{2+} in several types of diseases and disorders demonstrate an excellent correspondence between blood and cell values [21,24-29]. in this regard, using ISEs to measure free Mg^{2+} in fasting subjects with and without type 2 diabetes (NIDDM) and ^{31}P- nuclear magnetic resonance spectroscopy to measure free Mg^{2+} in red blood cells, we found that both Mg^{2+} levels were reduced significantly in diabetics compared with non diabetic subjects [21,24,26,27]. A very close relationship was noted between serum Mg^{2+} and intracellular free Mg^{2+} ($r=0.725$, $p<0.001$).

Studying women who develop diabetes during pregnancy (gestational diabetes), we have reported similar data as in the type 2 diabetic subjects [29]. Working with eugylcemic-clamped NIDDM insulin-resistant vs. insulin-sensitive subjects, we noted inverse correlations of Mg^{2+} (extracellular and intracellular) levels with arterial blood pressure and serum lipids in many of the insulin-resistant subjects only [11,27].

Mg^{2+} Measurements in Patients with End-Stage Renal Disease (ESRD)

If deficits in blood and cellular Mg^{2+} are causally-related in the etiology of the widespread atherogenesis and hypertensive disease noted in ESRD, then we should expect to observe significant reductions in both extra- and intracellular Mg^{2+}. Studying hemodialysis patients (HEMO) and continuous ambulatory peritoneal dialysis (CAPD) patients on dialysis for approximately 12 (HEMO) and 48 (CAPD) months, we did, indeed find significant reductions (e.g., 5-25%) in both serum and RBC Mg^{2+} using ISEs and ^{31}P-NMR [20]. There was no correspondence between total Mg values (extra-and intracellular).

Mg^{2+} Measurements in Patients with Varying Degrees of Ischemic Heart Disease

Studying patients with different degrees of IHD, as assessed by New York Heart Association criteria (stages I-IV), we found the greater the degree of cardiac damage, the lower the levels of Mg^{2+} in both blood and RBCs [24,26,27]. There was no correspondence looking at only total Mg levels.

Mg^{2+} Measurements in Migraine Headache Patients-treatment with Mg^{2+}

In 1981, we suggested that onset of many migraine headaches was associated with a fall in blood Mg^{2+} levels to be followed by deficits in brain Mg^{2+} as the headache and pain intensifies. Examination of more than two thousand migraine subjects demonstrated that more than 50% of these headache patients showed significant reductions in serum Mg^{2+} concomitant with reductions in free, intracellular RBC Mg^{2+}. No such correspondence was found on examination of total Mg levels [48-52]. Using such data, we hypothesized that intravenous injection of magnesium sulfate should break/reduce the intensity of the migraine headaches in those subjects that exhibited significant deficits in Mg^{2+}. We were able to confirm this hypothesis in several hundred migraine patients [50-52].

Conclusion

Novel ion-selective electrodes which can measure "true" ionized Mg in whole blood, plasma and serum are now available. These ISEs can measure, accurately, ionized Mg in conditions where pH is varying, and where heavy metals or lipids are present.

We believe these ISEs, when used under careful controlled laboratory conditions, should prove invaluable in settings where dietary intakes of Mg are variable, and in a number of clinical syndromes including diabetes, IHD, strokes, preeclampsia, neonatal stress conditions, toxic reactions to a number of drugs, and migraine headache patients.

Acknowledgement

Some of the original studies presented herein were supported, in part, by Research Grants from The National Heart Lung and Blood Institute, The National Institute on Drug Abuse, The National Institute of Mental Health, and The National Institute of Alcoholism and Alcohol Abuse.

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