Homeostasis of Magnesium in Man after Oral Supplementation: Results of a Placebo Controlled Blind Study

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Zusammenfassung

Magnesium (Mg^{++}) spielt eine vitale Rolle bei der Erhaltung vieler Stoffwechselwege, weil es mit organischen Substanzen, z. B. Proteinen, Nukleinsäuren und Nukleotiden reversible Komplexe bilden kann. Klinische Studien mit Mg^{++}-Supplementierung zeigten die Notwendigkeit einer Mg^{++}-Therapie bei zahlreichen Krankheiten. Therapeutische Reaktionen des Klinikers auf einen Mg^{++}-Mangel setzten eine zuverlässige Kenntnis der Bioverfügbarkeit von Mg^{++} voraus. Die vorliegende Studie wurde mit dem Ziel durchgeführt, Daten zur Mg^{++}-Homöostase bei oraler Mg^{++}-Supplementierung zu gewinnen. 14 Männliche Personen mit einer Hyperlipoproteinämie wurden in die Studie aufgenommen. Alle Teilnehmer erhielten 15 mmol Mg^{++}/Tag. Die blinde Studie schloß eine Placebophase von 2 Monaten, dann die zweimonatige Verumphase und letztlich eine erneute zweimonatige Placebophase ein. Während der Studie wurde eine intensive Ernährungsberatung durchgeführt. Blut und Urin wurde nach jedem Monat gewonnen. Die Mg^{++}-Konzentration im Plasma blieb während der gesamten Studienzeit unverändert. In den Erythrozyten stieg die Mg^{++}-Konzentration mit Beendigung der Verumphase von 1,87 mmol/l auf 2.29 mmol/l an und erhöhte sich weiterhin nach einem Monat der zweiten Placebophase auf 2.41 mmol/l. Die Ausscheidung von Mg^{++} stieg in der Verumphase um 42 % an und normalisierte sich erst am Ende der zweiten Placebophase. Die vorliegenden Daten zeigen, daß Mg^{++} während längerer Supplementierungsperioden von Körperzellen kontinuierlich aufgenommen wird. Nach Beendigung der Mg^{++}-Supplementierung wird Mg^{++} von aufgefüllten Körperpools an das Plasma abgegeben und damit biologisch weiterhin verfügbar gemacht.

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Summary

Magnesium (Mg^{++}) plays a vital role in the maintenance of many metabolic pathways due to its ability to form complexes with organic substances, such as proteins, nucleic acids and nucleotides. Clinical studies on the basis of Mg^{++} supplementation showed the need for an adequate therapy with Mg^{++} in various diseases. Therapeutic reactions of the clinician to a Mg^{++} depletion requires some knowledge on the bioavailability of Mg^{++} preparations. This study was undertaken to gain some data on Mg^{++} homeostasis in man after oral supplementation. 14 Male persons with hyperlipoproteinemia were included in the study. All participating persons obtained 15 mmol Mg^{++} per day. The double blind study included two months of placebo, followed by two months of verum, then again two months of placebo. Throughout the study a tight dietary consultation was carried out. Blood and urine was collected every months. Mg^{++} concentration in plasma remained constant throughout the study. Mg^{++} in red blood cells remained unchanged in the first placebo phase. During verum supplementation Mg^{++} in red blood cells increased from 1,87 mmol/l to 2.29 mmol/l and continued to increase to 2.41 mmol/l after switch over to the second placebo phase. Mg^{++} excretion in urine increased during the verum phase by 42 % and was normalized again at the end of the second placebo phase. The observed data suggest that cells take up Mg^{++} continuously during longer periods of Mg^{++} supplementation. Afterwards, Mg^{++} seems to spill over to plasma from body pools, presumably bone, and hence become biologically available thereafter.

Résumé

La magnésium (Mg^{++}) joue en rôle vital dans le mantien de nombreuses fonctions métaboliques, de par son aptitude à former des boliques, de par son aptitude à former des complexes avec des substances organiques telles que les protéines, les acides nucléiques et les nucléotides. Des essais cliniques d'une supplémentation en magnésium ont montré la nécessité d'une administration appropriée de magnésium dans le traitement de différentes pathologies. La réaction thérapeutique du clinicien devant une déplétion en magnésium dépend ses connaissances sur la biodisponibilité des préparations de magnésium. Cette étude a été entrepriise dans le but d'obtenir des donnéres supplémentaires sur l'homéostase magnésique chez l'homme après une supplémentation orale. Quatorze sujets de sexe masculin présentant une hyperlipoprotéinémie ont été inclus dans cette étude et one reçu15 mmol de Mg^{++} par jour, L'étude en double-insu incluait une phase placebo de 2 mois, suivie d'une période d'administration de deux mois du principe actif, puis d'une nouvelle phase placebo de deux mois. Un régiome alimentaire strict a été observé tout au long de l'etude et des prélèvements sanguins et urinaires ont été effectués chaque mois. La magnésémie est restée inchangée tout au long de l'étude. La concentration intra-érythrocytaire de Mh^{++} n'a pas varié jusqu'a la période d'administration du principe actif ôu elle a augmenté de 1,87 mmol/l à 2,29 mmol/l, pour augmenter à nouveau jusqu'à 2,m41 mmol/l au bout d'un mois de la deuxième phase placebo. L'extrétion urinaire de magnésium augmenté de 42 % au cours de la période d'administration de principe actif, puis s'est normalisés à la fin de la deuxième phase placebo. Les résultats montrent que les cellules absorbent la magnésium de façon continuelle lors de longues périodes de supplémentation. Le magnésium semble ensuite quitter le pool organique pour se répandre dans le plasma et devenir ainsi biologiquement disponible.

Introduction

Mg^{++} plays a vital role in maintenance of numerous metabolic pathways by binding to organic substances, such as proteins, nucleic acids and nucleotides. In general, Mg^{++} is active in three main metabolic complexes: homeostasis of intracellular calcium, membrane function, and activation of enzymes (Fig. 1).

The concentration of Mg^{++} in biological fluids is dependent on its balance in the body, i. e. its uptake from nutrition and its excretion by urine, sweat, etc. on the one hand, and by the concentration of cellular Mg^{++} binding molecules on the other hand. In man, the estimated Mg^{++} content of about 1 mol Mg is located practically in all organs, but at variable amounts (Fig. 2). Almost 75 % of total body Mg^{++} is contained in skeletal muscle and bone. A disturbed Mg^{++} balance in man will eventually result in an intracellular Mg^{++} depletion, accompanied by corresponding disturbances in biochemical effectiveness of cells and organs.

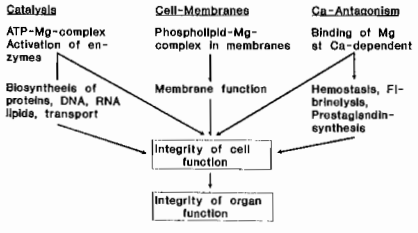

Fig. 1: Biochemical Effects of Magnesium.

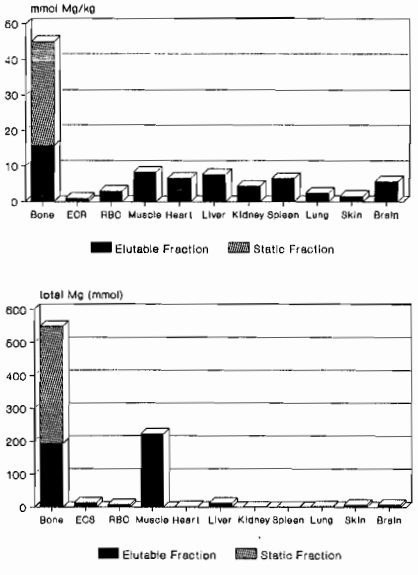

Fig. 2: Distribution of Magnesium in the Human Body.

Clinical studies with Mg^{++} supplementation indicated the necessity of a Mg^{++} therapy in numerous pathological conditions in man. Therapeutic reactions of the clinician to a Mg^{++} deficiency need a sufficient knowledge on bioavailability of Mg^{++} preparations. The presented data were obtained in connection with a Mg^{++} therapy in hyperlipidaemia.

Methods

14 Male persons (age 25–60 years) with a total serum cholesterol concentration of < 220 mg/100 ml and a LDL-cholesterol concentration of > 170 mg/100 ml participated in the study. Exclusion criteria included hyperlipidaemia type I, III, V according to Frederickson, kidney diseases, diabetes, thyroid diseases, intake of drugs, competitive athletes, persons on special diets, disturbances of hemostasis, drug therapy of hypertonus.

The persons (age 25–60 years) obtained 6 tablets per day for six months (24 weeks). In the 3. and 4. month the tablets contained 2.5 mmol Mg/tablet as Mg^{++} aspartate hydrochloride (Magnesiocard®, Verla-Pharm, Tutzing).

At the beginning of the study, and after every 4 week period, EDTA-blood, serum and 24-h-urine was collected.

During the study a dietician controlled the participants by monthly consultations.

Clinical Chemistry

Determination of blood hemoglobin concentration, hematocrit, count of erythrocytes, leucocytes, and thrombocytes was carried out with a Sysmex-E5000 automatic counter (Digitana, Frankfurt, Germany). Mg^{++} concentration in EDTA-plasma and EDTA containing blood was determined by atomic absorption spectroscopy (Evans Electroselenium, Sussex, England). Mg^{++} concentration in the erythrocytes was calculated from the corresponding Mg^{++} concentrations in plasma and blood [1]

Quality control of clinical chemistry was carried out with commercially available control sera from Behring, Marburg and control blood from Kabe, Nümbrecht, Germany. The coefficients of variation from day to day for the methods in question were below 5 %.

Statistics

HO-hypothesis was tested with students t-test with logarithmized data.

Results

Mg^{++} concentration in plasma remained unchanged during the verum and placebo periods. In the erythrocytes Mg^{++} concentration increased only during the verum phase from 1.84 ± 0.31 mmol/l to 1.97 ± 0.22 mmol/l after one months and to 2.29 ± 0.06 ($P < 0.05$) mmol/l after two months of Mg^{++} supplementation. In the second placebo phase, Mg^{++} concentration in the erythrocytes continued to increase to 2.41 ± 0.35 mmol/l after one month. At the end of the second placebo phase, erythrocyte magnesium concentration had decreased to 2.15 ± 0.13 mmol/l.

Excretion of Mg^{++} in urine increased during the verum phase by 42 % and was normalized again in the middle of the second placebo phase.

All other measured parameters shown in tab. 1 remained unchanged during the study.

Discussion

Mg^{++} is present in the earth crust to about 1.9 %. It was therefore natural that Mg^{++} obtained a crucial role in metabolism in Ca^{++} homeostasis, in enzyme activation, and in chelat formation with organic phosphate compounds during evolution of man.

Several observations point to the possibility of an increasingly deficient Mg^{++} supply of man. The chain of conclusion is still fragmentary, however, a certain logical connection is not to be neglected.

Mg^{++} bioavailability to agricultural plants is continuously decreasing by Mg^{++} loss in the soil, caused by acidic rains and by a decreased Mg^{++} supply of plants through the air due to reactions of man to air pollution includ-

Tab. 1: Biochemical parameters in human blood and urine after a six-month placebo-magnesium-placebo supplementation.

	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
HK (ml/dl)	46,2 ± 3,8	46,5 ± 2,5	46,1 ± 2,4	46,1 ± 2,4	46,2 ± 2,6	46,4 ± 2,8	46,2 ± 2,7
Mg in Plasma (mmol/l)	0,91 ± 0,18	0,96 ± 0,20	0,94 ± 0,11	0,80 ± 0,11	0,87 ± 0,03	0,87 ± 0,07	0,91 ± 0,08
Mg in Erythrocytes (mmol/l)	1,84 ± 0,31	1,91 ± 0,27	1,88 ± 0,36	1,97 ± 0,22	2,29 ± 0,06	2,41 ± 0,35	2,15 ± 0,23
Ca in Serum (mmol/l)	2,42 ± 0,07	2,39 ± 0,14	2,42 ± 0,08	2,37 ± 0,09	2,42 ± 0,09	2,50 ± 0,38	2,42 ± 0,08
Na in Serum (mmol/l)	141 ± 1	142 ± 3	142 ± 2	142 ± 3	142 ± 2	142 ± 3	142 ± 2
K in Serum (mmol/l)	4,49 ± 0,35	4,47 ± 0,52	4,32 ± 0,25	4,37 ± 0,33	4,46 ± 0,34	4,34 ± 0,29	4,36 ± 0,2
Urea in Serum (mg/dl)	34 ± 8	34 ± 9	35 ± 8	35 ± 9	33 ± 8	35 ± 7	34 ± 7
Creatinin in Serum (mg/dl)	1,03 ± 0,14	1,04 ± 0,13	1,04 ± 0,11	1,06 ± 0,14	1,04 ± 0,12	1,01 ± 0,12	1,01 ± 0,11
Uric acid in Serum (mg/Dl)	5,8 ± 1,3	5,9 ± 1,1	5,8 ± 1,1	5,8 ± 1,3	5,6 ± 1,1	5,8 ± 1,4	5,6 ± 0,9
Urine volume (ml/24 hours)	1478 ± 658		1508 ± 568	1531 ± 523	1380 ± 676	1535 ± 647	1468 ± 596
Creatinine in urine (mg/dl)	134 ± 51		121 ± 52	122 ± 44	241 ± 605	107 ± 51	113 ± 45
Mg in urine (mmol/l)	2,87 ± 1,24		2,78 ± 1.28	3,24 ± 1,44	3,74 ± 1,76	2,61 ± 0,91	2,66 ± 1,16
Mg in urine (mmol/day)	3,67 ± 2,28		3,73 ± 1,42	4,39 ± 1,79	4,64 ± 1,86	3,61 ± 1,77	2,98 ± 1,66
Mg in urine (mmol Mg/mmol creatinine)	0,26 ± 0,12		0,28 ± 0,08	0,32 ± 0,13	0,34 ± 0,14	0,32 ± 0,13	0,27 ± 0,09

ing elimination of detrimental and beneficial elements and molecules [2, 3]. Allergic reactions of man, which are caused by a disturbance of Ca^{++}-homeostasis have been rapidly increasing in the last years; this might be an indication of a parallel disturbance of the homeostasis of Mg^{++}, the natural Ca^{++} antagonist.

A comparison of the reference values of Mg^{++} concentration in the cells, such as the erythrocytes, of today [4] to the values observed 35 years ago [5], show the existence of an unexplained difference, which might be due to an insufficient Mg^{++} supply to man in recent years.

Mg^{++} Status

The Mg^{++} status of man might be easily assessed by the Mg^{++} content of the bones, which contain about 50 % of total body Mg^{++}.

Mg^{++} concentration in bones of healthy persons varies with age. In young persons, bone Mg^{++} content is observed between 132 and 144, in adults between 115 and 132, in geriatric patients between 107 and 119, in geriatric persons with bone fractures between 40 and 120 mmol/dry kg [6, 7]. This Mg^{++} depletion in man of up to 45 % of bone Mg^{++} is impressive and might be explained by an insufficient Mg^{++} balance. In addition to an increased Mg^{++} loss by various clinical condition [6], Mg^{++} supply by nutrition is often marginal [6, 8, 9, 10]. Various publications indicate, that the normal diet of teenagers, adults, old people contains insufficient Mg^{++} contents [6, 13, 14, 15].

Due to its central role in metabolism and Ca^{++} antagonism, a Mg^{++} supplementation seems to be advisable in numerous diseases [14]. Therapeutic aims include the optimization of cellular metabolism [1], as well as a pharmacological effect of Mg^{++} [15].

Mg^{++} abides to the classical pharmacodynamic and pharmacokinetic rules [16] which must include a two-compartment system with the extracellular and intracellular space, and the entry and elimination from the organism.

Mg^{++} Absorption and Excretion

Claasen et al. [17] showed in the rat and Lücker et al. [18] observed in man that the filling status of extracellular and intracellular spaces determines the extent to which Mg^{++} is absorbed from the intestines or excreted into urine. Urinary Mg^{++} concentration varies between 0.5 mmol/day in Mg^{++} deprivation and 6 or more mmol/day when the body Mg^{++} pools are filled [6]. Excretion of Mg^{++} in urine is maximal after 2 hours and almost reaches base line values after 10 hours [19]. Jahnen et al. observed a similar time course of Mg^{++} excretion in man after oral Mg supplementation [20].

A healthy person, which takes up 15 mmol Mg^{++}/day of nutrition, then intestinally absorbs 40 %, and excretes all of it in urine, will have an urinary Mg^{++} excretion of 6 mmol/day.

Our study indicates an increase in urinary Mg^{++} excretion with the beginning of verum supplementation (fig. 3). Two months later, Mg^{++} excretion has reached 3.74 mmol/l urine, and only about 15 % of the participants have passed the minimal target value of 5 mmol Mg excretion/l urine [16]. The target range of magnesium concentration with minimal and maximal values in urine had been defined by Stendig-Lindberg as that range, where urinary magnesium concentration should be located, when magnesium supply and body magnesium content are normal. An extrapolation of urinary Mg^{++} excretion during the verum phase indicate, that another two months of Mg^{++} supply

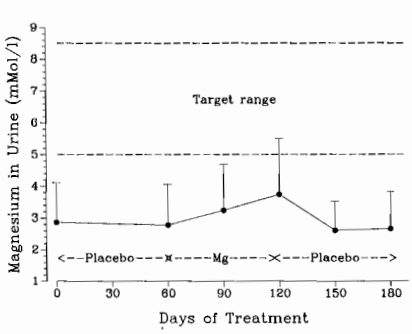

Fig. 3: Time course of magnesium concentration in human urine after a six-month placebo-magnesium-placebo supplementation.

would be needed for the average value to reach the target range of urinary Mg^{++} excretion.

Mg^{++} Retention by Organs

In recent studies from Morris and Rasmussen it was shown that orally and intravenously administered Mg^{++} is retained to a limited and variable degree between 5.6 % and 36 % [21, 22]. Several factors contribute to the degree of retention. Among these are the filling status of cells, the rate of Mg^{++} influx and efflux, as well as time course of Mg^{++} concentration in plasma.

Schuette showed by stable isotope tracer technology in the rat, that Mg^{++} exchange between intraperitoneum and organs varies according to type of organ. While heart and plasma have maximal uptake of Mg^{++} after 10 hours, skeletal muscle and brain have not reached maximal values even after 50 hours.

Fig. 4 shows the time course of Mg^{++} concentration in red blood cells and plasma during the study. While plasma Mg^{++} concentrations remains unchanged during the study, Mg^{++} concentration increases in the erythrocytes with the beginning of the verum phase (day 60) and continues to increase after switch over to the second placebo phase (day 120). As indicated in the double reciprocal plot (fig. 5) Mg^{++} concentration in the erythrocytes would reach the reference value as determined in 1958 of 2.78 mmol/l erythrocytes (5) only after 84 days of supplementation.

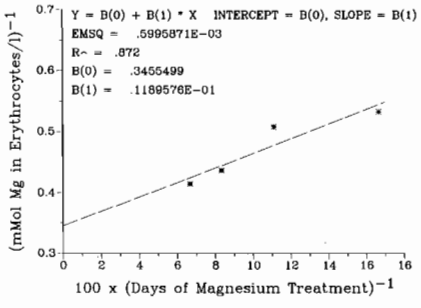

Fig. 4: Double reciprocal plot of magnesium concentration in human red blood cells versus days of magnesium supplementation.

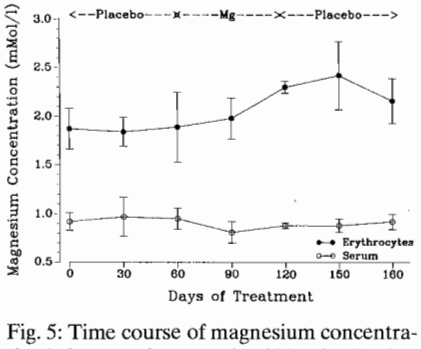

Fig. 5: Time course of magnesium concentration in human plasma and red blood cells after a six-month placebo-magnesium placebo supplementation.

Mg^{++} Transfer Between the Compartments

Mg^{++} in plasma, extracellular and intracellular space are in constant exchange. Transport of Mg^{++} from cellular or bone compartments to plasma and vice versa varies with the Mg^{++} state of the organism. Data in the literature indicate the existence of a rather slow transfer of Mg^{++} from the organs and from bone to plasma, however.

In rest Mg^{++} transport from erythrocytes to plasma is 0.004 mmol/litre cell/h [23]. It takes 3–4 days for Mg^{++} transfer from the functional bone fraction to plasma [24]. In stress situations which involve accumulation of acidic compounds such as lactic acid Mg^{++} is shifted faster from cells to plasma [25]. In isolated strips of the taenia of guinea-pig caecum intracellular free Mg^{++} decreased from 300 µmol/l to 8 µmol/l within 2 hours, when extracellular Mg^{++} was low [26].

In single barnacle giant muscle fibers immersed in Ca- and Na-free isoosmotic media, the initial influx rate varied in direct linear proportion to the Mg^{++} concentration, and was 11.8 pmol/cm²s when Mg^{++} was 6 mMol. However, the initial efflux rate appeared to increase nonlinearly with Mg^{++}, varying from 13.4 pmol/cm²s to approximately 80 pmol/cm²s (Mg^{++} = 60 mmol). The results are consistent with a model that assumes Mg influx to be mainly an electrodiffusive inward leak with PMg = 0.07 cm/s and Mg efflux to be almost entirely by active transport processes [27].

Nevertheless, our data indicate that after two months of Mg^{++} supplementation Mg^{++} is transferred from bone or intracellular pools to the extracellular space, where it is biologically available to the erythrocytes (fig. 4), even when Mg^{++} excretion is already decreasing.

Conclusions

Oral Mg^{++} only becomes biologically available, when it is first absorbed, and secondly when it is retained by the organs and by bone. The slow transfer rate of Mg^{++} from plasma to organs or to bone and the rather rapid urinary excretion of Mg^{++} indicate the necessity of a continuous Mg^{++} supplementation during the day. In addition, resorption should be delayed during the passage of the diet through the intestinal tract.

The presented data show that a consisting Mg^{++} deficiency in man cannot be normalized by a Mg^{++} therapy of short duration. A simple calculation on the basis of rates of Mg^{++} retention and urinary excretion indicates the necessity to supplement Mg^{++} for several months. If 40 % of orally administered Mg^{++} (15 mmol/day) and of dietary Mg^{++} (10 mmol/day) is intestinally resorbed, and an average 20 % of absorbed Mg^{++} is retained by body Mg^{++} pools, then a Mg^{++} depletion of 20 % (200 mmol Mg) will be normalized only after three months of Mg^{++} supplementation.

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