Effects of Magnesium Treatment on Hyperlipidaemia

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Zusammenfassung

Erhöhte Konzentrationen der Plasma-Lipide in der Ratte wurden bei einer Magnesiummangel-Diät beobachtet. Im Menschen ist das Plasmamagnesium mit der Cholesterinkonzentration negativ korreliert. Die Studie sollte mögliche Zusammenhänge zwischen einer Magnesiumbehandlung und den Plasmalipiden aufklären. 14 männliche Personen mit einer Hyperlipoproteinämie (Frederickson Typ IIa, IIb oder IV) wurden in die Studie aufgenommen. Alle Teilnehmer erhielten 15 mmol Magnesium/Tag. Die doppelt-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. Die Cholesterinkonzentration im Plasma erniedrigte sich durch Magnesium von 269 mg/dl um 2.3 % und erhöhte sich nach der letzten Placebophase um 7.5 %. LDL-Cholesterin wurde während der Magnesiumphase von 188 mg/dl um 0.5 % vermindert und erhöhte sich in der letzten Placebophase um 5.5 %. HDL-Cholesterin wurde während der Magnesiumphase von 57.6 mg/dl um 2 % erhöht und blieb in der letzten Placebophase erhöht. Die Triglyceridkonzentration im Plasma wurde während der Magnesiumbehandlung von 200 mg/dl um 30 % vermindert und stieg nach „switch-over" zu Placebo um 18.1 % an.

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Summary

Elevated concentration of plasma lipids has been associated with dietary magnesium deficiency in rats. In man, plasma magnesium and cholesterol are negatively correlated. This study tried to clarify possible effects of a magnesium treatment on plasma lipid concentrations. 14 Male persons with hyperlipoproteinemia, type IIa, IIb or IV according to Frederickson were included in the study. All participating persons obtained 15 mmol magnesium 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 diet protocol was carried out. Blood was collected every month. Cholesterol concentration in plasma decreased during the magnesium period from 269 mg/100 ml by 2.3 % and increased again by 7.5 % after the switch over to placebo. LDL-Cholesterol decreased during the magnesium period from 188 mg/100 ml by 0.5 % and increased again by 5.5 % after the switch over to placebo. HDL-Cholesterol increased during the magnesium period from 57.7 mg/100 ml by 2 % and stayed stable after switching over to placebo. Triglyceride concentration decreased during magnesium treatment from 200 mg/100 ml by 30 % and increased again by 18.1 % after switching over to placebo.

Résumé

Chez le rat, une carence en magnésium alimentaire a été associée à l'apparition d'une hyperlipidémie. Chez l'homme, la magnésémie est inversement corrélée à la cholestérolémie. Le but de la présente étude était d'élucider les éventuels effets d'un traitement par le magnésium sur les concentrations plasmatiques des lipides. Quatorze sujets de sexe masculin, atteints d'une hyperlipoprotéinémie de type IIa, IIb ou IV selon la classification de Frederickson, sont entrés dans l'étude et ont reçu 15 mmol de magnésium par jour. L'étude, menée en double-insu, se composait de deux mois sous placebo, puis deux mois sous traitement actif et, enfin, de deux mois à nouveau sous placebo. Un régime alimentaire strict a été imposé pendant toute la durée de l'étude et des prélèvements sanguins ont été effectués chaque mois. La cholestérolémie, initialement de 269 mg/100 ml, a baissé de 2,3 % pendant la période sous magnésium et a augmenté de 7,5 % après le passage sous placebo. La valeur du cholestérol des LDL, de 188 mg/100 ml avant magnésium, a diminué de 0,5 % lors des deux mois de traitement par le magnésium puis a augmenté de 5,5 % pendant la seconde administration de placebo.
Pour le cholestérol des HDL, la valeur initiale de 57,6 mg/100 ml a augmenté de 2 % sous l'influence du magnésium et est restée stable au cours de la deuxième administration de placebo. La triglycéridémie était de 200 mg/100 ml avant l'administration de magnésium; elle a diminué de 30 % sous magnésium puis a augmenté de 18,1 % après le passage sous placebo.

Introduction

Acute magnesium deficiency increases concentration of lipids in plasma of the rat, and augments disturbances of hemostasis and of vascular endothelium [1, 2]. Corresponding experiments in man are sparce and the published results are often in disagreement. Correlation studies of Speich indicated a negative correlation between serum magnesium and total cholesterol, and a positive correlation between serum magnesium and HDL-cholesterol concentration [3]. Meysing lowered serum cholesterol concentration by 16 % after 3 weeks of oral magnesium supplementation (30 mmol magnesium/day) to patients with hyperlipidaemia [4].
Other studies were not able to show a connection between magnesium status and lipid metabolism [5, 6, 7].
On the other hand, clinical observations of diabetics [8], alcohol abusus [9], and of patients after diuretics therapy [10] indicated that hyper-

lipidaemia and magnesium deficiency are simulatneously occuring.
While effects of ethanol on lipid metabolism are well known [11], a direct effect of magnesium, or of a magnesium deficiency on serum lipid concentration in man are still not completely proven [12].
This study was set up to clarify these interactions between lipid metabolism and magnesium in man.

Methods

14 Male persons (age 30–60 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 were hyperlipidaemia type I, III, V according to Frederickson, kidney diseases, diabetes, thyroid diseases, intake of drugs, competitive exercise, intake of 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 und 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, Hamburg, Germany). Mg^{++} concentration in EDTA-plasma and EDTA containing blood was carried out by atomic absorption spectroscopy (Evans Electroselenium, Sussex, England). Mg^{++} concentration in the erythrocytes was calculated from the corresponding Mg^{++} concentrations in plasma and blood [13]. Cholesterol and triglyceride concentration was determined using a Hitachi 737 Analyser and reagents from Boehringer, Mannheim, Germany. LDL-cholesterol was determined by precipitation with heparin and subsequent cholesterol determination. Lipoprotein electrophoresis was carried out using equipment from Immuno, Heidelberg, Germany.
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

The average values (arithmetic mean ± standard deviation) of all measured parameters are shown in Tab. 1. If the average of each phase is considered, then cholesterol concentration in plasma decreased by magnesium supplementation from 269 ± 35 mg/100 ml by 2.3 %, and increased after switch over to placebo by 7.5 %. LDL-cholesterol concentration was lowered during the magnesium phase from 188 ± 25 mg/100 ml by 0.5 %, and increased after switch over to placebo by 5.5 %. HDL-cholesterol concentration increased during the magnesium supplementation from 58 ± 10 mg/100 ml by 2 % and remained at that level after switch over to placebo. VLDL-cholesterol concentration in plasma decreased from 26 ± 23 mg/100 ml during the magnesium phase by 27 % ($P < 0.1$) and increased after switch over to placebo by 16 % (Fig. 1). The triglyceride concentration in serum was lowered by magnesium supplementation from 200 ± 158 mg/100 ml by 30 % and increased again by

Tab. 1: Effect of magnesium on serum lipid and lipoprotein concentration (avg = arithmetic mean, std = standard deviation. The double blind study included 2 months of placebo, followed by 2 months of magnesium treatment (15 mmol/day), again followed by placebo. N = 14.

	Pretest	Day 0	Day 30 Placebo	Day 60 Placebo	Day 90 Verum	Day 120 Verum	Day 150 Placebo	Day 180 Placebo
Cholesterol (mg/100 ml)								
avg	271,75	270,92	274,92	262,08	258	268,42	280,44	285,33
std	25,39	26,71	43,23	34,55	36,84	43,17	45,15	33,65
LDL-Cholesterol (mg/100 ml)								
avg	191,17	195,65	189,69	177,54	180,92	192,67	193,56	200,67
std	16,98	28,63	38,71	25,44	36,35	44,10	29,73	27,63
HLDL-Cholesterol (mg/100 ml)								
avg	51,17	55,60	56,62	61	60,17	57,58	60,89	62,67
std	7,68	12,89	9,92	11,42	17,31	13,18	17,77	11,08
VLDL-Cholesterol (mg/100 ml)								
avg	24,60	27,16	27,15	23,92	18,25	18,45	26,11	21,78
std	13,58	22	28,70	18,91	8,71	7,03	19,65	16,93
α-Lipoprotein (%)								
avg	39,80	39,64	39,61	44,45	43,31	40,13	41,10	43,68
std	4,10	7,88	7,15	7,14	10,13	10,86	7,97	5,96
prae-β-Lipoprotein (%)								
avg	10,75	12,08	11,42	11,19	8,40	8,40	10,50	8,28
std	5,44	8,28	9,06	6,28	3,74	3,76	5,98	1,36
β-Lipoprotein (%)								
avg	49,45	48,28	48,98	46,84	48,29	51,44	48,40	48,05
std	9,55	7,83	8,79	6,71	8,29	9,06	6,87	5,84
Triglycerides (mg/100 ml)								
avg	186,58	235	201,38	162,46	136,75	142,42	158,67	170,89
std	119,79	225,04	190,64	117,51	76,28	55,60	117,66	139,02
Mg in Plasma (mmol/l)								
avg		0,91	0,96	0,94	0,80	0,87	0,87	0,91
std		0,18	0,20	0,11	0,11	0,03	0,07	0,08
Mg in Erythrocytes (mmol/l)								
avg		1,84	1,91	1,88	1,97	2,29	2,41	2,15
std		0,31	0,27	0,36	0,22	0,06	0,35	0,23

18.1 % after switch over to placebo (Fig. 2) ($P < 0.05$). Prae-β-lipoprotein concentration in plasma decreased from 11 ± 7 % during the magnesium phase by 18 % ($P < 0.1$) and increased after switch over to placebo by 11 % (Fig. 3). Magnesium concentration in plasma remained unchanged during the combined placebo-magnesium supplementation period. In the red blood cells, magnesium concentration started to raise with beginning of verum phase from 1.88 ± 0,36 mmol/l to 2.29 ± 0.06 mmol/l at the end of the magnesium period ($P < 0.05$). After switch over to placebo, magnesium concentration in the erythrocytes continued to increase for one month to 2.41 ± 0.35 mmol/l ($P < 0.05$), and was decreased again at the end of the study.

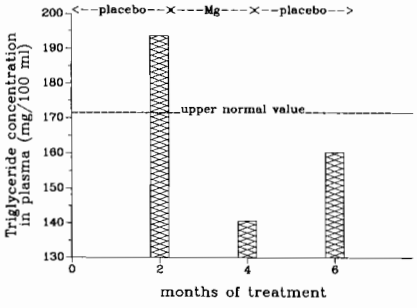

Fig. 1: Effects of magnesium treatment on VLDL-cholesterol concentration (arithmetic mean of phase values) in human serum.

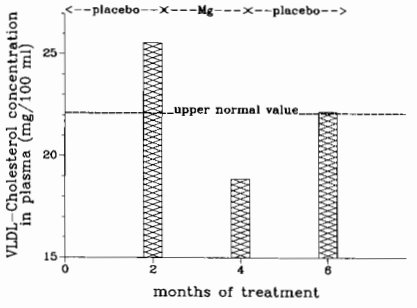

Fig. 2: Effects of magnesium treatment on triglyceride concentration (arithmetic mean of phase values) in human serum.

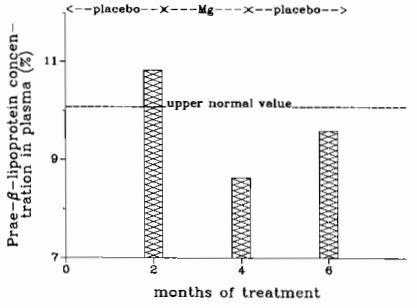

Fig. 3: Effects of magnesium treatment on relative prae-β-lipoprotein concentration (arithmetic mean of phase values) in human serum.

Discussion

Magnesium Status

According to reports from the „Deutsche Gesellschaft für Ernährung" a dietary magnesium deficiency of the german population is unlikely [14]. On the other hand, several recent publications point to the fact, that the adult population in the western world is characterized by a dietary magnesium deficiency [15, 16, 17, 18]. In addition, excessive magnesium losses by sweat (physical exercise), urine (diabetic persons), pregnancy and dietary misbehaviour, such as alcohol and nicotine abusus increase magnesium deficiency [19, 20, 21, 22, 23].

Arteriosclerosis and Lipids

The occurrence of arteriosclerosis is the most important contributor to mortality as well as to early invalidity in Germany [24]. Certain risc factors promote these developments [25, 26]. Risc factors of first order are hyperlipidaemia, nicotin abusus and hypertonia, risc factor of second order is among others diabetes mellitus.
The mechanism of arteriosclerosis is based on a deposition of lipids in the endothelium, accompanied by an injury of the cells, which is thought to hold a central role in the reactions. Eventually, these events lead to arteriosclerosis [27, 28]. Among the reactions occuring after an injury of endothelium are an activation of coagulation [23], a thrombocyte aggregation [29], an increased permeability of membranes to Ca^{++} [30], and an activation of macrophage reaction with the arterial wall [24].

Treatment of Arteriosclerosis

It is evident, that a reduction of serum lipids to values below 200 mg/100 ml [31] is the first therapeutic aim in prophylaxis and treatment of arteriosclerosis. Various therapeutic protocols are available, including diet, physical exercise, restriction of nicotine abusus [31, 32], and lipid lowering drugs [33], which, however, have considerable side effects, such as gastrointestinal disturbances, increase of transaminase catalytic concentration in serum, etc. [33].
In search for alternative therapeutic effective substances, the attention is focussed on magnesium, which shows close connections to lipid metabolism [21, 1, 2], as well as to accompanying causes of arteriosclerosis. Magnesium activates numerous enzymes including enzymes of lipid and prostaglandin metabolism [34, 35, 36], it stabilizes membranes [37, 38] by reaction with phospholipids and by activation of membrane Na^{+}-K^{+}-ATPase [38], and it reduces thrombocyte aggregation [39] and regulates hemostasis on a lowered level [40].

Magnesium and Lipids

In animal studies it was shown, that additional dietetic magnesium either lowers lipid concentrations, or an experimental magnesium deficiency increases lipid concentration in serum [2, 30, 41, 42, 43]. Correlation studies by Speich indicated a positive connection between serum magnesium and HDL-cholesterol and a negative connection between serum magnesium and total cholesterol [3].
Epidemiological studies clearly point to the fact high dietary magnesium is correlated with low serum total lipid concentrations [1] and high lipid fractions of the HDL-cholesterol type [44]. These studies were confirmed in several countries, where a reduction of mortality by vascular injuries was observed with dietary hard drinking water, which is rich in magnesium [45].

Human Studies

Meysing [4] was able to lower total cholesterol by 16 % in human hyperli-

pidaemia after magnesium supplementation. Recent studies from Kinnunen [46], Rasmussen [47], Motoyama [48], and Kirsten [49] demonstrated a significant reduction of serum concentrations of triglycerides, VLDL-lipoproteins, and free fatty acids in man after magnesium supplementation.

Our study clearly shows, that a therapeutic magnesium supplementation to male persons with hyperlipidaemia type II a, II b, and IV according to Frederickson is effective in decreasing significantly triglyceride concentration. For the measured parameters total cholesterol, LDL-cholesterol, VLDL-cholesterol, prae-β-lipoprotein, and triglycerides, a characteristic time course is observed. During the first placebo phase of two months, the corresponding concentrations start to decrease (Fig. 1). After switch over to verum, the decrease of serum concentration is accelerated (significantly in case of triglycerides). After the next switch over to the second placebo phase, all concentrations started to increase again (Tab. 1).

Statistical calculations between placebo and verum values were complicated by the unexpected placebo effect of decreasing lipid concentrations. This might be the reason for the obvious inefficiency of magnesium to effect lipid metabolism in some studies [7]. For this reason we have shown the phase average values of concentration of triglycerides, VLDL-cholesterol and relative concentration of prae-β-lipoprotein in Fig. 1–3. In addition, magnesium would only be effective in treatment of hyperlipidaemia if

1. the tested subjects are characterized by cellular hypomagnesaemia, and
2. the magnesium preparation is readily absorbed in the intestinal tract and retained by the organs.

Magnesium retention by the organs is a very slow process and might need several months of corresponding magnesium supplementation [18]. Some of these requirements might have been absent in other studies [6]. Our data concerning magnesium resorportion and retention by organs show a significant biological availability of the magnesium preparation (Tab. 1).

Biochemical Reactions of Magnesium In Lipid Metabolism

The possible mechanisms of effects of dietary magnesium on lipid metabolism include direct actions on enzymes of corresponding metabolic pathways, as well as general effects of magnesium on protein synthesis [50] and possibly hormonal glands such as the thyroid.

Cholesterol

Magnesium is known to affect several enzymes of lipid metabolism. Hydroxy-methylglutaryl-coenzym A reductase (HMG-CoA-reductase) is the rate limiting enzyme in endogenous cholesterol biosynthesis. Its metabolic control is achieved through phosphorylation and dephosphorylation by a magnesium dependent reductase kinase [51]. A magnesium deficiency would therefore keep HMG-CoA-reductase in an activated state and thus increase cholesterol biosynthesis. In addition it is known, that cholesterol is absorbed from the intestines in its free, unesterified form. 80–90 % of the cholesterol absorbed is esterified with long-chain fatty acids, taken up by liver when the remnant reacts with the apo E-receptor and is hydrolyzed to free cholesterol. Cholesterol ester hydrolase is activated by cyclic AMP dependent protein kinase and protein kinase C. Deactivation is accomplished by dephosphorylation catalyzed by a phosphoprotein phosphatase, dependent on magnesium [34]. A magnesium deficiency in the liver would thus keep rate of free cholesterol formation in the liver high and concomitantly formation of VLDL-cholesterol high.

Triglycerides

On the other hand, it has been reported, that divalent cations such as magnesium in the diet would decrease intestinal lipid resorption because of the complex binding capacity of the cation with anionic lipids [2]. Since mainly triglyceride concentration was decreased in our study, a corresponding effect should be concentrated on triglyceride resorption. Bernard was able to show in the rat that magnesium significantly improved the esterification of oleic acid phospholipids and triacylglycerols, as shown by the increase in triacylglycerol synthesis in rat isolated intestinal loops or by the increase in triacylglycerols recovered from the incubation media of mouse jejunal explants. Magnesium did not impede oleic acid absorption processes but, on the contrary, enhanced them.

The fatty acids used in the synthesis of hepatic triglycerides and therefore of triglycerides contained in serum VLDL are derived from the endogenous biosynthesis via acetyl-CoA and from free fatty acids in the circulation. During feeding high-fat diets, in diabetes mellitus and in magnesium deficiency [48], the level of circulating free fatty acids is elevated and lipogenesis is inhibited, and free fatty acids are the main source for triglyceride synthesis in liver. In magnesium deficiency an increased triglyceride and VLDL concentration would thus occur.

Conclusions

Therapeutic magnesium causes direct and indirect effects, which are related to a reduction or prevention of arteriosclerosis in man.

The presented data from the literature and our own data clearly indicate, that a magnesium supplementation of two months lowers serum triglyceride concentration in man by ca. 30 %. The effects on cholesterol are less clear.

The direct and close correlation of dietary magnesium arteriogenic lesions [52] might be based additionally on multifactorial events. Among these are beneficial effects of magnesium on blood pressure [19], blood glucose homeostasis and regulation of coagulation [22] and thrombocyte aggregation [1, 2].

References

[1] *Rayssiguier, Y.:* Magnesium, Lipids and Vascular Diseases. Magnesium **5** (1986) 182–190.

[2] *Rayssiguier, Y.:* Lipoprotein metabolism: Importance of magnesium. Mg.-Bull. **8** (1986) 186–193.

[3] *Speich, M., S. Gelot, P. Arnaud, N. Van Goc, N. Robinet, A. Pineau, A.:* Multiple and simple correlations between magnesium, calcium, zinc, potassium total and HDL-Cholesterol in 111 reference subjects. Mg.-Bull. **6** (1984) 137–141.

[4] *Meysing, R.:* Wirkung von Magnesiocard auf den Lipidstoffwechsel. Ther. d. Gegenw. **118** (1979) 1392–1407.

[5] *Manthey, J., M. Stoppeler, W. Morgestern, W. Kübler:* Magnesium in Serum bei Patienten mit koronarer Herzkrankheit. Dtsch. med. Woschr. **107** (1982) 732–735.

[6] *Marken, P. A., C. W. Weart, D. S. Carson, J. G. Gums, M. F. Lopes-Virella:* Effects of magnesium oxide on the lipid profile of healthy volunteers. Atherosclerosis **77** (1989) 37–42.

[7] *Zemel, P. C., M. B. Zemel, M. Urberg, F. L. Douglas, R. Geiser, J. R. Sowers:* Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension. Am. J. Clin. Nutr. **51** (1990) 665–9.

[8] *Mather, H. M., J. A. Nisbeth, G. H. Burton, G. J. Poston, J. M. Bland, P. A. Bailea, T. R. E. Pilkington:* Hypomagnesemia in diabetics. Clin. Chem. **95** (1979) 235–242.

[9] *Durlach, J. Y. Rayssiguier:* Donnees nouvelles sur le magnesium et l'alcoolisme chronique. Rev. Alc. **25** (1980) 1–26.

[10] *Reyes, A. L., W. Leary:* Diuretics and magnesium. Magnesium Bulletin **6** (1984) 87–99.

[11] *Baraona, E., C. S. Lieber:* Effects of ethanol on lipid metabolism. J. Lipid. Res. **20** (1979) 289–315.

[12] *Rayssiguier, Y., F. Chevalier, F. Bonnet, J. Kopp, J. Durlach:* Influence of magnesium deficiency on liver collagen after carbon tetrachloride or ethanol administration to rats. J. Nutr. **115** (1985) 1656–1662.

[13] *Golf, S. W.:* Magnesium – Diagnostik und Indikationen zur Therapie. Hospitalis **5** (1989) 331–3397.

[14] DEUTSCHE GESELLSCHAFT FÜR ERNÄHRUNG Empfehlungen für die Nährstoffzufuhr. Frankfurt/M: Umschauverlag, 1198, p. 34–36.

[15] *Seelig, M. S.:* Magnesium requirements in human nutrition J. med. Soc. N. J. **79** (1982) 849–850.

[16] *Marier, J. R.:* Magnesium content of the food supply in the modern-day world. Magnesium **5** (1986) 1–8.

[17] *Morgan, K. J., G. L. Stampley:* Dietary intake levels and food sources of magnesium and calcium for selected segments of the US population. Magnesium **7** (1988) 225–233.

[18] *Golf, S. W., H. Riediger, S. Matthes, D. Kuhn, V. Greaf, H. Temme, N. Katz, L. Róka:* Homeostasis of magnesium in man after oral supplementation: results of a double-blind study. Mg.-Bull. **12,4** (1990) 144–148.

[19] *Altura, B. T., B. M. Altura:* Cardiovascular Actions of Magnesium: Importance in Etiology and Treatment of High Blood Pressure. Mg.-Bull. **9** (1987) 6–15.

[20] *Bertschat, F., S. W. Golf, H. Riediger, V. Graef:* Protective effects of magnesium on release of proteins from muscle cells during a marathon run. Mg.-Bull. **8** (1986) 310–313.

[21] *Holtmeier, H.-J.:* Das Magnesiummangelsyndrom: Bedeutung für Mensch, Tier und Pflanze. Hippokrates Verlag, Stuttgart 1988.

[22] *Müller, D., H. Laube, G. Müller-Berghaus, S. Golf, H. Temme, V. Graef, L. Róka:* Magnesiumdepletion beim Diabetes – eine Ursache für Gerinnungsstörungen. Mg.-Bull. **9** (1987) 206-206.

[23] *Müller-Berghaus, G., U. Delvos:* Beitrag der Endothelzelle zur Aufrechterhaltung der Eukoagulabilität und Reaktion der Gefäßwand bei der Entstehung einer Thrombose. Schweizerische Gesellschaft für Phlebologie und praktische Angiologie. Jahrestagung 1985.

[24] STATISTISCHES BUNDESAMT. Statistisches Jahrbuch 1985. Fachserie 12 (Gesundheitswesen), Reihe 4 (Todesursachen). *Kohlhammer, W.,* Stuttgart, Mainz, 1985.

[25] *Assmann, G.:* Lipidstoffwechsel und Atherosklerose. Schattauer Verlag, Stuttgart, 1982.

[26] *Cremer, P., H. Wieland, D. Seidel:* Göttinger Risiko-, Inzidenz- und Prävalenzstudie (GRIPS). Muench. med. Wschr. **130** (1988) 268–274.

[27] *Kristenden, S. D., K. M. Roberts, J. Lawry, J. F. Martin:* Short Term High Cholesterol Diet Causes Changes in Megakaryocyte Size and in Vascular Ultrastructure. XIth ISTH-Congress, Brussels 612:–, 1987. (Abstract)

[28] *Mitropoulos, K. A., S. J. Walter, T. W. Meade, P. E. Esnouf:* Increase Faktor VII Reactivity in the Rabbit Following Diet Induced Hypercholesterolaemia. XIth ISTH-Congress, Brussels 1003:–, 1987. (Abstract)

[29] *Winocour, P. D., M. L. Rand, J. D. Vikkers, Kinlough-Rathbone, J. F. Mustard:* Enhanced Thrombin-Induced Aggregation and Inositol Triphosphate Formation of Platelets from Spontaneously Hypercholesterolemic Rats. XIth ISTH-Congress, Brussels 1012:–, 1987. (Abstract)

[30] *Ito, M., T. Toda, F. A. Kummerow, I. Nishimori:* Effect of magnesium on ultrastructural changes in coronary arteries in swine. Acta Pathol. Japon **36** (1986) 225–234.

[31] *Assmann, G. H., Schulte, U. Wahrburg:* Konzepte zur Atherosklerose-Prävention. Muench. med. Wschr. **130** (1988) 260–267.

[32] *Wolfram, G., W. Spann:* Ernährungstherapie der Dyslipoproteinämie. Münch. med. Wschr. **130** (1988) 248–250.

[33] *Richter, W. O., P. Schwandt:* Dyslipoproteinämie. Muench. med. Wschr. **130** (1988) 243–247.

[34] *Gosh, S., W. M. Grogan:* Activation of rat liver cholesterol ester hydrolase by cAMP-dependent protein kinase and protein kinase C. Lipids **24** (1989) 733–736.

[35] *Mahfouz, M. M., T. L. Smith, F. A. Kummerow:* Changes in phospholipid composition and calcium flux in LLC-PK cells cultured at low magnesium concentrations. Biochim Biophys Acta **1006** (1989) 75–83.

[36] *Weis, M. T., K. U. Malik:* The influence of mono- and divalent cations on the cardiac metabolism of arachidonic acid. Prostaglandins **37** (1989) 707–23.

[37] *Dyckner, T. H., P. O. Wester:* Magnesium. A Short Review. Malmo: *Searle, G. D.,* 1983, p. 1–23.

[38] *Ebel, H., T. Günther:* Magnesium Metabolism: A Review, J. Clin. Chem. Clin. Biochem. **18** (1980) 257–270.

[39] *Hettenbach, A., H. Patscheke:* Beeinflussung von Thrombozytenfunktion in vitro und ex vivo durch Magnesium. In: *Weidinger, H.* (ed.): Magnesium in Klinik und Forschung. Bayreuther Gespräch, Münchener Wissenschaftliche Publikationen. (1987) 224–231.

[40] *Pohlmann, U., M. Schmidt, S. Golf, V. Graef, L. Róka, H. Temme, H. Riediger, H. Neppl, C. Bortz:* Magnesiumeffekt auf die Hämostase von Leistungsschwimmern vor und nach einer Maximalbelastung. Mg.-Bull **12** (1990) 47–51.

[41] *el-Hindi, H. M., H. A. Amer:* Effect of thiamine, magnesium, and sulfate salts on growth, thiamine levels, and serum lipid constituents in rats. J Nutr Sci Vitaminol (Tokyo) **35** (1989) 505–10.

[42] *Luthringer, C., Y. Rayssiguier, E. Gueux, A. Berthelot:* Effect of moderate magnesium deficiency on serum lipids, blood pressure and cardiovascular reactivity in normotensive rats. Br. J. Nutr. **59** (1988) 243–50.

[43] *Mahfouz, M. M., F. A. Kummerow:* Effect of magnesium deficiency on delta 6 desaturase activity and fatty acid composition of on delta 6 desaturase activity and fatty acid composition of rat liver microsomes. Lipids **24** (1989) 727–732.

[44] *Fehily, A. M., J. W. Yarnell, C. H. Bolton, B. K. Butland:* Dietary determinants of plasma lipids and lipoproteins: the Caerphilly Study. Eur. J. Clin. Nutr. **42** (1988) 405–13.

[45] *Marier, J. R.:* Role or magnesium in the „hard-water story". Mg.-Bull. **8** (1986) 194–198.

[46] *Kinnunen, O., J. Salokannel:* Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, vitamins A and E, and minerals in geriatric hospital patients in the treatment of constipation. J. Int. Med. Res. **17** (1989) 442–54.

[47] *Rasmussen, H. S., P. Aurup, K. Goldstein, P. McNair, P. B. Mortensen, O. G. Larsen, H. Lawaetz:* Influence of magnesium substitution therapy on blood lipid composition in patients with ischemic heart disease. A double-blind, placebo controlled study. Arch. Intern. Med. **149** (1989) 1050–3.

[48] *Motoyama, T., H. Sano, H. Fukuzaki:* Oral magnesium supplementation in patients with essential hypertension. Hypertension **13** (1989) 227–32.

[49] *Kirsten, R., B. Heintz, K. Nelson, H. G. Sieberth, G. Oremek, J. Hasford, U. Speck:* Magnesium pyridoxal 5-phosphate glutamate reduces hyperlipidaemia in patients with chronic renal insufficiency. Eur. J. Clin. Pharmacol. **34** (1988) 133–137.

[50] *Terasaki, M., H. Rubin:* Evidence that intracellular magnesium is present in cells at a regulatory concentration for protein synthesis. Proc. Nat. Acad. Sci. USA **82** (1985) 7324–7327.

[51] *Murray, R. K., D. K. Granner, P. A. Mayes, V. W. Rodwell:* Cholesterol Synthesis, Transport & Excretion. In: Harper's Biochemistry, (21th ed.), edited by APPLETON & LANGE Norwalk, Conneticut: Appleton & Lange, 1988, p. 241–252.

[52] *Altura, B. T., M. Brust, S. Bloom, R. L. Barbour, J. G. Stempak, B. M. Altura:* Magnesium dietary intake modulates blood lipid levels and atherogenesis. Proc. Natl. Acad. Sci. USA; **87** (1990) 1840–1844.

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