Reactive hypoglycemia and magnesium*)

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Zusammenfassung

Bei Ratten wurden unter Mg-Mangel-Bedingungen erniedrigte Blutzuckerwerte beobachtet. Demnach könnte eine Beziehung zwischen Mg-Mangel und reaktiver Hypoglykämie bestehen, einer Krankheit mit unbekannter Genese. Entsprechende Patienten (14 weibliche, 8 männliche) wurden mittels Glucose-Toleranztest ermittelt. Die Mg-Gehalte wurden in Haar, Plasma, Erythrozyten und Urin ermittelt und mit entsprechenden gleichaltrigen Kontrollen verglichen. Anschließend wurde eine einfache Blind-Studie durchgeführt: 14 Patienten erhielten Mg (etwa 340 mg als $MgSO_4$ in Gelatinekapseln täglich), 8 andere erhielten Placebo. Nach 6 Wochen gaben 8 der Mg-behandelten Probanden (57 %) an, sich besser zu fühlen. Nur zwei Probanden der Placebo-Gruppe (25 %) fühlten sich besser. Glucose-Toleranz-Tests (6 Stunden) wurden bei drei Probanden vor und nach sechswöchiger Supplementation durchgeführt. Nach der Supplementation fiel in keinem Fall der Blutzucker unter die Nüchternwerte. Verglichen mit den Kontrollen waren Haar-Mg, Erythrozyten-Mg und, bei den weiblichen Probanden, auch das Plasma-Mg niedriger bei den Hypoglykämikern. Bei diesen bestand weiterhin ein schwacher aber nicht signifikanter Trend zu höheren Magnesium-Ausscheidungen. Es wird vermutet, daß die reaktive Hypoglykämie Folgeerscheinung eines gestörten Mg-Stoffwechsel ist.

Summary

In rats, magnesium (Mg) deficiency has been reported to result in decreased blood sugar levels. This suggested that Mg deficiency might be related to reactive hypoglycemia, a disease of unknown cause. Reactive hypoglycemics were recruited (14 female, 8 male) who had been previously diagnosed by glucose tolerance tests. Mg content of hair, plasma, erythrocytes and urine was determined in hypoglycemics and age-sex matched controls. Subjects then participated in a single blind study: 14 received Mg, 8 received the placebo. Subjects receiving Mg ingested about 340 mg elemental Mg (as Mg sulfate) in gelatin capsules each day. At the end of six weeks, 8 of the subjects (57 %) on the Mg reported 'feeling better'. Only two of the subjects (25 %) on the placebo reported 'feeling better'. Glucose tolerance tests (6 hr.) were carried out on three subjects before and after 6 weeks of supplementation. After supplementation, none of the blood glucose levels dropped below the fasting level. Compared to controls, hair Mg, erythrocyte Mg and in the females, plasma Mg, were lower in hypoglycemics. There was a trend for the hypoglycemics to have a slightly higher Mg excretion than the controls but not significantly. It is suggested that reactive hypoglycemia is a disease of disturbed Mg balance.

Résumé

Chez des rats, il a été rapporté que le déficit magnésique entraîne le développement de taux réduits du sucre sanguin. Ceci a suggéré que le déficit en magnésium pourrait être rapporté à une hypoglycémie réactive, affection d'origine inconnue. Des hypoglycémiques réactifs (14 femmes, 8 hommes) ont été recrutés; ils ont été diagnostiqués antérieurement par des tests de tolérance du glucose. La teneur en magnésium des cheveux, du plasma, des érythrocytes et de l'urine a été déterminée chez les hypoglycémiques et chez des sujets de contrôle d'âge et de sexe comparables. Les sujets ont alors participé à une étude à un seul insu: 14 ont reçu du magnésium, 8 ont reçu un placebo. Des sujets recevant du magnésium ont ingéré environ 340 mg de magnésium élément (sous forme de $MgSO_4$) dans des capsules de gélatine, chaque jour. A la fin des 6 semaines, 8 des sujets (57 %) avec magnésium ont rapporté une «sensation meilleure». Des tests de tolérance du glucose (6 h) ont été effectués chez 3 sujets avant et après 6 semaines de supplémentation. Après la supplémentation, aucun des taux du glucose sanguin ne s'est abaissé au-dessous du taux à jeun. Par comparaison avec les contrôles, le magnésium des cheveux, le magnésium érythrocytaire et chez les femmes, le magnésium plasmatique, ont été plus faibles chez les hypoglycémiques. Il a existé une tendance pour les hyperglycémiques à présenter une excrétion du magnésium légèrement plus élevée que chez les contrôles, mais de façon non significative. Nous suggérons que l'hypoglycémie réactive est une affection de perturbation de l'équilibre du magnésium, peut-être due à une absorption réduite du magnésium liée à une excrétion normale ou légèrement accrue du magnésium, ce qui entraîne un déficit magnésique. Des doléances subjectives, telles que la fatigue et la perturbation du contrôle du sucre sanguin sont des symptômes de ce déficit.

In rats, magnesium (Mg) deficiency has been reported to result in increased muscle uptake of sugar [4] which could result in decreased blood sugar levels. This suggested that reactive hypoglycemia [1, 3], a disease of unknown cause, might be related to Mg deficiency. In this study, Mg levels of hair, plasma, erythrocytes, and urine of reactive hypoglycemics (HPO) were compared to age-sex matched controls. The HPO also participated in a single-blind study of Mg or placebo supplementation.

Methods

Fourteen female and eight male HPO were recruited who had been previously diagnosed by glucose tolerance tests (GTT). An age-sex matched control was selected for each HPO.

Hair was clipped from the back of the head close to the scalp. Only the first 5 cm were used for analyses. Hair was washed using a nonionic detergent and disodium ethylenediaminetetraace-

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tate [5]. After drying the hair overnight, the hair was digested using a mixture of sulfuric and nitric acids with 30 % hydrogen peroxide being added drop wise until the hair was dissolved and the solution became clear [2]. The solution was then transferred to a 25 ml volumetric flask and made to volume with 1 % lanthanum chloride.

Blood was collected in heparinized trace mineral vacutainer tubes (Becton-Dickinson, Rutherford, New Jersey). Plasma was separated from the red cells, placed into polypropylene tubes, frozen and stored below 0° C until analyzed. Erythrocytes were washed twice with saline, then diluted with an equal volume of saline and the hematocrit taken. Diluted erythrocytes were frozen and held below 0° C until analyzed. A sample of urine from 24 hour collections was acidified to a 3 % concentration of hydrochloric acid, frozen and stored below 0° C until analyzed.

Minerals in all samples were determined, after appropriate dilutions where necessary, using atomic absorption spectrophotometry (Perkin-Elmer 306, Perkin-Elmer, Norwalk, Connecticut). Plasma and urine were diluted with 1 % lanthanum chloride; erythrocytes with 0,05 % Triton X [6]. All samples were analyzed for Mg. Hair, urine and plasma were also analyzed for calcium (Ca).

All HPO participated in a single blind study which lasted six weeks. Fourteen received Mg while eight received the placebo. Mg was provided as $MgSO_4$ in gelatin capsules with each capsule providing 85 mg elemental Mg. Subjects ingested 4 capsules a day with meals to provide a total of 340 mg elemental Mg. Those on placebo ingested 4 gelatin capsules a day that contained corn starch. At the end of six weeks, subjects were evaluated on their subjective responses as recorded in a daily record as 0, ±, +, or ++. Blood samples were drawn and a 24 hour urine collected. These samples were processed and analyzed as previously described. Three HPO had 6 hour glucose tolerance tests before and after Mg supplementation.

Results

Results of hair mineral analyses showed the HPO to have lower Mg than controls (table 1). This decreased Mg was significantly lower in females ($P<0{,}01$) but not in males ($0{,}10>P>0{,}05$). A sex difference was apparent (figure 1). The hair Ca of female HPO and controls were 975 ± 715 (S. D.) and 1154 ± 689; that of male HPO and controls was 460 ± 283 and 647 ± 452, respectively.

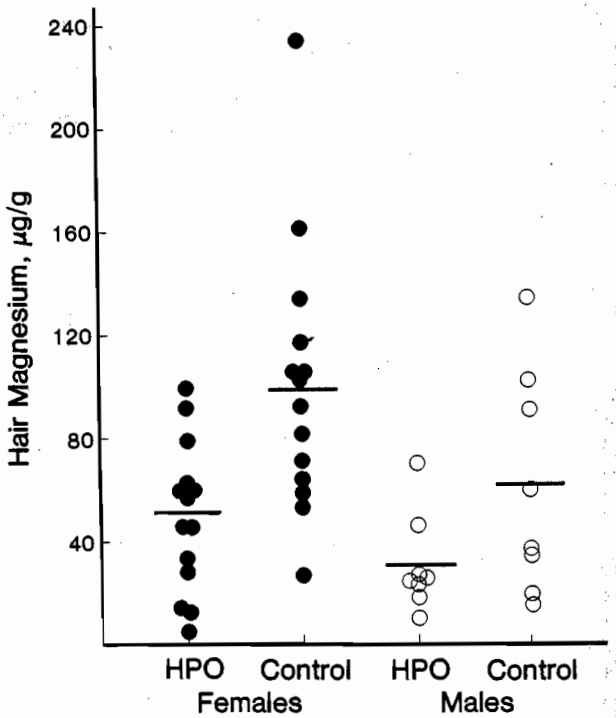

Fig. 1: Scattergram of hair magnesium of hypoglycemics and controls. Means are given by the solid line.

Erythrocyte and plasma Mg levels were significantly lower than controls in female HPO ($P<0{,}02$) but not in males (table 1). No differences were noted in plasma Ca. The urinary Mg of the HPO were the same or slightly higher than that in controls. The mean urinary Ca of HPO and controls were $8{,}5\pm3{,}5$ and $7{,}2\pm4{,}2$ meq/24 hours, respectively. Before and after Mg supplementation the nadirs of the GTT of the 3 HPO had means of -48 ± 15 (S. D.) and -5 ± 18 mg glucose/dl plasma, respectively, below the fasting levels. None of the nadirs were below 50 mg glucose/dl.

At the end of six weeks, 7 of the 14 HPO who received Mg were rated as + or ++. Only 2 of the 8 HPO on the placebo were rated as +. No significant or consistent trends in plasma or erythrocyte Mg levels occurred following supplementation.

Results were evaluated on the basis of characteristics of subjects who responded or did not respond to Mg supplementation (tables 2 and 3). Of the 7 HPO who showed improvement, 6 increased their urinary Mg excretion. The mean increase of the 7 HPO who showed improvement

was 41 ± 49 (S. D.). Only 3 of the 7 HPO who did not improve showed an increase in urinary Mg. The mean change in urinary Mg of this subgroup was −2 ± 21 %. This mean change in urinary Mg of the 8 HPO receiving the placebo was −2 ± 37 %.

Five of the seven responders had hair Mg less than 25 ug/g with hair Ca less than 400 ug/g. The remaining 2 responders had hair Mg of about 60 ug/g but hair Ca were high; 2405 and 1839 ug/g. All the + + responders had low hair Mg and Ca. Subjects with hair Ca concentrations less than 400 ug/g or over 1800 ug/g had + + or + responses. Those with hair Ca concentrations between 400 and 1800 ug/g had 0 or ± responses.

Tab. 1: Magnesium in hair, erythrocytes, plasma and urine of hypoglycemics and controls.

Group	Number	Magnesium				
		Age years	Hair ug/g	Erythrocytes meq/L	Plasma meq/L	Urine meq/24 hr
			Females			
Hypoglycemics	14	32,4 ± 10,0	51 ± 28[a]	3,9 ± 0,4[bc]	1,55 ± 0,09[b]	7,6 ± 3,3
Controls	14	31,1 ± 8,9	100 ± 52	4,5 ± 0,5	1,66 ± 0,12	5,7 ± 2,2
			Males			
Hypoglycemics	8	32,5 ± 9,6	30 ± 19	4,4 ± 0,3	1,56 ± 0,18	10,0 ± 3,2
Controls	8	32,1 ± 9,4	62 ± 43	4,4 ± 0,4	1,59 ± 0,13	8,7 ± 3,5

Mean differs from the control [a]$P < 0{,}01$ [b]$P < 0{,}02$ [c]Number = 12
(two tailed t test)

Tab. 2: Characteristics of hypoglycemics who responded to magnesium.

Subject	Age years	Response	Hair, ug/g		Urinary Mg, meq/24 hr		
			Mg	Ca	pre	post	% change
				Females			
4	27	+ +	15	275	10,8	14,6	+ 35
6	41	+ +	17	197	12,6	16,7	+ 32
9	42	+	13	84	5,5	5,2	− 5
1	28	+	59	2405	3,0	7,3	+ 143
2	46	+	58	1839	4,1	6,5	+ 59
				Males			
19	49	+ +	18	31	9,9	10,7	+ 8
16	37	+	24	358	12,0	14,1	+ 18

Tab. 3: Characteristics of hypoglycemics who did not respond to magnesium.

Subject	Age Years	Response	Hair, ug/g		Urinary Mg, meq/24 hr		
			Mg	Ca	pre	post	% change
				Females			
3	34	0	29	491	12,7	10,3	− 19
5	24	±	91	1508	8,0	9,7	+ 21
7	49	±	60	1398	8,2	6,1	− 26
8	43	0	80	505	5,1	6,4	+ 25
				Males			
15	43	0	10	786	8,7	8,3	− 5
17	25	±	27	469	6,0	6,8	+ 13
18	23	±	46	552	8,7	6,9	− 21

Discussion

Hair Mg levels of controls were lower than those previously reported [7] but a different hair washing procedure was used which may account for the difference. A low hair Mg has been suggested to be indicative of a Mg deficiency [7], if so, the low hair Mg of the HPO might be indicative of a Mg deficiency. This combined with the lower plasma and erythrocyte Mg levels in the women is suggestive that a Mg imbalance is occurring.

Why responders had both low and high hair Ca concentrations is unclear. Only 2 female controls had higher hair Ca levels and they had hair Mg concentrations greater than 130 ug/g. Three of the controls had hair Mg and Ca below 30 and 400 ug/g, respectively. These controls were between 43 and 49 years but had no hypoglycemic symptoms, showing that low hair Mg and Ca are not always associated with hypoglycemics.

The increased urinary Mg excretion of the responders suggested that they had absorbed Mg in excess of their body needs. Those who did not respond, generally, did not increase their Mg excretion. This could have been due to 1) not being able to increase Mg absorption, or 2) the Mg absorbed was taken up into tissues and was not available for excretion, or 3) a combination of these factors. If these reasons were valid, the nonresponding subjects might have responded to a longer or higher supplementation period or level, respectively. Those who did not respond could have had their symptoms caused by factors unrelated to Mg but in this case urinary Mg would be expected to increase unless the gut was able to decrease Mg absorption appreciably.

Since the 7 HPO who responded positively to Mg supplementation did not have a decreased urinary Mg excretion but had low hair Mg, it appears that these individuals may be showing a Mg deficiency with an inability of the kidney to conserve Mg. If these same individuals had a low to normal absorption of Mg, a negative Mg balance could ensue.

Mg supplementation appeared to prevent nadirs in plasma glucose that were significantly below fasting levels. This suggested that the hypoglycemia of reactive hypoglycemia would be a sign of a complex disorder and not the cause.

It is suggested that reactive hypoglycemia is related to a disturbed Mg balance. Mg-Ca interactions also appear to be important but the mechanisms are not clear. Subjective complaints, such as fatigue, and the disturbed blood sugar control would be symptoms and signs of this syndrome.

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