Hypomagnesemia in patients with essential arterial hypertension

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Zusammenfassung

Das Serum-Mg wurde bei 202 Patienten mit essentieller Hypertension (Klasse I: n = 40; Klasse II: n = 124; Klasse III: n = 38) sowie bei 38 normotensiven Kontrollpersonen gemessen. In Klasse II lagen bei behandelten Patienten die mittleren Serum-Mg-Werte signifikant unter den Spiegeln der unbehandelten Hypertoniker ($p < 0{,}001$). Auch im Vergleich zu den Kontrollen fanden sich signifikant häufiger Hypomagnesiämien, und zwar sowohl bei behandelten als auch bei unbehandelten Hypertonikern. Diese Befunde könnten zumindest teilweise mit durch Diuretika verursachten erhöhten renalen Verlusten erklärt werden. Hypomagnesiämien bei unbehandelten Hypertonikern können aus einer verminderten Aufnahme oder aus erhöhter adrenerger Aktivität resultieren. Bei Vorliegen einer Hypomagnesiämie fand sich in 62,5 % der Fälle eine Hypophosphatämie, in 19,64 % eine Hypokaliämie und in 12,5 % der Fälle eine Hypocalciämie. Die hohe Inzidenz von Hypomagnesiämien bei Hypertonikern und die Auswirkungen auf andere Serum-Elektrolyte sowie auf die Reaktivität der glatten Muskulatur auf Stimuli legen es nahe zu fordern, daß eine gezielte Therapie auch das Serum-Mg mitberücksichtigen sollte.

Summary

Serum magnesium was determined in 202 patients with essential arterial hypertension (40 in stage I, 124 in stage II und 38 in stage III) as well as in 38 normotensive control subjects. Mean value of serum magnesium was significantly lower ($p < 0.001$) in treated than in untreated hypertensive patients in stage II. Also when compared with control subjects the incidence of hypomagnesemia was significantly higher in both treated and untreated hypertensive patients. This finding could at least partially be explained by diuretics induced urinary loss of magnesium. Occurence of hypomagnesemia in untreated hypertensive patients may be subsequent to a decreased intake or by an increase adrenergic activity. Hypomagnesemia is accompanied by hypophosphatemia in 62.50 %, hypopotasemia in 19.64 % and hypocalcemia in 12.50 % of cases. The high incidence of hypomagnesemia in hypertensive patients and its effects upon other serum electrolytes and smooth muscle responsiveness to stimuli suggest, that a correct therapy should take into consideration the behaviour of serum magnesium levels.

Résumé

Les auteurs ont mesuré la concentration sérique de magnésium chez 202 patients atteints d'hypertension artérielle essentielle (40 au stade I, 124 au stade II et 38 au stade III) et chez 38 témoins normotendus. La concentration sérique moyenne de magnésium était significativement plus faible ($p < 0{,}001$) chez les patients traités que chez les hypertendus non traités de stade II. Par rapport aux résultats obtenus chez les témoins, les cas d'hypomagnésémie ont été significativement plus nombreux aussi bien chez les hypertendus traités que non traités. Cette différence peut, au moins partiellement, s'expliquer par la perte urinaire de magnésium induite par les diurétiques. Chez les hypertendus non traités, la survenue d'une hypomagnésémie peut être due à une réduction de l'apport ou à une augmentation de l'activité adrénergique. L'hypomagnésémie s'accompagne d'une hypophosphatémie dans 62,50 % des cas, d'une hypokaliémie dans 19,64 % des cas et d'une hypocalcémie dans 12,50 % des cas. La forte incidence de l'hypomagnésémie chez les hypertendus et ses effets sur les autres électrolytes sériques ainsi que sur la faculté de réponse des muscles lisses à des stimuli permettent de penser qu'un traitement convenable de l'hypertension artérielle doit tenir compte des taux sériques de magnésium.

Introduction

Magnesium had been used as a therapeutic agent in malignant arterial hypertension, arterial hypertension accompanying toxemia of pregnancy [17, 20, 27] and even in essential hypertension [9, 4] long before the effects of diuretics upon salt and water metabolism were known. Later on, it was demonstrated that diuretic drugs may lead to hypomagnesemia, which was was found to alter the responsiveness of vascular smooth muscle to stimuli probably by an effect upon intracellular calcium [1, 6, 17] or through changes affecting other electrolytes [10]. Recent data emphasize, that intracellular magnesium acts as a cofactor in about 300 enzymatic reactions [7], while the extracellular magnesium plays an important role in neuromuscular excitability [10].

It was also reported, that smooth muscle contractility and its responsiveness to stimuli are greatly dependent upon the relative concentrations of the various ions [2, 5, 17, 21] and a negative correlation between arterial tension and intracellular magnesium concentration could be established [17]. Higher doses of hypotensive drugs are usually required in hypomagnesemic hypertensive patients, than in those with normal serum magnesium level, in order to obtain the same decrease in blood pressure [25].

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In a recent paper [23] we have shown, that hypomagnesemia is more frequently encountered in treated hypertensive patients than in untreated ones.
Starting from these considerations the incidence of hypomagnesemia and its possible interrelationship with changes affecting other electrolytes was now studied in treated and untreated patients with essential arterial hypertension in relation to the stage of the disease.

Material and Methods

Serum magnesium was measured in 202 patients with essential arterial hypertension (40 in stage I: 21 men, 19 women; 124 in stage II: 54 men, 70 women; and 38 in stage III: 20 men and 18 women) as well as in 38 normotensive control subjects. Mean age is shown in Tab. 1.
WHO criteria were used for classifying the patients into the various stage of essential arterial hypertension [28]. Hypertensive patients affected by other diseases (severe hepatitis, enterocolitis, ect) that might have influenced serum electrolytes, were excluded.
Magnesium was measured in serum obtained from venous blood taken in fasting conditions and before any therapy was given, by a colorimetric method using Merk standardized reagents. In the 56 patients with hypomagnesemia (serum Mg < 0.80 mmol/l) serum sodium, potasium and calcium were investigated by means of a Zeiss flamephotometer. Also investigated was serum phosphorus using a colorimetric method. Zinc and copper were measured only in 31 patients with hypomagnesemia by means of a Perkin-Elmer model 300 atomic absorbtion photometer.
Statistical significance of the differences between mean values was calculated by the t-test according to Student and the significance of the incidence of hypomagnesemia was assessed by X^2.

Results

As shown in Tab. 1 serum magnesium levels tended to be lower in hypertensive patients treated with diuretics than in untreated ones. The difference between these treated and untreated patients reached statistical significance ($p < 0.001$) only for the larger group of hypertensives included in stage II. There was no statistical significant difference between hypertensive patients and normotensive control subjects with respect to the mean concentration of serum magnesium. However as shown in Tab. 2 the incidence of hypomagnesemia was significantly higher in both treated and untreated hypertensive patients.
Hypomagnesemia was accompanied by hypophosphatemia in 62.50 % of the cases while hypopotasemia and hypocalcemia occured in 19.64 % and 12.50 % of the cases respectively (Tab. 3). Concentration of the serum sodium lower than 130 mmol/l were noted only in two patients in stage III. Low concentration of serum zinc ($Zn < 10.5$ µmol/l) were noted only in two patients and another two patients were displaying copper levels lower than 10.5 µmol/l. A similar incidence of subjects with decreased Zn or Cu however noted among the controls. Determination of serum magnesium was repeated in 20 hypomagnesemic hypertensive patients after 10–20 days of therapy with nifedipine or clonidine. Although no magnesium salts were given the serum magnesium level returned to normal in 8 such patients.
No significant correlation between magnesium and systolic or diastolic value of arterial pressure were found in untreated hypertensive patients ($r = 0.114$; p NS).

Tab. 1: Mean values of serum magnesium in untreated (a) and treated (b) patients with essential arterial hypertension (EAHT)

Group		Number of patients	Age yr	Syst. blood pressure cm Hg	Diast. blood pressure cm Hg	Serum magnesium mmol/l
EAHT stage I	a	23	38.30 ±1.56	16.04 ±0.80	9.80 ±0.18	0.96 ±0.03
	b	17	48.69 ±2.53	15.28 ±0.94	9.70 ±0.13	0.88 ±0.06
EAHT stage II	a	56	52.55 ±1.07	18.75 ±1.21	10.46 ±0.26	0.98 ±0.02
	b	68	52.98 ±0.91	20.16 ±1.15	11.13 ±0.18	0.89 ±0.02
EAHT stage III	a	7	62.71 ±2.44	20.11 ±1.04	11.21 ±0.47	0.88 ±0.03
	b	31	61.09 ±1.48	18.88 ±1.13	10.48 ±1.33	0.96 ±0.03
Controls (C)		38	58.37 ±3.17	12.80 ±0.25	7.80 ±0.11	0.94 ±0.02

Statistical significance "p"

Ia	vs	Ib	p NS	IIa	vs	C	p NS
IIa	vs	IIb	$p < 0.001$	IIb	vs	C	p NS
IIIa	vs	IIIb	p NS	IIIa	vs	C	p NS
Ia	vs	C	p NS	IIIb	vs	C	p NS
Ib	vs	C	p NS				

Discussion

In agreement with previously reported data [23] we could not detect a significant differences between mean values of magnesium in hypertensive patients and normotensive subjects. It should however be noted, that the incidence of hypomagnesemia was significantly higher among hypertensive patients than among normotensive control subjects. Also data in the literature [26] report the occurence of low magnesium levels only in 6 – 12 % of the randomly selected patients with various complaints. This incidence is obviously lower than that of 27.72 % detected in our hypertensive patients. The above mentioned findings could be explained by urinary loss of magnesium following prolonged uncontroled diuretic therapy [5, 11, 24]. However this mechanism could not explain the occurence of hypomagnesemia in many untreated hypertensive patients. Recent epidemiological data provided evidence about a relationship between a lower magnesium content of the food, drinking water and soil in certain geographic areas on one side and the incidence of arterial hypertension on the other side [12, 13]. It was also emphasized that modern way of life has changed the ratio between magnesium intake and the increased necessities required by a diet richer in proteins, refined carbohydrate, fats, phosphorus, alcohol and vitamin D [13, 15, 18].

Other authors [25] consider, that the above mentioned factors do not provide a satisfactory explanation for the high incidence of hypomagnesemia in hypertensive patients and suggest, that acute or chronic stress and subsequent release of catecholamines would lead to a leak of cellular magnesium. Its elimination through the urine may then represent the main cause for the development of a negative magnesium balance.

Whether and to what extent hypomagnesemia may be involved in the pathogenetic mechanisms leading to sustained increased blood pressure are problems investigated by both experimental and clinical research groups. As previously reported by other authors [17], our study could not confirm the negative correlation between blood pressure and serum magnesium level found by Petersen and coworkers [16]. Perhaps the main clinical argument linking magnesium to pathogenic mechanisms involved in arterial hypertension are represented by the decrease of blood pressure in hypertensive patients given magnesium.

Experimental hypomagnesemia in animals leads to vasospasm in various territories and to an increase in blood pressure [1, 2]. These phenomena were mainly attributed to an increase of intracellular calcium as well as to a direct effect of magnesium upon the smooth muscle fibers [2, 17]. It was actually demonstrated, that the cellular influx and efflux of calcium is magnesium dependent [1, 17] and this electrolyte seems to be a natural antagonist in the smooth muscle and myocardium [3]. It was also shown, that hypomagnesemia increases the vascular responsiveness to the compounds causing an increase in blood pressure [1, 17].

Hypomagnesemia is often accompanied by other electrolytic disturbances and this correction depends upon the normalization

Tab. 2: Incidence of hypomagnesemia in patients with essential arterial hypertension

Group		Number of investigated subjects	Number of subjects with serum Mg < 0.80 mmol/l
EAHT stage I	untreated (a)	23	7
	treated (b)	17	9
EAHT stage II	untreated (a)	56	13
	treated (b)	68	15
EAHT stage III	untreated (a)	7	3
	treated (b)	31	9
Controls (C)		38	3

Statistical significance calculated by[2]

Ia vs C $p < 0.025$
Ib vs C $p < 0.001$
IIa vs C $p < 0.05$
IIb vs C $p < 0.05$
IIIa vs C $p < 0.02$
IIIb vs C $p < 0.025$

Tab. 3: Number of hypomagnesemic hypertensive patients (treated and untreated) displaying low levels of serum K, Ca und P. Number of investigated subjects in brackets

Group		Serum K < 3.6 mmol/l	Serum Ca < 2.10 mmol/l	Serum P < 0.80 mmol/l
EAHT stage I	untreated (7)	2	1	3
	treated (9)	2	2	5
EAHT stage II	untreated (13)	1	0	12
	treated (15)	4	2	10
EAHT stage III	untreated (3)	0	1	0
	treated (9)	2	1	5

of serum magnesium level [6, 23, 26]. In fact magnesium deficiency was found to alter the permeability of the cell membrane for other ions [2, 11, 17]. The most frequently encountered electrolyte abnormality accompanying hypomagnesemia was hypophosphatemia, which occured in 62.50 % of the cases. Mention should be made, that both the hypertensive and control groups included a rather large percentage of overweight subjects and it was shown that obesity is often accompanied by low levels of serum inorganic phosphate [22]. On the other hand experimental data demonstrate that magnesium deficiency always leads to an increase in phosphaturia [26], which returns to normal values after the administration of magnesium salts [26]. Magnesium deficiency leads to a decrease of the Na-K-ATP-ase activity, which might explain not only the loss of the cellular potasium but also the retention of sodium into the cells [19].

Hypomagnesemia may sometimes display a transient character. It is possible that the transient hypomagnesemia reflects a temporary intracellular shift of magnesium ions as a non specific response to stress [4].

The interaction between disturbances affecting the various ions is still poorly understood and it is very difficult if not impossible to isolate the effects of each individual ion [8]. It is actually shown, that hypomagnesemia may frequently occur in patients with hypopotasemia (42 %) or with hypophosphatemia (29 %) [26].

The above mentioned observations and considerations suggest, that the determination of serum magnesium should routinely be used for the correct control of therapy in hypertensive patients.

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