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Calcium and Magnesium in Hypertension: Current Evidence

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Zusammenfassung

Zunehmende Aufmerksamkeit wird der möglichen Rolle von Kalzium und Magnesium zur Regulierung erhöhten Blutdrucks entgegengebracht. Die Ergebnisse einer kleineren Untersuchung von 1982 haben gezeigt, daß zwischen Hypertonie und mangelnder Kalziumaufnahme mit der Nahrung ein Zusammenhang besteht. Seitdem ist in zahlreichen Veröffentlichungen eine umgekehrte Korrelation zwischen Nahrungskalzium und Blutdruck aufgedeckt worden. Über die Zufuhr von Magnesium mit dem Essen besitzen wir nur wenige Daten. In einigen Untersuchungen wurde ein umgekehrtes Verhältnis zwischen dieser und dem Blutdruck festgestellt. Die meisten epidemiologischen Studien zu den Zusammenhängen zwischen Ernährung und erhöhtem Blutdruck sind jedoch longitudinal, so daß sie schwer auszuwerten sind. Vor kurzem wurden die individuellen Korrelationen zwischen Kalziumzufuhr mit der Nahrung sowie Magnesium einerseits und Blutdruck andererseits in einer wichtigen prospektiven Studie mit Krankenschwestern in den USA bestätigt. Bei Testpersonen, die hohe Kalzium- und Magnesiumgaben in der Kost bekommen hatten, erwies sich das Risiko für die Entstehung einer Hypertonie im Gegensatz zur Nahrung mit geringer Mineralstoffzufuhr um 20 % geringer. Ein endgültiger Nachweis eines Verhältnisses zwischen Ursache und Wirkung wird nur durch klinische und nicht durch epidemiologische Studien erbracht werden können. Heute enthält die wissenschaftliche Literatur mindestens 18 Veröffentlichungen über kontrollierte klinische Doppelblindversuche mit Kalzium gegen Placebo und 8 ähnliche Untersuchungen mit Magnesium. Die Ergebnisse dieser Versuche gestatten jedoch keine eindeutige Aussage darüber, ob Kalzium oder Magnesium wirklich bei allen Patienten an der Blutdruckregulierung beteiligt ist. Vielleicht liegt die Unregelmäßigkeit der Ergebnisse an der relativ hohen Anzahl von Versuchen über einen kurzen Zeitraum oder mit nur wenigen Probanden. Sie kann teilweise aber auch auf der in bestimmten Studien beobachteten Heterogenität der Reaktion beruhen. Daher sind umfassendere und gut kontrollierte Studien, insbesondere über Magnesium, sicherlich geboten. Künftige Forschungsarbeiten sollten sich außerdem auf die Identifizierung von Untergruppen empfindlicher Individuen konzentrieren und Fortschritte unserer Kenntnisse über pathophysiologische Mechanismen ermöglichen.

Summary

Attention is growing for potential roles of calcium and magnesium in the regulation of blood pressure. Results of a small study in 1982 indicated that reduced intake of dietary calcium is related to hypertension. Since then, a large number of reports of an inverse association between dietary calcium and blood pressure appeared in the literature. Data on magnesium intake are limited; an inverse association with blood pressure has been observed in some studies. Most epidemiologic studies on diet and blood pressure, however, have been cross-sectional and are therefore hard to interpret. Recently, independent associations of calcium and magnesium intake with blood pressure were confirmed by a large prospective study among U.S. nurses. For both dietary calcium and dietary magnesium, the risk of developing hypertension was reduced by 20 % among those in the highest intake category compared to those in the lowest category. The final proof of a causal relationship is to be given by intervention studies. To date, at least 18 double-blind placebo controlled calcium intervention studies and at least 8 double-blind placebo controlled magnesium intervention studies have been published. The results of these trials do not unanimously support a contributing role for calcium, nor for magnesium, in the regulation of blood pressure in all subjects. The inconsistency in results may be due to the number of studies that were small or of short duration. It may also partly be due to a possible heterogeneity in response, as observed in some studies. There is clearly a need, especially with respect to magnesium, for larger, well-controlled studies. Further investigation should also try to indentify subgroups of susceptible persons, accompanied by developments in knowlegde of pathophysiologic mechanisms.

Résumé

Le rôle éventuel du calcium et du magnésium dans le contrôle de la pression artérielle suscite de plus en plus d'intérêt. Les résultats d'une étude restreinte menée en 1982 ont montré la liaison existant entre l'hypertension artérielle et une diminution de l'apport alimentaire en calcium. Depuis, un grand nombre de publications ont fait état d'une corrélation inverse entre le calcium alimentaire et la pression artérielle. Les données sur l'apport alimentaire en magnésium ne sont pas nombreuses. Quelques études ont rapporté l'existence d'une relation inverse entre cet apport et la pression artérielle. Cependent, la plupart des études épidémiologiques consacrées aux rapports entre l'alimentation et l'hypertension artérielle sont longitudinales, ce qui en rend l'interprétation difficile. Récemment, une importante étude prospective menée chez des infirmière aux Etats-Unis a confirmé les corrélations individuelles entre l'apport alimentaire en calcium et en magnésium d'une part et la pression artérielle d'autre part.

Le risque d'apparition d'une hypertension artérielle s'est avéré réduit de 20 % chez les sujets dont l'apport alimentaire était élevé tant en calcium qu'en magnésium par rapport aux sujets chez qui ces deux apports étaient faibles. La preuve définitive de l'existence d'une relation de cause à effet ne pourra être apportée que par des essais cliniques et non des études épidémiologiques. A l'heure actuelle, la littérature scientifique contient au moins 18 publications concernant des essais cliniques en double-insu contrôlés contre placebo relatifs au calcium et au moins 8 publications d'études similaires consacrées au magnésium. Les résultats de ces essais ne dégagent pas un consensus unanime en faveur d'une contribution du calcium ou du magnésium à la régulation de la pression artérielle chez l'ensemble des sujets. L'inconstance des résultats est peut-être due au nombre relativement important d'essais de courte durée ou ayant inclus de faibles effectifs. Elle peut également, en partie, être due à une éventuelle hétérogénéité de la réponse, observée dans certaines études. Il existe un besoin évident, en particulier en ce qui concerne le magnésium, d'entreprendre des études plus importantes et bien contrôlées. Les recherches devront également se focaliser sur l'identification de sous-groupes de sujets sensibles et s'accompagner de progrès dans la connaissance des mécanismes physiopathologiques.

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1. Introduction

A number of nutritional factors have been implicated in the development and treatment of hypertension. For a long time, research has mainly focussed on the potential effects of sodium and potassium intake. Recently, attention has been directed towards a possible role of the divalent cations calcium and magnesium. A variety of disorders of calcium and magnesium metabolism have been described in subjects with hypertension and in animal models. Whether intake of these minerals may exert an effect on blood pressure, however, is still debated. In this review, we will discuss the present evidence for a such a relationship provided by results from observational and intervention studies. Subsequently, we will discuss disturbances of calcium and magnesium metabolism in hypertension, followed by an examination of the literature on possible predictors of response to supplementation.

2. Observational studies

The hypothesis that intake of minerals may influence cardiovascular disease and hypertension was raised at an early time in studies of drinking water. *Kobayashi* in 1957, was the first to report lower death rates from cerebrovascular disease in area's with hard drinking water compared to area's with soft drinking water [1]. *Stitt* et al, among 12 towns in England and Wales, found a positive association between the town's hardness of drinking water and its mean blood pressure level [2]. These findings, however, were not confirmed by some other studies and remained subject to much debate [3].

Another type of epidemiological evidence supportive of the relationship between calcium and magnesium intake and blood pressure came from studies of gestational hypertension. The existence of a link between low calcium intake and pregnancy induced hypertension was postulated by some investigators as early as 1930. *Belizan* and *Villar* found less pregnancy induced hypertension in areas of increased calcium intake [4]. Comparable data relating dietary magnesium intake and pregnancy induced hypertension are not available to date. That magnesium deficiency contributes to hypertension in pregnancy is suggested by the succesful use of parenteral magnesium sulfate in the treatment of preeclampsia.

Great interest in the subject has been shown only recently. *McCarron* in 1982 was the first to report a low calcium intake in hypertensive compared to normotensive subjects [5]. Subsequently, an inverse association between calcium intake and blood pressure has been reported in a large number of population studies (Tab. 1). Most studies have been based on samples of US populations, but associations were also found in some European studies and among Japanese men living in Hawaii. The inverse association appears to be independent of age, gender, and race. The relationship was found both for total dietary calcium intake and for calcium intake from dairy products. Most studies controlled for potential confounding factors like body mass index and alcohol consumption. Some studies also controlled for intake of other nutrients, though it is doubted whether these can be fully accounted for [19].

Not all data are consistent however. In the first National Nutrition and Health Examination Study in the USA (NHANES I, 1971–1975) *McCarron* reported an inverse association of dietary calcium and blood pressure among a sample of 10, 372 subjects [17]. In reanalysis of the NHANES I data, and analysis of the NHANES II data (1976–1980), however, the association was either not found [23] or observed in subgroups only [10, 11]. A part of this discrepancy may be due to the varying inclusion of confounding and intermediary variables in the statistical models.

For magnesium intake fewer data are available. This is partly because interest in the hypothesis is of even more recent origin than for calcium and partly because of the more restricted availability of data on magnesium content in food composition tables. Population studies that did investigate the relationship with magnesium are noted in tab. 1. In a population sample in Belgium of 8, 058 men and women, an inverse association was observed between dietary magnesium intake and systolic blood pressure in women [13]. In a study among Japanese men living in Hawaii, a low magnesium intake was found to be the dietary factor most strongly associated with hypertension [12]. McCarron observed that among U.S. adults magnesium intake was lower in hypertensive compared to normotensive subjects [24], but no such relationship was observed among Scandinavian women [25].

With few exceptions, epidemiologic studies have been cross-sectional. Although most studies excluded subjects on a prescribed diet, these studies still might have included hypertensive subjects who changed their diet after the diagnosis. In 3 prospective analyses, no relationship could be observed between calcium intake and change in blood pressure during a follow-up period of some years [7, 15, 18]. The only prospective analysis that also presented data on the relationship between magnesium intake and blood pressure was performed among 58, 216 female U.S. nurses (Nurses' Health Study) [21]. In this study, dietary intake was measured by a mailed food frequency questionnaire. New cases of hypertension were ascertained during 4 years of follow-up by self-report of a physian's diagnosis of hypertension. After control for the effects of age, Quetelet's index, alcohol consumption and energy intake, significant inverse associations were found for dietary calcium and magnesium. Women with a calcium intake of at least 1000 mg/day had a 20 % reduction in risk of hypertension when compared with an intake of less than

Tab. 1: Poulation studies of calcium and magnesium and blood pressure.

References	Population	Design	Subjects No.	Sex	Age	Dietary data	Ca	Mg
Ackley et al. [6]	USA (CA)	C	5,050	M+F	30–79	ques	milk	–
Caggiula et al. [7]	USA, MRFIT	C, L	–	M	–	24-hr	diet	–
Folsom et al. [8]	USA (MN)	C	1,687	M+F	25–74	24-hr	diet	–
Garcia-Palmieri et al. [9]	Puerto Rico	C	7,932	M	45–64	24-hr	milk	–
Gruchow et al. [10]	USA, NHANES I	C	9,553	M+F	18–74	24-hr	diet	–
Harlan et al. [11]	USA, NHANES I	C	3,854	M+F	25–74	24-hr	diet	–
Joffres et al. [12]	Hawaii	C	615	M	61–82	24-hr	diet	diet
Kesteloot & Joossens [13]	Belgium	C	8,058	M+F	25–74	24-hr	diet	diet
Kok et al. [14]	Netherlands	C	2,291	M+F	40–65	history	diet	–
Kromhout et al. [15]	Netherlands	C, L	605	M	45–64	history	diet	–
Liebman et al. [16]	USA (SE)	C	532	F	14–16	24-hr	diet	–
McCarron et al. [17]	USA, NHANES I	C	10,372	M+F	18–74	24-hr	diet	–
Nichaman et al. [18]	USA (IL)	C, L	1,976	M	40–56	history	diet	–
Reed et al. [19]	Hawaii	C	6,496	M	46–68	24-hr	dairy foods	–
Trevisan et al. [20]	Italy	C	5,049	M+F	20–59	foodfr	milk	–
Witteman et al. [21]	USA, Nurses Study	L	58,218	F	34–59	foodfr	diet	diet
Yamamoto & Kuller [22]	USA	C	1,939	M+F	34–56	foodfr	diet	–

C = cross-sectionial; L = longitudinal; M = male; F = female; 24-hr = 24-hour recall; ques = questionnaire; history = dietary history; foodfr = food frequency questionnaire; Ca = calcium; Mg = magnesium.

400 mg/day. A comparable reduction in risk of hypertension was observed for women with a magnesium intake of 300 mg/day or more compared with an intake of less than 200 mg/day. These prospective data support the hypothesis that calcium and magnesium intake are related to blood pressure. Definite evidence of whether a change in intake of calcium and magnesium can induce a change in blood pressure, however, has to be provided by intervention studies.

3. Studies of calcium supplementation

Next to a number of calcium intervention studies that were not reported to be double-blind placebo controlled [26–32], 18 reports of double-blind placebo controlled studies have been published, covering studies in 24 hypertensive and nonhypertensive study-populations. For this review, only studies that presented data of baseline and final blood pressure measurements were regarded, thereby excluding two of the trials [33, 34]. Tab. 2 summarizes the main features of the studies. The duration of the trials varied from 1 week to 4 years. The number of subjects varied from 15 to 90. Thirteen studies were performed in mild to moderate hypertensive subjects, and 9 in normotensives, amongst 1 in pregnant women. In 3 studies subjects were on antihypertensive medication [38,45,49]. The dose of elemental calcium ranged from 400 mg/day to 2 160 mg/day.

The net mean changes in blood pressure are shown in fig. 1. Among the 22 studies presented, 4 showed a significant inverse effect on systolic blood pressure. The largest fall in systolic blood pressure, 21 mmHg, was found by *Johnson* et al., at the end of 4 years of calcium supplementation in patients who were on antihypertensive medication [38]. In the study of *Saito* et al., the rise in systolic blood pressure with the initiation of a high sodium diet was 10 mmHg less in subjects who concurrently received a high dose of calcium for 1 week compared to those who received placebo [43]. *Villar* observed a significant fall in systolic blood pressure of 4 mmHg in pregnant women supplemented from the 26th week of gestation onwards [47]. A significant fall in systolic blood pressure of 3 mmHg was found by *McCarron* and *Morris* among hypertensive subjects [40]. In this study, a significant fall in diastolic blood pressure of 3 mmHg was observed among normotensive subjects.

The response to calcium supplementation in the presented studies is not clearly related to age or sex of the subjects. In the study of *Lyle* et al., white and black subjects were studied separately but effects on blood pressure were observed in neither group [39]. The response does not seem to be related to initial blood pressure status, nor to concomitant administration of anti-hypertensive medication. Given that high blood pressure may represent a chronic disturbance of calcium homeostasis in some subjects, it might take at least several weeks before an effect of calcium supplementation becomes appearent. *McCarron* and *Morris* found that the antihypertensive effect was significant only after 8 weeks [40]. This finding warrants a careful interpretation of 'negative' findings in trials that are of short duration. *Nowson* and *Morgan* [42] found no effect from supplementation of 400 mg of elemental calcium and neither of 800 mg, but most studies used higher doses. The results do not seem to be related to the type of salt used. *Meese* et al. found no difference in response between supplementation with calciumcitrate versus calciumcarbonate [41]. Finally, the use of a low calcium diet for comparison [35, 44] does not discriminate between studies that showed an effect

and those that did not. In general, the studies differed in many variables and therefore it is hard to distinquish trial features that might be related to a favourable response.

4. Studies of magnesium supplementation

The studies using magnesium supplementation are less in number compared to those of calcium supplementation. There have been 5 studies published that were not placebo-controlled [51–55]. All studies were performed in mild to moderate hypertensive subjects. In 3, subjects were on anti-hypertensive medication, predominantly diuretics [51, 52, 55]. The salts used were either sulfate, oxide or aspartate hydrochloride in a dosis of 365 to 600 mg/day. *Karppanen* et al had used a potassium and magnesium enriched salt mixture with either 10 % or 20 % of magnesiumsulfate, to be used instead of the subjects usual table salt [52]. All studies observed a significant fall in systolic blood pressure. The largest fall in systolic blood pressure, 12 mmHg, was observed in the study of *Dyckner* en *Wester* after 6 months of supplementation in 20 hypertensive subjects on diuretic treatment [51]. Significant inverse associations were also observed for diastolic blood pressure, except for a significant increase in diastolic blood pressure among subjects with low plasma renin activity [54].

Since these studies were not placebo controlled, we should be careful with the interpretation. There have been 8 double-blind placebo controlled studies on magnesium supplementation and blood pressure published to date. The main features of these studies are presented in table 3. The duration of supplementation varied from 3 weeks to 6 months. Numbers of subjects involved were generally small, except in the study of *Sibai* et al., who investigated 374 pregnant women [63]. With the exception of the latter study, all were performed among adult hypertensive subjects; in 2 studies subjects used diuretics [58, 61]. The dose of elemental magnesium varied from 243 to 500 mg per day. The results of the studies are presented in fig. 2. In none of the studies a significant fall in systolic or diastolic blood pressure was observed.

Generally the effects shown in the controlled studies of magnesium intervention are far less convincing

Tab. 2: The effect of calcium supplements on blood pressure. A summary of double-blind placebo controlled studies.

Reference		Design	Duration	Subjects No.	Sex	Age (yrs) mean (range)	baseline BP (mmHg) mean	Condition	Ca salt	mg Ca/day
Beresteyn et al. [35]		P	6 wks	58	F	21 (20–23)	115/65 L	–	carb	1500*
Cappuccio et al. [36]		C	4 wks	18	M+F	49 (28–65)	153/103L	–	lact	1600
Grobbee & Hofman [37]		P	12 wks	90	M+F	25 (16–19)	143/83S	–	citr	1000
Johnson et al. [38]	a	P	4 yrs	81	F	– (35–65)	123/81S	–	carb	1500
	b			34	F	53 (35–65)	141/90S	treatment	carb	1500
Lyle et al. [39]	a	P	12 wks	54	M	33 (19–52)	117/73L	white	carb	1500
	b			21	M	28 (19–52)	118/71L	black	carb	1500
McCarron & Morris [40]	a	C	8 wks	32	M+F	48 (21–70)	121/75L	–	carb/citr	1000
	b			48	M+F	52 (21–70)	152/94L	–	carb/citr	1000
Meese et al. [41]	a	C	8 wks	26	M+F	49 (22–73)	142/96S	–	citr	800
	b								carb	800
Nowson & Morgan [42]	a	P	8 wks	47	M+F	55 (22–77)	154/91S	–	carb	400
	b								carb	800
Saito et al. [43]		P	1 wk	27	M+F	51 (39–67)	126/81L	low Na diet	glub	2160
Siani et al. [44]		C	4 wks	15	M+F	41 –	139/91L	–	carb/lact	1000*
Strazzullo et al. [45]		C	15 wks	18	M+F	43 –	153/96L	treatment	carb/lact	1000
Thomsen et al. [46]		P	1 yr	28	F	50 –	124/76L	–	carb/lact	2000
Villar et al. [47]		P	12 wks	52	F	21 (18–30)	106/67L	pregnant	carb	1500
Vinson et al. [48]	a	P	7 wks	15	M	– (19–24)	116/75L	–	gluc	500
	b								yeast	500
Waal-Manning et al. [49]		P	9 mos	52	M+F	61 (20–69)	143/84L	treatment	–	1000
Zoccali et al. [50]		C	8 wks	23	M+F	43 (27–59)	142/88S	–	carb/lact	1000

P = parallel group; C = crossover; wks = weeks, mos = months; yrs = years; M = male; F = female; BP = blood pressure; L = lying; S = sitting; Ca = calcium; carb = cabonate; lact = lactogluconate; citr = citrate; glub = glubionate; gluc = gluconate; * = versus low calcium diet. Lying blood pressure is presented when information was available.

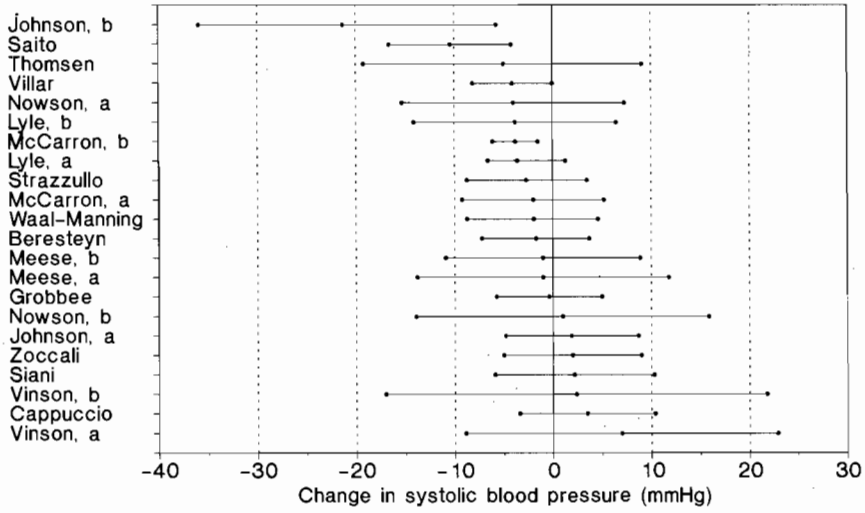

Fig. 1a

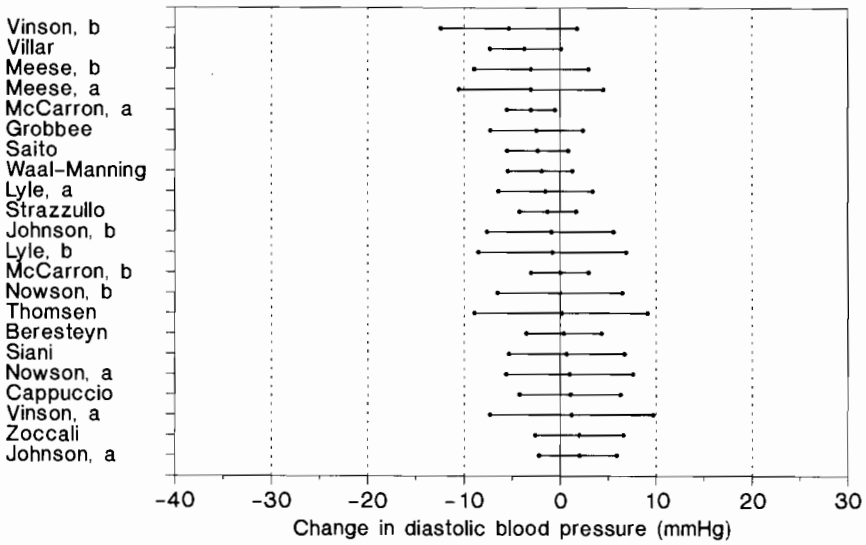

Fig. 1b

Fig. 1a + b: Effect of calcium supplements on systolic and diastolic blood pressure (mean and 90 % confidence interval) in double-blind placebo controlled studies. The figures are based on the difference in blood pressure change from baseline to final measurement between the placebo group and those receiving calcium supplements. The use of this strategy for data presentation may result in discrepancies between numbers and inferences in the original papers and those presented here.

compared to those in the studies that were not placebo controlled. While it is possible that the placebo controlled magnesium studies did not have enough power to detect an effect on blood pressure, the results of both the calcium and the magnesium supplementation studies performed to date provide no evidence of an effect of these minerals on blood pressure. How can this discrepancy with the results of population studies be explained? Blood pressure is affected by many genetic and environmental factors and their complex interactions. It is conceivable that calcium and magnesium supplements exert an effect differentially according to the specific underlying disturbance in metabolism of these minerals. In the next paragraphs, we will discuss disturbances of calcium and magnesium homeostasis in hypertension. Subsequently, we will examine the evidence for the existence of factors that may predict blood pressure response to supplementation.

5. Calcium and magnesium homeostasis in hypertension

5.1 Parameters of calcium and magnesium homeostasis

Urinary excretion of calcium and magnesium

Results of studies of calcium loading in hypertensive and normotensive subjects have suggested that increased urinary calcium excretion reflects renal calcium leak rather than high dietary intake of calcium [64]. A positive association between urinary calcium excretion and blood pressure has been reported in several large population studies: in 9 321 men on active duty in Belgian military forces [65] in 528 adults living in two Belgian towns [66], in 415 adult Bantu of Zaire [67] and among male farmers of three communities in China [68]. The relationship was also observed by studies comparing hypertensive and normotensive subjects [64, 69]. In contrast to the studies among adults, no relation of blood pressure with urinary calcium excretion was observed in young subjects [70].

In steady state, urinary magnesium excretion usually reflects dietary intake. An inverse association between urine magnesium and blood pressure has been found among 3 363 men and 1 262 women in Belgian Army troops [71], among 8,9 year old boys from 19 European centres [70] and among male farmers of three communities in China [68]. No relationship, however, was found in other large population studies [66, 67, 72].

Serum levels of calcium and magnesium

A positive association of total serum calcium with blood pressure has been observed among 4 167 men and 3 891 women of a Belgian population sample [73] and among 9 321 men on

Tab. 3: The effect of magnesium supplements on blood pressure. A summary of double-blind placebo controlled studies.

Reference	Design	Duration	No.	Sex	Subjects Age (yrs) mean (range)	baseline BP (mmHg) mean	Condition	Mg salt	mg Mg/day
Cappuccio et al. [56]	C	4 wks	17	M+F	52 (33–66)	154/100L	–	asp	365
Harris et al. [57]	P	12 wks	40	–	– –	≥140/≥90	–	oxide	500
Henderson et al. [58]	P	6 mos	41	M+F	62 –	156/90	diuretics	oxide	301
Nowson & Morgan [59]	P	8 wks	25	M+F	63 (50–77)	151/90L	low Na diet	asp	243
Olhaberry et al. [60]	P	4 wks	14	F	46 (24–64)	152/101L	low Na diet	chlor	385
Reyes et al. [61]	P	3 wks	21	M+F	57 (42–82)	158/110L	diuretics	chlor	385
Rüddel et al. [62]	P	12 wks	14	M	42 –	132/84S	low Mg i.c.	asp-HCl	365
Sibai et al. [63]	P	16–27 wks	374	F	18 (13–25)	110/60	pregnant	asp-HCl	365

P = parallel group; C = crossover; wks = weeks, mos = months; yrs = years; M = male; F = female; BP = blood pressure; L = lying; S = sitting; i.c. = intracellular; asp = aspartate; chlor = chloride; Mg = magnesium. Lying blood pressure is presented when information was available.

active duty in military forces [65]. In studies comparing hypertensive and normotensive subjects, however, no such relationship could be found [8, 64, 74]. Levels of serum ionized calcium were either reduced in hypertensives [8, 74] or were not different from normotensives [64], but also a weak positive association between serum ionized calcium and blood pressure has been reported [75].

An observation of low serum magnesium levels in subjects with hypertension compared to normotensive subjects was reported as early as 1958 [76]. The relationship was confirmed in a study of 73 Danish men and women [77]. No relationship, however, was observed in later studies that compared hypertensive and normotensive subjects [78], or examined the relationship in an adult population [79].

Intracellular levels of calcium and magnesium

Intracellular levels of the divalent cations may be of more importance than serum or urine levels. It is well established that the intracellular free calcium level plays a central role in smooth muscle cell contraction [80]. Increased levels of intracellulair free calcium in platelets [81] and in erytrocytes [82] have been observed in hypertensive subjects. Also depletion of intracellular free magnesium has been found in erytrocytes of subjects with essential hypertension, which has been suggested to be associated with increased intracellular free calcium levels [83]. It is an attractive hypothesis that increased intracellular concentration of free calcium in the vascular smooth muscle cell is the intermediary factor in the association of low intake of calcium as well as of magnesium with elevated blood pressure. *Turlapaty* and *Altura* [84] demonstrated an increase in total exchangeable and intracellular calcium in rat aortic tissue after withdrawal of extracellular magnesium. This finding agrees with the observation of an elevation of smooth muscle cell tension after acute withdrawal of extracellulare magnesium in in vitro studies [85]. It is possible that systems that are involved in the regulation of intracellular free calcium also modulate the effect of calcium and magnesium intake on blood pressure. These systems will be discussed in the next paragraph.

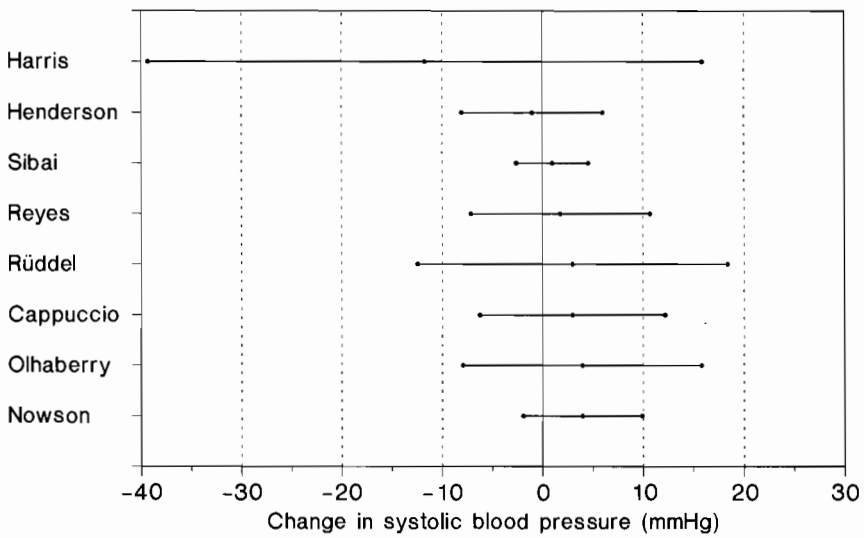

Fig. 2a

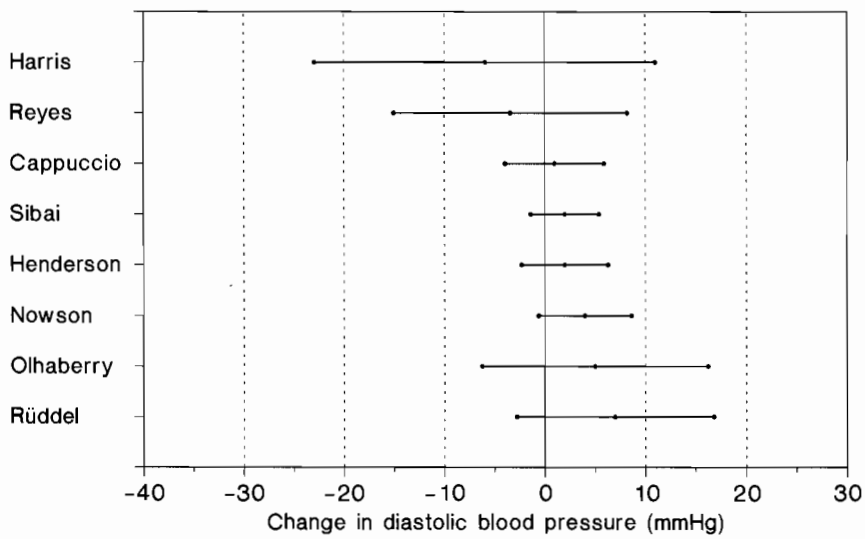

Fig. 2b

Fig. 2a + b: Effect of magnesium supplements on systolic and diastolic blood pressure (mean and 90 % confidence interval) in double-blind placebo controlled studies. The figures are based on the difference in blood pressure change from baseline to final measurement between the placebo group and those receiving magnesium supplements. The use of this strategy for data presentation may result in discrepancies between numbers and inferences in the original papers and those presented here.

5.2 Systems involved in the regulation of intracellular calcium

Ionic membrane transport

Extracellular free magnesium may alter ionic membrane transport, as reviewed by *Altura* [85]: magnesium possibly competes with calcium for binding sites on the membrane of

the vascular smooth muscle cell, magnesium may be involved in binding of calcium to intracellular organelles, and it may affect cell membrane permeability and stability. In addition to increasing vascular tone, a decrease in extracellular free magnesium has been shown to potentiate the contractile response of the vessel to vasoactive hormones; the latter may also be due to an enhanced influx of calcium into the cell [86]. Magnesium is known to be an important cofactor for activation of Na^+-K^+-ATPase activity, which plays an important role in determining vascular tone and reactivity. It is possible that a decrease in extracellular free magnesium may decrease Na^+-K^+-ATPase activity, finally resulting in an increase in intracellular free calcium [85]. Alternative contributing mechanisms could be a decreased formation of cyclic AMP within the cells or an inhibition of Ca^{2+}-ATPase activity at the membrane, which is also magnesium dependent [85]. Low calcium intake is also suggested to decrease activity of Ca^{2+}-ATPase and Na^+-K^+-ATPase [87] but few evidence exist to date.

Parathyroid hormone

The acute and long-term actions of parathyroid hormone (PTH) differ greatly. Acute infusions of PTH in supraphysiological quantities induce vasodilation in several vascular beds [88]. Longterm supplementation with PTH may elevate peripheral resistance and blood pressure in humans and in rats [89]. Several studies have shown elevated levels of circulating PTH in hypertensive subjects [64, 69, 90, 91]. PTH may act by increasing the intracellular free calcium levels in a variety of cells [92]. *Belizan* in pregnant women [32] and *Grobbee* in young mildly hypertensive subjects [37] found a positive association between the change in plasma PTH and the change in diastolic blood pressure associated with calcium supplementation.

Although calcium is the principal regulator of PTH, magnesium has also been observed to play a role. While extreme hypomagnesemia may inhibit the secretion of PTH, the regulation of PTH by magnesium generally seems to be similar to that of calcium, though its potency is much less. *Cholst* in pregnant women [93] and *Resnick* in hypertensive subjects [54] found a significant decrease in plasma PTH level after magnesium administration.

Renin-aldosteron system

Resnick [94] described 2 subgroups of hypertension according to the presence of a low or high plasma renin activity. In low renin hypertension there is an increased level of intracellular free calcium resulting from an influx of calcium from the extracellular calcium pool. Subjects are characterized by low plasma ionized calcium levels and high levels of plasma ionized magnesium. In this condition, calcium supplementation may be beneficial. In high-renin hypertension, the increase in intracellular free calcium results from intracellular disposition of calcium between the bound and free state. Subjects are characterized by high levels of plasma ionized calcium and low levels of plasma ionized magnesium. In this condition, magnesium supplementation may be beneficial.

6. Predictors of response to calcium and magnesium supplementation

6.1 Biochemical indicators

Urinary and serum levels of calcium and magnesium have only incidentically been found to be related to the response to supplementation. A high urinary calcium excretion [45], and a low serum total calcium [37, 95], have been reported to favour responsiveness to calcium supplementation, but these could not be confirmed as predictors of respons by other studies [36, 40, 50]. *Rüddel* et al. found low erytrocyte magnesium to be a prerequisite for an attenuated blood pressure response during stress following magnesium supplementation in labile hypertensives, but small subgroups were involved [62]. In this study no effect was observed on causual blood pressure; it thus may be that blood pressure reactivity is especially sensitive to magnesium supplementation. *Motoyama* et al. observed that subjects with the lowest sodium-efflux rate and the highest concentration of intracellular free sodium had the greatest benefit from magnesium supplementation [53]. In the study of *Grobbee* and *Hofman*, subjects with higher than median PTH levels had the greatest fall in blood pressure after calcium supplementation [37]. Accordingly, *Lyle* et al. found that subjects who responded to calcium supplementation had higher PTH levels compared to those that did not respond [95]. *Resnick* et al. observed that subjects with low-renin hypertension benefit preferentially from calcium supplementation and subjects with high-renin hypertension benefit from magnesium supplementation [31, 54]. These findings could not be reproduced by several other studies [36, 41, 56], but in most of these studies very small subgroups were compared. Among other biochemical indicators of response, serum estrogen levels may be considered. Evidence from different sources indicate that estrogens may be related to tissue retention of magnesium [96]. Postmenopausal women have been shown to have an increase in urinary magnesium excretion, which could be attenuated by use of substitution hormones [97]. In the Nurses' Health Study, the risk of hypertension associated with low dietary magnesium was highest among postmenopausal women who had never used substitution hormones. No such effect was shown for dietary calcium in this study [21].

6.2 Intake of nutrients

Studies that evaluated the influence of baseline dietary intake of calcium or magnesium on blood pressure response to supplementation found no evidence for a modifying effect

[40, 54]. However, the estimates of dietary intake are crude which might obscure real relationships. A possible interaction between calcium and magnesium intake on blood pressure has been investigated in animals [98], but no data are available from human studies. *Resnick* et al. found that subjects with high urinary sodium excretion tended to have the greatest decline in blood pressure after calcium supplementation [31]. Assuming that 24-hr urinary sodium extretion in part reflects sodium intake, the finding agrees with Resnick's postulate that high sodium diet suppresses renin activity, resulting in an increased intracellular calcium. Other calcium trials, however, observed no difference in effect according to level of baseline sodium excretion [36, 42, 50] or rather found the greatest blood pressure fall with calcium supplementation amongst subjects with a low sodium intake [40]. With respect to magnesium it is hard to predict whether the response to supplementation is conditional on salt intake. Two of the placebo controlled studies were performed in subjects on low salt intake [59, 60]. Although these studies showed rather an increase than a fall in blood pressure with supplementation, power is lacking to discriminate the results of these studies from those of other studies. Magnesium and potassium have been suggested to interact in many ways to control vascular tone and reactivity [99], but no data on a possible modifying effect of potassium intake are available to date. In an open uncontrolled study, coadministration of 1,25-dihydroxycholecalciferol prevented, instead of supported, a blood pressure lowering effect of calcium supplementation [100]. Amongst other nutrients, alcohol consumption may be important. A high level of alcohol consumption has been shown to increase the urine excretion of magnesium [101]. Results of the Nurses' Health Study showed that the risk of hypertension associated with a low magnesium intake was greatest in subjects with the highest level of alcohol consumption [21].

7. Conclusions

Although large population studies suggest a role of calcium and magnesium intake in hypertension, this is not supported by the majority of placebo controlled intervention studies performed to date. This may partly be due, especially for magnesium, to the number of studies that were small or of short duration. The heterogeneity of hypertension suggests that there may be subgroups that are susceptible to supplementation. The results of some of the intervention studies seem to confirm this, but in most studies numbers were too small for a powerful evaluation of predictors or response. Future studies should be large enough to examine possible subceptibility of subgroups defined a priori. The choice of subgroups should be based on insights in pathofysiological mechanisms and should also take into account other factors, like intake of nutrients known to interact with calcium and magnesium metabolism.

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