The effects of high oral magnesium supplementation on blood pressure, serum lipids and related variables in apparently healthy Japanese subjects

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In a double-blind, placebo-controlled study, thirty-three subjects were allocated to undergo either a 4-week treatment with oral Mg supplementation ($Mg(OH)_2$; 411–548 mg Mg/d) or a placebo. The urinary excretion of Mg increased significantly in both the first 2 weeks and the following 2 weeks of Mg supplementation, while the urinary Na excretion also increased significantly over the experimental period. The systolic and diastolic blood pressure values decreased significantly in the Mg group, but not in the placebo group. The urinary aldosterone excretion and packed cell volume increased significantly during the last 2 weeks of the experimental period compared with the run-in period and first 2 weeks of supplementation. There was a statistically significant positive correlation between the values for urinary noradrenaline excretion and diastolic blood pressure at the end of the supplementation period (both expressed as a percentage of the run-in value). Statistically significant increases in lecithin-cholesterol acyltransferase (*EC* 2.3.1.43; LCAT), HDL-cholesterol and apolipoprotein AI were also observed after Mg supplementation. A significant positive correlation was observed between the levels of LCAT and urinary Mg excretion for the experimental period (expressed as a percentage of the run-in value). The total cholesterol : HDL-cholesterol ratio decreased significantly during the last 2 weeks of Mg supplementation compared with the first 2 weeks and the run-in periods, but this did not occur in the placebo group. These results suggest that Mg supplementation may lower blood pressure through the suppression of the adrenergic activity and possible natriuresis, while also improving the serum lipids through the activation of LCAT in human subjects.

Magneisum: Hypertension: Lipids

Essential hypertension is one of the most common risk factors for cerebro- and cardiovascular diseases, which in turn are among the most common causes of death and disability in developed countries. The pharmacological treatment of essential hypertension has proven effective in lessening the mortality of stroke, but also has attendant risks due to its adverse effects. Therefore, the non-pharmacological treatment of essential hypertension has recently been attracting increasing interest. Lowering Na and/or increasing K intake has been established to exert beneficial effects on high blood pressure (Yamori *et al.* 1981; Kihara *et al.* 1984; Lai *et al.* 1989). On the other hand, epidemiological surveys, clinical investigations and experimental studies have recently reported that Mg may have some relationship to the pathogenesis of hypertension and atherogenesis (Wester & Dyckner, 1987; Kesteloot & Joossens, 1988; Witteman *et al.* 1994).

From an epidemiological point of view, Kobayashi (1960) first described a possible negative correlation between the hardness of drinking water and the prevalence of

hypertension and stroke. Since then, several epidemiological studies have suggested a relationship between the Mg content in drinking water or urinary Mg excretion and hypertension or IHD (Schroeder, 1960). Furthermore, animal experiments have also shown that Mg deficiency causes elevation of total cholesterol (Marier, 1982; Rayssiguier, 1984, 1986; Luthringer *et al.* 1988; Zhou *et al.* 1994) or triacylglycerol (Bussiere *et al.* 1995) concentration in the serum. In addition, Mg supplementation has decreased the levels of aortic cholesterol, and particularly cholesteryl ester, in mice (Yamaguchi *et al.* 1994), and also corrected hypertension in the rat (Rayssiguier *et al.* 1992; Laurant *et al.* 1995). These observations, combined with the knowledge that serum lipid composition is one of the major risk factors for the development of cardiovascular disease, have led to the suggestion that Mg deficiency may be involved in the development of IHD. While several studies have shown no benefit of Mg therapy (Cohen *et al.* 1984; Cappuccio *et al.* 1985; Henderson *et al.* 1986; Zemel *et al.* 1990; Durlach *et al.* 1992; Kisters *et al.* 1993; Mahfouz *et al.* 1994), other studies have demonstrated the effects of oral Mg supplementation on hypertension in human subjects (Saito *et al.* 1988; Motoyama *et al.* 1989). Therefore, the effects of oral Mg supplementation on blood pressure and lipid metabolism remain controversial. Thus, the present study was designed to investigate the effect of oral Mg supplementation on blood pressure, serum lipids and related variables in clinically healthy volunteers including borderline hypertensive and/or mildly hyperlipidaemic subjects under dietary control using a double-blind, placebo-controlled study.

SUBJECTS AND METHODS

Initially forty-one subjects were included in the study. The subjects were randomly divided into two groups at first; twenty-three received the Mg supplement, while eighteen received a placebo. However, eight subjects did not fulfill the study protocol for various reasons: in five subjects the energy and fat intakes were significantly different between the run-in and 4-week period, and three subjects withdrew for personal reasons (placebo group). Therefore these subjects were excluded from the analysis. Finally, twenty-three received the Mg supplement (Mg-group) and ten received a placebo (P-group). A total of thirty-three subjects were included in the present study. The subjects were all clinically healthy and active, normotensives or borderline hypertensives (World Health Organization criteria; 140–159 mmHg for systolic and/or 90–95 mmHg for diastolic blood pressure), normoglycaemic, and demonstrated no evidence of any other clinically overt diseases, but some did have moderately elevated serum lipid concentrations (total cholesterol: up to 6·96 mmol/l). Table 1 displays the clinical characteristics of the subjects investigated based on their particular group. No statistically significant differences were found between the P-group and the Mg-group with regard to age and sex distribution, the baseline blood pressure and serum variables. The serum Mg level was normal in all subjects. The dietary Mg intake was normal and was not significantly different between the two groups.

The Mg-group was given oral Mg supplementation, in the form of $Mg(OH)_2$, four tablets (548 mg Mg/d) for men and three (411 mg Mg/d) for women for 4 weeks.

The subjects were strictly instructed not to change their ordinary diet as far as possible during the entire 5-week test period including 1 week of run-in period. Therefore, food samples were collected from each subject for the last 2 d (run-in period), 2 weeks and 4 weeks of Mg supplementation or placebo administration in each group. In addition, all medications were kept constant during the 5-week test period when necessary.

The blood pressure and heart rate were measured three times in succession after the subjects sat quietly for at least 5 min in the morning, using an automated blood pressure

Table 1. *Characteristics of healthy Japanese subjects assigned to receive a supplement of magnesium or a placebo*

(Mean values and standard deviations)

	Placebo-group		Mg-group	
	Mean	SD	Mean	SD
No. of subjects	10		23	
Male : female	3 : 7		8 : 15	
Age (years)	66	18	64	9
Height (m)	1·549	0·065	1·564	0·076
Weight (kg)	56·0	7·8	57·4	7·7
Systolic blood pressure (mmHg)	121	15	130	14
Diastolic blood pressure (mmHg)	74	12	77	9
Heart rate (beats/min)	70	6	70	11
Total protein (g/l)	67	3	69	4
Total cholesterol (mmol/l)	5·24	0·62	5·38	1·06
Serum Mg (mmol/l)	0·85	0·06	0·86	0·07
Mg intake (mg/d)	222	17	229	23

device (BP-203N, Nippon Colin Co. Ltd, Komaki, Japan) at run-in, and after 2 and 4 weeks. The averages of three successive measurements were used as the individual blood pressure and heart rate values. The body weight was measured before blood sampling.

All subjects fasted for at least 12 h and were kept in a supine position for 30 min before blood sampling. Blood specimens were taken at the same time of day (08.00–09.30 hours) from the antecubital vein at the end of the run-in period and after 2 and 4 weeks of treatment.

The protocol was approved by the Human Investigation Review Committee of Nakamura Gakuen University. The subjects were fully informed of the purpose, procedures and hazards of the experiment, and written informed consent was obtained from all participants.

Measurements

The following serum variables were measured: total cholesterol, HDL-cholesterol, triacylglycerol, apolipoproteins (apo) AI, AII, B, CII, CIII, E, lecithin–cholesterol acyltransferase (*EC* 2.3.1.43; LCAT), total protein, glucose and insulin. The plasma renin activity was measured by a radioimmunoassay.

Urine samples were collected for 24 h on the day before each blood sampling, and the urinary volume and urinary excretions of Na, K, Ca, Mg, creatinine, aldosterone, noradrenaline and adrenaline were measured.

Electrolytes in the serum, urine and food were measured by use of atomic absorption spectrophotometry (Shimadzu AA660: Shimadzu Co. Ltd, Tokyo, Japan). The concentrations of total protein, total cholesterol, HDL-cholesterol and triacylglycerol in serum were measured by standard techniques using autoanalysers (Olympus AU-5000 and AUA-8000: Olympus Optical Co. Ltd, Tokyo, Japan; or ACP-5040; Eppendorf Co. Ltd, Germany) at the CRC Laboratory in Fukuoka. Urinary aldosterone was measured by radioimmunoassay. The urinary catecholamine concentrations were measured by HPLC at the Bristol Laboratory in Tokyo. Insulin was determined by an enzyme immunoassay using a commercial kit (Dinabot Laboratory, Tokyo, Japan). LCAT was measured by an enzyme assay using Anasolbu (Daiichi Laboratory, Tokyo, Japan), while the apolipoproteins were

measured by turbidimetric immunoassay using a commercial kit (Daiichi Laboratory) at the CRC Laboratory in Fukuoka. LDL-cholesterol was calculated by the formula of Friedewald *et al.* (1972).

Statistical analysis

The analysis required transformation of the data to a near-normal form before testing based on the logarithmic changes in the non-normal distribution. The differences between the data for the three periods were evaluated by Student's paired t test for variables which showed an approximately normal distribution. The differences in the variables between the run-in period and 2 weeks supplementation, the run-in period and 4 weeks supplementation and between 2 weeks and 4 weeks supplementation were evaluated by Student's t test. Differences between the two groups were evaluated by Student's t test for variables that had an approximately normal distribution. The correlation of the variables was determined using a least-squares fit linear regression analysis. All values were expressed as the mean and standard deviation. A value of $P < 0{\cdot}05$ was considered to be statistically significant. The statistical methods used to assess the relationship of the variables to the blood pressure and the LCAT activity also included Pearson's correlation analysis using the FACOM ANALYST program (Fujitsu, Tokyo, Japan).

RESULTS

The dietary intakes of Mg, Na, K and Ca were not significantly different among the run-in, 2 and 4 week measurements for both groups. As presented in Table 2, the 24 h urinary Mg excretion was significantly greater after 2 and 4 weeks of Mg supplementation, while the Na excretion after 4 weeks Mg supplementation was significantly greater than that during the run-in period. No significant changes, however, were observed in the 24 h urinary K, Ca or creatinine excretions in the Mg-group, or in any of the urine variables in the P-group.

Systolic and diastolic blood pressure expressed as absolute values and as a percentage of the values for the run-in period are shown in Table 3. The average systolic blood pressure was significantly decreased after both 2 weeks ($P < 0{\cdot}01$) and 4 weeks of Mg supplementation ($P < 0{\cdot}05$) compared with the run-in period, and the diastolic blood pressure also decreased significantly from 77 (SD 9) to 73 (SD 7) mmHg ($P < 0{\cdot}01$) after 2 weeks and 75 (SD 10) mmHg ($P < 0{\cdot}05$) after 4 weeks of Mg supplementation. However, the blood pressure did not change significantly over the experimental period in the P-group. In addition, the change in the systolic blood pressure from the run-in period to the experimental period was significantly greater in the Mg-group than in the P-group. No significant differences in the change in diastolic blood pressure were observed between the two groups.

Table 4 shows changes in the concentration of the serum electrolytes. The serum Mg concentration in the Mg-group increased significantly during supplementation compared with the run-in period. The serum K also increased significantly during the final 2 weeks of Mg supplementation compared with the run-in period, while the serum Na was lower during the final 2 weeks than during either the initial 2 weeks or the run-in period. Serum Na concentration increased during the final 2 weeks of the experimental period compared with the run-in period in the P-group. The serum Mg concentration for week 4 expressed as a percentage of the value from the run-in period was significantly greater ($P < 0{\cdot}05$) in the Mg group (104·0 (SD 6·5) %) than the P-group (99·1 (SD 6·9) %), while the serum Na

Table 2. *Urinary magnesium, sodium, potassium and creatinine excretion by healthy Japanese subjects receiving a magnesium supplement (Mg-group) or a placebo for 4 weeks*

(Mean values and standard deviations for ten subjects in the placebo-group and twenty-three subjects in the Mg-group)

	Placebo-group						Mg-group					
	Run-in		2 weeks		4 weeks		Run-in		2 weeks		4 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mg (mmol/d)	2·80	1·15	2·96	1·07	2·88	0·99	2·51	1·03	5·02***	1·56	4·69***	1·32
Na (mmol/d)	172	48	184	50	174	35	169	47	174	47	187*	49
K (mmol/d)	52·4	12·1	54·9	12·1	53	17·5	52·2	19·8	56·9	15·3	56·5	17·5
Creatinine (mmol/d)	10·96	5·39	9·20	2·01	9·28	2·38	10·79	3·50	10·04	2·72	10·57	4·92

Mean values were significantly different from those for the run-in period: * $P < 0·05$, *** $P < 0·001$.

Table 3. *Systolic blood pressure, diastolic blood pressure and heart rate in healthy Japanese subjects receiving a magnesium supplement (Mg-group) or a placebo for 4 weeks*

(Mean values and standard deviations for ten subjects in the placebo-group and twenty-three subjects in the Mg-group)

	Placebo-group						Mg-group					
	Run-in		2 weeks		4 weeks		Run-in		2 weeks		4 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Systolic BP (mmHg)	121	15	118	16	122	16	130	14	120**	11	125*†	13
Systolic BP (% run-in)§	100		98·6	6·2	101·6	6·6	100		92·1‡	8·2	95·6‡	7·4
Diastolic BP (mmHg)	74	12	72	10	73	10	77	9	73**	7	75*	10
Diastolic BP (% run-in)§	100		97·1	7·3	98·3	7·2	100		94·1	8·5	97·5	8·7
Heart rate (beats/min)	70	6	69	10	69	8	70	11	71	10	69	11

BP, blood pressure.

Mean values were significantly different from those for the run-in period: * $P < 0{\cdot}05$, ** $P < 0{\cdot}01$.

† Mean value was significantly different from that for the 2-week period, $P < 0{\cdot}05$.

‡ Mean values were significantly different from those for the placebo group, $P < 0{\cdot}05$.

§ Blood pressure value expressed as a percentage of that for the run-in period.

Table 4. *Serum magnesium, calcium, sodium and potassium concentration in healthy Japanese subjects receiving a magnesium supplement (Mg-group) or a placebo for 4 weeks*

(Mean values and standard deviations for ten subjects in the placebo-group and twenty-three subjects in the Mg-group)

	Placebo-group						Mg-group					
	Run-in		2 weeks		4 weeks		Run-in		2 weeks		4 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Serum Mg (mmol/l)	0·85	0·06	0·84	0·06	0·84	0·06	0·86	0·07	0·89*	0·07	0·90**	0·08
Serum Ca (mmol/l)	2·47	0·16	2·42	0·16	2·45	0·19	2·47	0·14	2·44	0·10	2·48†	0·11
Serum Na (mmol/l)	142·5	6·8	144·2	3·9	143·7*	3·5	144·1	2·3	144·6	3·5	142·0*†	4·8
Serum K (mmol/l)	4·74	0·73	4·53	0·49	4·61	0·31	4·60	0·45	4·68	0·41	4·85**	0·57

Mean values were significantly different from those for the run-in period: * $P < 0·05$, ** $P < 0·01$.
† Mean values were significantly different from those at 2 weeks, $P < 0·05$.

concentration was significantly lower ($P < 0·01$) in the Mg-group (98·5 (SD 2·7) %) than in the P-group (101·8 (SD 4·0) %).

As shown in Table 5, the urinary aldosterone excretion was significantly higher after 4 weeks Mg supplementation than during the run-in period, but not after only 2 weeks Mg supplementation. The urinary aldosterone excretion for week 4, expressed as a percentage of that for week 2, was also significantly greater ($P < 0·05$) in the Mg group; 115·6 (SD 3·79) % than in the P-group; 84·2 (SD 27·5) %. The packed cell volume was significantly higher during Mg supplementation than during the run-in period and reached the highest value after 4 weeks of Mg supplementation, while it was higher after 4 weeks than during the run-in period or week 2 in the P-group. The plasma renin activity did not change during Mg supplementation or placebo treatment. The urinary noradrenaline excretion tended to decrease during the experimental period in the Mg group, but there was no significant difference in comparison with the run-in period. However, there was a significant negative correlation between the values for urinary noradrenaline excretion and Mg excretion in weeks 2 and 4 (expressed as a percentage of the run-in value) (r − 0·432, $P < 0·05$; r − 0·533, $P < 0·05$ respectively) while no such correlation was detected in the P-group. In addition, a significant positive correlation was observed between the urinary noradrenaline excretion for week 4 expressed as a percentage of the run-in period and that of the diastolic blood pressure in the Mg-group (r 0·427, $P < 0·05$). However, no such correlation was found in the P-group. Table 6 shows the values for the serum lipid, LCAT and insulin concentrations during the various periods. During Mg supplementation the serum HDL-cholesterol increased significantly after 4 weeks and also increased after 2 weeks in the P-group, while the LDL-cholesterol decreased significantly in the Mg-group, whereas the serum cholesterol and triacylglycerol did not change significantly in either group. Although apo-AI increased significantly during the final 2 weeks of Mg supplementation compared with the other two periods, apo-AII, B, CII, CIII and E did not change in either group. The atherosclerosis index (total-cholesterol : HDL-cholesterol) was significantly lower during the final 2 weeks (3·84 (SD 1·04)) than during both the first 2 weeks (4·21 (SD 1·41)) and run-in period (4·38 (SD 1·37)) in the Mg-group, while no significant change was observed in the P-group. A statistically significant increase in LCAT from 2 weeks to 4 weeks was observed in the Mg-group, but not in the P-group, while neither the insulin concentration nor the body weight increased in either group. In addition, the difference in LCAT from week 2 to week 4 was significantly greater ($P < 0·01$) in the Mg-group (111·9 (SD 3·7) % run-in) than in the P-group (94·1 (SD 4·8) % run-in).

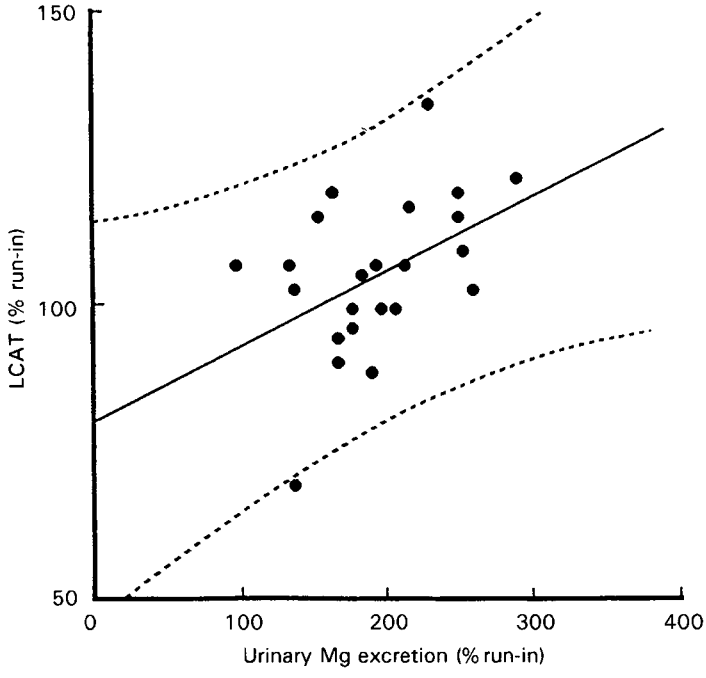

Fig. 1. Plot of urinary magnesium excretion (x) *v.* lecithin-cholesterol acyl transferase (LCAT) activity (y) in a group of Japanese subjects receiving a magnesium supplement for 4 weeks. Values are expressed as a percentage of those measured during the run-in period. The fitted line is: $y = 0{\cdot}1261x + 80{\cdot}95$, r 0·462.

Fig. 1 demonstrates the correlation between values for LCAT in week 4, expressed as a percentage of the run-in period and those for urinary Mg excretion in the Mg group. A significant positive correlation was observed between the two variables (r 0·462, $P = 0{\cdot}027$). The distribution of residuals had an approximately normal form. A significant positive correlation was also observed between the week 2 values for LCAT expressed as a percentage of those for the run-in period and those for urinary Mg excretion (r 0·471, $P = 0{\cdot}031$) in the Mg-group.

The doses of $Mg(OH)_2$ were well tolerated by both men and women and no complications of either diarrhoea or other adverse effects were observed.

DISCUSSION

The results of the present double-blind, placebo-controlled study indicated that, in middle-aged subjects of both sexes, oral Mg supplementation for 4 weeks produced significant increases in the urinary excretion of Mg and aldosterone, serum Mg, apo-AI, LCAT and packed cell volume, as well as significant decreases in the blood pressure and LDL-cholesterol in comparison with the run-in period. However, no such changes were found in the P-group.

Several reports (Marier, 1982; Rayssiguier, 1984, 1986; Luthringer *et al.* 1988; Zhou *et al.* 1994; Bussiere *et al.* 1995) have suggested that oral supplementation with Mg may be beneficial only in subjects with a low Mg status and, therefore, may have little or no effect in subjects with a normal Mg status. The average dietary intake of Mg in the subjects was

Table 5. *Body weight, urinary volume, urinary aldosterone and catecholamine excretion, plasma renin activity, total protein and packed cell volume in healthy Japanese subjects receiving a magnesium supplement (Mg-group) or a placebo for 4 weeks*

(Mean values and standard deviations for ten subjects in the placebo-group and twenty-three subjects in the Mg-group)

	Placebo-group						Mg-group					
	Run-in		2 weeks		4 weeks		Run-in		2 weeks		4 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Body wt (kg)	56·0	7·8	55·8	7·8	57·3	8·5	57·4	7·7	57·2	7·6	57·3	7·8
Urinary volume (ml/d)	1668	546	1552	538	1657	455	1656	568	1892	721	1785	539
Urinary aldosterone (nmol/d)	7·76	5·55	9·71	6·93	9·15	7·49	8·04	3·88	8·32	3·61	9·15**	4·16
Urinary adrenaline‡ (nmol/d)	102·5	38·2	89·0	40·4	102·5	94·4	77·5	40·9	73·7	56·8	87·3	73·1
Urinary noradrenaline‡ (nmol/d)	1300	567	975	508	981	408	1283	1040	946	378	934	467
PRA‡ (ng/l·s)	0·25	0·22	0·22	0·25	0·19	0·08	0·17	0·11	0·17	0·08	0·17	0·08
Total protein (g/l)	67	3	66	4	67	3	69	4	70	3	69	4
Packed cell volume	0·38	0·04	0·39	0·02	0·41	0·04	0·38	0·04	0·39**	0·04	0·40***††	0·03

PRA, plasma renin activity.

Mean values were significantly different from those for the run-in period: ** $P < 0·01$, *** $P < 0·001$.

†† Mean value was significantly different from that at 2 weeks, $P < 0·01$.

‡ Analysis was intended to transform the data to near normal form before testing by logarithmic change.

Table 6. *Serum total cholesterol, HDL-cholesterol, LDL-cholesterol, triacylglycerol, apolipoprotein (apo)-AI, lecithin-cholesterol acyltransferase (LCAT) and insulin concentrations in healthy Japanese subjects receiving a magnesium supplement (Mg-group) or a placebo for 4 weeks*

(Mean values and standard deviations for ten subjects in the placebo-group and twenty-three subjects in the Mg-group)

	Placebo-group						Mg-group					
	Run-in		2 weeks		4 weeks		Run-in		2 weeks		4 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total cholesterol (mmol/l)	5·24	0·62	5·11	0·48	5·09	0·58	5·38	1·06	5·29	1·09	5·34	1·09
HDL-cholesterol (mmol/l)	1·30	0·32	1·41*	0·34	1·35	0·34	1·28	0·35	1·28	0·37	1·37*†	0·34
LDL-cholesterol (mmol/l)	3·50	0·66	3·24	0·44	3·22	0·60	3·52	1·10	3·43	1·11	3·25**†	0·97
Triacylglycerol (mmol/l)	0·97	0·45	1·01	0·56	1·14	0·56	1·08	0·56	1·14	0·59	1·21	0·73
Apo-AI (mg/l)	1434	189	1392	195	1386	200	1362	203	1355*	211	1386†	195
LCAT (nmol/ml)	67·8	9·0	76·9	13·6	71·0	10·3	68·7	14·5	66·1	15·6	72·1†††	14·9
Insulin‡ (pmol/l)	28·7	12·2	30·1	17·2	28·7	10·0	40·9	17·2	42·3	22·2	45·9	17·9

Mean values were significantly different from those for the run-in period: * $P < 0·05$, ** $P < 0·01$.
Mean values were significantly different from those at 2 weeks: † $P < 0·05$, ††† $P < 0·001$.
‡ Analysis was intended to transform the data to near normal form before testing by logarithmic change.

about 225 mg/d. The recommended dietary allowance (Health Promotion and Nutrition Division, Health Service Bureau, Ministry of Health and Welfare, 1994) is 300 mg/d for Japanese people, so there is a considerable shortfall of Mg intake, but this is not an abnormal intake for Japanese individuals.

Previously Motoyama *et al.* (1989) found that a 4-week study of oral Mg supplementation to hypertensive patients significantly decreased both the blood pressure and intraerythrocyte Na concentration, although the plasma aldosterone level did change significantly after Mg supplementation. Saito *et al.* (1988) reported that the blood pressure decreased after Mg supplementation through an effect on Na–K ATPase (*EC* 3.6.1.3) in patients administered thiazide, although the urinary aldosterone and noradrenaline excretion levels were not measured.

In the present study the blood pressure decreased during Mg supplementation and this decrease was accompanied by an increase in urinary Mg excretion. Two of the main hormone systems involved in blood pressure regulation are considered to be the sympatho-adrenergic and renin–angiotensin–aldosterone systems. We found a significant negative correlation between the urinary noradrenaline excretion and the urinary Mg excretion values for week 2 (expressed as a percentage of the run-in value) and for week 4 (expressed as a percentage of the week 2 value). Moreover, a significant positive correlation was also observed between the values for urinary noradrenaline excretion and diastolic blood pressure measured in week 4 (% run-in value). These results together with our previous findings (Itoh *et al.* 1994) suggest that oral Mg supplementation might decrease the blood pressure through a decrease in the adrenergic activity which may be involved in the urinary excretion of noradrenaline. The vaso-relaxant activity of Mg is related to interference with Ca permeability in the cellular membrane. Ca binding and translocation in the vascular smooth muscle cells were obtained (Altura & Altura, 1995). The levels of serum Mg and urinary Mg excretion increased during Mg supplementation but not free Mg^{2+}, which is considered to decrease the blood pressure through the vaso-relaxant activity of Mg. These findings also suggest that the natriuretic phenomenon may occur through the activation of prostaglandin-I_2 (PGI_2) after Mg supplementation (Nadler *et al.* 1987) although PGI_2 was not measured in the present study.

A significant decrease in serum LDL-cholesterol and a significant increase in apo-AI concentration were observed after 4 weeks supplementation in the Mg-group. Only a few studies have evaluated the effects of oral Mg supplementation on blood lipid composition in human subjects (Davis *et al.* 1984; Rasmussen *et al.* 1988, 1989). Davis *et al.* (1984) found that the treatment of sixteen patients with hyperlipidaemia for a period of 118 d with an oral dose of 18 mmol Mg/d significantly reduced the total cholesterol, LDL-cholesterol, and VLDL-cholesterol concentrations and increased HDL-cholesterol, although their study was not placebo-controlled. Rasmussen *et al.* (1989) have reported that Mg treatment is associated with a decrease in the apo-B and LDL-cholesterol concentrations and an increase in the apo-AI : apo-B ratio. LCAT, however, was not measured in their study. Oral Mg supplementation in patients with hypertension has been reported to decrease significantly the concentrations of serum triacylglycerol and free fatty acid, but not total cholesterol (Rasmussen *et al.* 1989). None of the previous studies (Davis *et al.* 1984; Rasmussen *et al.* 1988, 1989), however, has suggested a mechanism for the hypolipidaemic effects of Mg supplementation. Thus, the physiological and biochemical background to the beneficial effect of Mg therapy on blood lipid concentrations still remains to be elucidated.

In the present study we found that the serum LCAT activity increased significantly during Mg supplementation. This is the first report relating Mg supplementation to LCAT activity in human subjects. In the Mg-deficient rat (Gueux *et al.* 1984) there was a reduced

activity of plasma LCAT, and a reduced insulin response after the intravenous administration of glucose, suggesting that Mg deficiency leads to a depressed insulin response after glucose administration (Gueux & Rayssiguier, 1983). Severe Mg deficiency in weanling rats produces a marked hypertriacylglycerolaemia, a decrease in cholesterol transport by HDL-cholesterol and a reduction of LCAT activity (Rayssiguier *et al.* 1981; Luthringer *et al.* 1988). In addition, the reduction of LCAT activity can reduce the formation of cholesterol esters in HDL and impair transport and disposal of triacylglycerol (Rayssiguier *et al.* 1981). The relationship between LCAT activity and serum lipid levels was investigated in patients with acute myocardial infarction, patients with CHD and healthy control subjects (Rayssiguier *et al.* 1981). The LCAT activity decreased significantly in the atherosclerotic patients, in comparison with the healthy control group (Solajic *et al.* 1991). A decrease in the LCAT activity was accompanied by elevated levels of phospholipids and LDL-cholesterol, a moderate increase in triacylglycerol and a decreased quotient of HDL3 : HDL2 cholesterol in atherosclerotic patients as compared with normal subjects (Solajic *et al.* 1991).

It is already well known that the LCAT reaction is activated by apo-AI and apo-C in human subjects (Soutar *et al.* 1975). The present study demonstrated an increased apo-AI concentration after 4 weeks of Mg supplementation similar to that reported by Soutar *et al.* (1975). The coefficient for urinary Mg excretion was also significantly associated with the LCAT activity based on a Pearson's correlation analysis. Recent findings also indicate that Mg deficiency modulates hepatic lipogenesis and apolipoprotein gene expression in the rat (Nasir *et al.* 1995), but the origin of the decrease in plasma apo-AI concentration is unclear. These findings may suggest that a clarification of the role of Mg in activating specific apoproteins may be of great future interest.

Some of the potential limitations of the present study include: the relatively small sample size, the short-term follow-up periods and the fact that no crossover study was performed.

It is well documented that high concentrations of HDL-cholesterol and apo-AI, and low concentrations of LDL-cholesterol, together with lower blood pressure, reduce mortality of strokes and IHD. While, in the present study, oral Mg supplementation has been documented to reduce blood pressure and improve the lipid metabolism, further studies are still required to confirm the beneficial effects of oral Mg supplementation on blood pressure and lipid metabolism in patients with hypertension and IHD.

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