British Journal of Nutrition (2010), **103**, 469–472
doi:10.1017/S0007114509992716

Short Communication

Effects of magnesium on postprandial serum lipid responses in healthy human subjects

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(Received 1 April 2009 – Revised 11 September 2009 – Accepted 19 September 2009 – First published online 27 November 2009)

Postprandial hyperlipidaemia has been recognised to be a risk factor for atherosclerosis development. Epidemiological and animal studies have shown that Mg intake is inversely associated with some risk factors of atherosclerosis, including lipid metabolism. The present study was performed to determine the effects of Mg supplementation on postprandial responses in serum lipid levels. We used bittern (*Nigari*, in Japanese), a natural $MgCl_2$ solution from sea or salt lake water, for Mg supplementation. In a two-way, randomised, crossover study, sixteen healthy male volunteers consumed 30 g butter with or without 5 ml bittern containing 500 mg of Mg. Fasting and postprandial blood samples were taken 2, 3, 4 and 6 h after ingestion. Postprandial lipid responses were evaluated by serum TAG, chylomicron TAG, apo-B48, remnant-like particle cholesterol (RLP-C) and NEFA concentrations. We found that the serum and the chylomicron TAG responses after the fat load were reduced and delayed by Mg supplementation. The concentrations of apo-B48 ($P<0{\cdot}05$), RLP-C ($P<0{\cdot}05$) and NEFA ($P<0{\cdot}05$) were significantly lower at 2 h after the fat-with-Mg meal compared with the fat-only meal. The present study indicated that Mg supplementation could inhibit fat absorption and improve postprandial hyperlipidaemia in healthy subjects.

Magnesium: TAG: Remnant lipoprotein: Postprandial hyperlipidaemia

CHD remains one of the leading causes of mortality in developed countries. Some prospective studies have shown the importance of postprandial TAG responses in the aetiology of CHD. Postprandial hyperlipidaemia is characterised by elevated levels and long residence of TAG-rich lipoproteins, such as chylomicron and VLDL remnants, in the circulation[1]. Recent data have shown that these postprandial TAG-rich lipoprotein remnants are atherogenic[2,3]. High TAG concentrations also evoked other atherogenic factors, such as low HDL-cholesterol concentrations, increase of small LDL particles and insulin resistance[4,5].The suppression of postprandial lipid responses is thus considered to be an important way to reduce the risk of CHD.

Epidemiological studies reported an inverse association between dietary Mg intake and incidence of CHD[6,7]. Since 1950, drinking water hardness has been known to associate with marked geographical variation in death rates from heart disease[8]. Mg is the fourth most abundant cation in the body and the second most abundant cation in intracellular fluid. Mg plays as a cofactor for over 300 cellular enzymes, many of which are involved in energy metabolism and is needed for normal vascular tone and insulin sensitivity. Mg is an essential mineral with several dietary sources, including whole grains, green leafy vegetables, legumes and nuts. Mg intake may be important in maintaining intracellular Mg homeostasis. In prospective studies, dietary Mg intake was inversely associated with the incidence of type 2 diabetes[9,10] and hypertension[11,12]. However, the pathophysiologic mechanisms underlying these observed beneficial effects of Mg intake are not fully understood.

In the present study, we used bittern (*Nigari*, in Japanese) for Mg supplementation. Bittern is a natural $MgCl_2$ solution from sea or salt lake water and is used in Japan as a coagulator of tofu (bean curd). We focused our attention on bittern with high Mg contents as a natural Mg supplement. Previous reports have evaluated the effect of oral bittern supplementation for 30 d on blood lipid composition in patients with type 2 diabetes[13].

Abbreviation: LPL, lipoprotein lipase.

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The present paper aimed to study the immediate effects of one-time Mg supplementation on postprandial hyperlipidaemia using a fat load test on healthy subjects.

Subjects and methods

Subjects

Sixteen healthy male volunteers were recruited for the study. Their mean age was 41·7 (SEM 2·6) years, and the average BMI was 24·5 (SEM 0·9) kg/m^2. Subjects with Mg metabolism disorders such as renal disease were excluded. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the ethics committee of Ochanomizu University. Written informed consent to participate in the study was obtained from all the subjects.

Experimentation protocol

All the subjects participated in two random order trials spaced at least 1 week apart. On the evening before an experiment, the subjects ate a standardised dinner. After over 12 h of fasting, blood samples were collected between 08.00 and 09.00 hours. Subjects then ingested a bread roll and 30 g butter with or without 5 ml bittern containing 500 mg of Mg. The meal contained 1369 kJ; energy derived was 74 % from fat, 22 % from carbohydrate, 4 % from protein. The bittern 'MAG21' was kindly obtained from Matier, Co. Ltd (Tokyo, Japan). This is a high-concentration $MgCl_2$ solution with low NaCl from a salt lake, Lake Deborah West (Australia). It contained 10·5 % (w/v) of Mg, 1·2 % of K, 0·2 % of Na, 0·01 % of Ca and small amounts of other trace elements, such as Zn, Mn, etc. Postprandial blood samples were taken 2, 3, 4 and 6 h after the end of ingestion.

Biochemical analyses

Serum was separated from whole blood by centrifuging at 3000 rpm for 20 min. We carried out biochemical analyses of serum TAG and NEFA using enzymatic methods. The lipoprotein lipid profiles were analysed using agarose gel electrophoresis (Helena Laboratories, Saitama, Japan). apo-B48 concentration was determined by using apo-B48 CLEIA kits (Fujirebio, Tokyo, Japan), and remnant-like particle cholesterol (RLP-C) concentration was analysed by immunoseparation assay with JIMRO-II RLP-C assay kits (Otsuka parmaceutical, Tokyo, Japan). Serum Mg and Ca concentrations were determined by enzymatic methods with Mg test kits (Wako Pure Chemical, Osaka, Japan) and calcium test kits (Roche Diagnostics, Mannheim, Germany).

Statistics

All data were expressed as means with their standard errors and analysed by repeated measures ANOVA followed by Dunnett's test using GraphPad Prism 5.0 (GraphPad Software, El Camino Real, CA, USA). Values of $P<0·05$ were considered statistically significant.

Results

All the subjects were able to follow the study protocol without difficulty. No adverse effects such as diarrhoea were reported during or after the testing sessions. There were no significant differences in the baseline levels of the serum TAG and cholesterol between the two different sessions (data not shown).

Fig. 1(a) shows the postprandial responses in the serum TAG following the ingestion of 30 g butter with or without 5 ml bittern. The serum TAG levels significantly increased over the first 4 h after the fat-only meal. When bittern had been added to the fatty meal, the serum TAG levels gradually increased and reached the maximum level at the 4 h after ingestion. The difference between the two sessions was statistically significant at the 2 and 3 h after ingestion ($P<0·05$, respectively). The chylomicron TAG responses reflect the absorption of fat from the intestine. As shown in Fig. 1(b), the maximum level of chylomicron TAG was 5·8-fold above the baseline in the fat-only session (at 3 h) and 3·6-fold in the fat-with-Mg session (at 6 h). Mg supplementation significantly decreased the chylomicron TAG responses at the 2, 3 and 4 h after ingestion and delayed the time it took to peak. The apo-B48 level was used to monitor acute chylomicron or chylomicron remnant changes over the postprandial period. As shown in Fig. 1(c), Mg supplementation produced a significant delay in the initial (0–2 h) postprandial apo-B48 response to the fat-only meal ($P<0·05$). Similar to the change in the serum TAG, the RLP-C concentrations were lower in the fat-with-Mg session during the 4 h after ingestion (Fig. 1(d)). Postprandial NEFA concentrations in the fat-with-Mg session were significantly lower than those in the fat-only session at 2–4 h (Fig. 1(e)).

We also measured serum Mg and Ca concentrations to investigate whether both major divalent cations in the bittern influence the postprandial lipid responses. The serum Mg levels in the fat-with-Mg session were significantly higher at all time points within the 6-h postprandial period than those in the fat-only session (Fig. 1(f)). In contrast, there were no significant differences in Ca levels between the two sessions (data not shown). Cholesterol levels in the serum and each lipoprotein particles were measured, but no significant changes were observed (data not shown).

Discussion

The present study evaluated the effects of Mg supplementation on postprandial fat absorption in a single fat load test. The major finding was that Mg supplementation improved postprandial hyperlipidaemia in healthy subjects.

Hyperlipidaemia is an independent risk factor for CHD and can occur even in healthy subjects in the postprandial state. Thus, suppression of intestinal absorption of dietary fat might be clinically useful. Recently, some food factors such as dietary fibres and flavonoids are known to attenuate the postprandial increase of serum TAG concentrations. We previously reported that tea catechins suppressed the postprandial TAG responses in human subjects[14].

In the present study, Mg supplementation reduced and delayed the postprandial increases of serum and chylomicron TAG. Several studies, in both animals and human subjects, have shown that dietary intake of divalent cations, such as Mg and Ca, increases the faecal excretion of fat[15–17].

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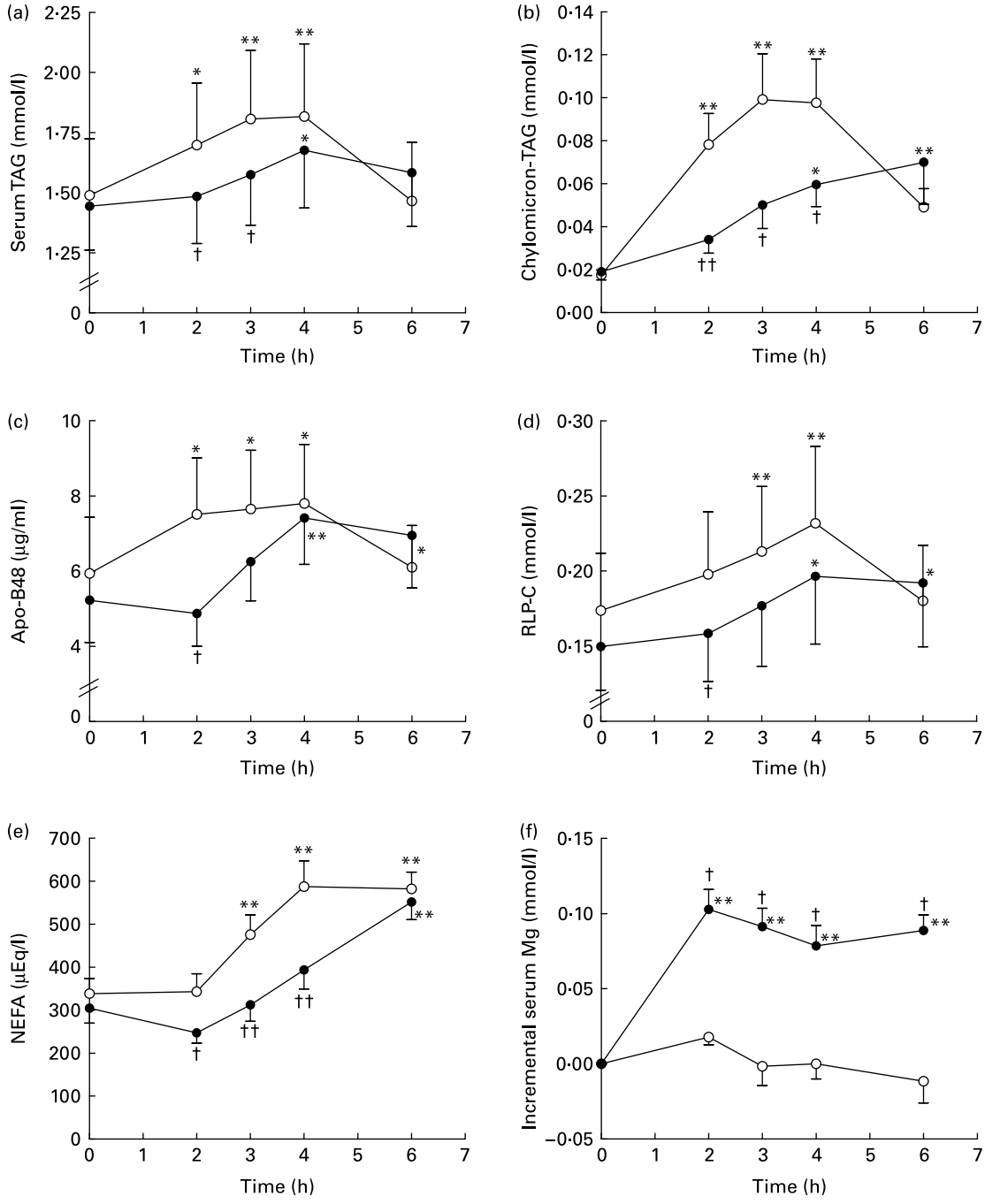

Fig. 1. Postprandial changes in serum TAG (a), chylomicron TAG (b), apo-B48 (c), remnant-like particle cholesterol (RLP-C) (d), NEFA (e) and Mg (f) after ingestion of the fat-only meal (○) and fat-with-Mg meal (●). Values are means with their standard errors. $^{**}P<0{\cdot}01$, $^{*}P<0{\cdot}05$ *v.* 0 h in each group. $\dagger\dagger P<0{\cdot}01$, $\dagger P<0{\cdot}05$ *v.* fat-only meal at each time point.

Such an effect has been attributed to the ability of these divalent cations to form insoluble salt complexes with fatty acids or form complexes with bile acid derivatives to reduce their absorption[18,19]. Bittern is the complex mixture containing a variety of minerals, mainly Mg. In the present study, serum Mg concentrations after bittern intake were significantly increased, while no significant changes in Ca concentrations were observed. These facts suggest that Mg may be responsible for the suppression of postprandial hyperlipidaemia by promoting the formation of insoluble compounds and the excretion of fat.

Another possibility is that Mg may increase chylomicron clearance. Chylomicron clearance, both lipolysis and hepatic uptake, is sensitive to lipoprotein lipase (LPL) activity. Mg is known to be a cofactor for LPL. Since decreased activity of LPL due to Mg deficiency causes hyperlipidaemia in diabetics[20], the reduced TAG levels after long-term Mg supplementation therapy in diabetics might reflect its increase of LPL activity. However, the present study was designed for a one-time ingestion test in healthy subjects, so it seemed that Mg supplementation might not influence the LPL activity.

In addition, the unaffected concentrations of NEFA suggested that Mg supplementation might not affect the chylomicron clearance. It is therefore most likely that the decreased postprandial lipid response by Mg supplementation was due to inhibition of fat absorption.

Experimental studies suggest that plasma accumulation of remnant lipoproteins is not just an associated feature of an atherogenic lipoprotein profile, but that TAG-rich lipoprotein remnants themselves contribute to the pathogenesis of atherosclerosis. Chylomicron remnants in the intima are derived from postprandial lipoproteins[21,22], and TAG-rich lipoprotein can be taken up directly by macrophages without prior modification to form foam cells[23]. apo-B48 containing chylomicron remnants may contain up to forty times more cholesterol per particle than do LDL particles, and consequently, exposure and retention of apo-B48 containing postprandial lipoproteins in the arterial wall may pose a significant atherogenic risk[21]. In addition, endothelial dysfunction is associated with hyperlipidaemia because NEFA and TAG-rich lipoproteins impair insulin action and endothelial dysfunction. In the present study, Mg supplementation also suppressed the apo-B48, RLP-C and NEFA concentrations in the postprandial state. These results suggest that Mg supplementation may contribute to reducing plaque formation and improving endothelial dysfunction. Indeed, Mg supplementation reduced plaque size and atherosclerotic lesions in rabbits fed a high cholesterol diet[24] and apoE-deficient mice[25].

In conclusion, we found that Mg supplementation reduced and delayed the postprandial serum and chylomicron TAG responses after fat loading. These data indicate that Mg supplementation may be effective for preventing the atherogenic process in healthy subjects.

Acknowledgements

The present study was supported in part by Grant-in-Aid (15300252 to K. K.) from Japan Society for the Promotion of Science. Y. K. is supported by research fellowships of the Japan Society for the Promotion of Science for young scientists. Y. K. was responsible for data collection, data analysis and writing of the manuscript. M. T. contributed significantly to the design of the study, the carrying out of the experiment, interpretation and critical reading of the manuscript. H. U.-K. contributed to the design of the study. E. S. and M. I. assisted with experimental design. H. S. provided critical review. K. Y. provided important information related to magnesium. K. K. supervised the results and manuscript writing. There are no personal or financial conflicts of interest.

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