Dietary Factors Influencing Magnesium Absorption in Humans

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Abstract: Decreased Mg intake and low Mg status have been associated with a number of major health concerns such as diabetes mellitus type II, coronary heart disease, and osteoporosis. While information on Mg intake is available, relatively little is known on dietary factors influencing Mg bioavailability. While it is established that Mg absorption is based on a combination of a non-saturable and a saturable pathway, the nature of especially the latter mechanism is not well understood. Recently, stable isotopes have improved techniques available for the determination of Mg absorption from single test meals or supplements. Some inorganic Mg forms such as MgO seem of limited solubility in the intestine, suggesting low bioavailability. Recent studies have further added evidence that some commonly consumed dietary compounds, such as phytate and oxalate, can inhibit Mg absorption, presumably via complexation, preventing absorption from the small intestine. Phytate for example has been shown to decrease Mg absorption by up to 60%, in a dose dependent manner. On the other hand, fermentable dietary fibre, such as fructo-oligosaccharides, have been demonstrated to increase Mg absorption in humans by 10-25%, even though the underlying mechanisms remain to be elucidated. Future studies to investigate factors impacting Mg absorption are warranted.

Keywords: Mg-absorption, small intestine, large intestine, protein transporters, dietary fibre, chelates.

INTRODUCTION

Mg is an essential mineral for the human body, required for the activation of >300 enzyme systems, predominantly for those involved in energy metabolism for the activation of phosphate groups [1]. Mg intake in developed countries is in the range of 250-350 mg per day and capita [2, 3], whereas the recommended daily dietary intake, for example the dietary allowances (RDA) within the dietary reference intakes (DRI) for men and women 19-30 y of age are 400 mg and 310 mg, respectively [4]. Even though Mg deficiency per se with neuromuscular symptoms such as cramping [5], is rare and usually observed only in cases of chronic alcohol abuse [6] or in hospitalized, critically ill patients [7], low Mg dietary intake and low Mg serum levels have been associated with a number of chronic diseases including diabetes mellitus type II [8, 9], cardiovascular disease [10-12], osteoporosis [13, 14] and the metabolic syndrome [15, 16].

The average dietary Mg intake in Westernized countries has been reported of having decreased from approx. 400 mg/d in the early 20th century to about 350 mg/d in the eighties [17], probably due to the increased consumption of more processed foods such as refined cereals with lower nutrient density [18]. Despite data present about the intake of Mg based on surveys of food intake, less is known about Mg bioavailability, i.e. the amount that can be absorbed and used for its specific functions. This relative paucity in knowledge has been partly due to a lack of methods to assess factors influencing Mg absorption, partly due to a lack of knowledge of Mg absorption and transport within the human body. In sight of the growing number of people diagnosed with chronic diseases both in developed and in developing countries associated with mineral, including Mg dietary intake, it appears prudent to continue investigating food factors influencing their absorption. This review aims to summarize the current knowledge on dietary factors with a potential impact on Mg absorption in humans.

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MECHANISM OF Mg ABSORPTION IN THE SMALL INTESTINE

As opposed to other minerals such as calcium and iron, Mg homeostasis is not known to be regulated by hormones but depends mostly on gastrointestinal absorption and reuptake by the kidney. Unlike Mg intestinal absorption, however, Mg re-absorption by the renal tubes has been shown to be influenced by hormones such as parathormone and norepinephrine [19-21], the presence of other salts and proteins [22], diuretic compounds such as caffeine [23] or alcohol [24], and many other factors. Due to the limited scope of the present review, renal handling of Mg is not discussed here, and the reader is referred to comprehensive reviews [25-27].

Intestinal Mg absorption in humans takes place primarily in the small intestine [28], and, according to the majority of studies [reviewed by 29, 30] especially in the more distal segments, i.e. the ileum. However, as Mg absorption starts already 1 hr following ingestion, as tested with the plasma appearance of ^{28}Mg radioisotopes [31] or stable isotopes [32], it can be concluded that some Mg can be absorbed in the proximal parts of the small intestine, i.e. the duodenum and jejunum. Recently, there is evidence that Mg can also be absorbed in the colon, as suggested by increased Mg absorption following the ingestion of dietary fibre fermentable by colonic bacteria, including fructo-oligosaccharides [33] and polyols [34]. However, the small increase in fractional Mg absorption based on these studies from 30.2% to 33.9% and 39.8% to 50.5% respectively, indicates that the potential for increased colonic absorption is limited. However, participation of the colon in Mg absorption is further supported by

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studies in ileostomists, which tend to have a low Mg absorption compared to healthy subjects, between 7 and 25 % apparent fractional Mg absorption [35, 36].

The mechanism of Mg absorption from the intestinal mucosa into the bloodstream is not entirely understood. Two major mechanisms of Mg absorption have been proposed, a saturable (transcellular) and a non-saturable (paracellular) process. Several authors have identified a curvelinear relation between the amount Mg ingested and its fractional intestinal absorption [37-39], which can be described as a combination of a hyperbolic function of absorption at low Mg doses (< 5 mmol) and a linear function dominating at higher Mg amounts (>5-10 mmol). The presence of a saturable process could indicate the presence of a transporter protein for transcellular uptake, as permeability of the lipid cell layers to hydrophilic Mg is very low, or a protein regulating at the level of the tight junctions between cells. In contrast, a non-saturable process would indicate passive (paracellular) diffusion. In fact, a protein regulating at the tight junctions and related to the occurrence of familial hypomagnesemia has been identified as paracellin-1, also known as claudin-16, so far however only in the kidney [40, 41]. However, the existence of an inherited genetic disorder for primary hypomagnesemia together with secondary hypocalcaemia (HSH) including decreased Mg intestinal absorption [42, 43] indicated the presence of an active transport system required for Mg uptake across the human epithelium in the intestine, which was later identified by Schlingmann *et al.* [44] and Walder *et al.* as TRPM6 [45]. It is only within the last years that we begin to gain some knowledge on the nature of this active, transcellular transport mechanism, as a number of transport proteins for Mg have been identified.

As of to date, at least four such transporter proteins for Mg cellular (re)uptake have been described in humans, Mrs2 [46, 47], the SLC41 homologue of MgtE [48], MagTI [49], and TRPM6/TRPM7 [50, 51]. These transporters lack similarity to other human mineral transporters, as these must possess unusual properties in order to regulate Mg up-take, due to the extreme ratio of the volume of the hydrated to the dehydrated Mg ion (>400), as the uptake through the transporters is thought to require removal of the hydrate shell [48]. While the importance of some of these transporters (TRPM6/TRPM7, MgtE and MagT1) for Mg re-uptake by the kidney is relatively well understood [50, 52, 53], only little is known about their contribution to active absorption in the intestine.

Mrs2 was the first transport protein described to be of importance for Mg transport in humans. In vertebrates, it seems to be restricted to regulate Mg transport through the mitochondria membrane [54]. Mrs2 belongs to the CorA family of Mg transporters which was first detected in *Escherichia coli* but is present in a variety of bacteria and yeast [48]. While the CorA homologue in yeast is well characterized, scant information is present about the Mrs2 essentiality in Mg homoeostasis in humans [48, 55]. As CorA in bacteria is also known to transport other minerals such as Co^{2+} and Ni^{2}+ [56], it seems likely that the Mrs2 is also not specific for Mg transport.

MgtE belongs to the SLC41 class of solute carriers. In contrast to CorA homologues, they are widespread in eukaryotes including humans, and are expressed at a high level in a variety of tissues [57]. SLC41A1 and SLC41A2 have been characterized in frog cells of *Xenopus laevis* oocytes [49, 58, 59] and were found to transport a variety of divalent ions through the cell plasma membrane, such as Zn^{2+}, Fe^{2+}, and Co^{2+}, suggesting SLC41A1 and SLC41A2 could play a role in the regulation of transcellular Mg transport in humans [60], including intestinal absorption.

MagT1 is homologue to the yeast OST (oligosaccharyl transferase) transporter. While relatively high concentrations of MagT1 are present in the tubes of the kidney, concentrations in especially the small but also the large intestine are relatively low [49]. This is in contrast to TRPM6 (transient receptor potential melastatin 6) which is apparently expressed in relatively high concentrations in the intestine [61]. There is evidence that MagTI is quite specific for Mg uptake [49], while TRPM6 is also known to regulate uptake of calcium and probably of zinc, cobalt and molybdenum [50]. Understanding more about the factors influencing uptake of Mg through these channels will help gaining more insight on dietary factors impacting Mg absorption.

For Mg uptake into the bloodstream following transcellular uptake, Mg has to leave at the basolateral site of the cell, against an electrochemical gradient. Thus, while no metabolic energy seems to be required for Mg uptake, cellular extrusion at the basolateral site of the enterocytes would be energy dependent [62]. This cell-exclusion would require either a primary Mg (ATP dependent) pump or a secondary active transport (Mg^{++} /$2Na^{+}$ exchange), however, no data is available on the favoured mechanism.

As the daily intake of Mg is usually in the range of 12-17 mmol, with meals contributing around 3-6 mmol, with the active absorption process becoming saturated at about 5-10 mmol, it can be speculated that a significant fraction of Mg is absorbed based on this saturable process, with passive diffusion dominating only at higher oral Mg loads. At present, SLC41 and TRPM6/7 seem transporter proteins which could be of relevance for Mg intestinal absorption.

DIETARY FACTORS IMPACTING Mg ABSORPTION

AMOUNT Mg INTAKE

Studies based on the chemical balance technique to assess Mg absorption have indicated that a high oral Mg load decreases fractional Mg absorption [37]. Similar results have been obtained earlier by studies using radioactive ^{28}Mg [38, 63], but, interestingly, have not been carried out with stable Mg isotope approaches. Nevertheless, the overall data for suggesting a lower fractional Mg absorption at a high Mg oral load is strong (Table **1**). However, the fact that Mg absorption is not saturable strongly suggests that Mg absorption can occur via a passive mechanism without participation of an active transporter. For a typical intake of Mg such as from a meal, Mg absorption can be assumed to be in the range of 20-60%.

Table 1. Relation of Oral Mg Load and Mg Absorption

study		Mg load		
		low	**medium**	**high**
Graham *et al.* (1960), [63]	intake (mg/d)	23	243	550
	% Mg apparent absorption	76	44	24
	subjects (n)	13	13	13
Roth and Werner (1979), [38]	intake (mg/d)	32	102	304
	% Mg apparent absorption	48	29	20
	subjects (n)	23	23	23
Fine *et al.* (1991), [37]	intake (mg/d)	36	273	974
	% Mg apparent absorption	65	21	11
	subjects (n)	8	8	8

Mg ABSORPTION FROM WATER VERSUS TEST MEALS

For Mg to be absorbed in the intestine, it has to be present in a soluble, i.e. hydrated form. Next to keeping Mg in solution, the presence and uptake of water in the intestine has been shown to increase Mg absorption in the rat ileum and colon [64], suggesting the participation of a solvent drag mechanism. In the same study, the addition of sugar and urea showed to enhance the water flow across the intestinal membrane and therefore Mg absorption. It appears that the presence of a more complex meal containing carbohydrates can similarly enhance Mg absorption compared to intake from water alone [65], given that this meal does not contain compounds that may bind Mg and therefore inhibit absorption. Liquid meals, especially water, typically have a less complex matrix and contain smaller quantities of potential inhibitors of mineral absorption, such as phytate and oxalate. On the other hand, solid meals, due to their higher viscosity, could further prolong gastrointestinal passage time and therefore increase Mg absorption through prolonged interaction in the intestine; liquid meals have been shown to have a shorter gastrointestinal passage time than solid meals in the majority of [66-68] though not all studies [69]. However, relative high Mg absorption (59%) from mineral water has recently been reported [31], indicating that water can also be a good source of Mg. Given that a meal can increase Mg absorption, presumably mostly via the passive solvent drag mechanism, its effect may be speculated to be more pronounced at higher Mg intake such as from supplements, as compared to snacks or small meals.

TYPE OF Mg SALT

Physical properties, especially the solubility of the salt used for supplementation or fortification have been discussed in relation to Mg absorption. Estimating Mg bioavailability from different supplements has been carried out by a variety of studies. In general, studies involving *in vitro*-tests such as dialysability [70, 71], Caco-2 cells [72], animals, typically rats [73-77], and humans [37, 78-83] have been performed. However, many of those studies have their own limitations. While the majority of studies only compared a low number of supplements, often ≤3, studies did typically not differentiate between a one-time and chronic intake of supplements and associated absorption, or have methodological limitations, such as measuring not directly absorption but urinary excretion [78, 84-86], or plasma levels [78].

Due to its low cost and non-hygroscopic properties, Mg oxide (MgO) has been a frequently used supplement. However, the poor solubility (Table **2**) has been associated with low Mg bioavailability in humans when compared to Mg citrate [80], citrate and an amino acid chelate [78], aspartate hydrochloride [86] and compared to chloride, lactate, and aspartate [79]. Compared to Mg hydroxide carbonate however, another poorly soluble salt, MgO did not result in a significant difference in bioavailability in healthy subjects [82]. However, doses given in those aforementioned studies were relatively high (containing more than 250 mg of Mg, Table **3**). Studies in which lower amounts of Mg (50 and 100 mg) were administered did not indicate a significant lower absorption of MgO compared to Mg diglycinate in subjects with Crohn's disease [87] or subjects with ileal resections [88]. These results are further supported by earlier studies in rats: Mg chloride and Mg hydroxide-carbonate had slightly but significantly higher absorption compared to Mg sulphate, hydrogen phosphate, and silicate, and, in addition, Mg hydroxide-carbonate as compared to oxide [76] when added at the same concentration to the diet (20 or 40 mg/100 g). However, the addition of lower amounts of 4 mg/100 g of Mg as lactate, citrate, acetate, sulphate, oxide, chloride, phosphate and carbonate did not result in any significant difference in Mg absorption in rats [77]. It can thus be suggested that a high oral load of MgO, or another poorly soluble form, could result in incomplete dissolution of Mg in the acid pH of the stomach, leading to low Mg absorption in the intestine. In addition to differing oral loads, varying particle size might also explain different study outcomes, as, for example, a larger particle size of MgO has been indicated to go along with reduced bioavailability, as shown in cows [89].

There is very limited evidence that besides poorly soluble Mg compounds, there are significant differences in Mg

Table 2. Solubility of a Number of Mg Salts

type of salt	solubility in water at 20-25 °C (g/L)
Mg orthosilicate	insoluble*[1]
Mg orthophosphate	insoluble[1]*
Mg pyrophosphate	insoluble[1]*
Mg hydroxide carbonate	insoluble[1]*
Mg oxide	0.006[2]
Mg hydroxide	0.007[1]
Mg oxalate	0.4[1]
Mg carbonate	1.8[1]
Mg hydrogenphosphate (heptahydrate)	3[2]
Mg lactate	33[2]
Mg gluconate	160[3]
Mg citrate	200[2]
Mg sulfate	357[1]
Mg chloride	560[1]
Mg acetate	656[1]
Mg nitrate	712[1]

*insoluble indicating a solubility of below 0.001 g/L in water
[1]Lide (2004), [115]
[2]Weast (1989), [261]
[3]Zief (1973), [262]

absorption due to the type of salt. In a more recent study by Coudray *et al*. in Mg depleted rats [73], Mg absorption from 10 organic and inorganic salts (Mg as oxide, chloride, sulphate, carbonate, acetate, pidolate, citrate, gluconate, lactate, aspartate) were compared, using both chemical balance and stable isotope approaches. As the salts themselves were not labelled with stable Mg isotopes (an additional ^{26}Mg solution was administered), it remains unclear whether full equilibrium between the salts and the added $^{26}MgCl_2$ solution occurred. However, both chemical balance and stable isotope approach indicated significantly higher absorption of Mg gluconate compared to Mg carbonate and Mg sulphate, and Mg absorption from organic salts tended to be higher than from inorganic sources. A similar higher absorption from Mg gluconate compared to chloride in rats was also found by Dolinska and Ryszka [90]. In healthy humans on the other hand, intake of 390 mg Mg in form of Mg gluconate did not suggest higher bioavailability compared to a Mg chloride solution or slow releasing Mg tablets [83]. However, bioavailability differences between organic and inorganic Mg salts might again be explained most likely by better dissolution of the salts in the gut, or alternatively, by absorption following a different uptake mechanism, such as suggested for Mg diglycinate [88] or Mg in form of aspartate [91, 92]. When comparing compounds possessing a sterio-genic center, it might further be important to take the stereo-configuration into account. When comparing the L-, D-, and DL- forms of K, Mg- aspartate, it was shown that in rats, upon infusing, the D- form was more rapidly excreted compared to the DL- and L- form, indicating that the L-form is more rapidly incorporated into cells and therefore more bioavailable [91]. Future human studies comparing the bioavailability of different Mg salts at physiologic concentrations, both one time challenges and chronic intake are needed.

INFLUENCE OF OTHER MINERALS AND TRACE ELEMENTS ON MG ABSORPTION

Many minerals and all trace elements are consumed in considerably lower amounts in the diet than Mg. Minerals consumed in the average Western diet in amounts equal or higher than Mg are calcium, potassium, sodium, phosphorus, chloride, and sulphur [93, 94]. Thus, it appears unlikely that trace elements such as iron and zinc could significantly effect Mg absorption in a regular diet. The same is not necessarily true for supplementing at pharmacological doses. The intake of 142 mg zinc/d decreased Mg apparent absorption and balance in humans significantly [95], suggesting that both minerals competed with the same transport mechanism in the small intestine, even though it has been reported that Mg is primarily absorbed in the distal [29] and zinc in the proximal parts of the intestine [96]. Likewise, adding calcium, Mg, phosphorus, iron, copper, and manganese in excess to a human diet decreased absorption of the respective other minerals in an early study by De and Basu [97]. For example, addition of calcium to the diet in amounts ranging from 300 to 1000 mg/d decreased Mg absorption significantly in healthy subjects at Mg concentrations typically ingested with the diet (370 mg/d).

The effect of calcium on Mg absorption has been subject to some discussion [22, 98-100]. In the majority of the > 2 dozen rat studies reported in the literature, high levels of dietary calcium decreased Mg absorption. Most of these diets however were marginal in Mg and contained relatively high amounts of both calcium and phosphorus. Mg concentration in the human diet is typically less marginal and calcium and phosphorus concentrations are lower than in the rat diets. The majority of studies in humans did not indicate an effect of consuming up to 2000 mg calcium/d on Mg absorption [101-106]. Studies showing a negative effect of calcium on Mg absorption were based on diets containing marginal amounts of Mg and high amounts of phosphorus [107], or were based on perfusion [108] and not normal dietary intake.

In theory, high calcium (or other mineral) intakes could reduce active Mg absorption via competition for a common carrier, modulation of such a carrier by calcium, or via the paracellular pathway via calcium-induced change in the tight junction permeability to Mg. This latter hypothesis is supported by an earlier rat study suggesting reduced Mg absorption due to increased calcium intake, going along with reduced rate of net sodium and water uptake, supporting a passive solvent drag mechanism via the paracellular pathway [109]. Competition or modulation of an active carrier on the other hand would indicate that calcium would inhibit Mg absorption predominantly at low Mg intakes, as at higher Mg

Table 3. Studies Comparing Bioavailability of Different Magnesium Salts

study	subjects	form of Mg tested	amounts tested (as elemental Mg)	method used	results and comments
Walter *et al*. (1998), [71]	na	various concentrations of citric acid	120 mg/100g meal	dialysability	improved dialysability with 1% citric acid
Hilleke *et al*. (1998), [70]	na	citrate, aspartate, oxide	varying amounts in aqueous solutions	dialysability	82%, 85%, 53% dialysability for citrate, aspartate, oxide, respectively
Ekmekcioglu *et al*. (2000), [72]	Caco-2 cells (n=8 wells per group)	solutions containing: hydrogen-carbonate, sulphate, chloride	1,1-7,0 mmol solutions for 90 min.	Caco-2 uptake	negative impact of high hydrogencarbonate concentrations on Mg uptake
Cook (1973), [76]	rats (n=8 per group)	carbonate, chloride, oxide, phosphate sulphate, silicate	17.7-19.9 mg/d for 2 wks	chemical balance, plasma Mg, urinary Mg	carbonate and chloride better absorbable than phosphate, sulphate, and silicate; oxide absorption in between the 2 groups
Ranhotra *et al*. (1976), [77]	rats (n=8 per group)	lactate, citrate, acetate, sulphate, oxide, chloride, phosphate, carbonate	19 mg/100 g in the diet for 4 wks	chemical balance	no significant difference in Mg absorption from various sources
Feillet-Coudray *et al*. (2003), [74]	rats (n= 8 per group)	sulphate rich water, bicarbonate rich water, magnesium chloride	11-14 mg/d for 4 wks	stable isotope techniques	no significant difference between 3 groups; however, only 1/3 of Mg coming from the Mg supplements
Dolinska &Ryszka (2004), [90]	rat small intestinal segments	gluconate, fumarate, chloride	1, 5, and 10 mmol	plasma area under curve	at 1 and 5 mM gluconate most positive effects, at 10 mmol fumarate
Coudray *et al*. (2005), [73]	Mg deprived rats (n=8 per group)	oxide, chloride, sulphate, carbonate, acetate, pidolate, citrate, gluconate, lactate, aspartate	12-14 mg/d for 2 wks	chemical balance and stable isotope techniques	gluconate absorption significantly higher than sulphate and carbonate in both studies, tendency for higher Mg absorption from organic salts; however, salts themselves were not labelled, ^{26}MgCl was added to diets
Lindberg *et al*. (1990), [80]	17 healthy humans	citrate, oxide	25 mmol in 1 dose	urinary excretion	significantly higher bioavailability of citrate form
Bohmer *et al*. (1990), [84]	18 healthy humans	tablets containing: citrate/lactate, citrate/lactate/hydroxide, hydroxide, chloride	15-21 mmol/d for 1d	urinary excretion	no statistical differences found
Muhlbauer *et al*. (1991), [86]	24 healthy adults	L-aspartate tablets and granules, oxide capsules	30 and 45 mmol/d for all 3 formulations for 1 wk	urinary excretion	lower urinary excretion from oxide form; however, results not statistically significant different
Fine *et al*. (1991), [37]	8 healthy adults	acetate capsules, enteric-coated chloride tablets	7 mmol in single dose	chemical balance	significant higher absorption from acetate form
White *et al*. (1992), [83]	12 healthy adults	chloride solution, slow-release chloride tablets, gluconate tablets	16 mmol/d for 1 wk	urine, blood, intraleucocyte	no overall difference in bioavailability of the 3 forms, but different plasma appearance kinetics

(Table 3) Contd….

study	subjects	form of Mg tested	amounts tested (as elemental Mg)	method used	results and comments
Schuette *et al*. (1993), [87]	10 adults with Crohn's disease	diglycinate, oxide	50 mg single dose	stable isotope techniques	no difference in absorption; however, Mg absorption low throughout groups (ca. 24%)
Schuette *et al*. (1994), [88]	12 adults with ileal resections	diglycinate, oxide	100 mg single dose	stable isotope techniques	no difference in absorption; however, Mg absorption low throughout groups (ca. 24%)
Tobolski *et al*. (1997), [82]	16 healthy adults	Mg oxide, Mg hydroxide carbonate	each 600 mg/d, for 3 d	plasma Mg, erythrocytes, urine	no significant difference between the 2 formulations
Martin *et al*. (1998), [263]	47 healthy adults	gluconate, chloride	640-650 mg/d for 6 month	serum Mg	no significant difference between the 2 formulations; however, tendency for higher absorption from chloride form
Firoz&Graber (2001), [79]	16 healthy adults	oxide, chloride, aspartate, lactate	11 mmol/d for 1 d	urinary excretion	significant lower bioavailability from oxide form
Walker *et al*. (2003), [78]	46 healthy adults	amino acid chelate, citrate, oxide	300 mg/d for 1 d and 60 d	plasma Mg	citrate form significant higher plasma appearance than other forms in both trials

intake, passive diffusion would dominate, however, studies investigating systematically the effect of calcium on absorption of different Mg amounts are missing. It is further possible that high calcium concentrations in the diet decrease plasma PTH concentrations [110]; higher PTH concentrations have been associated with increased intestinal Mg absorption in humans [111].

Studies investigating both the effect of calcium and phosphate on Mg absorption might explain some of the contradictory results. Similar as for calcium, there is no consensus on the influence of dietary phosphorus alone on Mg absorption [22, 98, 112], even though a negative correlation between Mg and P absorption was found in healthy human subjects in one study [113]. Phosphorus is usually consumed in form of phosphate [114], and Mg-phosphates are poorly soluble at the pH of the small intestine, but more soluble at the pH of the stomach [115]. Thus, a high phosphorus intake could, in theory, contribute to poor Mg absorption. In a rat study, Brink *et al*. [116] showed that intake of calcium and phosphorus, but not calcium alone, decreased apparent Mg absorption significantly, indicating that an insoluble Mg-calcium-phosphate complex was formed. Earlier, Heaton *et al*. [117] had shown that increasing the dietary phosphorus content from 1250 mg/d to 3890 mg/d during 6 d balance periods decreased Mg absorption significantly in human subjects with disorders of calcium metabolism; it could however be speculated whether an impaired calcium absorption contributed to the findings. Decreased apparent Mg absorption from both 43% to 34% was further found by Greger *et al*. [118] in healthy subjects consuming a standardized diet containing 780 mg calcium and 843 mg/d phosphorus compared to a diet containing 2382 mg calcium and 2443 mg phosphorus/d and a diet containing 780 mg calcium and 2443 mg phosphorus/d during 12 d. No influence on the other hand of supplemental phosphorus on apparent Mg absorption was found in an early study by Leichsenring *et al*. [102] between a diet containing 1500 mg calcium, 260 mg Mg, 800 mg phosphorus and a diet containing additional 600 mg phosphorus during 4 wk periods. However, the limited number of subjects (n=3) and the low amount of supplemented phosphorus might have limited the interpretation of the results. In conclusion, there are some indications that high amounts of phosphorus in the diet, especially together with high dietary calcium intake, might decrease Mg absorption.

No human studies have systematically investigated the influence of sodium on Mg absorption. Studies with rat gut sacs *in vitro* [119] or rat ileum *in vivo* [109] suggested that sodium ions might enhance Mg transport through the epithelial membrane, but balance studies in rats in which sodium was added to the diet at up to 3.1% (w/w) could not demonstrate a systematic effect on apparent Mg absorption. Similarly, dietary intake of potassium at 0.1-1.9% within the diet (w/w) showed no effect on Mg absorption in the majority of rat studies [22]. In humans, Fisler *et al*. [120] found no significant change in Mg faecal excretion in a group supplemented with 2300 mg potassium/d. It has been suggested earlier in sheep [121] and cows [122] that high amounts of potassium in the diet depolarize the apical membrane of the epithelial cells of the mucosa, reducing the driving force for Mg uptake. In summary, there is no evidence that sodium or potassium does influence Mg absorption in man.

PHYTIC ACID, OXALIC ACID, AND OTHER COMPLEXING AGENTS

a) Phytic Acid

Among the more potent inhibitors of mineral absorption in the diet is phytic acid, myo-inositol hexakisphosphate (Fig. **1**). Phytic acid is widely distributed in nature, all plant cells contain phytic acid [123]. In cereals, legumes, and oilseeds, it is the major storage form of phosphorus [124]. Foods based on wholemeal flour or bran contain high concentrations of phytic acid, typically in the range of 0.5% - 1.4% for wholemeal bread and up to 3.5% for bran, depending on the plant species [125]. In low extraction rate (white) cereal flours, the concentration of phytic acid is lower, as most phytic acid is removed with the outer layers of the grains. The daily dietary intake of phytic acid has been reported to be in the range of 180-800 mg/day in industrialized countries [126], and is therefore in a similar range than the Mg intake.

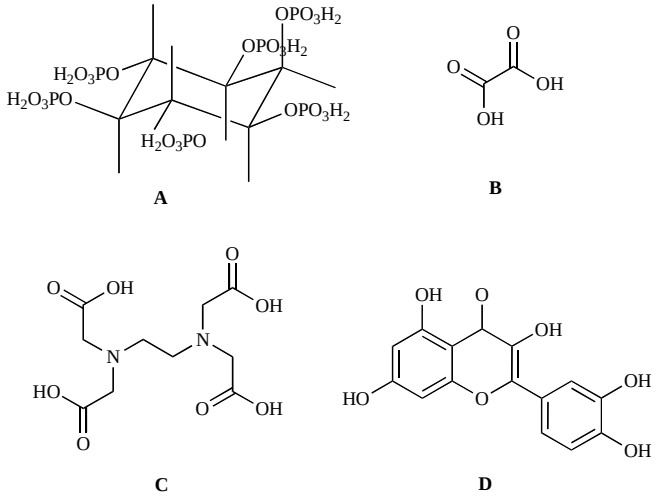

Fig. (1). Structure of phytic acid (A), oxalic acid (B), EDTA (C), and quercetin, a polyphenol (D).

It is assumed that insoluble complexes are formed in the gastrointestinal tract, both with dietary Mg and with endogenous Mg which are not absorbable. For Mg, it is assumed that Mg-phytate or protein-Mg-phytate complexes are formed which are insoluble >pH 6 [127, 128], even though it is assumed that Mg does not form very strong com-plexes with phytic acid. Based on calorimetric experiments at pH 3.6, the following order of stability between phytic acid and the respective mineral/trace element was suggested [129]: Cu>Zn>Mn>Mg>Co>Ni.

Phytate has been shown to decrease absorption of many nutritionally relevant minerals and trace elements in humans, including iron [130, 131], zinc [132, 133], calcium [134, 135], and manganese [136]. Studies in rats indicated reduced Mg apparent absorption when phytic acid was fed at concentrations between 0.6% and 1.2% mass in the diet [137-139], or from soybean protein at a molar ratio of phytic acid: Mg of ca. 0.5 [140]. However, not all rat studies found a significant negative effect of phytic acid on Mg absorption [141], although the Mg concentration in plasma in the latter study was decreased by 15%.

In an early study by McCance and Widdowson [142], phytate (0.6 g/d) added to white wheat bread indicated a significant reduction in Mg absorption from 47% to 29% in healthy volunteers when consumed during at least 14 d periods. Similarly, Mg absorption in humans was significantly lower when 3.5 g phytate/d in wholemeal bread was given compared to white bread in a study with 2 men over 20 d periods [143], however, other components in the bread such as fibre could have contributed to this observation, and Mg intake from the fibre rich diet was considerably higher. In a different study design, bran compared to dephytinized bran containing either 0.2 g or 2 g phytate/d reduced apparent Mg absorption in men significantly from 40 to 35% [144] when consumed during 15 d periods, even though dephytinization bears the risk of further changes in the bread matrix such as change of pH. In a more recent study using stable isotope techniques, the intake of phytic acid added to wheat bread in concentrations simulating brown and wholemeal bread significantly reduced Mg apparent absorption in a dose-dependent manner as opposed to phytate-free white bread, by up to 60% [145]. However, the lower fractional Mg absorption from wholemeal bread can be expected to be counterbalanced by the usually much higher Mg concentration present in wholemeal as opposed to white wheat bread [146, 147].

The exact mechanism by which phytic acid reduces Mg absorption remains to be elucidated. Brink *et al.* [148] found reduced apparent, but not true absorption in rats consuming soybean protein versus casein, suggesting higher endogenous Mg losses due to binding effects of phytic acid as the major cause of decreased apparent Mg absorption. Matsui *et al.* [137] on the other hand investigated the influence of a diet containing 0 versus 0.6% phytic acid on endogenous Mg losses in rats based on stable isotope techniques and found no significant increase in endogenous Mg. However, both methods were not based on dual isotope labelling approaches, and differences between the study designs, i.e. the methodological approaches and precision of isotopic ratio measurements might explain the different results. As phytic acid is only partly degraded in the rat and human gut [149], it seems likely that both Mg from the diet and Mg of endogenous origin might be chelated by phytic acid. The effect of phytic acid on mineral absorption depends on its degradation in the gastrointestinal tract. This can be influenced by natural phytase occurring in cereals and grains, or by bacteria present in the intestine. Rat studies suggested that the majority of phytate is broken down by dietary phytase [150, 151] rather than by endogenous phytase activity in the small intestine. The same would be valid for humans, as their bacterial phytase activity is much lower compared to rats [152]. However, as most diets possess no phytase activity because of inactivation by heat, it appears unlikely that phytate is broken down in the human intestine to a large extent. In conclusion, there is relatively strong data suggesting that phytate can reduce absorption of Mg, similarly as previously shown for Zn and Ca in humans. The degradation of phytic acid can also occur during food processing and preparation, leading to dephosphorylation of phytic acid and the reduction of its complexing capabilities

[153, 154]. Thus, ensuring long enough fermentation, as for example for bread, is a way to increase phytate breakdown and to increase mineral absorption [155], as is acidification [156].

b) Oxalic Acid

Oxalate (Fig.**1**) is ubiquitously found in plants, especially in the leafy parts, such as in spinach (over 1 g/100g, [157]) and rhubarb. However, there are also high amounts of oxalate in fruits, grains, nuts, tea, coffee, and cacao [147]. Daily dietary oxalate intake in industrialized countries such as the UK are in the range of 70-150 mg/d [158, 159], intake in developing countries consuming more vegetables could be higher, e.g. intake in India has been reported to vary between 78-2045 mg/d[160].

Oxalic acid can form poorly soluble complexes with a number of minerals at physiological pH, especially with divalent ions. For example, zinc, calcium, and Mg oxalates have low solubility in water at room temperature: 26, 6.1, and 400 mg/L, respectively [115]. Even though it is known that all 3 oxalate components are soluble in dilute acid, it is not known to what extent they dissolve in the stomach and release the minerals to mix with minerals of other dietary origin.

Oxalates in plants can be classified into insoluble (mostly calcium bound) and water soluble (potassium-, sodium-bound, or free) oxalates. Soluble oxalates are assumed to have a negative impact on mineral absorption due to the ability to bind free minerals in the small intestine, thus reducing their absorption. For spinach, around 15-20% of total oxalates have been reported to be soluble [147, 161], even though higher concentrations of soluble oxalic acid have also been reported, up to 93%; fruits usually contain about equal amounts soluble and insoluble oxalates [160].

Oxalate, especially its soluble forms, can partly be removed by cooking. In a study with Mg deficient rats by Kikunaga *et al*. [162], Mg absorption from a diet containing raw spinach was significantly lower compared to the same diet containing boiled spinach (about 50% of the oxalate was removed by boiling) or the control (same diet without spinach), even though the difference in absorption was small, absorption being 80.2% vs. 88.4% and 88.9%, respectively as deter-mined by chemical balance technique. On the other hand, supplementation of the control diet with 0.8% oxalate (as oxalic acid) had no significant effect on Mg absorption, suggesting that factors other than oxalic acid present in spinach reduced Mg absorption or different behaviour of added oxalic acid as compared to native oxalic acid, such as preferred binding of the added oxalic acid to calcium ions from the food matrix and incomplete dissolution of the complex in the gut.

Information regarding the influence of oxalate on Mg absorption in humans is scant. Mg has previously been shown to decrease absorption of oxalic acid in humans [163, 164], indicating that Mg oxalate complexes are formed which are not or only poorly absorbed. Kelsay and Prather [165] observed increased faecal Mg losses in human subjects when spinach was added to the diet during 4 wk periods containing 440 mg oxalate/d compared to the same diet containing cauliflower (175 mg oxalate/d). However, the Mg intake was significantly higher in the group receiving the spinach rich diet, increasing the risk of decreased fractional Mg absorption due to higher oral load.

Schwartz *et al.* [166] investigated Mg absorption from bran muffins containing spinach in healthy adults and found that is was not significant lower compared to muffins containing lettuce, bran, or turnip greens, but significantly lower than from collard greens, 48% vs. 54%. No information about the consumed amount oxalate or spinach was given, but from the data presented, it could be assumed that about 50-100 g of spinach were served [146, 147]. Thus, the amount oxalate consumed with the spinach based meal might have been too low to detect an effect on Mg absorption in only 4 subjects as compared to the other vegetable based meals. In a more recent study, Mg absorption from oxalate rich spinach was compared to kale, a botanically similar vegetable with a low oxalic acid content, using stable isotope techniques. This was similar as previously reported for decreased Ca absorption from high oxalate spinach versus kale or milk [167, 168]. Mg absorption from spinach was significantly lower, 26.7% as compared to 36.5%. However, the total amount Mg absorbed from spinach can be expected to be counterbalanced by the higher absolute amount of Mg typically present in spinach as compared to kale [146, 147]. In summary, there are a few studies suggesting that oxalate is likely to exert a negative impact on Mg absorption. Given the variable amounts of oxalate consumed within the diet, this fact deserves more attention and investigation.

c) Polyphenols

Polyphenols include a wide variety of aromatic compounds - over 8000 [169] - in plants containing at least 2 hydroxyl groups, such as flavones, anthocyanidines, lignins, and tannins (Fig. **1**). Only little information regarding the dietary intake of polyphenols are available, as a huge variety of chemical compounds are concerned and quantification is difficult. The major dietary sources of polyphenols include fruits and beverages, a total polyphenol intake of about 1 g/d has been estimated for the Western diet [170, 171] and the total polyphenol content in fruits, vegetables, and grains has been reported to be in the range of 0.04-0.6% [172]. This appears to be relatively low compared to other potential mineral inhibitors, e.g. phytate, especially when calculating molar ratios.

Polyphenols possess chelating properties and have been related to decreased absorption of iron in humans [173, 174], and zinc in rats [175]. However, no information is available on their influence on Mg absorption in humans. Because of the relative high amounts of Mg consumed within the diet and the lower stability of the Mg complexes as compared to iron and zinc [146, 147, 176], a potential negative effect on absorption may be assumed to be much lower. This has been confirmed in a rat study, where apparent Mg absorption was not influenced by up to 0.06 g/100g tannins in the diet [177], but by relatively high concentrations of 1 g/100g in the diet [178]. It could thus be hypothesised that diets rich in polyphenols, such as those in some developing countries, might have a somewhat negative impact on Mg absorption.

d) Other Compounds

Complexing agents might not necessarily enact a negative impact on mineral absorption. Weak chelators could also prevent minerals from being bound to other chelating complexes with a negative impact on absorption, given that they are weak enough to release the minerals in the small intestine or can be absorbed as a whole. For example, it has been shown that sodium EDTA can enhance absorption of iron from meals with a typical low iron bioavailability fortified with iron sulphate [179], probably by protecting iron from being complexed by phytic acid or other compounds with a negative impact on iron absorption. However, fortification of meals with sodium EDTA had no effect on Mg absorption in healthy infants [180], most likely due to the higher ratio of Mg to present potential inhibitors of absorption and the weaker strength of the Mg-EDTA complex as compared to iron-EDTA [181, 182].

Another reason for altered absorption can be the existence of different mineral pools of absorption. For iron, it is well known that heme-iron has a higher bioavailability than non-heme iron [183, 184]. It has further been speculated whether Mg in chlorophyll, a complex with structural similarity to the iron-protoporphyrin ring, could offer similar protection of Mg and be absorbed intact [185, 186]. It is known however that chlorophyll is unstable under acidic condition such as in the stomach [187], exchanging Mg as its central atom by 2 protons. In addition, it has also been demonstrated that Mg coming from chlorophyll constitutes only a minor source of dietary Mg, with probably less than 1% of total dietary Mg [188]. Furthermore, a human study comparing spinach intrinsically versus extrinsically labelled with stable Mg isotopes indicated no difference in the absorption between the labels, even though the analytical tools used to detect differences in absorption were rather of limited precision [166]. Another potential pool of Mg is Mg-bound to peptides. Mg-diglycinate has been suggested to be absorbed in part intact, predominantly in the jejunum, even though there was no significant difference in its absorption compared to Mg oxide in 2 studies by Schuette *et al.* [87, 88], but is has to be considered that these studies were carried out in subjects without or without a normal small intestine. In summary, there is no evidence that there exists a separate pool of Mg with higher Mg bioavailability.

PROTEIN AND FAT

A number of human studies have suggested a positive effect of proteins on Mg absorption. In an early human study by McCance *et al.* [189], dietary intake of 145-200 g protein/d as compared to the same diet containing 45-70 g protein/d during 14 d periods in a crossover study with healthy adults increased fractional apparent Mg significantly from 32% to 40%. Similarly, Schwartz *et al.* [190] found significantly increased absorption in adolescent boys consuming 265 compared to 125 mg protein/(kg x d) during 30 d periods in a randomized crossover trial. Even a lower difference in protein intake was found to influence Mg absorption; Hunt and Schofield [191] reported higher Mg apparent absorption in a balance study in subjects consuming 30 g as compared to 20 g protein/d and 48 g as compared to 34 g protein/d during 30 d periods, apparent Mg absorption being 46.1% versus 28.3% and 57.7% versus 42.4%, respectively. In support of these findings, Lakshmanan *et al.* [192] found that the amount protein consumed in self selected diets by healthy adults correlated negatively with Mg excretion in faeces, however, the effect was only significant in adults <35 years.

Studies showing no effect of dietary proteins on Mg absorption have also been reported, however, they tended to suffer from methodological limitations, namely that the Mg content in the diet was not standardized but was higher in the high protein diets, with the potential risk of decreasing fractional Mg due to higher oral Mg load [193-196]. Thus, a few human studies indicate a positive relationship between protein intake and apparent Mg absorption, even though the mechanism for this observation remains speculative. Verbeek *et al.* [193] found that a high as compared to a low protein (casein) diet balanced for Mg, calcium, and phosphorus increased apparent but not true Mg absorption in rats during 14 and 28 d periods, suggesting that a high protein intake might decrease endogenous Mg losses. It was suggested that phosphopeptides prevented the precipitation of calcium-magnesium-phosphate complexes in the ileum, increasing the solubility and absorbability of both dietary and endogenous Mg. However, it is important to consider the source of protein. Some vegetable proteins, such as soy, can be a source of phytate, with a potential negative impact on mineral, including Mg absorption [197]. In agreement with this consideration, a study with rats suggested higher Mg absorption from phytate-free soybean protein compared to soybean protein isolate [198]. Given the comparable high dietary protein intake compared to other food compounds, the potential impact of proteins on Mg absorption has attracted little attention.

In addition to proteins, lipids have been discussed to impact Mg absorption. In a study by Lopez- Aliaga *et al.* [199], casein was compared to casein given together with protein from cow milk and casein together with protein from goat milk, in small intestinal resected and transected rats. Mg absorption from casein and the casein plus cow milk was found to be significantly lower in both transected and resected animals, an effect which was attributed to the lower amount of medium chain triglycerides (MCT, C8-C12) present compared to the goat milk. Free fatty acids in the diet or those formed during enzymatic digestion of triglycerides can form insoluble soaps with Mg in the small intestine. MCT have been reported to form more soluble Mg soaps [22], and it has therefore been suggested that MCT increase Mg absorption compared to long chain triglycerides (LCT). It has further been reported that saturated fatty acids form more insoluble soaps with Ca and Mg than their corresponding unsaturated fatty acids [200]. In a rat study standardized for Mg intake, in which MCT were given together with olive and sunflower oil during 1 month periods, Mg absorption increased significantly as compared to olive oil alone [201]. Similarly, Mg absorption was higher in rats consuming a diet rich in palmitic acid as compared to a diet rich in long chain fatty acids [202]

No human studies have investigated the effect of MCT on Mg absorption in healthy adults. In patients with resections of the small intestine, no difference in Mg absorption was found when MCT replaced 50% of the LCT during 4 d

periods in a randomized crossover study [203]. However, absorption of Mg was very low, 5.4% with MCT versus 2.9% from LCT rich diets, impeding the finding of significant differences. In a study with healthy very low birth weight infants, Mg absorption increased significantly from 69 to 78% when a MCT instead of a LCT rich diet was given during 3 d balance periods standardized for Mg intake [204]. Similar results were obtained in a study including low birth weight infants consuming a diet standardized for Mg with either no, 40% or 80% fat as MCT's, a significant increase in Mg absorption from 58 to 85% was found in the group receiving the 80% MCT rich diet [205].

In addition to the fat composition, an increased fat intake per se has been discussed to increase Mg absorption [22], even though, due to formation of insoluble soaps, the opposite would have been expected. However, fatty acids can also form insoluble soaps with calcium, which has been controversially discussed to decrease Mg absorption. However, in the majority of rat balance studies [22] fat per se did not appear to influence Mg absorption. Human studies investigating fat intake and Mg absorption are scant and contradictory, due to differences in the diet and the type of fat ingested. Van Dokkum *et al*. [206] reduced dietary fat intake in otherwise similar diets during 1 month periods from 42 to 22% (energy) in healthy subjects and found no significant effect on Mg absorption. In addition, Ricketts *et al.* [207] also found no significant effect when decreasing dietary fat in US diets consumed by healthy subjects during 28 d periods in a crossover study. On the other hand, in a study by Kies *et al.* [208], subjects were given a diet high (40% of energy) and lower (30% of energy) in dietary fat during 28 d periods; Mg absorption was lower in the low fat diet (10 versus 27%), despite lower Mg intake in this group. In conclusion, although the replacement of MCT for LCT has been shown to increase Mg absorption in rats and infants, increasing the amount of dietary fat per se, has not shown a consistent effect on Mg absorption in the few studies conducted. As with proteins, the potential effect of fat on Mg absorption deserves more attention.

CARBOHYDRATES AND DIETARY FIBRE

Dietary fibre includes all substances that are not digested by human enzymes in the gastrointestinal tract. Dietary fibre can be categorized into non-fermentable fibre such as cellulose and lignin and fibre fermentable by some gut bacteria, such as oligosaccharides and resistant starch, even though there are many other classification possibilities. However, it appears that fermentability is a crucial property influencing mineral absorption, next to its solubility and phytic acid content. In the Western world, the majority (about 65-75%) of the fibre intake of about 15-23 g/d [93, 94, 209] consumed is insoluble fibre [94, 210].

Nonfermentable Fibre

The effect of nonfermentable dietary fibre on Mg absorption is not clear. Foods rich in dietary fibre are usually also rich in Mg, and a high oral Mg load can decrease fractional Mg absorption. In addition, foods rich in dietary fibre, such as cereals and legumes, are often also rich in phytate, a potential inhibitor to Mg absorption. Many studies investigating the effect of fibre on Mg absorption were not standardized for Mg and/or phytate content [22, 30].

Camire and Clydesdale [211] investigated the effect of wheat bran, cellulose and lignin on Mg binding ability *in vitro* at different pH values, lignin showing the highest binding abilities. The amount Mg bound to these compounds increased with increasing pH, indicating that the tested compounds are potentially able to bind free Mg in the small intestine, thus reducing Mg absorption. However, no human study could clearly demonstrate a negative effect of fibre on Mg absorption (Table 4). Mc Hale *et al.* [212] studied the effect of 10 and 20 g cellulose added to a diet on Mg urinary and faecal excretion in adolescent healthy subjects during 6 d periods, a non- significant tendency towards higher faecal Mg excretion was found. Likewise, Drews *et al*. [213] found no significant effect on faecal Mg excretion in adolescent male subjects fed a basal diet standardized for Mg content containing 14.2 g added cellulose during a 4 d crossover study. A significant increase in faecal Mg was found by Slavin & Marlett [214], when 16 g cellulose/d were added to a diet consumed by healthy adults during 30 d periods, but the high fibre rich diet contained about 9% more Mg. Behall *et al.* [215] studied the effect of different types of fibre (cellulose, Na-carboxymethylcellulose) added to a basal diet at 7.5 g per 1000 kcal on Mg absorption in men during 4 wk periods, fractional faecal Mg excretion increased non-significantly from 62.4% to 78.3%, however, Mg concentration in the diet was not standardized, and was higher from the basal diet. It appears that the varying nature of the fibre, its phytic acid and Mg content, and the study design such as length of intervention impede the finding of consistent results.

Fermentable Fibre

Fermentable carbohydrates include resistant starch, fructo-oligosaccharides, inulin, gums, lactulose and other non-digestible sugars and sugar alcohols, and, if not digested, due to lactase deficiency, lactose [216]. Hemicellulose and pectin are partly fermentable [217]. Many fermentable fibres are also water soluble, soluble dietary fibres are characterized by the ability to increase the viscosity of aqueous solutions, and are typically found in the cell walls of plants, and are therefore frequently consumed in vegetables, especially in roots or tubers, e.g. potatoes. Of the soluble fibres, especially fructooligosaccharides have been investigated with growing interest during the last years for their use as prebiotics.

The exact mechanism for enhanced absorption however remains speculative. Fermentation of the carbohydrates occurs mainly mainly by bifidobacteria in the caecum and colon [218, 219]. These bacteria produce short-chain carboxylic acids (acetate, propionate, butyrate) and lactate, decreasing the pH in the large intestine. This acidic fermentation and associated lower luminal pH has been reported to be associated with improved solubility and enhanced absorption of Mg [220, 221]. Another explanation is the existence of an exchange mechanism, i.e. an apical $Mg^{2+}/2H^{+}$ antiport, allowing an influx of Mg^{2+} into mucosal cells against H^{+} coming from passive uptake of undissociated short chain fatty acids [222]. Short chain fatty acids have also been speculated to increase directly the resorptive surface of the

gut's absorptive area [223], as caecum hypertrophy has been found in rats fed fermentable fibre [224]. More recently, it has further been shown that indigestible disaccharides do enhance Mg absorption in the rat via uptake through tight junctions in the jejunum, ileum, caecum, and colon, following the paracellular pathway [225], similar as suggested for calcium in rats [226]. Whether this effect is also present for other types of dietary fibre or the human intestine remains to be shown. A study with ileostomy subjects in which inulin and oligofructose were given in amounts of 17 g for 3 d, no effect on mineral absorption could be deduced [227], suggesting no effect of dietary fibre on small intestinal Mg absorption. Similarly, in another study with ileostomy patients, 15 g citrus pectin supplementation during 3 d did not alter apparent Mg absorption [228].

a) Hemicellulose, Pectin, and Gums

Hemicellulose encompasses partly water soluble polysaccharides [217] occurring in the cell wall of plants. In comparison to cellulose, they are of a smaller molecular mass and of a more branched chemical structure. The amount of hemicellulose in most vegetables and fruits is in the range of 1–2% [147]. Few studies have indicated reduced Mg absorption due to intake of hemicellulose. Drews *et al*. [213] found significantly increased faecal Mg excretion in adolescent male subjects fed a basal diet containing 14 g added hemicellulose from psyllium during a 4 d crossover study. Similar results were found by Taper *et al*. [229] in a randomized 11 d cross over study, in which healthy male subjects consumed a diet with either 0, 20, 30, or 40 g/1500 kcal soy polysaccharide rich in hemicellulose. The diet with the highest amount of fibre decreased fractional Mg absorption from 31 to 25%, however, the fibre rich diet contained also (5%) more Mg than the basal diet. It could be speculated whether the phytic acid content present in the diets contributed to the observed results.

Pectin consists mainly of galacturonic-acid units, the carboxyl group being partly esterified with methanol, and with a molecular weight between 10000 and 500000. Pectin is typically found in the cytosole and the cell membrane of plants, pectin concentration in fruits and vegetables is around 1% [230]. Several rat studies indicated bacterial fermentation of pectin and, similarly, of gums such as gum arab and guar gum [231, 232]. Demigné *et al*. [233] found that addition of 10% pectin to the diet over 21 d periods significantly increased Mg flux from the caecum to the blood. In contrast, no human study could demonstrate an effect of pectin on Mg absorption. No statistical significant difference for Mg absorption was found when feeding healthy adults 9 g citrus pectin/d during 5 wk periods versus subjects receiving a low-fibre control diet [234]. Similar results were found by Drews *et al*. [213] studying the effect of adding 14 g pectin/d to the diet of adolescent boys during 4 d periods. In summary, hemicellulose, pectin and gums have not demonstrated any positive effects on Mg absorption in humans. As these compounds have been suggested to bind minerals *in vitro* [211], it can be speculated that this effect might counterbalance potential positive effects on Mg absorption in the large intestine.

b) Oligo(Fructo)Saccharides

Oligosaccharides typically include carbohydrates of 2-60 monosaccharide units. In the case of fructose, a polymerization degree between 2 and 60 is classified as inulin, below <8, these compounds are referred to as oligofructosaccharides or oligofructose [222]. Wheat, onions, and bananas are the most important sources of oligofructose and inulin in Western diets. Western European intake was estimated to be in the range of 3-11 g/d for adults [reviewed by 235].

A number of rat studies have indicated a positive effect of these compounds on Mg absorption. However, in these studies, usually very high amounts of oligofructosaccharides were fed. Wolf *et al.* [236] found a significant increase in Mg absorption from 70% to 77% in rats given 0, 1, 3, or 5% (w/w, based on dry matter) oligofructosaccharides in the diet over 7d periods. Similar results, also for inulin, were found by other researchers [141, 237, 238].

The first study showing an effect of inulin on calcium absorption in humans was reported by Coudray *et al*. [239]; inulin addition increased calcium absorption significantly from 21% to 34% in healthy humans consuming up to 40 g/d inulin over 28 d periods, but had no significant effect on Mg, iron, and zinc absorption. Similarly, Van den Heuvel [240] could not detect an increase in Mg absorption in subjects consuming 15 g fructooligosaccharides for 9 d. It has been speculated that a longer adaptation period might be necessary to show an effect on mineral absorption because of the time it takes to stimulate bacterial growth and fermentation. A recent study by Tahiri *et al*. [33] showed that ingestion of 10 g/d short-chain oligofructosaccharides in postmenopausal women over 5 wk periods enhanced apparent absorption of Mg slightly but significantly from 30.2 to 33.9% in a randomized, double blind crossover study, using stable isotope techniques. In infants, supplementation of the diet with 0.75, 1 and 1.25g/d inulin significantly increased Mg absorption in infants during a 14 d feeding study in a dose dependent manner from 77 to 92% [241].

In conclusion, intake of oligofructosaccharides has been shown to improve Mg absorption in rats and in humans. However, relatively high amounts of oligofructose (about 10 g/d) seemed to be needed to increase Mg absorption.

c) Resistant Starch

Resistant starch is not or only partly broken down into digestible sugars by human enzymes such as α-amylase in the gastrointestinal tract. The reason is not completely understood, but protection of the starch through undisrupted cell walls, presence of amylose-lipid complexes, or the formation of an extensive network of intra-and interhelical hydrogen bonds may play a role [242]. The 4 major groups of resistant starch are physically inaccessible resistant starch (granules) (RS_1), occurring e.g. in partly milled grains and seeds; raw starch (RS_2) occurring e.g. in raw potatoes and bananas; retrogradiated resistant starch (RS_3) occurring in thermically treated products such as in bread, corn flakes, and cooked potatoes; and chemically modified resistant starch (RS_4), [243]. Global consumption of resistant starch has been reported to be in the range of 3-10g/d [244] and 4 g/d in Europe [245], which amounts therefore for about half of the non-digestible soluble carbohydrates consumed.

Especially RS_2 has been reported to positively stimulate Mg absorption in a number of rat studies, however, no studies in human subjects are available at present. RS_2 seems more fermentable in the large intestine than is RS_1 or RS_3 [246]. Demigné *et al.* [233] found that adding 10% amylose rich starch, which is incompletely broken down in the small intestine, to the diet during 21 d periods significantly increased fluxes of Mg from caecum to blood. Younes *et al.* [247] found a significant increase in Mg caecal solubility and absorption in rats fed a diet containing 10% inulin, 15% resistant starch (RS_2), or a blend of 5% inulin plus 7.5% (w/w) resistant starch versus a fibre-free diet, similar results were found by Lopez *et al.*, [248] with ingestion of 20% (w/w) raw potato starch and high amylase corn starch (both RS_2) during 21 d periods, counterbalancing the negative effect of phytic acid present in the wheat bran [249]. RS_2 increased Mg absorption in rats over a period of 13 d when added at 25% (w/w) in the diet [246] while RS_3 (17% in the diet) had no effect, in contrast to a study by Ebihara *et al.*[224] in which 50 g/kg diet higher substitution hydroxypropyl-distarch phosphate (RS_3) for 21 d increased apparent absorption of rats. No effect of resistant starch on Mg absorption was found in a study with rats and pigs fed a diet containing 6% RS_2 or RS_3, respectively, as compared to the control diet [250] over 5 wk (rats) or 1 wk (pigs) periods. However, the number of animals was low (n=8), and a non-significant increase in apparent Mg absorption during the RS_2 diet was seen in the rats. It could be assumed that only diets containing relatively high amounts of resistant starch showed a significant effect on Mg absorption. The influence of resistant starch on true Mg absorption was also evaluated in rats. In a study by Heijnen *et al.* [251], RS_2 increased apparent but not true Mg absorption significantly in rats fed a diet containing 12% RS_2 (w/w) compared to a diet containing 12% RS_3 (w/w) over 4 wk periods, true Mg absorption was estimated by using a ^{28}Mg tracer. It could be speculated that RS_2 might reduce intestinal fluid secretion, depress turnover of epithelial cells or reduce Mg influx in the lumen because of higher concentration of soluble Mg in the lumen. In conclusion, especially raw resistant starch (RS_2) increased Mg absorption in rats in the majority of studies. No studies with human subjects are available, however, a recent study with a product similar to resistant starch, Nutriose FB, investigated the effect of adding 100 g/d dry matter of this low digestible glucose-polymer to the diet of healthy adult men for 31 d and found a significantly increased apparent fractional Mg absorption from 30% to 51% [252].

d) Lactose, Lactulose, Sugar Alcohols

Lactose enhanced Mg absorption in a number of studies with adult rats lacking the enzyme lactase [reviewed by 22, 253, 254]. However, there is no agreement about the effect of lactose on human Mg absorption at present and studies are scant. A small but significant increased Mg absorption from 40% to 48% was found in healthy infants given 7% (w/w) lactose in a diet standardized for Mg content during at least 11 d, compared to a diet containing similar amounts of sucrose and polyose [255], while in preterm infants, a 50% reduction of lactose in the diet did not decrease Mg absorption significantly during 3 d periods [256]. Moya *et al.* [257] compared Mg absorption in term infants fed either a lactose-free or a lactose containing formula during 3 d balance periods and likewise found no significant difference in Mg absorption, even though a trend toward higher absorption was observed in the lactose group. Hardly any information is available on the influence of lactose on Mg absorption in adults. Urinary excretion as an indicator for Mg absorption was monitored by Brink *et al.* [258] in a double blind crossover study in lactose tolerant, healthy adults receiving 46 g lactose/d in the diet as compared to a lactose-free diet during 1 wk periods. No differences in urinary Mg excretion were found, indicating no differences in Mg absorption. A proposed mechanism for a potential increase in Mg absorption is not at hand. An early study by Kobayashi *et al.* [259] found that apparent Mg absorption in term infants was lower from a lactose free milk than from milk and the same milk containing lactase during 8-9 d periods, apparent Mg absorption being 39.3%, 57.7% and 80.9%, respectively. It was suggested that the hydrolyzed monosaccharides, rather than lactose, were responsible for increased Mg absorption in the intestine, even though it remains unclear how such an effect could be explained. Thus, there is little evidence of a positive effect of lactose on Mg absorption in humans; if such an effect exists, it can be assumed to be small and requiring longer supplementation periods.

Lactulose, a synthetic disaccharide consisting of galactose and fructose and which cannot be digested by the rat or human, has been shown to increase Mg absorption in rats, albeit no human studies have been carried out. Demigné *et al.* [233] found that feeding 10% lactulose (w/w) in the diet compared to a lactulose-free control diet in rats during 21 d periods significantly increased intestinal flow of Mg from the caecum into the blood. Heijnen *et al.* [253] found significantly increased Mg absorption when lactulose (14%) was added to the diet of rats during 21-23 d periods. Significantly increased Mg absorption was also found in dogs fed either 0, 1, or 3 g lactulose/MJ during 2 wk periods [260]. Similar as for lactulose, sugar alcohols have been studied for their effect on Mg absorption. A study by Coudray *et al.* [34] showed increased Mg absorption in healthy adults consuming two additional maltitol rich polyol preparations for 32 d, fractional Mg apparent absorption increased significantly from 40 to 51%.

In conclusion, it can be assumed that a number of non-digestible but fermentable carbohydrates (Table **4**) which induce a decrease in pH in the large intestine due to increased bacteria degradation could, in principle, increase Mg colonic absorption. Whether the predominant mechanism is a $Mg^{2+}/2H^{+}$ antiport, increased absorption via tight junctions, or an increased large intestinal surface, remains to be elucidated.

CONCLUSIONS

Despite the reported relation between Mg and a number of chronic diseases such as osteoporosis and metabolic syndrome, our present understanding on factors impacting Mg absorption remains limited (Fig. **2**). Even though recent human studies have demonstrated effects of dietary compounds on Mg absorption using adequate techniques such as stable isotopes, the effect and mechanisms of many dietary compounds on intestinal Mg absorption is poorly

Table 4. Studies Investigating the Effect of Dietary Fibre on Mg Absorption in Humans

study	subjects	fibre tested	amounts tested	method used	results and comments
Mc Hale *et al*. (1979), [212]	6 healthy adolescents	cellulose	10 g, 20 g/d added to diet for 6 d	chemical balance	trend toward higher Mg faecal excretion
Drews *et al*. (1979), [213]	8 adolescent boys	cellulose	14 g/d for 4 d	chemical balance	no significant effect
Slavin & Marlett, (1980) [214]	7 healthy adult males	cellulose	16 g/d for 30 d	chemical balance	significant increase in faecal Mg; however, high fibre rich diet contained 9% more Mg
Behall *et al*. (1987), [215]	11 healthy adult men	cellulose, Na-carboxymethylcellulose	7.5 g/1000 kcal for 4 wks	chemical balance	non-significant increase in Mg faecal excretion
Drews *et al*. (1979), [213]	8 adolescent boys	hemicellulose from psyllium	14 g/d for 4 d	chemical balance	significant increased Mg faecal excretion
Taper *et al*. (1988), [229]	22 healthy young men	soy polysaccharide rich in hemicellulose	0, 20, 30, or 40 g/1500 kcal for 11 d	chemical balance	significant decreased Mg absorption from 31 to 25% for diet with highest hemicellulose, however, this diet also contained 5% more Mg
Stasse.Wolhuis *et al*. (1979), [234]	16 healthy adults	pectin	9 g/d for 5 wks	chemical balance	no significant differences
Drews *et al*. (1979), [213]	8 adolescent boys	pectin	14 g/d for 4 d	chemical balance	no significant differences
Sandberg *et al*. (1983), [228]	6 ileostomy subjects	pectin	15 g/d for 3 d	chemical balance	no significant difference
Ellegard *et al*. (1997), [227]	10 ileostomy subjects	inulin, oligofructose	17 g/d oligofructose, 7 g/d inulin, for 3 d	chemical balance	no effect of supplementation
Coudray *et al*. (1997), [239]	9 healthy adults	inulin	40 g/d for 28 d	chemical balance	no significant effect
Van den Heuvel (1998), [240]	12 healthy adults	fructooligosaccharides	15 g/d for 9 d	stable isotope techniques	no significant effect
Tahiri *et al*. (2001), [33]	11 postmenopausal women	short-chain oligofructosaccharides	10 g/d for 5 wks	stable isotope techniques	significant increase of Mg absorption from 30.2 to 33.9%
Yap *et al*. (2005), [241]	36 healthy infants	inulin	0.75, 1 and 1.25 g/d for 14 d	chemical balance	increased Mg absorption from 77 to 92 % in dose-dependent manner
Vermorel *et al*. (2004), [252]	10 healthy young men	glucose-polymer	100 g dry matter/d for 31 d	chemical balance	increased Mg absorption from 30 to 51%
Ziegler and Fomon (1983), [255]	6 healthy infants	lactose	7% in diet for 11 d	chemical balance	significant increase of Mg absorption from 40 to 48%
Wirth *et al*. (1990) [256]	10 preterm infants	lactose	50 % lactose reduction of diet for 3 d	chemical balance	no significant effects
Moya *et al*. (1999), [257]	10 term infants	lactose	lactose-free vs. lactose diet for 3 d	chemical balance	no significant effects; however, trend toward higher Mg absorption in lactose group; no specific data on amount lactose intake

(Table 4) Contd.…

Study	subjects	fibre tested	amounts tested	method used	results and comments
Brink *et al.* (1993), [258]	24 healthy adults	lactose	46 g lactose/d for 1 wk	urinary Mg excretion	no significant differences
Kobayashi *et al.* (1975), [259]	15 term infants	lactose	milk (a), vs. lactose-free milk (b) vs. milk with lactase (c) for 8-9 d	chemical balance	39.3, 57.7 and 80.9% Mg absorption, however, low number of subjects, n=3 (c), n=4 (a)
Coudray *et al.* (2003a), [34]	9 healthy young men	maltitol	100 g dry matter/d for 34 d	chemical balance	significant increase in Mg absorption from 40 to 51%

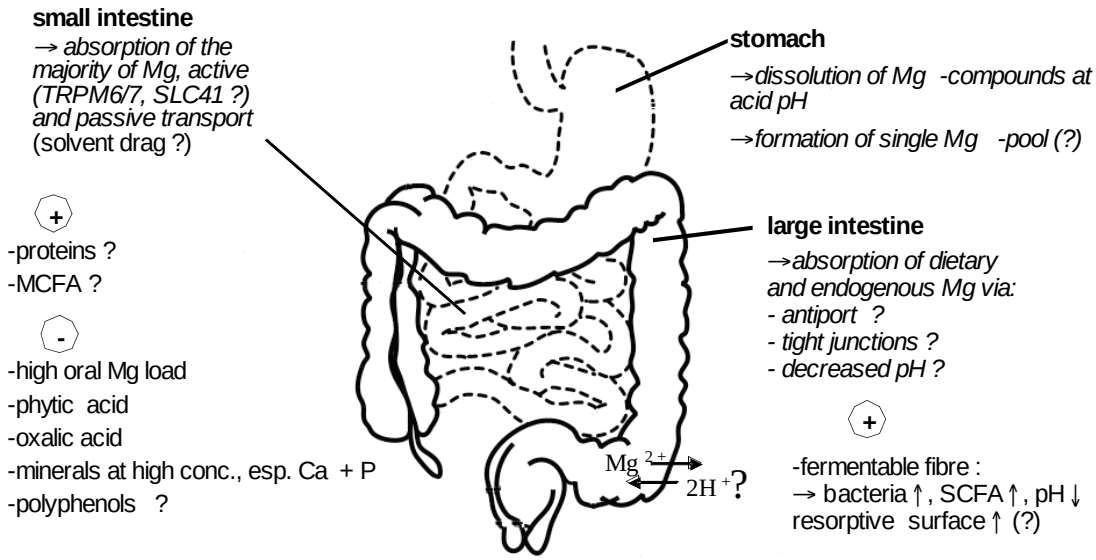

Fig. (2). Dietary factors influencing Mg absorption.

understood, as little is known on the active and passive transport of Mg in the intestine itself. Dietary factors with a negative impact on Mg absorption have been shown to include phytic acid and possibly oxalic acid, and calcium together with phosphate, the latter especially at low Mg intake. The ingestion of fermentable carbohydrates, given a low phytate content, can be expected to have beneficial effects on Mg absorption, while the effect of a large number of major dietary compounds, such as fats, proteins, and polyphenols, remains to be elucidated. In sight of the relation of low Mg consumption and low Mg status to a number of chronic health implications, future studies investigating dietary factors influencing Mg absorption in humans are warranted.

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