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REVIEW ARTICLE

Intestinal Absorption and Factors Influencing Bioavailability of Magnesium-An Update

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ARTICLE HISTORY

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Abstract: ***Background*:** Information on the bioavailability of the essential mineral Mg^{2+} is sparse.

***Objective/Method*:** Evaluation of the present knowledge on factors influencing the bioavailability and intestinal absorption of Mg^{2+}.

***Results*:** Mg^{2+} is absorbed *via* a paracellular passive and a transcellular active pathway that involves TRPM6/7 channel proteins. The bioavailability of Mg^{2+} varies within a broad range, depending on the dose, the food matrix, and enhancing and inhibiting factors. Dietary factors impairing Mg^{2+} uptake include high doses of other minerals, partly fermentable fibres (*e.g.*, hemicellulose), non-fermentable fibres (*e.g.*, cellulose, lignin), phytate and oxalate, whereas proteins, medium-chain-triglycerides, and low- or indigestible carbohydrates (*e.g.*, resistant starch, oligosaccharides, inulin, mannitol and lactulose) enhance Mg^{2+} uptake. The Mg^{2+} dose is a major factor controlling the amount of Mg^{2+} absorbed. In principle, the relative Mg^{2+} uptake is higher when the mineral is ingested in multiple low doses throughout the day compared to a single, large intake of Mg^{2+}. The type of Mg^{2+} salt appears less relevant than is often thought. Some studies demonstrated a slightly higher bioavailability of organic Mg^{2+} salts compared to inorganic compounds under standardized conditions, whereas other studies did not.

***Conclusion*:** Due to the lack of standardized tests to assess Mg^{2+} status and intestinal absorption, it remains unclear which Mg^{2+} binding form produces the highest bioavailability. The Mg^{2+} intake dose combined with the endogenous Mg^{2+} status is more important. Because Mg^{2+} cannot be stored but only retained for current needs, a higher absorption is usually followed by a higher excretion of the mineral.

Keywords: Mg-absorption, bioavailability, intestinal uptake, meal composition, dietary fibre, oligosaccharides.

1. INTRODUCTION

Magnesium (Mg^{2+}) is the second most abundant intracellular cation, after potassium, and is the fourth most abundant cation in the human body [1]. This essential mineral is needed for a broad variety of physiological and biochemical functions. As a co-factor in more than 300 enzymatic reactions, which often depend on ATP, Mg^{2+} is involved in many biochemical pathways of key importance, including the degradation of macronutrients, oxidative phosphorylation, DNA and protein synthesis, neuro-muscular excitability, and regulation of parathyroid hormone (PTH) secretion (for a review, see [2]). As a physiological calcium channel antagonist, Mg^{2+} affects processes that are regulated by intracellular calcium concentration fluxes and is therefore essential for normal neurological and muscular function [3, 4]. Furthermore, Mg^{2+} regulates membrane permeability *via* interactions with phospholipids and affects vessel tone and blood pressure.

Data vary on total body content of Mg^{2+} and its distribution in adults. The total Mg^{2+} amount varies between 22 and 26 g [3]. More than 99% of the total body Mg^{2+} is located in the intracellular space, mainly stored in bone (60-65%), muscle and soft tissues (34-39%), whereas less than 1% is located in the extracellular space [5, 6]. Up to 70% of all plasma Mg^{2+} exists in the ionized (free) active form, which is important for physiological processes, including neuromuscular transmission and cardiovascular tone [7].

The reference range for serum ionized Mg^{2+} is 0.54-0.67 mmol/l [3]. Deviations from this physiological Mg^{2+} range cause neural excitability, arrhythmia, bone formation and several other pathological consequences [8]. Thus, Mg^{2+} stores are tightly regulated *via* a balanced interplay between intestinal absorption and renal excretion under normal conditions. Renal elimination removes approximately 100 mg of Mg^{2+} per day, whereas the losses *via* sweat are generally low. However, during intense exercise, these losses can rise substantially.

Balance studies suggest a daily Mg^{2+} requirement of 3.0-4.5 mg per kg body weight. The recommended intake de-

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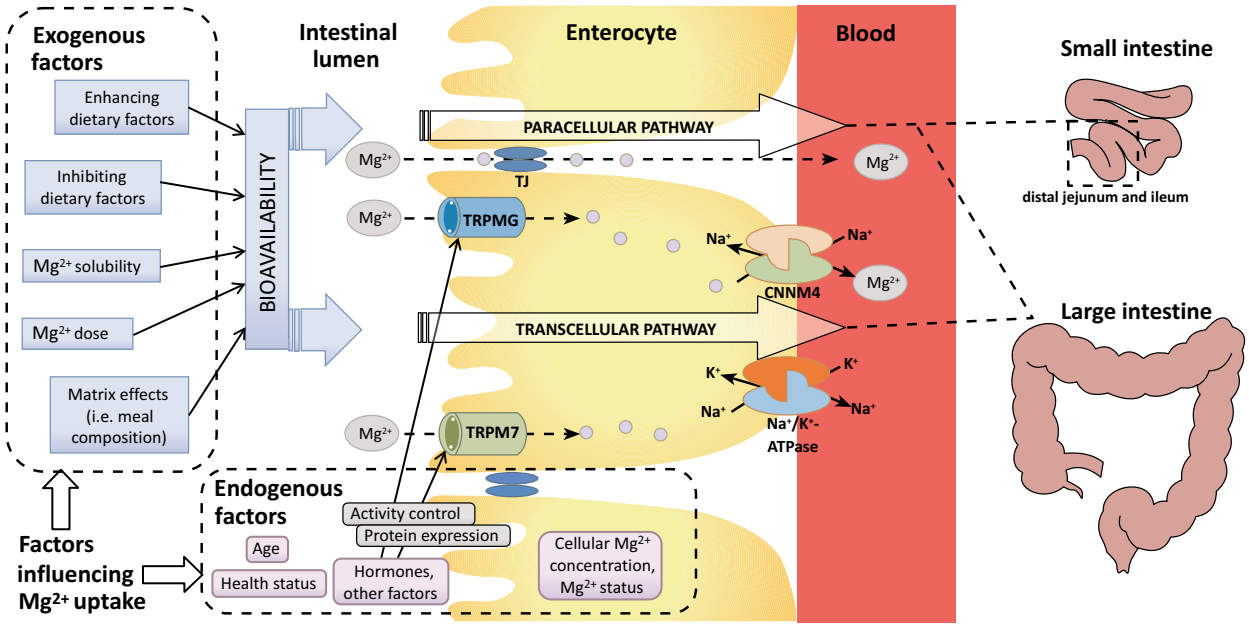

Fig. (1). Intestinal Mg^{2+} absorption and influencing factors.

The mechanism of Mg^{2+} absorption through the enterocytes into the bloodstream shows a dual kinetic process that involves two mechanisms: a saturable (transcellular) active pathway and a non-saturable (paracellular) passive pathway. The intestinal absorption occurs predominantly in the small intestine-mainly in the distal jejunum and ileum [11] *via* the paracellular pathway, which is regulated by the paracellular Tight Junctions (TJ). The fine-tuning of Mg^{2+} uptake occurs in the caecum and colon of the large intestine *via* the transcellular pathway mediated by membrane TRPM6/7 channel proteins and the paracellular pathway. It has been suggested that the basolateral Mg^{2+} extrusion mechanism of the enterocyte is performed *via* CNNM4, a Na^{+}/ Mg^{2+}-Antiporter [12]. The driving force is a Na^{+}-gradient that is established *via* the Na^{+}/K^{+}-ATPase. The bioavailability and intestinal absorption efficacy of orally ingested Mg^{2+} are influenced by various endogenous and exogenous factors. For more details, see the text.
CNNM4, cyclin M4; TRPM6, transient receptor potential melastatin type 6; TRPM7, transient receptor potential melastatin type 7.

rived from these data varies in different countries. Whereas the Institute of Medicine [9] recommends 310-320 mg per day for women and 400-420 mg per day for men as adequate, the European Food Safety Authority [10] recently defined an adequate intake of 300 and 350 mg per day for women and men, respectively.

Various factors influence the intestinal uptake of Mg^{2+} and are of substantial importance for the supply of the mineral. Dietary Mg^{2+} uptake in the intestine varies within a broad range and depends on dose, the food matrix, and enhancing and inhibiting factors. Furthermore, several studies have shown that the absorption of Mg^{2+} from food supplements and pharmaceutical preparations under standard conditions is slightly influenced by the type of Mg^{2+} salt. Nevertheless, an approach that focuses on one or a few aspects is insufficient from a nutritional and medical point of view. To understand the true absorption of Mg^{2+}, numerous endogenous and exogenous factors must be considered. Overall, the understanding of Mg^{2+} absorption and its influencing factors is still limited, which has been due to methodological limitations. This article gives an overview of this issue.

2. MECHANISMS OF Mg^{2+} ABSORPTION IN THE INTESTINE

Intestinal Mg^{2+} absorption (Fig. **1**) [11, 12] occurs predominantly in the small intestine *via* a paracellular pathway, and smaller amounts are absorbed in the colon, mainly *via* a transcellular pathway [13]. In humans, Mg^{2+} absorption starts approximately 1 h after oral intake, reaches a plateau after 2-2.5 h up to 4-5 h and then declines. At 6 h, the Mg^{2+} absorption is approximately 80% complete [14].

With a daily intake of 370 mg, the absorption rate of Mg^{2+} in the intestine ranges from 30-50% [13]. However, the efficiency of Mg^{2+} uptake is dependent on the ingested dose [15, 16]. For example, early studies with a low dietary Mg^{2+} intake showed that the relative absorption rate can reach 80% [17], whereas it is reduced to 20% with Mg^{2+} surfeits [18].

In general, Mg^{2+} is absorbed as an ion. It is not known if the mineral is absorbed together with other nutrients or if Mg^{2+} is absorbed in the form of complexes [19].

2.1. Transcellular Pathway

With the identification and characterization of the Mg^{2+} transporters TRPM6 and TRPM7, which are members of the Transient Receptor Potential (TRP) melastatin family of cation channels, our understanding of Mg^{2+} absorption mechanisms has greatly improved (for a review, see [18]). TRP channels contribute to the saturable active transcellular movement of divalent cations from the intestinal lumen into the cells [8]. The tight regulation of TRPM6, induced by intracellular Mg^{2+}, provides a feedback mechanism in Mg^{2+}

influx and implies that intracellular Mg^{2+} buffering and Mg^{2+} extrusion mechanisms strongly impact channel functioning [20].

2.2. Paracellular Pathway

It has been hypothesized that the paracellular pathway exclusively contributes to Mg^{2+} absorption in the small intestine because a) Mg^{2+} absorption in this region linearly correlates with luminal Mg^{2+} concentrations [13, 18, 21]; and b) the TRPM6 channel is not expressed in the small intestine [22].

Paracellular Mg^{2+} absorption occurs *via* simple diffusion and involves the transport of Mg^{2+} through small spaces between the epithelial cells. The driving force for the passive Mg^{2+} transport in the distal jejunum and ileum is established by the high luminal Mg^{2+} concentration and the lumen-positive transepithelial voltage of ~15 mV [23]. The process relies on tight junction permeability, which is still poorly understood [10]. The small transmembrane proteins, claudins, are the key components of the paracellular channel because they control ion permeability. The relatively low expression of 'tightening' claudins 1, 3, 4, 5 and 8 in the small intestine enables Mg^{2+} permeability [24].

3. INTESTINAL ABSORPTION OF MG^{2+}-METHODOLOGICAL ASPECTS

Studies on the absorption and bioavailability of Mg^{2+} have produced different results and are often not comparable because of the different methods used. Different parameters, such as retention and urinary excretion must be used to evaluate Mg^{2+} bioavailability.

3.1. Direct Bioavailability Studies

The investigation of Mg^{2+} absorption and its kinetics is complex. Conventional bioavailability studies, which monitor the plasma Mg^{2+} levels after oral administration **(direct method)**, are insufficient to investigate the rate and amount of Mg^{2+} absorption because the plasma Mg^{2+} levels are subject to rapid homeostasis, which is mainly driven by renal excretion and storage in compartments such as bone [25]. The active reabsorption of Mg^{2+} from primary urine in the kidney produces approximately 20 times more Mg^{2+} transported into the plasma compared to Mg^{2+}, which is absorbed in the intestinal tract. The remaining Mg^{2+} is excreted in urine. In the net balance, the complete amount of Mg^{2+} absorbed in the intestinal tract is excreted *via* the kidney. Therefore, the basic plasma Mg^{2+} levels are quickly regulated, thereby impeding evaluation of precise concentration time curves.

3.2. Indirect Chemical Balance Studies

The absorption of Mg^{2+} should be studied in human studies by using **indirect methods** of dietary balance that are based on measuring **faecal or urinary Mg^{2+} excretion** after oral Mg^{2+} administration. However, such **chemical balance studies** also have a number of limitations. Usually, these studies are carried out over a period of several days or weeks, where a strict diet has to be followed. Long-term balance studies are susceptible to low compliance, and it is questionable whether the results of such long-term balance studies are suitable for extrapolation on bioavailability. These studies instead provide data on the required intake amounts. However, a short balance period may yield inaccurate absorption results because the meals given during the balance period might mix with preceding meals in the intestine, an effect that might vary between subjects due to varying gastrointestinal passage time. At a minimum, probands must be given food low in Mg^{2+} throughout the studies, especially through beverages (*e.g.*, water). Nevertheless, mineral excretion in faeces cannot be strictly related to intake. In addition, endogenous faecal Mg^{2+} is lost through bile, the pancreas, and other ways; thus, 'true absorption' cannot be determined because there is no ability to distinguish between endogenous and dietary Mg^{2+}.

3.3. Isotopic Methods

In contrast, absorption studies using labelled Mg^{2+} **(isotopic methods)** allow the amount of Mg^{2+} that is absorbed from a certain food or drink to be calculated. Because the addition of radioisotopes ($^{28}Mg^{2+}$) in meals is not useful in terms of either ethical considerations or its half-life (21 h), **stable isotope techniques** are preferable [26]. Combined with inductively coupled plasma mass spectrometry (ICP-MS), $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$ can be used to follow exogenous Mg^{2+} in plasma, urine, or faeces after the oral administration of labelled test meals and to calculate the absolute bioavailability of Mg^{2+} [26]. However, the two isotopes of Mg^{2+}, $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$, are highly abundant in nature (10 and 11%, respectively), which reduces the sensitivity [26]. Furthermore, it remains unclear whether the addition of isotopes to a food leads to similar properties in terms of solubility and binding to the matrix compared to the unlabelled Mg^{2+} in the respective source.

3.4. Other Issues

The long-term collection of urine and faeces is very cumbersome. Therefore, Sabatier *et al*. (2003) compared several multiple blood sample protocols with complete urine and faecal samples [27]. All protocols were combined with stable-isotope-tracer methods. The authors found that double-labelling methods are an alternative to faecal monitoring methods, which are simpler and less invasive [27].

Hansen *et al*. (2014) performed a bioavailability study with stable Mg^{2+} isotopes to identify a more convenient method of measuring Mg^{2+}absorption that did not require 72-h urine or ≥ 6-d stool collection [28]. Mg^{2+} absorption values using means of the 0-24 h urine collection and 3-h serum samples were found to most accurately reflect 72-h Mg^{2+} absorption.

Mg^{2+} retention depends on absorption and other mechanisms that contribute to homeostasis, such as excretion *via* the renal pathway, which is the most important organ for regulating Mg^{2+} homeostasis. Therefore, to prevent any sub-Mg^{2+} deficiency and minimise the differences in Mg^{2+} status, subjects of Mg^{2+} bioavailability studies need to be supple-

Table 1. Overview of endogenous and exogenous factors affecting absorption of Mg^{2+}.

	Improve Absorption	Impair Absorption
Endogenous Factors	• Low Mg^{2+} status	• Increasing age
		• Balanced Mg^{2+} status
		• Intestinal dysfunction (*e.g.*, in CD, IBD, or SBS)
Exogenous Factors	• MCT (SFA) (?) • Proteins (?) • Casein phosphopeptides (?) • Low- or indigestible carbohydrates (*i.e.* oligosaccharides, inulin, mannitol and lactulose) • High solubility of Mg^{2+} • Solubilized Mg^{2+} (*e.g.*, effervescent tablets)	• High single Mg^{2+} intake dose • Partly fermentable fibers (hemicellulose) • Non-fermentable fibers (cellulose and lignin) • LCT (?) • Phytate • Oxalate • Pharmacological doses of calcium, phosphorus, iron, copper, manganese and zinc • Slow-release formulations (?)

CD, celiac disease; IBD, inflammatory bowel disease; LCT, long chain triglycerides; MCT, medium chain triglycerides; SBS, short bowel syndrome; SFA, saturated fatty acids.

mented for ≥ 4 weeks before evaluation [29]. Indeed, under this condition, Mg^{2+} bioavailability is comparable. However, the observation is meaningless because the additional absorbed Mg^{2+} is immediately eliminated renally in case of sufficient Mg^{2+} status. Such data are only limitedly transferable to a situation where the Mg^{2+} supply status in insufficient. It is unclear whether the type of Mg^{2+} salt or other exogenous factors influencing Mg^{2+} bioavailability are important under conditions of insufficient Mg^{2+}.

4. DATA ON INTESTINAL Mg^{2+} ABSORPTION

The absorption rate of orally ingested Mg^{2+} for healthy individuals is influenced by various endogenous and exogenous factors (Table **1**). In particular, the amount of ingested Mg^{2+} and, to a variable extent, the presence of inhibiting and enhancing dietary components (Fig. **1**) are important. Moreover, the meal composition (*i.e.*, matrix effects), the type of Mg^{2+} salt and galenic formulation (*e.g.*, gastric acid resistant capsules, pH-dependent release systems, or retard formulation) may influence the absorption efficacy.

In previous balance studies, various protocols have been applied, including true bioavailability studies with stable Mg^{2+}-isotopes [30-39]. Furthermore, the Mg^{2+} load administered varied widely among studies (from <100 to >1,000 mg/d), notwithstanding the age of subjects (infants to adults), their physical condition or the proximity of meals to administration. As a result, the data often appear confusing and conflicting.

The absorption of Mg^{2+} and other minerals is impaired in patients with gastrointestinal disorders such as Celiac Disease (CD) [40], Inflammatory Bowel Disease (IBD) [41] and Short Bowel Syndrome (SBS) [42] due to a malabsorption syndrome. Hence, a Mg^{2+}-enriched diet and a thorough Mg^{2+} supplementation is therefore advised to prevent or treat Mg^{2+} deficiency. Little is known on the bioavailability of dietary Mg^{2+} and other minerals in CD, IBD and SBS patients. The following data outline the Mg^{2+} absorption in healthy subjects.

4.1. Endogenous Factors Influencing Absorption

4.1.1. Homeostasis and Mg Status

The kidney is the primary organ that regulates Mg^{2+} homeostasis [39]. Approximately 2,400 mg of the mineral is filtered through the glomeruli, and 15-20% of the filtered Mg^{2+} is reabsorbed in the proximal convoluted tubule. Approximately 65% is reabsorbed in the Henle loop *via* active transport [39], and approximately 10% is reabsorbed in the distal convoluted tubule [11]. Thus, only approximately 5% of the filtered Mg^{2+} is excreted under normal conditions. Excessive Mg^{2+} is almost entirely excreted through the kidneys, which is also the case in hypermagnesaemia. Consequently, supplementation with Mg^{2+} usually increases renal Mg^{2+} excretion to varying degrees, depending on the quantity absorbed. Renal handling of Mg^{2+} is comprehensively discussed elsewhere [43]. Systematic studies comparing the intestinal uptake efficiency of Mg^{2+} between Mg^{2+} depleted and saturated subjects cannot be executed for ethical reasons.

4.1.2. Age

The efficiency of the gastrointestinal tract in absorbing micronutrients is negatively affected by increasing age [44]. This trend also applies to Mg^{2+}. Coudray *et al*. (2006) investigated the effect of ageing on mineral absorption in the intestine using a stable isotope approach in rats [45]. The authors showed that aged rats exhibited less efficient intestinal absorption of $^{25}Mg^{2+}$. Young and adult rats absorbed 56%, whereas Mg^{2+} absorption decreased to 45% in old and very old rats. Additionally, a human study found a significant, inverse relation between $^{28}Mg^{2+}$ absorption from mineral water and age [46]. However, the study by Verhas *et al*. [46] had a restricted sample size, and the subjects had only a two-decade age range, which are limitations of their study.

4.2. Exogenous Factors Influencing Absorption

4.2.1. Absolute Mg Intake Per Dose

In studies with humans, a wide range (10-75%) of Mg^{2+} absorption rates have been reported. Such variability is most

likely due to the Mg^{2+} load than to the analytical method, the formulation or the food matrix [29]. It is generally thought that the relative absorption of Mg^{2+} is inversely related to the ingested dose; in other words, the quantity of Mg^{2+} in the digestive tract is the major factor controlling the amount of Mg^{2+} absorbed. For example, in 1991, Fine *et al.* showed that in humans, the relative Mg^{2+} absorption rate from a daily dose of 36 mg was 65%, whereas, only 11% was absorbed from a daily dose of 973 mg, apparently due to the greater restriction of intestinal permeability to Mg^{2+} [47]. However, it should be noted that absolute absorption increased with each increment in intake [47].

Nakamura *et al*. (2012) conducted two experiments where the effects of the Artificial Mineral Water (AMW) serving volume and consumption pattern and the Mg^{2+} concentration on Mg^{2+} absorption in rats were examined [48]. In experiment 1, rats received 1 ml of AMW containing 200 mg Mg^{2+}/l at 4 times, 400 mg Mg^{2+}/l twice, or 800 mg Mg^{2+}/l at 1 time. In experiment 2, the rats received 1 ml of AMW containing 200 mg Mg^{2+}/l or 0.25 ml of AMW containing 800 mg Mg^{2+}/l at 4 times or 1 ml of AMW containing 800 mg Mg^{2+}/l at 1 time. The absorption of Mg^{2+} decreased with increasing Mg^{2+} concentrations in the same serving volume of AMW with different serving frequencies. When the AMW containing 800 mg Mg^{2+}/l was portioned into 4 servings, Mg^{2+} absorption increased to the level of absorption in the group exposed to AMW containing 200 mg Mg^{2+}/l served at the same frequency. These results suggest that the Mg^{2+} concentration and the volume of AMW do not affect Mg^{2+} absorption per se but that Mg^{2+} absorption from AMW decreases when the amount of Mg^{2+} in each serving is increased. Thus, frequent consumption is preferable for mineral water that is rich in Mg^{2+} when the total consumption of mineral water is the same.

Additionally, several human studies observed higher bioavailabilities when a given amount of Mg^{2+} was distributed over the span of a day rather than being consumed in a single bolus [29, 47, 49, 50]. Ekmekcioglu *et al*. (2000) showed that the upper range of Mg^{2+} absorption was obtained for the lowest ingested amount of Mg^{2+} in a study with adults [31]. Likewise, in a study with infants, the fractional absorption of Mg^{2+} of the same Mg^{2+} load (20 mg) was increased after distributed (64.0±3.9%) *vs*. bolus administration (54.3±5.9%) [49].

In a 2-d, cross-over, single-dose study with 12 healthy men, Sabatier *et al*. (2011) determined that the mode of administration (bolus *vs*. consumption throughout the day) could influence Mg^{2+} bioavailability from Mg^{2+}-rich natural mineral water comparing the same nutritional Mg^{2+} amount (126 mg from 2x750 ml or 7x212 ml) [29]. Two stable isotopes ($^{25}Mg^{2+}$ and $^{26}Mg^{2+}$) were used to label the water and distinguish both regimens. Fractional apparent Mg^{2+} absorption was determined by faecal monitoring, and Mg^{2+} retention was determined by measuring the urinary excretion of Mg^{2+} isotopes. The authors confirmed the results of the rat study by Nakamura *et al*. (2012) [48] and observed higher Mg^{2+} absorption and retention from Mg^{2+}-rich mineral water when it was consumed in seven servings compared with two larger servings, suggesting that regular water consumption throughout the day is an effective way to increase Mg^{2+} bioavailability from Mg^{2+}-rich mineral water. This increase in Mg^{2+} absorption after distributed *vs*. a bolus administration can most likely be explained by the absorption of low Mg^{2+} amounts *via* the TRPM6 channels [51, 52].

4.2.2. Meal Composition/Matrix Effects

Mg^{2+} is typically consumed as a part of complex meal, even in the case of supplementation. Hence, it is important to design studies with real food systems.

In a cross-over study with $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$ isotopes, Sabatier *et al*. (2002) investigated the bioavailability of mineral water consumed **with or without a simultaneous meal** [53]. Apparent Mg^{2+} absorption was determined by faecal monitoring, and Mg^{2+} retention was determined from urinary excretion of Mg^{2+} isotopes. The mean Mg^{2+} absorption from mineral water consumed alone was 45.7±4.6% but was significantly greater ($p = 0.0001$) when consumed with a meal (52.3±3.9%), which is a relative difference of 14.4%. Therefore, the Mg^{2+} bioavailability from mineral water is enhanced when the water is consumed with a meal, perhaps because of a slower gastrointestinal transit time or the presence of other food constituents (or both). A slower transit time may lead to an increased exposure of the mucosal cells of the intestine to Mg^{2+} and thus a higher total absorption. Surprisingly, Verhas *et al*. (2002) [46] observed a mean Mg^{2+} bioavailability rate of 59±13.6% from carbonated water consumed without a meal, which lies in the upper reported range for solid foods. However, in this study, the bioavailability of Mg^{2+} from water was not compared to solid food.

Bergillos *et al*. (2015) determined the bioavailability of Mg^{2+} from **ultrafiltered goats' milk fermented** with the probiotic *L. plantarum* C4 in an *in vitro* model with Caco-2 cells combining simulated gastrointestinal digestion and mineral retention [54]. The highest Mg^{2+} bioavailability was found in the probiotic-fermented goats' milk compared with ultrafiltered fermented goats' milk without the probiotic and commercial fermented goats' milks. The authors indicated that the casein concentration from the ultrafiltration process could increase the Mg^{2+} bioavailability.

In many western countries, bread is an important source of Mg^{2+}. Lopez *et al*. (2004) compared the effects of different kinds of bread fermentation on Mg^{2+} bioavailability in rats [55]. The authors found that although yeast fermentation minimizes the unfavourable effects of phytic acid on Mg^{2+} bioavailability, **sourdough bread** is the better source of available Mg^{2+}. Consumption of **Maillard reaction products** present in food (*e.g.*, bread crust) has been related to deterioration of protein digestibility and changes in mineral bioavailability [56-58]. However, in a balance study with rats, no influence of Maillard reaction products from bread crust on Mg^{2+} balance was observed [59].

4.2.3. Enhancing Factors

Various dietary factors that promote Mg^{2+} bioavailability have been investigated in animal and human studies. Several early human studies showed that higher **protein** intake increased Mg^{2+} absorption compared to lower intake [60-63], possibly by preventing the precipitation of calcium-Mg^{2+}-phosphate complexes in the ileum resulting in an increased

solubility of Mg^{2+} [64]. Likewise, **lipids** impact the absorbability of Mg^{2+}, whereby the lipid composition is suggested to be the influencing factor. Rat studies showed that a replacement of Medium Chain Triglycerides (MCT) for Long Chain Triglycerides (LCT) increased Mg^{2+} absorption [65, 66], possibly due to more soluble Mg^{2+} soaps of saturated fatty acids compared to insoluble Mg^{2+} salts formed with unsaturated fatty acids [67]. Conversely, studies on the influence of absolute fat mass on Mg^{2+} absorption have not produced consistent results ([68-70], reviewed in [64]).

Many studies examined the effect of **low or indigestible carbohydrates** (Table **2**) and of lactose. A stimulatory effect of these carbohydrates on Mg^{2+} absorption has been predominantly shown in animal studies [37, 71-79] and some human studies [31, 80, 81]. The tested carbohydrates include **resistant starch** (especially raw resistant starch) [67-70], **short-chain fructo-oligosaccharides** [30, 80], **resistant maltodextrin** [82], a mixture of **chicory oligofructose** and **long-chain inulin** [31], **galactooligosaccharides (GOS)** [75, 76], **inulin** [37, 77, 78], **polydextrose** [78], **maltitol** and the hydrogenated polysaccharide fraction of Lycasin®HBC [81], **mannitol** [79] or **lactulose** [36]. Only one human study with short-chain fructo-oligosaccharides found no effect on Mg^{2+} uptake [30].

The stimulatory effect of **GOS**-and possibly other low- or indigestible carbohydrates-on mineral uptake might be attributed to the effects of short-chain fatty acids (lactate, acetate, propionate, butyrate) and reduced pH in the large intestine produced through fermentation of the carbohydrates by intestinal bacteria (mainly bifidobacteria) [75, 83]. The resulting lower caecal pH may increase solubility of minerals, thereby enhancing their absorption from the colon and caecum [84]. A rat study observed that the promoting effect of GOS on Mg^{2+} absorption was diminished by neomycin treatment (bacteria-suppressing), suggesting that the GOS-effect is dependent on the action of intestinal bacteria [75]. Weaver *et al*. (2011) observed that supplementing rats with GOS stimulates Mg^{2+} absorption and results in a decreased caecal pH, increased caecal wall and content weight and an increased proportion of bifidobacteria [76]. The authors proposed that these effects were either directly or indirectly attributed to changes in caecal pH, caecal content and wall weight (increased surface area available for Mg^{2+} absorption) and to the number of bifidobacteria. The proposed explanations cannot be verified, especially because the bulk of Mg^{2+} is absorbed in the small intestine and not in the large intestine. However, the increased Mg^{2+} absorption following prebiotic exposure associated with a shift in gut microbiome would occur in the large intestine. Moreover, there may be further explanations. For example, Rondón *et al*. (2008) showed that inulin ingestion also modulated TRPM6 and TRPM7 expression in the large intestine of mice, which suggests ameliorated active Mg^{2+} absorption in the large intestine [85].

An enhancing effect of **lactose** on Mg^{2+} absorption has been demonstrated in two studies with lactase-deficient rats [86, 87], but human studies have shown mixed results. An early study by Ziegler and Fomon (1983) observed an enhanced Mg^{2+} absorption of lactose in healthy infants compared to sucrose and polyose [88], whereas other studies with preterm infants [89] or term infants [90] did not find significant differences. There have been no studies with human adults investigating the effect of lactose on Mg^{2+} absorption. Xiao *et al*. (2013) observed that resistant sugar **mannitol** improves apparent Mg^{2+} absorption in growing Wistar rats, possibly by the fermentation of mannitol in the caecum resulting in a reduced pH [79]. Moreover, **lactulose**-an indigestible synthetic disaccharide of D-galactose and fructose-increased Mg^{2+} absorption in rat studies [81, 86] and a human study [36]. Seki *et al*. (2007) performed a clinical trial with a double-blind, randomized cross-over design and stable isotopes $^{24}Mg^{2+}$ and $^{25}Mg^{2+}$ to evaluate the effect of lactulose on Mg^{2+} absorption in healthy men. The test foods contained lactulose at a dose of 0 g (placebo), 2 g (low-dose), or 4 g (high-dose) [36]. The authors demonstrated that lactulose enhanced the absorption of Mg^{2+}. The stimulatory effect on Mg^{2+} absorption is possibly also due to acidification in the ileal lumen [86].

4.2.4. Inhibiting Factors

The number of studies investigating dietary factors with a negative influence on the availability and uptake of Mg^{2+} is limited (Table **3**). Early studies reported that increasing **calcium** in the diet significantly depressed Mg^{2+} absorption [91, 92]. The same depressive effect on Mg^{2+} absorption was shown with excess **phosphorus, iron, copper, manganese** [93] and **zinc** [94]. However, in these studies, unphysiological doses of the minerals were used. When these substances are consumed within a physiological range, such as present in a regular diet, the inhibiting effects have not been observed [64]. For example, long-term Mg^{2+} balance studies with calcium doses >1.000 mg/d did not produce a negative effect on Mg^{2+} uptake [35, 94, 95]. Andon *et al*. (1996) demonstrated in a human study with 26 adolescent girls that high calcium intake (1.667 mg/d) had no relevant impact on measures of Mg^{2+} utilization, including the absorption rate or urinary or faecal excretion [95]. Likewise, a balance study with adolescent girls showed that high calcium intake (1.800 mg/d) did not alter Mg^{2+} kinetics or balance compared to a calcium intake of 800 mg/d [35].

Oxalic Acid (OA) is present in high amounts in members of the spinach family and in brassicas (cabbage, broccoli, brussels sprouts). The conjugate base of OA, oxalate, is a chelating agent for metal cations and thus affects the gastrointestinal bioavailability of Mg^{2+}. The effect of OA on Mg^{2+} absorption has been studied in rats [96] and humans [32]. Kikunaga *et al*. (1995) investigated Mg^{2+} availability from OA-rich spinach in Mg^{2+}-deficient rats [96]. The authors demonstrated that OA in spinach impairs Mg^{2+} absorption. In a cross-over study with healthy humans and stable isotopes $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$, Bohn *et al*. (2004) evaluated Mg^{2+} absorption from a test meal served with an OA-rich vegetable, spinach (6.6 mmol OA), compared to a test meal with kale, a vegetable with low OA content (0.1 mmol) [32]. The authors demonstrated that Mg^{2+} absorption from the OA-rich spinach meal was significantly lower compared to the kale meal. The same group investigated the effect of **Phytic Acid (PA)** on Mg^{2+} bioavailability in another human study. PA is typically found in the outer layers of cereal grains (aleurone layer). Therefore, high amounts of PA are present in cereal products such as bran and whole-meal bread. PA, a myo-inositol hex-

Table 2. Low- or indigestible carbohydrates supposed to enhance bioavailability of Mg^{2+}.

Studies are sorted by dietary factors. Mg^{2+} intake is consistently indicated in mg. Specifications in mmol were converted to mg.

Species	Design	Duration	Dietary Factor Investigated	Diet/Doses	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
11 Healthy Postmenopausal Women	Randomized, placebo-controlled, double-blind, cross-over (3 weeks wash-out), stable isotope $^{25}Mg^{2+}$	5 weeks	Short-chain fructo-oligosaccharides (sc-FOS)	Diet with sc-FOS (10 g/d) or sucrose (placebo) 250 mg Mg^{2+} + 87.5 mg $^{25}Mg^{2+}$	Mg^{2+} excretion in faeces and urine, Mg^{2+} in blood	sc-FOS increase Mg^{2+} absorption	[80]
14 Healthy Girls	Randomized, placebo-controlled, double-blind, cross-over (12 days wash-out), stable isotopes $^{24}Mg^{2+}$, $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$	36 days (8-d of c-FOS intake)	sc-FOS	Diets with maltodextrin (placebo) or 10 g sc-FOS 41.0 mg Mg^{2+} + 52.5 mg $^{25}Mg^{2+}$ + 21.1 mg $^{26}Mg^{2+}$ intravenously	Mg^{2+} excretion in urine	No significant differences	[30]
15 Post-menopausal Women	Randomized, placebo-controlled, double-blind, cross-over (6 weeks wash-out), stable isotopes $^{25}Mg^{2+}$ $^{26}Mg^{2+}$	6 weeks	Mixture of chicory oligofructose (c-OF) and long-chain inulin (lc-In)	Diet with digestible maltodextrin (placebo) or 5 g c-OF and lc-In 58.0 mg total Mg^{2+} incl. 23.0 mg of $^{26}Mg^{2+}$ + 11.5 mg $^{25}Mg^{2+}$ intravenously	Mg^{2+} excretion in urine	c-OF and lc-Is increase Mg^{2+} absorption	[31]
20 Male Fischer Rats	Parallel group, control-diet	7 days	Galactooligosaccharides (GOS)	Control diet or diet with 5 g GOS/ 100 g Control: 20.0±2.0 mg Mg^{2+}/3 d GOS: 18.7±2.7 mg Mg^{2+}/3 d	Mg^{2+} excretion in faeces	GOS increase Mg^{2+} absorption, action of intestinal bacteria is necessary for the stimulatory effect of GOS	[75]
75 Male Sprague Dawley Rats	Randomized, parallel group, control-diet	8 weeks	GOS, dose-response effect	Control diet or diet containing 2, 4, 6 or 8% GOS Control: 30.4±2.7 mg Mg^{2+}/3 d 2% GOS: 27.9±1.6 mg Mg^{2+}/3 d 4% GOS: 30.2±2.6 mg Mg^{2+}/3 d 6% GOS: 30.9±2.1 mg Mg^{2+}/3 d 8% GOS: 31.2±3.6 mg Mg^{2+}/3 d	Mg^{2+} excretion in faeces and urine	GOS increase Mg^{2+} absorption	[76]
80 Male Wistar Rats	Randomized, control-diet, stable isotope $^{25}Mg^{2+}$	25 days	Inulin (In)	Control diet or diet with 3.75% In for 4 days and then 7.5% In for 21 days Control: 495 mg Mg^{2+}/kg (+ once ~ 2.5 mg $^{25}Mg^{2+}$) In diets: 514 mg Mg^{2+}/kg (+once 2.5 mg $^{25}Mg^{2+}$)	Mg^{2+} excretion in faeces and urine	In increase Mg^{2+} absorption	[37]

(Table 2) contd….

Species	Design	Duration	Dietary Factor Investigated	Diet/Doses	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
60 Male Wistar Rats	Randomized, parallel group, control-diet	40 days	In + different calcium levels	Control diet or diet with 5% In for 4 days and then 10% In, each group divided in 3 subgroups receiving 0.25%, 0.50% and 0.75% calcium short-term balance study: 0.25%: 9.9±1.1 mg Mg^{2+} 0.50%: 9.9±0.6 mg Mg^{2+} 0.75%: 9.5±0.6 mg Mg^{2+} 0.25%+In: 8.2±1.0 mg Mg^{2+} 0.50%+In: 8.1±0.8 mg Mg^{2+} 0.75%+In: 7.4±0.7 mg Mg^{2+} long-term balance study: 0.25%: 10.1±1.4 mg Mg^{2+} 0.50%: 9.2±0.7 mg Mg^{2+} 0.75%: 9.3±0.8 mg Mg^{2+} 0.25%+In: 8.3±1.3 mg Mg^{2+} 0.50%+In: 8.4±1.0 mg Mg^{2+} 0.75%+In: 8.0±1.0 mg Mg^{2+}	Mg^{2+} excretion in urine	In increase Mg^{2+} absorption, efficiency of intestinal Mg^{2+} absorption (%) was negatively affected by calcium intake levels	[77]
Ovariectomized (OVX) Sprague-Dawley Rats	Parallel group, control-diet	4 weeks	In polydextrose	6 treatment groups: Control, OVX-Control, OVX rats receiving daily estradiol (E2) injections, and OVX rats receiving a diet supplement with either In-based fiber (SYN or Fruitafit HD) or polydextrose fiber at 5% wt. of diet no information on Mg^{2+} intake	Mg^{2+} excretion in faeces and urine	In and polydextrose increase Mg^{2+} absorption	[78]
50 Male Wistar Rats	Parallel group, control-diet	3 weeks	Lactulose, pectin, guar gum, amylomaize starch	6 treatment groups: control, 10% lactulose, 10% pectin, 10% guar gum, 25% amylomaize starch, 50% amylomaize starch no information on Mg^{2+} intake	Mg^{2+} excretion in faeces	Fermentable carbohydrates increase Mg^{2+} absorption	[71]
36 Female Wistar Rats	Parallel-group, control-diet	3 weeks	Lactose, lactulose	3 treatment groups: control: 4.8±0.2 mg Mg^{2+}/d, lactose: 4.6±0.1mg Mg^{2+}/d, lactulose: 4.6±0.1 mg Mg^{2+}/d	Mg^{2+} excretion in faeces and urine	Lactose and lactulose increase Mg^{2+} absorption	[86]
36 Female Wistar Rats	Parallel-group, control-diet	13 days	Maize starch Resistant Starch (RS)	3 treatment groups: Low RS[1]: 4.1 mg Mg^{2+}/d High RS_2[2]: 4.1 mg Mg^{2+}/d High RS_3[3]: 4.4 mg Mg^{2+}/d	Mg^{2+} excretion in faeces and urine	RS_2 increases Mg^{2+} absorption, no differences in RS_3	[74]
64 Male Wistar Rats	Parallel-group, control-diet	3 weeks	Raw potato starch (RPS), high amylose starch (HAS)	3 treatment groups: Control: 14.5±0.6 mg Mg^{2+}/d RPS: 15.8±0.7 mg Mg^{2+}/d HAS: 16.1±0.8 mg Mg^{2+}/d	Mg^{2+} excretion in faeces	RPS and HAS increase Mg^{2+} absorption	[73]

(Table 2) contd….

Species	Design	Duration	Dietary Factor Investigated	Diet/Doses	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
32 Male Wistar Rats	Parallel-group, control-diet	3 weeks	In, RS	4 treatment groups: Control: 20.8±1.1 mg Mg^{2+}/d In: 22.4±1.2 mg Mg^{2+}/d RS: 23.0±1.0 mg Mg^{2+}/d In+RS: 21.9±1.1 mg Mg^{2+}/d	Mg^{2+} excretion in faeces and urine	In and RS increase Mg^{2+} absorption	[72]
Exp. 1: 40 Male Sprague-Dawley Rats Exp. 2: 32 Male Sprague-Dawley Rats	Parallel-group, control-diet	Exp. 1: 2 weeks Exp. 2: 1 week	Resistant maltodextrin (Fibersol 2, FS2), hydrogenated resistant maltodextrin (Fibersol 2H, FS2H)	Exp. 1: 5 treatment groups: control: 17.3±0.6 mg Mg^{2+}/d 1.5% FS2: 15.0±0.6 mg Mg^{2+}/d 3%FS2: 15.7±0.6 mg Mg^{2+}/d 1.5%FS2H: 16.0±0.4 mg Mg^{2+}/d 3% FS2H: 15.4±0.5 mg Mg^{2+}/d Exp. 2: 4 treatment groups CX-Ct: 13.3±0.1 mg Mg^{2+}/d CX-FS2H: 13.2±0.1 mg Mg^{2+}/d Sham-Ct: 13.5±0.1 mg Mg^{2+}/d Sham-FS2H: 13.6±0.1 mg Mg^{2+}/d	Mg^{2+} excretion in faeces	Resistant maltodextrin and hydrogenated resistant maltodextrin increase Mg^{2+} absorption	[82]
Exp. 1: 35 Male Wistar Rats Exp. 2: 21 Male Wistar Rats	Parallel-group, control-diet	Exp. 1: 4 weeks Exp. 2: 7 days	Mannitol	Exp. 1: 5 treatment groups: Control, 2M (2% Mannitol), 4M, 6M, 8M Exp. 2: 3 treatment groups: Control, 4M, 8M no information on Mg^{2+} intake	Mg^{2+} excretion in faeces	Mannitol increases Mg^{2+} absorption	[79]
9 Healthy Young Men	Placebo-controlled, Latin-square (3x3) with three repetitions	32 days (each)	Hydrogenated polysaccharide fraction of Lycasin®HBC (polyol)	Diet with dextrose (control) or hydrogenated polysaccharide fraction of Lycasin®HBC 320-330 mg Mg^{2+}/d	Mg^{2+} excretion in faeces and urine	Hydrogenated polysaccharides increase Mg^{2+} absorption	[81]
10 Healthy Young Men	Randomized, cross-over (4 weeks wash-out)	31 days	Glucose-polymer (NUTRIOSE FB)	2 diets 1) control (+ 212±6.0 mg Mg^{2+}/d) 2) 100 g NUTRIOSE FB/d (+ 232±7.0 mg Mg^{2+}/d)	Mg^{2+} excretion in urine and faeces	NUTRIOSE FB enhanced Mg^{2+} absorption	[97]
24 Healthy Adult Males	Randomized, placebo-controlled, double-blind, cross-over (2 weeks wash-out), stable isotopes $^{24}Mg^{2+}$ and $^{25}Mg^{2+}$	Single test meals	Lactulose	Test foods containing lactulose at a dose of 0 g (placebo), 2.0 g (low-dose), or 4.0 g (high-dose) 150 mg Mg^{2+} + 28.0 mg $^{25}Mg^{2+}$	Mg^{2+} excretion in urine	Lactulose increase Mg^{2+} absorption	[36]

[1] Cooked normal starch, [2] Uncooked high amylose starch, [3] Cooked and cooled high amylose starch.

Table 3. Dietary factors supposed to inhibit bioavailability of Mg^{2+}.
Studies are sorted by dietary factors. Mg^{2+} intake is consistently indicated in mg. Specifications in mmol were converted to mg.

Species	Design	Duration	Dietary Factor Investigated	Diet/ Doses	Target Parameter For Mg^{2+} Bioavailability	Core Result	Refs.
9 Healthy Adults	Cross-over (1 day wash-out), stable isotopes $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$	Single test meals	Oxalic acid (OA)	2 diets: 1) 300 g spinach (6.6 mmol OA; 122 mg Mg^{2+} incl. 17.0 mg $^{25}Mg^{2+}$) 2) 300 g kale (0.1 mmol OA; 117 mg Mg^{2+} incl. 29.2 mg $^{26}Mg^{2+}$)	Mg^{2+} excretion in faeces	OA reduce Mg^{2+} absorption	[32]
Male Wister Rats	Parallel group, control-diet	8 days	OA	6 diets: 1) Mg^{2+}-deficient diet (control, 0.3 mg Mg^{2+}) 2) raw powdered spinach (R-sp + 34.5 mg Mg^{2+}) 3) boiled powdered spinach (B-sp + 34.8 mg Mg^{2+}) 4) fried powdered spinach (F-sp + 35.9 mg Mg^{2+}) 5) control diet with OA (Ox-C + 33.6 mg Mg^{2+}) 6) control diet + 31.1 mg Mg^{2+}	Mg^{2+} excretion in faeces and urine	OA reduce Mg^{2+} absorption Rate of absorbed Mg^{2+}: control 88.9%, R-sp 80.2%, B-sp 88.4%, F-sp 90.4%, Ox-C 88.1%, + Mg^{2+} 87.7%	[96]
20 Healthy Adults	Cross-over (1 day wash-out), placebo-controlled, stable isotopes $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$	Single test meals	Phytic acid (PA)	2 diets with 200 g wheat bread: 1) 0.75 mmol PA (+ 88.5 mg Mg^{2+} incl. 17.0 mg $^{25}Mg^{2+}$) 2) 1.49 mmol PA (+ 88.5 mg Mg^{2+} incl. 26.7 mg $^{26}Mg^{2+}$)	Mg^{2+} excretion in faeces	PA reduce Mg^{2+} absorption, PA inhibiting effect was dose dependent	[33]
78 Male Sprague-Dawley Rats	Randomized, control-diet	1, 3, or 5 weeks	Potato starch (PS) with esterified phosphorus (EP)	4 diets: 1) EP-free control diet (+ 11.0 mg Mg^{2+}) 2) 600 g Cornstarch (+ 8.0 mg Mg^{2+}) 3) 600 g Benimaru PS (+ 8.3 mg Mg^{2+}) 4) 600 g Konafubuki PS (+ 9.3 mg Mg^{2+})	Mg^{2+} excretion in faeces	PS-EP reduce Mg^{2+} absorption	[98]
40 Premenopausal and Post Menopausal Women	Randomized, placebo-controlled, single-blind, cross-over (2 weeks wash-out), stable isotope $^{26}Mg^{2+}$	2 weeks + single test meals for Mg^{2+} absorption	Wheat dextrin (WD)	Cookies with 15.0 g WD/d or without (placebo) 120 mg Mg^{2+} incl. 29.2 mg $^{26}Mg^{2+}$	Mg^{2+} excretion in urine	No significant differences	[34]
26 Adolescent Girls	Randomized, placebo-controlled, double-blind, parallel-group	2 weeks	Calcium	3 diets with basal Mg^{2+} intake of 176 mg Mg^{2+}: 1) Placebo diet 2) low calcium (667 mg/d) 3) high calcium (1,667 mg/d)	Mg^{2+} excretion in urine and faeces	No significant differences	[95]
5 Adolescent Girls	Randomized, cross-over (5 weeks wash-out), stable isotopes $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$	2 weeks	Calcium	2 diets (each + 40.0 mg $^{26}Mg^{2+}$ oral + 20.0 mg $^{25}Mg^{2+}$ intravenously): 1) low calcium (800 mg/d) + 305±30.0 mg Mg^{2+}/d 2) high calcium (1,800 mg/d) + 286±9.0 mg Mg^{2+}/d	Mg^{2+} excretion in urine and faeces	No significant differences	[35]

akisphosphate, has a strong binding affinity to important minerals and forms insoluble precipitates, which are not absorbable in the intestine. In a bioavailability study, Bohn *et al*. (2004) demonstrated that PA dose-dependently lowers Mg^{2+} absorption [33]. The amounts of PA tested in the study were similar to those naturally present in whole-meal (1.49 mmol) and in brown bread (0.75 mmol) [97, 98].

Human studies also found an inhibiting effect of partly and non-fermentable fibres such as **wheat bran, cellulose** and **lignin** on Mg^{2+} absorption [99, 100]. Two other human studies also observed a significant increase in faecal Mg^{2+} when cellulose was added to the diet [101, 102]. However, neither study matched the Mg^{2+} concentrations between the diet groups. Fibres such as **hemicellulose** and **pectin** are partly fermentable by intestinal bacteria. Two human studies with healthy males showed an inhibitory effect of hemicellulose on Mg^{2+} absorption [100, 103]. The effect of pectin on Mg^{2+} absorption remains controversial. A rat study observed a positive effect of pectin on Mg^{2+} flux from the caecum to the blood [81]. In contrast, two human studies found no significant difference in Mg^{2+} absorption when feeding healthy subjects citrus pectin [100, 104].

Unlike starch derived from cereals or other plants, **potato starch** contains considerable amounts of phosphorus [105], which is esterified on the carbon-6-hydroxyl group of the glucose molecule [106]. Other **esterified phosphorus**-bonded compounds in food sources, *e.g.*, casein phosphopeptide, are known to enhance the absorption of calcium and other minerals [107]. Therefore, Mineo *et al*. (2009) examined the effect of potato starch feeding for 1, 3, and 5 weeks on apparent Mg^{2+} absorption in bone using a balance study in rats [98]. Two kinds of potato starch (Benimaru potato starch and Konafubuki potato starch) containing different phosphorus contents were used as carbohydrate sources. However, instead of increasing the absorption rate, the ingestion of potato decreased the absorption of Mg^{2+}. The inhibiting effect is likely due to the binding effect of esterified phosphorus on Mg^{2+} and, thus, to enhanced faecal excretion. The study results, which were obtained in growing male rats, are difficult to extrapolate directly to humans. To evaluate the effect of potato starch and esterified phosphorus on Mg^{2+} bioavailability in humans, further experiments are needed.

Two human intervention studies investigated the effect of **low-digestible carbohydrates** on Mg^{2+} absorption [34, 97]. Armas (2011) determined the effect of chronic ingestion of **Wheat Dextrin (WD)** on Mg^{2+} absorption in premenopausal and postmenopausal women [34]. WD is a non-viscous soluble fibre that is used as a supplement to increase fibre intake. In a randomized, two-way cross-over, placebo-controlled, single-blind trial over two weeks, the authors showed that 15 g WD per day had no effect on Mg^{2+} absorption. Supplementation with a low-digestible glucose-polymer (NUTRIOSE FB, 100 g/d) *versus* dextrose in experimental meals was tested by Vermorel *et al*. (2004) in 10 healthy young men [97]. This study, likewise, reported no inhibiting effects of the low-digestible carbohydrate. Instead, the apparent Mg^{2+} absorption increased from 30.4% in the control group to 50.9% in the NUTRIOSE FB group. A possible explanation for the improvement in Mg^{2+} absorption is a high-regulation of the active intestinal absorption in the upper part of the intestine after ingesting fermentable carbohydrates for several weeks [81].

4.2.5. Type of Mg^{2+} Salt/Chemical and Physical Properties

In the past, attention has been given to the type of Mg^{2+} salt that should be administered, especially with respect to supplements. This aspect should be critically discussed in view of other factors influencing bioavailability and retention of the mineral. Surprisingly, there are only a few animal and human studies investigating the bioavailability of different Mg^{2+} salts (Table **4**). In a rat study, Coudray *et al*. (2005) determined the intestinal Mg^{2+} absorption and urinary excretion of various **organic and inorganic Mg^{2+} salts** using stable isotopes ($^{26}Mg^{2+}$) [38]. Eighty male Mg^{2+}-depleted Wistar rats were fed the same diet replete with Mg^{2+} (550 mg Mg^{2+}/kg) as oxide, chloride, sulphate, carbonate, acetate, pidolate, citrate, gluconate, lactate or aspartate. The Mg^{2+} absorption values obtained varied from 50% to 67%. Organic Mg^{2+} salts were slightly more available than inorganic Mg^{2+} salts, whereas Mg^{2+} gluconate exhibited the highest Mg^{2+} bioavailability. However, the study demonstrated that all Mg^{2+} salts were equally efficient in restoring rats' blood Mg^{2+} levels in plasma and red blood cells. Although humans and rats have some differences in intestinal physiology, these results may be extrapolated to human Mg^{2+} nutrition with necessary precautions.

The few human studies, which were predominantly conducted in the early 1990's, that compared the bioavailability of different Mg^{2+} salts led to mixed results (Table **4**). Several chemical balance studies investigating urinary Mg^{2+} excretion in humans found no significant differences between various Mg^{2+} salts, including the comparison of organic with inorganic Mg^{2+} salts [108-120], which indicated that all types of Mg^{2+} are suitable to maintain or restore the Mg^{2+} status. Some other studies observed a slightly better bioavailability of organic Mg^{2+} salts under standardized conditions [112-116].

Lindberg *et al*. (1990) compared Mg^{2+} citrate and Mg^{2+} oxide with respect to *in vitro* solubility and *in vivo* gastrointestinal absorbability in healthy volunteers [112]. The authors observed that the bioavailability of Mg^{2+} citrate was higher than that of Mg^{2+} oxide, possibly due to its better solubility. Likewise, a product study by Kappeler *et al*. (2017) observed a slightly higher bioavailability of Mg^{2+} citrate as compared to Mg^{2+} oxide using 24-h urinary Mg^{2+} excretion as biomarker [116]. However, the difference in urinary Mg^{2+} levels between Mg^{2+} citrate (7.2±1.48 mmol) and Mg^{2+} oxide (6.7±1.43 mmol)-although statistically significant-is marginal. The difference of 0.565 mmol Mg^{2+} is equivalent to 13.7 mg (!) and, thus, physiologically irrelevant, especially with regard to a total Mg^{2+} intake of about 800 mg or more in the study during the test day. Walker *et al*. (2003) compared the bioavailability of Mg^{2+} oxide, Mg^{2+} citrate and Mg^{2+} amino acid chelate after single ingestion (24 h) and chronic administration (2 months) [113]. The authors also reported that the bioavailabilities of Mg^{2+} citrate and Mg^{2+} amino-acid chelate were higher that of Mg^{2+} oxide. Mühlbauer *et al*. (1991) observed that Mg^{2+} L-asparate was more bioavailable than Mg^{2+} oxide in healthy volunteers [114]. Firoz & Graber (2001) determined the Mg^{2+} bioavailability in four commercial Mg^{2+} preparations (Mg^{2+} oxide,

Table 4. Comparative studies on Mg^{2+} bioavailability from different types of Mg^{2+} salts.

Mg^{2+} intake is consistently indicated in mg. Specifications in mmol were converted to mg.

Species	Design	Duration	Type of Mg^{2+} Salt/Formulation Doses	Mg^{2+}-Intake on Empty Stomach or with Diet	Assessment/Adjustment of Mg^{2+}-Status Before Intervention	Control of Mg^{2+} in Diet During Treatment/Intervention Period	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
18 Healthy Female Adults	Randomized, placebo-controlled, cross-over (4 d wash out)	Single intake	3 Mg^{2+} salts: 1) 330 mg Mg^{2+} as Mg-lactate + 30.0 mg Mg^{2+} as Mg-citrate tablets 2) 270 mg Mg^{2+} as Mg-lactate + 90.0 mg Mg^{2+} as Mg-hydroxide tablets 3) 500 mg Mg^{2+} as Mg-chloride solution 4) 500 mg Mg^{2+} as Mg-hydroxide tablets	Before meals	No information ("normal Mg-status")	Subjects were asked to avoid Mg rich foods (no control)	Mg^{2+} excretion in 24-h urine	No significant differences	[108]
17 Healthy Adults	Randomized, parallel-group	Single intake	2 Mg^{2+} salts: 1) 607.6 mg Mg^{2+} as Mg-oxide 2) 607.6 mg Mg^{2+} as Mg-citrate	Sober	Restricted diet 3 d before (200 mg Mg^{2+})	Subjects were asked to avoid Mg preparations	Mg^{2+} excretion in urine (4-h and 2nd 2-h post-load)	Mg-citrate showed significantly greater absorption than Mg-oxide	[112]
8 Healthy Male Adults	Randomized, placebo-controlled, parallel-group	Single intake	2 Mg^{2+} salts: 1) Placebo: 36.5±0.6 mg Mg^{2+} 2) Mg acetate (MgAc) 1130 mg: 162±1.0 mg Mg^{2+} 3) MgAc 2,145 mg: 273±2.4 mg Mg^{2+} 4) MgAc 4,289 mg: 510±2.4 mg Mg^{2+} 5) MgAc 8,578 mg: 974±7.3 mg Mg^{2+} 6) Slow-Mag® (MgCl): 164±0.7 mg Mg^{2+} 7) Almonds: 177±2.4 mg Mg^{2+} 8) Fast: 0 mg Mg^{2+}	Unclear condition	No information ("normal Mg-status")	Standardized diet	Mg^{2+} excretion in urine (4-h, 10-h urine collection)	Mg-acetate showed greater absorption than Mg-chloride, Mg from almonds was as bioavailable as from MgAc supplement	[47]
14 Healthy Adults	Randomized, cross-over (3 d wash out)	Single intake	2 Mg^{2+} salts: 1) 304 mg Mg^{2+} as Mg-citrate 2) 304 mg Mg^{2+} as K-Mg-citrate	With diet	Constant metabolic diet 3 d before (no information on Mg^{2+})	No information on Mg^{2+}	Mg^{2+} excretion in 24-h urine	No significant differences	[110]

(Table 4) contd….

Species	Design	Duration	Type of Mg^{2+} Salt/Formulation Doses	Mg^{2+}-Intake on Empty Stomach or with Diet	Assessment/Adjustment of Mg^{2+}-Status Before Intervention	Control of Mg^{2+} in Diet During Treatment/Intervention Period	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
24 Healthy Adults	Randomized, placebo-controlled, parallel-group	7 days	3 Mg^{2+} salts/ 2 concentrations: 1) 729 mg/d Mg^{2+} as Mg-L-aspartate-HCl tablets 2) 1,093 mg/d Mg^{2+} as Mg-L-aspartate-HCl tablets 3) 729 mg/d Mg^{2+} as Mg-L-aspartate-HCl granules 4) 1,093 mg/d Mg^{2+} as Mg-L-aspartate-HCl granules 5) 729 mg/d Mg^{2+} as Mg-oxide capsules 6) 1,093 mg/d Mg^{2+} as Mg-oxide capsules	With usual diet	One control and one placebo week before	No special diet	Mg^{2+} excretion in urine (7-d cumulative)	Mg-L-aspartate-HCl showed significantly greater absorption than Mg-oxide	[114]
18 Healthy Male Adults 40 Healthy Age-Matched Controls	Randomized, cross-over (2 d wash out)	Single intake	3 Mg^{2+} formulations: 300 mg Mg^{2+} as 1) Mg-phosphate + Mg-oxide 2) Mg-oxide in smooth gelatin capsules 3) Mg-oxide in hard gelatin capsules	After standardized breakfast	6 d Mg^{2+}-saturation period	Standardized diet rich in Mg^{2+}	Mg^{2+} excretion in urine (2-h intervals first in first 12-h, 4-h intervals in next 12-h intervals, 8- and 12-h intervals until 48-h post-load)	No significant differences	[109]
12 Healthy Adults	Randomized, cross-over (1 week wash out)	Single intake	3 Mg^{2+} formulations: 389 mg Mg^{2+} as 1) Mg-chloride solution 2) slow release Mg-chloride tablets 3) Mg-gluconate tablets	Standard low Mg diet intake after fasting state	1 day Mg^{2+} low diet	Low Mg diet	Mg^{2+} excretion in urine at baseline, 0 to 4, 4 to 8, 8 to 12, 12 to 24 h Mg^{2+} in blood at baseline, 1, 2, 3, 4, 8, 12, and 24 h	No significant differences	[111]
16 Healthy Adults	Randomized, cross-over (3 d wash out)	Single intake	3 Mg^{2+} salts: 1) 243 mg Mg^{2+} as Mg-oxide 2) 267 mg Mg^{2+} as Mg-l-lactate 3) 267 mgl Mg^{2+} as Mg-aspartate	With usual diet	No supplement intake ("normal Mg-status")	Subjects were asked to avoid Mg rich foods (no control)	Mg^{2+} excretion in 24-h urine	Mg-chloride, Mg-l-lactate, Mg-aspartate showed a significantly higher bioavailability than Mg-oxide, Mg^{2+} bioavailability from Mg-chloride, Mg-l-lactate and Mg-aspartate was equivalent	[115]

(Table 4) contd….

Species	Design	Duration	Type of Mg^{2+} Salt/Formulation Doses	Mg^{2+}-Intake on Empty Stomach or with Diet	Assessment/Adjustment of Mg^{2+}-Status Before Intervention	Control of Mg^{2+} in Diet During Treatment/Intervention Period	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
46 Healthy Adults	Randomized, parallel-group, placebo-controlled, double-blind	60 days	3 Mg^{2+} salts: 1) 269±34.4 mg/d Mg^{2+} as Mg-amino acid chelate 2) 255±18.3 mg/d Mg^{2+} as Mg-citrate 3) 280±29.8 mg/d Mg^{2+} as Mg-oxide	With usual diet	Subjects were asked to avoid Mg rich foods	Subjects were asked to avoid Mg rich foods (no control)	Mg^{2+} excretion in 24-h urine Mg^{2+} in saliva and plasma	Mg-citrate and Mg-amino-acid chelate showed significantly greater absorption than Mg-oxide	[113]
16 Healthy Adults	Cross-over (5 days wash-out)	Single intake	2 Mg^{2+} salts: 1) 600 mg Mg-oxide 2) 600 mg Mg-hydroxide carbonate	Sober	10 days strict diet with 350 mg Mg^{2+}, first 3 days + 300 mg Mg-citrate	Standardized diet (350 mg Mg^{2+})	Mg^{2+} excretion in 24h urine Mg^{2+} in plasma	No significant differences	[117]
20 Healthy Male Adults	Randomized, cross-over	Single intake	2 Mg^{2+} salts: 1) Mg citrate 2) Mg oxide	With diet	Supplementation with Mg^{2+} to saturate Mg-pools (5 days)	Balanced, mixed diet (300-400 mg Mg/d)	Mg^{2+} excretion in 24-h urine, Mg^{2+} in serum, red blood cells, leukocytes	Mg-citrate showed greater absorption than Mg-oxide	[116]
120 Male Sprague-Dawley Rats	Parallel-group	2 weeks	6 Mg^{2+} salts: 1) Mg-carbonate: 2.8 mg Mg^{2+}/d 2) Mg-chloride: 2.7 mg Mg^{2+}/d 3) Mg-oxide: 2.8 mg Mg^{2+}/d 4) Mg-phosphate: 2.5 mg Mg^{2+}/d 5) Mg-sulfate: 2.6 mg Mg^{2+}/d 6) Mg-silicate: 2.6 mg Mg^{2+}/d	With diet	5-day pretest period with 9 g diet per day (400 mg Mg^{2+}/kg) 8 g diet per day during the experimental period (200 or 400 mg Mg^{2+}/kg)	Yes, same diet	Mg^{2+} excretion in faeces and urine, Mg^{2+} in plasma	No significant differences	[118]
80 Sprague-Dawley Rats	Parallel-group, control-diet	4 weeks	8 Mg^{2+} salts: 1) Control: 4.0 mg Mg^{2+}/100 g 19.0 mg Mg^{2+}/100 g (2-10) 2) wheat flour 3) Mg-sulfate 4) Mg-oxide 5) Mg-chloride 6) Mg-phosphate 7) Mg-carbonate 8) Mg-lactate 9) Mg-citrate 10) Mg-acetate	With diet	No information (“normal Mg^{2+}-status”)	Yes, same mild Mg^{2+}-deficient diet	Mg^{2+} excretion in faeces and urine, Mg^{2+} in plasma	No significant differences	[119]

(Table 4) contd….

Species	Design	Duration	Type of Mg^{2+} Salt/Formulation Doses	Mg^{2+}-Intake on Empty Stomach or with Diet	Assessment/Adjustment of Mg^{2+}-Status Before Intervention	Control of Mg^{2+} in Diet During Treatment/Intervention Period	Target Parameter for Mg^{2+} Bioavailability	Core Result	Refs.
40 Male Wistar Rats	Parallel-group, control-diet	4 weeks	1 Mg^{2+} salt: 1) Control: 10.7±0.7 mg Mg^{2+}/d 2) Mg-chloride: 12.5±1.2 mg Mg^{2+}/d 3) sulphate rich water: 13.7±1.2 mg Mg^{2+}/d 4) carbonate rich water: 13.6±2.0 mg Mg^{2+}/d Day 24: 3 mg of $^{26}Mg^{2+}$ orally + 0.5 mg ^{25}Mg intravenously	With diet	No information	Yes, same diet	Mg^{2+} excretion in faeces and urine, Mg^{2+} in plasma, red blood cells	No significant differences	[120]
80 Male Wistar Rats	Randomized, parallel-group, stable isotope $^{26}Mg^{2+}$	2 weeks	10 Mg^{2+} salts: 600 mg Mg^{2+}/kg diet for two weeks + 1.8 mg $^{26}Mg^{2+}$ 1) Mg-oxide 2) Mg-chloride 3) Mg-sulphate 4) Mg-carbonate 5) Mg-acetate 6) Mg-pidolate 7) Mg-citrate 8) Mg-gluconate 9) Mg-lactate 10) Mg-aspartate	With diet	Run in phase: 3 w 150 mg Mg^{2+}/kg diet	Yes, same diet	Mg^{2+} excretion in faeces and urine, Mg^{2+} in plasma	Organic Mg-salts were slightly more available than inorganic Mg-salts, Mg-gluconate exhibited the highest Mg^{2+} bioavailability	[38]

Mg^{2+} chloride, Mg^{2+} lactate and Mg^{2+} aspartate) in human subjects by using urinary Mg^{2+} excretion [115]. They observed a relatively poor bioavailability of Mg^{2+} oxide but a greater or equivalent bioavailability of the other three Mg^{2+} salts. Dolinska & Ryszka (2004) studied the influence of three different salts at different concentrations on Mg^{2+} absorption in the small intestine of rats using the area under the curve as the endpoint for Mg^{2+} bioavailability [121]. Mg^{2+} absorption was shown to be most efficient from Mg^{2+} gluconate compared to Mg^{2+} fumarate or Mg^{2+} chloride forms.

Together, most of the studies have shown that the availability of organic Mg^{2+} salts is slightly higher than that of inorganic compounds. However, the results of the different studies are hardly comparable because the designs of the studies were different (Table **4**). For example, Mg^{2+} supplements were ingested together with a meal in some studies [38, 108-111, 113-116] or on an empty stomach or unclear conditions in others [47, 112, 117]. A study by Sabatier *et al*. (2002) demonstrated higher Mg^{2+} bioavailability when Mg^{2+}-rich mineral water was consumed with a simultaneous meal [53]. It is questionable whether such food matrix effects similarly affect the bioavailability of Mg^{2+} salts and formulations. The target parameters used to evaluate Mg^{2+} bioavailability vary between studies. Most studies used Mg^{2+} excretion in urine but at different time points ranging from 2 h to 24 h. Another study used the 7-d cumulative Mg^{2+} excretion in urine [114].

Moreover, the validity of numerous studies is limited due to methodological weaknesses. Several studies did not adjust (or did not even assess) Mg^{2+} status by using a Mg^{2+}-defined diet before the intervention period [108, 113, 115]. A similar Mg^{2+} status between the probands is a prerequisite to compare the bioavailability of Mg^{2+}. In other words, several studies did not adequately control Mg^{2+} intake in the background diet or water intake during the treatment or intervention period [110, 112, 114, 116]. Other studies simply encouraged subjects to avoid Mg^{2+}-rich foods or avoid Mg^{2+} supplements [108, 113, 115]. In a recent study [116], the concomitant diet during the test day contained more Mg^{2+} (300-400 mg) than the actual Mg^{2+} content in comparable supplements (300 mg Mg^{2+} citrate or Mg^{2+} oxide). Likewise, the drinking volume was not standardized over the 24 h test day. For example, subjects were allowed to drink Mg^{2+}-containing water ad

libitum until 1 h prior to administration. Moreover, the consumption of Mg^{2+}-containing water was not adequately controlled during the test day. As a result, variations in the Mg^{2+} intake during the test day could have taken place, which question the standardization of the study conditions. In several cross-over studies with a single intake of Mg^{2+}, the wash-out periods were very short (1-3 days) between the treatments [109, 110, 115]. Finally, only one study (with Wistar rats) used stable isotopes ($^{26}Mg^{2+}$), in contrast to all human studies.

Against this background, it is quite difficult to judge the importance of the type of salt for Mg^{2+} absorption. It has to be assumed that it is only one factor in the complex process and not of importance to maintain or restore Mg^{2+} status. Consequently, for legal reasons, several inorganic and organic Mg^{2+} salts are allowed for use in Mg^{2+}-containing drugs and food supplements because they are all suitable for restoring Mg^{2+} status under physiological conditions.

4.2.6. Galenic Properties

In a randomized, controlled, cross-over trial with 22 healthy male volunteers, Karagülle *et al.* (2006) showed that the Mg^{2+} absorption from a single dose of mineral water with comparable pH value (test water I with 120 mg Mg^{2+}/l, or test water II with 281 mg Mg^{2+}/l) was similar to that from a pharmaceutical Mg^{2+} oxide (150.8 mg Mg^{2+}) preparation [122]. The complete ionization of Mg^{2+} in the mineral water and the Mg^{2+} intake in diluted form might account for the good absorbability of Mg^{2+} from mineral waters [123, 124]. In addition, it has been suggested that Mg^{2+} in water, which appears as hydrated ions, can be more readily absorbed than Mg^{2+} from food [125].

This result is consistent with data from a randomized cross-over study with 13 healthy male volunteers that investigated the bioavailability of two different pharmaceutical Mg^{2+} oxide formulations (each 450 mg Mg^{2+}) using urinary Mg^{2+} excretion (24-h urine) as an endpoint [126]. Better bioavailability of Mg^{2+} from Mg^{2+} oxide-effervescent tablets than from Mg^{2+} oxide-capsules was observed. The results showed that although the same Mg^{2+} amount was given with each preparation, the increase in Mg^{2+} excretion with effervescent tablets was twice that obtained with capsules. The authors assumed that the dissolution of Mg^{2+} tablets in water before ingestion results in an ionization of Mg^{2+}, which is an important precondition for absorption. During solution CO_2 production, acidic pH and excess citric acid achieve complete solubility of the Mg^{2+} salt such that Mg^{2+} becomes readily ionized. As a result, the bioavailability of Mg^{2+} from Mg^{2+} oxide effervescent tablets is comparable to that of the organic Mg^{2+}salts, *e.g.*, Mg^{2+} lactate, aspartate, amino acid chelate, and citrate [113, 115].

The few studies examining the effect of slow-release formulations on Mg^{2+} absorption produced different results. In a randomized, cross-over study with 12 healthy volunteers, White *et al.* (1992) compared the bioavailability of a Mg^{2+} chloride solution and slow-release Mg^{2+} chloride tablets by using urinary Mg^{2+} excretion (24-h urine) as the endpoint [111]. The authors observed no significant differences between the galenic forms, which suggests that the delayed-release tablet formulations had no influence on intestinal Mg^{2+} uptake. In contrast, Fine *et al.* (1991) showed that "slow release" Mg^{2+} formulations such as gastric acid resistant capsules also impacted the bioavailability of Mg^{2+} [47]. In their study, it was demonstrated that the Mg^{2+} absorption from enteric-coated tablets (cellulose acetate phthalate) of Mg^{2+} chloride was 67% less than that from Mg^{2+} acetate in gelatin capsules, suggesting that an enteric coating can impair Mg^{2+} bioavailability. Cellulose acetate phthalate requires 3-5-h before it is completely dissolved and the Mg^{2+} chloride is expelled. This delay would presumably reduce the absorptive area in the small intestine, where Mg^{2+} is predominantly absorbed.

SUMMARY AND CONCLUSION

The intestinal absorption of Mg^{2+} is a complex process that involves a saturable (transcellular) active pathway and a non-saturable (paracellular) passive pathway. At physiological luminal concentrations of the mineral, an active, saturable, and transcellular process dominates, whereas at higher doses, the passive, paracellular pathway gains importance. In principle, the relative bioavailability of Mg^{2+} is higher when the mineral is taken up in multiple low doses throughout the day compared to a single intake of a high amount of Mg^{2+}. However, absolute absorption increases with the dose. The uptake of Mg^{2+} can be influenced by physiological factors, such as age and the other food components in a meal. Inhibitory effects can be exerted by high levels of partly fermentable fibres (*i.e.*, hemicellulose), non-fermentable fibres (*i.e.*, cellulose and lignin) and phytate and oxalate. In contrast, the inhibitory effect of other minerals, such as calcium, was not supported because it only occurs when unphysiological amounts are given within a meal. In addition to inhibiting factors, several dietary factors are known to enhance Mg^{2+} uptake, including proteins, MCT, and low- or indigestible carbohydrates such as resistant starch, oligosaccharides, inulin, mannitol and lactulose. Some studies have demonstrated a slightly higher bioavailability of organic Mg^{2+} salts compared to inorganic compounds under standardized conditions, which is probably due to variations in solubility. Other studies did not find significant differences between various Mg^{2+} salts. The design of the few studies investigating the differences in Mg^{2+} salts was heterogeneous. In addition, many of these studies had methodological weaknesses that limited the significance of the results. Due to the lack of standardized tests to assess Mg^{2+} status and intestinal absorption, it remains unclear which Mg^{2+} binding form shows the highest bioavailability. Animal studies showed that organic and inorganic Mg^{2+} salts were equally efficient at restoring depleted Mg^{2+} levels in plasma and red blood cells, despite a slightly higher bioavailability of organic Mg^{2+} compounds. Because Mg^{2+} cannot be stored but only retained for current needs, this aspect is less relevant than it is often thought to be. Higher absorption is followed by higher excretion of the mineral in most cases. In practice, especially in the case of additional administration of Mg^{2+} with a meal, absorption is superimposed by individual physiological conditions and the other food compounds. Due to the importance of passive paracellular Mg^{2+} absorption, the quantity of Mg^{2+} in the intestinal tract is the major factor controlling the amount of Mg^{2+} absorbed from the diet. In addition to standardized markers for Mg^{2+} uptake and status, there is a need for further studies investigating the intestinal absorption and

bioavailability of Mg^{2+} that also include endogenous and exogenous factors.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that this article content has no conflict of interest.

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