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Review

Interaction of divalent minerals with liposoluble nutrients and phytochemicals during digestion and influences on their bioavailability – a review

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A B S T R A C T

Several divalent minerals, including the macroelements calcium and magnesium, are essential nutrients for humans. However, their intake, especially via high-dose supplements, has been suspected to reduce the availability of lipophilic dietary constituents, including lipids, liposoluble vitamins, and several phytochemicals such as carotenoids. These constituents require emulsification in order to be bioavailable, and high divalent mineral concentrations may perturb this process, due to precipitations of free fatty acids or bile salt complexation, both pivotal for mixed micelle formation. Though in part based on *in vitro* or indirect evidence, it appears likely that high-dose supplements of divalent minerals around or even below their recommended dietary allowance perturb the availability of certain liposoluble miroconstituents, in addition to reducing absorption of dietary lipids/cholesterol. In this review, we investigate possible negative influences of divalent minerals, including trace elements (iron, zinc), on the digestion and intestinal uptake of lipophilic dietary constituents, with a focus on carotenoids.

1. Introduction

For the past two decades, there has been an increasing interest in phytochemicals and recognition of their potential benefits in human nutrition and health. Phytochemicals cover a wide range of secondary plant compounds that are considered not to be essential for humans, i.e. their absence in the diet does not cause any deficiency symptoms. However, the intake of several dietary phytochemicals has been associated with the prevention of certain chronic conditions, such as cancer (Giovannucci, 2002; Surh, 2003), type 2 diabetes and insulin resistance (Coyne et al., 2005), and cardiovascular diseases (Voutilainen, Nurmi, Mursu, & Rissanen, 2006). Some of these phytochemicals and other food microconstituents are highly lipophilic molecules, i.e. with high octanol-water partition coefficients (log $P_{oct} > 8$), and tend to readily dissolve in oil. These include, among other, carotenoids, mono- and diterpenes, and triterpenes/triterpenoids such as phytosterols, as well as fat soluble vitamins (A, E, D, and K) (Fig. 1).

Given their highly lipophilic nature, these food microconstituents tend to share similar crucial steps during their digestion, including the transfer from the food matrix into a lipid phase, emulsification, inclusion into mixed micelles, diffusion through the mucus to the unstirred water layer, binding to the enterocyte, and cellular uptake (Gropper & Smith, 2013). The transfer of lipophilic food microconstituents from the food matrix via lipid droplets into mixed micelles is especially important and a limiting step in their bioavailability, i.e. the fraction of a nutrient/non-nutrient that is absorbed and available for use and/or storage in body organs. In recent years, dietary aspects influencing the bioavailability of highly lipophilic food microconstituents, especially carotenoids, have been reviewed comprehensively (Borel, 2003), highlighting the importance of sufficient lipids (Unlu, Bohn, Clinton, & Schwartz, 2005) and a limited amount of dietary fibre (Palafox-Carlos, yala-Zavala, & Gonzalez-Aguilar, 2011) as crucial factors influencing their bioavailability.

One dietary factor that has recently been proposed to affect *in vitro* carotenoid bioaccessibility and cellular uptake is the presence of divalent minerals, especially at concentrations that are common for dietary supplements, usually at half to full the recommended dietary allowance (RDA). For example, calcium at concentrations between 12.5 and 25 mM reduced the bioaccessibility of beta-carotene from a spinach based meal by approximately 80% (Biehler, Hoffmann, Krause, & Bohn, 2011; Corte-Real, Bertucci et al., 2017 Table 1). Very recently, a human trial corroborated the potential negative effects of divalent minerals on carotenoid absorption, showing that a dietary supplement containing 500 mg of calcium reduced lycopene absorption from tomato paste by

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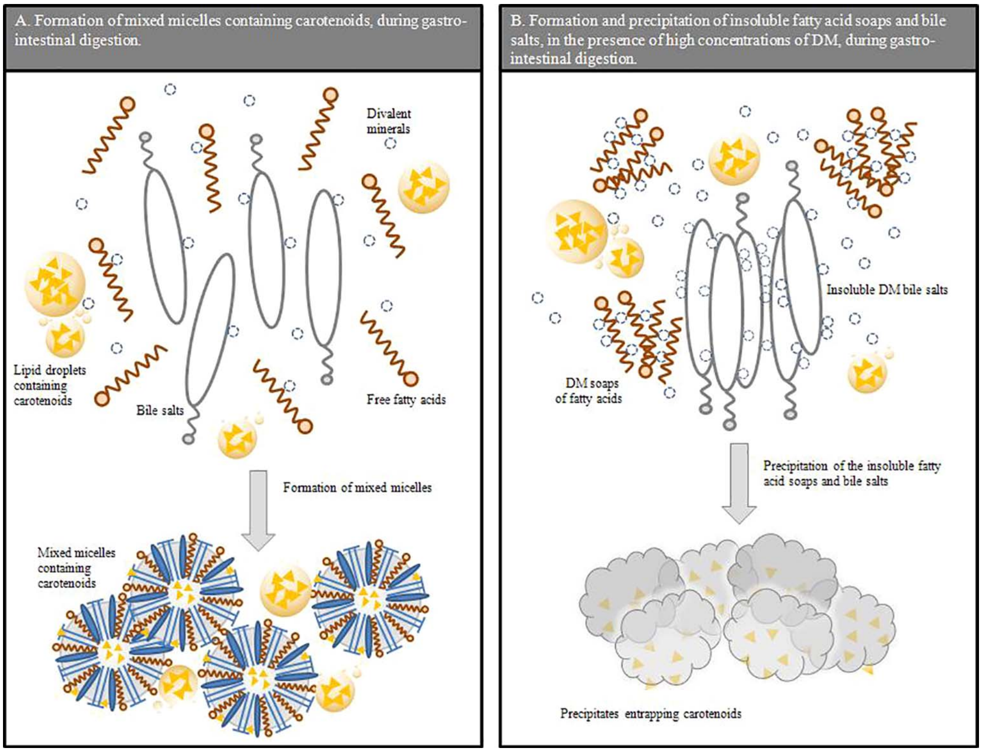

Fig. 1. Possible interactions of divalent minerals and liposoluble dietary constituents during digestion, exemplified for carotenoids.

up to 83%, as measured by plasma appearance (Borel et al., 2016). The ability of divalent minerals to bind free fatty acids and bile acids, leading to the formation of poorly soluble soaps (Govers & Van der Meet, 1993) and salts (Hofmann & Mysels, 1992), respectively, may in fact inhibit the transfer of lipophilic food microconstituents from the food matrix into mixed-micelles, limiting eventually their bioavailability. The non-absorbed fraction would then pass on to the colon, where they will likely not become available either, or are in part degraded by the microbiota (Goni, Serrano, & Saura-Calixto, 2006), and are finally excreted via the faeces.

Dietary divalent minerals include several essential macrominerals, such as calcium and magnesium, and microminerals, also termed trace elements, such as iron and zinc, as the most predominant ones. Due to their participation in many essential functions in the human body, a sufficient intake of these minerals is paramount. While calcium is especially of relevance for bone metabolism, magnesium plays a crucial part in many energy-related metabolic functions, acting as a cofactor for many enzymes. Iron is part of haemoglobin and required for the formation of functional erythrocytes, and zinc is likewise required for energy metabolism and constitutes a cofactor for many enzymes (Gropper & Smith, 2013).

The RDA for calcium, magnesium, iron and zinc are 1000, 400, 8 and 11 mg/d, respectively, for adult men (age category 19–40). Yet, a significant percentage of the population fails to meet 100% of the RDA for mineral and trace element intake, as well as of certain vitamins. For example, it is estimated that in the United States, more than half of the population aged ≥ 2, does not meet the RDAs for vitamin B-6, vitamin A, magnesium, calcium, and zinc (Cordain et al., 2005). As a solution, due to their dietary importance and convenience, supplements are widely offered on the market and are frequently consumed. For calcium, typical dietary supplements contain between 250 and 1200 mg per unit (mostly, a tablet), for magnesium these are 100–600 mg, and for iron and zinc up to 65 and 50 mg, respectively.

Especially in developed Westernized countries, up to 66% of the population consumes regularly dietary multimineral/multivitamin supplements (Skeie et al., 2009), at least in several, though not all of these countries. Given their frequent use in today's society, and the potential inhibitory effects of divalent minerals on the bioavailability of dietary lipophilic microconstituents, we aimed at providing an overview of literature, shedding evidence on the interaction between dietary minerals/trace elements and lipophilic food microconstituents during intestinal digestion and cellular uptake. This would also be of interest for subjects with digestive malfunctions, such as those with pancreatitis, or for subjects with already poor absorption of certain micronutrients, such as those with inflammatory bowel disease. Often, these conditions are associated with deficient bile and pancreatic enzyme secretion, causing steatorrhea and absorption deficiencies of certain nutrients, such as of vitamin E, most likely due to the impeded ability to form mixed-micelles during the small intestinal passage (Stahl et al., 2002). It could be hypothesised that intake of divalent minerals as supplements would worsen the effects of these conditions. For this purpose, literature (Pubmed, Medline databases) was searched for English reports, from all years until today, employing the search terms: ("minerals" or "calcium" or "magnesium" or "iron" or "zinc") and ("digestion" or "bioavailability" or "bioaccessibility" or "intestine") and ("carotenoid" or "vitamin" or "lipid" or "fat").

2. Effect of divalent minerals on digestion

Dietary mineral release typically starts in the stomach, where digestive enzymes (pepsin, gastric lipase) and peristaltic movements work towards the food matrix breakdown, and the rather acidic gastric pH (fasting 1-5-2.0; with food 3–5) (Alminger et al., 2014) aids in releasing the minerals from their bound forms, such as in organic complexes including phytic acid or oxalic acid. Solubilized minerals, present in their free ionised form, can be taken up in the small intestine, both via passive transport and facilitated uptake, via e.g. calcitriol-regulated transporters such as for calcium (Gropper & Smith, 2013), though a smaller fraction may also reach the colon (Gopalsamy et al., 2015). Trace elements (e.g. iron and zinc) are principally absorbed in the upper small intestine (duodenum and jejunum), while the macrominerals calcium and magnesium appear to be absorbed throughout the small intestine, either by active or passive transport, but especially in the latter sections of the small intestine, the ileum (Gropper & Smith,