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Prebiotics and the Bioavailability of Minerals and Trace Elements[#]

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ABSTRACT

Promising evidence exists for a stimulatory influence of prebiotic carbohydrates (non-digestible oligosaccharides (NDO) and lactulose) on the bioavailability of minerals and trace elements, although most information is available from rat experiments. Because the number of human studies is limited, additional research is needed, especially studies that focus on the long-term effects of prebiotics on bone metabolism. The hypothesized mechanisms suggest that prebiotics that result in a strong pH reduction, a pronounced osmotic effect, a stimulation of the exchange of protons, an increased level of butyrate and calbindin, and an enlarged surface area in the colon may be promising candidates for increasing the absorption of minerals and trace elements. Because the place of colonic fermentation seems to be of influence in these mechanisms, the use of mixtures of different types of prebiotics is of special interest. Probiotics are involved in most prebiotic-related mechanisms, possibly mediated in part by the production of polyamines. Therefore, the combined use of pre- and probiotics may yield promising results. More detailed information on the present state-of-the-art concerning the effects of prebiotics on the bioavailability of minerals and trace elements in different life

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stages, discussed by study design and its underlying mechanisms, can be found in this review.

Key Words: Bioavailability; Minerals; Non-digestible carbohydrates; Prebiotics; Trace elements.

1. INTRODUCTION

Carbohydrates that become available for the colonic fermentation process are most interesting if they can be defined as prebiotics: "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or the activity of one or a limited number of bacteria in the colon" (Gibson, 1995). Of the currently available fermentable carbohydrates, non-digestible oligosaccharides (NDO) are the only carbohydrates that convincingly can be regarded as prebiotics (Roberfroid, 2001). These components include raffinose, stachyose, fructo-, galacto-, isomalto- and xylo-oligosaccharides, maltodextrins, polydextrose, polydextrins, and some inulins (Blackwood et al., 2000; Cummings and Englyst, 1995), which exhibit a different degree of polymerization, mostly varying from 3 to 10. Although the role of lactulose in enhancing specific microorganisms has not been validated effectively, this disaccharide is commonly also regarded as prebiotic (Collins and Gibson, 1999; Salminen and Salminen, 1997).

Promising research evidence exists for a beneficial effect of prebiotics on the bioavailability of dietary minerals and trace elements, which refers to the proportion of such nutrients that are absorbed, retained, and used for normal body functions (Fairweather-Tait, 1998; Lönnerdal, 1985). This health benefit of prebiotics is discussed in this review, with special attention for conditions of high nutrient requirements, such as growth, adolescence, and postmenopause. In addition, the importance of study design and possible underlying mechanisms of the effects is described.

2. PREBIOTICS AND THE BIOAVAILABILITY OF MINERALS AND TRACE ELEMENTS DURING CONDITIONS OF HIGH-NUTRIENT REQUIREMENTS

2.1. Growth

Adequate bioavailability of minerals and trace elements is of particular importance during growth when the requirement for minerals and trace elements is high. Prebiotics may positively influence bioavailability and hence, extensive research has been performed in young growing rats (defined by us as ≤ 7 weeks old and/or ≤ 200 g). Information from infant studies is scarce, but some studies have been performed in adolescents, which are of interest because of the pubertal growth spurt.

2.1.1. Growing Rats

Table 1 shows an overview of the reported effects of prebiotic components on the bioavailability of minerals and trace elements in young growing rats. The studies have

Table 1. Reported effects of prebiotic components on the bioavailability of minerals and trace elements in young growing rats (defined as ≤7 weeks old and/or ≤200 g)[a].

Authors	Dietary % prebiotic	Effect on absorption	Effect on bone/status	Effect on mineral retention
Delzenne et al. (1995)	10% FOS		[b]	Ca↑ Mg↑ Fe↑ Zn↑ Cu−
	10% inulin			Ca↑ Mg↑ Fe− Zn↑ Cu−
Lopez et al. (2000)	10% FOS	Ca↑ Mg↑ Fe↑ Zn− Cu↑	Ca tibia− Mg tibia↑ Zn tibia− Fe[c]− Cu[d]−	[b]
Kashimura et al. (1996)	5% IBO	Ca↑ Mg↑ Fe↑ P↑	[b]	Ca↑ Mg↑ Fe↑ P↑
Vanhoof and Schrijver (1996)[e]	6% inulin	Ca− Mg− Fe− Zn− P↓	[b]	Ca− Mg↓ Fe− Zn− P−
Heijnen et al. (1993)	14% lactulose	Ca↑ Mg↑ P↑	[b]	Ca− Mg↑ P↑
Ohta et al. (1998a)	5% FOS	Ca↑	[b]	[b]
	10% FOS	Ca↑		
Chonan and Watanuki (1995)	5% GOS	Ca↑	[b]	Ca↑
	10% GOS	Ca↑		Ca↑
Ohta et al. (1995b)	5% FOS	Ca↑ Mg↑	[b]	[b]
Ohta et al. (1996)	5% FOS	Ca↑ Mg↑	Ca femur↑ Mg femur−	Ca↑ Mg↑
Takahara et al. (2000)	5% FOS	Ca↑ Mg↑	Ca femur↑ Mg femur↑ P femur↑	[b]
Morohashi et al. (1998)[e]	5% FOS	Ca↑	Ca−	Ca↑
Chonan and Watanuki (1996)	5% GOS	Ca↑[f]	Ca tibia↑[f] Ca femur↑[f]	[b]

[a]Stimulatory (↑), no (−), or negative (↓) effects are indicated. FOS, fructooligosaccharides; GOS, galactooligosaccharides; IBO, isomaltulose-based oligomers.
[b]Not measured.
[c]Measured by plasma iron concentration, transferrin saturation, and liver iron content.
[d]Measured by plasma copper concentration and liver copper content.
[e]Rats weighing about 200 g.
[f]Only in rats fed a normal-calcium diet (0.5%), not in rats fed a low-calcium diet (0.05%).

mainly shown positive effects on the absorption of calcium, magnesium, and iron, although this was not confirmed by Vanhoof and Schrijver (1996). The absence of effects in their study may be due to the full-grown state of the rats or the relatively low dose of inulin. Contradicting results were found for the effects of prebiotics on the bioavailability of phosphorus, zinc, and copper. Because the number of studies is limited, further research is needed. Next to absorption, the rat experiments indicate physiological importance of prebiotics for bone metabolism during growth.

2.1.2. Infants

During the vulnerable period of infancy, an optimal bioavailability of minerals and trace elements is very important, because requirements are high due to the rapid rate of growth and development. Preterm infants are especially at risk of developing deficiencies, which can lead to serious adverse, effects. Worldwide, iron and zinc deficiency are the most prevalent micronutrient deficiencies in infants (Fomon et al., 2000; Hercberg et al., 2001; Lönnerdal, 1997; Krebs and Westcott, 2002). An association has been established between iron deficiency anemia during the first years of life and delayed cognitive development (Hurtado et al., 1999). A mild zinc deficiency has been associated with adverse effects on growth, immune function, development, and activity (Lönnerdal, 1997; Kerbs and Westcott, 2002), and an adequate calcium supply in infants is important because inadequate calcium nutrition has been associated with a reduced bone mineral content (Lönnerdal, 1997).

Knowledge of magnesium absorption in infants is limited, but preterm infants are at risk for magnesium deficiency and may consequently exhibit hypomagnesemia (Caddell et al., 1999; Lönnerdal, 1995). Although the fortification of infant formulas with iron, zinc, and calcium is widely recommended, this may reduce the absorption of other elements due to interaction effects (Chierici et al., 1992; Davidsson et al., 1991; Hallberg et al., 1992; Haschke, 1989; Lönnerdal, 1997; Sandström, 2001; Wood and Zheng, 1997). Human milk contains substantial quantities of oligosaccharides, especially galacto-oligosaccharides (GOS) (Coppa et al., 1993; Kunz et al., 2000). Therefore, to simulate the nutritional value and beneficial effects of human milk, some infant food companies include NDO in their infant formulas (Rivero-Urgell and Santamaria-Orleans, 2001), which is also interesting because of the potential of these components to optimize the absorption and utilization of iron, zinc, calcium, and magnesium.

Although no studies have been performed on the effects of NDO or lactulose on the bioavailability of minerals and trace elements from infant formulas, some studies have addressed the effects of lactose. This is of importance in the context of prebiotics, because in people who are not (completely) capable of hydrolysing lactose, this disaccharide may become available for colonic fermentation, as shown in preterm infants (Kien et al., 1996; 1998). Lactose did not increase calcium absorption in preterm infants (Stathos et al., 1996; Wirth et al., 1990), whereas a positive relationship between lactose and the absorption of calcium was observed in term infants (Abrams et al., 2002; Kobayashi et al., 1975; Moya et al., 1992; Ziegler and Fomon, 1983) and lactase-deficient infants (Saarela et al., 1995). The inconsistency in results may be explained by the extent of lactose degradation by available lactase. Considering the positive effects lactose can exert, it is plausible that research in (pre)term infants into the effects of prebiotics on the absorption of calcium and possibly other minerals and trace elements could yield promising results.

2.1.3. Adolescents

Pubertal growth spurt is associated with a rapid increase in calcium gain by the skeleton, stressing the importance of adequate calcium nutrition during adolescence (Abrams et al., 2000). An optimal bioavailability of calcium is not only important to achieve maximal peak bone mass but also to prevent bone loss and osteoporosis-related fractures in adulthood (Anderson, 2001). However, many adolescents do not consume calcium in amounts that are optimal for bone mineralization, which are assumed to be 1000–1200 mg/day (Guéguen and Pointillart, 2000). Therefore, some studies have been performed on the effects of prebiotics on the bioavailability of calcium in adolescents. One study also looked at the effects on the absorption of magnesium, which seems to be the second most important mineral necessary for skeletal development (Martini, 1999).

In a study by van den Heuvel et al. (1999a), 12 male adolescents (mean age of 15.3 years) consumed either 5 g fructooligosaccharides (FOS) or a control substrate containing orange juice three times per day (breakfast, lunch, and dinner) for a period of 9 days. The effect on true calcium absorption was measured by using the dual stable isotope technique. Subjects received an oral dose of a stable calcium isotope, added to the orange juice drunk at breakfast, followed by an intravenous administration of another stable calcium isotope. Urine was collected for 36 hr; by determining the relative ratio of the oral vs. the intravenous isotope in this urine pool, true calcium absorption was calculated. The treatments were given according to a randomized, double-blind crossover design, separated by a 19-day washout period. The FOS increased calcium absorption from 47.8% ± 16.4% during the reference treatment ($n = 12$) to 60.1% ± 17.2% during the FOS treatment ($n = 11$) (mean ± SD).

Most of the research in adolescents has focused on girls. Griffin et al. (2002) investigated female adolescents (11.0–13.9 years old), who were instructed to maintain a calcium intake aimed at providing a total of about 1500 mg/day, by consuming a glass of calcium-fortified orange juice with breakfast and dinner, and a glass of milk, calcium-fortified orange juice or a serving of yoghurt with lunch. The study had a double-blind crossover design with treatment periods of 3 weeks, separated by a washout period of 2 weeks. The girls were randomized to receive two 4-g servings of NDO or two 4-g servings of placebo daily, one added to the morning glass of orange juice and the other to the evening glass of orange juice. Two similar protocols were carried out simultaneously. In protocol I ($n = 30$), FOS were investigated, whereas in protocol II ($n = 29$), the NDO used were a mixture of inulin and FOS. Calcium absorption was determined at the end of the 3-week intervention by using a modification of the dual stable isotope technique. For this technique, subjects consumed together with a low-calcium breakfast and the evening meal, the calcium-fortified orange juice to which, next to the 4-g serving of NDO, a dose of calcium isotope had been added. Immediately after breakfast, another calcium isotope was infused intravenously, and 48-hr urine collection was begun. No effect was found for 8 g FOS, but the daily consumption of 8 g of the inulin/FOS mixture increased calcium absorption from 32.3% ± 9.8% to 38.2% ± 9.8% (mean ± SD).

Van den Heuvel et al. (submitted (b)) also selected adolescent girls (mean age of 12.7 years), but only girls with a low calcium intake (316–858 mg/day) were selected. In this study, the short- and long-term effects of FOS on the absorption of calcium and magnesium were studied. Fourteen subjects received a FOS or placebo treatment for 37 days according to a randomized, double-blind, crossover design with a washout period of 12 days. For the first 9 days, subjects were instructed to ingest two sachets per day, one at breakfast and one at dinner, each consisting of 5 g FOS or 5 g placebo. After that period, FOS were given according to an intermittent mode, on average 7 g/day. Both on day 8 (short-term) and on day 36 (long-term), the dual stable isotope technique was applied to determine the absorption of calcium and magnesium. Immediately after the administration of the isotopes at breakfast, subjects were instructed to collect urine for 46 hr. The FOS did not affect calcium absorption after 8 or 36 days of treatment. The absorption of magnesium was affected neither after 8 days, but FOS increased magnesium absorption after 36 days of treatment, from 30.1% ± 9.1% in the placebo group to 35.4% ± 12.8% in the FOS group (mean ± SD).

Prebiotics seem to be promising components for increasing the absorption of calcium and magnesium in adolescents, although results are sometimes contradictory. This may be due to differences in study design, which is discussed later. The studies that found a positive effect of NDO on the absorption of calcium or magnesium did not find an increase in urinary excretion of these minerals (Griffin et al., 2002; van den Heuvel et al., 1999a, submitted (b)), which suggests that the increase in absorption may have led to a higher level of mineral that was taken up by the bone tissue and may have helped to maximize peak bone mass. Several studies in young growing rats underscore this suggestion (Chonan and Watanuki, 1996; Ohta et al., 1996; Takahara et al., 2000). However, whether a NDO-induced increase of calcium and magnesium absorption indeed has physiological relevance for bone metabolism of adolescents remains to be established. In the study of van den Heuvel et al. (submitted (b)), consumption of FOS increased magnesium absorption, but no effects on parameters of bone metabolism were found. The absence of effects on these parameters was possibly due to the absence of an effect on calcium absorption or to the relatively small change in magnesium absorption (18%). In addition, the number of subjects ($n = 14$) may have been too small to find an effect on bone parameters.

2.2. Postmenopause

Postmenopause is, next to growth, another stage of life in which subjects with a high nutrient requirement can benefit from the potential benefits of prebiotics. In postmenopausal women, substantial bone loss and consequently osteoporosis are commonly observed as a consequence of a change in bone turnover. The incidence of osteoporosis and morbidity associated with osteoporosis, such as bone fractures, are increasing worldwide and makes osteoporosis one of the main medical and social problems for the elderly in Western countries. Although the most important cause of postmenopausal osteoporosis is estrogen deficiency, nutritional factors also play a primary role in bone health; especially an adequate bioavailability of calcium, phosphorus, and magnesium is of paramount importance (Tranquilli et al., 1994). In this, prebiotics may be beneficial. This has been studied in ovariectomized rats, a model for the human postmenopausal state. Some studies have been performed in postmenopausal women.

2.2.1. Ovariectomized Rats

Chonan et al. (1995) studied 4-week-old ovariectomized rats (about 170 g body weight) and found that 5% GOS feeding increased calcium absorption after 8–10 days and 18–20 days, although no effect was found after 28–30 days. In addition, GOS feeding had a positive effect on bone (femur and tibia) ash weight and tibia calcium content, whereas femur calcium content was unaffected. In 8-week-old ovariectomized mice (about 25 g), a diet containing 5% FOS did not affect the femoral contents of calcium, magnesium, and phosphorus but efficiently prevented femoral bone loss (Ohta et al., 2002). Other studies showed that 5% FOS feeding prevented ovariectomy-induced loss of trabecular structure (Scholz-Ahrens et al., 2001a) and positively affected femur calcium levels (Scholz-Ahrens et al., 2001b) in 5-month-old ovariectomized rats on a diet containing 1% calcium, although neither study observed effects of 2.5%, 5%, or 10% FOS when the diet contained 0.5% calcium. However, a positive trend toward a linear relation between the dosage of FOS and bone mineralization was found (Scholz-Ahrens et al., 2001b). These studies indicate that there is convincing evidence for a positive effect of prebiotics on bone health in ovariectomized rats.

2.2.2. Postmenopausal Women

Van den Heuvel et al. (1999b) investigated whether lactulose would affect true calcium absorption in postmenopausal women. Twelve women (mean age of 60.5 years) received a solution with a reference substance or 5 or 10 g lactulose per day at breakfast for 9 days. These three treatments were given according to a randomized, double-blind, crossover design with two 19-day washout periods. At day 8 of each treatment period, true intestinal calcium absorption was measured by applying the dual stable isotope technique, for which subjects collected urine for 36 hr. A linear relationship was found between the dose of lactulose and its positive effect on calcium absorption. The highest dose of lactulose increased true calcium absorption from 27.7% ± 7.7% to 32.2% ± 7.0% (mean ± SD). In another study with a similar design, the effect of GOS was investigated. Twelve postmenopausal women (mean age of 62 years) received a daily dose of GOS or the reference treatment divided over breakfast and lunch. Adaptation to GOS was ensured by gradually increasing the daily dose from 10 g GOS on days 1–2 to 15 g on days 3–4, followed by 20 g daily on days 5–9 of treatment. The GOS increased true calcium absorption from 20.6% ± 7.0% during the reference treatment to 23.9% ± 6.9% (mean ± SD) during the GOS treatment (van den Heuvel et al., 2000). Both lactulose and GOS increased calcium absorption without an accompanied increase in urinary calcium excretion. Therefore, it was suggested that these prebiotics may have increased the uptake of calcium by the bones or may have inhibited bone resorption (van den Heuvel et al., 1999b; 2000), which is supported by studies in ovariectomized rats (Chonan et al., 1995; Ohta et al., 2002; Scholz-Ahrens et al., 2001a; 2001b).

One human study looked at the effect of FOS on markers for bone metabolism during human postmenopausal conditions. In this study, the effect of FOS on the absorption of magnesium was investigated in 11 postmenopausal women (mean age of 59 years). Volunteers received either 5 g FOS or the reference substance at lunch for the first 4 days of the study, followed by consumption of 10 g/day (5 g at lunch and 5 g at dinner) for the rest of the treatment period to obtain the best adaptation. The study had a randomized double-blind crossover design and treatment periods lasted 5 weeks each, separated by a washout period of at least 3 weeks. Subjects ingested a stable magnesium isotope together with a fecal marker at lunch on day 28 and intestinal magnesium absorption was determined by isotopic label monitoring of feces, plasma, and urine. The addition of FOS increased intestinal magnesium absorption from $30.2\% \pm 5.0\%$ to $33.9\% \pm 7.2\%$ (mean $\pm$ SD). This increase was accompanied by an increase in plasma magnesium isotope level and a higher retention and urinary excretion of magnesium isotope (Tahiri et al., 2001). Recently, another publication on the same study showed that FOS did not have an effect on intestinal calcium absorption (Tahiri et al., 2003). Furthermore, markers of bone formation and bone resorption had not been changed by FOS (Tahiri et al., 2001; 2003), which may be explained by the very variable age of the subjects (50–70 years old) and, consequently, postmenopausal status. Because individual variability in the skeletal response to menopause is great (Kleerekoper, 1996) and bone loss is largely age-related (Tohmé et al., 1991), it would be better to include postmenopausal women who show less variation in postmenopausal age to minimize the variation in parameters of bone metabolism.

It can be concluded that prebiotics are capable of increasing the absorption of calcium and magnesium in postmenopausal women. This may be promising with regard to the prevention of osteoporosis, because deficiency of calcium or magnesium is recognized as a risk factor for postmenopausal osteoporosis. Although such a benefit of prebiotics for bone health after menopause was observed in ovariectomized rats (Chonan et al., 1995; Ohta et al., 2002; Scholz-Ahrens et al., 2001a; 2001b), this has not been confirmed by human studies yet, and long-term studies are needed.

2.3. Other Conditions of High Nutrient Requirements

Besides growth and postmenopause, a specific deficiency is another condition of increased requirements for minerals and trace elements. In addition, after gastrectomy, the surgical treatment of peptic ulcers and stomach cancer, the use of prebiotics may be beneficial. Because gastric acid is thought to facilitate absorption, malabsorption of minerals and trace elements is often observed after gastrectomy and may be one of the factors that contributes to complications such as postgastrectomy anemia and osteopenia. Whether prebiotics can increase the bioavailability of minerals and trace elements during deficiency or after gastrectomy has been investigated in several rat experiments.

2.3.1. Iron

To detect effects of absorption aids on the bioavailability of iron, a high iron requirement is probably necessary, because iron homeostasis is primarily regulated through its absorption (Rucker et al., 1994); iron cannot be excreted via other ways. In iron-deficient anemic rats, 5% FOS improved recovery from anemia and resulted in an increased absorption of iron, calcium, and magnesium, regardless of the level of iron in the diet (Ohta et al., 1995a). In addition, the development of postgastrectomy anemia was completely prevented after 7.5% FOS feeding (Ohta et al., 1998e; Sakai et al., 2001a; 2001b). This was confirmed in another study in gastrectomized rats, in which 7.5% FOS feeding also increased iron absorption in rats fed a non-heme iron-containing diet. In rats fed the heme diet, the increase in iron absorption was only slight and non-significant, although FOS improved hematocrit values and hemoglobin levels and increased hemoglobin regeneration efficiency (HRE) in these rats (Ohta et al., 1999). In contrast to FOS, 7.5% inulin feeding did not lead to recovery of postgastrectomy anemia in gastrectomized rats (Sakai et al., 2000b).

2.3.2. Magnesium

As for iron, stimulatory effects of prebiotics on magnesium absorption were observed under conditions of increased nutrient requirements. Diets containing 1% or 5% FOS have been found to increase apparent magnesium absorption in magnesium-deficient rats. Moreover, FOS reduced inflammation in these rats, such as peripheral hyperemia and hemorrhage (Ohta et al., 1994a). Another study in magnesium-deficient rats showed that consumption of 5% GOS resulted not only in an increased magnesium absorption but also in increased magnesium levels in serum and femur, and a reduced accumulation of calcium in kidneys and heart (Chonan et al., 1996). In addition, 10% FOS feeding increased magnesium absorption in gastrectomized rats (Ohta et al., 1998b).

2.3.3. Calcium

Calcium homeostasis is known to proceed via the skeleton, the kidneys, and the gastrointestinal tract. The potential effect of prebiotics on calcium bioavailability is probably best observable under conditions of increased calcium requirements. Ohta et al. (1998b; 1998d) found that 10% and 7.5% FOS increased calcium absorption in gastrectomized rats. The increases were higher than those found in studies with normal rats, which was possibly related to the level of the calcium-binding protein calbindin in the colon (Ohta et al., 1998b); this was increased more effectively by FOS in gastrectomized rats (Ohta et al., 1998b) than in normal rats (Ohta et al., 1998a; Takasaki et al., 2000). Moreover, the condition of post-gastrectomy osteopenia was completely prevented after 7.5% FOS feeding (Ohta et al., 1998d; 1998e). One study, performed in calcium-deficient rats, showed that isomaltulose-based oligomers increased the calcium, magnesium, and phosphorus levels in the tibia, whereas the iron content was decreased (Kashimura et al., 1996).

2.3.4. Conclusion

It can be concluded that prebiotics are promising agents for increasing the bioavailability of iron, magnesium, and calcium under conditions of increased requirements in rats (e.g., in deficiency and after gastrectomy). It seems that the fermentation of prebiotics in the colon and the accompanying decrease in pH are remarkable enough to compensate for the absence of gastric acid secretion after gastrectomy. Some human studies found positive effects of prebiotics on the absorption of calcium and magnesium under conditions of increased requirements, such as adolescence and postmenopause, but such data are not available for iron. Two studies have been performed in healthy young men who found no