Review

Effects of inulin on calcium metabolism and bone health

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Abstract: Inulin, a dietary fibre found in the roots of many plants, has positive effects on health. It is particularly noteworthy due to its positive impact on calcium metabolism. Inulin has significant functions, such as improving calcium absorption through passive diffusion, bolstering calcium absorption via ion exchange and expanding the absorption surface of the colon by stimulating cell growth. In addition, inulin boosts calcium absorption by increasing calcium solubility, stimulating levels of calcium-binding protein expression and increasing useful microorganisms. It increases calbindin levels and stimulates transcellular active calcium transport. An inulin intake of least 8–10 g/day supports calcium absorption and total body bone mineral content/density in adolescents through its known mechanisms of action. It also significantly enhances calcium absorption and improves bone health in postmenopausal women and adult men. Sustained and sufficient inulin supplementation in adults has a positive effect on calcium metabolism and bone mineral density.

Keywords: inulin, inulin-calcium interaction, calcium absorption, calcium balance, bone health

Introduction

Inulin, which is considered a dietary fibre, is a fructan with low energy density (1.5 kcal/g) and a beta (2-1)-D-fructosyl-fructose glycosidic bond structure. It is recognised as the energy storage polymer in plants of the families *Compositae* and *Lilialiaceaes*. While chicory root is considered the biggest source of inulin, the fibre can be found in approximately 36,000 plant species [1, 2]. A study of its nutritional sources reveals that white and red onions, shallots, garlic, Chinese garlic, barley, chicory, sunchokes and asparagus are quite rich in inulin [3, 4]. The inulin content of some foods is summarised in Table 1 [1, 5–11]. The metabolic journey of a nutrient rich in inulin is arduous. Inulin is resistant to salivary and enzymatic hydrolysis due to its beta bond configuration and alpha-glycosidic bonds. Since it is not digested in the small intestine, it is completely metabolised in the colon through fermentation by colonic microflora. Gases (i.e. carbon dioxide and hydrogen), short-chain fatty acids (SCFAs) (acetate, propionate and butyrate) and lactate are formed as end-products of this fermentation [2, 12].

Inulin varies based on its distinctive functionality and structural divergence. Inulin functionality is enabled by the degree of polymerisation (DP), which is defined as the number of repeating units in a polymer or oligomer chain, and its branches. Consequently, inulin can be classified according to its DP value and content [13]. Plant-based inulin has low DP (2–60) depending on the plant and environmental factors [14]. Inulin molecules with a DP of 3–10 are called oligofructose or fructooligosaccharides (FOS) [1]. While the term 'high degree of polymerisation inulin' (inulin-HP) is used to define only long-chain and high-molecular-weight inulin-type fructan combinations, the term 'FOS-inulin' means FOS-enriched inulin. Inulin-HP is classified as FOS-inulin HP when it is specifically supplemented by various FOS sources. Additional types of inulin, such as oligofructose-enriched inulin and oligofructose-inulin HP, also exist [13].

Inulin's various functional characteristics may lead to significant advances in promoting and preserving better health. The specific characteristics of inulin that promote better health are its low energy value (1.5 kcal/g); its positive impact on lipid metabolism, constipation and bowel movement frequency; and its role in controlling body weight and boosting the immune system [2]. It also reduces the risk of cardiovascular disease (CVD) by lowering triglyceride (TG) and low-density lipoprotein cholesterol (LDL-c) levels [15].

In addition to reducing the risk of CVD, inulin decreases the risk of obesity by regulating food intake and appetite. It plays an active role in food intake and regulating appetite by controlling glucagon-like peptide 1 (GLP-1) and ghrelin secretion [16]. In addition to its role in preventing obesity, it also may decrease the risk of diabetes and gastrointestinal system diseases through epigenetic effects on colonic microflora by stimulating the growth and metabolism of *Bifidobacteria* and *Lactobacilli* in particular, thus creating a bifidogenic effect [17–20]. Owing to its prebiotic action,

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Table 1. Inulin content of some foods

Nutrients	Amount (g/100 g)	References
Yacon/tuber (dry weight) (Smallanthus sonchifolius)	35	[5]
Stevia (wet weight) (Stevia rebaudiana)	18–23	[6]
Garlic & Chinese garlic (wet weight) (Allium sativum)	14–23	[7]
Barley (dry weight) (Hordeum vulgare)	1–5	[8]
Chicory (fresh) (Cichorium intybus)	11–20	[9]
Jerusalem artichoke (fresh) (Helianthus tuberosus)	12–19	[10]
Asparagus (fresh) (*Asparagus officinalis*)	15	[11]
Leeks (fresh)	6.5	[1]
Wheat bran (fresh)	2.5	[1]
Wheat flour (baked)	2.4	[1]
Rye (baked)	0.7	[1]
Banana (fresh)	0.5	[1]

inulin acts as a substrate for probiotics. Chicory inulin has a sufficiently cathartic result in relieving constipation [2]. While prebiotics have been shown to improve a number of chronic, inflammatory conditions, growing evidence exists for prebiotic effects on calcium metabolism and bone health. The main effect is improvement of calcium absorption in the lower intestines [21]. Apart from its potential preventive effects against cardiovascular and metabolic diseases, inulin has many positive effects on cancer metabolism [1]. It also has active role in preventing colorectal cancer as an anti-cancer component, because it improves colonic microflora, reduces reactive oxygen species and prevents colonic carcinogenesis [2, 22, 23].

Inulin plays quite an important role in boosting the immune system and contributes to bone mineral density. Although it has positive effects on mineral absorption mechanisms in general, it is especially effective in increasing calcium, magnesium and iron absorption. Its active role in calcium mineral metabolism stands out when compared to other minerals [24]. Inulin was determined to have a positive impact on calcium balance by increasing calcium absorption due to its significant effect on the transcellular and paracellular calcium transport route [25, 26]. This review examines the interaction between inulin and calcium metabolism, and its effects on calcium absorption. It includes results from studies on human and rat models of all age groups.

Methods

To explore the effects of inulin on calcium metabolism and bone health, searches were conducted in PubMed, Science Direct, Nature, Web of Science, Clinical Keys and Google Scholar databases between March and June 2019 using the keywords 'inulin and calcium metabolism', 'inulin and bone health', 'inulin and calcium absorption' and 'inulin and bone mineral density'. Clinical studies and review articles that were conducted in the last decade and accessible in full text were included in this study. Theses and oral or poster presentations were not included.

Results

The potential role of inulin in calcium metabolism

The active role inulin-type fructans play in mineral metabolism is especially dominant in the case of calcium metabolism. During its metabolic journey, inulin interacts with calcium in various metabolic pathways (Figure 1). This interaction boosts calcium absorption by increasing calcium solubility through passive diffusion in the small intestine and the first part of the large intestine [2]. The resulting increase in calcium absorption may have a positive effect on calcium balance [25–29]. Inulin's major role in calcium metabolism is a result of its contribution to the transcellular and paracellular calcium transport route along the colon [30]. Suzuki and Hara (2004) have determined that a 300% to 400% increase in paracellular calcium absorption in Caco-2 human intestinal cells was due to inulin [31]. Inulin boosts calcium absorption by increasing levels of calbindin-D9 k (CaBP9 k), which binds intracellular calcium and acts as a transport protein for calcium from apical to basolateral membrane via cytoplasm, and by regulating the expression of other proteins involved in transcellular absorption [27, 32]. Inulin also supports calcium absorption along the transcellular active calcium transport route by altering the vitamin D mechanism of action [2]. As a result, its effects on the gene expression of proteins involved in mucosal calcium binding and uptake are viewed as a functional link to increased calcium absorption [30]. Furthermore, an increase in short-chain fatty acids (SCFAs), mainly acetate, propionate and butyrate, which are end-products of inulin-type fructan fermentation, increases calcium solubility by lowering intraluminal pH. This increase stimulates transepithelial calcium gradients and passive calcium uptake [30].

As noted, it has been reported that inulin can improve calcium absorption in the small intestine and in the first section of the large intestine through passive diffusion. Furthermore, its stimulation of cell growth and expansion of the absorption surface of the colon explains its possible effects on calcium metabolism [2]. Among the numerous mechanisms through which inulin-type fructans facilitate absorption of the mineral calcium are the acidification of the intestinal lumen through SCFAs that increase the

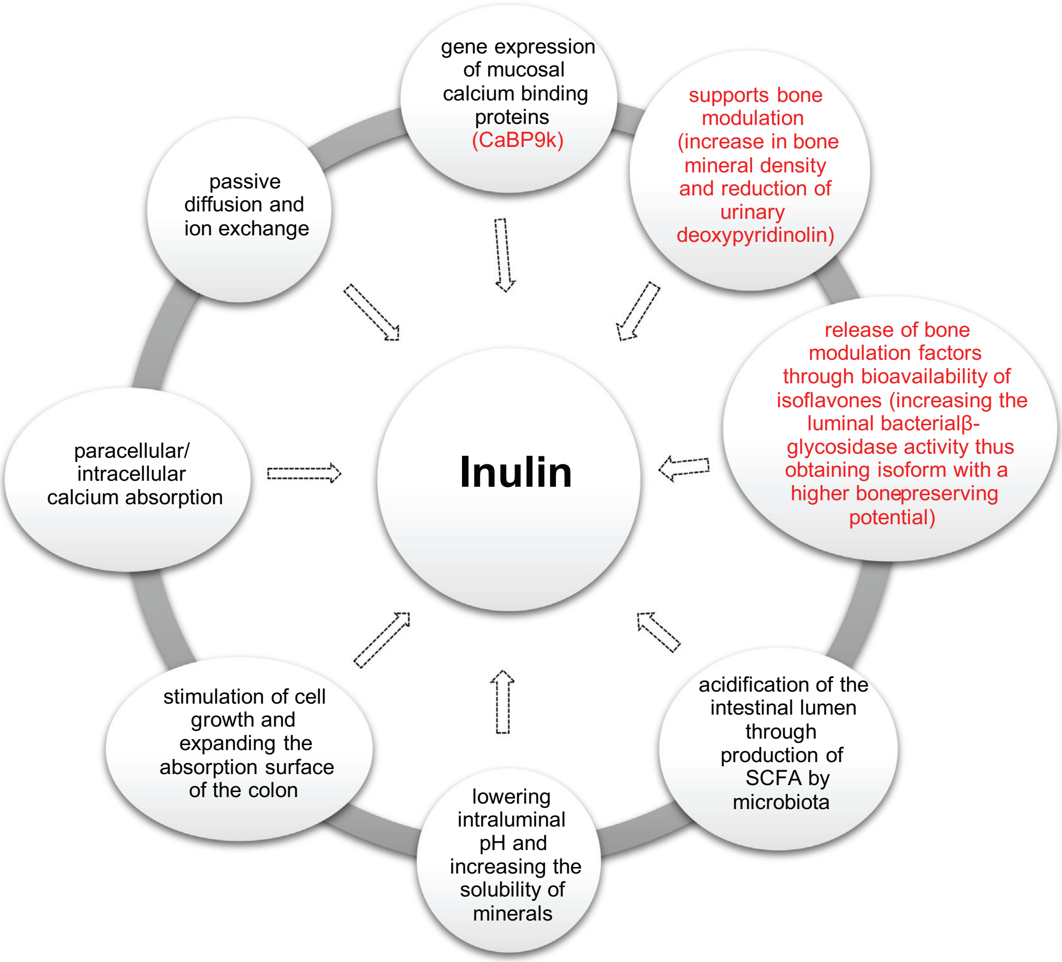

Figure 1. Potential role of inulin in calcium metabolism.

solubility of minerals; the expression of increased calcium-binding proteins, mostly in the colon; the boosting of calcium uptake through the stimulation of useful microorganisms, suppression of bone resorption; and the increasing of the bioavailability of phyto-oestrogens [33].

The effect of inulin on human calcium etabolism and bone health

Rivera-Huerta et al. (2017) have provided tangible data that inulin-type fructans promote good health through improved calcium absorption, increased bone mineral density, potential anti-cancer characteristics and anti-inflammatory components. Synergy-1, which is an inulin-type fructan derived from chicory, can be especially effective in prevent chronic diseases such as osteoporosis by promoting calcium absorption and uptake [26]. Similarly, in-vitro research by Krupa-Kozak et al. (2016) has shown that thanks to inulin, cellular calcium uptake in Caco-2 cells is increased by about 30% (6.1±0.27 μg/mL vs. 7.3±0.45 μg/mL) [25]. Butyric (160.1±11.56 mM/mL vs. 180.9±6.35 mM/mL), valeric (35.8±1.72 mM/mL vs. 42.3±2.50 mM/mL) and lactic acid (457.5±22.36 mM/mL vs. 519.0±24.21 mM/mL) concentrations, in particular, are significantly higher in the media surrounding the Caco-2 cells [25]. All these findings show that inulin-type fructans increase in-vitro cellular calcium retention [25]. In human models, supplementing with a daily dose of 8 g of inulin-type fructans with high DP over an eight-week period improved calcium absorption by 3%, increased colonic calcium absorption in the acute phase by 69.6±18.6% and increased overall calcium absorption by 49±28 mg/day [27]. Given inulin's positive impact on calcium balance, favouring foods with sufficient inulin content is essential for sustainable bone health [27].

Healthy bones are especially important for adolescent growth and development. Promoting calcium uptake is a basic requirement for sustaining good health, ensuring growth and development and bone growth. It has been claimed that inulin acts as a bone preservative by releasing of bone-modulating factors. In addition, it promotes the bone-protection effect of phytoestrogens through improvement of isoflavone bioavailability [34]. Inulin also improves the luminal bacterial b-glycosidase activity that hydrolyses the glycosidic bond of isoflavone conjugates through stimulation of *Bifidobacteria* and *Lactobacilli*, thus improving the absorption of isoflavone metabolites [34]. Inulin can prevent bone loss by stimulating *Bifidobacterium* and *Lactobacillus*, which can convert daidzein to equol, an estrogen receptor β agonist [34, 35]. Equol could be the major isoflavone metabolite responsible for a clinically important effect in bone [36]. Equol has bone-building activity, it has been associated with a positive outcome for vasomotor symptoms and osteoporosis (an increase in bone mineral density) [37]. Finally, inulin suppresses *Lactococcus garvieae*, associated with infective bone involvement [38, 39]. Thus, inulin supports bone-modulating factors. Moreover, it suppresses bone resorption relative to the rate of bone formation [34]. It is strongly believed that due to its interaction with calcium metabolism, inulin has a positive effect on bone mineral density in adolescents. A study of young adolescents in the growth stage has shown that calcium absorption and total body bone mineral content were higher in adolescents who were administered 8 g/day of Synergy-1 type inulin mixture [28]. An additional 30 mg/day of calcium through inulin supplementation corresponds to 11 g of the skeletal calcium required for pubertal growth each year. According to dual energy X-ray absorptiometry (DXA) results, inulin supplementation can provide 15 g of additional calcium to the bone mineral deposits of the skeleton every year. This amount of calcium makes up roughly 10–15% of the yearly skeletal calcium deposit. Other findings further show that inulin can play an active role in preserving skeletal integrity and maintaining mineral density. Furthermore, inulin supplementation equals at least 250 mg of additional calcium intake [28]. Martin et al. (2010) have determined that 9 g/day of oligofructose-enriched inulin supplementation is equivalent to consuming a calcium-fortified cereal in female adolescents between the ages of 11 and 13. The adolescent group has shown varying results in terms of short- and long-term effects of inulin supplementation [40]. The administration of 8 g/day of oligofructose-enriched inulin-HP supplement over a three-week period resulted in a significant increase in calcium absorption in adolescents [41, 42]. Use of the supplement over a period of one year not only resulted in an astounding increase in calcium absorption, but also led to a significant increase in total bone mineral density and content [43]. Supplementation with inulin (10 g/day) for three months can alter bone metabolism beneficially by increasing bone formation rates and decreasing bone resorption process rates [44]. At this point, it is possible to surmise that long-term inulin supplementation has a positive impact on bone mineral density and content. Therefore, long-term use of 8–10 g/day of inulin may be more effective in adolescents [44].

Another group for which skeletal health and sufficient calcium intake should be considered is postmenopausal women. Due to menopause, preserving bone health and ensuring sufficient calcium and vitamin D intake is of utmost importance in this population. Bone resorption is common, and inulin supplementation can lessen this adverse effect [29]. A double-blind intervention study on postmenopausal women has shown that when a diet with approximately 900 mg/day of calcium is supplemented with an additional 175 ml of fermented milk consumed at night, bone turnover is slowed down and bone resorption is decreased due to a decrease in plasma bone-specific alkaline phosphatase activity [29]. While a 500 mg calcium supplement in addition to the fermented milk had no positive effect other than on the luminal calcium solubility threshold, inulin-type fructan and casein phosphopeptide supplementation in addition to calcium-fortified fermented milk increased calcium absorption. Calcium supplemented by milk minerals showed no additional effect unless fortified with inulin and casein phosphopeptides [29]. Similarly, 8 g/day of inulin supplementation over a three-month period resulted in increased calcium absorption in postmenopausal women, but had no effect on bone mineral density [45]. In another study, regular use of oligofructose-enriched inulin-HP over six weeks led to an increase in serum osteocalcin levels, and an incremental increase in calcium absorption was also reported [46]. Evaluation of tangible data suggests that an inulin- and casein-phosphopeptide-fortified diet may lead to increased calcium absorption, resulting in calcium balance and decreased bone resorption. Table 2 shows a brief summary of studies focusing on the correlation between inulin and calcium absorption, metabolism and bone health [27–29, 40–52].

While inulin presented positive effects in adolescents and postmenopausal women with regards to calcium balance, no effect on calcium absorption was observed in infants. While a 1.25 g/day inulin supplementation increased zinc, iron and magnesium uptake in 5- to 12-month-old infants, it had no effect on calcium absorption or uptake [49]. However, there is not enough research available to reach a definitive conclusion. Dose-dependent long-term human studies are needed. Similar to the infant study, administering 15 g/day of inulin supplement for 21 days had no discernible effect on calcium absorption and metabolism in adult men [48]. However, a dose of 40 g/day of inulin for 26 days dramatically increased calcium absorption and had a positive effect on calcium balance in adult men [47]. Similarly, an eight-week-long course of 8 g/day of

Table 2. The human studies focusing on the correlation between inulin and calcium absorption, metabolism and bone health

Study	Year	Sample & Method	Findings	Result
Coudray et al. [47]	1997	Healthy young men (n=9) have received standard diet or standard diet with soluble inulin (40 g/day) during 28 days.	Intake of inulin significantly has enhanced Ca absorption (58% increase) and the balance of Ca.	Inulin can significantly improve Ca absorption (278±101 mg/day vs. 179 ±115 mg/day, 33.7±12.1% vs. 21.3 ±12.5%) and balance (91.8±115 mg/day vs. 10.1±136 mg/day) and does not have negative effects on other mineral retention.
Van den Heuvel et al. [48]	1998	Healthy men (n=12) aged between 20-30 years have received; a basal diet or a basal diet supplemented with inulin (15 g/day) or GOS, or FOS during 21 days.	There are no differences in Ca absorption.	It is deduced that 15 g/day inulin does not affect Ca absorption at a significant level in young healthy men.
Griffin et al. [41]	2002	Healthy girls (near menarche, n=59) randomly have received 8 g/day placebo, oligofructose or inulin+oligofructose for 3 weeks. All of diets contain Ca 1500 mg/day, two glasses orange juice (fortified with Ca).	In the inulin+oligofructose group, Ca absorption has showed a higher level than placebo.	Calcium absorption was significantly higher in the group receiving the inulin +oligofructose mixture than others (approximately 6%, p=0.01). Inulin+ oligofructose mixture supports Ca absorption in girls.
Griffin et al. [42]	2003	Healthy girls (n=54) aged between 10-15 years have received 8 g/day inulin (long-chain) enriched with oligofructose for 3 weeks.	Inulin notably enhanced Ca absorption from 33.1% to 36.1%.	In young girls, ITF intake (8 g/day) leads to a significant 3% increase in Ca absorption (p=0.027).
Kim et al. [45]	2004	Healthy postmenopausal women (n=26) have received maltodextrin (8 g/day) or chicory fructan fiber (8 g/day).	In postmenopausal women, administration of inulin (8 g/day) during 3 months has increased Ca absorption (42%) but caused no difference in bone mineral density.	Apparent calcium absorption significantly increased by 42% in the fructan group, while that of the control group decreased by 29% as compared to the values at baseline. Inulin increases Ca absorption in postmenopausal women.
Abrams et al. [43]	2005	Pubertal adolescents (n=100) between 9.0 and 13.0 years of age have received 8 g/day ITF for a year or not supplemented.	In group ITF, Ca absorption was significantly (difference at 8 weeks: 8.5±1.6%, at 1 year: 5.9±2.8%) greater than control group. After a year, the ITF group had a significant rise (difference: 35±16 g) in whole-body BMC than did the control group. Besides, ITF group had a greater increase (difference: 0.015±0.004 g/cm^2) in whole-body bone mineral density than did the control group.	ITF contributed approximately 35 g to BMC. Administration of ITF notably contributes Ca absorption and improves bone mineralization in pubertal growth.
Yap et al. [49]	2005	Healthy infants (n=36) received different amounts of inulin (0.75/ 1.00/1.25 g/day)	All the doses of inulin did not show a significant enhancement in absorption/retention of Ca.	No remarkable increase in Ca absorption/retention were detected.
Abrams et al. [28]	2007a	Healthy young adolescents (n=98) between 9-13 years of age were given 8 g/day ITF or maltodextrin during 8 weeks.	Adolescents who enhanced calcium absorption by at least 3% thanks to ITF had a greater Ca accumulation to the skeleton over a year. Total absorbed Ca had a greater (87 mg/day) in ITF group compared to placebo. Difference in whole-body BMC accumulation between ITF group and control group was 47.9±23.0 g/year.	Inulin supplementation equals at least 250 mg of additional calcium intake. It may be useful for rise peak bone mass.

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oligofructose-enriched inulin-HP led to a significant increase in calcium absorption [27]. The duration and dosage of inulin supplementation impacts inulin effectiveness. Long-term use of 8–10 g of inulin supplementation per day may lead to significant improvement in calcium absorption in adult men and women [27].

Table 2. (Continued)

Study	Year	Sample & Method	Findings	Result
Abrams et al. [27]	2007b	Young adults (n=13) have received 8 g ITF for 8 weeks.	The absorption of Ca enhanced from 22.7±11.3% mg/dL to 31.0 ±15.3% mg/dL thanks to ITF. The rise in colonic absorption was 49.0 ±28.0 mg/day.	The effectiveness of ITF on Ca absorption mainly comes from colonic pathway. The ITF attribution to colonic calcium absorption was ~70%. These results showed that a significant increase in calcium absorption from the colon occurred thanks to ITF.
Holloway et al. [46]	2007	Postmenopausal women (n=15) were administered ITF or placebo during 6 weeks.	The absorption of Ca was higher (5%) in ITF group than placebo group. The marker of bone formation (serum osteocalcin) showed to an upward trend at 3 weeks. A significant increase in serum osteocalcin emerged at 6 weeks.	Two-thirds of the subjects demonstrated an significant increase in absorption after ITF consumption. In postmenopausal women, ITF (during 6 weeks) can support mineral balance and affect bone turnover.
Adolphi et al. [29]	2009	Healthy postmenopausal women (n=85) were given calcium fortified fermented milk or fermented milk fortified with calcium, ITF and caseinphosphopeptides or control milk during 2 weeks.	The ITF group showed more positive result in the Ca balance. Milk which contains ITF+casein phosphopeptides has diminished the nocturnal bone resorption by deceleration of its turnover. Calcium fortified milk had no positive effect without ITF and casein.	Supplementation of a fermented milk +Ca with ITF diminished bone alkaline phosphatase levels (−2.8±4.95 U/l). Fortification with ITF and casein phosphopeptides to milk can be important for bone health.
Martin et al. [40]	2010	Healthy adolescent girls (n=14) have received Ca-fortified cereal with 9 g/day inulin or the cereal without inulin. All diets contain 1500 mg/day Ca.	In the diet containing inulin, Ca absorption and retention was not significantly different than control group.	Calcium absorption (67% vs. 66%) and retention (409 mg/day vs. 464 mg/day) were not significantly different. In adolescent girls, daily consumption of cereal containing FOS was not useful for Ca absorption or retention.
Bevilacqua et al. [50]	2013	Healthy post-menopausal women (n=28) have received a mixture contains calcium (500 mg), 25-Hydroxyvitamin D (300 UI), inulin (3 g) and soy isoflavones (40 mg), taken once daily for 3 months.	After supplementation, women have improved Ca absorption and bone metabolism. PTH level has significantly decreased (18%). IGF1 level which is bone anabolism indicator has significantly enhanced (16%), whereas CTx level (indicative of osteoclastic activity) was significantly reduced by approximately 17% ($p<0.05$)	Because of relatively low amount of supplemented Ca and unchanged 25-Hydroxyvitamin D level, the detected positive effects are most likely due to both inulin and soy isoflavones.
Farhangi et al. [51]	2016	Diabetic female patients (n=46) received chicory (10 g/day) or placebo for two months.	In supplementation group, serum Ca concentrations significantly increased (approximately 0.4 mg/dL) but no change was observed in placebo treated group.	Chicory had a significant role on Ca homeostasis in female diabetic patients (serum calcium levels 9.78 ±0.51 mg/dL vs. 9.43±0.54 mg/dL, p=0.02).
Kruger et al. [52]	2016	Premenopausal (n=136) and postmenopausal women (n=121) have received fortified milk (Ca premenopausal women: 1000 mg, postmenopausal: 1200 mg, magnesium (96 mg), zinc (2.4 mg), vitamin D (15 μg), FOS-inulin (4 g/day) or regular milk (500 mg Ca) for 12 weeks.	In premenopausal intervention group, Ca level was significantly higher than the other group throughout the trial. Besides, Ca level has significantly increased between at the final stage. While in postmenopausal control group PTH level has increased from 3.62 to 3.86 pmol/L, in the intervention group PTH level has decreased from 3.72 to 3.55 pmol/L. In the intervention group, CTx level has diminished from 0.46 to 0.36 μg/L.	While regular milk have significantly reduced bone resorption 11%, inulin fortified milk was measurably more effective than regular milk (17%, $p<0.05$). Procollagen type I N propeptide decreased by 13% in the inulin fortified groups ($p<0.05$).

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Table 2. (Continued)

Study	Year	Sample & Method	Findings	Result
Drabińska et al. [44]	2019	Children with CD (n=34) have received inulin (10 g/day) or maltodextrin during three months, together with a GFD.	Osteocalcin concentration increased significantly in children receiving inulin. After inulin intake, the level of pyridinoline enhanced significantly in the maltodextrin group. In inulin group, the tartrate-resistant acid phosphatase 5b level has increased.	The supplementation of inulin beneficially has altered bone metabolism, through increased bone formation rates (bone alkaline phosphatase levels from 0.49 to 0.88 ng/mL, p=0.005; osteocalcin levels from 2.73 to 9.86 ng/mL, p=0.018) and diminished bone resorption process rates (N-terminal telopeptides of type I collagen levels from 63.54 nM BCE to 54.71 nM BCE, p=0.038).

Abbreviations: BMC: Bone mineral content, Ca: Calcium, CD: Celiac disease, CTx: Collagen telopeptide, FOS: Fructo-oligosaccharide, GFD: Gluten-free diet, GOS: Galacto-oligosaccharide, IGF1: Insulin-like growth factor 1, ITF: Inulin-type fructans, nM BCE: nanomoles bone collagen equivalents, PTH: Parathormone.

The effect of inulin on calcium metabolism and bone health in rat models

Evaluation of the effects of inulin on laboratory animals shows positive effects regarding calcium absorption and bone mineral density/content. In a study on rat models, rats on a diet containing a 10% inulin supplement showed higher levels of calcium, magnesium, zinc and iron absorption compared to the other group. Their calcium balance was also at higher levels. Inspection of calcium levels in the femur and the tibia showed significantly higher levels of bone calcium in the group that received the inulin supplement. Inulin supplementation also resulted in higher bone mineral content (calcium and zinc) and increased bone strength. This data confirms that inulin has a positive effect on mineral bioavailability [24]. Similarly, it has been reported that an increase in the absorption of calcium (approximately 25%), soluble calcium levels (20 to 30 times) in caecum and total caecum calcium levels (128–158%) in the rats supplemented with inulin. [53].

Supplementation of the diet with inulin has resulted in 7–12 times increase in soluble-form caecal calcium. The biggest increase (about 30 times) was in the inulin group. In another study supporting these findings, a significant increase in calcium balance percentage and calcium absorption levels was reported in rat models that received 10% inulin supplementation for 33 days [55]. Optimum benefits of inulin can be observed in older rat models. A study has shown inulin intake to improve calcium absorption in all rat groups, and to have a numerically larger effect on calcium absorption in older rats compared to younger ones [54]. There is tangible data to show the contribution of inulin-based fibres to a healthy colon, as well as their positive chronic effects on calcium metabolism. While inulin supplementation of four weeks or longer improves chronic calcium absorption, polydextrose supplementation increases calcium absorption in the acute phase the most [56]. Long-term (four weeks or longer) inulin supplementation may benefit calcium metabolism and bone mineral density [56]. Table 3 shows a brief summary of studies focusing on the correlation between inulin and calcium absorption, metabolism and bone health in rat models [26, 30, 31, 53–59].

The safe dose and uration of inulin intake

While there is conclusive evidence of the benefits of inulin in rat models, results in human trials differ. These differences may result from variations in the dosage and duration of inulin intake. The dose administered in rat models is usually around 10 g/kg/day, whereas the dose in humans usually corresponds to less than 0.3 g/kg/day. As a result, the impact of the low dosage on mineral absorption is minimal in human trials. This is not to suggest that inulin has no physiological effect on calcium absorption [1]. Further dose-dependent long-term human studies should provide clear findings. In studies regarding daily tolerance dosage of inulin, a 20 g/day intake of inulin with an average 9 DP caused only minor gastrointestinal side effects such as gas and bloating [1]. Throughout the studies on effects of inulin on calcium absorption, inulin intake levels are observed to have been planned as under 10 g/day. Current studies show that moderate doses (5–10 g/day) of chicory inulin and agave-based inulin are tolerated [60, 61].

While inulin is highly resistant to digestive enzymes, the glycosidic bonds of inulin are sensitive to processing by acid or heat. Dry heating of inulin (60 minutes, 135 and 195 °C) results in a significant degradation of the fructan, ranging from 20 to 100%. Therefore, inulin degradation is a problem when fructan is used as a prebiotic ingredient in thermally treated foods [62]. Glibowski and Bukowska (2011) reported that the chemical stability of inulin decreases in an acidic environment at pH$\leq$4 due to the heating time

Table 3. The experimental animal studies focusing on the correlation between inulin and calcium absorption, metabolism and bone health

Study	Year	Sample & Method	Findings	Result
Coudray et al. [53]	2003	Male Wistar rats (n=50) have received a fiber-free basal diet or diet containing 10% oligofructose, or 10% HP-inulin for 28 days.	Inulin caused to an increase in the soluble Ca pool (20–30 times). HP-inulin has significantly increased intestinal Ca absorption and balance ($p<0.05$).	The cecal Ca soluble form in rats fed inulin and control diet was respectively 23–44% and 3.5%. HP-inulin had positive influences on Ca absorption and balance such as an increase in Ca pool (20–30 times) and soluble Ca form ($p<0.05$). The rats receiving HP-inulin absorbed significantly more Ca than the control rats (47.9% vs. 51.9%, $p<0.05$)
Coudray et al. [54]	2005	Male Wistar rats (n=80) have been randomized into either a control group or a group receiving 3.75% inulin in their diet for 4 days and then 7.5% inulin for 3 weeks.	Inulin had numerically more effect on Ca absorption in elderly rats than on younger rats.	Inulin intake (7.5% inulin for three weeks) has significantly improved net relative Ca absorption (47.8% vs. 66.1%), urinary Ca excretion (15.3 μg vs. 23.5 μg) and Ca retention (46.9% vs. 64.6%) compared to the control group ($p<0.05$).
Raschka et al. [30]	2005	Sprague-Dawley rats (n=48) have received a standard diet or a diet containing 10% inulin-oligofructose mixture.	ITF has increased the large intestinal Ca absorption and soluble and ionized Ca in the pools.	As a result, in rats fed inulin-oligofructose, apparent total net calcium transport activity in caecum approximately doubled. Soluble calcium ratio was significantly higher in the ITF group than control (2.1±2.1% vs. 18.0±7.0%, $p<0.05$).
Lobo et al. [31]	2009	Male Wistar rats (n=24) have received 15% lipid diet or 15% lipid diet supplemented with 10% ITF for 15 days.	In group supplemented with 10% ITF, Ca absorption has improved. The addition of ITF to the diet has resulted in higher BMC (especially Ca) and bone strength.	ITF significantly increased Ca absorption (approximately from 40% to 70%) and Ca balance (<30 mg/dL to 40 mg/dL) compared to the control group ($p<0.05$). ITF had positive influences on mineral bioavailability.
Vaz et al. [55]	2010	Wistar rats (n=24) have received ITF (0 and 100 g/kg) for 33 days.	ITF consumption has increased Ca absorption.	ITF carried Ca absorption and balance from approximately 50% to over 60% ($p<0.05$). ITF consumption has enhanced Ca balance.
Legette et al. [56]	2012	Female Sprague-Dawley rats (n=60) have received a standard diet or a standard diet with 5% inulin.	Administration of inulin for 4 weeks and longer duration has assisted rise in chronic Ca absorption.	Inulin significantly increased bone mineral density compared to the control group (0.173± 0.001 g/cm^2 vs. 0.171± 0.001 g/cm^2, $p<0.05$). ITF had a positive chronic effect on Ca metabolism.
Hess et al. [57]	2015	Hypocalcemia model mice (n=40) have received inulin (10% (weight/weight)) or a standard diet.	Administration of inulin has improved serum Ca concentration. Inulin has abolished increment colonic Trpv6 and S100 g expression by omeprazole. Besides, intestinal and renal mRNA level of the Trpm6 gene has reduced thanks to inulin.	Inulin has prevented upregulation of calciotropic genes. In colon Trpv6 expression was significantly increased to 170±14% compared to the control group ($p<0.05$).

(Continued on next page)

Table 3. (Continued)

Study	Year	Sample & Method	Findings	Result
Bueno-Vargas et al. [58]	2016	Pregnant Sprague-Dawley rats (n=30) have received a standard rodent diet or a Ca-fortified diet (1 g Ca^{2+}/100 g) or a prebiotic oligofructose-enriched inulin supplemented diet (7.5% of the total carbohydrates as prebiotic oligofructose-enriched inulin) during the second half of gestation and lactation.	Dams in the enriched inulin group had significantly higher trabecular thickness, trabecular bone volume fraction and smaller specific bone surface of the tibia in comparison with dams in the standard diet group. Offspring in enriched inulin group had an increase of the lumbar vertebra bone mineral density during early adulthood when compared to offspring of standard diet group and Ca-fortified group. In enriched inulin group, offspring have also showed a significant increase versus standard diet group in cancellous and cortical structural parameters of the lumbar vertebra 4 such as trabecular thickness, cortical bone mineral density and decreased bone volume fraction ($p<0.05$).	Administration of oligofructose-enriched inulin can be considered as a potential nutritional strategy for protecting against maternal bone loss, preventing bone fragility and optimizing peak bone mass. Besides, it can establish architecture of the offspring in order to increase bone strength.
Krupa-Kozak et al. [59]	2017	Wistar rats (n=32) have been divided into four experimental groups: GFD with the recommended Ca content; GFD with the recommended Ca content and inulin; GFD with reduced Ca content; and GFD with reduced Ca content and inulin.	Growing a significant luminal acidification, a decrease in ammonia concentration and stimulation of short chain fatty acids formation has been detected after inulin administration for six-weeks. Inulin has importantly stimulated *Bifidobacteria B. animalis* species. Increased Ca absorption was seen in rats fed Ca-restricted GFD and inulin.	Only inulin effect was important in Ca absorption and faecal excretion. Inulin significantly diminished faecal Ca excretion (22.6±4.08 mg/day vs. 20.0±4.43 mg/day, $p<0.05$) whereas it enhanced Ca absorption (73.2±3.13% vs. 74.6±4.86%, $p<0.05$).
Rivera-Huerta et al. [26]	2017	Ovariectomized Wistar rats (n=60) have received a standard diet or a standard diet with isoflavones and inulin from Mexican blue agave or chicory inulin.	Inulin treatment has significantly increased bone densitometry (femur and vertebra) in rats. Bone densitometry has been significantly raised (0.243 g/cm^2, $p<0.05$) by the inulin (Mexican agave) treatment. ITF has increased bone densitometry in femur and vertebra.	Femur and vertebra bone mineral density was significantly higher in the isoflavone inulin group compared to the group without inulin (respectively 0.243±0.003 g/cm^2 vs. 0.233±0.003 g/cm^2, and 0.220±0.004 g/cm^2 vs. 0.205±0.004 g/cm^2 $p<0.05$). Inulin intake can improve health and prevent osteoporosis.

Abbreviations: BMC: Bone mineral content, Ca: Calcium, GFD: Gluten-free diet, HP-Inulin: High polymerization inulin, ITF: Inulin-type fructans, mRNA: Messenger ribonucleuc acid, S100 g: S100 calcium binding protein G, Trpm6: Transient receptor potential cation channel subfamily M member 6, Trpv6: Transient receptor potential cation channel, subfamily V, member 6.

and temperature increase, thus limiting inulin applications in acidic foods, especially those heated at temperatures above 60 °C [63]. The effects of heat treatment applied to inulin on inulin-calcium interaction are unknown. Furthermore, quantitative studies are needed to learn about the degradation of the substituent that plays a calcium-supporting role in inulin during food processing.

Conclusion

Through known mechanisms of action, inulin has been found to increase calcium absorption and to positively impact calcium balance in adolescents, adult women (including postmenopausal women), adult men and laboratory animals. Providing sustained and sufficient inulin supplementation is considered to offer great potential benefits to calcium metabolism and bone mineral density. In addition to its effects as a source of fibre, its positive impact on calcium metabolism makes opting for foods rich in inulin important for all age groups. For bone health, onions, shallots, garlic, Chinese garlic, barley, chicory, sunchokes and asparagus can be preferred due to their being primary sources of inulin. Including various foods with high inulin content in one's diet, as well as ensuring 8–10 g/day of inulin intake, will result in substantial health benefits.

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