Current Data with Inulin-Type Fructans and Calcium, Targeting Bone Health in Adults[1–3]

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Abstract

In humans, there is increasing evidence that the colon can absorb nutritionally significant amounts of calcium, and this process may be susceptible to dietary manipulation by fermentable substrates, especially inulin-type fructans. Inulin-type fructans can modulate calcium absorption because they are resistant to hydrolysis by mammalian enzymes and are fermented in the large intestine to produce short-chain fatty acids, which in turn reduce luminal pH and modify calcium speciation, and hence solubility, or exert a direct effect on the mucosal transport pathway. Quite a few intervention studies showed an improvement of calcium absorption in adolescents or young adults by inulin-type fructans. In the same way, a positive effect has been reported in older women. J. Nutr. 137: 2527S–2533S, 2007.

The rationale for calcium need

Calcium is the most abundant mineral in the human body, accounting for 1.5–2.0% of our body weight. Indeed, the adult skeleton contains 1000–1200 g calcium, and ~1 g/d is required to maintain that level. This mineral has some very important life-supporting functions because it is a structural component of bones, teeth, and soft tissues and is essential in many of the body's metabolic processes. On the cellular level, calcium is involved in the regulation of the permeability and electrical properties of biological membranes, which in turn control muscle and nerve functions, glandular secretions, and blood vessel dilation and contraction. Calcium is also essential for proper blood clotting.

Consequently, maintaining a balanced blood calcium level is essential to life. A normal level is ~10 mg/100 mL. If there is not enough calcium in the diet to maintain sufficient amounts of calcium in the bloodstream, the parathyroid glands will be activated to release more parathyroid hormone, which will then draw calcium out of the bones as well as increase intestinal absorption of available calcium. So even though most of our body's calcium is in the bones, the blood and cellular concentrations of this mineral are maintained first. Indeed, bones are not only our most basic physical support structure; they are the main reservoir for calcium. Most minerals are in a state of dynamic activity and function, and even the calcium in bones is being added to and removed depending on the calcium balance in the body.

The obligatory calcium losses in sedentary adults on typical diets are generally in the range of 160–240 mg/d (1), and the requirement for calcium relates to the size of the calcium reserve, in other words, to total skeletal and regional bone mass. Because the size of the calcium reserve is limited (by genetic and mechanical factors), calcium functions as a threshold nutrient: above this threshold no further benefit will accrue from additional increases in intake. Thus, because the body cannot store bone above the level of current need, the calcium requirement remains high throughout life. Indeed, it is critical during infancy and childhood because it translates to gain in bone mass and, with genetic factors, to achievement of peak bone mass at the completion of physiological growth, but it is also important lifelong to keep our bones, which are primarily calcium phosphate and a protein matrix, healthy. Indeed, over the long term, dietary deficiency eventually depletes bone stores, rendering the bones weak and prone to fracture, a hallmark for osteoporosis (2,3), which has been defined by the World Health Organization as the second leading health care problem after cardiovascular diseases.

There is an overwhelming body of evidence emphasizing that nutrition is an important modifiable factor in the development and maintenance of bone mass (4,5). It is now generally accepted that an adequate calcium intake is important for building the skeleton. Moreover, because bone remodeling triples from age 50 to 65 y in women and is now recognized to have a

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[3] In these proceedings, the term inulin-type fructan shall be used as a generic term to cover all β–(2←1) linear fructans. In any other circumstances that justify the identification of the oligomers vs. the polymers, the terms oligofructose and/or inulin or eventually long-chain or high-molecular-weight inulin will be used, respectively. Even though the oligomers obtained by partial hydrolysis of inulin or by enzymatic synthesis have a slightly different DP_{av} (4 and 3.6, respectively), the term oligofructose shall be used to identify both. Synergy will be used to identify the 30/70 mixture (wt:wt) of oligofructose and inulin HP otherwise named oligofructose-enriched inulin.

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homeostatic basis that contributes to structural weakness of bone, high calcium intakes in postmenopausal and older women reduce this homeostatic remodeling to approximately premenopausal values and improve bone strength well before any appreciable change in bone mass. In addition to these cellular processes in bone, calcium (but phosphorus and magnesium as well) plays a more passive role in any mass changes that occur in bone because it must be present at physiological concentrations in extracellular fluids for bone mineralization to occur normally (6).

Consequently, the primary goal of a nutritional strategy to prevent osteoporosis is to provide sufficient bioavailable calcium to optimize the genetic potential. Actually, calcium was present in abundance in the environment in which the human species evolved. The plant foods eaten by hunter-gatherers provided a calcium intake that, adjusted for differences in body size, would have been in the range of 2000–4000 mg/d (7). It is likely that human physiology developed mechanisms to protect the organism from getting too much calcium. By contrast, current exposure in contemporary humans is often only a small fraction of what their primitive ancestors experienced and even slightly less than the recommended daily allowance of calcium. This is why, with our physiology no longer being adapted, and nearly 30% of people eating calcium-deficient diets, osteoporosis is so prevalent (8). In fact, elderly people usually have less calcium in their diets than others do, and calcium deficiency particularly affects postmenopausal women. Moreover, calcium absorption becomes less efficient as we age. The resulting dietary calcium deficiency may be addressed in different ways. Calcium intake may be inadequate for the straightforward reason that it is low; however, even when intake is normal, it may still be inadequate because of subnormal absorption or greater than normal excretory loss. In fact, calcium bioavailability is frequently equated to its absorption; that is the first barrier. Thus, given its low absorbability, and because it is commonly believed that nutrients interact, thereby altering one another's requirements, the prospect of finding substances that might improve calcium bioavailability has enticed many scientists.

Many factors are involved in making calcium available and in improving its deposition for its many essential functions. Intestinal calcium absorption occurs throughout the intestine through both transcellular and paracellular pathways (9), even though the highest rates of absorption are found in the duodenum. Vitamin D is, of course, most essential to calcium absorption. However, there appears to be an age-related altered vitamin D metabolism: a decline in renal $1,25(OH)_2D$ production caused by a defect in the renal 1α-hydroxylase leading to impaired renal conversion of the molecule into its bioactive form, associated with a decrease in vitamin D receptor (VDR) creating a relative resistance state. A lower plasma level in the elderly has been considered to be a contributing factor in the development of osteoporosis, which could be explained by a low vitamin D state from inadequate diet and decreased exposure to sunlight, as people age. All of these factors coordinately contribute to an impaired calcium absorption and bone loss (10,11). In fact, in the NHANES III study, it appears that the percentage of non-Hispanic whites, Mexican Americans, and non-Hispanic blacks with serum 25(OH)D concentrations above 50 nmol/L (the optimal value being 80 nmol/L (12)) is 87, 69, and 41% in older men, respectively, and 67, 57, and 31% in older women, respectively (13).

Various factors in addition to vitamin D can improve calcium absorption: vitamins A and C can help support normal membrane transport of calcium. However, a high intake of vitamin A has been associated with increased risk of hip fracture in Sweden (14). Protein intake helps absorption of calcium, but, in some cases, too much protein can elicit urinary calcium loss. Some dietary fat may also help absorption, but high fat may reduce it. Lactose helps calcium absorption, and because of this as well as the protein-fat combination, the calcium content of milk is a reliable source of easily assimilated calcium. Nevertheless, ~70% of blacks and 6% of whites are lactose-intolerant. Therefore, it is very important to provide a wide array of options to improve calcium absorption. Actually, among calcium absorption enhancers that have been identified, emerging evidence has shown that some nondigestible oligosaccharides such as inulin or oligofructose could be an interesting tool (15–17).

The rationale for inulin and oligofructose

Nondigestible carbohydrates are short-chain carbohydrates that are not digestible by human enzymes (18). These range from small sugar alcohols and disaccharides to oligosaccharides and large polysaccharides. Among those molecules, inulin-type fructans have been most extensively studied (19–22), and it has been speculated that they might optimize passive calcium absorption (16,17,23–25). In fact, intestinal calcium absorption can also occur via a passive paracellular route through the tight junctions between mucosal cells over the whole length of the small and large intestine (9). Thus, increasing paracellular absorption is promising because it is not limited by saturation; it is vitamin D independent and occurs throughout the length of the intestine.

The colonic fermentation of inulin-type fructans produces SCFA (essentially acetate, propionate, and butyrate) and other organic acids (e.g., lactate) that contribute to lower luminal pH in the large intestine (**Fig. 1**). The reduction in pH simply leads to a change of calcium speciation and hence solubility in the luminal phase so that the bioavailable amount is increased (26,27). It is also possible that SCFA contribute directly to the enhancement of calcium absorption via a cation exchange mechanism (increased exchange of cellular H^+ for luminal Ca^{2+}) (28). Further,

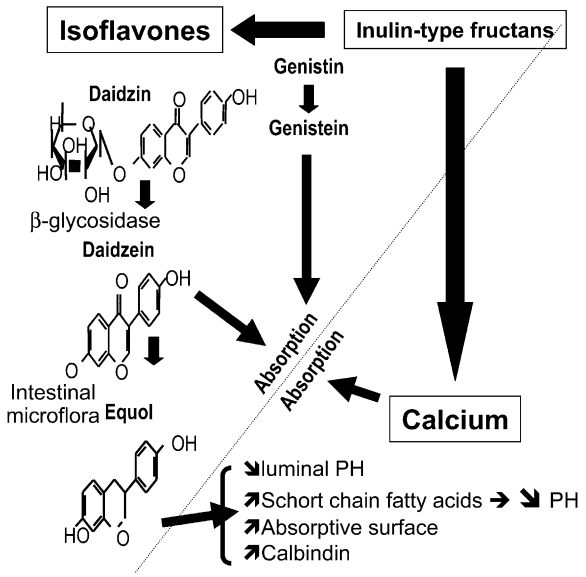

FIGURE 1 Effect of inulin-type fructans in the human intestine: possible mechanisms of action leading to modulation of both isoflavones and calcium bioavailability, both involved in bone health. Inulin-type fructans will improve isoflavone bioavailability by converting genistein to genistin or daidzin to daidzein by modulating β-glycosidase or by stimulating the intestinal microflora involved in daidzein conversion into equol.

inulin-type fructans may also improve transcellular active calcium transport by altering the activity of vitamin D receptor and increasing calbindin D_{9K} (the intracellular ferry protein involved in the translocation of calcium to the basolateral membrane of mucosal epithelial cells) (29).

Another way to contribute to the enhanced mineral absorption is the increased production of butyrate and/or certain polyamines, which might indirectly induce histological (cell growth) and functional (enhancement of the gut's absorptive area) changes in the intestinal epithelium (20,30).

Indeed, numerous investigations performed in animal models in the past 10 y have shown repeatedly that nondigestible oligosaccharides and especially inulin-type fructans stimulate mineral absorption (31). Long-term beneficial effects on bone health have been indicated by both increased bone mineral content in growing rats and bone-sparing effects in ovariectmized rats, an animal model for osteoporosis (32). However, human studies are more limited.

Effect of inulin and oligofructose on calcium bioavailability, clinical trials

Inulin-type fructans in young adults. In a pivotal study to demonstrate the proof of this principle in adult humans, Coudray et al. (33) performed a balance study with 9 healthy volunteers (mean age 25.5 y), who where given up to 40 g/d chicory inulin for a period of 26 d, according to a crossover design (2 d of control diet followed by 14 d of progressive increase in inulin amount and then 12 d at maximal inulin consumption). Using the metabolic balance methodology, they found that, on inulin ingestion, apparent calcium absorption increased significantly from 21.3 ± 12.5 to 33.7 ± 12.1% (i.e., a 58% increase).

However, opposing this, a study carried out by Van den Heuvel et al. (34) in healthy young adults found no significant differences in mineral absorption, irrespective of the treatment (which consisted of a constant basal diet supplemented for 21 d with 15 g/d inulin, oligofructose, or galacto-oligosaccharide, or not supplemented). It was hypothesized that a 24-h period of urine collection, as used in the present work, was too short to include the colonic component of calcium absorption and thus to make up a complete balance necessary to detect the effect of fructans.

Teuri et al. (35) investigated the effect of inulin on calcium metabolism using a randomized, 2-period crossover design (each period consisting of 1 test day) in 15 young healthy women (mean age 23.7 y, range 20–29 y). The volunteers were given cheese containing 210 mg of calcium together or not with 15 g inulin. The authors concluded that this kind of treatment did not acutely affect the markers of calcium metabolism, as compared with a corresponding breakfast without inulin. Nevertheless, they measured parathyroid hormone and ionized calcium plasma concentrations, which are not the best parameters to assess the effect of such a treatment on intestinal calcium absorption.

To summarize, in adult humans, it appears that as long as the right methodology is used, it is possible to see an improvement of intestinal calcium absorption after inulin-type fructan consumption Moreover, such molecules did not alter this process in small intestine, probably because the modulation of mineral absorption by fructans originates mainly in the colon. This is why Ellegard et al. (36) have shown that they do not affect mineral digestion in volunteers with an ileostomy, even though another explanation for the lack of effect in such patients could be an increased transit rate, eliciting reduced opportunities of inulin-type fructans to stimulate the fermentation process.

Inulin-type fructans in early postmenopausal women. In a randomized double-blind crossover trial in 12 postmenopausal women, Tahiri et al. (37) failed to show an effect of oligofructose consumption (10g/d for 5 wk) on calcium absorption. However, the length of menopause was quite different among subjects: 8.3 ± 7.1 y. This corresponds to huge differences in terms of bone metabolism, and this could explain the lack of any significant effect.

Actually, because menopausal status is the overriding factor determining bone loss in women in their early 50s, given the tremendous impact of gonadal hormones on bone health, calcium intake during the first 5 y of menopause is not effective in retarding bone loss, and this may be why oligofructose failed to modulate calcium absorption during that period.

Inulin-type fructans in late postmenopausal women. Even though Tahiri et al. (37) failed to show a significant effect of oligofructose on calcium absorption in 12 postmenopausal women, the results from the subgroup of women who were >6 y after menopause suggest that this nondigestible carbohydrate may influence calcium absorption in the late postmenopausal phase (37.4 ± 9.7% vs. 34.5 ± 9.4% in the placebo group; SD).

In the same way, in 12 healthy women (at least 5 y past the onset of menopause), Van den Heuvel et al. (38) investigated the effect of 2 doses of lactulose (5 and 10 g/d for 9 d). The highest dose was associated with a 32.2 ± 7.0% calcium absorption (against 27.7 ± 7.7% in controls, SD).

In a double-blind, randomized, crossover study consisting of 2 consecutive 9-d treatment periods separated by a 19-d washout period, performed in 12 postmenopausal women (age ranged from 55 to 65 y, mean 62 y), the same authors (39) reported same results with *trans*-galacto-oligosaccharides (20 g/d). Indeed, true calcium absorption was significantly increased by 19% (to 29.6 ± 7.0% from 23.9 ± 6.9% during the treatment). This increase in calcium absorption was not accompanied by increased urinary calcium excretion.

Using a parallel, randomized, double-blind design, Kim et al. (40) investigated the effects of supplementation of chicory fructan fiber on apparent absorption of minerals in Korean postmenopausal women (mean age 60–61 y) who were not receiving any kind of hormonal replacement therapy. All women received 2 doses (at breakfast and dinner) of 4 g of chicory fructan fiber or a placebo (maltodextrins/sucrose mixture) for 3 mo. After 3 mo of treatment, apparent calcium absorption in the fructan group increased from 38.6 ± 7.3 at baseline to 54.9 ± 4.7% ($P < 0.05$, i.e., a 42% increase), without any change in urinary calcium loss. In the control group of volunteers, such a parameter moved from 43.2 ± 9.3 to 30.7 ± 6.4.

Finally, in a recent study, 15 women (who were a minimum of 10 y past the onset of menopause and had taken no hormone replacement therapy for those years) were given 10 g/d of a mixture of long-chain inulin and oligofructose (known as Synergy) for 6 wk, according to a double-blind placebo-controlled crossover design (41). True fractional calcium absorption, measured by dual isotopes before and after treatment, was significantly increased [+5.1 (SE 2.1)% vs. −3.3 (SE 2.2)%, $P < 0.05$, comparison to the placebo group]. Further, the efficacy of treatment seems to be improved in women with lower initial vertebral bone mineral density.

Consequently, if inulin-type fructans have failed to modulate calcium absorption during the first 5 y after the onset of menopause, they appear to be efficient, later in life, probably because hormonal changes occurring during menopause become less important, leaving some room for other mechanisms of

regulation. However, it is important to know if the extra absorbed calcium is deposited in bones. For that purpose, long-term studies are needed.

Inulin and oligofructose and bone health, clinical trials

In their clinical trial conducted in postmenopausal women, Tahiri et al. (37) failed to show any significant differences in plasma osteocalcin concentrations (a marker for osteoblast activity) and urinary deoxypyridinoline excretion (a marker for bone resoprtion) between oligofructose-treated women and those who received the placebo.

Dahl et al. (42), in an attempt to develop thickened beverages that contain soluble inulin with acceptable consistency, taste, and texture, supplemented institutionalized adults who were bound to wheelchairs and had dysphagia or not, according to a double-blind, 3-wk, crossover design, with 13 g/d inulin-fortified vs. isocaloric standard modified starch-thickened beverages. They failed to induce any change in bone resorption rate, as assessed by the measurement of cross-linked N-telopeptides.

In their study performed in postmenopausal women (mean age 60–61 y), Kim et al. (40) investigated the effects of chicory fructan fiber supplementation on serum bone parameters related to bone turnover and bone mineral density as well. After 3 mo of consumption, the level of serum alkaline phosphatase, a marker for bone formation, was significantly lower in the inulin-type fructan group than in controls, whereas urinary deoxypyridinolin exhibited a trend toward a slight reduction, indicative of a slower bone turnover. However, they failed to show any significant effect on bone mineral density, which is not surprising, a longer study period of exposure being required to modulate such a parameter.

In their clinical trial in postmenopausal women with Synergy, Hollaway et al. (41) provided evidence of an improvement of intestinal calcium absorption and also showed that the mixture of inulin and oligofructose was able to impact on biomarkers for bone metabolism as well. In fact, changes in those parameters occurred only in volunteers who increased mineral absorption in response to oligosaccharides.

Consequently, it appears that inulin-type fructans can modulate calcium bioavailability, and few studies have shown that the benefits of these ingredients can impact on bone metabolism in the human species as well (depending on the physiological status). Nevertheless, an important consideration is whether the retained calcium can be translated into benefits to bone health; in others words, whether bone mineral density can be increased by those compounds. The only available trial in humans has been carried out in 9- to 13-y-old children by Abrams et al. (43) with the main objective to assess the biological effects of 8 wk and 1 y of supplementation at the daily dose of 8 g. In fact, at the end of the experimental period, the inulin-type fructan group had a greater increment in both whole-body bone mineral content (change after 1 y: 245 $\pm$ 11 vs. 210 $\pm$ 10 g) and bone mineral density (change after 1 y: 0.047 $\pm$ 0.004 vs. 0.032 $\pm$ 0.004 g/cm^2) than did the control group. Given these promising results in the adolescents, we need to fully investigate the long-term effect of such compounds in adults or the elderly.

Targeting bone health, another possible interest for inulin and oligofructose

Albright and Reifenstein (44) have underlined the importance of sex steroids in maintenance of skeletal integrity. This is why health professionals used to strongly advocate estrogen replacement therapy. However, prophylaxis is now limited to only a small minority of eligible women because of a number of factors that are unlikely to be resolved in the near future. In this light, there is a need for "the ideal estrogen," which would exhibit the beneficial effects of estrogens on bone mass and cardiovascular disease in the absence of stimulation of reproductive tissue, most notably the breast and uterus (45). This explains the renewed interest in materials from botanical sources for promoting health and preventing osteoporosis and other hormone-dependent diseases as well: scientists have targeted phytoestrogen consumption as a possible way to achieve this goal (46,47).

In fact, phytoestrogens deserve special mention as food supplements because of evidence of their estrogenic properties in postmenopausal women (48–50) and a very similar biological signature to that of estrogens (51). Substantiation of their importance came from emerging data supporting a potential preventive effect for a range of hormone-dependent conditions including postmenopausal symptoms, prevention of breast and prostate cancer, and coronary heart disease (49).

Basically, phytoestrogens belong to a broad group of edible plant-derived compounds called polyphenols that may display both estrogenic and antiestrogenic effects. A substantial body of work in animal models in the past few years has provided convincing evidence for significant improvement of bone mass or other endpoints following soy feeding or isoflavone consumption. (52). In addition, epidemiological studies, primarily comparing Asian and Western populations, have been interpreted to indicate that consumption by postmenopausal women of a diet rich in phytoestrogens ameliorates estrogen deficiency symptoms such as osteoporosis (53). Finally, based on randomized, placebo-controlled clinical trials, a number of scientists point toward a bone-sparing effect of soy, attributed to its isoflavone component, even though it can still not be recommended because of the lack of data targeting the risk of fracture (53,54).

Targeting phytoestrogen consumption for their possible bone-sparing activity, nondigestible carbohydrates still remain a source for putative new and innovative dietary health interventions to prevent postmenopausal osteoporosis. Actually, they may have a beneficial effect on isoflavone metabolism and improve their health protective effect because gut metabolism (the main target for inulin-type fructans) appears to be key to the determination of their potency of action.

Indeed, bioavailability of phytoestrogens, naturally occurring as a glycosidic form, seems to require an initial hydrolysis of the sugar moiety to allow the uptake by enterocytes. Glucosidases of intestinal bacteria such as *Lactobacilli, Bacteroides,* and *Bifidobacteria* are involved in this process (55,56). It has been shown that dietary oligofructose may increase β-glucosidase activity in the large intestine, leading to an enhancement of the large-intestinal absorption of these compounds (57). Furthermore, isoflavones and aglycones [daidzein (4′,7-dihydroxyisoflavone) and genistein (4′,5,7-trihydroxyisoflavone)] undergo extensive phase 2 metabolism by intestinal microflora, presumably in the colon (58), into several other products, including equol, O-desmethylangiolensin, and *p*-ethyl phenol (59,60). Equol is not produced with the same efficiency by all individuals (61,62). However, according to Setchell's theory (63), the clinical effectiveness of soy protein may be a function of the ability to convert soy isoflavones to their more potent equol intestinal metabolite.

Indeed, equol has a longer half-life and a much higher affinity for the estrogen receptor than its precursor (daidzein) and has the highest antioxidant capacity among isoflavones (63). This could explain the results from a 2-y study carried out in postmenopausal women randomized to consume 500 mL of soy milk either with or without isoflavones. Greater effects on bone

health were elicited when volunteers were able to produce equol, a 2.4% increase in lumbar spine BMD being demonstrated, compared with control group, whereas no significant difference was shown in nonproducers (64).

Consequently, because a greater efficacy of phytoestrogens can be expected if they are converted into more potent molecules by the intestinal microflora, there is a good rationale for considering every strategy that will enhance equol production. It has been established that concurrent dietary intake, in particular high dietary fibers, exert a major influence on isoflavone metabolism (57,65). Moreover, Uehara et al. (57) reported that oligofructose is able to increase plasma equol concentrations in rats given isoflavone conjugates. On the other hand, Tamura et al. (66) have shown that difructose anhydride III, a newly manufactured nondigestible disaccharide, is able to efficiently enhance plasma equol concentrations (which may be associated with an increase in equol production and a decrease in equol degradation by enterobacteria) in isoflavone-fed rats. In the same way, according to Tamura et al. (67), soy oligosaccharides have an impact on the metabolic activity of intestinal microflora, plasma concentrations of isoflavones, and amount of isoflavones in the intestine. In contrast, inulin was reported to lower serum equol concentrations in rodents (68). Nondigestible carbohydrates are thus receiving great scrutiny for the purpose of improving the bone-sparing effects of isoflavones.

In fact, in ovariectomized mice, oligofructose consumption has been shown to augment the bone-sparing effect of isoflavones by improving equol production (69). In the same way, in ovariectomized female rats (the established animal model for postmenopausal osteoporosis), Mathey et al. (70) have shown that addition of nondigestible oligosaccharides such as oligofructose significantly increases bone protection exhibited by daidzein, as shown by a higher femoral bone mineral density. In a recent animal experiment, carried out by Devareddy et al. (71), although the combination of dietary oligofructose and soy failed to exhibit additive effects on bone mineral density of the whole body, tibiae, and lumbar vertebrae, in terms of architecture, both nutrients, when given together, had a greater effect in reversing the impairment of some microarchitectural parameters such as tibial trabecular number, separation, and thickness. Finally, in a clinical trial carried out on 39 healthy postmenopausal women, Mathey et al. (72) have shown that inulin-type fructans (as well as probiotics), when given at the dose of 7 g/d for 1 mo, increase plasma equol concentrations and may augment the prevention elicited by isoflavones, as shown by a significantly reduced osteoclastic activity, when compared with women given soy isoflavones alone.

Consequently, a dietary combination of prebiotic and/or probiotic and isoflavones may have a potential promise for maintaining or improving bone health.

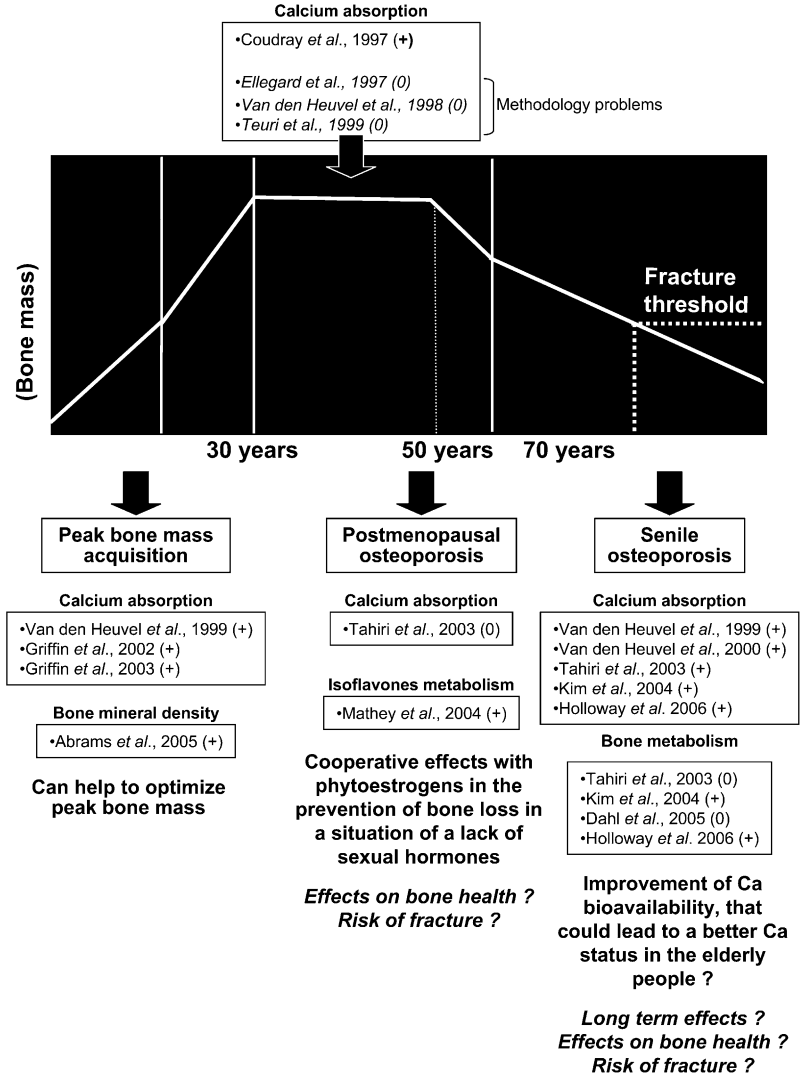

FIGURE 2 Targeting bone health throughout life: effect of inulin-type fructans in the human species. (+) means positive effect; (0) means no effect.

Because bone is mainly built up with calcium for which deficiency is common, the primary goal of a nutritional strategy is to provide sufficient bioavailable calcium to optimize the genetic potential. However, given the generally low absorbability of calcium, the prospect of finding substances that might improve its bioavailability has enticed many scientists. Toward that purpose, quite a few intervention clinical trials have shown an improvement in calcium absorption in humans with inulin-type fructans, depending on the physiological status. Nevertheless, before health professionals can actively advocate the increased consumption of inulin-type fructans to prevent osteoporosis, it is necessary to expand those promising results and to prove that the benefits of these nondigestible carbohydrates on calcium absorption persist and can be translated into a bone-sparing effect, as has been recently shown in adolescents (43) (**Fig. 2**). Such data are necessary to substantiate type B claims (reduction of the risk of bone disease).

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