Young Adolescents Who Respond to an Inulin-Type Fructan Substantially Increase Total Absorbed Calcium and Daily Calcium Accretion to the Skeleton1–3

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Abstract
Calcium absorption and whole-body bone mineral content are greater in young adolescents who receive 8 g/d of Synergy, a mixture of inulin-type fructans (ITF), compared with those who received a maltodextrin control. Not all adolescents responded to this intervention, however. We evaluated 32 responders and 16 nonresponders to the calcium absorptive benefits of ITF. We found no differences in usual dietary calcium intakes. Responders who increased their calcium absorption by at least 3% after 8 wk of Synergy had a greater accretion of calcium to the skeleton over a year based on whole-body dual-energy x-ray absorptiometry data. The absorptive benefit to ITF use in responders is substantial and would be comparable to increasing daily calcium intake by at least 250 mg. Increased intake of ITF may be an important aspect of a multifaceted approach to enhancing peak bone mass. J. Nutr. 137: 2524S–2526S, 2007.

Introduction
Determinants of peak bone mass include calcium intake and absorption, other dietary components such as magnesium and zinc, and lifestyle factors, especially physical activity. Increasingly, it is recognized that genetic factors are also important in interacting with diet and lifestyle in determining peak bone mass. The current recommended dietary intake of calcium or adequate intake (AI)4 of 1300 mg/d for adolescents is designed to maximize calcium absorption and retention (1). This intake, however, is not achieved by the vast majority of young adolescents in the United States (2). Therefore, it is important to consider other factors, such as calcium absorptive efficiency, that may affect total calcium absorption and improve bone mineral mass accumulation at a calcium intake less than the current AI.

We have recently published the results of a blinded, controlled trial into the effects of a mixture of inulin-type fructan5 (ITF) on calcium absorption and bone mineral mass accumulation in young adolescents (3). We found a significant benefit to calcium absorption after both 8 and 52 wk compared with placebo controls. However, not all subjects who received the ITF responded with an increase in calcium absorption. In particular, we found that about two-thirds of subjects who received the ITF responded with an increase in calcium absorption >3%. This result was similar to our previous studies in this age group (4,5). In this article, we consider further this aspect of the response to ITF and the implications of these findings for dietary and nutritional guidance.

Methods
By public advertising, we identified 50 girls and 50 boys for this study. Of these, 49 boys and 49 girls completed the 1-y intervention study. All

1 Published in a supplement to The Journal of Nutrition. Presented at the conference “5th ORAFTI Research Conference: Inulin and Oligofructose: Proven Health Benefits and Claims” held at Harvard Medical School, Boston, MA, September 28–29, 2006. This conference was organized and sponsored by ORAFTI, Belgium. Guest Editors for the supplement publication were Marcel Roberfroid, Catholique University of Louvain, Brussels, Belgium and Randal Buddington, Mississippi State University, USA. Guest Editor disclosure: M. Roberfroid and R. Buddington, support for travel to conference provided by ORAFTI.

2 Sources of Financial Support: This work is a publication of the U.S. Department of Agriculture/Agricultural Research Service (ARS) Children’s Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children’s Hospital, Houston, TX. This project has been funded in part with federal funds from the U.S. Department of Agriculture/ARS under Cooperative Agreement number 58-6250-6-001, the NIH, NCRR General Clinical Research for Children Grant number RR00188, NIH AR43708 and NIDDK P30 DK56338. Orange juice used in the study was provided by The Coca-Cola Company, Houston, TX, and the inulin-type fructan by ORAFTI, N.V., Tienen, Belgium. Contents of this publication do not necessarily reflect the views or policies of the U.S. Department of Agriculture, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

3 Author disclosures: S. A. Abrams, I. J. Griffin, and K. M. Hawthorne, no conflicts of interest.

4 Abbreviations used: AI, adequate intake; BMC, bone mineral content; DXA, dual-energy x-ray absorptiometry; ITF, inulin-type fructan.

5 In these proceedings, the term inulin-type fructan shall be applied 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 DPω (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.
Calcium absorption at 8 wk, \( P \) when Daily change in calcium accretion, Calcium intake at study initiation, Tanner stage at enrollment were included as covariates in all models; did not receive the ITF with post-hoc paired analysis performed when the generalized linear model (ANOVA). Analysis also included those who provide some dietary variation, subjects were also allowed to use milk to mix the carbohydrate supplement. Dietary recalls and discussions with families demonstrated that all subjects primarily used orange juice, and this accounted for over 95% of total study days.

After 8 wk of receiving the carbohydrate supplement to which they had been randomized, subjects returned for a calcium absorption study. Twelve months after the initial baseline study, they returned for a follow-up visit in which measurements of calcium absorption and bone mineral content (BMC) were performed.

Stable isotope studies were performed as previously described (4–6). Most subjects received a breakfast that contained approximately one-third of their daily intake of calcium (including the tracer-containing juice). Toward the end of breakfast, subjects were given 20 \( \mu g \) of \( ^{46}\text{Ca} \) that had been mixed with 240 mL of calcium-fortified orange juice. Whole-body BMC was determined using a Hologic QDR-4500A dual-energy x-ray (DXA) absorptiometer scanning in the fan-beam mode. Comparisons of responders and nonresponders were made using a generalized linear model (ANCOVA). Analysis also included those who did not receive the ITF with post-hoc paired analysis performed when the initial differences were significant (\( P < 0.05 \)). Gender, ethnicity, and Tanner stage at enrollment were included as covariates in all models; other covariates depended on the specific analysis being carried out. Analyses were performed using SPSS 13.0 for Windows (SPSS). All data are presented as the mean \( \pm \) SEM, and values are considered significant when \( P < 0.05 \).

### Results

We used an increment of \( >3.0\% \) in calcium absorption at 8 wk compared with baseline to define “responders” to the interven-

### TABLE 1 Baseline subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders, ( n = 32 )</th>
<th>Nonresponders, ( n = 16 )</th>
<th>Non-ITF (placebo), ( n = 50 )</th>
<th>Additional covariates</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>12.0 ( \pm ) 0.2</td>
<td>11.4 ( \pm ) 0.2</td>
<td>11.4 ( \pm ) 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>44.1 ( \pm ) 1.6</td>
<td>39.9 ( \pm ) 2.3</td>
<td>41.4 ( \pm ) 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, ( n )</td>
<td>17 M, 15 F</td>
<td>8 M, 8 F</td>
<td>25 M, 25 F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner stage 2, %</td>
<td>75</td>
<td>69</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( 1 \) All data are mean \( \pm \) SEM. Covariates in all models were Tanner stage at baseline, gender, and ethnicity. Additional covariates for specific analyses are shown.

\( 2 \) Pairwise comparison \( P < 0.001 \) for Responders vs. Nonresponders and for Responders vs. Non-ITF. \( P = 0.83 \) for Responders vs. Non-ITF.

\( 3 \) Pairwise comparison, \( P < 0.01 \) for Responders vs. Nonresponders and for Responders vs. Non-ITF, \( P = 0.79 \) for Responders vs. Non-ITF.

\( 4 \) One missing urinary calcium excretion value for Non-ITF.

\( 5 \) Calcium accretion determined from 1 y and baseline DXA whole-body BMC data using conversion factor of 0.322 for the fraction of bone mineral that is calcium. One missing case (responders) for calcium accretion results. Pairwise comparisons, \( P = 0.026 \) for Responders vs. Nonresponders, \( P = 0.04 \) for Non-ITF vs. Responders and \( P = 0.45 \) for Nonresponders vs. Non-ITF.

To evaluate differences between responders and nonresponders, we compared both percentage and total calcium absorption in these groups (Table 2). There was no significant difference between groups in calcium intake. Total absorbed calcium was 95 mg/d greater in responders compared with nonresponders (\( P < 0.01 \)) and 87 mg/d greater in responders compared with placebo. No significant difference was seen in urinary calcium excretion.

Endogenous fecal calcium excretion was not assessed in this study, but based on available data relating absorbed calcium and endogenous excretion, one could expect that the greater absorbed calcium in the ITF group led to a greater level of endogenously excreted calcium of 10–20 mg/d (7,8). Thus, it is reasonable to calculate the net benefit in retained calcium from the ITF intervention as \( \sim 65–75 \) mg/d in responders.

We further considered whether a response in calcium absorption at 8 wk (as previously defined by an increase in calcium absorption from baseline of \( >3.0\% \)) was predictive of a benefit to bone mineral accretion over the entire year. In this case, using ethnicity, Tanner stage, and gender as covariates, we found that responders at 8 wk had a significantly greater increment in whole-body BMC over the entire year (\( n = 31 \) responders and 16 nonresponders because DXA data were not available for 1 responder). The net difference in whole-body BMC accumulation was 47.9 \( \pm \) 23 g/y (\( P = 0.04 \)). Calculating the net
difference in daily calcium accretion to the skeleton based on the DXA data demonstrated that responders had a greater daily calcium accretion (retention) compared with nonresponders and those who did not receive Synergy 1 (Table 2).

Discussion

We previously reported a net benefit for all young adolescents supplemented with 8 g/d of Synergy compared with placebo of ~30 mg of additional daily calcium accretion to the skeleton, which was equivalent to ~11 g of calcium for each year of pubertal growth. In this analysis, we found that an increase in calcium absorption at 8 wk predicted a substantial benefit in both short-term calcium absorption compared with placebo or to nonresponders and long-term whole-body bone mineral accumulation. From the values derived from DXA results, it can be calculated that ~15 g of additional calcium would be added to the skeleton each year in responders compared with nonresponders. This amount of calcium is about approximately equal to 10–15% of the annual rate of skeletal calcium accretion.

The magnitude of this change may be a result of the definition of response used. However, the finding that our definition of response at 8 wk was associated with longer-term advantages in bone mineralization compared with subjects who did not respond to ITF lends support to this general type of definition. With this analysis we confirm that a short-term marker of ITF response is associated with a longer-term change in a physiological important parameter (whole-body BMC).

Although the primary analysis of placebo vs. all subjects who received the Synergy remains the principal outcome of the study, this newer analysis of responders is a reasonable approach to consider as well. Multiple investigations into the effect of ITF on calcium absorption (4–6) have identified populations of both responders and nonresponders. Response may be affected by genetics, usual inulin intake, other aspects of diet, and/or unidentified factors including compliance with the intervention or diet. It is reasonable to consider the relative ITF benefit and how it might relate to other potential interventions. There are no dietary or other interventions in children or adolescents other than increasing calcium intake that have been shown to have this magnitude of long-term effect (1). Data regarding vitamin D supplementation are minimal at this point in young adolescents (9). The net benefit in retained calcium of ~65 mg/d, if one assumes a retention fraction of 25% (dietary calcium source) or 20% (if given as a pill supplement), would require a dietary increase in calcium intake or calcium supplement of ~250–320 mg/d.

It is advocated that young adolescents achieve an intake of calcium at the current AI of 1300 mg/d. However, calcium intakes of ~900 mg/d, as seen in our study, are consistent with population data for adolescent girls in the United States and many other countries. Only a very small percentage of adolescent girls achieve intakes of 1300 mg/d (1,2). The effect of ITF to increase calcium absorption by an amount similar to what might occur with an increase in calcium intake of 250–320 mg/d would be the equivalent of moving the 50th percentile calcium intake in this population close to the 80th percentile of usual intakes for girls (1).

This magnitude of effect may not be maintained over a long period of time, but this may also be true for the use of dietary and other supplemental forms of calcium. A significant benefit to Synergy is maintained during the crucial pubertal bone growth peak. Thus, multiple strategies can and should be advocated to enhance the achievement of peak bone mass including both enhancement of calcium intake and calcium absorptive efficiency. As further understanding of the underlying mechanism determining response or nonresponse to interventions such as ITF is achieved, these strategies and their public health role will become more apparent.

Literature Cited