Do oligosaccharides affect the intestinal absorption of calcium in humans?

Dear Sir:

We read with interest the paper of van den Heuvel et al (1), who studied the effect of nondigestible oligosaccharides on calcium and iron absorption in young men. They concluded that 15 g inulin, fructooligosaccharide, or galactooligosaccharide/d had no effect on the intestinal absorption of these minerals. Their results seem to disagree with our findings. In a recent study (2), we investigated the effect of 40 g inulin/d on the intestinal absorption of calcium, magnesium, iron, and zinc in young men by using the chemical balance method. Our results showed that inulin greatly increased calcium absorption in these subjects (by 58%). This was the first time that such an effect of inulin on calcium absorption was reported in humans. Our results agree well with those from animal studies indicating that inulin increases the absorption of calcium and magnesium (3). It is possible that the small oligosaccharide doses used by van den Heuvel et al explain the differences between their results and ours. However, other explanations deserve to be looked for.

To evaluate calcium absorption, van den Heuvel et al used the dual isotope-tracer approach and simultaneously administered 44Ca orally and 45Ca intravenously. Abrams et al (4) showed that calcium absorption can be measured correctly with use of either the chemical balance method or the isotopic method, but that the isotopic approach may be preferred for its convenience. The approach used by van den Heuvel et al is known to be appropriate for assessing the true absorption of calcium from serum or urine samples. For determining calcium absorption, van den Heuvel et al collected urine over the first 24 h after isotope administration and measured the isotope enrichment of both isotopes in this urine pool. The 24-h urine pool may not be appropriate for determining calcium absorption in humans, however, which may explain the discordance between our results and those of van den Heuvel et al.

The dual isotope-tracer technique is based on the assumption that the orally and intravenously administered isotopes are metabolized at the same rate once equilibrium has been reached. Mineral absorption is generally determined from serum or urine collections starting ≥24–48 h after isotope administration (5). After such time, one can be sure that the required equilibrium has been attained. However, it is essential that minimal quantities of isotopes be administered both orally and intravenously so as to not perturb mineral metabolism and also to make isotopic studies less expensive. This is why in some studies mineral absorption was assessed earlier than 24 h, sometimes in urine collected during the first 8 h after isotope administration, when the isotope enrichment is high enough to be reliably measured. Unfortunately, such early measurements can often lead to erroneous results.

Yergey et al (6) measured fractional calcium absorption by the dual isotope-tracer approach. In their study, all urine excreted after isotope administration was collected and pooled for 48 h (6 pools of 8 h each). Their results showed that the pools collected during hours 0–8, 9–16, and 17–24 were not suitable for measuring calcium absorption. The calculated absorption in these urine samples was 35%, 45%, and 53%, respectively, whereas the accurate absorption value, obtained in urine spots sampled > 24 h after isotope administration, was 56%. In another study, Yergey et al (7) determined the fractional absorption of dietary calcium in an 8-h urine pool (16–24 h) and compared the absorption value with that obtained in a urine pool collected 0–24 h after isotope administration. The absorption value was lower in the 0–24-h urine pool (27.3%) than in the 16–24-h urine pool (35.9%). Smith et al (8) reported that the ratio of concentration of oral to intravenous tracer in urine samples can be calculated and used to determine the true fractional absorption of the oral tracer. They concluded that during the first 24 h after tracer administration, the assumption that both tracers enter the mineral exchangeable pool at the same rate does not hold and the data points are scattered. Only after 24 h does this assumption become valid and the data points form an approximately straight line with a slope of zero.

In an animal study (9), we investigated magnesium absorption by using the dual isotope-tracer approach and analyzed 12-h urine pools over 5 d. We observed that > 40% of total urinary 25Mg was excreted within the first 12 h when the tracer was given intravenously in rats, whereas only 18% of total urinary 26Mg was excreted in the first 12 h when the tracer was given orally; thus, the 2 isotopes did not behave similarly during this period. Magnesium absorption, calculated on the basis of the urine collected

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in sporadic cases, as reviewed recently by Boers et al (4). These preliminary studies indicate that oral administration of pharmacological amounts of betaine of 1.7–6 g/d reduce substantially the homocysteine concentration in blood.

For the moment, there are no reports showing that dietary intake of choline or betaine nor their blood concentrations nor decreased BHMT activity are determinants of plasma homocysteine in a healthy population or even in vascular patients with hyperhomocysteinemia. Therefore, they were not included in my recent editorial in the Journal (5). However, I agree with Canty (1) that molecular genetic analysis of BHMT should be conducted and that dietary intake of betaine and its precursor choline, and their blood concentrations, should be explored for their possible role in mild hyperhomocysteinemia.
0–12 h after isotope administration, was only 11%. But when we considered the urine spot samples collected 12–24 h after isotope administration, absorption was 37%, which was closer to the other absorption values obtained from urine spots after 24 h (38%). If we had considered the urine collected over 0–24 h, we would have obtained an absorption value of ~22% or less, which is far from the correct magnesium absorption value.

These studies in humans and in animal models can perhaps explain not only why van den Heuvel et al did not observe an effect of oligosaccharides on calcium absorption, but also why they obtained a lower value (27%) than would be expected for calcium absorption in young men. For example, Fairweather-Tait et al (10) may have obtained a higher value for calcium absorption because they used plasma collected 24 h after isotope administration or 24-h urine collections 2 and 3 d postdosing. However, the high amount of calcium in the breakfast consumed by the subjects in van den Heuvel et al’s study may also be responsible for the low calcium absorption value because it is well known that calcium absorption is increased with a low-calcium diet and reduced with a high-calcium diet (5).

We conclude that, when the dual isotope-tracer approach is used, the urine pool collected 0–24 h after isotope administration should not be used for determining the fractional absorption of calcium in humans. This is particularly true when the effect of the studied product on mineral absorption is expected to be exerted in the distal part of the intestine as in the case of oligosaccharides. Allowing a reasonable period of ≥24 h for equilibrium to be reached is necessary before collecting plasma or urine samples for the measurement of calcium absorption because of the high urinary excretion of the intravenously administered isotope in the first hours after its administration. In this way, the risk of obtaining inappropriately low values for calcium absorption can be avoided. Moreover, in some cases, the effect of a dietary compound or a nutritional condition may be reduced or even masked when the correct protocol is not used. This is true also for magnesium absorption studies in which the dual isotope-tracer approach is used.

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Reply to C Coudray and SJ Fairweather-Tait
Dear Sir:

We thank Coudray and Fairweather-Tait for their comments on our study, in which we did not find an effect of 15 g inulin, fructooligosaccharides, or galactooligosaccharides/d on true iron and calcium absorption in men (1). In contrast with these results, Coudray et al (2) showed that 40 g inulin/d increased apparent calcium absorption in men. Coudray and Fairweather-Tait ascribe the discrepancy between the 2 studies to the fact that we used an improper measurement of calcium absorption. We used the dual stable-isotope technique. With this technique, true calcium absorption was estimated from the relative ratio of orally to intravenously administered calcium isotope in urine collected over 24 h, starting immediately after isotope administration. The main criticism of Coudray and Fairweather-Tait is that, for a correct estimation of calcium absorption, urine should be collected starting from 24 h after isotope administration instead of directly after isotope administration. Coudray and Fairweather-Tait, referring to the papers of Smith et al (3) and Yergey et al (4), state that measurements in urine collected before 24 h after isotope administration will underestimate actual calcium absorption. However, in the studies mentioned, isotope enrichment was measured in spot urine samples or single blood samples and not in complete urine collections.

Use of complete urine collections over a period of time (0–24 h) instead of a single spot urine or blood sample gives a better estimate of the correct value of fractional calcium absorption (5, 6). This is because calculation of absorption from a spot urine or a single blood sample is based on the assumption that the intravenously injected isotope and the absorbed orally administered isotope arrive in the bloodstream at about the same time and are metabolized in parallel. In this case, the correct time to meas-