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## The gut: a regulatory hall governing fat-soluble micronutrient absorption

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The gut has long been considered a simple entry gate into the body for nutrients and micronutrients, including the fat-soluble molecules that flow into the blood via chylomicrons initially released into the lymph. However, recent research has emphasized that the gut can actually be considered a hall, with entry doors, waiting rooms, and exit gates (1).

The present issue of the Journal contains elegant work by Traber et al. (2) presenting for the first time vitamin E absorption kinetics using a dual-isotope technique. In this study, healthy women consumed 30 mg D3-labeled vitamin E while 30 mg D6-labeled vitamin E was simultaneously injected intravenously. This work is particularly relevant in understanding vitamin E intestinal absorption, because it clearly shows that the amount of vitamin E absorbed is not dependent on the presence of fat within the meal in which it is consumed, but depends on successive fat-containing meals. Indeed, vitamin E secretion into chylomicrons after a vitamin E-rich meal can be delayed to a subsequent postprandial period, and can likely be regulated by the fat composition of this second meal.

A similar process of pulsed secretion was first described in healthy men for  $\beta$ -carotene absorption ~20 years ago (3). When given a pharmacological dose of  $\beta$ -carotene (120 mg) within a fat-rich meal, the release of  $\beta$ -carotene was higher after the second fat-rich meal than after the first. This effect was not observable at high dietary doses of  $\beta$ -carotene (~15 mg) (4). Two years later, the use of D7-cholesterol in 7 subjects highlighted that this labeled cholesterol also reached a maximum in chylomicrons secreted after a second meal, and that it was still present in chylomicrons after a third meal (5).

These observations underline the fact that when given at high doses, and if the necessary fat is not already present in the enterocytes, (micro)nutrients may be temporarily stored, waiting for the time where conditions necessary for chylomicron synthesis and secretion are met. Thus, this phenomenon leads to the regulation of (micro)nutrient appearance into the blood after a massive oral load, which may be of interest considering the putative pro-oxidant potential of vitamin E (6) or carotenoids (7) when circulating at high doses. Further research to understand both the mechanisms of micronutrient retention in the enterocyte, and its consequences, is deeply needed.

Traber et al.'s (2) work also emphasizes that the time between the first vitamin E-rich meal and the subsequent fat-containing

meal determines the kinetics of appearance of vitamin E in the blood.

Most of the studies conducted thus far to appreciate vitamin E (and other fat-soluble micronutrient) bioavailability mainly focused on the total amount absorbed, rather than the absorption kinetics. However, discrepancies in terms of kinetics and, in turn, in terms of circulating micronutrient concentrations may have physiological consequences that have not yet been estimated.

Based on *in vitro* and rodent data, the possible secretion of vitamin E in intestinal lipoproteins other than chylomicrons, and in particular in intestinal HDL, was suggested a few years ago (8, 9). However, in patients presenting with altered chylomicron secretion, this putative HDL pathway does not significantly compensate (10), possibly owing to concomitant dysfunctional HDL synthesis. Thus, investigations are required to evaluate the effectiveness of this HDL pathway to aid in vitamin E absorption in healthy subjects. Traber et al.'s work highlights that HDLs are rapidly enriched in labeled vitamin E during the postprandial period. This enrichment seems largely due to vitamin E exchange between circulating lipoproteins, providing further evidence that vitamin E absorption via an intestinal HDL pathway may be minimal in humans.

Finally, the work by Traber et al. (2) presents data on vitamin E recovery in feces. Interestingly, 2% of the D6-vitamin E was excreted after 96 h. This amount appears to be low, but may be underestimated owing to microbiota metabolism. This excreted D6-vitamin E may originate from the bile, from desquamation of enterocytes that have absorbed this vitamin E from the blood, or from putative transintestinal excretion. The concept of transintestinal cholesterol excretion has emerged in the past few years. It was first characterized in rodents and healthy humans (11), and was also recently observed in patients with complete common bile duct obstruction (12). Interestingly, our group has also discovered that plasma vitamin D can also be effluxed through the intestine to the digestive lumen in mice (13). Even if the recent report by Traber et al. suggests that transintestinal vitamin E excretion may be nonsignificant in healthy women,

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such an excretion pathway may exist under certain conditions that still remain to be fully defined.

Thus, beyond the results presented, the work by Traber et al. opens new lines of questioning, and further extends interest in investigating micronutrient transport through the intestine.

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