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3 **Vitamin E bioavailability in humans: State of the art**

4

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20

21 **Running title:** Vitamin E bioavailability.

22

1 *Abstract*

2

3 Vitamin E is essential for human health and may prevent some degenerative diseases.

4 However its bioavailability is wide-ranging and affected by numerous factors. Recent findings

5 showing that vitamin E intestinal absorption involves proteins have raised new relevant

6 questions about the factors that can affect its bioavailability. It is therefore opportune to

7 present a state of the art on this topic. This review begins with what is known/unknown about

8 the fate of vitamin E in the human upper gastrointestinal tract. A methodical evaluation of the

9 factors assumed to affect vitamin E bioavailability is then presented. Three main conclusions

10 can be drawn: (i) ABCA1, NPC1L1 and SR-BI are implicated in absorption of vitamin E; (ii)

11 absorption efficiency is widely variable, not accurately known (i.e. between 10% and 79%),

12 and affected by several dietary factors (e.g. food matrix, fat, some other fat-soluble

13 micronutrients); (iii) numerous questions, suggested in this review, still remain to be

14 answered on the fate of vitamin E in the intestinal lumen and on the factors that affect its

15 absorption efficiency.

16

17 **Key words:** α -tocopherol, absorption, intestine, micelle, enterocyte

18

1 *Introduction*

2
3 Vitamin E is one of the main liposoluble antioxidants (1), but it also shows non-
4 antioxidant activities, *e.g.* gene expression modulation, cell proliferation inhibition, platelet
5 aggregation, monocyte adhesion (2) and bone mass regulation (3). Vitamin E is the generic
6 term for molecules that possess the biological effects of α -tocopherol. Four tocopherols (α , β ,
7 γ and δ) and four tocotrienols (α , β , γ and δ) occur naturally, α - and γ -tocopherol being the
8 main vitamers found in Western diets. Dietary vitamers of vitamin E are present as RRR
9 stereoisomers and are not esterified. However, vitamin E used in supplements and as an
10 antioxidant food additive, currently taken by more than 10% of the US adult population (4), is
11 usually a racemic mixture of the eight stereoisomers and is esterified (*e.g.* *all-rac- α -*
12 *tocopheryl acetate* and *all-rac- α -tocopheryl succinate*) to protect the phenol group against
13 oxidation. Food containing high concentrations of this vitamin include vegetable oils and
14 nuts, but vitamin E is also found in other food matrices, *e.g.*, wheat germ and lettuce (5).

15 The average vitamin E intake of Americans is still below the recommended dietary
16 allowances (15 mg/d for persons of age 14 years and older) and it was reported ten years ago
17 that about 3/4 of Americans (19 to 30 years old) consumed less than 10 mg/d. In Europe, 8%
18 of men and 15% of women failed to meet 67% of the European recommended dietary
19 allowances for vitamin E (12 mg/d) (6). In addition, it is assumed that the US Institute of
20 Medicine recommendations to replace dietary saturated fatty acids with monounsaturated
21 fatty acids and polyunsaturated fatty acids will rise vitamin E needs and thus increase vitamin
22 E deficiency (7).

23 The potential benefit of vitamin E on several diseases have been extensively studied
24 (8-14). Yet surprisingly, the fundamental mechanisms that govern its absorption and the
25 factors that influence its absorption efficiency and its postprandial blood concentrations,

1 *i.e.* its bioavailability, are not accurately known. This review will focus on the factors
2 assumed to affect vitamin E bioavailability, which is taken to be the fraction of ingested
3 vitamin E recovered in the blood after absorption of a known dose of vitamin E. The factors
4 studied are therefore those that affect bioaccessibility, *i.e.* release from the food matrix,
5 absorption by the enterocytes, enterocyte intracellular transport, and enterocyte secretion first
6 into the lymph and then into the blood compartment. The review begins with what is
7 known/unknown about the fate of vitamin E in the human upper gastrointestinal (GI) tract. A
8 methodical evaluation of the factors hypothesized to affect vitamin E bioavailability is then
9 presented.

10

11 ***Fate of vitamin E in the upper gastrointestinal tract***

12

13 Since vitamin E is fat-soluble and is mainly absorbed in vegetable oils, it is assumed,
14 and it has been shown (15), that it follows the fate of major lipids (triacylglycerols,
15 cholesterol and phospholipids) in the upper GI (gastrointestinal) lumen (16, 17), although it is
16 not as efficiently absorbed as triacylglycerols. This fate includes emulsification, incorporation
17 in micelles, transport through the unstirred water layer, uptake by the apical membrane of the
18 enterocyte, solubilisation into intestinal lipoproteins, and secretion out of the intestinal cell
19 into the lymph or into the portal vein.

20

21 Foods are mixed with saliva in the mouth and in the stomach it is mixed with gastric
22 secretions and subjected to acidic conditions and gastric enzymes. It has been shown that free
23 *all-rac- α -tocopherol* is not significantly degraded in this organ (18) where it is thought that
24 vitamin E is partially released, by the action of pepsin, from food matrices in which it is
25 embedded. It is also assumed that the fraction of vitamin E already incorporated in vegetable
oils, *e.g.* vitamin E in vegetables or in nuts, is transferred to dietary fat. It is reasonable to

1 suggest that this process depends on the characteristics of the food matrix and on the
2 amount/type of dietary fat. There is little data on the role of gastric lipase on vitamin E ester
3 hydrolysis, but it has been suggested that some esters of vitamin E are at least partially
4 hydrolyzed by this lipase. This could be of importance when vitamin E is ingested as
5 supplements and when pancreatic lipase activity is not optimal (*e.g.* neonates and pancreatic
6 insufficiencies).

7 In the duodenum, digestive enzymes, *i.e.* proteases, amylases and lipases, continue to
8 release vitamin E from food matrices. It is hypothesized that vitamin E not naturally
9 incorporated in vegetable oils is transferred from food matrices to dietary fat and then into
10 micelles, but it can be hypothesized that there is a direct transfer of vitamin E from the food
11 matrices into micelles (**Figure 1**), as shown for carotenoids (19). Tocopheryl esters are
12 hydrolyzed, at least partly, by carboxyl ester hydrolase (also called bile salt-dependent lipase,
13 carboxyl ester lipase, and bile salt-stimulated lipase), secreted by the exocrine pancreas and
14 whose activity requires bile salts (20, 21). However, by analogy with retinol esters, some
15 other candidate enzymes exist: pancreatic lipase, pancreatic lipase-related protein 2, (22) and
16 phospholipase B. This hydrolysis could also be carried out by some brush border enzymes of
17 enterocytes (23-25). Brush border enzyme candidates could include an esterase localized in
18 the membrane or in the endoplasmic reticulum. Experiments on homogenates of jejunal rat
19 enterocytes showed that an esterase able to hydrolyse tocopheryl acetate was located in the
20 endoplasmic reticulum (25). The relative percentage of tocopheryl esters hydrolyzed by the
21 candidate esterases is not known, but it is suggested that most of tocopheryl esters are
22 hydrolyzed in the lumen of the intestine.

23 Although it is hypothesized that most vitamin E released from food matrices is localized
24 in mixed micelles in the GI lumen, we cannot exclude the possibility that some vitamin E is
25 incorporated in other lipid structures that coexist with micelles during digestion, *i.e.* lipid

1 droplets and vesicles. Vesicles, like liposomes, are constituted of either single bilayers of
2 phospholipids (unilamellar vesicles) or multiple bilayers of phospholipids (multilamellar
3 vesicles). The assumption that vitamin E could be incorporated in vesicles during digestion
4 is supported by the fact that vitamin E is incorporated in phospholipid bilayers *in vitro* (26).
5 Furthermore, it has been shown that α -tocopherol facilitates the assembly of phospholipid
6 bilayers. Conversely, without α -tocopherol, phospholipids generate micelles (27). Finally,
7 the stability of vesicles to sodium deoxycholate was improved by fat-soluble vitamins (26).
8 The distribution of vitamin E between triglyceride droplets, uni or multilammellar vesicles
9 and mixed micelles, and its location within these vehicles, *i.e.* in the lipid surface or core of
10 the droplets, or across or inside the phospholipid bilayers, depends on its solubility and its
11 ability to react with the different lipids that constitute these vehicles (28-30). This
12 distribution is unknown, but it is likely involved in vitamin E absorption efficiency.

13 To summarize, it is likely that vitamin E is not only solubilized in micelles, but it also
14 distributes between different lipid structures in the intestinal lumen during digestion. It can
15 also be suggested that absorption mechanisms are affected by the structure with which
16 vitamin E is associated: micelles may interact with proteins located in membranes, while
17 vesicles might have a different transport pathway. Thus knowledge of the distribution of
18 vitamin E between the different vehicles allowing its solubilization in the intestinal lumen is
19 required to better understand the mechanisms governing its absorption.

20
21 The main site of vitamin E absorption is assumed to be in the mid-GI tract, although
22 its precise localization in humans is still unknown. Indeed the only data available were
23 obtained using everted small bowel sacs in rats and mice. The Hollander's team found that
24 the highest efficiency of vitamin E absorption in the rat took place in the medial portion of
25 the small bowel, assumed to be the jejunum (31). This is in agreement with a recent study in

1 mice showing that the main site of absorption of vitamin E is the distal part of the jejunum
2 (32). A first hypothesis explaining why the efficiency of vitamin E absorption is not similar
3 along the intestine is that the proteins involved in vitamin E absorption, *i.e.* SR-BI
4 (scavenger receptor class B type 1), NPC1L1 (Niemann-Pick C1 like protein 1) and ABCA1
5 (ATP-binding cassette, sub-family A) (33), are not evenly distributed. It is likely that the
6 absorption efficiency of vitamin E is maximal where its intestinal transporters are mostly
7 expressed. The intestinal distribution of transporters involved in cholesterol absorption–
8 transporters also involved in vitamin E absorption – was recently measured in intestinal
9 samples from 11 subjects. Results showed bell-shaped distribution, with the highest
10 concentrations in the ileum for NPC1L1 and ABCA1 (34). Another significant variable that
11 can modulate vitamin E absorption is the repartition of vitamin E transporters between the
12 basolateral and apical membranes of the intestinal cell. This repartition is different along the
13 | gut: SR-BI, which is involved in vitamin E absorption, is present mainly on the apical
14 | membrane of the proximal intestine, but mainly on the basolateral surface of the distal
15 intestine (35). Better knowledge of the localization of transporters implicated in absorption
16 of vitamin E along the gut, and within the intestinal cell, would likely improve our
17 knowledge of vitamin E absorption. Another hypothesis explaining why efficiency of
18 vitamin E absorption is not similar along the intestine is that the major sites of absorption
19 might be those where the bioaccessibility of vitamin E is the highest, *i.e.* where its
20 concentration in micelles, and possibly vesicles, is the highest.

21 Data on efficiency of vitamin E absorption are scant and have been obtained with
22 widely different models (laboratory animals, healthy volunteers, subjects with intestinal
23 malabsorption, ileostomy subjects...). They have also been obtained with wide-ranging
24 doses of vitamin E, which were embedded into different matrices and assimilated in very
25 different test meals or diet. Because (i) absorption of vitamin E is modulated by numerous

1 factors, (ii) absorption is likely mediated by gut proteins at dietary doses, but is likely
2 passive at pharmacological doses (33), and (iii) there is an important variability between
3 inter-individual with regard to its absorption efficiency (36), the wide variability in published
4 data is unsurprising.

5 Available studies report efficiency of absorption in the range 10–79% (37–41). In a
6 recent study using deuterium-labeled vitamin E to estimate absorption, the range was found
7 to be between 10–33%, depending on the amount of fat in the meal (38). However, the
8 authors acknowledged that this percentage would have been larger with a breakfast richer in
9 fat (>11 g fat) and that the method they used, *i.e.* labeled vitamin E only in food, was not
10 optimal, suggesting for future studies the injection of another labeled dose of vitamin E to
11 the subjects and calculation of the ratio of the consumed dose divided by the injected dose.

13 ***Vitamin E absorption mechanisms***

14
15 Intestinal absorption of vitamin E was assumed to occur by passive diffusion: the
16 transport of vitamin E was found as non-ATP-dependent, because the use of chemicals that
17 inhibit ATP synthesis did not impair its absorption. Also, the observation that vitamin E
18 absorption was linear up to 1.2 mM was a further result in favor of passive diffusion (31).
19 However, the passive diffusion hypothesis cannot explain the higher absorption of vitamin E
20 in the middle of the intestine compared with other segments of the intestine (31, 32). Nor can
21 it explain the high inter-individual variability in bioavailability observed during studies
22 performed in the postprandial period (36). Nor indeed can it explain the competition between
23 carotenoids and vitamin E observed in rodents (42) and suggested in humans (43).

24 The discovery of the *Drosophila* gene *ninaD* (neither inactivation nor afterpotential
25 D) that encodes a class B scavenger receptor involved in tocopherol metabolism was the first

1 evidence supporting the involvement of a membrane protein in the cellular uptake of vitamin
2 E (44). Recent studies, performed mainly in Caco-2 cells and in transgenic mice, have shown
3 that at least two proteins are involved in uptake of vitamin E at the apical membrane of the
4 intestinal cell and one in its secretion at the basolateral side (33, 45). These proteins are
5 NPC1L1 and SR-BI, which are implicated in apical uptake (46-49), and ABCA1, which is
6 involved in the secretion of a fraction of vitamin E at the basolateral side *via* an apoAI
7 pathway (50, 51). The main fraction is secreted in chylomicrons via the apoB pathway.

8 The intracellular mechanisms of vitamin E transport in the enterocyte are not known.
9 In hepatocytes, the α -tocopherol-transfer protein (α -TTP) binds RRR- α -tocopherol with the
10 highest affinity (tocopherol > tocotrienols, α - > β - > γ - > δ -tocopherol, RRR- α -tocopherol >
11 2R- α -tocopherol > 2S- α -tocopherol) and is responsible for the preferential secretion of this
12 stereoisomer onto nascent hepatic VLDL (52, 53) and thus for its preferential distribution to
13 peripheral tissues (54, 55) (**Figure 2**). Mutations in the gene that encodes this protein can
14 impair the transfer of tocopherol from the liver into blood lipoproteins, resulting in a disease
15 called ataxia with isolated vitamin E deficiency. It is hypothesized that other proteins than α -
16 TTP are involved in the intracellular transport of vitamin E in other tissues (56). A protein
17 that binds vitamin E, and which is called SPF (supernatant protein factor) or TAP
18 (tocopherol-associated protein), has been found in bovine (57) and human tissues (58). This
19 protein belongs to a family of proteins that bind hydrophobic ligands and that share a
20 homologous substrate-binding pocket, commonly referred to as the “sec14 domain”. It was
21 shown by Northern that *SPF/TAP* mRNA is ubiquitously expressed. Therefore this protein
22 was suggested to be involved in intracellular transport of vitamin E in various tissues,
23 although its expression in enterocyte has not been evaluated (57). Nevertheless, a systematic
24 review of substrate specificity among this protein has shown that it has a weak non-selective
25 affinity towards tocopherols (59, 60) suggesting that it is not a good candidate for

1 intracellular transport of vitamin E. Other candidates for intracellular transport of vitamin E
2 within the enterocyte could be the sec14p-like proteins (encoded by *TAP1*, 2 and 3 in
3 humans). Indeed these proteins are detected in several tissues and have been shown *in vitro*
4 to improve the transport of α -tocopherol to mitochondria with the same efficiency than α -
5 TTP (61). As α and γ -tocopherol are absorbed with similar efficiency (46, 52), and with no
6 firm evidence that the other forms of vitamin E, *i.e.* β and δ -tocopherol and tocotrienols are
7 absorbed with different efficiencies, we hypothesize that if a vitamin E-binding protein is
8 involved in the transport of vitamin E within the intestinal cell, it is probably a transporter
9 that has no specificity for the RRR isomer of α -tocopherol, unlike α -TTP. Finally, it has
10 recently been found that NPC1/2 (Niemann-Pick type C1/C2) proteins are involved in the
11 intracellular transport of tocopherol in fibroblasts and hepatocytes (62). However, it is not
12 known whether these proteins are expressed in enterocytes or whether they are involved in
13 vitamin E absorption .

14 Finally, it is important to state that the two absorption mechanisms, *i.e.* the protein-
15 mediated absorption and the passive absorption, may be complementary, with protein-
16 mediated absorption occurring at dietary doses (**Figure 3**) and passive diffusion taking over
17 at pharmacological doses.

18 *Possible factors affecting absorption*

19
20
21 In order to be absorbed, vitamin E has to be released from the matrix in which it is
22 incorporated and presented to the brush border in a state allowing its absorption by
23 enterocytes. Absorption efficiency depends on an array numerous variables including: (i)
24 food matrix, (ii) nature and amount of macronutrients, (iii) activity of digestive enzymes, (iv)
25 transport efficiency across the intestinal cell, etc. The mnemonic “SLAMENGGHI”, listing the

1 factors assumed to govern carotenoid absorption (63), is used here to review the factors
2 suspected to affect vitamin E absorption. Each letter stands for one factor: Species of vitamin
3 E (i.e. the form of vitamin E, e.g. α -tocopherol, γ -tocopherol or α -tocotrienol), molecular
4 Linkage (e.g. esterification of vitamin E), Amount of vitamin E consumed in a meal, Matrix
5 in which vitamin E is incorporated (e.g. vegetable oil or supplement), Effectors of absorption
6 and bioconversion (e.g. lipids, dietary fibers, drugs), Nutrient status of the host (in this case
7 vitamin E status), Genetic factors (e.g. mutations or genetic polymorphisms in genes involved
8 in vitamin E metabolism), Host-related factors (e.g. gender, age), and mathematical
9 Interactions (to refer to the differences in effects observed when two factors play a joint role
10 compared with the sum of the effects observed separately). The effect of each SLAMENGHI
11 factor on vitamin E absorption efficiency was reviewed by querying the on-line US National
12 Library of Medicine in February 2012. Results are presented below.

13
14 a. *Species of vitamin E*

15 Three comparisons are of interest: (i) relative absorption of α -tocopherol stereoisomers,
16 (ii) relative absorption of tocopherol vitamers (α , β , γ , δ) and (iii) relative absorption of
17 tocopherols and tocotrienols. Concerning the first comparison, no significant difference
18 between the absorption efficiency of RRR and SRR α -tocopherol stereoisomers has been
19 found in humans (64) and to our knowledge, the other stereoisomers have not been tested.
20 Concerning the second comparison, two studies found no major difference in intestinal
21 absorption of labeled α - and γ -tocopherol in humans (52, 53), while another study suggested
22 that α -tocopherol was better absorbed than γ - and δ -tocopherol (65), although it was
23 performed in rats without labeled tocopherols. Finally, regarding the third comparison, a study
24 in thoracic duct-cannulated rats suggested a preferential absorption of α -tocotrienol compared
25 with γ - and δ -tocotrienols and α -tocopherol (66), but this needs to be confirmed in humans.

1 In conclusion, the small number of studies on this factor does not allow any firm
2 conclusion to be drawn on the effect of vitamin E species on its absorption efficiency in
3 human.

4

5 *b. Molecular Linkage*

6 Although most dietary vitamin E is free, supplements of vitamin E usually contain vitamin
7 E esters because of the greater stability conferred to the reactive hydroxyl group of vitamin E/
8 α -tocopherol. The relative absorption of RRR- α -tocopherol compared with its esters (RRR- α -
9 tocopheryl acetate and RRR- α -tocopheryl succinate) was found to be similar in humans (67,
10 68).

11 These two studies suggest that vitamin E esterification does not have a marked effect on
12 its intestinal absorption, at least in subjects not suffering from a deficiency in gastrointestinal
13 lipolytic enzymes (*e.g.* pancreatic insufficiencies or cystic fibrosis). It seems reasonable to
14 hypothesize that absorption efficiency of vitamin E esters would be lower when intestinal
15 esterolytic activity is impaired, but this has unfortunately never been assessed.

16

17 *c. Amount consumed in a meal*

18 It is generally assumed that the absorption efficiency of vitamin E decreases with
19 increasing doses because of blood saturation . However, the lack of a dose-dependent increase
20 in blood vitamin E concentration does not necessarily indicate a decreased absorption
21 efficiency, because blood concentration largely reflects redistribution by the liver of newly-
22 absorbed vitamin E, not absorption. Plasma vitamin E concentration increased linearly in
23 response to doses up to 150 mg (69). Also, by measuring vitamin E in chylomicrons following
24 vitamin E-rich meals, it was shown that absorption efficiency did not decrease with increasing
25 doses of *all-rac*- α -tocopheryl acetate between 432 mg and 937 mg (70).

1 Thus there is no evidence that vitamin E absorption efficiency decreases with increasing
2 doses. This does not conflict with the involvement of proteins in enterocyte uptake of vitamin
3 E: it is likely that passive diffusion, which is not affected by concentration, occurs at
4 pharmacological doses of vitamin E.

5
6 *d. Matrix in which vitamin E is incorporated*

7 This factor is hypothesized to be one of the most important ones, because it is assumed
8 that vitamin E extraction is not very efficient in some food matrices, a necessary step for
9 vitamin E to become bioaccessible, *i.e.* to become available for absorption. To support this
10 hypothesis, an *in vitro* study measured the bioaccessibility of α - and γ -tocopherol in various
11 food matrices and showed that it was widely variable, ranging from 0.5% in apples to around
12 100% in bananas, bread and lettuce (71). Furthermore, it was recently shown that although the
13 bioaccessibility of vitamin E from durum wheat pasta was quite high (about 70%), adding
14 eggs to the pasta diminished tocopherol bioaccessibility (down to about 50%) (72). We note
15 that although it was thought that vitamin E from seeds was not bioaccessible because seeds
16 are not digested in the human GI tract (73), the bioaccessibility of almond and hazelnut α -
17 tocopherol was measured at around 10–15% (71) and at 45% in finely ground almonds (74).
18 The efficient bioavailability of α -tocopherol in nuts is supported by a recent clinical trial that
19 showed a significant increase in plasma α -tocopherol after consumption of 30 g/d of either
20 ground, sliced or whole hazelnuts for 4 weeks (75). The bioavailability of vitamin E (α - and
21 γ -tocopherol) from broccoli was assessed *in vitro* and in healthy volunteers and results
22 suggested that α -tocopherol was weakly bioavailable from this vegetable matrix (76)..

23 In summary, the food matrix is probably a key factor with regard to absorption
24 efficiency of vitamin E, but most dietary vitamin E occurs in vegetable oils and too few data
25 are available in humans to rank foods as a function of vitamin E absorption efficiency.

1

2 *e. Effectors of absorption*

3

4 I. Dietary lipids

5 Lipids are assumed to affect vitamin E absorption by several mechanisms. First, they may
6 facilitate the release of vitamin E from its food matrix by providing a hydrophobic phase
7 where vitamin E can be solubilized. Second, it has been demonstrated that lipids stimulate
8 biliary secretion and consequently micelle formation. They may thus increase the proportion
9 of micellarized vitamin E, *i.e.* vitamin E available for absorption. Third, lipid digestion
10 products, e.g. fatty acids, monoglycerides and lysophospholipids are micelle components, and
11 the higher the lipid digestion, the higher the amount of micelles that can solubilize vitamin E
12 (77). Finally, by inducing chylomicron synthesis, lipids may enhance vitamin E transport
13 outside the enterocytes and thus prevent the accumulation of vitamin E in enterocytes (78).
14 Several characteristics of dietary lipids are suspected to affect vitamin E absorption: (a) the
15 amount of triacylglycerols ingested with vitamin E, (b) the species of triacylglycerol fatty
16 acids (c) the amounts of phospholipids, (d) the species of phospholipids and (e) lipid
17 emulsification. The effect of this latter characteristic has been studied in only one study and
18 there was no significant effect of emulsion lipid droplet size on vitamin E bioavailability (18).

19

- 20 • Amount of fat (triacylglycerols)

21 Dimitrov et al. (79) have observed higher plasma α -tocopherol levels in human
22 subjects given vitamin E (as *all-rac*- α -tocopherol) with a high fat diet for 5 d in comparison
23 with subjects receiving a low-fat diet. Nevertheless, no difference in plasma vitamin E
24 concentrations was observed following a 50 mg supplement (as α -RRR-tocopherol) taken
25 with either 3 g or 36 g fat for 7 d in another study (80). A recent study compared vitamin E

1 bioavailability from a capsule with that from a fortified breakfast cereal (81) and found a
2 lower bioavailability from the latter. This was explained by the lack of fat in the supplement,
3 although the supplement and the fortified breakfast cereal were different for several factors.
4 Finally, the bioavailability of vitamin E in whole milk (3.6% fat), whole milk fortified with
5 vitamins A and E, and skimmed milk (0.3% fat) fortified with vitamins A and E was
6 compared in healthy subjects. Results showed no significant difference in tocopherol
7 response (area under the curve) after the ingestion of any of these milks, suggesting that the
8 fat fraction of the milk had no marked effect on vitamin E bioavailability (82). These four
9 studies give inconsistent results and so do not allow any conclusion on the effect of fat on
10 vitamin E absorption, probably because of the low sensitivity of the parameter used to study
11 this effect (variation in blood α -tocopherol).

12 The best studies to assess the role of fat on vitamin E absorption are those using stable
13 isotopes, because this allows the discrimination of newly-absorbed from endogenous vitamin
14 E. A first study using this method compared RRR- α -tocopheryl acetate absorption following
15 meals comprising: toast with butter (17.5 g fat), cereal with full-fat milk (17.5 g fat), cereal
16 with semi-skimmed milk (2.7 g fat), and water (no fat) (83). Vitamin E uptake was highest
17 after the toast with butter meal (17.5 g fat), followed by the cereal with full-fat milk (17.5 g
18 fat). Vitamin E uptake was the lowest for the water (no fat) and the cereal with semi-skimmed
19 milk (2.7 g fat). The authors concluded that both the food matrix and the amount of fat
20 influenced absorption of vitamin E. In the second study using labeled vitamin E, apples were
21 fortified with deuterium-labeled RRR- α -tocopheryl acetate and given to five volunteers in
22 breakfasts containing 0, 6 or 21% kcal from fat (38). Results showed that vitamin E
23 absorption increased from 10% after the 0% fat meal to 20% and 33% after the 6% and 21%
24 fat meal, respectively. It was estimated in this study that an increase of 1 g in fat increased
25 tocopherol absorption by 0.43 mg. Finally, we note that in this study, a lunch eaten 5 h after

1 the consumption of the vitamin E-rich breakfast, and which contained 36% fat, had no
2 apparent effect on vitamin E absorption.

3
4 The finding of increased absorption of vitamin E in the presence of dietary fat is
5 consistent with results on other lipid micronutrients: compared with steamed tomatoes, the
6 bioavailability of lycopene provided in oil increased threefold, although other factors, *i.e.*
7 tomato matrix and potential lycopene *cis*-isomerization under steaming, could participate in
8 this difference (84). Likewise, carotenoid bioavailability was higher with full-fat salad
9 dressing than with reduced-fat salad dressing (85).

10

- 11 • Type of fatty acid (within triacylglycerols)

12 The type of fat in which vitamin E is presented to the gut seems to be important because
13 solubilization of the vitamin in long-chain, as opposed to medium-chain triacylglycerols
14 seemed to diminish absorption efficiency in the rat (86). This has been attributed to an
15 increased oxidation of tocopherol due to peroxidation of polyunsaturated fatty acids during
16 digestion. A study in poultry supported this hypothesis by showing that polyunsaturated fatty
17 acids did not limit vitamin E absorption, but may have increased its degradation in the GI tract
18 (87). Nevertheless the lack of clinical studies prevents any conclusion on the effect of this
19 dietary factor in humans. Finally, it has recently been shown that consumption of conjugated
20 linoleic acid by mice leads to an increase in concentrations of vitamin E in several tissues, *e.g.*
21 the liver and kidney. This increase was not due to any effect on absorption, but to an effect on
22 α -tocopherol transfer protein expression in the liver (88).

23

- 24 • Phospholipids

25 It has been shown that phosphatidylcholine can diminish vitamin E absorption (89, 90).

1 The hypothesis is that because of its high hydrophobicity, vitamin E is associated with the
2 long-chain fatty acids of phospholipids in mixed micelles, leading to a lower uptake by
3 enterocyte. The inhibitory effect of phosphatidylcholine on α -tocopherol absorption
4 disappear when they are substituted by lysophosphatidylcholine (89). As
5 lysophosphatidylcholine micelles are smaller than micelles of phosphatidylcholine, it has
6 been suggested that the size of micelles might affect absorption of vitamin E. However, a
7 comparison of cholesterol absorption from lysophosphatidylcholine and phosphatidylcholine
8 micelles, which had similar size, showed that absorption was still lower in
9 phosphatidylcholine micelles (91). Although all these studies suggest that phospholipids may
10 impair vitamin E bioavailability, dedicated clinical studies are required to assess whether
11 they can significantly impair intestinal vitamin E absorption in humans.

12

13 II. Dietary Fiber

14 Dietary fiber is suspected to affect vitamin E absorption (i) by affecting micelle formation,
15 (ii) by inhibiting lipases and thus affecting the release of vitamin E embedded in fat droplets
16 and (iii) by increasing the viscosity of the chyme and thus limiting the diffusion of vitamin E-
17 containing micelles to the brush border.

18 Data on the effects of fiber on vitamin E absorption are limited. A recent *in vitro* study
19 suggested that carrageenan slowed down the release of tocopherol from soybean oil body
20 emulsions stabilized by this fiber (92). However, the impact on tocopherol absorption was not
21 evaluated. Studies in rats suggested that pectin impaired vitamin E bioavailability (93, 94).
22 However, there was apparently no effect of various fiber types (pectin, guar, alginate,
23 cellulose or wheat bran (0.15 g kg⁻¹ body weight)) on the mean increase of plasma α -
24 tocopherol concentration over 24 h in women (95). A prospective cohort study in 283 middle-

1 aged women showed that higher intakes of fiber were not associated with lower plasma
2 concentrations of vitamin E (96).

3 Thus it seems that a normal intake of fiber does not markedly affect blood vitamin E
4 levels in humans.

6 III. Inhibitors of fat/cholesterol absorption

7 Since obesity and cardiovascular diseases are both major health problems, several drugs
8 have been proposed to diminish the absorption of fat and cholesterol. Given the solubilization
9 of vitamin E in dietary fat and the common pathways involved in enterocyte uptake of vitamin
10 E and cholesterol, it has been hypothesized that these drugs could impair vitamin E
11 absorption. It has been suggested and confirmed that Orlistat, a non-absorbed inhibitor of
12 gastric and pancreatic lipases also known as Xenical, Alli or tetrahydrolipstatin, as well as
13 Olestra, a sucrose polyester used as a fat substitute, can reduce absorption of vitamin E (97-
14 100). Phytosterols, known inhibitors of cholesterol absorption, have also been thought to
15 impair vitamin E absorption because they could impair tocopherol solubilization within mixed
16 micelles and/or compete with tocopherol for transport by NPC1L1 (101). Two studies were
17 designed to test this hypothesis. The study by Richelle et al. concluded that phytosterols
18 reduced tocopherol absorption (102), but another study failed to find any significant effect of
19 phytosterol esters on blood vitamin E levels (103). Different doses and species of phytosterols
20 together with different doses of tocopherol may explain this discrepancy. Cholestyramine, an
21 anion exchange resin used to lower cholesterol absorption by sequestering bile acids in the
22 intestinal lumen, apparently impaired α -tocopherol absorption (104). In mice, it has been
23 shown that ezetimibe, a cholesterol-lowering drug that specifically targets NPC1L1 (105), can
24 also lower γ -tocopherol absorption *in vivo* (32). However, there have not yet been any

1 dedicated clinical studies, and further research is required to assess the effects of cholesterol
2 absorption inhibitors.

3

4 IV. Microconstituents

5 Because α -tocopherol is generally ingested together with other vitamin E species
6 (*i.e.* γ -tocopherol, tocotrienols, etc.) and other lipid micronutrients (other fat-soluble vitamins,
7 carotenoids and phytosterols), and because common mechanisms of absorption are generally
8 involved, it has been hypothesized that interactions, including competition, might affect their
9 absorption. A study performed in Caco-2 cells showed that γ -tocopherol, carotenoids and a
10 polyphenol (naringenin) significantly impaired α -tocopherol absorption (43). Three clinical
11 trials also reported competition between α - and γ -tocopherol with regard to their
12 bioavailability. In a first clinical trial in 184 adult non-smokers, supplementation with α -
13 tocopheryl acetate significantly reduced serum γ -tocopherol concentration (106). In a second
14 clinical trial, plasma α -tocopherol concentration significantly decreased during γ -tocopherol
15 administration (376 mg/d for 28 days) (107). In a third clinical trial, both RRR- and *all-rac*-
16 α -tocopherol (free or esterified) significantly diminished serum γ -tocopherol levels to the
17 same extent (108). There are apparently no data on the interaction between tocotrienols and
18 tocopherols and their absorption. Concerning other lipid micronutrients, a high vitamin A
19 intake has been shown to diminish plasma tocopherol levels (109). This can be explained by
20 the fact that retinoic acid, a vitamin A metabolite, reduces the intestinal uptake of α -
21 tocopherol, possibly by promoting its oxidation during absorption (110) or by downregulating
22 *SR-BI*, which is involved in vitamin E uptake (46), and whose activity has recently been
23 shown to be controlled by retinoid signaling (111-113). In fact retinoic acid induces the
24 expression of *ISX* (intestine-specific homeobox), an intestinal transcription factor that
25 represses the expression of *SR-BI*. Thus a diet-responsive regulatory network may control

1 absorption of vitamin E *via* negative feedback regulation of *SR-BI*. We say “may” because
2 ISX null mice have normal blood cholesterol concentrations although there was an
3 overexpression of *SR-BI* in the intestine (111, 113). Lutein, a xanthophyll that belongs to the
4 carotenoid family, impaired α -tocopherol bioavailability in a postprandial study in eight
5 subjects (43). Conversely, canthaxanthin, another xanthophyll, did not affect vitamin E
6 absorption, but this study was carried out in the rat (42).

7 The broad range of possible interactions makes it difficult to draw general rules about
8 the effects of other lipid micronutrients on vitamin E absorption. Each suspected interaction
9 must be studied separately and no generalization can be made.

10

11 V. Milk and milk-derived products

12 Dairy products are generally assumed to be a significant source of vitamin E.

13 However, the contribution of these products to the Recommended Dietary Intake (RDI) of
14 vitamin E was evaluated (114) and it was calculated that the consumption of three standard
15 portions/d of dairy products could provide about 3% of the RDI for vitamin E (15 mg/d). The
16 same consumption, but using fortified/supplemented milk and yoghurt, may increase the
17 contribution to up to 24% of the RDI for elderly subjects. Thus the inclusion of fortified dairy
18 products in the diet may offer a sensible approach to improving vitamin E intake and status.

19 Several clinical studies did not report any inhibitory effect of milk on vitamin E
20 absorption (81-83, 115). In addition, an *in vitro* study showed (i) that α -tocopherol
21 bioaccessibility from fruit juices was increased in the presence of milk, and (ii) that
22 consumption of fruit juices with milk did not significantly modify serum tocopherol increase
23 in response to fruit juices. The authors concluded that the presence of milk did not markedly
24 influence the bioavailability of α -tocopherol from fruit juices (116).

1 Bovine milk fat globule membranes were purified and used to stabilize oil-in-water emulsions
2 containing α -tocopherol. Interestingly, the bioaccessibility of vitamin E in these vehicles was
3 double that in emulsions stabilized by milk proteins (whey proteins and caseinate) (117).

4 In conclusion, milk does not seem to significantly affect vitamin E absorption for the
5 general population.

6 7 *f. Vitamin E (Nutrient) status of the host*

8 Because vitamins are essential and because large amounts of fat-soluble vitamins can
9 be toxic, it has been suggested that vitamin E absorption could be regulated by its status. The
10 mechanism could involve a vitamin E mediated regulation of the expression of membrane
11 proteins implicated in its absorption, *e.g.* ABCA1, SR-BI. This hypothesis is supported by the
12 fact that α -tocopherol reduces the transcriptional activity of LXR α (Liver X receptor α) and
13 thereby the expression level of ABCA1 (118). α -tocopherol is also suggested to mediate the
14 regulation of SR-BI expression. Indeed treatment of HepG2 cells with agonists of PXR
15 (Pregnane X receptor), which recognizes most vitamin E vitamers as ligands (119),
16 diminished SR-BI expression (120). Furthermore, it has been shown that the expression of SR-
17 BI protein was regulated post-transcriptionally by vitamin E (121). Thus it has been
18 hypothesized that vitamin E could control cellular vitamin E levels by a negative feedback
19 regulation mechanism of SR-BI expression. Nevertheless, there is no, to our knowledge, study
20 dedicated to the effect of vitamin E status on vitamin E absorption efficiency.

21 22 *g. Genetic factors*

23 The involvement of intestinal proteins in vitamin E absorption has prompted the
24 hypothesis that genetic variants (most common genetic variants being single nucleotide
25 polymorphisms) in these proteins can modulate its absorption efficiency. This is supported by

1 several studies. Concerning *NPC1L1*, it has been shown, in Caco-2 cells transiently
2 transfected with expression vectors containing different variants, that *NPC1L1* non-
3 synonymous variants transport less α -tocopherol than the wild-type *NPC1L1* (49).
4 Concerning *SR-BI*, it was shown in a cohort of 128 volunteers that single nucleotide
5 polymorphisms in *SCARB1*, the gene coding for SR-BI, were related to the plasma status of
6 α - and γ -tocopherol (122), suggesting an effect of these variants on α -tocopherol distribution
7 in the body. Another scavenger receptor, CD36 (cluster of differentiation 36), which has been
8 found to be involved in cellular uptake of carotenoids (123, 124), but not yet in cellular
9 uptake of α -tocopherol, has been associated with blood vitamin E levels in humans (125).
10 Because CD36 recognizes a broad variety of lipid ligands, including FAs, oxidized LDLs,
11 apoptotic cells and carotenoids, we hypothesize that recognition of vitamin E by CD36 is
12 plausible, as like SR-BI, CD36 may function as a docking port and thus facilitate the transfer
13 of lipid molecules (including tocopherols) from mixed micelles to the apical membrane of the
14 enterocyte.

15 Other genetic factors that can affect vitamin E absorption are those which affect
16 absorption of lipids. Indeed vitamin E intestinal absorption requires normal digestive
17 functions, and thus subjects with genetic disease leading to impaired fat absorption, e.g. cystic
18 fibrosis, abetalipoproteinemia, are liable to have impaired vitamin E absorption. An example
19 is abetalipoproteinemia that is characterized by the defective assembly and secretion of apoB
20 containing lipoproteins caused by mutation in *MTTP* (Microsomal Triglyceride Transfer
21 Protein). Indeed, it has been hypothesized (126) that polymorphisms in *MTTP*, which is also
22 involved in intracellular metabolism of vitamin E (78), may influence the absorption
23 efficiency of vitamin E.

24

1 Altogether, these observations suggest that variants in genes involved in vitamin E or
2 lipid absorption may modulate vitamin E absorption efficiency and perhaps its disease-
3 preventive effects (126). We can speculate that ongoing results in the field of nutrigenetics
4 will lead to more personalized recommended dietary allowances that take into account the
5 genetic characteristics of subgroups in the population.

6 7 *h. Host-related factors*

8 Several studies suggest that some host-related factors (mainly gender, age and health
9 disorders) have an effect on vitamin E absorption.

10 11 I. Gender

12 The effect of gender on vitamin E absorption is difficult to assess in human studies
13 because female hormones affect lipid and lipoprotein metabolism (127), and thus differences
14 in blood vitamin E responses between males and females may be due to different rates of
15 lipoprotein clearance rather than to differences in absorption efficiency. However, no
16 significant difference was found in the plasma vitamin E concentration between 3 males and 3
17 females following vitamin E administration in the apparently only one study dedicated to this
18 topic (128).

19 20 II. Age

21 Age-related maturation or alterations of GI tract functions (129-131) have been
22 suggested to modify the efficiency of vitamin E absorption. Nevertheless, although it has been
23 hypothesized that the immature GI tract of premature babies is unable to efficiently absorb
24 lipids and fat soluble vitamins, these babies seem to maintain their vitamin E status on
25 unsupplemented milk (132). In children, it has been shown that a vitamin E supply (10.2 mg/d

1 for 42 months on average) allowed plasma levels of vitamin E to return to normal in home
2 parenteral nutrition children aged 5 months to 11 years (133). Concerning the effect of aging,
3 it has been shown that the bioavailability of *all-rac- α -tocopheryl acetate* is apparently lower
4 in healthy older subjects than in younger ones (70). However, this result was not confirmed in
5 another study performed in about 100 healthy 20- to 75-year-old male volunteers (134). This
6 apparent discrepancy can be explained by the fact that in the former study, vitamin E was
7 provided at pharmacological amounts of tocopheryl acetate, which might have overwhelmed
8 the capacity of elderly carboxyl esterase to hydrolyze vitamin E acetate. This hypothesis
9 needs to be checked in a further study.

10 In conclusion, absorption efficiency of free α -tocopherol is probably similar in young
11 and in elderly healthy adults and apparently not significantly diminished in children, while
12 absorption efficiency of pharmacological amounts of α -tocopheryl acetate is possibly less
13 efficient in elderly persons.

14 III. Health disorders

15 The intestinal absorption of vitamin E requires normal digestive functions, and so
16 subjects with impaired fat absorption, which can be caused by several disorders
17 (*e.g.* obstructive jaundice, pancreatic insufficiency, cystic fibrosis or adult coeliac disease) are
18 liable to have impaired vitamin E absorption. Patients with cholestatic liver disease (135), or
19 patients with cystic fibrosis (136), exhibited impaired vitamin E absorption. Conversely, no
20 significant difference was observed between patients with chronic pancreatitis and healthy
21 controls (137). Another disease has been suspected to affect vitamin E bioavailability:
22 *Helicobacter pylori* infection. However, in a recent clinical trial, it was concluded that this
23 infection, at least in its asymptomatic stages, did not significantly affect either vitamin E or C
24 bioavailability (138). Chemoradiation used as anticancer therapy in patients with rectal
25

1 carcinoma can be toxic for the GI tract and may affect its ability efficiently to absorb several
2 nutrients/drugs, including vitamin E (139). Finally, it has been shown recently that vitamin E
3 accumulates in lysosomes when expression of *NPC1* (Niemann-Pick C1) or *NPC2* (Niemann-
4 Pick C2) is diminished (62). It has been suggested that these proteins play a key role in
5 intracellular transport of vitamin E, thus explaining the altered vitamin E status in Niemann-
6 Pick type C disease (62).

7 In conclusion, host-related factors have a marked effect on vitamin E bioavailability.
8 This can partly explain the large interindividual differences in plasma vitamin E response to
9 single doses of vitamin E in the same population category (140).

10

11 *i. Mathematical Interactions*

12 These refer to synergistic interactions between two factors (63). Although no data are
13 available on these interactions, they probably occur under certain circumstances. For example,
14 an interaction may occur between “host-related factor” and “molecular linkage” in subjects
15 suffering from fat malabsorption (host-related factor) with impaired activity of gut esterases
16 (where the molecular linkage factor can play a role).

17

18 **Conclusions**

19

20 The aim of this review is to provide an overview of vitamin E absorption/bioavailability
21 and its modulating factors in humans. It clearly emphasizes that several crucial questions still
22 remain unanswered. Although recent findings have shown that the absorption mechanisms
23 involve proteins, it is probable that not all of these have yet been identified. The wide
24 interindividual variability observed in absorption efficiency suggests that genetic factors are
25 implicated but again, most of these await identification. Concerning non-genetic factors, there

1 is convincing evidence on the effect or absence of effects of some of them, *e.g.* esterification,
2 amount consumed in a meal, amount of fat consumed, dietary fiber, milk products, etc., while
3 few data are available on other important factors, *e.g.* food matrix, microconstituents,
4 cholesterol and lipid absorption inhibitors, etc., underlining the vast amount of work still
5 needed to improve our knowledge of vitamin E absorption and its modulating factors. This
6 knowledge will ultimately allow the optimization of vitamin E absorption, for example in
7 subjects on low-fat diets and carrying polymorphisms that alter antioxidant vitamin
8 requirements (14, 141).

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Figure legend

Figure 1

Distribution and transfer of vitamin E between the different vehicles assumed to transport vitamin E in the human intestinal lumen.

Figure 2

Fate of vitamin E in the human body showing the key role of α -TTP (α -tocopherol transfer protein).

Figure 3

Proteins involved in vitamin E uptake by human intestinal cell. From the recent papers of Reboul et al. (34) and Takada et al. (47). SR-BI: scavenger receptor class B type 1. NPC1/2: Niemann-Pick type C1/C2. NPC1L1: Niemann-Pick C1-like 1. NL-FABP: Liver Fatty-Acid-Binding Protein. hTAP 1,2,3: sec14p-like proteins 1, 2 et 3. ABCA1: ATP Binding Cassette A1.