Bioavailability of vitamin E in humans

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Abbreviations used: **ABCA1**, ATP binding cassette A1; **ABCG1**, ATP-binding cassette sub-family G member 1; **ASBT**, apical sodium–bile acid transporter; **CD36**, CD36 molecule; **NPC1L1**, NPC1 like intracellular cholesterol transporter 1; **SR-B1**, scavenger-receptor class B-type I; **SREBP2**, sterol regulatory element-binding protein 2; **VE**, vitamin E.

Introduction

The term vitamin E (VE) is the generic descriptor for all tocol and tocotrienol derivatives exhibiting qualitatively the biological activity of α-tocopherol. It refers to a group of 8 naturally-occurring fat-soluble micronutrients: 4 tocopherols (α, β, γ and δ) and 4 tocotrienols (α, β, γ and δ) (**Figure 1**). VE is composed of a substituted chromanol ring linked to a C16 isoprenoid side chain. Tocotrienols differ from tocopherols by the presence of 3 double bonds in their side chain. Tocopherol and tocotrienol isomers differ in the location of the methyl groups on the chromanol ring. Due to the presence of 3 asymmetric carbons in their side chains, tocopherols can form 8 stereoisomers (*RRR*, *RRS*, *RSR*, *RSS*, *SRR*, *SRS*, *SSR*, *SSS*). Naturally occurring tocopherols exist as *RRR* stereoisomers (formerly known as d-tocopherol) and are not esterified. However, when supplemented to the diet, tocopherol is usually a racemic mixture of the eight possible stereoisomers (all-*rac*-tocopherol, formerly known as dl-tocopherol) and is esterified to protect the phenol group against oxidation (*e.g.* α-tocopheryl acetate) (**Figure 1**) (1).

α- and γ-tocopherol are the most abundant VE forms in Western diets and are found at the highest concentrations in human blood and tissues (2). VE is found at relatively high concentrations in vegetable oils and nuts but it is also present in other food matrices such as wheat germs and salad. In the US, γ-tocopherol represents ≈70% of VE intake, due to the high consumption of food sources rich in γ-tocopherol in the typical diet (*e.g.* soybean oil, corn oil) (3). The respective contribution of α- and γ-tocopherol to VE intake in Europe is not precisely known. The current US recommended daily allowance (RDA) for healthy adults is 15 mg/day but it is estimated that >90% of men and >96% women in the US do not consume the estimated average requirements (EAR) (4). Recent data point at similar inadequacies in several European countries (5). A recent systematic review of global α-tocopherol status has pointed at a relatively high prevalence of VE deficiency with 13% of the subjects exhibiting serum α-tocopherol concentration <12 µmol/l, which has been proposed as a criterion for VE deficiency (6), and only 21% of the subjects reaching serum α-tocopherol concentrations >30 µmol/l (7), which has been proposed as a criterion for VE adequacy (8).

VE is quantitatively the main lipid-soluble antioxidant in mammalian tissues and blood (9). It acts as a chain-breaking antioxidant, especially against peroxyl radicals, and is thus essential in maintaining the integrity of long-chain polyunsaturated fatty acids found in cell membranes (9). Recently, it has been shown to also exert non-antioxidant activities (10): modulation of gene expression (11, 12), inhibition of cell proliferation (13), regulation of bone

mass (14)… Since oxidative stress has been implicated in the aetiology of several diseases, *e.g.* cardiovascular diseases and cancers, numerous epidemiological studies have investigated the association between VE dietary intake or status (usually evaluated as the fasting blood α-tocopherol concentration) and the incidence of these diseases and reported negative associations (15-17). However, most randomized controlled trials have failed to show a benefit of VE supplementation on the incidence of these diseases (18, 19). Several explanations have been put forward, including an absence of effect of VE supplementation on these diseases (20), a negative effect of α-tocopherol supplementation on the bioavailability of other VE isomers (21) or the absence of population stratification by VE status or oxidative stress in these negative studies (19). Recently, it has also been suggested that the high interindividual variability of α-tocopherol bioavailability may have interfered with the effects of VE supplementation (22) and that benefit from VE supplementation depends on a subject's genotype (23-25).

VE is a lipid and it shares common transport mechanisms with other lipids: in the lumen of the human upper gastrointestinal tract, it is found in structures allowing the solubilisation of lipids, *i.e.* micelles and possibly vesicles. It is transported in the blood via lipoproteins and it is found in membranes and lipid droplets in cells. Its bioavailability, *i.e.* the proportion of VE that is available for use or storage by the organism, has been reported to range between 10 and 81% (26-29). Numerous factors affect its bioavailability: dietary factors, such as composition of the food matrix or the presence of fat, but also host-related factors, such as pathologies or genetic factors (*see* section 3 for an overview thereof) (30). Its fate in the gastrointestinal tract includes emulsification, incorporation into mixed micelles, transport through the unstirred water layer, uptake by the enterocyte, incorporation into intestinal lipoproteins, and secretion out of the intestinal cell into the lymph or into the portal vein. This chapter will present an overview of what is known/unknown about the fate of VE in the human upper gastrointestinal tract and then list some of the factors hypothesized to affect VE bioavailability.

1. Vitamin E fate in the lumen of the upper gastrointestinal tract during digestion

Digestion of foods, or supplements, that contain VE starts in the mouth where the diet is subjected to the action of saliva coupled with mechanical processing, leading to a partial disruption of the food matrix and an increase of the surface area. In the stomach, the food matrix is submitted to an acidic pH (between 2 and 6 during digestion) and to the action of gastric

secretions, which contain several enzymes (pepsin, amylase, gastric lipase…) able to further degrade the food matrix. VE, if not naturally incorporated in vegetable oils, is assumed to transfer, at least partly, from its food matrix to the oil phase of the meal. The extent of this phenomenon depends most likely on the food matrix in which VE is incorporated and on the quantity and the nature of lipids present at the same time as VE in its food matrix. It has been shown that there is no significant degradation or metabolism of α-tocopherol in the stomach during digestion (26). There is a lack of data on the role gastric lipase could play on the hydrolysis of VE esters (*e.g.* tocopheryl acetate). This process could be significant when VE is consumed as a supplement and when pancreatic secretions are impaired (*e.g.* in newborns or in patients with cystic fibrosis).

In the duodenum, digestive enzyme (lipases, proteases, amylases…) participate in the release of VE from the food matrix by degrading it further. The importance of the contribution of pancreatic lipase, which is responsible for the intestinal hydrolysis of triglycerides, to VE bioavailability has been recently emphasized by the association of SNPs in its encoding gene with the postprandial chylomicron VE concentration, an acknowledged marker of VE bioavailability, following consumption of a VE-rich meal (22). It is widely accepted that, to some extent, VE transfers to the lipid phase, if not naturally incorporated in vegetable oils, and then to mixed micelles. However, the possibility that some VE could be transferred to other structures that solubilize lipids in the duodenum, *i.e.* vesicles (31), cannot be ruled out (32). Only one *in vitro* study has investigated VE (as α-tocopheryl acetate) distribution between the different structures present in the lumen of the small intestine during digestion, *i.e.* mixed micelles, vesicles, oil droplets and nonsolubilized food debris: most VE was found in matrices where its hydrolysis and its uptake by a model of human enterocytes was less efficient than in mixed micelles, suggesting this distribution could affect VE absorption efficiency (32). Its location within these structures, *i.e.* at the surface or in the core of lipid droplets, or across or inside phospholipid bilayers, are not currently known and likely depend on VE interaction with the different components of these structures. Nevertheless, a computational study has suggested that, at 37°C, α-tocopherol remains in one leaflet of phospholipid bilayers, with its hydroxyl group located between the third and the fifth carbon atom in the sn-2 acyl chains of the lipids (33). As it is accepted that only free VE is taken up by enterocytes, VE esters need to undergo hydrolysis to be absorbed. This hydrolysis is carried out, at least partly, by cholesteryl ester hydrolase (CEH; also known as carboxyl ester lipase, CEL; bile salt-dependent lipase, BSDL; bile salt-stimulated lipase, BSSL), secreted by the exocrine pancreas and whose activity requires the presence of bile salts (34). Contrarily to what is observed with retinyl esters, we

have shown that pancreatic lipase and pancreatic lipase-related protein 2 are not involved in this process (32). Nonetheless, other luminal candidate enzymes exist, *e.g.* phospholipase B, and the participation of brush border enzyme has been suggested as well (32, 35-38). Actually, Nagy *et al.* have recently shown that α-tocopherol and α-tocopheryl acetate exhibited the same bioavailability in the absence of digestive enzymes and bile salts in healthy subjects, even at supplemental doses (38). This study thus stressed the high potential contribution of either brush border enzymes, enzyme released after cellular damage or enzymes on the exterior of shed cells to the cleavage of α-tocopheryl acetate. These processes are summarized in **Figure 2**. Interestingly, a recent study has revealed the existence of a VE-ω-hydroxylase activity in human intestinal mucosa with the following rank order of activity on tocopherol isomers: $\gamma = \delta >> \alpha$ (39). The ω-hydroxylase activity in human intestinal mucosa was 20–30% of that found in the liver. In mice, it was found that only one enzyme, namely cytochrome P450, family 4, subfamily f, polypeptide 14 (Cyp4f14), was responsible for this activity. The quantitative, and qualitative (*i.e.* isomer specificity), contribution of this pathway to VE bioavailability warrants further investigation.

2. Uptake, metabolism and secretion of vitamin E by enterocytes

After its extraction from the food matrix and incorporation into mixed micelles, or vesicles, bioaccessible VE can be taken up by enterocytes. It needs to be reminded here that this extraction is only partial (32) and as a consequence, VE bioaccessibility can be relatively low and is highly variable between food matrices (40) (*see* section 3 for more details). VE is then transported across the enterocyte before its incorporation into chylomicrons, and also intestinal HDL, and secretion in the blood circulation via the lymph and the portal vein. These processes are summarized in **Figure 3**.

2.1 Vitamin E uptake at the apical membrane of the enterocyte

VE uptake by the enterocyte was long thought to occur only by simple passive diffusion (41) but several proteins, which are temporarily present at the apical membrane, have been shown to facilitate the uptake of VE (42). NPC1 like intracellular cholesterol transporter 1 (NPC1L1), which was first identified as an intestinal protein involved in cholesterol absorption (43), has been shown to be involved in the uptake of α-tocopherol into the enterocyte (44). Moreover, SNPs in the gene encoding sterol regulatory element–binding protein 2 (SREBP2),

a modulator of *NPC1L1* expression (45), have been shown to be associated with the postprandial chylomicron VE concentration following consumption of a VE-rich meal (22). Scavenger-receptor class B-type 1 (SR-B1) facilitates the uptake of several molecules with fairly different chemical structures, *e.g.* cholesterol (46), vitamin K (47) carotenoids (48) and α-tocopherol (49). Since mixed micelles are assumed to dissociate in the unstirred water layer bordering the apical membrane of the enterocyte (50), VE incorporated in mixed micelles is supposed to reach the apical membrane as free molecules. Given that SR-B1 facilitates the uptake of fairly different molecules and that it has been shown to act as a sensor of mixed micelles (51) promoting the assembly and secretion of chylomicrons (52), we hypothesize that a possible mechanism may be that this protein, by increasing the basolateral secretion of these molecules, increases their gradient between the intestinal lumen and the enterocyte, therefore promoting their uptake at the apical membrane. Another hypothesis might be that this protein interacts with mixed micelles rather than with free VE molecules and that micelle components and VE then diffuse towards the apical membrane (50). The mechanisms by which these molecules then cross this membrane and are secreted into the cytoplasm are not known. CD36 molecule (CD36) has also been associated with the uptake of α- and γ-tocopherol *in vitro* (53) but since it has also been shown to promote the assembly and secretion of chylomicrons (54), a mechanism similar to the one we propose for SR-B1 could explain this association. Finally, the apical sodium–bile acid transporter (ASBT) (55) has also been suggested to be involved in VE uptake following the association of SNPs in its encoding gene (*solute carrier family 10 member 2*, *SLC10A2*) with the postprandial chylomicron VE concentration following consumption of a VE-rich meal (22). Other membrane proteins might be involved but they are yet to be discovered. To summarize, both simple and facilitated diffusion mechanisms are involved in the apical uptake of VE by the enterocyte. Future studies will clarify if facilitated diffusion of VE is directly or indirectly, *i.e.* by promoting basolateral secretion, mediated by proteins such as SR-B1 and CD36. We hypothesize that their respective contribution probably depends on VE concentration in mixed micelles, which depends to some extent on the amount of VE ingested with the diet: at pharmalogical doses (*e.g.* when VE is provided by a supplement), simple diffusion is likely to be preponderant while at nutritional doses, the contribution of facilitated diffusion is likely to increase. Additionally, SR-B1 has been shown *in vitro* in Caco-2 cells (a cell line derived from a human colon adenocarcinoma used as a model for enterocytes) to be involved in the efflux of VE from the enterocyte towards the apical side, a process greatly enhanced by the presence of VE-free mixed micelles (49). The *in vivo* contribution of this pathway to VE absorption efficiency is unknown.

2.2 Intracellular transport of vitamin E in the enterocyte

Data are lacking on the trafficking of VE from the apical membrane of the enterocyte to the Golgi apparatus (where chylomicrons are assembled, in which a fraction of VE is incorporated). VE is a hydrophobic molecule and it is thus unlikely to cross the aqueous intracellular compartment without being bound to (a) transport protein(s). Although no protein has been clearly identified, several candidates exist. Liver fatty acid binding protein (L-FABP), which can transport large molecules in its hydrophobic pocket, and which has been implicated in cholesterol trafficking in the enterocyte (56) could participate in VE intracellular transport. If VE does indeed bind to SR-B1, it is also possible for SR-B1-associated VE to be transported from the apical membrane towards cytoplasmic lipid droplets since it has been shown that during fat absorption, SR-B1 is internalized via clathrin-coated vesicles (57). A similar mechanism could occur with NPC1L1-associated VE, again if VE does indeed bind to NPC1L1 (58). A protein called supernatant protein factor (SPF) or tocopherol-associated protein (TAP) has been found to bind VE in bovine (59) and human tissues (60). Its mRNA is ubiquitously expressed, although there are no data regarding its expression in the small intestine (59). However, a systematic study of substrate specificity has shown that it had a weak non-selective affinity towards tocopherols (61, 62), thus questioning its implication in intracellular VE transport. Other candidates for intracellular transport of VE within the enterocyte could be the sec14p-like proteins TAP1, 2, 3 (which are encoded by *TAP1*, *2* and *3* in humans). The proteins are expressed ubiquitously, including in the small intestine, and they have been shown *in vitro* to improve the transport of *α*-tocopherol to mitochondria with the same efficiency as α-tocopherol transfer protein (*α*-TTP), the main tocopherol binding protein in hepatocytes (63). Finally, the Niemann-Pick disease, type C1 and C2 proteins (NPC1/2) have been shown to be involved in the intracellular transport of tocopherol in fibroblasts and hepatocytes (64) and neurons (65). However, it is not known whether these proteins are expressed in enterocytes or whether they are involved in VE absorption.

2.3 Vitamin E secretion from the basolateral side of the enterocyte to the blood circulation

VE follows the fate of other newly absorbed lipid molecules (fatty acids, monoglycerides, cholesterol…) but contrarily to what is observed for retinol or cholesterol, VE is not re-esterified before its basolateral secretion from the enterocyte. Most VE is incorporated into chylomicrons in the Golgi apparatus before secretion in the lymph (apolipoprotein B-dependent route). Patients with abetalipoproteinemia, homozygous hypobetalipoproteinemia,

or chylomicron retention disease, which are caused by mutations in *microsomal triglyceride transfer protein* (*MTTP*), *apolipoprotein B* (*APOB*) (66) and *secretion associated Ras related GTPase 1B* (*SAR1B*) (67) respectively, three genes critically involved in the assembly and secretion of chylomicrons, exhibit dramatically impaired VE absorption efficiency and need to be aggressively supplemented with VE to prevent occurrence of neurologic abnormalities (68, 69). This highlights the major contribution of the apolipoprotein B-dependent route to VE absorption. However, it has been suggested in mice that the small intestine is able to secrete HDL directly into the portal vein via the basolateral membrane protein ATP binding cassette A1 (ABCA1) (70), although earlier studies in rats had suggested intestinal secretion of HDL occurred into the mesenteric lymph (71, 72). ABCA1 has been shown to participate in the basolateral secretion of VE towards apolipoprotein A1-containing HDL (apolipoprotein A1-dependent route) (73, 74). Whether this secretion occurs in the lymph or in the portal vein remains to be determined. Recently, it has been suggested that the basolateral membrane protein ATP-binding cassette sub-family G member 1 (ABCG1) could also be involved in VE basolateral efflux to HDL (75, 76) and a SNP in its encoding gene has been shown to be associated with the postprandial chylomicron VE concentration following consumption of a VE-rich meal (22). The qualitative or quantitative contribution of non-apolipoprotein B-dependent routes to VE absorption efficiency are not known and further investigations are warranted. Additionally, it has been suggested that SR-B1 present at the basolateral membrane could participate in HDL-VE uptake from the basolateral side (75).

2.4 Intestinal absorption localization of vitamin E

The precise localization of the main VE absorption sites in humans is not known. A study in everted small intestine sacs in rats showed that VE absorption rates were as follows: jejunum > duodenum, ileum (41). A more recent study in mice showed that 2h after oral administration of an emulsion containing 5 mg γ-tocopherol, the highest γ-tocopherol concentration was found in the distal part of the jejunum (77). VE absorption efficiency along the intestine likely depends on bioaccessible VE luminal concentration (which is probably not constant along the intestine as absorption occurs) and the rate of apical uptake, intracellular transport and basolateral secretion. Several of these processes are, at least partly, mediated by proteins. Interestingly, the distribution of some of these proteins is not homogeneous. A study of post-mortem intestinal samples from 11 subjects revealed that jejunal and ileal levels of NPC1L1, CD36 and ABCA1 were higher than those found in the duodenum or colon (78). Another study in mice showed a gradual decrease in SR-B1 levels along the gastrocolic axis

of the intestine. Interestingly, the SR-B1 apical/basolateral localization ratio was not constant along this axis with SR-B1 present mostly in the apical membrane in the duodenum, in both apical and basolateral membranes in the duodenum and almost exclusively present in the basolateral membrane in the ileum (79).

3. Factors modulating the bioavailability of vitamin E

To be absorbed, VE has to be extracted from the food matrix in which it is ingested (usually oil, a vegetable matrix, or a dietary supplement) and presented to enterocytes in a structure enabling its absorption, *i.e.* in mixed micelles or possibly vesicles. VE absorption depends on many variables: (i) food processing, (ii) meal composition, (iii) the activity of digestive enzymes, (iv) transport efficiency across the enterocyte, etc. The mnemotechnic term "SLAMENGHI" has been proposed to list all factors susceptible to affect carotenoid bioavailability (80) and it has been used since then for other lipid micronutrient, including VE (30, 81). Each letter represents one factor:

– S for "**S**pecies of VE" (referring to the relative bioavailability of the different forms of VE, *e.g.* α-tocopherol, γ-tocopherol, or α-tocotrienol)

– L for "molecular **L**inkage" (*e.g.* esterification of VE)

– A for "**A**mount of VE consumed in the meal" (referring to the relative absorption efficiency as a function of the quantity of VE consumed in a meal)

– M for "**M**atrix in which VE is incorporated" (referring to the effect of the matrix in which VE is incorporated, *e.g.* vegetable oil or supplement)

– E for "**E**ffectors of absorption" (referring to the effect of nutrients, *e.g.* lipids, dietary fibers, and drugs on VE absorption)

– N for "**N**utrient status of the host" (referring to the effect of the VE status of the host)

– G for "**G**enetic factors" (representing the effect of genetic polymorphisms or epigenetic modifications)

– H for "**H**ost-related factors" (referring to individual characteristics such as age, gender, pathologies…)

– I for "mathematical **I**nteractions" (referring to the differences in effects observed when two of the above-mentioned factors play a joint role compared with the sum of their effects observed separately).

Since genetic factors are host-related factors *per se*, we have decided to include them in this section and we are thus using the mnemotechnic term "SLAMENHI". We will provide readers with an overview of all factors susceptible to affect VE bioavailability, with emphasis on new studies and *in vivo* results, as a relatively recent review can be found elsewhere (30).

3.1. Species of vitamin E

Regarding the relative bioavailability of VE stereoisomers, only *RRR*- and *SRR*-α-tocopherol bioavailability in humans have been compared and no difference was found (82).

Regarding the relative bioavailability of VE isomers (α, β, γ, δ), 2 studies did not observe any difference between α- and γ-tocopherol bioavailability in humans, although they were carried out in a low number of subjects (n=2 and n=4 respectively) (83, 84). A recent study observed a 2.3-fold higher absorption of α-tocopherol compared to γ-tocopherol when raw vegetables with 3 g canola oil were consumed together with 3 cooked whole eggs (85). The food matrix used in this study could have influenced these results (40) since α- and γ-tocopherol localization may differ in the salad items used (tomatoes, shredded carrots, baby spinach, romaine lettuce and Chinese wolfberries), which can in turn influence their respective release during digestion. Hence, this study needs to be considered with caution regarding the comparison of α- *vs* γ-tocopherol bioavailability. Another possible explanation for this discrepancy might come from the fact that the last study provided dietary VE doses (≈ 3.2 mg) whereas the first 2 used pharmalogical doses (1000 and 50 mg respectively). Interestingly, a study in humans and mice found VE-ω-hydroxylase activity in the intestine with activities differing between tocopherol isomers ($\gamma = \delta >> \alpha$) which could partly explain differences in isomer bioavailability (39). Additionally, a study in rats found a higher α-tocopherol absorption efficiency compared to γ- and δ-tocopherol (86). To conclude, this point would deserve to be further exanimated in a clinical trial with a higher number of subjects and dietary or supplemental doses of α- and γ-tocopherol provided in the same matrix or as a supplement.

Regarding the relative bioavailability of tocopherols *vs* tocotrienols, α-tocopherol has been shown to be more bioavailable than α- and γ-tocotrienol in humans (87). A study in rats has reported a higher bioavailability of α-tocopherol *vs* γ-tocotrienol (88) but another study has reported higher absorption of α-tocotrienol compared with γ- and δ-tocotrienol and α-tocopherol (89).

3.2. Molecular Linkage

Most dietary VE is consumed as free molecules but VE supplements are usually VE esters in order to protect the hydroxyl group against oxidation. In humans, no difference were found between *RRR*-α-tocopherol, *RRR*-α-tocopheryl acetate and *RRR*-α-tocopheryl succinate regarding their bioavailability (90, 91), suggesting intestinal esterase activity towards VE esters is not a limiting factor across a wide range of doses. Nonetheless, VE ester esterase activity could become limiting in patients with pancreatic defects (*e.g.* pancreatic insufficiency, cystic fibrosis) (*see* section 3.9 for a discussion thereof).

3.3 Amount of vitamin E consumed in a meal

At large pharmalogical doses, VE absorption efficiency is thought to remain constant: the increase in chylomicron VE concentrations following meals containing 318 and 689 mg all-*rac*-α-tocopheryl acetate was linear (92). Studies comparing nutritional doses with supplemental or pharmalogical doses are lacking.

3.4 Matrix in which vitamin E is incorporated

This factor is considered to be a key factor governing VE bioavailability because, to be absorbed, VE first needs to be bioaccessible, *i.e.* to be extracted from its food matrix and to be incorporated into mixed micelles in the upper part of the digestive tract. Two studies have compared VE bioaccessibility in various food matrices and it can be concluded that it is highly variable (from 0.5% in apples to close to 100% in bananas, bread and lettuce) (40, 93). A recent study did not find any correlation between α-tocopherol bioaccessibility in several leafy vegetables and their biochemical composition (parameters tested: cell-wall content, pectin, protein, tannin content) (94). Unfortunately, data are scarce and the effect of several factors on VE bioaccessibility and bioavailability needs to be investigated further in order to provide better nutritional recommendation. These include the effect of technological treatments (*e.g.* thermal treatment and high-pressure processing) or VE localization (*e.g.* plants *vs* other origins such as oils or animal products). For example, it has been shown that VE bioaccessibility and bioavailability increased with grinding (95). Thermal treatment (90°C/30 s) has been shown to decrease the bioaccessibility of α-, γ- and δ-tocopherol from fruit juices *in vitro*, while high-pressure processing (400 MPa/40°C/5 min) had no impact when whole and skimmed milk were added to the food matrix, but led to a decrease in bioaccessibility when soy milk was added to the food matrix (96).

3.5 Effectors of absorption

Dietary lipids

Lipids can affect VE absorption by several mechanisms:

- They can facilitate the extraction of VE from its food matrix by providing a hydrophobic phase in which VE can be solubilised.
- They stimulate biliary secretion and consequently micelle formation. They may thus increase the quantity of VE solubilised in micelles and hence available for absorption.
- Lipid digestion products, *e.g.* fatty acids, monoglycerides, lysophospholipids, are micelle components and thus participate in the solubilisation of VE into micelles prior to its absorption.
- By promoting chylomicron secretion, partly via SR-B1 and CD36 (*see* section 2.1), triglycerides could increase VE secretion outside the enterocyte and thus prevent their intracellular accumulation, which would in turn increase their absorption.

Several characteristics of dietary lipids are thought to affect carotenoid bioavailability:

- The amount of triglycerides ingested with VE. Studies using stable isotopes or measuring postprandial chylomicron VE concentrations are more sensitive to detect variation in VE bioavailability since they allow discrimination between newly absorbed *vs* endogenous VE. Two studies using stable isotopes have investigated the effect of the amount of dietary fat on VE absorption efficiency. Jeanes *et al.* showed that ^{2}H-labelled *RRR*-α-tocopheryl acetate bioavailability (provided in a capsule containing 150 mg thereof) was highest when consumed in a meal consisting of toast with butter (17.5 g fat) or cereal with full-fat milk (17.5 g fat) *vs* cereal with semi-skimmed milk (2.7 g fat) or water (no fat) (97). Chylomicron α-tocopherol concentration remained negligible following the last 2 meals. Bruno *et al.* showed that d_6-*RRR*-α-tocopheryl acetate (provided in apples containing 22 mg thereof) bioavailability increased from 10% after consumption of a test meal without fat, to 20% after consumption of a test meal with 6% fat, to 33% after consumption of a test meal with 21% fat (fat was provided by cream cheese) (27). The authors estimated that an increase of 1 g in dietary fat increased tocopherol absorption by 0.43 mg. Recently, Kim *et al.* showed that when raw vegetables with 3 g canola oil were consumed together with 3 cooked whole eggs (each egg provided ≈4.8 g lipids and each meal provided 3.24 and 3.11 mg α- and γ-tocopherol respectively), α- and γ-tocopherol absorption increased ≈7.5 and 4.5 fold respectively, compared to raw vegetables with 3 g canola oil alone (85). Adding only 1.5 eggs increased α- and γ-tocopherol absorption by 1.7 and 2.1 respectively but it did not reach statistical significance, most likely due to a lack of statistical power (the study group was composed of

16 healthy young men). Surprisingly however, no effect of dairy fat addition (bovine milk) was observed on d_6-*RRR*-α-tocopherol (15 mg) bioavailability in another recent study (0.2 to 7.9 g fat) (98).

- the species of fatty acids from triglycerides. There is no clinical study dedicated to investigate the effect of this dietary factor. Polyunsaturated fatty acids peroxidation during digestion can lead to VE oxidation and it is thus important to differentiate effects on VE bioavailability from effects on VE degradation during digestion. A recent study in cockerels showed that a meal rich in linseed oil (majority of polyunsaturated fatty acids) led to a greater bioavailability of added all-*rac*-α-tocopheryl acetate than a meal rich in coconut oil (majority of saturated fatty acids) (99). A recent *in vitro* study showed that addition of 3% fat (w/w) to a mixed vegetable salad increased α-tocopherol micellarisation from 8% to 42-45% but no difference was observed between butter (majority of saturated fatty acids), soybean oil (majority of polyunsaturated fatty acids), olive oil and canola oil (majority of monounsaturated fatty acids) (100). However, the authors showed that α-tocopherol absorption by Caco-2 cells was increased by both mono- and polyunsaturated *vs* saturated fatty acids, mostly due to their effect on increased assembly and secretion of chylomicrons. In another *in vitro* study, it was shown that the bioaccessibility of both α-tocopherol and α-tocopheryl acetate increased when they were dispersed in corn oil (majority of polyunsaturated fatty acids) *vs* medium chain triglyceride oil (101).
- the amounts of phospholipids. There is again no clinical study dedicated to investigate the effect of this dietary factor. Studies in rats have shown that phosphatidylcholine decreased α-tocopherol absorption efficiency (102, 103), possibly due to the association of VE, a highly hydrophobic molecule, with the long chain fatty acids of phospholipids in mixed micelles, leading to a lower uptake by enterocyte. Conversely, lysophosphatidylcholine has been shown to increase α-tocopherol absorption efficiency (102), an effect not due to the lower size of lysophosphatidylcholine *vs* phosphatidylcholine micelles (104).
- lipid emulsification. In the only study on this factor, no significant effect of emulsion lipid droplet size on VE bioavailability in humans was found (26). A nanoemulsion formulation (mean droplet diameter: 277 nm) has been shown to increase VE bioavailability in rats when compared to a conventional emulsion (mean droplet diameter: 1285 nm) with the same composition (105). This is likely due to a larger surface area in the smaller-size droplets which would in turn increase the VE transfer rate efficiency. Indeed, it has been shown in humans that gastric and duodenal lipolysis were higher when the emulsion droplet size decreased (106).

Dietary Fiber

Dietary fibers were hypothesized to affect VE absorption by several mechanisms:

- by sequestering micelle components (107).
- by inhibiting pancreatic lipase (108) and thus limiting the release of VE from lipid droplets.
- by increasing the viscosity of the intestinal content (109) which would impair the diffusion of VE-rich micelles towards the brush border. Studies in rats suggested that VE bioavailability was impaired by the presence of pectin (110, 111). However, no effect of various fiber types (pectin, guar, alginate, cellulose or wheat bran) were observed on the mean increase of plasma α-tocopherol concentration over 24 h in women (112). Additionally, higher intakes of fiber were not associated with lower plasma VE concentrations in a prospective cohort of 283 middle-aged women (113). Hence, VE bioavailability or blood VE concentrations are not significantly affected by a normal intake of fibers.

Inhibitors of fat/cholesterol absorption

Since obesity and cardiovascular diseases are major health problems, several drugs have been designed to decrease fat and cholesterol absorption. However, these drugs could decrease lipid micronutrient absorption as well.

Orlistat (also known as tetrahydrolipstatin), an inhibitor of gastric and pancreatic lipase, as well as Olestra, a saccharose polyester used as a lipid substitute, have been shown to decrease VE absorption (114-117). Similarly, phytosterols, which are used to decrease cholesterol absorption efficiency, have been shown to decrease α-tocopherol absorption (118). However, in another study, no effects of phytosterol esters were found on blood VE levels (119). Cholestyramine, an anion exchange resin used to lower cholesterol absorption by sequestering bile acids in the intestinal lumen, has been suggested in a study in 3 patients to lower α-tocopherol absorption (120). Studies in mice have shown that the cholesterol-lowering drug ezetimibe, which targets NPC1L1 (121), can also lower γ-tocopherol absorption (77). A recent study in rats also showed that α-tocopherol absorption efficiency was inhibited by ezetimibe co-administration. Interestingly, this effect was not seen for an administration interval of 4h (122). Whether this translates to decreased VE absorption in humans has not been properly investigated. No study on the effect of liver X receptor agonists, used in the treatment of dyslipidemia, on VE bioavailability has been carried out, although this nuclear receptor controls several genes and proteins involved in VE absorption (*see* section 3.6).

Micronutrients

Since different VE species are often consumed together (*i.e.* tocopherols and tocotrienols) and since VE is consumed together with other micronutrients (*e.g.* other fat-soluble vitamins, carotenoids, phytosterols), and since common absorption mechanisms are involved (42), it is hypothesized that some micronutrients compete with VE absorption. Three clinical trials have reported interactions between α- and γ-tocopherol regarding their bioavailability: α-tocopheryl acetate (123) and α-tocopherol (both *RRR*- and all-*rac*-) (124) supplementation were shown to significantly decrease serum γ-tocopherol concentration. γ-tocopherol supplementation (376 mg/day for 28 days) was shown to significantly decrease serum α-tocopherol concentration (125). No study has investigated the interaction between tocopherols and tocotrienols regarding their bioavailability.

Regarding interactions with other microconstituents, plasma tocopherol levels have been shown to be decreased when ruminants were fed very high doses of vitamin A (126), an effect which could be due to increased VE oxidation during absorption (127) or by downregulation of SR-B1 (128). A study in 8 subjects showed that lutein, a carotenoid belonging to the xanthophyll class, decreased α-tocopherol bioavailability (129). However, a study in rats did not observe any effect of canthaxanthin, another xanthophyll, on VE absorption efficiency (130). A recent study showed that α-tocopherol uptake by Caco-2 cells was decreased in a dose-dependent manner by retinol (vitamin A) and cholecalciferol (vitamin D) from dietary and supplementation doses onwards respectively, and by phylloquinone (vitamin K_1) at pharmalogical doses only (131). There is thus a wide variety of possible interactions between VE species and between VE and other micronutrients but data are lacking to draw practical conclusions.

3.6 Vitamin E (Nutrient) status of the host

By analogy to what has been observed with vitamin A status and regulation of provitamin A carotenoids absorption efficiency (128), we suggest that VE absorption efficiency could be modulated by the VE status of the host, or enterocyte VE concentration. Indeed, VE can modulate, directly or indirectly, several nuclear receptors, which in turn can act as transcriptional factors for genes encoding proteins involved in VE uptake and secretion in the enterocyte. More precisely, α- and γ-tocopherol have both been shown to indirectly decrease liver X receptor α (LXRα) activity in an *in vitro* enterocyte cell model (132), which can in turn inhibit the expression of ABCA1 and ABCG1 (132, 133). ABCA1 is involved in enterocyte VE

basolateral efflux to apolipoprotein A1-containing HDL while ABCG1 is a candidate for enterocyte VE basolateral efflux to HDL (76, 134). Additionally, pregnane X receptor (PXR), whose expression can be modulated by most VE vitamers (135), has been shown to decrease SR-B1 and ABCA1 expression in an *in vitro* model of hepatocytes (136). There are thus several mechanisms by which an elevated VE status or enterocyte concentration could inhibit VE intestinal absorption efficiency. Nevertheless, it has recently been shown that the liver X receptor could modulate triglyceride absorption via regulation of SR-B1: LXR agonists caused intestinal SR-B1 relocalization, from apical membranes to intracellular organelles, which decreased chylomicron secretion, and also reduced SR-B1 levels via a post-transcriptional mechanism involving microRNAs (52). Since α- and γ-tocopherol have been shown to indirectly decrease liver X receptor α activity (132), a higher intracellular concentration of these VE isomers in the enterocyte could then lead to a relocalization of SR-B1 to apical membranes and no inhibition of SR-B1 levels, which could then lead to higher VE absorption. Hence, enterocyte VE concentration can modulate several metabolic pathways involved in VE absorption, some with opposing effects, and it is thus hard to draw any firm conclusion without a dedicated *in vivo* study.

3.7 Host-related factors

Genetic factors

Numerous proteins are involved in VE bioavailability: this includes proteins/enzymes involved in the digestion of typical food matrices where VE is incorporated, proteins involved in enterocyte uptake, transport and basolateral secretion of VE and proteins involved in postprandial lipoprotein metabolism (*see* (137) for a recent review). This suggests that variations in the genes encoding these proteins could modulate VE absorption efficiency. Since single nucleotide polymorphisms (SNPs) represent ≈90% of genetic variations in the human genome, they have been the focus of studies investigating the effect of genetic variations on VE bioavailability. First, studies investigated the effect of SNPs on the variability in VE status: SNPs in *apolipoprotein A-IV*, *apolipoprotein E*, *SCARB1* (138), *apolipoprotein C-III*, *cholesteryl ester transfer protein* (139) and *CD36* (140) were associated with fasting blood α-tocopherol concentration while a SNP in *hepatic lipase* was associated with fasting blood γ-tocopherol concentration (139). Nevertheless, some of these genes are expressed ubiquitously and do not necessarily point at an effect on VE bioavailability. Moreover, VE status is affected by numerous factors, *e.g.* dietary VE intake, VE absorption efficiency, VE catabolism. Hence,

in a recent clinical trial from our group, the association of SNPs involved in VE metabolism and transport with the postprandial chylomicron α-tocopherol concentration, an acknowledged marker of VE bioavailability, following the consumption of a VE-rich meal was assessed in a group of 38 healthy subjects (22). The interindividual variability in VE bioavailability was associated with a combination of 28 SNPs in or near 11 candidate genes. Seven of these genes were involved in the postprandial chylomicron triacylglycerol response in the same group of subjects (141). Indeed, most newly absorbed VE is carried from the intestine to the liver via chylomicrons. Four of these genes were more specifically associated with VE metabolism and transport: *ABCG1*, *PNLIP* (*pancreatic lipase*), *SLC10A2* (*solute carrier family 10 member 2*) and *SREBF2* (*sterol regulatory element binding transcription factor 2*) (*see* (22, 137) for discussion). ABCG1 is a candidate protein in the basolateral efflux of VE to HDL in enterocytes (75, 76). *Solute carrier family 10 member 2* encodes for ASBT, which functions as an apical membrane enterocyte transporter responsible for the uptake of luminal bile acids in the ileum (55). Mutations in this gene have been shown to cause primary bile acid malabsorption, and SNPs have been associated with lower ASBT mRNA and protein expression (142). Since bile acids are essential for normal VE absorption (143), SNPs in this gene could affect VE bioavailability. The association of SNPs in the gene encoding for pancreatic lipase, which is responsible for the intestinal hydrolysis of triglycerides, with the variability in VE bioavailability is most likely due to the role of this enzyme in the release of VE from lipid droplets for its incorporation into mixed micelles. *Sterol regulatory element binding transcription factor 2* encodes for a transcription factor, SREBP2, which controls numerous genes involved cholesterol homeostasis, including NPC1L1 (45), which is involved in the apical uptake of VE by enterocytes. Thus, the association of SNPs in its encoding gene and the variability in VE bioavailability could originate from an indirect effect on NPC1L1 expression. To date, there has only been one study dedicated to identify genetic variants involved in VE bioavailability. These results need to be confirmed and other study groups need to be investigated (women, non-European subjects…). Nevertheless, this opens the door to more personalised dietary recommendation, taking into account one's individual genetic characteristics in order to improve the benefit from VE consumption or supplementation.

Gender

Only one study has investigated the effect of gender on VE bioavailability and no difference was observed between males and females following consumption of 150 mg of *RRR*- or all-*rac*-α-tocopheryl acetate (144). Although women exhibited slightly higher fasting serum

α-tocopherol concentrations compared to men (27.9 *vs* 26.9 µmol/l) in the National Health and Nutrition Examination Survey (1999-2000), this difference was abolished after correction by serum total cholesterol concentration. Moreover, no difference was observed regarding fasting serum γ-tocopherol concentration, before or after correction by serum total cholesterol concentration (145). In the French SU.VI.MAX study, men volunteers exhibited a slightly higher fasting serum α-tocopherol concentration compared to women but no correction for blood lipids was applied (146). It needs to be reminded that VE status is influenced by other factors beside VE bioavailability, *e.g.* dietary VE intake, VE catabolism.

Age

Healthy old subjects (64-72 years old) exhibited lower VE bioavailability compared to healthy young subjects (20-30 years old) following consumption of pharmalogical doses of all-*rac*-α-tocopheryl acetate (318 and 689 mg) (92). Another study did not observe a significant effect of age on VE bioavailability following the consumption of 30 mg *RRR*-α- and *RRR*-γ-tocopheryl acetate (147). Hence, except at pharmacological doses, older age does not seem to affect VE bioavailability.

Disease status

The intestinal absorption of VE requires normal digestive functions, and so subjects with impaired fat absorption, which can be caused by several disorders (*e.g.* obstructive jaundice, pancreatic insufficiency, cystic fibrosis or adult coeliac disease) are liable to have impaired VE absorption. Patients with cholestatic liver disease (148), or patients with cystic fibrosis (143, 149-151), exhibited impaired VE absorption. Patients with abetalipoproteinemia, homozygous hypobetalipoproteinemia or chylomicron retention disease exhibit dramatically impaired VE absorption efficiency and need to be aggressively supplemented with VE to prevent occurrence of neurologic abnormalities (68, 69). Conversely, no significant difference was observed between patients with chronic pancreatitis and healthy controls (152). No effect of *Helicobacter pylori* at asymptomatic stages of infection was observed on VE, or vitamin C, bioavailability (153). Recently, it was shown that patient with metabolic syndrome had lower d_6-*RRR*-α-tocopherol (15 mg) absorption efficiency than healthy subjects (26.1 *vs* 29.5%) (98).

3.8 Mathematical Interactions

Several of the above-mentioned factors can interact together, with additive, synergistic or antagonist effects. For example, we hypothesize that the effect of the amount of fat (factor E) will not be observed in subjects who exhibit abetalipoproteinemia (factor H), or that the effect of ezetimibe (factor E), which is the chemical inhibitor of NPC1L1, will be modulated by genetic variants that affect the expression/activity of this protein (factor H). Interestingly, two recent studies have dismissed the possibility of an interaction between VE esterification (factor L) and lipid malabsorption in patients with low pancreatic secretion (factor H): no difference was observed between α-tocopherol *vs* α-tocopheryl acetate absorption in a small group (n=6) of patients diagnosed with chronic pancreas insufficiency (using 18 and 27 mg of d_6-*RRR*-α-tocopherol and d_6-*RRR*-α-tocopheryl acetate) (154) or in 6 healthy subjects in the absence of digestive enzymes and bile salts (using 51 and 76.5 mg of d_6-*RRR*-α-tocopherol and d_3-*RRR*-α-tocopheryl acetate) (38). Another possible interaction could be between species of VE and the food matrix since it has been shown *in vitro* that the bioaccessibility of α- *vs* γ-tocopherol was highly dependent on the food matrix: α-tocopherol was >10 times more bioaccessible than γ-tocopherol in white wheat bread but 2.5 times less bioaccessible in hazelnuts (40).

Conclusion

The absorption mechanisms of VE are complex. This review underlines the vast amount of work still needed to improve our knowledge of VE absorption and its modulating factors ("SLAMENHI"). Indeed, several key points still need to be investigated:

- Is a fraction of VE solubilised in the vesicles present in the lumen of the duodenum during digestion and if so, how does this affect its absorption?
- What are the other proteins involved in VE absorption?
- What are the intracellular enterocyte transport proteins of VE?
- Does VE and/or vitamin A status modulate VE absorption efficiency?
- What are the best dietary sources of VE as far as absorption efficiency is concerned?
- Possible interactions between VE and the gut microbiota have not been investigated. Yet, since VE bioavailability can be fairly low, significant amounts reach the colon. To what extent does the microbiota contribute to VE metabolism? Can VE or putative VE metabolites be taken up in the colon?

Several strategies can be applied in order to improve VE bioavailability, *e.g.* to modify technological treatments or to provide food preparation advice, to provide nutritional recommendations (*e.g.* to consume VE with lipids), to create formulations protecting VE or improving their absorption (*e.g.* nanoencapsulation). There is a high interindividual variability of VE bioavailability, which is partly due to genetic polymorphisms. The identification of additional SNPs and epigenetic factors involved in this variability is a promising area of research which, together with the identification of other factors might lead to propose more personalised recommendations in order to increase the health effects of VE.

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Figure 1. Chemical structures of vitamin E.

To be absorbed by the enterocyte, tocopheryl esters need to be hydrolysed to tocopherols. This cleavage is carried out partly by cholesteryl ester hydrolase, secreted by the pancreas, and possibly by unidentified brush border enzymes.

Figure 2. Vitamin E fate in the lumen of the upper gastrointestinal tract during digestion.

Transfer of VE between the different vehicles assumed to transport VE in the human upper gastrointestinal lumen. Dashed arrows indicate putative transfers.

Figure 3. Proteins involved in uptake, transport and secretion pathways of vitamin E across the enterocyte.

(A) Putative unidentified protein involved in uptake; (B) Putative unidentified protein involved in apical efflux; (C) passive diffusion; (D) Putative unidentified protein involved in basolateral efflux. The transport into the enterocyte of VE following digestion is facilitated by proteins that are located, at least temporarily, in the apical membrane: CD36 (CD36 molecule), NPC1L1 (NPC1 like intracellular cholesterol transporter 1), SR-B1 (scavenger receptor class B type I) and possibly other proteins. CD36 and SR-B1 have been shown to increase chylomicron assembly and secretion (dashed arrows). A fraction of VE taken up might be effluxed back to the intestinal lumen via apical membrane proteins (SR-B1 and possibly other transporters). The remaining fraction is transported to the site where it is incorporated into chylomicrons (apolipoprotein B-dependent route) or HDL (apolipoprotein A1-dependent route), involving the transporter ATP binding cassette A1 (ABCA1). Although some proteins are hypothesized to be involved in intracellular transport of VE, none has been identified yet.

Other abbreviations: L-FABP, liver fatty acid binding protein; NPC1/2, Niemann-Pick disease, type C1 and C2 proteins.