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1 **Vitamin D bioavailability: State of the art**

2

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20

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

22

23 **Key words:** cholecalciferol, ergocalciferol, 25-hydroxyvitamin D , bioaccessibility,
24 absorption, intestine.

25

1 **List of abbreviations:**

- 2 25OHD: 25-hydroxy vitamin D, i.e. 25-hydroxy cholecalciferol or/and 25-hydroxy
3 ergocalciferol
- 4 25OHD₂: 25-hydroxy ergocalciferol
- 5 25OHD₃: 25-hydroxy cholecalciferol
- 6 1,25(OH)₂D₃: dihydroxy cholecalciferol
- 7 1,25(OH)₂D₂: dihydroxy ergocalciferol
- 8 FSM: fat-soluble microconstituents, e.g. fat soluble vitamins, carotenoids and phytosterols

1 ***Abstract***

2

3 There has been renewed interest in vitamin D since numerous recent studies have suggested
4 that besides its well-established roles in bone metabolism and immunity, vitamin D status is
5 inversely associated with the incidence of several diseases, e.g. cancers, cardio-vascular
6 diseases and neurodegenerative diseases. Surprisingly, there is very little data on factors that
7 affect absorption of this fat-soluble vitamin, although it is acknowledged that dietary
8 vitamin D could help to fight against the sub-deficient vitamin D status that is common in
9 several populations. This review describes the state of the art concerning the fate of vitamin D
10 in the human upper gastrointestinal tract and on the factors assumed to affect its absorption
11 efficiency. The main conclusions are: (i) ergocalciferol (vitamin D₂), the form mostly used in
12 supplements and fortified foods, is apparently absorbed with similar efficiency to
13 cholecalciferol (vitamin D₃, the main dietary form), (ii) 25-hydroxyvitamin D (25OHD), the
14 metabolite produced in the liver, and which can be found in foods, is better absorbed than the
15 non-hydroxy vitamin D forms cholecalciferol and ergocalciferol, (iii) the amount of fat with
16 which vitamin D is ingested does not seem to significantly modify the bioavailability of
17 vitamin D₃, (iv) the food matrix has apparently little effect on vitamin D bioavailability, (v)
18 sucrose polyesters (Olestra) and tetrahydrolipstatin (orlistat) probably diminish vitamin D
19 absorption, and (vi) there is apparently no effect of ageing on vitamin D absorption efficiency.
20 We also find that there is insufficient, or even no data on the following factors suspected of
21 affecting vitamin D: (i) effect of type and amount of dietary fibre, (ii) effect of vitamin D
22 status, and (iii) effect of genetic variation in proteins involved in its intestinal absorption.
23 In conclusion, further studies are needed to improve our knowledge of factors affecting
24 vitamin D absorption efficiency. Clinical studies with labelled vitamin D, e.g. deuterated or
25 ¹³C, are needed to accurately and definitively assess the effect of various factors on its
26 bioavailability.

1 *Introduction*

2

3 Vitamin D is the generic name for compounds exhibiting the biological activity of

4 cholecalciferol (vitamin D₃). Cholecalciferol is the main dietary source of vitamin D and it is

5 present mostly in foods of animal origin. A significant fraction of vitamin D₃ (estimated at

6 around 80%, but depending on sun exposure) is produced endogenously in the skin from 7-

7 dehydrocholesterol by the action of UV light. Diet can also contain 25-hydroxy cholecalciferol

8 (25OHD₃) and trace amounts of dihydroxy cholecalciferol (1,25(OH)₂D₃). It is assumed that

9 most people need dietary vitamin D to reach the recommended serum level, i.e. greater than

10 30 ng/mL (75 nmol/L) (Wimalawansa, 2012). The chemical structures of these vitamin D

11 forms are recalled in **Figure 1**. Very few naturally-occurring foods contain vitamin D. The

12 flesh of fatty fish and fish liver oils are among the best sources. Small amounts of vitamin D

13 are found in beef liver, dairy products and egg yolk. Vitamin D in these foods occurs primarily

14 as vitamin D₃ and its metabolite 25OHD₃. Some mushrooms provide vitamin D₂ in variable

15 amounts. In some groups, e.g. infants, elderly persons not sufficiently exposed to sunlight, and

16 patients suffering from fat malabsorption, consumption of vitamin D supplements or vitamin

17 D fortified foods are required to meet the daily need, i.e. approximately 2000 IU/day to

18 maintain serum 25(OH)D levels greater than 30 ng/mL (Wimalawansa, 2012), for vitamin D.

19 In supplements and fortified foods, vitamin D can be available as either vitamin D₂ or vitamin

20 D₃. Vitamin D₂ (ergocalciferol) is manufactured by the UV irradiation of ergosterol in yeast,

21 and vitamin D₃ by the irradiation of 7-dehydrocholesterol from lanolin and the chemical

22 conversion of cholesterol. The mechanisms involved in vitamin D absorption and the factors

23 assumed to affect this process have been under-researched. Vitamin D is assumed to follow

24 the fate of lipids in the human upper gastrointestinal tract. It is also assumed that it is secreted

25 in the chylomicrons and then transported to the liver. The absorption efficiency of vitamin D

26 is lower than that of triacylglycerols, and varies widely. Some factors suspected of affecting

1 its absorption efficiency have been extensively studied, while there is scant or even no data on
2 others. After a review on the fate of vitamin D in the upper human gastrointestinal tract and
3 on recent discoveries concerning mechanisms involved in its absorption, factors known or
4 thought to affect its bioavailability, which is acknowledged as the fraction of ingested vitamin
5 D that is recovered in the blood during the postprandial period after absorption of a known
6 dose of vitamin D, are presented.

7

8 *Fate of vitamin D in the human upper gastrointestinal tract*

9

10 The fate of vitamin D in the human upper gastrointestinal tract consists of several
11 sequential steps including physicochemical and enzymatic events. It is assumed that vitamin D
12 absorption is governed by the same intraluminal factors as those that have been described for
13 major lipids (triacylglycerols, cholesterol and phospholipids) (Tso and Fujimoto, 1991). These
14 include emulsification, solubilisation in mixed micelles, diffusion across the unstirred water
15 layer and permeation through the enterocyte membrane.

16 Vitamin D metabolism may begin in the stomach, where foods are subjected to acid
17 conditions and gastric enzymes. There is apparently no data on the sensitivity of the main
18 dietary forms of vitamin D (cholecalciferol, ergocalciferol, 25OHD₃) to the acidic pH of the
19 stomach. It can be hypothesised that pepsin plays a role in vitamin D absorption by releasing
20 the fraction of vitamin D associated with proteins. Because vitamin D is fat-soluble it can also
21 be hypothesised that a fraction of dietary vitamin D not incorporated in oils, e.g. vitamin D in
22 fish flesh, transfers to the fat phase of the meal during digestion. This might improve
23 vitamin D bioavailability, assuming that vitamin D in oil is more bioaccessible than vitamin D
24 in a complex matrix. It is reasonable to suggest that the transfer efficiency depends on the
25 characteristics of the food matrix and on the presence of fat, but no data is available on this
26 topic. Finally, there is no data on the role of gastric lipase on vitamin D ester hydrolysis, but it

1 can be suggested that vitamin D esters (Hollis et al., 1996) are at least partially hydrolysed by
2 this lipase. This could be of importance when vitamin D is ingested as vitamin D esters, and
3 when pancreatic lipase activity is not optimal (e.g. neonates and pancreatic insufficiency).

4 In the duodenum, digestive enzymes, e.g. proteases, amylases and lipases, continue to
5 release vitamin D from the food matrix. It is assumed that vitamin D not incorporated in oils,
6 i.e. present naturally in dietary fat or transferred from a non-food matrix to the fat phase of the
7 meal in the stomach, is transferred from the food matrix to dietary fat and then into micelles,
8 but it is not known whether there is a direct transfer of vitamin D from the food matrix into
9 micelles. In the duodenum, it is assumed that vitamin D esters, if present, are hydrolysed by
10 bile salt stimulated lipase (Lombardo and Guy, 1980), also called carboxyl ester lipase, but it
11 is not known whether other hydrolytic enzymes, such as pancreatic lipase (Mathias et al.,
12 1981a), pancreatic lipase related proteins (Reboul et al., 2006a), or enzymes of the brush
13 border (Mathias et al., 1981b) are also involved in their hydrolysis. It is assumed that vitamin
14 D₃ is solubilised in mixed micelles (Rautureau and Rambaud, 1981) and absorbed by the
15 lymphatic route, while 25OHD₃, being more polar, is less dependent on bile acids, and being
16 water-soluble, is mainly absorbed *via* the portal route (Maislos et al., 1981). This has been
17 confirmed by an Israeli team who studied the effect of absence of bile salts on the absorption
18 of non-hydroxylated and hydroxylated vitamin D forms. Their results showed that
19 1,25(OH)₂D₃ absorption was unaffected by the lack of biliary salts. Conversely, absorption of
20 25OHD₃ was decreased and that of vitamin D₃ was fully impaired (Maislos and Shany, 1987).
21 Fat-soluble entities can be theoretically solubilised in structures other than micelles in the gut.
22 More precisely, as vesicles have been observed in the human duodenal lumen during digestion
23 (Staggers et al., 1990), it is hypothesised that they can incorporate fat-soluble substances in
24 their phospholipid membranes (Urano et al., 1987; Kirilenko and Gregoriadis, 1993).
25 However, it is not known whether a significant proportion of the different forms of vitamin D
26 is incorporated in vesicles, and whether this has any effect on their absorption.

1 The main site of vitamin D absorption in humans is not accurately known, but in the
2 rat, uptake was observed in both jejunum and ileum (Hollander et al., 1978; Reboul et al.,
3 2011), the ileum being the main site of absorption (Reboul et al., 2011). Absorption efficiency
4 of vitamin D₃ given in peanut oil was found to range between 55 % and 99 % (mean 78%) in
5 healthy subjects (Thompson et al., 1966). These rates are similar to those from animal
6 experiments, where rates between 66% and 75% were reported. Vitamin D is detected in the
7 bile. However, the significance of a conservative enterohepatic circulation of vitamin D is
8 controversial. **Figure 2** summarises current knowledge on the fate of vitamin D in the human
9 upper gastrointestinal tract. In addition, although the metabolism of vitamin D lies outside the
10 scope of this review, we need to know how vitamin D metabolism modifies the forms of
11 vitamin D that circulate in the blood; a figure is therefore presented that summarises the
12 current knowledge of vitamin D metabolism in the human body (**Figure 3**).

13

14 *Absorption mechanisms of vitamin D*

15

16 From early studies using everted rat gut sacs (Hollander and Truscott, 1976) and
17 perfusion of rat small intestinal loops (Hollander et al., 1978), the mechanism of absorption of
18 the non-hydroxylated forms of vitamin D, i.e. cholecalciferol and ergocalciferol, had been
19 assumed to be a non-saturable passive diffusion process. However, recent results using the
20 human intestinal cell line Caco-2 and HEK transfected cells have shown that intestinal cell
21 membrane proteins are involved in the uptake of these non-hydroxylated forms at the apical
22 side of the enterocyte (Reboul et al., 2011). These proteins are SR-BI (Scavenger Receptor
23 class B type 1), CD36 (Cluster Determinant 36) and NPC1L1 (Niemann-Pick C1-Like 1), also
24 involved in apical uptake of cholesterol and of other lipidic micronutrients: vitamin E (Reboul
25 et al., 2006b; Narushima et al., 2008) and carotenoids (Reboul et al., 2005; van Bennekum et
26 al., 2005; Moussa et al., 2008). The results of Reboul et al. (Reboul et al., 2011) also suggest

1 that vitamin D uptake is mainly protein-mediated at low, dietary concentrations of vitamin D,
2 while it is also passive at high, pharmacological concentrations. Finally, the fact that
3 cholecalciferol uptake was higher in the rat jejunum than in the duodenum suggests that
4 another transporter specifically expressed in the jejunum might play an important role in
5 vitamin D uptake (Reboul et al., 2011). There is no data concerning absorption mechanisms of
6 the hydroxylated forms of vitamin D. However, it can be hypothesised that the mechanisms
7 are different, because these entities (25OHD_3 and $1,25(\text{OH})_2\text{D}_3$) are less dependent on bile
8 acids for absorption, and their absorption efficiency is considerably higher, about three times
9 that of the non-hydroxylated forms (Compston et al., 1981). **Figure 4** shows the current
10 knowledge on proteins involved in absorption of vitamin D by human intestinal cells.

11

12 *Possible factors affecting absorption*

13

14 Before it can be absorbed, vitamin D has to be released from the food matrix,
15 e.g. fish oil, fish flesh, or mushrooms, in which it is embedded, and be presented to the brush-
16 border in a state such that it can be absorbed by intestinal cells. It is assumed that absorption
17 efficiency depends on an array of variables including: (i) the food matrix, (ii) the composition
18 of the meal, (iii) the activities of digestive enzymes, and (iv) the efficiency of transport across
19 the enterocyte. The mnemonic “SLAMENGHI”, listing the factors thought to govern
20 carotenoid absorption (de Pee and West, 1996), was used to review the factors suspected to
21 affect vitamin D absorption. Each letter stands for a factor: Species (molecular forms) of
22 vitamin D, molecular Linkage of vitamin D (e.g. esterification), Amount of vitamin D
23 consumed in a meal, Matrix in which vitamin D is incorporated, Effectors of absorption and
24 bioconversion, Nutrient status of the host, Genetic factors, Host-related factors, and
25 mathematical Interactions. Each SLAMENGHI factor was reviewed by querying the on-line
26 US National Library of Medicine (last review January 31, 2012). It appeared that some factors

1 had been extensively studied, e.g. the effect of ageing or the effect of diseases that lead to fat
2 malabsorption, while there is no data on other factors, e.g. effect of gender or genetic factors.
3 Results from the available literature are presented here.

4

5 *a. Species of vitamin D*

6

7 Although cholecalciferol is the main dietary form of vitamin D, foods can also contain
8 ergocalciferol and 25OHD₃. Several studies have compared the bioavailabilities of these two
9 vitamin D species with that of vitamin D₃.

10 • Ergocalciferol vs. cholecalciferol: In a first study, bioavailability was evaluated
11 by administering single doses of 50,000 IU of either cholecalciferol or ergocalciferol to 20
12 healthy male subjects. The two forms produced similar initial rises in serum 25OHD over the
13 first 3 days, suggesting equivalent intestinal absorption (Armas et al., 2004). In a second study
14 (Holick et al., 2008), healthy subjects received either placebo, or 1000 IU vitamin D₃, or 1000
15 IU vitamin D₂, or a mixture of 500 IU vitamin D₃ and 500 IU vitamin D₂. 25OHD increased
16 similarly in all the vitamin D supplemented groups, again suggesting similar bioavailabilities
17 of the two forms. A consistent result was obtained recently when vitamin D₂ and vitamin D₃,
18 incorporated in orange juice or in a supplement, gave similar serum 25OHD responses
19 (Biancuzzo et al., 2010). However, two clinical studies (Romagnoli et al., 2008; Khazai et al.,
20 2009a) suggested a higher bioavailability of vitamin D₃ than of vitamin D₂. However, there
21 was a confounding variable in the study of Khazai et al. (Khazai et al., 2009a): vitamin D₃ was
22 in a powder-based supplement while vitamin D₂ was in oil. Furthermore, the subjects had
23 cystic fibrosis, and the effect of the vehicle in which vitamin D is solubilised can be more
24 critical, especially when it is oil, in subjects with fat malabsorption than in healthy subjects.
25 The study of Romagnoli et al. (Romagnoli et al., 2008) found that vitamin D₃ was apparently

1 almost twice as potent as vitamin D₂ in increasing serum 25OHD after 60 d. However, as
2 discussed by the authors themselves, the 25OHD increased in parallel, suggesting a
3 comparative absorption. Thus the difference in 25OHD levels after 60 d was attributed to a
4 more rapid metabolism/clearance of vitamin D₂ than of vitamin D₃ metabolites (see below).
5 The best way to avoid the effect of liver and kidney metabolism on blood vitamin D
6 concentration is to compare absorption in cultures of human intestinal cell. This was recently
7 done (Reboul et al., 2011) and it was shown that vitamin D₃ and vitamin D₂ were absorbed
8 with similar efficiencies by Caco-2 cells.

9 The biological equivalence between vitamin D₃ and vitamin D₂ is still a matter of
10 debate (Armas et al., 2004; Khazai et al., 2009b; Binkley et al., 2012; Youssef et al., 2012).
11 Thus the fact that absorption efficiencies of vitamin D₃ and vitamin D₂ are apparently similar
12 contrasts with the finding in the clinical study by Armas et al. (Armas et al., 2004) that serum
13 25OHD continued to rise in the vitamin D₃-treated subjects, peaking at 14 d, while 25OHD
14 fell rapidly in the vitamin D₂-treated subjects and was not different from baseline at 14 d.
15 Consequently, area under the curve (AUC) to day 28 was 151 nmol.d/L for vitamin D₂ and
16 512 for vitamin D₃. It was concluded that vitamin D₂ potency was less than one third that of
17 vitamin D₃. This conclusion is supported by three studies from another team who showed that
18 treatment with vitamins D₂ and D₃ in the same doses produced considerably different serum
19 concentrations of vitamin D metabolites (Tjellesen et al., 1985b; Tjellesen et al., 1986), and
20 not the same action of the two vitamins on bone metabolism (Tjellesen et al., 1985a), and also
21 by the results of a study with very large doses of vitamin D₂ and D₃ given to elderly subjects
22 (Romagnoli et al., 2008). The mechanisms explaining the different biological effects of
23 vitamin D₂ and D₃ are apparently not linked to their first hydroxylation by the liver, as similar
24 increases in serum 25OHD levels were observed after intravenous injection of either vitamin
25 D₂ or D₃. Other mechanisms have been suggested, e.g. different affinities of 1,25(OH)₂D₂ and

1 1,25OHD₃ for the VDR nuclear receptor, but these hypotheses remain to be addressed in
2 dedicated studies.

3 • 25OHD₃ vs. cholecalciferol and ergocalciferol: The relative bioavailability of
4 vitamin D₃ and 25OHD₃ is well-documented. In healthy subjects, the total amount of
5 [3H]vitamin D₃ recovered in plasma 6 h after [3H]25OHD₃ intake was considerably higher
6 after [3H]25OHD₃ than after [3H]cholecalciferol intake. Conversely, a much higher
7 percentage of [3H]vitamin D₃ was found in the chylomicron fraction after ingestion of
8 [3H]vitamin D₃ than after ingestion of [3H]25OHD₃ (Compston et al., 1981). This apparent
9 discrepancy was explained by the fact that vitamin D₃ absorption occurs *via* chylomicrons,
10 while that of 25OHD₃ occurs *via* the portal route. However it is also possible that a significant
11 fraction of newly absorbed cholecalciferol and ergocalciferol is quickly stored in adipose
12 tissue leading to lower blood concentrations of these forms as compared to 25OHD₃. The
13 higher bioavailability of 25OHD₃ than of vitamin D₂ and D₃ was confirmed in another study in
14 which ten times more vitamin D, either as ergocalciferol or as cholecalciferol, than 25OHD₃
15 was required to produce equivalent plasma 25OHD₃ concentrations (Stamp et al., 1977). As
16 patients suffering from diseases that lead to fat malabsorption also malabsorb vitamin D (Lo
17 et al., 1985; Heubi et al., 1989; Lark et al., 2001), several studies were dedicated to assessing
18 whether 25OHD₃ could be used to improve vitamin D absorption in these patients: the results
19 were positive. The absorption of cholecalciferol and 25OHD₃ was compared in normal
20 subjects and in patients with mild and severe cholestatic liver disease. Results showed that
21 absorption of 25OHD₃ was greater than that of cholecalciferol in all three groups (Sitrin and
22 Bengoa, 1987). In another study in patients with Crohn's disease and resections of the small
23 bowel, it was also observed that 25OHD₃ was better absorbed than cholecalciferol
24 (Leichtmann et al., 1991).

25

1 In conclusion, 25OHD is better absorbed than the non-hydroxylated forms
2 cholecalciferol and ergocalciferol. These forms are apparently absorbed with the same
3 efficiency, but metabolism and biological activities of the hydroxylated metabolites of vitamin
4 D₂ and D₃ are apparently different, and lead to an apparent lower biological activity of vitamin
5 D₂ compared with vitamin D₃.

6

7 *b. Molecular Linkage*

8

9 Dietary vitamin D is non-esterified, but because some supplements may contain
10 vitamin D esters (Hollis et al., 1996), the question arises of whether esterification affects
11 vitamin D bioavailability. Only one study is dedicated to comparing the relative absorption
12 efficiency of free vitamin D and vitamin D esters (Hollis et al., 1996). In this study, performed
13 at various postnatal ages, the abilities of vitamin D₃-palmitate and non-esterified vitamin D₂ to
14 elevate circulating vitamin D₃ and vitamin D₂, respectively, were compared. It was concluded
15 that the two forms approached equivalence when the gastrointestinal tract was mature.
16 Conversely, vitamin D₃-palmitate bioavailability was lower below age 10 days, probably due
17 to the lack of maturation of the digestive tract. This confirms the need for an efficient
18 digestion of lipids to efficiently absorb vitamin D, in particular vitamin D esters.

19

20 *c. Amount consumed in a meal*

21

22 It is generally assumed that like other vitamins, the absorption efficiency of vitamin D
23 decreases with increasing dose. The effect of the dose of vitamin D on its absorption
24 efficiency was studied in the rat. In both the jejunum and ileum, a linear relationship was
25 found between the absorption rate of the vitamin and its intraluminal concentration (Hollander
26 et al., 1978). This suggests that at least in the range of the studied concentrations, vitamin D

1 absorption efficiency does not significantly decrease with dose. This result is supported by the
2 result of a clinical study in which 116 subjects were placed in nine treatment groups that
3 ingested vitamin D₃ (25, 250 or 1250 µg/d for 8 weeks), 25OHD₃ (10, 20 or 50 µg/d for 4
4 weeks) or 1,25(OH)₂D₃ (0.5, 1.0 or 2.0 µg/d for 2 weeks). Results showed that serum levels of
5 all three forms increased linearly with the dietary dose, showing a similar efficiency of
6 absorption, at least in the range of doses studied (Barger-Lux et al., 1998). A recent study,
7 performed in the human intestinal cell line Caco-2, has shown that at low concentrations of
8 vitamin D₃ in micelles, i.e. between 0.1 and 2-3 µmole/L, higher than the physiological
9 concentration in the human duodenum, calculated to be about 0.01 µmole/L (Reboul et al.,
10 2011), the uptake of both vitamin D₃ and D₂ was saturable, while it was linear at high
11 pharmacological concentrations, i.e. up to 10 µmole/L. This result supports the involvement
12 of intestinal proteins in vitamin D absorption at dietary concentrations and a passive diffusion
13 that becomes preponderant at pharmacological concentrations.

14

15 *d. Matrix in which vitamin D is incorporated*

16

17 This factor is thought to be important because it is assumed that vitamin D needs to be
18 extracted from its food or supplement matrix to become bioaccessible, i.e. to become
19 solubilised in micelles and available for absorption.

20 Vitamin D bioavailability in foods was measured in some foods only, i.e. meat,
21 mushrooms, orange juice, milk and fortified cheese. This was done in different studies and it
22 is therefore difficult to compare the values obtained. In a clinical study, the relative
23 bioavailability of vitamin D₂ from pig meat sources was estimated to be about 60% compared
24 with a vitamin D₂ supplement (van den Berg, 1997). In two studies, performed in the rat, it
25 was concluded that vitamin D₂ from UV-irradiated mushrooms (*Agaricus bisporus* or
26 *Lentinula edodes*) was bioavailable (Jasinghe et al., 2005; Koyyalamudi et al., 2009), but there

1 was no comparison of the bioavailability with any other matrix. The bioavailability of vitamin
2 D₂ from mushrooms (*Cantharellus tubaeformis*) was confirmed in a clinical study involving
3 27 volunteers. The volunteers were randomly divided up into three groups of nine persons.
4 For 3 weeks, group 1 received mushrooms providing 14 µg ergocalciferol/d with their lunch,
5 group 2 received an ergocalciferol supplement providing 14 µg/d, and group 3 received no
6 supplementation. Serum 25OHD concentrations at 3 weeks were higher in groups 1 and 2 than
7 in group 3, and did not significantly differ between groups 1 and 2, suggesting that the vitamin
8 D₂ in mushrooms had the same bioavailability as the vitamin D₂ in supplement (Outila et al.,
9 1999). A recent controlled trial confirmed this finding, showing that vitamin D₂ from UV-B-
10 irradiated button mushrooms had the same bioavailability as that of a vitamin D₂ supplement
11 (Urbain et al., 2011). A clinical study found similar bioavailabilities of 25000 UI vitamin D₂
12 ingested with either milk (whole or skimmed) or 0.1 mL corn oil on toast (Tangpricha et al.,
13 2003), suggesting no effect of milk nutrients on vitamin D bioavailability. Four years ago, a
14 clinical study compared the bioavailability of vitamin D₃ from fortified wheat bread, fortified
15 rye bread and a supplement (Natri et al., 2006). Both fortified breads increased serum 25OHD
16 as effectively as the supplement. It was concluded that bread matrix did not significantly
17 affect vitamin D bioavailability. The bioavailability of vitamin D in bread was confirmed
18 recently in a study that showed that vitamin D₂-rich yeast baked into bread was bioavailable
19 and improved bone quality in vitamin D-deficient rats (Hohman et al., 2011). Recently, a
20 clinical study involving 80 subjects was dedicated to comparing the bioavailability of vitamin
21 D₃ between fortified cheeses and a supplement (liquid vitamin D₃). It was concluded (from
22 measurement of blood 25OHD) that vitamin D₃ was equally bioavailable from both sources
23 (Wagner et al., 2008). Finally, a recent study showed that vitamins D₂ and D₃ were equally
24 bioavailable in orange juice and in supplement (Biancuzzo et al., 2010).

25 Concerning vitamin D bioavailability in supplements, the effect of the vehicle
26 substance used in vitamin D supplements on vitamin D bioavailability was recently reviewed

1 (Grossmann and Tangpricha, 2010). It is concluded that although limited studies are available,
2 vitamin D in an oil vehicle is more bioavailable than when incorporated in a powder-based
3 vehicle (cellulose or lactose) or in ethanol. However, a recent clinical trial has concluded that
4 vitamin D is more bioavailable from a lactose capsule than from an oily drop formulation
5 (Coelho et al., 2010).

6 In summary, most data suggest that food matrix has no marked effect on vitamin D
7 bioavailability. The effect of supplement matrix is less clear.

8

9 *e. Effectors of absorption*

10

11 A very recent study found that taking vitamin D supplement with the largest meal of
12 the day improved vitamin D absorption (Mulligan and Licata). This suggests that one or more
13 components of the meal, or gut enzymes secreted after meal intake, improve vitamin D
14 absorption. However, another study did not confirm this finding, showing no significant
15 difference in blood 25OHD levels between subjects consuming a vitamin D supplement with
16 or without food (Wagner et al., 2008). As foods contain a multitude of substances (nutrients,
17 micronutrients, fibre, phytochemicals, etc.) it is likely that the different results of these two
18 studies were due to the different composition of the meals. To evaluate whether food
19 components can affect vitamin D bioavailability, it is necessary to perform dedicated
20 experiments to study the effect of each food component. Some studies presented here have
21 used this approach.

22

23 I. Dietary lipids

24

25 Lipids are assumed to improve absorption of fat-soluble microconstituents (FSM) by
26 several mechanisms. First, they can facilitate the release of FSM from food matrices by

1 providing a hydrophobic phase where FSM can be solubilised. Second, because lipids
2 stimulate biliary secretion, and consequently micelle production, they can increase the
3 proportion of micellarised FSM, i.e. of FSM available for absorption. Third, lipid digestion
4 products, e.g. fatty acids, monoglycerides and lysophospholipids, are micelle components and
5 so the more lipids digested, the more micelles are available to solubilise FSM (Hofmann,
6 1963). Finally, by inducing chylomicron synthesis, lipids can enhance FSM transport outside
7 the enterocytes and thus prevent the accumulation of vitamin D in enterocytes. This in turn
8 will theoretically increase FSM absorption. Several characteristics of dietary lipids are thought
9 to affect FSM absorption: (i) the amount of triacylglycerols ingested with vitamin D, (ii) the
10 species of fatty acids that constitute triacylglycerols (iii) the amounts of phospholipids, d) the
11 species of phospholipids, and (iv) the emulsification of lipids. However, data on the effect of
12 only two of these characteristics is available.

13

- 14 • Amount of fat (triacylglycerols)

15 Surprisingly, adding 2.5 mM fatty acids of varying chain length and degree of
16 saturation resulted in a decrease in the rate of vitamin D₃ absorption in rats (Hollander et al.,
17 1978). This suggests that conversely to what is observed for other fat-soluble vitamins
18 (vitamin E and β -carotene), fat may diminish vitamin D absorption. However, four clinical
19 studies did not find any significant effect of fat on vitamin D bioavailability. The first one,
20 mainly designed to compare the bioavailability of vitamin D in two beverages (orange juice
21 and milk), showed that the fat content of milk did not significantly affect vitamin D₂
22 bioavailability in 18 adults (Tangpricha et al., 2003). The second study did not find any
23 difference between vitamin D₃ fortified cheddar cheese (~33% fat) and vitamin D₃ fortified
24 low-fat cheese (~7% fat) in their ability to increase blood 25OHD (Wagner et al., 2008). The
25 third study found no difference between vitamin D in multivitamin tablets and vitamin D in
26 fish oil in their ability to increase serum 25OHD (Holvik et al., 2007). In the fourth trial,

1 consumption of vitamin D with 2 g fish oil once weekly did not improve vitamin D absorption
2 (Korkor and Bretzmann, 2009). We note that in a recent clinical study (Raimundo et al.,
3 2011), it was concluded that a high-fat meal (25.6 g fat/meal) increased vitamin D absorption
4 compared with a low fat meal (1.7 g). However, a close look at the results obtained reveals
5 that there was no effect of either the low fat or high fat meals, which contained 50000 UI
6 vitamin D₃, on serum 25OHD 7 days after intake. Furthermore, it was not a crossover study
7 and the authors acknowledged that some of the subjects may have had secondary
8 hyperparathyroidism. Thus the available data suggests that the amount of fat ingested with
9 vitamin D has no major effect on vitamin D bioavailability.

10

- 11 • Type of fatty acid (within triacylglycerols)

12 The pioneering work on this topic was performed by Hollander's team (Hollander et
13 al., 1978). It was shown in rat perfusate intestine that addition of fatty acids of varying chain
14 length and degrees of saturation, i.e. butyric, octanoic, oleic and linoleic, resulted in a
15 decrease in the rate of vitamin D₃ absorption. More precisely, the inhibitory effects of the
16 oleic and linoleic acids were higher than that of octanoic acid in the distal part of the intestine.
17 The authors suggested that unlike medium-chain fatty acids, which are not incorporated in
18 micelles, long-chain fatty acids hinder vitamin D absorption by causing enlargement of the
19 micellar size, thereby slowing their diffusion towards the enterocyte. However, this result was
20 not confirmed in a clinical trial: absorption of a pharmacological dose of vitamin D₃ was
21 compared when ingested with either medium-chain triacylglycerols or long-chain
22 triacylglycerols (peanut oil). Results showed that the serum levels of vitamin D₃ were
23 significantly higher after administration in peanut oil (long-chain triglycerides) than after
24 administration in medium-chain triglycerides. (Holmberg et al., 1990). Concerning the
25 comparison between different types of fatty acids, a recent clinical study has concluded that

1 diets rich in monounsaturated fatty acids may improve the effectiveness of vitamin D₃
2 supplements in healthy older adults, while those rich in polyunsaturated fatty acids may
3 reduce it (Niramitmahapanya et al., 2011).

4 Taken together, these results suggest that the type of fatty acid can affect vitamin D
5 bioavailability. However, further studies are required to draw firm conclusions on the
6 compared effects of each type of fatty acid on vitamin D bioavailability.

7

8 II. Dietary Fibre

9

10 Dietary fibre has been suspected of affecting FSM absorption by several mechanisms:
11 (i) by affecting micelle formation; (ii) by altering emulsification and triacylglycerol lipolysis
12 (Pasquier et al., 1996) and thus affecting the release of FSM embedded in fat droplets, and
13 (iii) by increasing the viscosity of the chyme and thus limiting the diffusion of FSM
14 containing micelles to the brush border. Compston suggested that the high dietary fibre intake
15 of Asian immigrants caused vitamin D bioavailability to diminish, thus explaining the higher
16 incidence of rickets and osteomalacia in this population (Compston, 1979). However, there
17 are only two clinical studies on the effect of fibre on vitamin D absorption. The first study
18 compared the rate of plasma disappearance of radiolabelled 25OHD in healthy volunteers on
19 either normal or high-fibre diets (20 g/d). The authors observed that the mean plasma half-life
20 of 3H-25OHD₃ in the high-fibre group was 19.2 ± 1.7 d, significantly shorter than in the group
21 on normal diet (27.5 ± 2.1 d). They suggested that fibre enhanced elimination of 25OHD by
22 an action in the intestinal lumen (Batchelor and Compston, 1983). However, a recent clinical
23 study did not find any significant differences between vitamin D fortified low-fiber wheat
24 bread (3 g/100 g) and high-fiber rye bread (12 g/100 g) consumed for 3 weeks, in their ability
25 to increase blood 25OHD in 41 healthy subjects (Natri et al., 2006). However, the authors

1 acknowledged that there was no significant difference in daily total fiber intake among the
2 two groups of subjects, because they were allowed to eat other breads. In conclusion, there is
3 too little data to conclude on the effect of this factor on vitamin D bioavailability.

4

5 III. Inhibitors of lipid absorption

6

7 Since obesity is a major health problem, several antiobesity drugs have been proposed
8 to diminish the absorption of triacylglycerols and cholesterol. Because of the closely similar
9 fate of lipids and vitamin D in the gastrointestinal lumen, it has been hypothesised that these
10 drugs can also impair vitamin D absorption. It has been shown that tetrahydrolipstatin
11 (orlistat), a non-absorbed inhibitor of gastric and pancreatic lipases, and olestra, a sucrose
12 polyester used as a fat substitute, reduce absorption of vitamin D (Schlagheck et al., 1997;
13 McDuffie et al., 2002). Phytosterols, the plant sterols used to diminish cholesterol absorption,
14 might also impair vitamin D absorption by impairing its solubilisation in mixed micelles. This
15 hypothesis was supported both by results obtained in rats that showed a decrease in both
16 blood and liver vitamin D levels after dietary levels of stanol esters for 13 wks (Turnbull et
17 al., 1999), and by recent results obtained *in vitro* and in mice that showed that phytosterols
18 compete with vitamin D₃ for incorporation into mixed micelles as well as for apical uptake
19 (Goncalves et al., 2011). Surprisingly, phytosterols were claimed to have no effect on vitamin
20 D status in different clinical trials [32, 33]. However, in all these studies, vitamin D status
21 was evaluated as plasma 25OHD, which is highly variable depending on factors such as
22 season and sun exposure. As a consequence, 25OHD levels can display a high variability
23 between the beginning and end of the study or between the different groups (Gylling et al.,
24 2010). In addition, the intervention periods may have been too short to reveal a significant
25 effect on vitamin D homeostasis. Finally, we note that a close look at one of these studies
26 reveals a significant lowering effect of a sitostanol ester enriched margarine on vitamin D

1 plasma level after a long-term treatment (Gylling et al., 1999). We note that the negative
2 effect of inhibitors of lipid absorption on absorption of fat soluble vitamins can be offset by
3 adding vitamin supplements to the diet. This was demonstrated in a clinical study in 102
4 subjects in whom serum concentrations of vitamin E and 25OHD₂ were restored to control
5 concentrations by adding 2.1 mg d- α -tocopheryl acetate and 0.06 μ g ergocalciferol per gram
6 of olestra, respectively, to the diet (Schlagheck et al., 1997).

7

8 IV. Microconstituents

9

10 As the main dietary source of vitamin D, i.e. cholecalciferol, can be ingested together
11 with other vitamin D species (vitamin D₂, vitamin D esters, etc.) and other lipid
12 micronutrients (other fat-soluble vitamins, carotenoids and phytosterols), and because
13 common mechanisms of absorption are involved (Reboul and Borel, 2011), it has been
14 hypothesised that interactions can occur that affect their absorption (Reboul and Borel, 2011).
15 A study performed in our laboratory in Caco-2 cells supports this hypothesis by showing that
16 high concentrations of vitamin D₂ significantly impair cholecalciferol absorption (Reboul et
17 al., 2011). However, this competition should be re-assessed *in vivo*, as conflicting results have
18 been published: in a first clinical study, oral administration of 400 IU/d of vitamin D₂ for 1
19 week led to very small variations of plasma vitamin D₃ and its metabolites (Matsuoka et al.,
20 1989). Furthermore, in a recent study, a mixture of 500 IU of vitamin D₃ and 500 IU of
21 vitamin D₂ led to a similar rise in 25OHD as 1000 IU of vitamin D₃ (Holick et al., 2008),
22 suggesting no inhibition of D₃ absorption by D₂ at relatively low doses. Conversely, in another
23 study, vitamin D₂ treatment (4000 IU/d for 8 weeks) decreased blood 25OHD₃ and
24 1,25(OH)₂D₃ (Tjellesen et al., 1986). Finally, a recent study in cows has shown that vitamin
25 D₃, given as an oral bolus of 250 mg (1.0×10^7 IU) after vitamin D₂, is less efficient in
26 increasing the plasma status of 25OHD₃ than the same dose of vitamin D₃ given without

1 previous vitamin D₂ administration (Hymoller and Jensen, 2011). Thus high doses of vitamin
2 D₂ supplements might decrease vitamin D₃ absorption, but available data are in different
3 species and therefore further studies are needed to definitely conclude on the effect of high
4 doses vitamin D₂ on vitamin D₃ absorption in humans.

5

6 V. Milk and milk-derived products

7

8 The bioavailability of vitamin D naturally present in milk has never been measured,
9 probably owing to the low concentration of the vitamin in it (about 25 IU of vitamin D/L
10 human milk). By contrast, studies were performed to measure bioavailability of vitamin D in
11 fortified milk or cheeses. In a first study in 18 subjects, it was shown that milk, either whole
12 or skimmed, did not significantly modify vitamin D₂ bioavailability compared with its intake
13 without milk (Tangpricha et al., 2003). In a second study in young and older adults, it was
14 observed that vitamin D bioavailability was higher when incorporated in cheese than when
15 solubilised in water (Johnson et al., 2005). In a third study, dedicated to comparing vitamin D
16 bioavailability between fortified cheeses and supplement, it was concluded that vitamin D was
17 equally absorbed between fortified cheese and water (Wagner et al., 2008). In conclusion, it
18 appears that milk or cheese do not significantly affect vitamin D bioavailability.

19

20 VI. Absorption enhancers

21

22 Some substances, e.g. β -cyclodextrine, nanoparticles and compounds able to form
23 micelles, are used to improve absorption efficiency of liposoluble drugs or fat-soluble
24 vitamins. Their ability to enhance absorption efficiency of vitamin D was assessed in some
25 studies. The first absorption enhancer studied was a water-soluble form of vitamin E
26 (tocopheryl succinate polyethylene glycol 1000 (TPGS)). This substance was a good candidate

1 for improving vitamin D absorption as it is able to form micelles that can solubilise lipophilic
2 compounds including vitamin D. This was assessed in a clinical study with eight children
3 (aged 5 mo to 19 y) suffering from severe chronic cholestasis. Results showed a significantly
4 higher absorption of vitamin D administered in a mixture with TPGS (Argao et al., 1992). The
5 ability of β -cyclodextrine to enhance absorption of vitamin D was studied in rats. Results
6 showed a 2.5-fold increase in absorption compared with vitamin D alone (Szejtli et al., 1983).

7

8 *f. Nutrient status of the host*

9

10 As vitamin D has numerous biological effects, and as large amounts of vitamin D can
11 be toxic, it can be hypothesised that as observed for vitamin A (Lobo et al., 2010), vitamin D
12 absorption is regulated by vitamin D status. Surprisingly, only one study in rats has been
13 dedicated to testing this hypothesis. In this study it was observed that the intestinal absorption
14 of vitamin D₃ and its hydroxylation in the liver were higher in vitamin D-deficient rats than in
15 vitamin D-treated ones (Apukhovskaia et al., 1990). This very interesting finding requires
16 support from further experiments.

17

18 *g. Genetic factors*

19

20 A line of results has suggested that genetic variants play a key role in modulating
21 25OHD blood concentrations (Orton et al., 2008; Fu et al., 2009; Sinotte et al., 2009; Ahn et
22 al., 2010; Karohl et al., ; McGrath et al., 2010). The fact that proteins are involved in cellular
23 uptake of vitamin D raises the question of the impact of modulations in the expression or
24 activity of these proteins on blood and tissue concentrations of vitamin D. The expression and
25 activity of proteins can be modulated by several factors, including genetic ones. Genetic
26 variations in or near genes that encode proteins may affect protein expression, e.g. a genetic

1 variation that affects the binding of a transcription factor in the promoter region of a gene
2 (Hernandez-Romano et al., 2009), or protein activity, e.g. a genetic variation that leads to a
3 functional modification in the amino acid sequence of the protein, and in turn the ability of
4 these proteins to accurately perform their function in the metabolism (Lindqvist et al., 2007;
5 Borel, 2011). However, no result has been published on this exciting topic.

6

7 *h. Host-related factors*

8

9 A line of evidence suggests that host-related factors (mainly age and diseases) can
10 have an effect on vitamin D absorption. Thus several studies have been performed to assess
11 their effect in order to optimise RDA as a function of age and disease.

12

13 I. Age

14

15 Ageing, by affecting numerous physiological processes, may directly or indirectly
16 affect vitamin D absorption. More precisely, age-related alterations of gastrointestinal tract
17 functions (Vellas et al., 1991; Russell, 1992; Ikuma et al., 1996) may modify the efficiency of
18 vitamin D absorption, as suggested for vitamin E (Borel et al., 1997). As most elderly people
19 have a low vitamin D status, it has been hypothesised that absorption efficiency of vitamin D
20 is less efficient in elderly persons than in young adults.

21 The first study dedicated to testing this hypothesis was performed in 20 elderly
22 women, most of whom were vitamin D-depleted. Because the plasma [3H]cholecalciferol
23 response after oral ingestion was significantly lower than that of a group of younger female
24 subjects, it was suggested that there was a defect in intestinal absorption of cholecalciferol in
25 the elderly (Barragry et al., 1978). However, subsequent studies on this topic did not confirm
26 this finding: a study in rats pointed to a normal absorption of vitamin D₃ in ageing animals

1 (Hollander and Tarnawski, 1984). In another study, serum vitamin D₂ concentrations were
2 compared after oral administration of 50,000 IU of vitamin D₂ in both healthy vitamin D-
3 sufficient elderly subjects and young adults. Again, no evidence of malabsorption of vitamin
4 D in the elderly subjects was observed (Clemens et al., 1986). In a third study, involving four
5 young (23 to 50 yr) and four older (72 to 84 yr) subjects, peak serum 25OHD and 25OHD
6 areas under the curve were not significantly different between the younger and older adults
7 (Johnson et al., 2005). Finally, a study by Harris and coworkers involving 25 young men (18
8 to 35 yr) and 25 older men (62 to 79 yr) supplemented with 800 IU of vitamin D₃ per day
9 (Harris and Dawson-Hughes, 2002), found that the magnitude of blood 25OHD increase was
10 identical between the two age groups. In conclusion, there is apparently no significant effect
11 of ageing on vitamin D absorption efficiency. The frequent lower vitamin D status in elderly
12 than in young subjects may be due to lower dietary intakes, lower exposure to sunlight, lower
13 efficiency of vitamin D synthesis in the skin or lower hydroxylation of vitamin D by the liver.

14

15 II. Diseases/digestive tube surgery

16

17 The intestinal absorption of vitamin D requires normal digestive functions, and so
18 subjects with impaired fat absorption caused by any of several diseases (obstructive jaundice,
19 pancreatic insufficiency, cystic fibrosis or adult coeliac disease) have been suspected of
20 impairing vitamin D absorption. This is supported by the results of several studies: serum
21 vitamin D₂ and D₃ were undetectable in infants and children (age 4-22 mo) with extrahepatic
22 biliary atresia, whose portoenterostomy failed to produce bile flow, despite supplements of
23 2500-5000 IU/day (Heubi et al., 1990). Also, serum vitamin D₂ concentrations were
24 undetectable despite oral supplementation with 2,500 to 50,000 IU per day of vitamin D₂ in
25 children with cholestasis since infancy (Heubi et al., 1989). Finally, cystic fibrosis patients
26 absorbed less than one third (Farraye et al.), or one half (Lark et al., 2001) the amount of oral

1 vitamin D₂ that was absorbed by healthy subjects. However, we note that the negative effect
2 of these diseases on vitamin D bioavailability can be partially corrected by sun exposure
3 (Robberecht et al.) or by using hydroxylated vitamin D. Patients with intestinal fat
4 malabsorption syndromes have a relatively well-preserved absorption of 25OHD₃, which is
5 absorbed directly *via* the portal vein (Leichtmann et al., 1991).

6 The effect of gastric surgery on vitamin D bioavailability has been studied by Aarts et
7 al. (Aarts et al., 2011). This team showed that peak serum cholecalciferol levels were about
8 30% lower after Roux-en-Y gastric bypass than before.

9

10 III. Obesity

11

12 As obesity is usually associated with vitamin D insufficiency, a study was dedicated to
13 assessing the effect of obesity on the cutaneous production of vitamin D₃ and on vitamin D
14 bioavailability, evaluated by the blood response in vitamin D after a vitamin D-rich meal.
15 Obese and matched lean control subjects received either whole-body ultraviolet radiation or a
16 pharmacologic dose of vitamin D₂ orally. Results showed that body mass index was inversely
17 correlated with serum vitamin D₃ concentrations after irradiation, and with peak serum
18 vitamin D₂ concentrations after vitamin D₂ intake. It was concluded that obese subjects had
19 lower blood concentrations of vitamin D (coming either from the skin or the food) because of
20 its deposition in the body fat compartment (Wortsman et al., 2000), and not because of lower
21 skin synthesis or bioavailability. This was supported by a very recent study suggesting that
22 dilution of ingested or cutaneously synthesised vitamin D in the large fat mass of obese
23 patients explains their typically low vitamin D status (Drincic et al., 2012).

24

25 *i. Mathematical Interactions*

26

1 These are the interactions that can occur when several factors are involved (West and
2 Castenmiller, 1998). One recent study (Khazai et al., 2009a) shows a good example of
3 interactions between factors: in this clinical study, bioavailability of vitamin D₃ was better
4 than that of vitamin D₂, but this was probably not due to any difference in absorption
5 efficiency of the two forms of vitamin D (see chapter on the S factor), but rather to an effect
6 of the vehicle in which vitamin D was incorporated (M factor), an effect probably exacerbated
7 in patients with fat malabsorption (H factor).

8

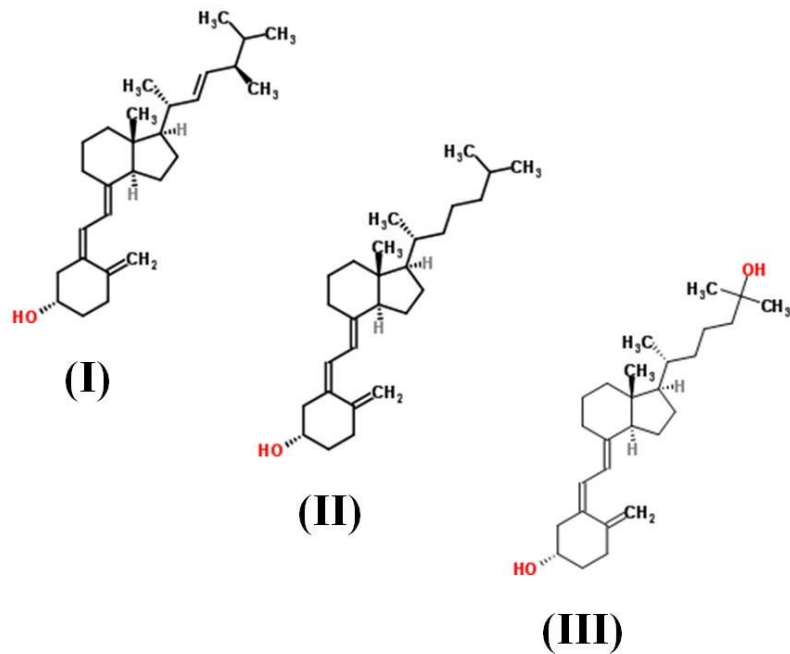
9 *Conclusions*

10

11 This review shows that the intraluminal fate of vitamin D and the fundamental
12 mechanisms involved in vitamin D absorption are far from fully understood. It also shows that
13 although the effects of some factors on vitamin D bioavailability are well documented, little
14 data is available on numerous factors that may affect vitamin D bioavailability, e.g. genetic
15 factors, effect of dietary fibre, and effect of vitamin D status. Clinical studies with labelled
16 vitamin D (deuterated or ¹³C) are needed to accurately and definitively assess the effects of
17 these factors on vitamin D bioavailability.

1 **Figures**

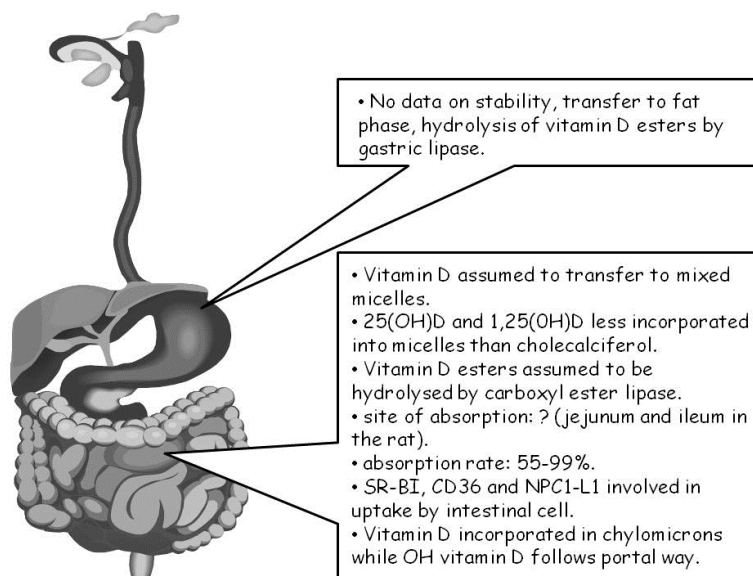
2

3 *Figure 1*

4

5 Chemical structures of natural dietary forms of vitamin D: (I) ergocalciferol (vitamin D₂), (II)6 cholecalciferol (vitamin D₃), (III) 25-hydroxy-cholecalciferol.

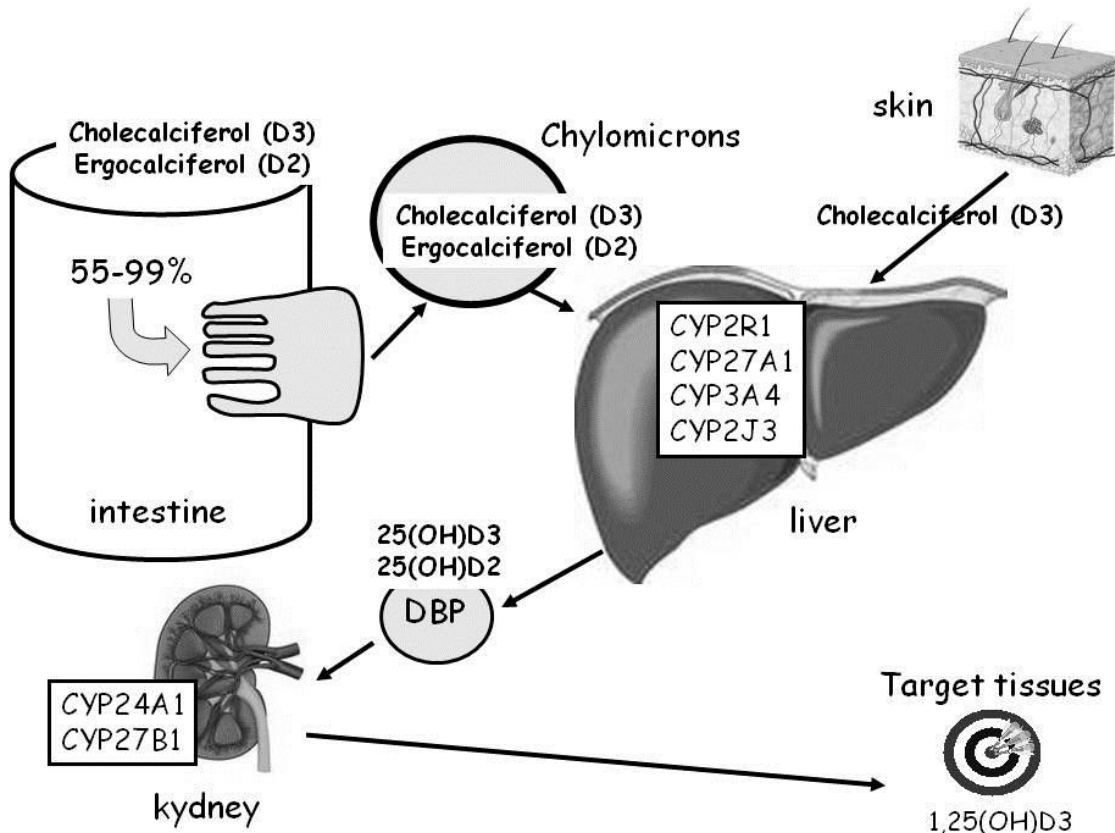
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8 *Figure 2*

1 Some important knowledge and lack of knowledge, on the fate of vitamin D in the human
 2 upper gastro-intestinal tract lumen.

3

4 *Figure 3*



5

6 Vitamin D metabolism in the human body. 25(OH)D₃: 25-hydroxy cholecalciferol.

7 25(OH)D₂: 25-hydroxy ergocalciferol. 1,25(OH)₂D₃: dihydroxy cholecalciferol, DBP:

8 vitamin D binding protein. CYPxyzw: cytochrome P450, family x, subfamily y, polypeptide

9 zw.

10

11

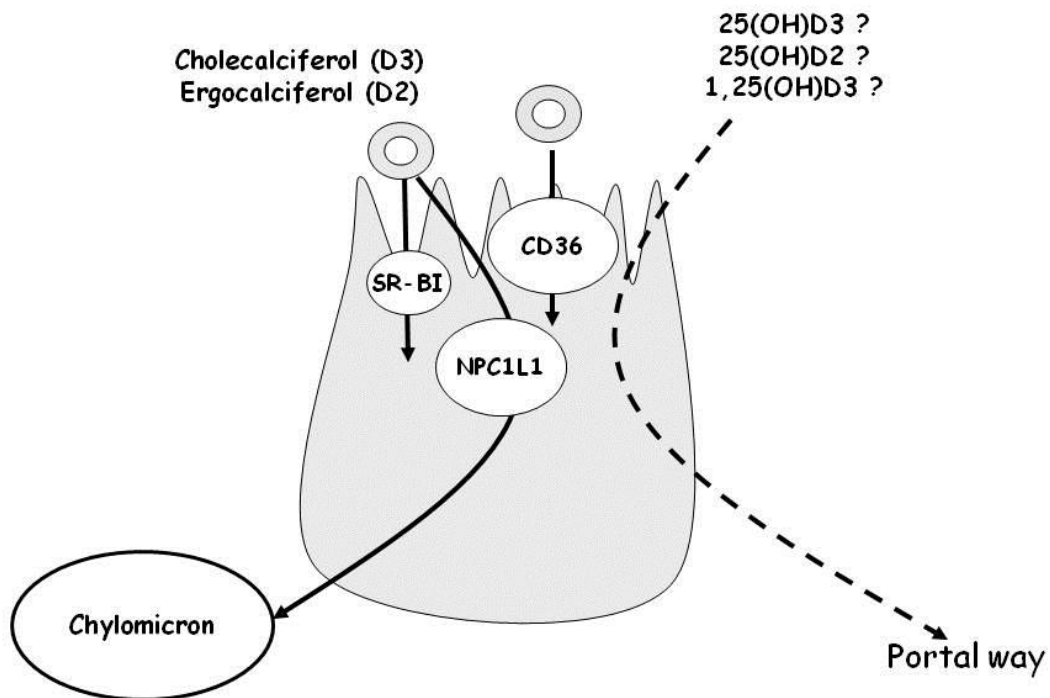
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13

1

2

3

4 *Figure 4*

5

6

7 Current knowledge on vitamin D absorption by human intestinal cells. From the paper of

8 Reboul et al. (Reboul and Borel, 2011). SR-BI: scavenger receptor class B type 1. CD36:

9 Cluster Determinant 36. NPC1L1: Niemann-Pick C1-like 1. The dashed arrow means that

10 there is no data on the molecular mechanisms involved in absorption of the hydroxy

11 metabolites of vitamin D. It has been hypothesized (Reboul and Borel, 2011) that protein

12 mediated uptake takes place at dietary doses of vitamin D while passive diffusion probably

13 occurs at high, non-physiological doses.

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2

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