Factors affecting the mechanism and modelling of vitamin D absorption in designing fortified foods – A review

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Summary
Vitamin D is an essential nutrient for human health, which can be either synthesized inside the body when exposed to sunlight or enter the body via the oral root by food or supplement consumption. This review aims to provide information on possible factors and mechanisms that may interfere with the absorption of the vitamin along the gastrointestinal tract. This information is valuable in food and nutrition science, as it can provide a useful guidance in designing fortified foods with enhanced bioavailability of the vitamin. Multiple databases were searched including Scopus (Elsevier, Amsterdam, Netherlands), PubMed (National Center for Biotechnology Information, Bethesda, Maryland, USA), ResearchGate (ResearchGate, Berlin, Germany) and Google Scholar (Google, Mountain View, California, USA), between December 2019 and November 2020. The research gaps that arose included possible interactions between the food composition or structure and the vitamin's bioavailability, the details of the fate of the vitamin in the gastrointestinal tract as well as the limitations occurring in the mathematical models of digestion, which may simplify the simulation but also insert some uncertainty concerning the accuracy of results.

Keywords
vitamin D; fortified foods; enriched foods; bioavailability; digestion; mathematical modelling

Vitamin D is an essential micronutrient for human health. However, its deficiency is a global phenomenon even in countries with abundant sunlight exposure [1]. Supplementation has been used in order to cope with vitamin D deficiency or insufficiency. As there are not many foods that naturally contain vitamin D or the amount of the vitamin naturally present is small, there is a prominent need for food fortification, either by enhancing the content of some foods or by exogenously adding the vitamin. Food fortification and biofortification were considered as an alternative way to deal with vitamin D deficiency or insufficiency [2].

Several studies showed that food fortification can increase vitamin D serum concentration (Tab. 1). To properly design fortified foods, several factors must be considered. These factors are related to human physiology, food matrix in which vitamin D is incorporated as well as the processing and storage conditions encountered before consumption. Modelling the processes that take place during digestion of vitamin D containing foods is potentially an important tool for the prediction of vitamin D's fate in the gastrointestinal tract and the associated bioavailability. Additionally, these models can lead to better designed fortified foods that will contribute to the fight against vitamin D deficiency.

The aim of this review was to analyse the factors affecting the mechanism and modelling of vitamin D absorption in designing fortified foods. Factors affecting its bioavailability, such as food matrix, composition and gastrointestinal tract conditions, are explained and analysed. The review focuses on filling research gaps of previous reviews on similar topic, including more recent studies with new information, i.e. how lipids can affect vitamin D absorption, and highlighting some contradictions between studies. Special reference is made to the available mathematical models developed so far for the simulation of the digestion process. In the concluding remarks, research gaps

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Tab. 1. Studies on vitamin D content and bioavailability of enriched or fortified foods (2000-2020).

Form of vitamin	Quantity		Bioavailability – final serum concentration (species, dosage, duration of intervention)	Ref.
	Natural	After treatment		
Mushrooms				
D_2	0.18×10^{-5} μg·kg^{-1} fresh weight	Post-harvest UV-B: 491×10^{-5} μg·kg^{-1} fresh weight	25(OH)D: 56.7 ± 7.2 nmol·l^{-1} (humans, 0.70 mg mushroom D_2, 4 times a week, 5-week)	3
D_2	–	Post-harvest UV-C (2.5 min, 5 min, 10 min): $(6.7–23.1) \times 10^{-3}$ μg·kg^{-1} dry solids	25(OH)D_2: 3.13 nmol·l^{-1} (rats, 50 mg·kg^{-1} body weight, 3-week) 4.7 nmol·l^{-1} (rats, 100 mg·kg^{-1} body weight, 3-week) 5 nmol·l^{-1} (rats, 200 mg·kg^{-1} body weight, 3-week)	4
D_2	–	UV: 29.20 μg·kg^{-1}	25(OH)D: 55-67 mmol·l^{-1} (mice, 1.35 μg·kg^{-1} D2 in feed, 7-month)	5
D_2	–	UV: 491×10^{-5} μg·kg^{-1} fresh weight	25(OH)D: 59.6 ± 12.2 nmol·l^{-1} (humans, 491×10^{-5} μg·kg^{-1} per week, 4-week)	6
			25(OH)D_2: 46.1 ± 7.1 nmol·l^{-1} (humans, 491×10^{-5} μg·kg^{-1} per week, 4-week)	
			25(OH)D_3: 17.7 ± 4.0 nmol·l^{-1} (humans, 491×10^{-5} μg·kg^{-1} per week, 4-week)	
Eggs				
D_3	0.63 ± 0.22 μg per egg	D_3-enhanced: 1.04 ± 0.54 μg per egg 25(OH)D_3-enhanced: 0.14 ± 0.08 μg per egg	25(OH)D: 34.8 ± 11.4 nmol·l^{-1} (humans, ≤ 2 eggs per week, 8-week) 50.1 ± 21.4 nmol·l^{-1} (humans, 7 D_3-enhanced eggs per week, 8-week) 49.2 ± 16.5 nmol·l^{-1} (humans, 7 25(OH)D_3-enhanced eggs per week, 8-week)	7
25(OH)D_3	0.56 ± 0.22 μg per egg	D_3-enhanced: 0.50 ± 0.10 μg per egg 25(OH)D_3-enhanced: 0.88 ± 0.26 μg per egg		
Milk				
D_3	–	Feed supplementation: D_3 0.45 mg·d^{-1}: 471 pg·ml^{-1} to 324 pg·ml^{-1} (1st to 6th milking) D_3 0.45 mg·d^{-1} + DCAD –139 mEq·kg^{-1}: 340 pg·ml^{-1} to 295 pg·ml^{-1} (1st to 6th milking) 25(OH)D_3 6 mg·d^{-1} + DCAD –138 mEq·kg^{-1}: not detected	25(OH)D_3: 45.7 ng·ml^{-1} to 37.1 ng·ml^{-1} (calves, milk from cows fed D_3 0.45 mg·d^{-1}, birth to 6th feeding) 42.3 ng·ml^{-1} to 35.5 ng·ml^{-1} (calves, milk from cows fed D_3 0.45 mg·d^{-1} + DCAD –139 mEq·kg^{-}), birth to 6th feeding) 80.2 ng·ml^{-1} to 57.6 ng·ml^{-1} (calves, milk from cows fed 25(OH)D_3 6 mg·d^{-1} + DCAD –138 mEq·kg^{-1}, birth to 6th feeding)	8
25(OH)D_3		Feed supplementation: D_3 0.45 mg·d^{-1}: 1021 pg·ml^{-1} to 458 pg·ml^{-1} (1st to 6th milking) D_3 0.45 mg·d^{-1} + DCAD –139 mEq·kg^{-1}: 891 pg·ml^{-1} to 340 pg·ml^{-1} (1st to 6th milking) 25(OH)D_3 6 mg·d^{-1} + DCAD –138 mEq·kg^{-1}: 3690 pg·ml^{-1} to 1088 pg·ml^{-1} (1st to 6th milking)		
D_3	–	2.50 μg D_3 per 250 ml milk	25(OH)D: 57 nmol·l^{-1} (humans, 2.50 μg D_3/250 ml milk + 0.75 μg D/93 ml yoghurt beverage, 12-week) 65 nmol·l^{-1} (humans, 2.50 μg D_3/250 ml milk + 2×1.05 μg D/93 ml yoghurt beverage + 200 IU D/21 g cheese, 12-week) 62 nmol·l^{-1} (humans, 2.50 μg D_3/250 ml milk + 2×3.13 μg D/93 ml yoghurt beverage + 5.00 μg D/21 g cheese, 12-week)	9
D_3	–	Micronutrient-fortified milk: 6.3×10^{-5} μg·kg^{-1} powder Vitamin D-fortified milk: 6.0×10^{-5} μg·kg^{-1} powder	25(OH)D: 70.5 nmol·l^{-1} (humans, vitamin D fortified milk, 20-week intervention) 69.8 nmol·l^{-1} (humans, micronutrient fortified milk, 20-week intervention)	10
D_3	–	2.50 μg per 236 ml	25(OH)D: $(20 \pm 6)–(29 \pm 10)$ ng·ml^{-1} (humans, 7.50 μg·d^{-1}, 49-day)	11

Tab. 1. *continued*

Form of vitamin	Quantity		Bioavailability – final serum concentration (species, dosage, duration of intervention)	Ref.
	Natural	After treatment		
D_2	–	625 μg per 240 ml	Serum D_2: 68–75 nmol·l^{-1} (humans, 625 μg, peak serum concentration after 12 h of ingestion)	12
D_3	–	5 μg or 10 μg per sachet	25(OH)D_3: 50 nmol·l^{-1} (humans, 25 g·d^{-1} – 5 μg D_3, 4-week) 58 nmol·l^{-1} (humans, 25 g·d^{-1} – 10 μg D_3, 4-week)	13
			25(OH)D_2: 3 nmol·l^{-1} (humans, 25 g·d^{-1} – 5 μg D_3, 4-week) 3 nmol·l^{-1} (humans, 25 g·d^{-1} – 10 μg D_3, 4-week)	
D_2		5 μg or 10 μg per sachet	25(OH)D_3: 37 nmol·l^{-1} (humans, 25 g·d^{-1} – 5 μg D_2, 4-week) 36 nmol·l^{-1} (humans, 25 g·d^{-1} – 10 μg D_2, 4-week)	
			25(OH)D_2: 12.5 nmol·l^{-1} (humans, 25 g·d^{-1} – 5 μg D_2, 4-week) 20 nmol·l^{-1} (humans, 25 g·d^{-1} – 10 μg D_2, 4-week)	
D_3	–	Fortified dairy drink with crystalline D_3 dissolved in oil: 20 μg per 300 ml dairy drink	25(OH)D_3: 35 nmol·l^{-1} (humans, 20 μg D_3, 24 h) 39.5 nmol·l^{-1} (humans, 20 μg 25(OH)D_3, 24 h)	14
25(OH)D_3		Fortified dairy drink with crystalline 25(OH)D_3 dissolved in oil: 20 μg per 300 ml dairy drink		
Yoghurt				
D_3	–	Fortified yoghurt: 5 μg D_3 per 125 g yoghurt	25(OH)D_3: 60 mmol·l^{-1} (humans, 2·5 μg·d^{-1}, 3-month)	15
D_3	–	Emulsified or non-emulsified vitamin D: 0.2 μg·g^{-1}	25(OH)D: (93.4 ± 17.5)–(96.6 ± 22.7) nmol·l^{-1} (rats, 2 g of yoghurt per day, 14-day)	16
D_3		Powder vitamin D_3: 25 × 10^{-5} μg·kg^{-1} yoghurt	25(OH)D_3: 30.79 ± 12 ng·ml^{-1} (humans, 20 packs of 100 g yoghurt/10 days, 3-month)	17
Cheese				
D_3	–	Fortified low fat cheese and cheddar: 20.85 μg·g^{-1} and 16.90 μg·g^{-1}	25(OH)D: 125 nmol·l^{-1} (humans, low fat cheese – 700 μg per serving once a week, 8-week) 115 nmol·l^{-1} (humans, cheddar cheese – 700 μg per serving once a week, 8-week)	18
D_3	–	Water dispersible D_3: 5 μg per 28.3 g cheese	25(OH)D: 21 ± 1.4 ng·ml^{-1} (humans, 15 μg·d^{-1}, 2-month)	19
D_2		147 μg per 57 g cheese	Serum vitamin D_2: 15 ± 1 ng·ml^{-1} (humans, fortified cheese (147 μg) in day 0 – fortified water (818.75 μg) in day 14, 14-day)	
Formula and growing-up milk				
D*	–	1.7 × 10^{-5} μg·l^{-1}	25(OH)D: 77.8 ± 26.6 nmol·l^{-1} (humans, 1.7 μg/100 ml, 20-week)	20
D*	–	2.85 × 10^{-5} μg·l^{-1}	25(OH)D: 24.8 ng·ml^{-1} (humans, milk 350 ml·d^{-1}, 9-month, after winter) 27.6 ng·ml^{-1} (humans, milk 350 ml·d^{-1}, 9-month, after summer)	21
D_3	–	1.2 μg per 100 ml	25(OH)D: 92.0 ± 25.5 nmol·l^{-1} (humans, milk 300 ml·d^{-1}, 12-month)	22

Tab. 1. *continued*

Form of vitamin	Quantity		Bioavailability – final serum concentration (species, dosage, duration of intervention)	Ref.
	Natural	After treatment		
Orange juice				
D_3	–	Cold-water soluble vitamin: 25 μg D_3 per 236.6 ml	25(OH)D: 30.7 ± 8.5 ng·ml^{-1} (humans, juice 236.6 ml·d^{-1}, 11-week)	23
D_2	–	Cold-water soluble vitamin: 25 μg D_2 per 236.6 ml	25(OH)D: 26.4 ± 7.4 ng·ml^{-1} (humans, juice 236.6 ml·d^{-1}, 11-week)	
D	–	700 mg calcium + 5 μg vitamin D	25(OH)D: 92.8 ± 36.0 nmol·l^{-1} (humans, juice 2× 240 ml·d^{-1}, 12-week)	24
		700 mg calcium, 5 μg vitamin D, 12 IU vitamin E, 2000 IU vitamin A	25(OH)D: 95.9 ± 27.7 nmol·l^{-1} (humans, juice 2× 240 ml·d^{-1}, 12-week)	
D_3	–	25 μg D_3 per 240 ml	25(OH)D: 94.0 ± 20 nmol·l^{-1} (humans, juice 240 ml·d^{-1}, 12-week)	25
Plant oils				
D_3	–	12.5 μg D_3 per 30 g	25(OH)D: 44.0 ± 12.4 ng·ml^{-1} (humans, 30 μg oil per lunch, 12-week)	26
D_2	–	625 μg dissolved in 0.1 ml corn oil	Serum D_2: 75 nmol·l^{-1} (humans, 625 μg, peak serum concentration after 12 h of ingestion)	27
D_3	–	UV-B, 4 min: 0–50 ng·g^{-1} UV-B, 8 min: 5–80 ng·g^{-1}	25(OH)D: 45 nmol·l^{-1} (mice, UVB-exposed oil, D_2 83.7 μg·kg^{-1} feed, 4-week) 80 nmol·l^{-1} (mice, D_3-supplemented oil, D_3 80 μg·kg^{-1} feed, 4-week)	28
D_2	–	UV-B, 4 min: 250–1000 ng·g^{-1} UV-B, 8 min: 450–1500 ng·g^{-1}		
Bread				
D_3	–	Flour fortification: 125 μg D_3 per bun	25(OH)D: (123.5 ± 38.1)–(128.5 ± 41.1) nmol·l^{-1} (humans, D_3 in fortified buns 125 μg·d^{-1}, 12-month)	29
D_3	–	Flour fortification: 125 μg D_3 per bun	25(OH)D: 125.6 ± 38.8 nmol·l^{-1} (humans, D_3 in fortified buns 125 μg·d^{-1}, 12-month)	28
D_3	–	Flour fortification: 125 μg D_3 per bun	25(OH)D: 127.3 ± 37.8 nmol·l^{-1} (humans, D_3 in fortified buns 125 μg·d^{-1}, 12-month intervention) 64.9 ± 24.8 nmol·l^{-1} (humans, D_3 in fortified buns 125 μg·d^{-1}, 12-month – 1-year follow-up) 28.0 ± 15.0 nmol·l^{-1} (humans, D_3 in fortified buns 125 μg·d^{-1}, 12-month – 3-years follow-up)	29
D_3	–	Flour fortification: Wheat: (12.0 ± 0.7) × 10^{-5} μg·kg^{-1} bread Rye: (12.0 ± 0.8) × 10^{-5} μg·kg^{-1} bread	25(OH)D: 16.3 ± 6.6 nmol·l^{-1} (increase from baseline, humans, fortified wheat – bread 85 g·d^{-1}, 10 μg D_3, 3-week) 14.9 ± 6.2 nmol·l^{-1} (increase from baseline, fortified rye – bread 85 g·d^{-1}, 10 μg D_3, 3-week)	30
D_3	–	Flour fortification: 25 ± 2.0 μg D_3 per 50 g bread	25(OH)D: 72.9 ± 23.1 nmol·l^{-1} (humans, bread 50 g·d^{-1}, 8-week)	31
D_2	–	Yeast-fortified bread: 25 μg D_2 per 87 g bread	25(OH)D: no significant change from baseline (humans, fortified bread 87 g·d^{-1}, 8-week)	32
			25(OH)D_3: no significant change from baseline (humans, fortified bread 87 g·d^{-1}, 8-week)	
			25(OH)D_2: +6.4 nmol·l^{-1} from baseline (humans, fortified bread 87 g·d^{-1}, 8-week)	

Tab. 1. *continued*

Form of vitamin	Quantity		Bioavailability – final serum concentration (species, dosage, duration of intervention)	Ref.
	Natural	After treatment		
D_2	–	Yeast-fortified bread (spray-dried): Intact yeast cells: 39250×10^{-5} μg·kg^{-1} Yeast cell walls: 138500×10^{-5} μg·kg^{-1}	25(OH)D: 40 nmol·l^{-1} (rats, intact yeast cell 7.5 μg·d^{-1}, 8-week) 70 nmol·l^{-1} (rats, intact yeast cell 15 μg·d^{-1}, 8-week) 60 nmol·l^{-1} (rats, yeast cell wall 7.5 μg·d^{-1}, 8-week) 80 nmol·l^{-1} (rats, yeast cell wall 15 μg·d^{-1}, 8-week)	33
D_2	–	Yeast-fortified bread: 0–0.11 μg·g^{-1} bread	25(OH)D: 2 nmol·l^{-1} (rats, 0.63 μg D_2 in bread per kilogram of diet, 8-week) 5 nmol·l^{-1} (rats, 2.5 μg D_2 in bread per kilogram of diet, 8-week) 8 nmol·l^{-1} (rats, 5 μg D_2 in bread per kilogram of diet, 8-week) 25 nmol·l^{-1} (rats, 25 μg D_2 in bread per kilogram of diet, 8-week)	34
Biscuits				
D_3	–	Flour fortification: 1250×10^{-4} μg·kg^{-1} biscuit	25(OH)D: 42.09 ± 21.30 ng·ml^{-1} (humans, 1 biscuit (1 250 μg D_3) twice a week 3 consecutive weeks, 4-month)	35

* – not specified D vitamin, 25(OH)D – 25-hydroxyvitamin D, 25(OH)D_2 – 25-hydroxyvitamin D_2, 25(OH)D_3 – 25-hydroxyvitamin D_3, UV-B – ultraviolet B radiation, UV-C – ultraviolet C radiation, UV – ultraviolet radiation, DCAD – dietary cation-anion difference.

are pointed out and suggestions for future research are made.

MATERIALS AND METHODS

A thorough literature search was conducted using the databases Scopus (Elsevier, Amsterdam, Netherlands), PubMed (National Center for Biotechnology Information, Bethesda, Maryland, USA), ResearchGate (ResearchGate, Berlin, Germany) and Google Scholar (Google, Mountain View, California, USA), between December 2019 and November 2020. The research was focused on the past 2 decades (2000–2020), including official or government agencies and scientific papers or books in English language. Unpublished data and conference proceedings were not included.

The terms or keywords used were: "vitamin D" AND ("foods" AND "bioavailability" AND ("milk", OR "juice", OR "oil", OR "bread", OR "eggs", OR "mushrooms")), OR ("absorption" AND ("food structure", OR "lipids", OR "fiber", OR "inhibition", OR "phytosterols", OR "plant stanols", OR "polyphenols", OR "enhancers", OR "interactions", OR "vitamin E", OR "vitamin K", OR "vitamin A", OR "gastrointestinal", OR "bile salts", OR "pH")), "digestion modelling", "absorption modelling". For example, for the first line of keywords presented, the term "vitamin D foods bioavalability milk" was used.

The results obtained were categorized in sections and subsections, depending on the content of each study, using Mendeley Reference Manager (Elsevier). Any duplicate papers were removed. Information was extracted and evaluated by two independent researchers. Relevance and date of publication were the two main criteria. Initial screening was conducted by one author (EP), followed by screening from two authors (EP, PV) independently. If consensus was not reached following a discussion, a third author (VP) reviewed these manuscripts and a decision was made whether to include them in this review. The final count of literature sources was 90. A diagram of the search strategy and screening is presented in (Fig. 1).

RESULTS

Fortified foods

Fortified foods are foods in which vitamin D is added externally at certain concentration. Common examples are milk, yogurt, cheese, orange juice, plant oils, flour and bread, and

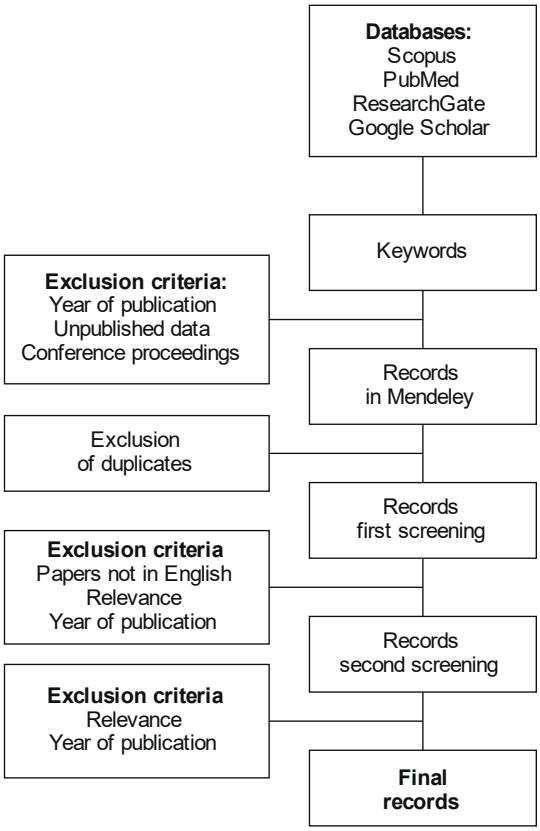

Fig. 1. Search process and screening diagram.

cereals. In Tab. 1, the studies that combine vitamin D enrichment or fortification and determination of its bioavailability are summarized. The studies presented include foods which may (e.g. mushrooms) or may not (e.g. flour) naturally contain vitamin D and have been enriched or fortified with the vitamin. The information given in Tab. 1 includes the food, the form in which the vitamin was added, the initial content of vitamin D in food and the content after fortification as well as the method of fortification (e.g. UV-B radiation). The separate column of Tab. 1 presents the bioavailability observed from consumption of the food as well as some information concerning the characteristics of each study (species in which the study was conducted, dosage and duration of study). It was evident that, except for the amount of vitamin D present in food, the type of food matrix as well as the form (D_3 or D_2) of vitamin D and the method by which is added can affect the final serum concentration. Serum concentration was, generally, proportional to the vitamin's content in food. However, when vitamin D_3 was added, the increase in total serum concentration was higher than the increase observed with D_2. This increase was even greater when the active metabolite 25-hydroxycholecalciferol ($25(OH)D_3$) was added.

Before and after vitamin D reaches consumers, it is subjected to a series of processes and exposed to various storage conditions, which may affect its stability. Heat treatment, UV- or γ-radiation, high pressure, extrusion, ripening and fermentation as well as storage conditions, such as duration, exposure to light and packaging, may affect vitamin D stability and ultimately its bioavailability. However, these parameters were out of the scope of this review, since we were focusing on food matrix factors that can affect vitamin D absorption.

Factors affecting vitamin D absorption

Matrix associated factors and component interactions

The consumption of vitamin D along with a meal has been studied in order to identify the influence of the meal in the absorption of vitamin D along the gastrointestinal tract (GIT). Mulligan and Licata [36] found that vitamin D supplementation was more efficient when consumed with the largest meal and provided a 50% increase in serum 25-hydroxyvitamin D (25(OH)D). In another study, it was found that vitamin D absorption was higher with a low-fat meal, compared to high-fat or no meal [37]. However, in a study testing the absorption of vitamin D from an oily solution, no difference was observed between fed and fast conditions [38]. The complexity of a food matrix can interfere with the release and absorption of a nutrient. The different components as well as the range of each component's content in foods, can affect vitamin D absorption to a different degree and lead to variable results among studies.

Structural factors

The structure of the food matrix may influence the bioavailability of a nutrient. Aguilera [39] reviewed the effect of food matrices on digestion processes occurring in the GIT and the interactions between food components. The chain length, the stereochemical structure as well as the degree of unsaturation of fatty acids and triglycerides can affect the digestion of lipids and the subsequent structure of mixed micelles and chylomicrons [40]. Ye et al. [41] found that the hydrolysis of fatty acids is dependent on chain length and stereochemical structure. Lipid interactions with other food components as well as the physical state of the food influence the digestion processes. Liquid foods demonstrated better bioavailability of vitamin D than solid foods [42], which may be attributed to the higher complexity and lower diffusiv-

ity of a solid matrix compared to a liquid one, as it can influence the vitamin release.

Dietary lipids

BOREL et al. [43] as well as MAURYA and AGGARWAL [44] reviewed several studies regarding the effect of fat content and concluded that vitamin D absorption was not affected by it, except for one study. However, the results of this study may not be reliable due to its type (single-blind, parallel, randomized trial-not crossover), the possible secondary parathyroidism of some of the participants as well as the observation that, after 7 days of intake of either low or high fat meal containing 50 000 IU vitamin D, the 25(OH) D, serum levels were not affected. In addition to their previous results, RAIMUNDO et al. [45], found that the consumption of 15 g or 30 g of fat led to a higher vitamin D serum level after 2 weeks. As mentioned before, DAWSON-HUGHES et al. [37] also observed a dependence between vitamin D absorption and fat content of meal, though in their study vitamin D was better absorbed with a low-fat meal. As mixed micelle formation is crucial for vitamin D absorption, lipid concentration may interfere with vitamin D absorption. Critical micellar concentration (*cmc*) must be reached for the mixed micelles to be formed. However, *cmc* of mixed micelles is not the same observed for the lipids alone, as there are other components present. Incorporation of the vitamin in mixed micelles can also be influenced by the size of micelle as well as the type of the lipids present.

BOREL et al. [43] also reviewed the effect of the type of fatty acids in vitamin D absorption. It was concluded that the type of fatty acids, regarding chain length and degree of saturation, plays an important role in the absorption of the vitamin. GONCALVES et al. [46] suggested that monounsaturated fatty acids (MUFA) increase the effectiveness of vitamin D supplementation, whereas polyunsaturated fatty acids (PUFA) reduce it. It was assumed that PUFAs increased the solubility of the vitamin and altered the partition coefficient in a manner that vitamin D was not released from the mixed micelles, or the size of the produced micelles was increased causing a reduction of the diffusion rate through the unstirred water layer. They also reported an increased chylomicron synthesis, which was attributed to the possible interaction of oleic acid (monounsaturated) with the cholesterol transporters Scavenger Receptor class B type 1 (SR-BI), Cluster Determinant 36 (CD36) and Niemann-Pick C1-Like 1 (NPC1L1) [46]. Additionally, SCHOENER et al. [47] found that vitamin D was better absorbed when encapsulated in MUFA-rich oils than in PUFA-rich oils. This was attributed to the possible obstruction of lipase action due to kinked chains of PUFA and, therefore, the formation of mixed micelles. On the other hand, DAWSON-HUGHES et al. [48] concluded that fat content increases the absorption regardless the MUFA to PUFA ratio. Furthermore, ITARIU et al. [49] showed that *n*-3 PUFA did not influence vitamin D status in obese patients and could counterbalance for the adverse effects of vitamin D deficiency. However, these results refer to obese patients and may not be applicable to healthy subjects, due to changes in metabolic parametes. NAESGAARD et al. [50] investigated the correlation between vitamin D and *n*-3 or *n*-6 fatty acids intake in patients with acute myocardial infarction. Even though they observed a prior positive correlation between *n*-3 fatty acids and 25(OH)D, the correlation was abolished after 12 months of intervention. For the *n*-6 fatty acids and vitamin D, no positive correlation was observed. These conflicting results suggest that the mechanism of vitamin D absorption and the role of dietary lipids are not yet fully understood. More studies, carefully designed to account for physiological factors as well as for food matrix and composition, should be conducted to draw safer conclusions.

Regarding chain length, GONCALVES et al. [46] showed that long chain fatty acids have a negative effect on vitamin D absorption, which was diminished when they were mixed with other fatty acids. Conversely, OZTURK et al. [51] investigated the effect of carrier oil type of nanoemulsions in vitamin D bioaccessibility and found that long chain triacylglycerols showed higher bioaccessibility of the vitamin than the medium chain ones. The authors speculated that mixed micelles derived from long chain fatty acids could more efficiently incorporate lipophilic bioactive compounds. This can be attributed to the fact that long chain fatty acids can activate chylomicron formation and ameliorate lymphatic transport [52]. YAO et al. [53] suggested that although medium chain triacylglycerols led to better bioaccessibility of a lipophilic compound, long chain triacylglycerols transported better through the lymph.

Inhibitors of fat absorption

Obesity is a clinical condition, which often requires the use of antiobesity drugs. The purpose of these drugs is to reduce the total amount of triacyglycerols and cholesterol absorbed. Due to the similarity of the absorption pathways of vitamin D and of these compounds, consumption of fat inhibitor drugs, which decrease fat absorption, may interfere with vitamin D absorption.

Orlistat, an inhibitor of gastric and pancreatic lipases, as well as olestra, a saccharose polyester used as a fat inhibitor, can reduce vitamin D absorption, as mentioned in the reviews of Borel et al. [43] and Maurya and Aggarwal [44]. Protonated nanostructured aluminium silicate (NSAS), a cholesterol absorption inhibitor, also decreased vitamin D absorption in in vitro lipolysis [54]. Recently, Tan et al. [55], investigating the effect of chitosan in vitamin D absorption within oil-in-water emulsions, found that chitosan reduced the vitamin's absorption by binding to mixed micelles and leading them to precipitation.

Some studies in mice and in vitro showed that phytosterols can impair vitamin D absorption, though clinical studies suggested that such an obstruction did not occur. However, the results of the latter studies may not be reliable, as there are factors, such as season, sun exposure or short intervention period, that can affect the outcome [43]. A meta-analysis study of randomized controlled trials concluded that vitamin D absorption was not affected by plant sterols or plant stanols [56]. Additionally, Gylling [57] found that plant stanols do not interfere with the absorption of vitamin D. Nevertheless, it was found that phytosterols can interfere with vitamin D's incorporation in mixed micelles, resulting in decreased bioavailability [58]. Concerning polyphenols, Goncalves et al. [59] found that pinoresinol, a lignan contained in olive oil, can decrease vitamin D absorption in rats and Caco-2 cells.

Multiple studies demonstrated the ability of a probiotic bile salt hydrolase-active bacterium *Lactobacillus reuteri* NCIMB 30242 to decrease cholesterol absorption. However, Jones et al. [60] studied its effect on fat-soluble vitamins and found that serum 25(OH)D increased when the probiotic supplement was consumed. The authors attributed these results to either increased intraluminal lactic acid production or increased synthesis of 7-dehydrocholesterol, or both. They also postulated that 25(OH)D changes were associated with high-sensitivity C-reactive protein changes, rather than with low-density lipoprotein cholesterol changes.

Interactions between lipophilic vitamins

Vitamins E and K are absorbed by the same mechanisms and receptors as vitamin D [61]. Therefore, it is possible that there is a competition for absorption. Vitamin E hinders vitamin D absorption in Caco-2 cell culture [62]. In the same study, vitamin K's absorption was correlated to that of vitamin D, where vitamin K's absorption was reduced. Regarding vitamin E, Hymoller et al. [63] observed that the consumption of one stereoisomer, RRR-α-tocopherol (an isomer of α-tocopherol), resulted in smaller concentration of 25-hydroxyvitamin D_3 (25(OH)D_3) in plasma of minks than *all-rac*-α-tocopherol.

Vitamin A also decreased the absorption of vitamin D, though in an unknown manner [62]. The same results were observed in minks, where high concentrations of vitamin A in the feed led to reduced 25(OH)D_3 plasma levels [63]. Interestingly, there was a differentiation in the effect of vitamin A on vitamin D, when comparing dietary to endogenous vitamin D. Endogenous vitamin D was unaffected by vitamin A, while the dietary one was reduced [64], which may indicate that there is an interaction between the mechanisms of absorption of the two vitamins.

Enhancers of vitamin D absorption

The absorption of vitamin D may be facilitated by substances such as β-cyclodextrin, β-lactoglobulin or other micelle-inducing substances. The methods used to produce these micelles were reviewed by Maurya et al. [65]. Maurya and Aggarwal [44] included in their review the results of some studies of vitamin D absorption enhancement and the possible mechanism of absorption. A capsule vehicle, consisting of bile salts and pancreatic lipase, also demonstrated enhanced bioavailability of the vitamin, compared to tablets [66]. Nanoparticles, generally, improve vitamin D bioavailability [67]. Microencapsulation of vitamin D in gelatin and cress seed mucilage micelles increased the vitamin's bioavailability [68]. Encapsulation of vitamin D in a β-lactoglobulin coagulum also increased the bioavailability of the vitamin in rats [69]. Yeast cell microcapsules were studied as a vitamin D carrier, though its bioavailability was not tested [70]. Nanoemulsions of vitamin D showed higher bioavailability than coarse emulsions [71]. Apart from the protection of the nutrient inside emulsion droplets, nanoemulsions are more stable as the droplet size is much smaller, which results in a reduction of gravity force and Brownian motion and, therefore, in a decrease in possible precipitation. Binding vitamin D in reassembled casein micelles increased the vitamin's bioavailability by protecting it from the degrading conditions encountered in the gastrointestinal tract [72]. In a recent study, vitamin D was loaded in nanostructure lipid carriers, along with raloxifene hydrochloride, and it was found that its in vivo bioavailability was better than that of the reference product used (Raloxifene hydrochloride tablets 60 mg – vitamin D capsule 800 IU) [73].

Physico-chemical interactions with gastrointestinal tract secretions

Studies regarding the effect of gastric pH and bile salts on vitamin D absorption are scarce and rather old. In their review, MAURYA and AGGARWAL [44] mentioned some in vivo and in vitro studies from 1974 to 1978 regarding bile salts concentration and pH variations. They suggested that the excessive raise in bile salts concentration leads to a decrease in vitamin D absorption, while a decrease in pH causes an increase in absorption, by changing the micelle and cell membrane surface charge.

As vitamin D is absorbed by incorporation in mixed micelles, bile acids concentration, which are components of mixed micelles, may play a key role in its absorption. Complete absence of bile salts may decrease vitamin D absorption, as micelle formation may be hindered. Therefore, bile acid concentration in the intestinal lumen is essential in vitamin D absorption. POLAT and BEYAZAL [74] tested the effect of cholecystectomy, which induces bile salts malabsorption, on vitamin D absorption and found lower serum 25(OH)D in patients than in non-patients. Vitamin D interferes with bile acids synthesis by suppressing the 7α-hydroxylase (CYP7A1) gene expression, which is associated with bile acids synthesis [75]. Another indirect interaction between vitamin D and bile salts has been found, involving vitamin D receptor. Vitamin D receptor was ligated by lithocholic acid, a secondary bile acid with high toxicity, and interfered in its metabolism, by inducing the expression of the gene coding enzyme cytochrome P450 3A4 (CYP3A), which is involved in its detoxification [76]. The interaction between lithocholic acid and vitamin D reduced its influence on vitamin D 24-hydroxylase (CYP24A), bone γ-carboxyglutamate protein (BGLAP) and tumor necrosis factor ligand superfamily member 11 (TNFSF11) gene expression, which take part in vitamin D metabolism [77]. Furthermore, vitamin D receptor activation by lithocholic acid exerts a protective effect on intestine epithelial barrier [78]. However, lithocholic acid was shown to cause vitamin D Receptor (VDR) gene expression mainly in the ileum, rather than the duodenum or the jejunum [79]. COPPLE and LI [80], in their review, mentioned several interactions observed between vitamin D, vitamin D receptor, bile acids and some genes.

Concerning gastric pH variations and the influence on vitamin D absorption, the studies are scarce, indicating the need for more research on that area. A rather old in vivo study in rats suggested that an increase in hydrogen ion concentration, which leads to lower pH, causes an increase of vitamin D absorption rate, which was attributed to the possible change of surface charge of micelles and the absorptive cell membrane [81].

Host-related factors

Host-related factors include vitamin D status of the host, gender, age, obesity or other pathological conditions as well as genetic variants. These were analysed by BOREL et al. [43] as well as MAURYA and AGGARWAL [44] in their reviews.

Modelling of digestion

Mathematical modelling of digestion can offer an affordable and quick way to predict the degradation and absorption of food and nutrients in the gastrointestinal tract, which can lead to the production of more efficiently designed fortified or enriched foods or supplements. MUTTAKIN et al. [82] reviewed several in silico models of gastric emptying and secretions as well as that of the small intestine. Modelling of small intestine was achieved through single compartment models, multiple compartment models and plug flow reactor models. VAN WEY and SHORTEN [83] reviewed the models used to describe the degradation of food in stomach.

BASTIANELLI et al. [84] developed a model for pig digestion comprised of four compartments. The first one represented the stomach, the second and third the small intestine (divided to duodenum and proximal jejunum (2nd compartment) and medial and distal parts of jejunum and ileum (3rd compartment)) and the fourth the cecum and large intestine. The compartments were divided further into a total of 44 subcompartments with homogenous digestive behaviour. The hypotheses made to develop this model were analysed thoroughly by BASTIANELLI et al. [84]. One of the assumptions made was that the digestion processes depended only on the dry matter of food. Except for the action of enzymes in the small intestine, they considered the action of the microbes located in large intestine. The equations describing digestion are presented in Tab. 2 for the stomach, small intestine and large intestine (Eq. 1–4, respectively).

The authors also implemented some equations describing the abovementioned flows. The absorption in small and large intestine were assumed to follow Michaelis-Menten kinetics. The flow of each constituent was supposed to be a portion of the dry matter flow, which was the product of the quantity of the dry matter in each compartment and the fractional rate of flow, either the dry matter flow rate or the endogenous flow rate. Degradation flow was the product of the quantity

Tab. 2. BASTIANELLI et al. [84] model equations.

Equation	No.
$\frac{dQ_{i,STO}}{dt} = AL_{i,STO} + E_{i,STO} - F_{i,STO.SI1}$	1
$\frac{dQ_{i,c}}{dt} = F_{i,bc} + D_{ji,c} + E_{i,c} - (F_{i,cd} + D_{ij,c} + A_{i,c})$	2
$\frac{dQ_{i,LIC}}{dt} = F_{i,SI2.LIC} + D_{ji,LIC} + E_{i,LIC} - (F_{i,FEC} + D_{ij,LIC} + A_{i,LIC} + U_{i,LIC})$	3
$\frac{dQ_{MIC}}{dt} = G_{MIC} - F_{MIC,FEC}$	4

$A_{i,c}$ – absorption flow of constituent i in compartment c, AL_i – alimentary flow of constituent i, $D_{ij,c}$ – degradation flow of constituent i to constituent j, $D_{ji,c}$ – degradation flow of constituent j to constituent i, E_i – endogenous flow of constituent i in each compartment, F_i – flow of constituent i from one compartment to the next one, G_{MIC} – growth of microbial dry matter, t – time, Q_i – quantity of constituent i in each compartment, $U_{i,LIC}$ – uptake of constituent i for microbial growth in the large intestine. Subscripts: STO – stomach, LIC – large intestine, MIC – microbial subcompartment in large instestine, FEC – fecal, SI1 – first compartment of small intestine, SI2 – second compartment of small intestine, c – compartment considered, b – previous compartment to compartment considered c, d – next compartment to compartment considered c.

of each constituent in the compartment and the fractional rate of its degradation flow. The growth of microbial dry matter was the product of the efficiency of microbial growth with response to glucose and the quantity of soluble sugars in the large intestine. Lastly, the uptake for microbial growth was the product of growth of microbial dry matter and the fractional rate of uptake for microbial growth.

The simplifications made for the development of this model may interfere with its accuracy in predicting the digestion outcome. The assumption regarding the dry matter does not consider the effect of water in the bolus' physico-chemical characteristics, such as variation in viscosity, therefore it cannot predict the possible effect of food structure on digestion. Viscosity may affect the gastric emptying rate (meals with higher viscosity have a lower rate) as well as the mass transfer. Also, viscosity may be variable during digestion, due to gradual hydrolysis and lipolysis of food. Chyme viscosity can affect the movement and mixing processes through peristalsis across the small intestine. Additionally, the food component interactions are not considered. As the authors mentioned, the one compartment model for stomach may not be sufficient for larger feed particles. Moreover, the model did not consider the effect of peristaltic movements and propulsion of the bolus in the small intestine. Peristaltic movement of the small intestine leads to better mixing of the chyme and, therefore, to better interaction between food components and nutrients. Neglecting the effect of peristaltic movement can result in different bolus composition, which affects the physico-chemical characteristics of the bolus and, concequently, its movement across the intestine as well as the absorption of nutrients. Furthermore, the concentration of nutrients in each compartment cannot represent the real concentrations in each portion of the small intestine. As the authors mentioned, the applicability of the model can be expanded to humans, as they are also monogastric, with some changes in its structure and different parametrization. Pig digestion is more similar to human than any other model, as its gastrointestinal tract structure and function is close to humans. However, there are some differences, such as nutrient absorption and gut microbiota [85]. Other digestion models based on pigs have been successfully used to predict human digestion [86].

TAGHIPOOR et al. [87] developed a model describing the transport and degradation of food in the small intestine, which they later tried to improve by inserting the effect of dietary fibre in degradation and absorption processes, using a system of ordinary differential equations [88]. The model contained an equation of transport of the bolus inserted in the small intestine, which included the effect of pulses in the motility of the bolus through the small intestine (Eq. 5 and Eq. 6 in Tab. 3). There, $x(t)/c$ is the time required for a pulse to reach the bolus in the position $x(t)$, which is produced in time $(t - x(t)/c)$, c_0 and c_1 are determined under the assumption that the acceleration depends linearly on $v(t)$, a and b are constants, values of which result from experimental data. The last term represents the friction occurring in the small intestine, which is related to the viscocity of the bolus.

Digestion procedures were modelled based on some simplifications. The bolus was per-

ceived as a cylinder of length l and variable radius $R(t)$, which was located in the small intestine by the position $x(t)$ of its center. The mass of the bolus (A) consisted of four parts, the solubilized part (A_s), the non-solubilized part (A_{ns}), the non-digested part (A_{nd}) and water (W) – $A = A_s + A_{ns} + A_{nd} + W$. A_s and A_{ns} are connected through Eq. 7 (Tab. 3).

They also implemented Eq. 8–11 (Tab. 3). Eq. 8 represents the variation in the proportion of water in the bolus. Eq. 9 represents the variation of the solubilized part of the bolus. The first term represents the equilibrium of the insoluble part. The second term represents the enzyme activity, which depends on pH and on the presence of enzymes at each time point. The third term represents the volumic and surfacic degradation, while the fourth one the influence of intestinal secretions in the bolus.

Eq. 10 represents the variation of the absorbable nutrients, which depends on the enzymatic hydrolysis of A_s and B_{int} (first term) and its absorption through the intestine (second term). B_{abs} emerges from either the volumic degradation of A_s to B_{int} (and the subsequent surfacic degradation of B_{int} to B_{abs}, or the direct surfacic degradation of A_s to B_{abs}. The absorption of the nutrients is represented by a Michaelis-Menten mechanism. $K(t)$ represents the lubrication of the bolus, which depends on the proportion of water in the bolus.

The authors also developed a model in which they simplified the transport equation, by averaging out the pulses that reach the stomach. The model had good correlation with experimental data. However, the model contained some extra simplifications, such as neglecting the spatial aspects as well as the different components of food. The latter can interfere with absorption processes, as they can change the viscocity of the bolus as well as the action of enzymes. Different enzymes catalyse different reactions thoughout digestion. The components and their concentrations may interfere with the enzymes activity, as obstructions may occur, either due to the ability of the enzyme to reach a particular molecule, or due to the competition for binding. Furthermore, mixed micelles

Tab. 3. Taghipoor et al. [87] model equations.

Equation	No.
$\frac{d^2}{dt^2}x(t) = \frac{d}{dt}[y(t - x(t)/c)]\frac{c_0 + c_1 V(t)}{a + bx(t)} - K(t)\frac{dx}{dt}(t)$	5
$\frac{dx}{dt}(0) = v_0, x(0) = 0$	6
$\frac{dA_{ns}}{dt} = -k_s(\mu([W])A_{ns} - A_s)$	7
$\frac{d[W]}{dt} = -k_W([W] - [W_0]) + \ln(1.\beta)\frac{1}{a}\frac{dx}{dt}\chi((x(s) - 0.85)/\alpha)[W]$	8
$\frac{dA_s}{dt} = k_s(\mu([W])A_{ns} - A_s) - Ck_{(x,e)}A_s(t) - 2C_{abs}\sqrt{\frac{\pi l}{\rho}}\frac{A_s}{(A_s + A_{ns} + A_{nd} + B_{int} + W + B_{abs})^{1/2}}[W] + + \ln(1.25)\frac{1}{a}\frac{dx}{dt}\chi((x(s) - 0.85)/\alpha)A_s$	9
$\frac{dB_{abs}}{dt} = 2\sqrt{\pi l/\rho}\frac{C_{abs}A + C_{iabs}B_{int}}{(A_s + A_{ns} + A_{nd} + B_{int} + W + B_{abs})^{1/2}}[W] - k_{abs}\frac{B_{abs}}{k + B_{abs}}$	10
$K(t) = \frac{\widetilde{K}}{[W](t)}$	11

a – distance travelled by the bolus in which the secretions stop, A_{nd} – non-digested part of bolus, A_{ns} – non-solubilized part of bolus, A_s – solubilized part of bolus, b – constant obtained from experimental data, B_{abs} – directly absorbable product, B_{int} – intermediate product, product of volumic hydrolysis, β – percentage of the mass of secretions in comparison to the bolus mass, c – average velocity of peristaltic waves of the small intestine, c_0, c_1 – constants that are determined under the assumption that the acceleration depends linearly on the volume of the bolus, C – degradation rate, C_{abs} – degradation coefficient per unit of surface and time for A_s, C_{iabs} – absorption coefficient per unit of surface and time for B_{abs}, k – Michaelis-Menten constant, k_{abs} – maximal rate of absorption at saturation, k_s – consant representing the return to equilibrium, k_W – equilibrium constant, $k_{(x,e)}$ – enzyme activity, depends on pH of small intestine and presence of enzymes at each point along it, K – friction coefficient, $\widetilde{K}$ – constant, l – bolus length, μ – linear function of water, ρ – bolus density, s – bolus position between 0.85 cm and (0.85 + a) cm, t – time, v_0 – bolus velocity in $x = 0$, V – volume of bolus, W – mass of water in the bolus, $[W]$ – proportion of water in the bolus, $[W_0]$ – proportion of water in bolus in equilibrium, χ – localization function which represents that the secretions arrive in the small segment of the intestine between 0.85 cm and (0.85 + a) cm.

derive from digestion products, consequently food components are of great importance for their formation and subsequent absorption. In a later work, Taghipoor et al. [88] incorporated in their previously developed model the effect of dietary fibre, and its water holding capacity, on the composition of the bolus and the degradation as well as absorption processes. Some aspects, such as the interactions between various food molecules or the dependence of enzyme activity on the composition of the bolus, were neglected.

Moxon et al. [89] developed a model in which the stomach and small intestine were approached as a continuous stirred tank reactor (CSTR) and a plug flow reactor (PFR), respectively. The model was based on glucose metabolism and is represented by Eq. 12 and Eq. 13 in Tab. 4. The first term of Eq. 12 represents the gastric emptying rate, the second term represents the movement across the small intestine due to advection and the third is the absorption of glucose. The mass transfer coefficient K is calculated using Eq. 14,

Tab. 4. Moxon et al. [89] model equations.

Equation	No.
$\frac{\partial G(z,t)}{\partial t} = \begin{cases} \gamma G_s - \bar{u}\frac{\partial G(z,t)}{\partial z} - \frac{2f}{r_m}KG(z,t), & \text{if } z = l_0 \\ -\bar{u}\frac{\partial G(z,t)}{\partial z} - \frac{2f}{r_m}KG(z,t), & \text{otherwise} \end{cases}$	12
$G(z,0) = 0, \quad \left.\frac{\partial G}{\partial z}\right\|_{z=0} = \left.\frac{\partial G}{\partial z}\right\|_{z=L} = 0$	13
$K = 1.62\left(\frac{\bar{u}D^2}{Ld}\right)^{1/3}$	14
$\frac{\partial S(z,t)}{\partial t} = \begin{cases} \gamma S_s - \bar{u}\frac{\partial S(z,t)}{\partial z} - \frac{V_{max}S(z,t)}{K_m + S(z,t)}, & \text{if } z = l_0 \\ -\bar{u}\frac{\partial G(z,t)}{\partial z} - \frac{V_{max}S(z,t)}{K_m + S(z,t)}, & \text{otherwise} \end{cases}$	15
$\frac{\partial G(z,t)}{\partial t} = -\bar{u}\frac{\partial G(z,t)}{\partial z} + \frac{V_{max}S(z,t)}{K_m + S(z,t)} - \frac{2f}{r_m}KG(z,t)$	16

d – diameter of small intestine, D – diffusivity of glucose, which is derived from Einstein-Stokes equation and is inversely proportional to the viscosity of the bolus, f – increase in the absorptive surface area due to villi and microvilli present in the small intestine, γ – decay constant expressed as the half emptying time ($t_{1/2} = \ln(2)/\gamma$), G_s – mass of glucose in the stomach, $G(z,t)$ – glucose concentration in the small intestine at time t and distance z, K – overall mass transfer coefficient, K_m – Michaelis-Menten constant, l_0 – position of bolus entrance, L – length of small intestine, $(2/r_m)$ – ratio of surface area to volume of a cylinder, which approaches the small intestine, S_s – mass of starch in the stomach, $S(z,t)$ – starch concentration at time t and distance z, t – time, $\bar{u}$ – mean velocity along the small intestine, V_{max} – maximum rate of Michaelis-Menten equation, z – distance.

which emerges from the correlation of Sherwood number to Reynolds and Schmidt numbers.

The authors further developed a model, in which they assumed that glucose is produced from the hydrolysis of starch in the small intestine, which is achieved through Michaelis-Menten kinetics. That model is represented by Eq. 15 and Eq. 16 in Tab. 4. Eq. 15 represents the change in starch mass $S(z,t)$ with time and Eq. 16 the change in glucose mass with time. The model described above has some limitations due to the simplifications made. The gastric processes, other than the emptying in the small intestine, were not considered. Furthermore, the model was developed based on a liquid meal and not considering the complexity of a solid meal. As the authors mentioned, the characteristic emptying, the mass transfer rate and the reaction rate were assumed independent of the others, though in reality changes in viscosity of a meal may influence the gastric emptying and mass transfer of nutrients and enzymes.

Later, Moxon et al. [90] tried to link the gastric emptying rate to chyme viscosity and nutrient feedback mechanism. Furthermore, the interaction between food components as well as the inhibition of enzymes by additives can affect the absorption of nutrients. The effect of mixing due to peristaltic contractions was not considered, as the model was developed through the assumption of laminar flow.

The aforementioned models are examples of the efforts made to mathematically describe digestion. In respect to vitamin D, these models may constitute a starting step. However, vitamin D is mainly absorbed through lacteals. During digestion, vitamin D is incorporated in mixed micelles, consisting of phospholipids, cholesterol, lipid digestion products and bile salts, and is absorbed through the enterocyte, where mixed micelles are disassembled and reassembled into chylomicrons, consisting of triacylglycerols, cholesterol, phospholipids and apolipoproteins. Therefore, the formation as well as the absorption kinetics of mixed micelles should be considered in order to better predict the outcome of vitamin D consumption. Incorporation of micelle formation and absorption in digestion modelling can lead to a model applicable in vitamin D absorption through the gastrointestinal tract. Furthermore, vitamin D absorption is mediated by intestinal cell membrane proteins (SR-BI, CD36, NPC1L1) [62], at the apical side of the enterocyte. These proteins participate in the absorption of cholesterol and other lipophilic nutrients, therefore antagonism for absorption may occur, which could be considered to further improve the model.

CONCLUSIONS

Bioavailability of vitamin D from fortified foods is crucial because vitamin D plays an important role in human health, especially for people in more vulnerable groups, such as the elderly. This review focused on presenting the available information on the effect of food matrix or composition and GIT on vitamin's D bioavailability and on the available mathematical approaches to modelling the digestion process, focusing on recent data. Various studies concluded different results concerning the quantity of vitamin D contained in food. The differences could be attributed to many factors, such as the different species existing between the same food category, the access to sunlight, the feed of animals intended for consumption as well as the different techniques used to detect vitamin D. To our knowledge, the studies investigating both the amount contained in foods and the bioavailability of the vitamin are summarized in Tab. 1. It is evident that, except for milk, there are only a few studies for the other types of food. The food matrix as well as vitamin's content, form (D_3, D_2) and physical state (crystalline, emulsion or other) can affect the resulting bioavailability. Vitamin D deficiency has surfaced as an important health issue even in the developed world and becomes of paramount importance nowadays due to the potential role it can play against Covid-19. More research is needed in order to connect bioavailability of vitamin D to the food matrix as well as how it can be enhanced by food processing.

The release of a nutrient from the food matrix is highly connected to its bioaccessiblity. It is influenced by the food component interactions and structure of food matrix as well as the conditions encountered along GIT. This review revealed parameters that need further research including the physical state of the food in combination with its composition. Little information is available on the effect of dietary fibre in vitamin D absorption and no information is available on its possible interaction with dietary proteins. Furthermore, little information is available regarding vitamin's D bioavailability in fortified gel-like or emulsion-type foods. Finally, more attention should be given to the physico-chemical interactions along GIT, such as the interactions between vitamin D and GIT's secretions and particularly to the effect of pH variations encountered.

After the release from food matrix, the incorporation in mixed micelles and chylomicrons and the absorption of chylomicrons through the enterocytes is of great importance, too. The mathematical modelling of these processes, along with the processes concerning digestion, starting from the oral cavity down to small intestine, may greatly contribute to predicting vitamin D bioavailability and lead to better design and production of enriched or fortified foods or planning of supplementation dosage.

The models for digestion presented in this review contain certain limitations. The simplifications made by the models can affect the results and their predictive ability. Factors concerning food, such as the different components and their interactions, the structure and complexity of the food matrix and the viscosity as well as factors concerning the physiology of GIT, such as the absorption sites of the nutrient, enzyme activity, the secretions and pH conditions along GIT and the peristaltic movement of the intestine, play a crucial role and should be considered in modelling the digestion process. Further studying and incorporation of these parameters in a model could enhance its accuracy and predictive ability.

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