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REVIEW PAPER

Factors influencing the absorption of vitamin D in GIT: an overview

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Abstract Vitamin D refers to a group of secosteroid compounds and recognized as the antirachitic vitamin, as it counters rickets, mineral desorption from fully-grown bones (Osteodistrophy), bone, joint disorders, and fragility of bones. On one hand, there is scarcity of vitamin D rich food while on other hand a number of factors negotiate its absorption efficiency in human gastrointestinal tract (GIT). These factors include variations in the physiochemical state of the vitamin D (molecular forms, potency and their physiological linkages), the complexity of food matrix (the amount and type of fatty acids, dietary fibers and presence/absence of vitamin D enhancer and inhibitor), and its interaction of other fat soluble compounds with vitamin D as well as the host-associated factors (age, disease, surgery, obesity, genetic variation etc.). It is hypothesized that the bioavailability of vitamin D in GIT is compromised if there changes within these factors. Present article is intended to review the contribution of these factors anticipated to be influencing vitamin D absorption in GIT.

Keywords Vitamin D · Ergocalciferol · Cholecalciferol · Vitamin D_2 · Vitamin D_3 · Bioavailability · GIT

Introduction

Vitamin D is the generic name for a group of compounds imparting antirachitic functions. Although vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are the two major physiological forms of vitamin D but vitamin D_3 is considered as major dietary source for vitamin D. A significant portion of vitamin D (estimated around 80% but varies with sun exposure) is synthesized endogenously in the skin from 7-dehydrocholecalciferol as the function of UV light. While 25-hydroxy cholecalciferol and 1, 25-dihydroxycholecalciferol are source of vitamin D from diet. The liver oil and flesh of fatty fish are the best known source of vitamin D. It can also be obtained from beef liver, dairy product, egg yolk in small quantity. The few sources of plant origin are also reported such as mushrooms and it is present in form of vitamin D_2 (ergocalciferol).

Particular population subsets such as neonates, elderly person (not adequately exposed sun radiation), patient (affected by fat metabolism and genetic variations in protein associated to vitamin D uptake in intestine) obligated to get vitamin D from supplements and fortified food in order to meet the recommended daily allowance (RDA) and to retain plasma 25(OH)D level above 30 ng/ml (Wimalawansa 2012). Mechanism of vitamin D absorption and the factors suspected to influence the absorption process have been reviewed by the time. Vitamin D seems to follow league of lipid metabolism in human GIT thus it is assumed that fat does influence the fate of vitamin D. Moreover, vitamin D is diffused in chylomicron which does facilitate its transportation to liver. It seems that the bioavailability of vitamin D is a function of various factors such as absorption, transportation and metabolism.

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Bioavailability

It is defined as the proportion of ingested amount (total vitamin in food) which ultimately ends up in the systemic circulation. It is significant to illustrate the major factors limiting the bioavailability of lipophilic bioactive compounds since this information may help in the designing the efficacious excipient foods (Fig. 1).

Bioavailability of lipophilic agents

The knowledge about how vitamin D released from food matrix and absorbed in GIT (Fig. 4), can help in designing the efficient delivery system. For any lipophilic agent incorporated in food, the bioavailability (F) could be defined as

$$F = F_B \times F_T \times F_M$$

where F_B: Bioavailability coefficient/proportion of the lipophilic agents which released from food matrix into the gastric juice in GIT, F_T: Transport coefficient/ratio of the release lipophilic agent which is transported through the intestinal epithelium, F_M: The proportion of the lipophilic agent that reaches the blood circulation without being metabolized, The F_M depends on the route taken by lipophilic agent to reach the blood circulation. Before reaching the systemic circulation these lipophilic vitamins transported through the portal vein system and metabolized in liver (Drevon 1991).

Vitamin D status in GIT

The fate of the vitamin D in GIT is monitored by those factors which have been intimately involved with major lipid (phospholipid and triglycerides) (Tso and Fujimoto 1991). These involve emulsification, dissolution in micelles, diffusion through the stagnant water layer and penetration across enterocytes membranes. The future of vitamin D in GIT seems to be a multistep process including physiochemical as well as enzymatic involvement (Fig. 2). The acidic pH of gastric juice may affect the bioavailability of vitamin D. It is apparent that no data available on the susceptibility of major dietary forms of vitamin D to GIT pH conditions. Further, a hypothesis can be made that protein digestive enzymes (pepsin and trypsin) are also intimately involved in vitamin D absorption as they cleave vitamin D binding proteins present in food and thus facilitate its release. Further, in duodenum digestive enzyme (amylases, lipase and protease) continues the release of vitamin D from food matrix.

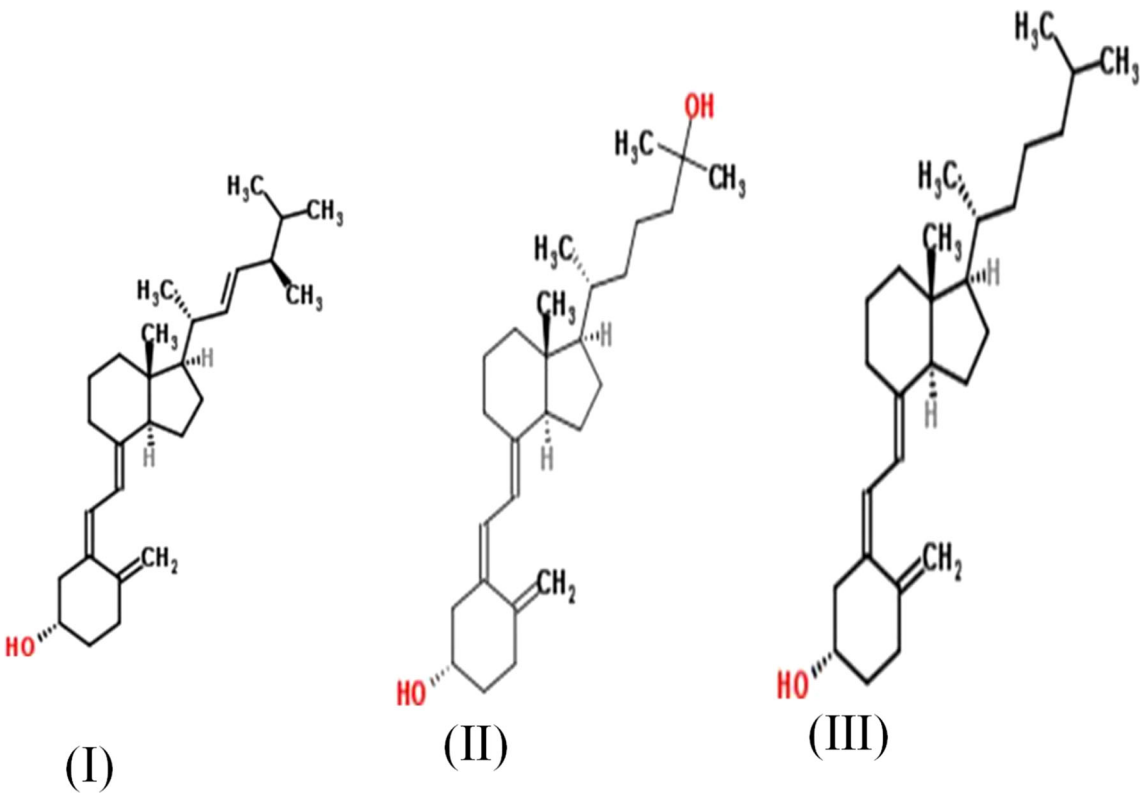

Fig. 1 Chemical structures of naturally occuring dietary forms of vitamin D (*I*) Cholecalciferol, (*II*) 25(OH) cholecalciferol, and (*III*) ergocalciferol

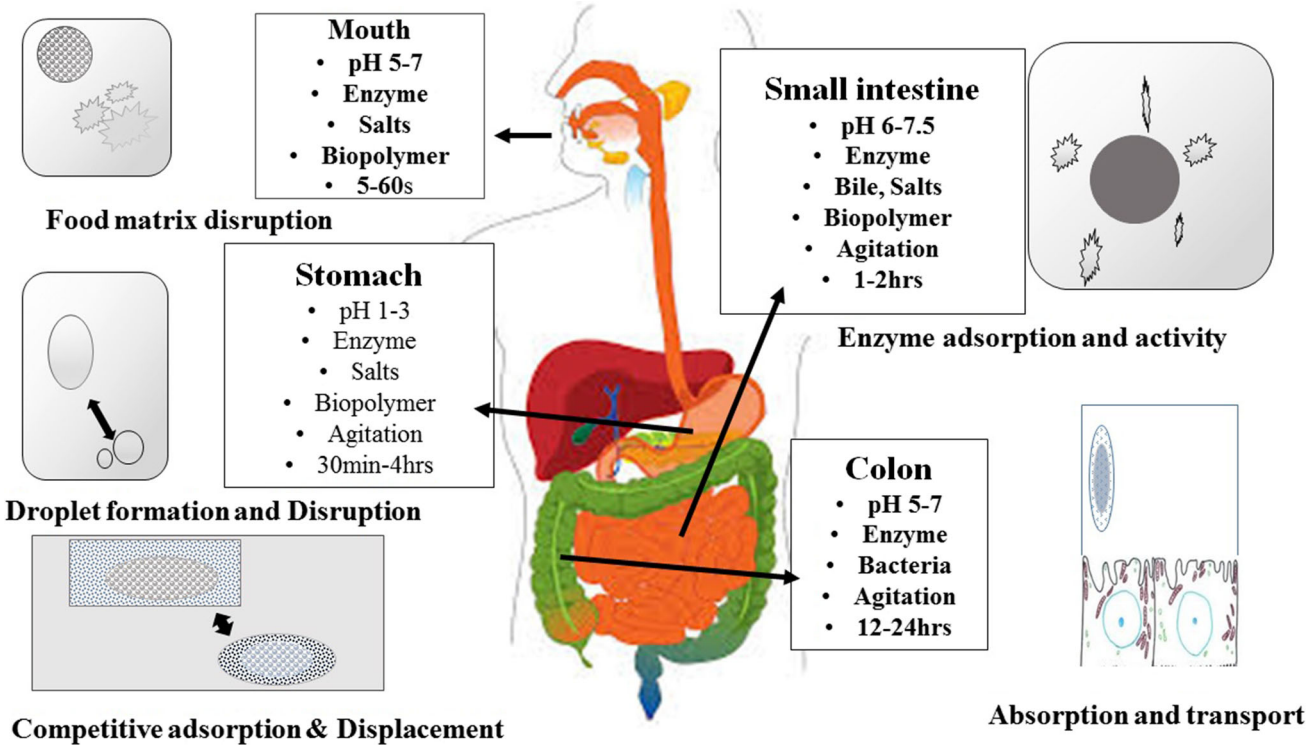

Fig. 2 Schematic diagram of the human digestive system and the various physiochemical and physiological processes involved in digestion and absorption of vitamin D

Mechanism of vitamin D absorption

The mechanism of absorption of nonhydroxylated species of vitamin D (i.e. vitamin D_2 and vitamin D_3) are suspected to be medicated by an unsaturable passive diffusion process. Furthermore, recent studies on human intestinal cell line $CaCO_2$ (Caucasian colon adenocarcinoma) and HEK (Human embryonic kidney) transfected cells clearly demonstrated the intimacy of intestinal cell membrane protein in the absorption of these nonhydroxylated forms at the border side of the enterocytes. Absorption of cholesterol and other lipophilic compounds (tocopherol, carotenoids) is also facilitated by these proteins which are SR-BI (scavenge receptor class B type 1), CD 36 (cluster Determinant 36) and NPC1L1 (Neimann-Pick C1-Like 1).

The observations made from these proteins postulate that there is a mode shift in absorption of vitamin D from protein mediated transport to passive diffusion, depending on the concentration of vitamin D: protein mediated transport at low concentration (dietary concentration of vitamin D) and passive diffusion at high concentration (pharmacological concentration) (Reboul et al. 2011). Further, the difference in vitamin D uptake between jejunum and duodenum clearly indicates the presence of another transporter particularly expressed in the jejunum (Goncalves et al. 2015). Conversely absorption efficiency of hydroxylated forms of vitamin D is significantly higher than that of the nonhydroxylated forms but there is not a single report dealing with uptake mechanism of hydroxylated species of vitamin D. A Figure 3 is depicted to summarize the available literature on vitamin D bioavailability.

Possible variables influencing absorption of vitamin D

Vitamin D needs to be released from food matrix, in which it is physically or chemically bound, in order to get accessed to enterocytes and get absorbed in human GIT. It is hypothesized that absorption efficiency of vitamin D is controlled by a syndicate of factors.

Status of vitamin D in food

It is believed that the vitamin D, synthesized in skin, alone suffice to meet the daily vitamin D requirement but there are profound evidence that sun exposure does not fulfil RDA of vitamin D which could be due to variation in sun exposure depending on atmospheric components, clothing, skin pigmentation, age, obesity, latitude, season and time of day. This obligates patient to get vitamin D via dietary sources to meet the RDA. The major dietary vitamin D comprised of vitamin D_2 and vitamin D_3 that could be

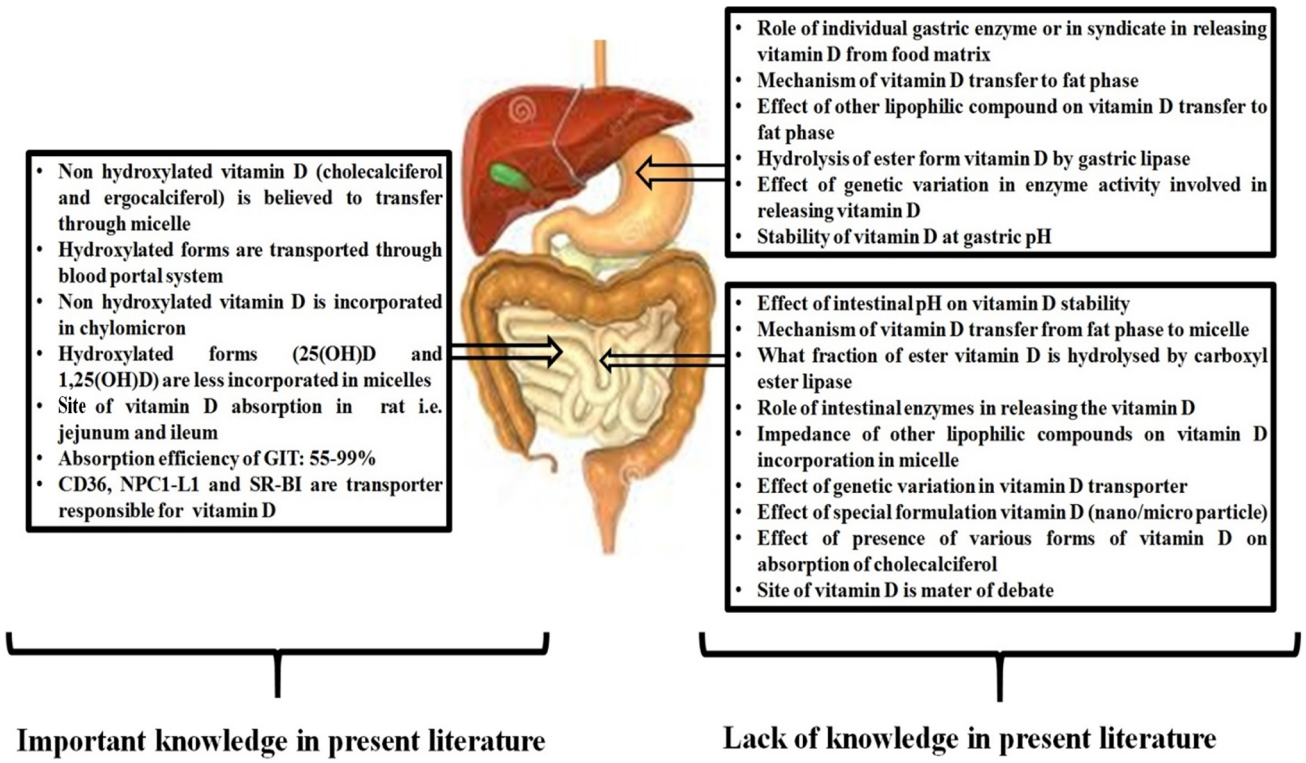

Fig. 3 Summary of important information and lack of information on vitamin D status in GIT

derived from pharmaceutical supplements, fortified foods or foods from plant or animal origin. Diet and cutaneous in vivo synthesis are being two lateral routes for vitamin D needs to be highly regulated by each in order to avoid the overriding of vitamin D in body. To avoid the overdosing, the 1997 RDA standing committee of the US Department of Agriculture, therefore, have recommended various vitamin D dose depending upon the age i.e. 200 International Unit/day (IU/day) for children, 400 IU/day for adults and 600–800 IU/day for elders (70 years). Further, Food and Nutrition Board declared 2000 IU/day as the upper limit to be safe to consume. Due to lack of representative survey data, it is hard to estimate vitamin D daily intake accurately as the food consumption pattern varies with social economic status. A study carried out to speculate the daily intake of vitamin D via food alone and combining supplements and foods. The daily intake of vitamin D was found to be 153–213.6 IU (African American), 174–278 IU (White American), 158–251.6 IU (Mexican) via food alone while 209.6–330 IU (African American), 258.8–383.2 IU (white American) and 227.6–320.4 IU (Mexican via combining supplements and foods (Calvo et al. 2004). In addition to this, several excellent studies clearly suggest that the daily vitamin D intake via food alone and combining food and supplements, differs with target population and the food consumption pattern (Calvo et al. 2005; Moore et al. 2005).

Molecular forms of vitamin D: vitamin D_2, vitamin D_3 and 25(OH)D

Vitamin D_2, vitamin D_3 and hydroxylated vitamin D (25(OH) D_3) contribute significantly in dietary vitamin D and in combination referred as total dietary vitamin D. Molecular structure is recalled in Fig. 1. The absorption of vitamin D is facilitated by protein mediated transport depending upon its concentration and the affinity of these transporters which may vary depending upon the molecular forms of vitamin D (Fig. 4).

Bioavailability and potency of various forms of vitamin D

The first report comparing bioavailability of vitamin D_2 and vitamin D_3 was produced by injecting a high dose of 5000 IU in male subjects and it was observed that they follow same pattern in elevating the serum 25(OH)D level. From this study it can be hypothesized that there is no intestinal discrepancy between absorption efficiency of these two forms of vitamin D. The data produced by further studies followed similar pattern in elevating serum vitamin D level when vitamin D_2 and vitamin D_3 were administrated through vitamin D fortified orange juice or through vitamin D supplement.

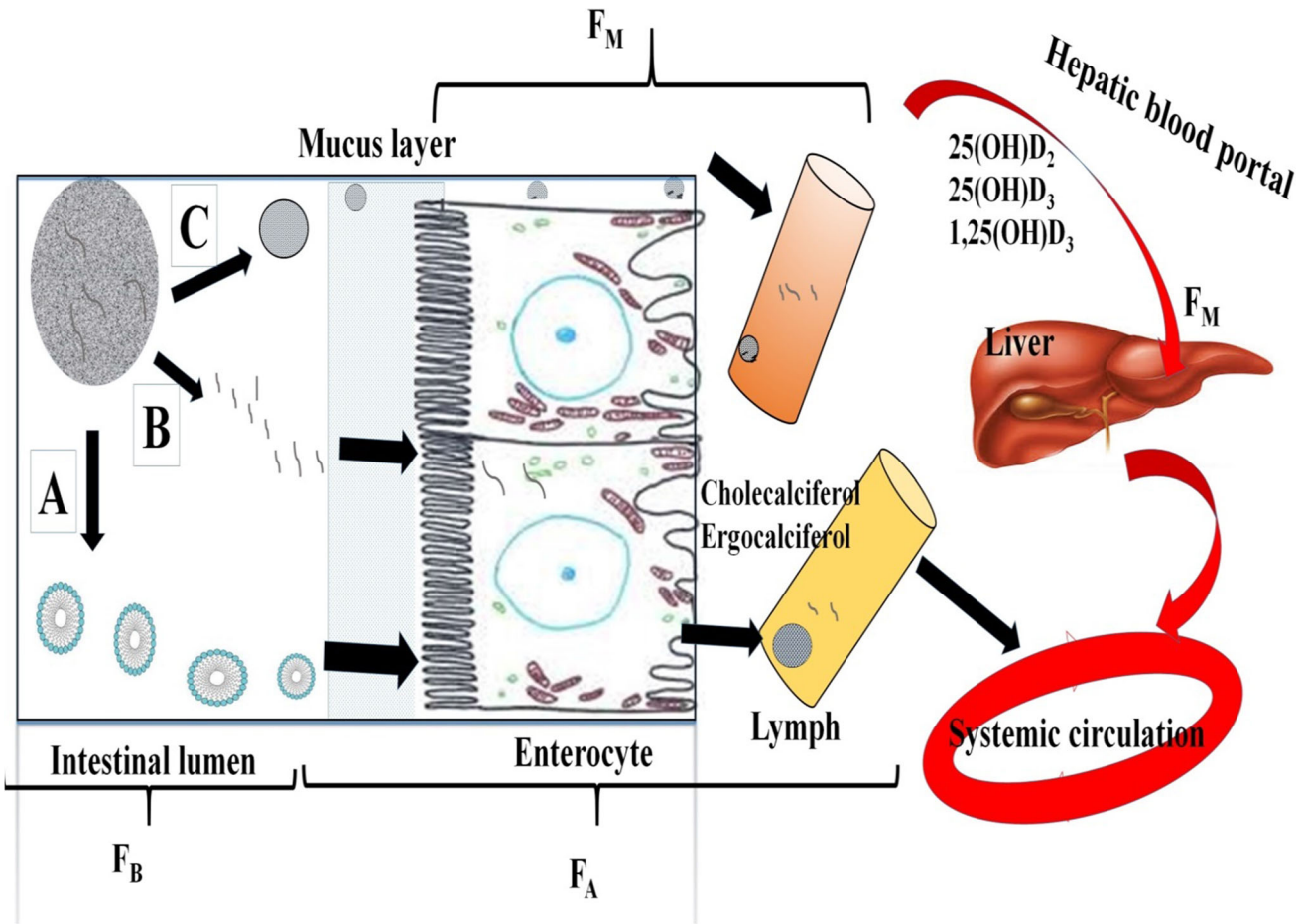

Fig. 4 The bioavailability of lipophilic agent. Where, F_B: bioavailability coefficient/proportion of the lipophilic agents which released from food matrix into the gastric juice in GIT, F_T: Transport coefficient/ratio of the release lipophilic agent which is transported through the intestinal epithelium, F_M: The proportion of the lipophilic agent that reaches the blood circulation without being metabolized

The variation in potency of vitamin D_2 and vitamin D_3 to enhance the serum vitamin D level could be due to high metabolism and clearance of vitamin D_2 than that of vitamin D_3 in liver and kidney respectively. In order to avoid the influence of these organs (kidney and liver) intestinal cell line $CaCO_2$ cell were used and similar absorption efficiency was documented for both vitamin D_2 and vitamin D_3 in these cells.

Hydroxylated versus non hydroxylated vitamin D: Bioavailability and potency

Apart from vitamin D_2 and vitamin D_3, hydroxylated vitamin D (25(OH) D_3) also contributes significantly in dietary vitamin D if food derived from animal origin. Further, the literature reports about the higher bioavailability of vitamin D if it is administrated in hydroxylated form (25(OH)D_3) than that of the non hydroxylated forms (vitamin D_2 and vitamin D_3). However, the relative bioavailability of nonhydroxylated (vitamin D_2 and vitamin D_3) and hydroxylated (25(OH)D_3) forms of vitamin D is well documented. Several reports suggest that the higher bioavailability of hydorxylated vitamin D (25(OH)D_3) could be due to greater retention than that of non nonhydroxylated vitamin D (vitamin D_2 and vitamin D_3).

The difference in their polarity (polar-hydroxylated form and nonpolar-nonhydroxylated form) may contribute to their biological equivalence inconsistency. From these results an assumption can be made that the mechanism absorption and storage for nonhydroxylated and hydroxylated vitamin D significantly varies. The hypothesis was tested on the patient suffering from lipid metabolism by administrating hydroxylated and nonhydroxylated vitamin D and it was found that bioavailability of hydroxylated form (25(OH)D_3) is 10 times greater than that of the non hydroxylated forms (vitamin D_2 and vitamin D_3) vitamin D.

Physiochemical linkage of vitamin D

The patients suffering from vitamin D deficiency are bound to consume vitamin D via pharmaceutical supplements and fortified food. Calcitriol (25-hydroxyvitamin D), calcidiol (1,25- dihydroxyvitamin D), cholecalciferol (previtamin D_3), ergocalciferol (previtamin D_2) and 7-dehydrocholecalciferol (provitamin D) are the major pharmaceutical supplements available in market with various brand names. Calcitriol (25-hydroxyvitamin D) is considered as most active form while calcidiol (1,25- dihydroxyvitamin D) is an inactive form of vitamin D which helps in storage of vitamin D in tissue. Further, vitamin D_2 and vitamin D_3 are precursor of the active vitamin D. These various form of vitamin D supplements are supposed to follow the same route in GIT as they share same physiochemical behavior. Nevertheless, there is scarcity of data addressing the relative absorption of these supplements in GIT. These supplements are designed to exhibit high bioavailability of vitamin D. The bioavailability of vitamin D in oil vehicles is greater than that of powder-based vehicles such as starch and cellulose. In contrast to this the bioavailability of vitamin D in lactose capsule is higher than that of oily drop formulation. These supplements are made by changing physical properties (encapsulation of vitamin D) as well as chemical alteration of vitamin (vitamin D ester and salt).

The effect of physical modification such emulsification, encapsulation and nanoparticle of vitamin D is well documented and it was found that these physical modifications make vitamin D more accessible to enterocyte and helpful to penetrate the lipid bilayer thus enhancing the absorption efficiency. But very scant data is available addressing the chemical modification (ester and salt of vitamin D).

Though the absorption of vitamin D is facilitated by protein mediated/passive diffusion transport depending upon the concentration of vitamin D, therefore the variation in these protein transporters and vitamin D receptors may change their structure thus their affinity to vitamin D. But there is no data present addressing this issue. The difference in affinity of VDR Vitamin D Receptor (VDR) between vitamin D_2 and vitamin D_3 suggests the involvement of some other mechanism of transport which yet to be discovered. Furthermore, there is not a single data produced how concentration of vitamin D_3 can affect the affinity of these protein transporters to vitamin D_2 and vice versa.

Food matrix and its complexity

Since food is multitude of nutrients and their supportive matrix in which these nutrients are embedded. Before absorption vitamin D need to be released from its matrix and get accessible to enterocytes. An assumption can be made that the bioavailability of vitamin D is affected by amount of ingested food and its complexity.

Amount of ingested food in meal

This factor has not been discussed much in present literature. Recently one study reported the improvement of vitamin D (vitamin D_2 and vitamin D_3) absorption with the largest meal of day and in consequences about a 50% rise of serum level of 25(OH)D. The data obtained from this study could be result of either high secretion of digestive enzymes (after heavy meal) or some specific food components (Mulligan and Licata 2010). These results were not reproduced when subjects were served vitamin D with and without food (Wagner et al. 2008). More supplementary studies are required to understand the effect of food amount on bioavailability of vitamin D.

Food matrix

Vitamin D needs to be extracted from the food matrix in which it is embedded in order to get bioavailable to enterocytes i.e. need to solubilize in micelles and accessible for absorption. It is essential to determine the bioavailability of food in which vitamin D is delivered. Though several foods (fortified such as bread, milk, meat, orange juice, vegetable oil, other dairy products and naturally rich in vitamin D i.e. meat, fish oil, mushroom etc.) have been used as potential candidate for vitamin D vehicle. But it is remarkable that the bioavailability of these foods is not well reported.

When vitamin D was supplied through meat, its bioavailability was estimated to be 60% as compared to vitamin D supplement. The vitamin D_2 from UV radiated mushroom was also tested. The reports on two mushrooms (*Lentinula edoes* and *Agaricus biosporus*) suggest the high bioavailability of its vitamin D (Jasinghe et al. 2005; Koyyalamudi et al. 2009) but their bioavailability were not compared with any other food matrix. Furthermore, the 25(OH)D serum level was higher in group 1 and group 2 when 27 subjects, randomized in 3 groups each having 9 persons, were assigned to receive no supplementation (group 3), 14 µg vitamin D_2/day (group 2) through pharmaceutical formulation and mushroom containing 14 µg vitamin D_2/day (group 1) in lunch for 3 weeks, excluding Saturdays and Sundays (Outila et al. 1999). These results were further supported by a five week single blinded, randomized, placebo controlled study in 26 healthy Caucasian adults with 25(OH)D serum level below 20 ng/ml (Urbain et al. 2011). Further the trials, conducted by serving capsules containing 2000 IU vitamin D_2, 2000 IU vitamin D_3 or 2000 IU mushroom vitamin D_2 (dried white extract of button mushroom or Monterey mushrooms),

demonstrate that the mushrooms containing vitamin D_2 have similar biological equivalence as supplemental vitamin D_2 and vitamin D_3 (Keegan et al. 2013).

Results of clinical study demonstrate no significant difference in rise of total 25(OH)D serum levels in healthy subjects who were served orange juice (fortified with 1000 IU of vitamin D_2 or 1000 IU of vitamin D_3) as compared to ingesting a supplement containing either 1000 IU of vitamin D_2 or 1000 IUs of vitamin D_3 (Biancuzzo et al. 2010). The high bioavailability of vitamin D in mushroom was confirmed by several studies (Calvo et al. 2013; Ko et al. 2008). It is remarkable that the difference in food matrix does not impose any variation of bioavailability of vitamin D and it was found as effective as vitamin D_3 supplements in increasing the 25(OH)D serum level (Natri et al. 2006). These results were supported by another study when vitamin D_2 rich yeast were baked in bread (Hohman et al. 2011).

Dietary lipids

In general lipids are most widely used vitamin D delivery medium and considered crucial for fat soluble micronutrients. It facilitates the absorption lipophilic components of food through a multisequence process. First lipids mediate diffusion of these fat soluble food components from food matrix as it behaves as hydrophobic phase within which fat soluble nutrients get solubilized. Then these lipids stimulate the secretion of bile juice resulting into micelle formation. In next step the digestive enzymes catalyze the lipids and release fatty acid, monoglycerides and phospholipid which again generate more micelles available for lipophilic nutrients to solubilize (Hofmann 1963). At last these lipids mediate lipophilic nutrients out the enterocyte avoiding the accumulation of vitamin D in enterocytes thus increasing the vitamin D absorption in GIT. These steps depend on the amount of fat (triglycerides), type of triglycerides, amount of phospholipids, types of phospholipids etc.

Amount of lipids (triglycerides)

This factor is believed to be important because it is hypothesized that vitamin D absorption is facilitated by lipid. Several studies are conducted to verify this hypothesis (Johnson et al. 2005; Weber 1980). In contrast, the absorption rate of vitamin D was found to be decreasing when rats were served with 2.5 mM fatty acid differing in chain length and degree of saturation (Hollander et al. 1978). When the bioavailability of vitamin D was evaluated in two beverages (orange and milk), it was noticed that the lipid content of milk does not significantly affect the bioavailability of vitamin D (Tangpricha et al. 2003). Similar results were obtained in the case of two vitamin D fortified foods (cheddar cheese with 33% fat and low fat cheese 7%) (Wagner et al. 2008). These results were reproduced by two multivitamin supplements (one supplement with vitamin D in tablet and other vitamin D in fish oil) (Holvik et al. 2007). Recently a team of researchers has also disbanded this hypothesis when they observed, the consumption of vitamin D with 2 g fish oil per week did not increase vitamin D absorption (Korkor and Bretzmann 2009). Thus reports available till date clearly neglect the hypothesis that high amount of fat in meal improves the vitamin D bioavailability.

Type of fatty acids

The first report on this factor came from Hollander's study when the decrease in vitamin D uptake was registered by addition of fatty acids of different chain length and degree of saturation i.e. butyric acid, octanoic acid, oleic acid and linoleic acids (Hollander et al. 1978). In this study the oleic and linoleic acids exhibited greater inhibition of vitamin D absorption as compared to octanoic acid. Authors propose that unlike medium chain fatty acids (do not integrated in micelles), long chain fatty acids impair the vitamin D absorption by increasing the micellar size hence decelerating their diffusion towards the enterocytes. However this result was not reproduced at pharmacological dose of vitamin D when it was ingested with either long chain triacylglycerols (peanut oil) or medium chain triacylglycerol. In contrast to this, the improvement in the serum level of vitamin D_3 was registered when it was served in peanut oil (long chain triglycerides) than when it was served in medium chain triglycerides (Holmberg et al. 1990). More clear observations were made in experimental trials conducted to evaluate the bioavailability of vitamin D in monounsaturated and polyunsaturated fatty acids. It was found that monosaturated fatty acid rich diet may increase the efficacy of vitamin D supplements than that of polyunsaturated fatty acids (Niramitmahapanya et al. 2011).

In summary, literature suggests that the species of fatty acids can affect the bioavailability of vitamin D. Nevertheless more research is needed to draw firm conclusion on bioavailability of vitamin D.

Dietary fibers

Dietary fibers have been assumed a key player in deciding the fate of vitamin D in GIT. It affects the bioavailability of vitamin D in following ways:

Impairs the micelle formation

Affects triacylglycerol lipolysis and emulsification of fat soluble food component
Affects the release of lipophilic food nutrient from fat droplet (oil phase)
Increases the viscosity of chyme hence confines the diffusion of lipophilic food nutrients containing micelles to enterocytes

High fiber intake was suspected the reason for the reduced bioavailability of vitamin D for higher prevalence of rickets and osteomalacia in Asian immigrant's population (Compston et al. 1981). This assumption was supported by a study on relative disappearance of radiolabelled 25(OH)D_3 in healthy volunteers served with either higher fiber diet (20 g/day) or normal diet. Result reveals that the mean serum half-life of 3H-25(OH)D_3 in the normal diet group was longer (27.5 ± 2.1 day) than that of high fiber diet group (19.2 ± 1.7 day). High clearance of 3H-25(OH)D_3 in high fiber diet group could be due to interference of the fiber metabolite in enterohepatic circulation i.e. binding of 3H-25(OH)D_3 to dietary fibers.

In contrast, the serum levels of 25(OH)D in two groups (consuming vitamin D fortified low fiber wheat bread (3 g/100 g) and high fiber rye bread (12 g/100 g)) were not significantly different from each other. Conversely, these results could be refuted as volunteers in these groups were allowed to consume other breads. Due to very scant data available on uptake of vitamin D in presence of fibers, it could be too early to conclude the role of fibers. Likewise more dedicated studies are required to understand the effect of fibers on vitamin D bioavailability.

Nutrient status in the host

It can be hypothesized that absorption of vitamin D in GIT is also controlled by nutrient status of host.

Status of vitamin D in the host

The complete vitamin D status of host is comprised of both food derived as well as cutaneous synthesized vitamin D. However, it is very difficult to establish the correlation between the contribution of orally ingested and cutaneous synthesized vitamin D. Due to lipophilic nature vitamin D stored in adipose tissue and release at its need. High intake as well as high de novo synthesis of vitamin D could be toxic, therefore, it can be hypothesized that high intake of oral vitamin D and excessive radiation with UV may cause hypervitaminosis D so there will be feedback inhibition between absorption of orally ingested vitamin D and cutaneous synthesis. Nevertheless, there is not a single study performed to investigate of impact of absorption of vitamin D on cutaneous synthesized vitamin D. The main problem in establishing correlation between dietary and cutaneous synthesized vitamin D is the variation in the surface area of skin exposed and in the frequency and duration of UV exposure.

Interaction with micronutrients

Vitamin E and K follow common pathway used in vitamin D uptake so they may impose competitions for vitamin D absorption in intestine. This assumption was verified by a study on $CaCO_2$ cell line which confirms the role of vitamin E in impairing the vitamin D absorption (reduced 15% at medium concentration of vitamin E and 17% at high concentration of vitamin E) absorption in intestine (Goncalves et al. 2015). Phytosterols, plant sterols traditionally, are applied as functional ingredients to reduce cholesterol absorption in GIT. As vitamin D possesses a steroid structure and parades common absorption pathways as cholesterol, we hypothesized that phytosterols could also hamper vitamin D_3 uptake. This assumption was confirmed by an in vitro study on $CaCO_2$ intestinal cell where phytosterol was found to be potential candidate to impair the vitamin D_3 absorption by 16–36% (depending on micellar composition) in these cell line (Goncalves et al. 2011).

Concentration of vitamin A was also found to be antagonist to vitamin D absorption (Aburto and Britton 1998). In addition, vitamin A also discriminates dietary D_3 (coming from food) and endogenous D_3 (synthesized in skin by action of sunlight) in their utilization i.e. negatively affect the utilization of dietary vitamin D_3, but not the endogenous vitamin D_3 (Johansson and Melhus 2001). Recently a research demonstrated that high concentration of vitamin A reduce bioavailability of vitamin D by 30%. However the mechanisms, how vitamin A hampers the vitamin D absorption, does remain unknown and requires further investigation.

Enhancers and inhibitors for vitamin D absorption

Literature reports about various agents which can stimulate or impair the vitamin D absorption in GIT. These agents could be present in food naturally or could be added to improve absorption efficiency of vitamin D. Data from available literature is presented here.

Inhibitors of fat absorption

Person suffering from obesity consumes several antiobesity drugs and fat substitutes to reduce the fat quantity. These drugs and fat substitutes reduce the absorption of triglycerides. Since vitamin D follows the similar league of triglyceride in GIT lumen it can be assumed that these

antiobesity drugs could impede vitamin D bioavailability leading to reduction in absorption. The absorption of vitamin D was found to be impaired when vitamin D was served with a fat substitute (olestra: sucrose polyester) was ingested in 102 healthy males and females (James et al. 1997; Schlagheck et al. 1997). The serum level of vitamin D in African-American and Caucasian adolescents was significantly reduced after 1 month supplementation of 400 IU vitamin D with orlistat (Tetrahydrolipstatin: inhibitors of gastric and pancreatic lipases) 120 mg 3 times/day (McDuffie et al. 2002). Furthermore, the cholesterol derivatives from plant origin, used as reduce the cholesterol absorption, may affect the bioavailability of vitamin D. This assumption was confirmed by various studies. The decrease in vitamin D level both in serum as well as in liver was registered in rats when they assigned stanol ester for 13 weeks (Turnbull et al. 1999). Even these results were reproduced for various phytosterols in mice and in vitro and found that phytocholesterols do hinder the micelles formation and its diffusion in enterocytes thus reducing the bioavailability. Though some recent findings of clinical trials have disowned this hypothesis by negating the effect of phytosterol on bioavailability of vitamin D (Gylling et al. 2010; Gylling and Miettinen 1999; Gylling et al. 1999; Hendriks et al. 2003; Korpela et al. 2006; Nguyen et al. 1999). But these conclusions could be refuted as the evaluation was made on the basis of the serum level of 25(OH)D which could be altered by endogenous vitamin D synthesis depending on the several factors i.e. sun exposure and season. Furthermore this hypothesis was again supported by results of two clinical trials in which the serum level of 25(OH)D was observed significantly different in subjects, who assigned plant sterol ester enriched spread. Although these fat reducing agents limit the fat absorption hence hamper the absorption of vitamin D (James et al. 1997; McDuffie et al. 2002) but the exact amount of lipid needed for maximal absorption of vitamin D has not been optimized.

Enhancers of vitamin D

It is thought that the vitamin D delivery in specialized formulation (encapsulated in micro/nano particles, micellar/liposomal form, embedded in β-cyclodextrin and some proteins β-lactoglobulin) may enhance the bioavailability of vitamin D in GIT. Their ability to improve the uptake of vitamin D was tested in various studies. Higher absorption rate of vitamin D in children affected with severe chronic cholestasis was registered when it was administered with tocopherol succinate polyethylene glycol 1000 (TPGS) (Argao et al. 1992). Similar observation was made when vitamin D was served with β-cyclodextrin in rat (Szejtli et al. 1983). It is hypothesized that encapsulated vitamin D remain embedded within non digested nano/microparticles, rather being released. These micro/nanoparticles may transport paracelluarly to the blood portal through tight junction, thus bypassing the liver. This may result in the greater bioavailability for micro/nano encapsulated vitamin D than that of its fortified food and supplement. Limited literature is available on this factor thus it will too early to conclude about the effect of these formulations on the bioavailability of vitamin D and this assumption should be varied by extensive clinical trials.

Physiochemical interaction with GIT secretions

It is assumed that the absorption of vitamin D in GIT remains maximal within a range of salt ionic strength and pH beyond which the vitamin D uptake could be affected. This assumption was addressed in various studies. It was observed that the uptake of vitamin D_3 is affected with variation of salt concentration within physiological concentration. For example the progressive reduction in vitamin D_3 absorption was noticed as the sodium taurocholate salt concentration was increased above the 5 mM (10 or 15 mM) n (Hollander et al. 1978).

High concentration may facilitate the conversion of monomeric vitamin D into its micellar form thus enhances the solubility of vitamin D_3. Since lipophilic compounds such as vitamin D_3 have greater penetration power in enterocyte's membrane in monomer form than that of micellar particles (Simmonds 1974), The high salt concentration may cause the decrease the vitamin D absorption (Simmonds 1974)

The variation in the hydrogen ion concentrations (pH 5.3–8.3) in the perfusate decreases the negative charge of both the micelle and the luminal cell membrane, therefore, reduces the repulsion between the micelles and the cell membrane thus increasing the absorption of vitamin D (Hollander et al. 1978).

Host associated factors

Literature clearly suggests the involvement of various host associated factors which could be suspected players in deciding the bioavailability of vitamin D. Thus several studies have been conducted to optimize recommended dietary allowance (RDA) as the functions of these factors (age and disease obesity).

Age of host

Physiological changes in body function have been witnessed with aging. It is assumed that the age stimulated physiological (age associated GIT functions) changes may

directly or indirectly influence vitamin D bioavailability. Aging associated variations in lipoprotein metabolism was suspected for reduction of absorption and postprandial transport of vitamin E (Borel et al. 1997). Several studies have conducted to find out the reason for low vitamin D status in elderly people than that of young adults (Clemens et al. 1986; Ikuma et al. 1996; Russell 1992; Vellas et al. 1991). The first report on this factor was made in 20 elderly women, who had low serum [3H]cholecalciferol than that of younger females. This was explained that GIT of elderly women was less efficient as compared to younger ones (Barragry et al. 1978). Nevertheless, this result was not reproduced in mice study (Hollander and Tarnawski 1984). Conclusive statements regarding changes in serum 25OHD levels in elderly than in young adults could be due to low endogenous vitamin D synthesis in skin, lower sunlight exposure and low dietary intake.

Obesity

Obesity is generally negatively correlated to vitamin D deficiency. This was supported by Liel et al. (1988) work in which they observed improved absorption and higher clearance of vitamin D by obese subjects than that of normal weights. Conversely vitamin D is deposited in adipose tissue and does not released when required (Wortsman et al. 2000) resulting into high supplementation of vitamin D. This was confirmed by a study on elderly subjects served with 700 IU of vitamin D per day for every addition 15 kg of weight above normal subjects (Blum et al. 2008). The low serum level in obese subjects could be due to dilution of vitamin D (ingested or cutaneous vitamin D) in their large fat mass (Drincic et al. 2012). The inference of these findings is that vitamin D stored in fat tissue is not easily available, and obese individuals may oblige larger dose of vitamin D to meet a serum 25OHD level equivalent to that of their normal weight counterparts (Wortsman et al. 2000). The rise in serum 25(OH)D level during weight loss in obese individual verifies this hypothesis (Riedt et al. 2005; Zittermann et al. 2009)

Digestive tube surgery/diseases

Several clinical and experimental animal studies confirmed that vitamin D is most efficiently absorbed when consumed with foods containing fat (Johnson et al. 2005; Weber 1980). Early studies suggested that subjects suffering from impaired GIT i.e. obstructive jaundice (low bile juice release) or pancreatic insufficiency, cystic fibrosis or adult coelic disease and gastric surgery could demonstrate significantly reduced absorption of vitamin D. Reduction of serum level vitamin D_3 by 30% was registered in case of Roux-en-Y gastric bypass surgery than before (Aarts et al. 2011). Despite of high dose of vitamin D supplementation (2500–5000 IU/day) vitamin D_2 and D_3 were not detected in infants and children suffering from extrahepatic biliary atresia (whose portoenterostomy failed to produce bile flow) (Heubi et al. 1990). Similarly in children with cholestasis serum vitamin D_2 level remained undetectable instead of high dose of vitamin D supplementations (2500–5000 IU/day) (Heubi et al. 1989). Furthermore, the patients affected with cystic fibrosis were found to be less efficient in vitamin D absorption than that of their normal counterparts (Farraye et al. 2011; Lark et al. 2001). Likewise it is also hypothesized that the vitamin D positively alter the gut microbiota and $CD8^+$ cells which may lead to retain the integrity of the GIT mucosal barrier by controlling the intercellular junctions thus controlling mucosal permeability and increasing the $CD8^+$ cell (Bashir et al. 2016; Kanhere et al. 2016). Additionally some clinical studies also demonstrated the role of vitamin D in inhibiting the various cancers including GIT cancer by modulating cancer stem cell markers and VDR polymorphism and other VDR regulation (Lappe et al. 2017; Li et al. 2017; P Peppelenbosch et al. 2017). Though these studies do verify the involvement of vitamin D in different disease prevention but there is scarcity of data how vitamin D absorption in GIT is influenced under these diseases (Messa et al. 2017; Scragg et al. 2017; Yao et al. 2017). Nevertheless, the deleterious effect of diseases was partially rectified by sunlight exposure or by applying 25(OH)D which does not depend on the fat assimilation in GIT and take portal vein.

Genetic variations

The absorption of vitamin D is monitored by various factors such as vitamin D protein transporter, nuclear vitamin D binding protein, enzyme involved in fat digestion, bile secretion, liver enzyme catalyzing vitamin D. Literature has described the key role of genetic variations in modulating serum level 25(OH)D (Fu et al. 2009). It is clear now that vitamin D is absorbed in enterocyte through protein mediated transport. The expression and activity of these proteins can be modulated by altering the genetic code which may result into complete or partial loss of its activity. Furthermore, variation in genetic code of nearby gene may also interrupt binding of transcription factor leading into absence of these protein transporters. Till date literature lacks data addressing this factor (Hernández-Romano et al. 2009). Similarly any genetic variation in fat digestive enzyme and vitamin D binding protein may also affect the vitamin D absorption.

Research gaps and future prospects

After thorough review of literature the gaps in present literature were identified and these research gaps could be addressed by future dedicated studies. The future research prospects identified from present literature are as follows:

1. The acidic pH of gastric juice may affect the bioavailability of vitamin D. It is apparent that no data available on the susceptibility of major dietary forms of vitamin D with respect to pH variation in GIT.
2. It have been observed that various digestive enzymes facilitate the release of vitamin D from food matrix but the role of these enzyme is not fully recognized with respect to bioavailability of vitamin D. The evaluation of effect of enzymes individually or in syndicate and their concentration on vitamin D bioavailability will aid in better understanding their impact on vitamin D uptake.
3. It has been assumed that vitamin esters are at least partially cleaved by gastric lipase, but this problem in not addressed in present literature. Thus further studies needed to evaluate the effect of gastric lipase on vitamin D ester hydrolysis.
4. In duodenum digestive enzyme (amylases, lipase and protease) continues the release of vitamin D from food matrix. Vitamin D released from food matrix during digestion need to transfer from oil (naturally retained in dietary lipid) to the fat phase of meal (micelles). But kinetics of vitamin D transfer from food matrix into micelles is not completely understood. More dedicated research is needed to get better understanding about the impact of vitamin D transfer from food oil phase to micelle on the bioavailability of vitamin D.
5. Since these micelles incorporate lipophilic nutrients in their phospholipid bilayer but there is limited reports on these nutrients (other lipophilic vitamins, phytosterol etc.) addressing how they affect the transfer of vitamin D in micelle. More focused studies, discussing the impact of concentrations of these lipophilic nutrients on vitamin D uptake in GIT, will aid better understanding on bioavailability of vitamin D.
6. Though within physiological concentration, vitamin D is absorbed in enterocyte via protein mediated transport but there is shift in transport mode from protein medicated to passive diffusion at pharmacological concentration (high dose of vitamin D). The optimal concentration of vitamin D at which this mode shift in vitamin D transport occurs is still unknown.
7. Difference in vitamin D uptake efficiency in jejunum of rat than that of it ileum clearly suspects about the presence of another transporter particularly expressed in the jejunum (Goncalves et al. 2015). More research on these transporters is required to understand complete mechanism of vitamin D uptake in intestine.
8. Hydroxylated vitamin D forms do take different path for their absorption by enterocytes but the mechanism of hydroxylated species of vitamin D absorption is still remains unaddressed.
9. Vitamin D remains embedded in lipid phase of food as well as bound with specific proteins. The various food items differ in their complexity to retain vitamin D. There is limited documents available dealing with effect of food matrix complexity on bioavailability of vitamin D. Conversely more studies comparing bioavailability of vitamin D are required in order to know the effect of complexity of food matrix on vitamin D bioavailability.
10. Non hydroxylated vitamin D forms are absorbed through protein mediated transporters but their affinity may vary with variation in molecular forms (vitamin D_2 or vitamin D_3). Effect of concentration of vitamin D_2 on the absorption of vitamin D_3 and vice versa is still not much discussed.
11. The mechanism how the esters of vitamin D does effect the absorption of vitamin D is still remained unaddressed
12. Though vitamin E impairs the vitamin D absorption (reduced 15% at medium concentration of vitamin E and 17% at high concentration of vitamin E) in intestine but the concentration at which vitamin E completely cease the vitamin D absorption is not optimized.
13. Compressive review of relative bioavailability of vitamin D in different food matrix is essential to evaluate the bioavailability of vitamin D in different food.
14. Effect of special vitamin D formulations (encapsulated vitamin D in micro/nanoparticle) on bioavailability of vitamin D is not addressed in present literature.

Conclusion

Wide range of food products are available in different parts of the world; each food product displays variations in their matrix due to difference vitamin content, fat content, dietary fibers etc. All these factors contribute difficulty in determining the bioavailability of vitamin D in particular food. The present literature lacks complete knowledge about the mechanism of vitamin D absorption. Although some factors governing fate of vitamin D in GIT is well documented but several factors i.e. genetic variation, dietary fiber, host vitamin D status, effect of nano/

microparticle of vitamin D which may influence the bioavailability of vitamin D, are either not addressed or have very little data to conclude. For better understanding about bioavailability of vitamin D more dedicated studies with labeled vitamin D are required addressing the future research prospects mentioned above.

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