

## REVIEW ARTICLE

# Transdermal vitamin D supplementation—A potential vitamin D deficiency treatment

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## Abstract

Vitamin D deficiency has high prevalence worldwide. Vitamin D<sub>3</sub>, the active form of vitamin D, exhibits array of roles in body, from calcium homeostasis and bone mineralization to cancer, neurological disorders, immunomodulatory action, and cardiac health. Current approaches for supplementing vitamin D<sub>3</sub> are restricted to oral and parenteral routes. This review highlights recent research in the field of transdermal delivery of vitamin D, its active form and analogues with the aid of penetration enhancers and novel carrier system as nutritional supplement in case of vitamin D deficiency. The penetration of vitamin D<sub>3</sub> is challenging; however, by means of reducing hydrophobicity of the active and encapsulating vitamin D<sub>3</sub> in a suitable carrier system, penetration is achieved. The results show that penetration of vitamin D<sub>3</sub> through skin is feasible. Further clinical trials could strengthen these results. However, the present research till date shows transdermal vitamin D<sub>3</sub> a promising way of supplementation.

## KEYWORDS

carrier, penetration enhancers, transdermal vitamin D, vitamin D deficiency, vitamin D<sub>3</sub>

## 1 | INTRODUCTION

Vitamin D is a hormone, is steroidal in nature, and is synthesized in the skin on exposure to UVB radiations. The UVB radiations enable conversion of precursor, 7-dehydrocholesterol, into cholecalciferol, that is, vitamin D<sub>3</sub>. Besides endogenous synthesis, exogenously, vitamin D is obtained in two forms, that is, vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol). Vitamin D, in the body, is metabolized to several metabolites, most active of which is 1, 25-dihydroxycholecalciferol (commonly called as calcitriol) that has a vital role in the regulation of calcium homeostasis and bones mineralisation.<sup>1</sup> Vitamin D and its analogues have an intricate relationship with the skin. They are well known and used for the treatment of topical condition such as psoriasis. They work by regulating keratinolytic differentiation and enforcing immunomodulatory actions. The vitamin is also involved in controlling multiple intracellular pathways which are responsible for the melanin synthesis and melanocyte survival.<sup>2</sup> Maxacalcitol, an active analogue of vitamin D<sub>3</sub>, is proved

to effectively treat comedones,<sup>3,4</sup> and a few studies also report anti-neoplastic activity<sup>5</sup>.

Low vitamin D levels in the serum are associated with increased risk of chronic diseases such as hypertension, inflammation, diabetes, and cancer. The hypotheses that local conversion of vitamin D<sub>3</sub> into its active metabolite 1, 25-dihydroxycholecalciferol in healthy cells in colon, breast, and prostate can prevent malignancy by inducing cellular maturation, apoptosis, and inhibiting angiogenesis while enhancing the expression of genes that control cellular proliferation is established.<sup>6</sup> Observational studies in humans showed that level of vitamin D<sub>3</sub> metabolites is inversely related to coronary artery calcifications. Vitamin D metabolites displayed promising effect in significantly reducing the incidences of angina and myocardial infarction.<sup>7</sup> In another study, it was reported that vitamin D acts as a natural modulator or regulator of immunity. The epidemiologic studies indicate the essential role of vitamin D in the pathogenesis of several systemic and organ-specific diseases such as type 1 diabetes mellitus, rheumatoid arthritis, and

Crohn's disease.<sup>8</sup> Apart from this, vitamin D3 has been effective in controlling fatal infections like tuberculosis. Vitamin D in adults show neuro-protective action by way of inducing remyelination of endogenous progenitor cells and stimulation of amyloid beta clearance brought about by macrophages in Alzheimer's disease.<sup>9</sup> Since vitamin D is an extremely vital nutrient and has multifarious role in the prevention and treatment of several diseases, its deficiency is a matter of serious concern. Even though new therapies have become available to manage and treat the above-mentioned diseases, Vitamin D supplementation is majorly used as a critical and adjuvant therapy. Hence, vitamin D has prophylactic as well as therapeutic significance.

### 1.1 | Current mode of supplementation and associated drawbacks

There is an array of oral and parenteral products that are supplements for vitamin D3 deficiency. Fortified foods are available but are seldom an option in treatment of vitamin D3 deficiency. They are rather prophylactic in action. Therapeutic vitamin D3 supplementation is majorly given in case of osteoporosis and osteomalacia as an adjuvant treatment. However, these are limited to oral tablets, capsules, granules, and parenteral products.

When given orally, the absorption of the vitamin D occurs in the proximal part of small intestine with the aid of bile acids. Several factors affect vitamin D3 absorption that result in inconsistent bio-availability of vitamin D3 supplements in many populations. Certain diseases causing fat malabsorption hamper the absorption of vitamin D3.<sup>10,11</sup> In a study, it was found that, in patients with celiac disease, biliary obstruction and chronic pancreatitis, the absorption of tritium-labeled (3H) vitamin D3 fell to 50%, <28%, and <18%, respectively. This was significantly lower than normal subject absorption, which ranged from 62% to 91%. The study also stated that chronic use of bile acid binding medications such as cholestyramine will reduce vitamin D3 absorption to significant extent.<sup>12</sup>

The systemic absorption that takes place in the duodenum does not take place in patients who have undergone gastric bypass surgery (digestive tube surgery) as the absorption window for vitamin D3 is not available for them. The effect of gastric bypass surgery on vitamin D3 bioavailability was studied by Aarts E. et al<sup>13</sup> Study revealed significant decrease in the levels of cholecalciferol in patients after surgery. For such patients, alternate route of administration is required to be envisaged.<sup>14,15</sup>

In addition to these drawbacks, patient compliance in supplementation therapies is a major concern. Many oral supplements need to be taken multiple times a day, and this reduces patient compliance in cases of geriatric patients and Alzheimer's patients. Also, parenteral administration of vitamin D3 requires continuous medical supervision, which causes less comfort to the patients.

Giving due consideration to these limitations of oral route of administration, a new route of delivery for vitamin D3 and its analogues for vitamin D3 supplementation could overcome these limitations and prove to be a potential route of administration.

### 1.2 | Transdermal vitamin D3

Skin, acting as a strong barrier, nevertheless provides innumerable advantages as a route for drug delivery. Skin not only facilitates topical delivery wherein localisation of a large concentration of therapeutic moiety in the skin layers to treat dermatological conditions can be attained but also facilitates systemic absorption of the active moiety so as to enable therapy for underlying systemic ailments. The effectiveness of topically and transdermally administered drugs depends on the physicochemical characteristics of the drug as well as the carrier system.

Physicochemically, vitamin D3 has a molecular weight of 384.64 g/mol, the recommended daily dose being approximately 0.01 mg-5 mg, and the measured lipid/water partition coefficient is about 10. It is, hence, a highly potent lipophilic drug, and its intricate relationship with the skin serves as an advantage to consider transdermal route for systemic absorption of vitamin D.

Advancement in this approach is observed in the currently Vitamin D3 Patches (Patch MD), and creams (SeaBlue) are available in the United States and Europe as nutritional supplements. However, there are no marketed products available under prescription category worldwide.

## 2 | RECENT STUDIES CONDUCTED TO EXPLORE THERAPEUTIC TRANSDERMAL DELIVERY OF VITAMIN D3

Researchers have explored various possibilities for enhancing penetration of vitamin D3 through skin. In one study, G. Costa et al studied the feasibility of transdermal use of vitamin D3 for providing nutritional supplementation. They also studied the effect of few penetration enhancers in improving systemic levels of vitamin D3. The group used female abdomen skin for ex vivo permeation study. Comparative evaluation was done on gel-based formulation comprised of primary penetration enhancers, viz. soybean lecithin, isopropyl palmitate, and ethoxydiglycol, and a cream-based formulation without penetration enhancers. The permeation data were verified by performing skin integrity test by trans-epidermal water loss. Both the formulations did not show any detectable level of vitamin D3 in the receptor medium. On performing skin retention studies, it was observed that gel formulation exhibited significant quantity of vitamin D3 in stratum corneum at the end of 4 hours and the levels continued to penetrate in dermis and epidermis at the end of 24 hours. However, no such penetration was observed from cream-based formulation. These results were attributed to high log P (10.34) and lipophilicity of vitamin D3 hampering its transdermal penetration. The group concluded that topical use of vitamin D3 was appropriate for skin retention and more apt for the treatment of psoriasis where localization of the drug was required. They also concluded that the transdermal delivery should be explored by using more potent penetration enhancers and less lipophilic vitamin D3 analogues or derivatives.<sup>16</sup>

Ahmed Alsaqr et al investigated ex vivo skin penetration of cholecalciferol using oleic acid and dodecylamine as penetration enhancers. The group formulated three types of ointment containing no penetration enhancer, oleic acid, and dodecylamine. Porcine skin was used to experiment diffusion. It was found that the amount of vitamin D3 penetrated from formulation containing no penetration enhancer and that containing dodecylamine were 170 ng/cm<sup>2</sup>, and 360 ng/cm<sup>2</sup>, respectively. The formulation containing oleic acid did not show any detectable penetration. The group further investigated the penetration by pretreating the skin with ethanol prior to the application of ointment. Significant increase was observed in the results after pretreatment with ethanol. It was observed that penetration was higher in ethanol pretreated skin as proven to disrupt the skin structure and provide rapid penetration.<sup>17</sup> However, concomitant use of such penetration enhancer is not preferred as it could eventually lead to toxicity. The data depicted that without pretreatment of ethanol, the ointment comprised of dodecylamine showed greater penetration and could be used in combination with other penetration enhancers for enhancing the vitamin D3 penetration. The study concluded that transdermal route could be potential site for vitamin D3 supplementation.

T. Ramezanli et al investigated topical delivery of vitamin D3-loaded polymeric nanospheres. The polymeric nanoparticles, termed as TyroSphere, were made from amphiphilic tyrosine-derived ABA-triblock copolymers comprised of a hydrophobic block of oligomers of desaminotyrosyl-tyrosine ester (DTR) and di-acid, and hydrophilic poly (ethylene glycol) (PEG) A-blocks. The drug encapsulation efficiency of nanospheres was observed to be about 70%. The ratio of drug to polymer had significant impact on drug loading. The high drug loading capacity was attributed to affinity of vitamin D3 to hydrophobic portion of the polymer. The average diameter of TyroSpheres was 60-70 nm. Skin release and retention study was performed on dermatomed human cadaver skin samples by separately carrying out experiments for stratum corneum, epidermis, and dermis. Drug distribution was measured at 3, 6, and 12 hours to check TyroSphere permeation. Vitamin D3 solution in Transcutol was used as control to compare delivery efficiency of TyroSphere. About 40% of the drug was released in the receptor media through the stratum corneum at 20 hours, and was about 80% released at 80 hours. The skin distribution was found to be 3 mcg/cm<sup>3</sup> and 10 mcg/cm<sup>3</sup> of epidermis at end of 3 hours and 12 hours, respectively. The results were significantly higher than those obtained with Transcutol control.<sup>18</sup> The study finding indicated that TyroSphere comprised of hydrophilic and hydrophobic copolymer can serve as potential novel delivery carrier for transdermal penetration of vitamin D3. In addition, the carrier provided prolonged release of vitamin D3 and enhanced its chemical stability. However, it has reiterated that the polymers used as carriers for the drug have to be thoroughly investigated for biocompatibility and biodegradability.

Hsu T. et al in their patent have mentioned about approaches to enhance transdermal penetration of different vitamins by the use of penetration enhancers. The inventors have mentioned the improving permeation across skin or mucosal tissue by enhancing

the flux of the active pharmaceutical ingredient through the tissue. Amongst different vitamins mentioned in the patent, the inventors have included vitamin D as calcitriol and calcipotriene in the form of prodrug or active metabolite. The permeation enhancement approach mentioned includes the use of inorganic base comprised of inorganic hydroxides and oxides or inorganic salts of weak acids in the formulation that can provide pH of about 8.0-13.0 at the application site.<sup>19</sup> Choi Y. et. al. have patented matrix-based transdermal patch of vitamin D. The system involves drug dissolved or diffused in nonpolar polymer base comprised of polyethylene, polyisobutylene, styrene or isoprene copolymers or synthetic rubbers. The nonpolar adhesive polymers were selected on the basis of their values solubility parameters. The nonpolar polymers having solubility parameter in the range of 15.4-17.9 (J/cm<sup>3</sup>)<sup>1/2</sup> showed maximum skin penetration of calcitriol in the range of 29.5-246.8 ng/cm<sup>2</sup>/day. The inventors have claimed the permeation rate of vitamin D and its analogue for their developed matrix type transdermal patch in the range of 0.005-20 µg/cm<sup>2</sup>/d for period up to 7 days.<sup>20</sup>

Schwarzrock, T. and Cleary, Gary have formulated vitamin D as reservoir type transdermal adhesive patch. The components of the formulation included polymers belonging to polyisobutylene, silicone adhesive, or acrylate adhesive, organic solvent triglyceride, and permeation enhancer transcutool. Permeation studies showed delivery of more than 20 000 µg of vitamin D through 40 cm<sup>2</sup> of intact unbroken living skin at the end of 24 hours. When the transdermal patch was tested on subjects having 25-hydroxyvitamin D3 blood serum level in the range of 1-25 ng/mL, the blood level of 25-hydroxyvitamin D3 increased to about 30 ng/mL in 5 hours.<sup>21</sup>

N. Yamagishi et al studied penetration of active metabolite of vitamin D3, that is, calcitriol directly. In the study, the group applied three types of patches on three groups of experimental dairy cattle models, viz. nonpregnant Jersey heifers. Group I was considered as vehicle control, whereas Group II and III received a dose of 10 µg/µL using ethanol as solvent in reservoir patch and 10 µg/µL using ethanol with dodecylamine in reservoir patch, respectively. Patches were administered to the cattle once in 3 days for a period of 2 weeks. It was observed that, in Group II receiving calcitriol in ethanol reservoir patch, average plasma calcitriol concentrations increased significantly from 41.3 pg/mL on the 0th day to 169.6 and 274.7 pg/mL on 1st and 2nd day ( $P < .05$ ), respectively. However in Group III receiving Calcitriol in ethanol along with dodecylamine reservoir patch, the mean calcitriol concentrations in plasma increased from 69.3 pg/mL on 0th day to 236.6 pg/mL on the 2nd day.<sup>22</sup> The study indicated that dodecylamine did not show any significant contribution toward enhancing penetration of calcitriol.

However, interesting observations and conclusions can be drawn from the study results conducted by G. Costa et al and Yamagishi et al. The chemical form of vitamin D can also be a major factor affecting transdermal penetration of vitamin D. Calcitriol as explored in studies conducted by Yamagishi being more hydrophilic in comparison with cholecalciferol evaluated in study conducted by G. Costa et al showed higher penetration than the latter. Lower hydrophobicity of calcitriol as compared to cholecalciferol facilitated the release

with further partitioning and penetration across deeper layers of skin to reach systemic circulation. This phenomenon was not seen in hydrophobic cholecalciferol.

K. Yamaguchi et al studied *in vitro* and *ex vivo* skin permeation of another type of vitamin D3 analogue oxacalcitriol (OCT). 22-oxacalcitriol (OCT) is also a vitamin D receptor activator (VDRA), and it is clinically used for treatment of secondary hyperparathyroidism (SHPT). The group formulated ointment of OCT and evaluated the penetration of the drug across dorsal skin of Sprague Dawley rat. In the first part of the study, penetration across stratum corneum was evaluated, and in the second part, penetration across full thickness skin was evaluated. Results depicted that 25% of drug permeated across stratum corneum and about 15%-17% drug permeated through the skin having full thickness at the end of 24 hours. The group concluded that oxacalcitriol another hydrophilic analogue of vitamin D3 can be further investigated clinically as potential transdermal supplement.<sup>23</sup> From the above findings, it can be interpreted that although ointment did not contain any penetration enhancer, it displayed considerable penetration across full thickness skin. The low penetration could be also attributed to the absence of carrier system in the formulation.

A clinical study report was published by J. Lyftogt wherein he evaluated patients receiving transdermal treatment of vitamin D3 cream. The patients had etiology of inferior heel pain, known as plantar fasciitis, a peripheral neuropathic pain syndrome due to persistent neurogenic inflammation of the medial calcaneal branches of the tibial nerve. The dose of cholecalciferol 12.0 IU/gram was applied to the affected area twice daily. The study findings showed alleviation of pain associated with the ailment. It was concluded that the application of a transdermal cream with the pro-hormone vitamin D3 (25-hydroxyvitamin D3) near neuropathic cutaneous nerves was contributing to up-regulate the local production of calcitriol. This resulted in more effective neuroimmune modulatory effect than oral vitamin D supplementation.<sup>24</sup> This report gives a new insight that applying 121 U of vitamin D3 cream twice daily on skin could trigger subcutaneous synthesis and release of calcitriol and exert its analgesic effect which was otherwise not experienced by the patients receiving oral supplement. Although the plasma levels were not quantified in this study, the findings further provide evidence of transdermal penetration of vitamin D3 and its beneficiary neurologic effect.

M. Sadat-Ali et al conducted clinical trials of a topical vitamin D3 gel on 48 healthy unmarried female students of average age of  $22.58 \pm 1.95$  with the body mass index (BMI) of mean  $19.95 \pm 3.15$  kg/M<sup>2</sup>. The participants received a dose of 5000 IU vitamin D3 in form of aloe vera gel which comprised of aromatic oil as penetration enhancer. It was depicted from the study that the average 25-hydroxyvitamin D3 in the study group pretreatment was 12.05 ng/mL and post-treatment was 37.95 ng/mL. The team concluded the study by declaring that vitamin D3 was safe for transdermal use.

25-hydroxyvitamin D3, a slightly hydrophilic analogue of vitamin D3 when applied in the form of gel, could effectively reach the systemic circulation in the body when applied on skin.<sup>25</sup>

Also, the reason for lesser penetration through the skin could be lack of a novel carrier system that could enable penetration of the active ingredient through skin without damaging the skin structure.

Hye-Gyeong Kim et al developed delivery system for transdermal vitamin D3 by synergistically using PLGA nanoparticles and microneedles. Particle size of PLGA nanoparticles was 240 nm, and the *in vitro* release study of the PLGA nano particles showed a release in burst pattern of 61.24% at 4 hr and 82.22% at the end of 48 hours. These vitamin D3-loaded PLGA nanoparticles were coated to stainless steel microneedles. The microneedles showed delivery efficiency to be 81.08%, which was significantly greater compared with that of the cream at around 16.3% which was used as control. Despite the fact that the cream contained a penetration enhancer, the microneedle systems showed fivefold better delivery. The study concluded that a micro-device may give convenient and effective vitamin D3 supplementation with good patient compliance. However, the release of vitamin D3 through PLGA nanoparticles alone was higher than that obtained by further usage of microneedles.<sup>26</sup> This proves that in comparison with providing physical passage for the drug, a carrier system can be proved as a better mode of penetration enhancement.

### 3 | CONCLUSION

It was concluded that vitamin D3 strongly tends to get retained in the dermis and epidermis layers of skin due to its higher lipophilicity and log P. Decreasing the hydrophobicity of the molecule is seen to enhance the penetration in case of vitamin D3 metabolites, viz. 1, 5-dihydroxyvitamin D3 and 25-hydroxyvitamin D3 as well as vitamin D3 analogues like 22-oxacalcitriol. Penetration enhancers such as dodecylamine and aromatic oils contribute to increased diffusion of the vitamin D3 across the skin. The use of polymers as carrier system could be an innovative way to strike a balance in the hydrophilicity and hydrophobicity of vitamin D3. Polymers used in the recent study depict this phenomenon with increased diffusion of vitamin D3 and its stability. Recent research shows evidence that vitamin D3 is safe and effective when administered through transdermal route. Further investigations are required to enhance penetration possibly by combination of penetration enhancers and suitable carrier system. Clinical studies have to be carried out to produce substantial evidence of transdermal absorption of vitamin D3. Hence, vitamin D3 can be potentially given as a nutritional supplement via transdermal route.

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