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Vitamin D: The Family Physician And Super Specialist Healthcare Of Human Being

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ABSTRACT:- Vitamin D is considered a steroid hormone with a broad spectrum of action in the human body. Its action arises from the binding of its active metabolite (1a, 25- dihydroxyvitamin D) toits receptor (VDR), which is present throughout the body, including vascular smooth muscle cells and cardiomyocytes. regulated mineral ion homeostasis. Vitamin D plays several roles in the body, influencing bone health as well as serum calcium and phosphate levels. health outcomes, including risk of rickets in children or osteomalacia in adults, increased risk of fractures, falls, cancer, autoimmune disease, infectious disease, hypertension and heart disease disease, and other diseases such as thyroid, prostate cancer. So we should understand the use of vitamin D well so that we can avoid the diseases. And here we have given detailed information about Vitamin D.

I. INTRODUCTION:-

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological effects[1][2]In humans, themost important compounds in this group are vitamin D3 (also known as cholecalciferol) andvitamin D2 (ergocalciferol).[1][2][3]

DISCOVERY:-

The first clear description of rickets was by Whistler in 1645. However, it was not until the Industrial Revolution with the mass movement of the population from the farms to the smoke filled cities that rickets became a public health problem, most notably in England where sunlight intensity was already marginal for much of the year. Mellanby in Great Britain and McCollum in the United States developed animal models for rickets and showed that rickets could be cured with cod liver oil. McCollum heated the cod liver oil to destroy its vitamin A content and found that it still had antirachitic properties; he named the antirachitic factor vitamin D. Steenbock and Black then demonstrated that UV irradiation of food, in particular non saponifiable lipids, could treat rickets. Meanwhile, clinical investigations revealed that rickets could be prevented or cured in children with sunlight or artificial UV exposure suggesting that what subsequently became known as vitamin D could be produced by irradiation of precursors in vivo. Ultimately, Askew et al. isolated and determined the structure of vitamin D_2 (ergocalciferol) from irradiated plant sterols (ergosterol), and Windaus et al. determined the structures and pathway by which 7-dehydrocholesterol (7-DHC) in the skin is converted to vitamin D_3 (cholecalciferol). The name vitamin D_1 refers to what proved to be an error of an earlier identification, and is not used. The structures and pathways of production of vitamin D_2 and D_3 are shown in figure 1. The structures of vitamins D_2 and D_3 differ in the side chain where D_2 contains a double bond (C_{22-23}) and an additional methyl group attached to C_{24}. In this chapter the designation of D will refer to both D_3 and D_2. [30]

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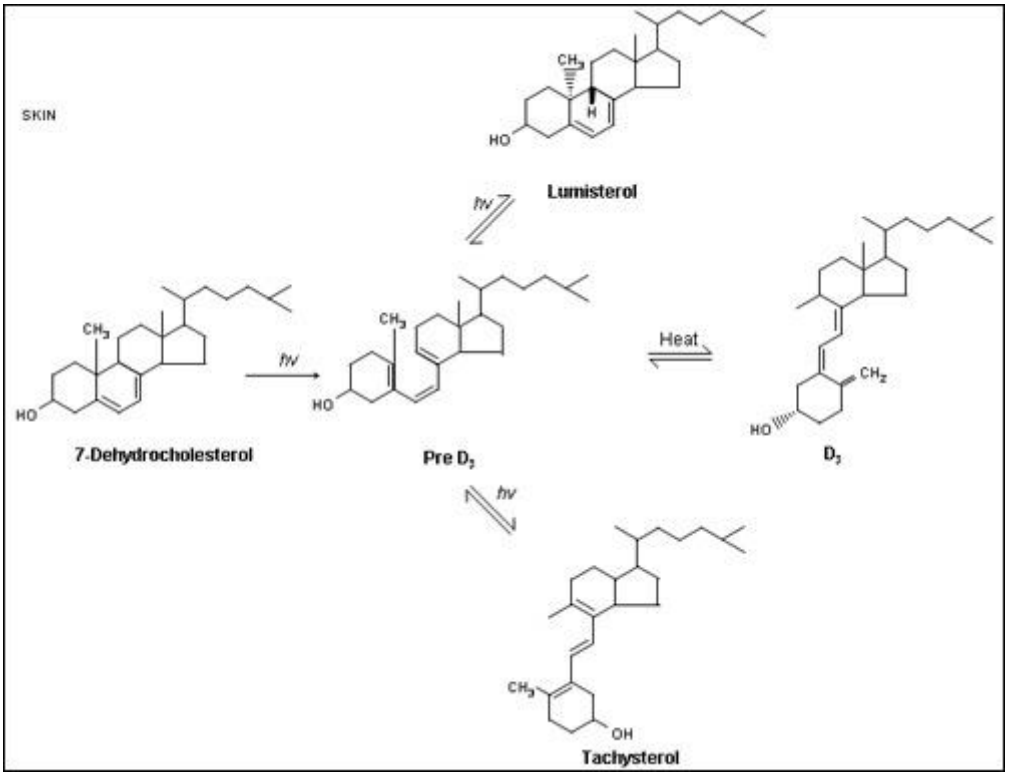

Figure 1.

The production of vitamin D3 from 7-dehydrocholesterol in the epidermis. Sunlight (the ultraviolet B component) breaks the B ring of the cholesterol structure to form pre- D3. Pre-D3 then undergoes a thermal induced rearrangement to form D3. Continued irradiation of pre- D3 leads to the reversible formation of lumisterol3 and tachysterol3 which can revert back to pre-D3 in the dark.[30]

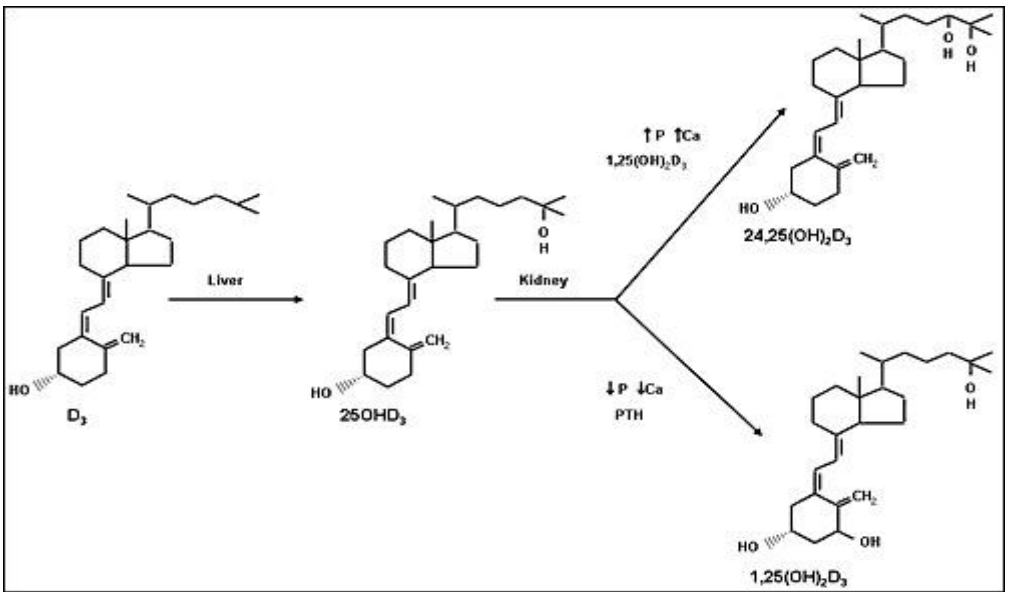

Figure 2.

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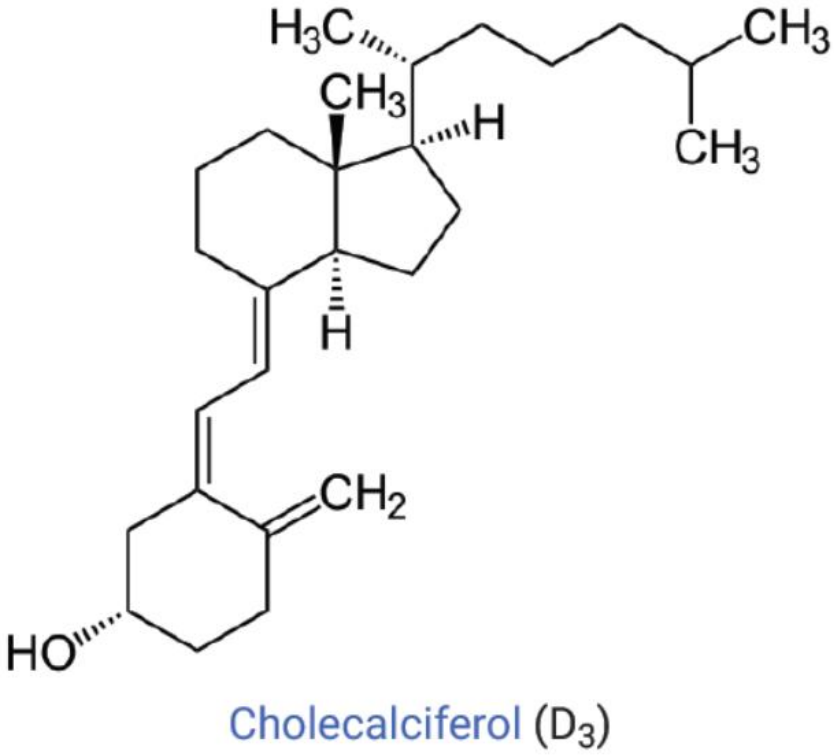
The metabolism of vitamin D. The liver converts vitamin D to 25OHD. The kidney converts 25OHD to 1,25(OH)2D and 24,25(OH)2D. Other tissues contain these enzymes, but the liver is the main source for 25-hydroxylation, and the kidney is the main source for 1-hydroxylation. Control of metabolism of vitamin D to its active metabolite, 1,25(OH)2D, is exerted primarily at the renal level where calcium, phosphorus, parathyroid hormone, FGF23, and 1,25(OH)2D regulate the levels of 1,25(OH)2D produced.[30]

VITAMIN D CHEMICAL STRUCTURE:-



Cholecalciferol (D_3)

Molecular Formula :-

$C_{27}H_{44}O_2$[22]

Synonyms**:-**

Calcifediol
Calcidiol
25-hydroxyvitamin D3
25-Hydroxycholecalciferol
19356-17-3[23]

Molecular Weight :

400.6[24]

IUPAC Name:-

(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-1-[(2R)-6-hydroxy-6-methylheptan-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol[25]

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The major natural source of the vitamin is synthesis of cholecalciferol in the lower layers of skin epidermis through a chemical reaction that is dependent on sun exposure (specifically UVB radiation). [4][5]Cholecalciferol and ergocalciferol can be ingested from the diet and fromSupplements. [6][2]Onlya few foods, such as the flesh of fatty fish, naturally contain significantamounts of vitamin D. [1][7]Vitamin D from the diet, or from skin synthesis, is biologically inactive. It is activated by twoprotein enzyme hydroxylation steps, the first in the liver and the second in the kidneys. [3]As vitamin D can be synthesized in adequate amounts by most mammals if exposed to sufficientsunlight, it is not essential, so technically not a vitamin. [2]Instead it can be considered ahormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol,which then produces effects via a nuclear receptor in multiple locations. [2]

TYPE:-

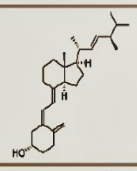
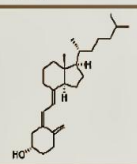
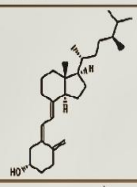
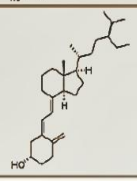
Name	Chemical composition	Structure
Vitamin D_1	Mixture of molecular compounds of ergocalciferol with lumisterol, 1:1	
Vitamin D_2	ergocalciferol (made from ergosterol)	
Vitamin D_3	cholecalciferol (made from 7-dehydrocholesterol in the skin).	
Vitamin D_4	22-dihydroergocalciferol	
Vitamin D_5	sitocalciferol (made from 7-dehydrositosterol)	

Fig.3 Type of vitamin D

Several forms (vitamers) of vitamin D exist. The two major forms are vitamin D2 or ergocalciferol, and vitamin D3 or cholecalciferol. Vitamin D without a subscript refers to either D2 or D3, or both, and is known collectively as calciferol. [8]

Chemically, the various forms of vitamin D are secosteroids, that is, steroids in which one of the bonds in the steroid rings is broken.[9]

Physiology of Vitamin D:-

Vitamin D can be produced in the skin as vitamin D_3 on exposure to ultraviolet-B (UVB) from the sun or obtained from the diet as vitamin D_2 or vitamin D_3. After vitamin D enters the body, it circulates bound to vitamin D-binding protein and is rapidly converted to its major circulating form, 25-hydroxyvitamin D (25(OH)D), by the liver. Under the influence of PTH, 25(OH)D is converted by the 1-alpha-hydroxylase (1α-OHase) in the kidney to form the hormonal form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Other tissues in the body have the 1α-OHase and can convert 25(OH)D to $1,25(OH)_2D$. However, only the renal 1α-OHase significantly contributes to circulating $1,25(OH)_2D$ levels. It is speculated that

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the presence of the extrarenal 1α-OHases allow 25(OH)D to be converted to $1,25(OH)_2D$ to work as a paracrine or autocrine hormone.

Circulating $1,25(OH)_2D$ enters the target cell, either in its free form or facilitated by megalin, and binds to the VDR in the cytoplasm, which then translocates to the nucleus and heterodimerizes with the retinoic × receptor. The $1,25(OH)_2D$-VDR-retinoic × receptor complex then binds to vitamin D response elements on DNA to increase transcription of vitamin D-regulated genes. Classic functions regulated by vitamin D include genes important for mineralization of bone and calcium transport in the intestine. Nonclassic or novel functions of vitamin D under investigation include genes important for innate immunity, cancer proliferation, muscle (both skeletal and smooth) function, and endothelial cell proliferation.

Vitamin D status is best determined by a serum 25(OH)D as opposed to $1,25(OH)_2D$, for several reasons including its long circulating half life (~3 weeks versus ~8 hours); the concentration of 25(OH)D is 1000× higher in circulation compared with $1,25(OH)_2D$ (ng/mL versus pg/mL); and the production of $1,25(OH)_2D$ is mainly under the influence of PTH, which tightly regulates calcium levels. Thus, $1,25(OH)_2D$ levels could be elevated in individuals with severe vitamin D deficiency to maintain normal serum calcium levels. As a mediator of CVD, it is believed that 25(OH)D is the best biomarker to describe vitamin D status, although this has not been proven. [28]

Pharmacology:-

Calcidiol is the precursor of vitamin D3. Vitamin D3 is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, in mineralization of bone, and for the assimilation of vitamin A. The classical manifestations of vitamin D deficiency is rickets, which is seen in children and results in bony deformaties including bowed long bones. Deficiency in adults leads to the disease osteomalacia. Both rickets and osteomalacia reflect impaired mineralization of newly synthesized bone matrix, and usually result from a combination of inadequate exposure to sunlight and decreased dietary intake of vitamin D. Common causes of vitamin D deficiency include genetic defects in the vitamin D receptor, severe liver or kidney disease, and insufficient exposure to sunlight. Vitamin D plays an important role in maintaining calcium balance and in the regulation of parathyroid hormone (PTH). It promotes renal reabsorption of calcium, increases intestinal absorption of calcium and phosphorus, and increases calcium and phosphorus mobilization from bone to plasma [26]

FUNCTION:-

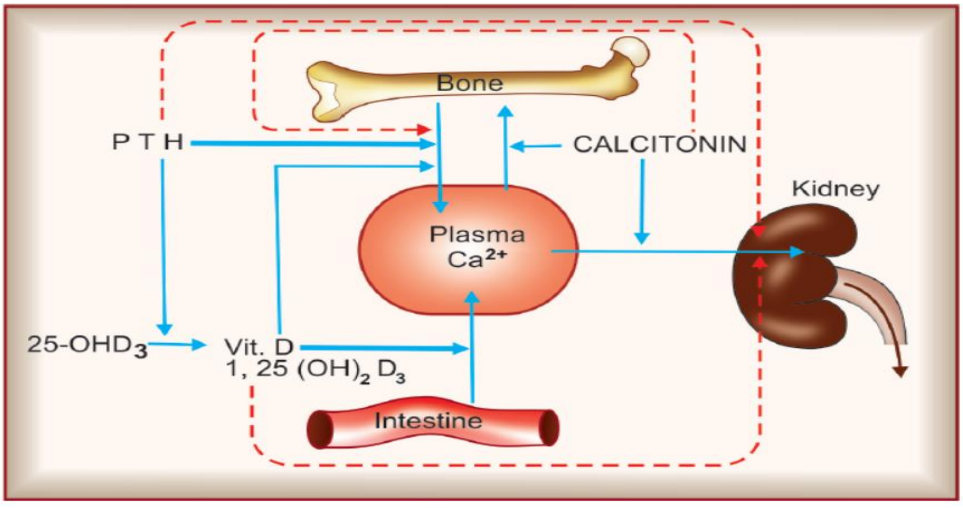

Fig.4 Calcium regulation in the human body. The role of active vitamin D (1,25-dihydroxyvitamin D, calcitriol) is shown in orange.

The active vitamin D metabolite calcitriol mediates its biological effects by binding to thevitamin D receptor (VDR), which is principally located in the nuclei of target cells [9]The bindingof calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the geneexpression of transport proteins (such as TRPV6 and calbindin), whichare involved in

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calciumabsorption in the intestine.[10]The vitamin D receptor belongs to the nuclear receptorsuperfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in mostorgans, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, andparathyroid gland cells leads to themaintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroidhormone and calcitonin) and to the maintenance of bone content.[11]One of the most important roles of vitamin D is to maintain skeletalcalcium balance bypromoting calcium absorption in the intestines, promoting boneresorption by increasingosteoclast number, maintaining calcium and phosphate levels for bone formation, and allowingproper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin Ddeficiency can result in lower bone mineral density and an increased risk of reduced bonedensity (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism inthe body.[12] Thus, vitamin D is also critical for bone remodeling through its role as a potentstimulator of bone resorption.[12]

BIOSYNTHESIS:-

Synthesis of vitamin D in nature is dependent on the presence of UV radiation and subsequentactivation in the liver and in the kidneys. Many animals synthesize vitamin D3 from 7-dehydrocholesterol, and many fungi synthesize vitamin D2 from ergosterol.[13][14]

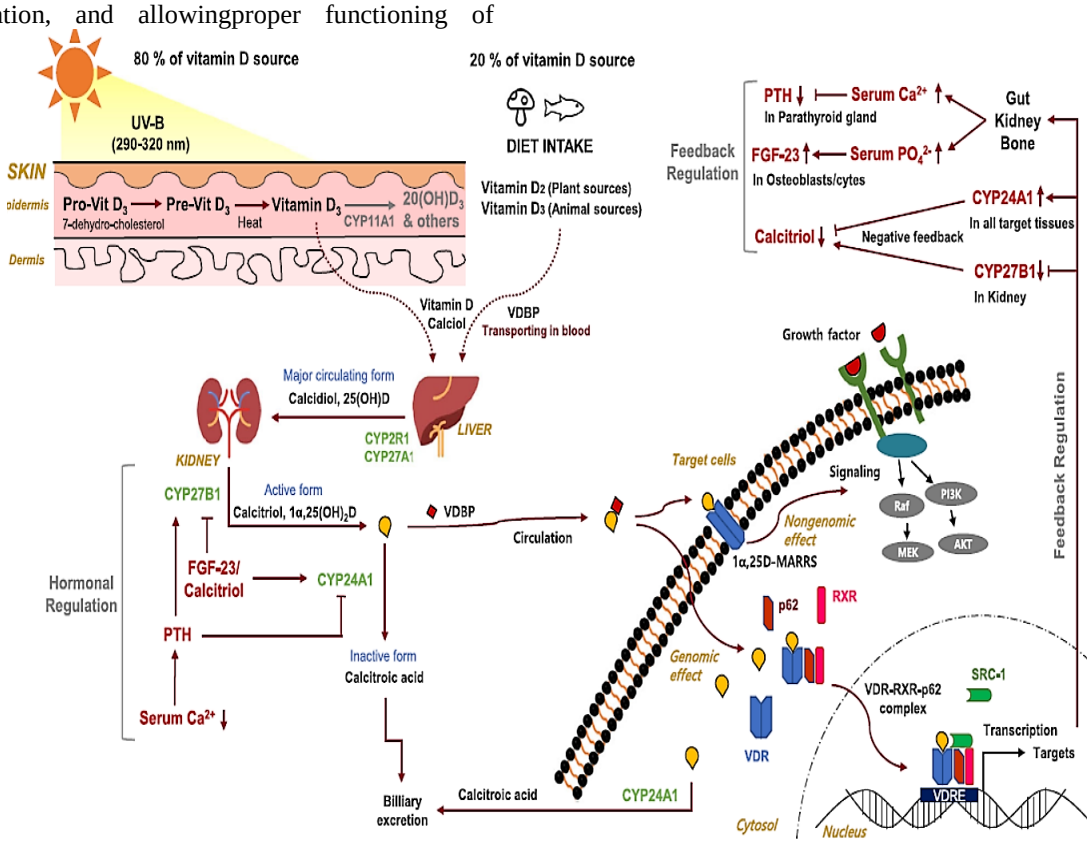

Fig.5 synthesis of vitamin d in body through solar radiation

Vitamin D2 is synthesized from ergosterol by UVBradiation in plants, yeasts, and fungi and can be ingestedin a diet containing plant source foods, such as mushrooms.Vitamin D3 is synthesized from 7-dehydrocholesterol by UVB radiation in the epidermisof skin and can be also ingested in a diet of animal sourcefoods, such as cod liver oil. Vitamin D (both vitamin D2and D3, calciol) originating from either the diet or the skinbinds to vitamin D-binding protein (VDBP) in circulationand is first delivered to the liver. In the liver, vitamin D is metabolized by vitamin D 25-hydroxylase (CYP2R1 and CYP27A1) to 25(OH)D (calcidiol),which is the major circulating form of vitamin D inserum. 25(OH)D is further metabolized by 25(OH)D1α-hydroxylase (CYP27B1) mainly in the proximal tubule of the kidney to 1α,25-dihydroxyvitamin D

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[1α,25(OH)2D,calcitriol], which is the most biologically active form ofvitamin D23,24. Calcitriol then enters the circulation and,after binding to VDBP, is delivered target tissues such asintestine, bone, and kidney, where vitamin D is known toregulate absorption, mobilization, and reabsorption,respectively, of calcium and phosphate21.

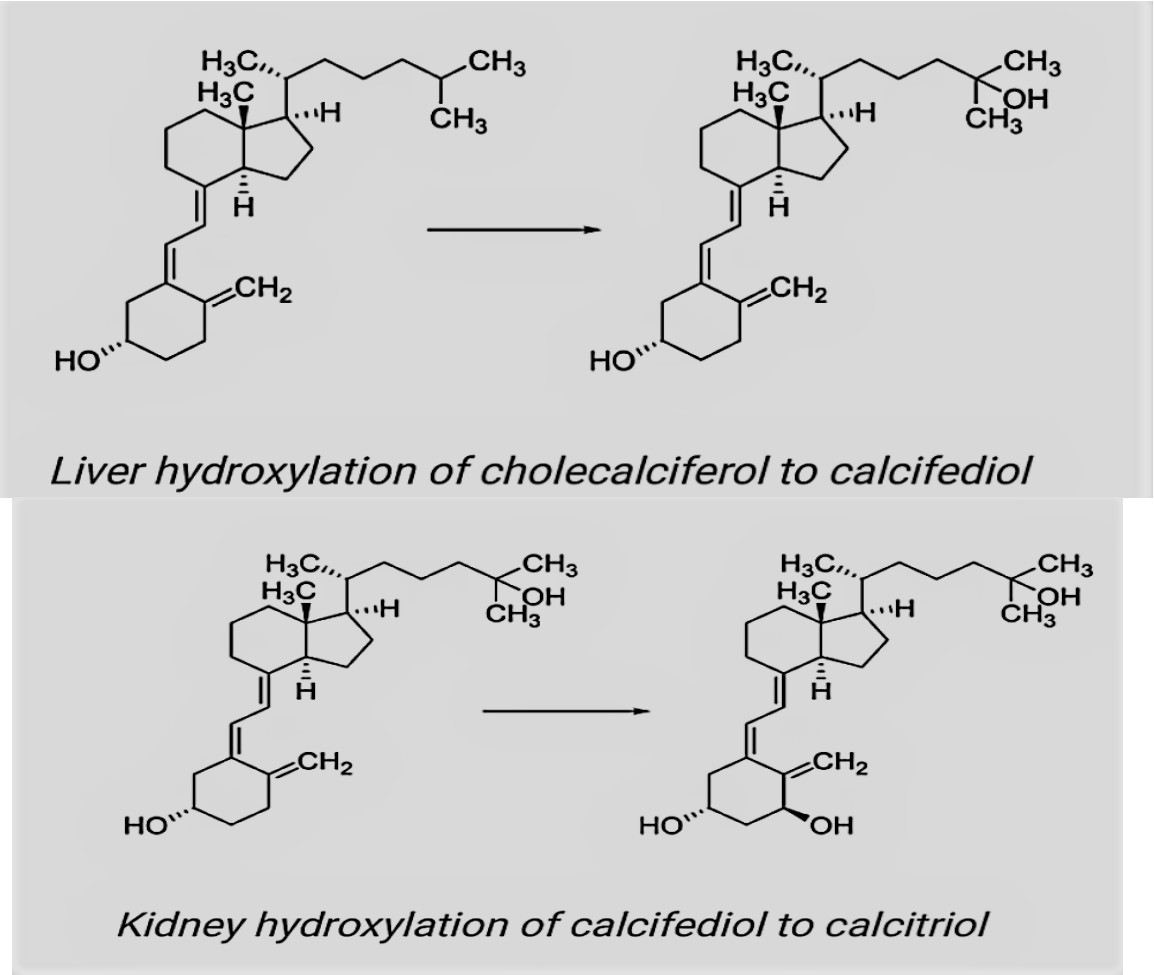

Fig.6 Vitamin D biotransformation in liver and kidney

METABOLISM:-

Vitamin D_3 produced in the epidermis must be further metabolized to be active. The first step, 25-hydroxylation, takes place primarily in the liver, although other tissues have this enzymatic activity as well. As will be discussed below, there are several 25-hydroxylases. 25OHD is the major circulating form of vitamin D. However, in order for vitamin D metabolites to achieve maximum biologic activity they must be further hydroxylated in the 1α position by the enzyme CYP27B1; $1,25(OH)_2D$ is the most potent metabolite of vitamin D and accounts for most of its biologic actions. The 1α hydroxylation occurs primarily in the kidney, although as for the 25-hydroxylase, other tissues have this enzyme. Vitamin D and its metabolites, 25OHD and $1,25(OH)_2D$, can also be hydroxylated in the 24 position. In the absence of 25-hydroxylation this may serve to activate the metabolite or analog as $1,25(OH)_2D$ and $1,24(OH)_2D$ have similar biologic potency. However, 24-hydroxylation of metabolites with an existing 25OH group reduces their activity and leads to further catabolism. The details of these reactions are described below. [31]

MECHANISM OF ACTION:-

The hormonal form of vitamin D, $1,25(OH)_2D$, is the ligand for a transcription factor, the vitamin D receptor (VDR). Most if not all effects of $1,25(OH)_2D$ are mediated by VDR acting primarily by regulating the expression of genes

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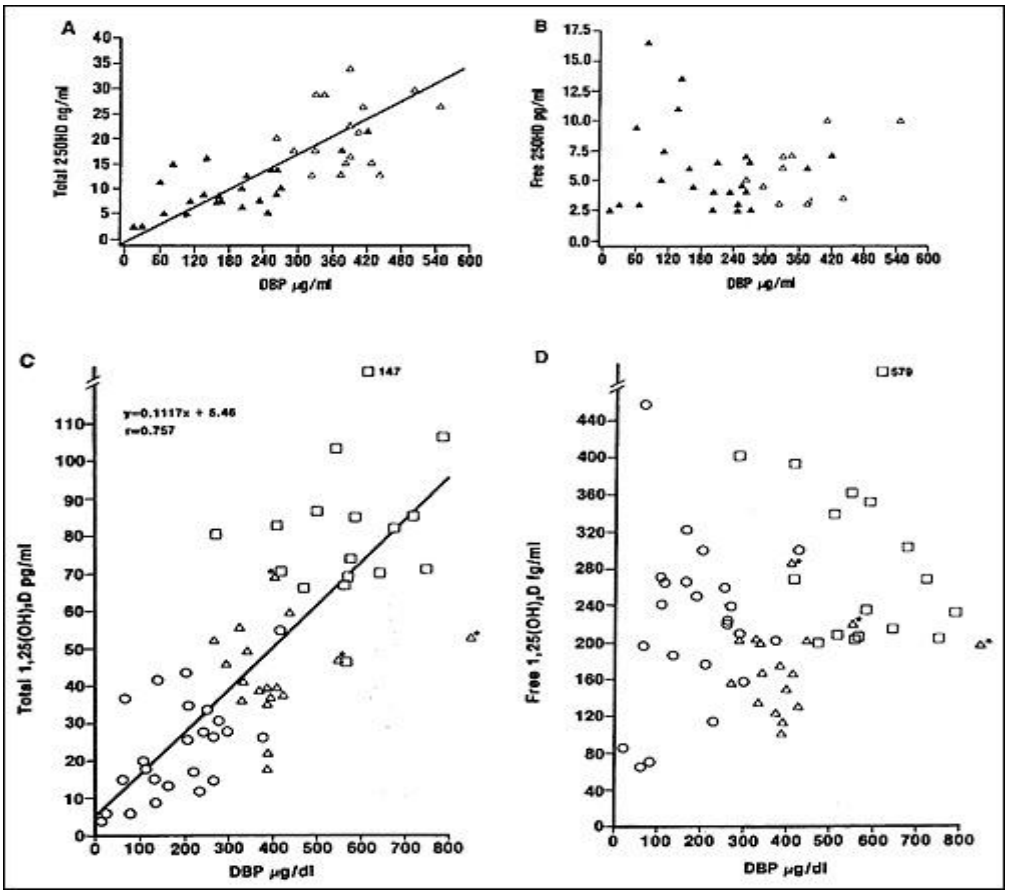
whose promoters contain specific DNA sequences known as vitamin D response elements (VDREs). There are thousands of VDREs throughout the gene, often thousands of base pairs away from the coding portion of the gene regulated. However, some actions of $1,25(OH)_2D$ are more immediate, and may be mediated by a membrane bound vitamin D receptor that has been less well characterized than the nuclear VDR or by the VDR acting outside of the nucleus. On the other hand some actions of VDR do not require its ligand $1,25(OH)_2D$. Our understanding of the mechanism by which VDR regulates gene expression has increased enormously over the past few years. [33]

TRANSPORT IN BLOOD:-

The vitamin D metabolites are transported in blood bound primarily to vitamin D binding protein (DBP) (85-88%) and albumin (12-15%) . DBP concentrations are normally 4-8mM, well above the concentrations of the vitamin D metabolites, such that DBP is only about 2% saturated. DBP has high affinity for the vitamin D metabolites ($Ka=5x10^8M^{-1}$ for 25OHD and $24,25(OH)_2D$, $4x10^7M^{-1}$ for $1,25(OH)_2D$ and vitamin D), such that under normal circumstances only approximately 0.03% 25OHD and $24,25(OH)_2D$ and 0.4% $1,25(OH)_2D$ are free . Conditions such as liver disease and nephrotic syndrome resulting in reduced DBP and albumin levels will lead to a reduction in total 25OHD and $1,25(OH)_2D$ levels without necessarily affecting the free concentrations (figure). Similarly DBP levels are reduced during acute illness, potentially obscuring the interpretation of total 25OHD levels . Earlier studies with a monoclonal antibody to measure DBP levels suggested a decreased level in African Americans consistent with their lower total 25OHD levels, but these results were not confirmed using polyvalent antibody based assays . Vitamin D intoxication can increase the degree of saturation sufficiently to increase the free concentrations of $1,25(OH)_2D$ and so cause hypercalcemia without necessarily raising the total concentrations. [32]



https://www.ncbi.nlm.nih.gov/books/NBK278935/bin/vit-d-prod-metab-moa_figure.jpg

Figure.7

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Correlation of total 25OHD (A) and 1,25(OH)2D (C) levels to DBP; lack of correlation of free 25OHD (B) and 1,25(OH)2D (D) levels to DBP. Data from normal subjects (open triangles), subjects with liver disease (closed triangles, open circles), subjects on oral contraceptives (open triangles*), and pregnant women (open squares) are included. These data demonstrate the dependence of total 25OHD and 1,25(OH)2D concentrations on DBP levels which are reduced by liver disease. However, the free concentrations of 25OHD and 1,25(OH)2D are normal in most patients with liver disease. Reprinted with permission from the American Society for Clinical Investigation. [32]

Correlation with varius condition /disease:

❖ **VITAMINS AND ANDROGEN:**

Men with sufficient 25(OH)D levels (> or =30 microg/l) had significantly higher levels oftestosterone and FAI and significantly lower levels of SHBG when compared to 25(OH)D insufficient(20-29.9 microg/l) and 25(OH)D-deficient (<20 microg/l) men ($P < 0.05$ for all). In linear regressionanalyses adjusted for possible confounders, we found significant associations of 25(OH)D levels withtestosterone, FAI and SHBG levels ($P < 0.05$ for all). 25(OH)D, testosterone and FAI levels followed asimilar seasonal pattern with a nadir in March (12.2 microg/l, 15.9 nmol/l and 40.8, respectively) andpeak levels in August (23.4 microg/l, 18.7 nmol/l and 49.7, respectively) ($P < 0.05$ for all).[15]

❖ **VITAMINS AND THYROID:**

that patients with hypothyroidism suffered from hypovitaminosis D with hypocalcaemia that is significantly associated with the degree and severity of the hypothyroidism. That encourages the advisability of vit D supplementation and recommends the screening for Vitamin D deficiency and serum calcium levels for all hypothyroid patients. [16]

❖ **PSA:**

Vitamin D inhibits the development and growth of prostate cancer cells. Epidemiologic results on serum vitamin D levels and prostate cancer risk have, however, been inconsistent. Scientist and doctor conducted a longitudinal nested case-control study on Nordic men (Norway, Finland and Sweden) using serum banks of 200,000 samples. they studied serum 25(OH)-vitamin D levels of 622 prostate cancer cases and 1,451 matched controls and found that both low (</=19 nmol/l) and high (>/=80 nmol/l) 25(OH)-vitamin D serum concentrations are associated with higher prostate cancer risk. The normal average serum concentration of 25(OH)-vitamin D (40-60 nmol/l) comprises the lowest risk of prostate cancer. The U-shaped risk of prostate cancer might be due to similar 1,25-dihydroxyvitamin D(3) availability within the prostate: low vitamin D serum concentration apparently leads to a low tissue concentration and to weakened mitotic control of target cells, whereas a high vitamin D level might lead to vitamin D resistance through increased inactivation by enhanced expression of 24-hydroxylase. It is recommended that vitamin D deficiency be supplemented, but too high vitamin D serum level might also enhance cancer development.[17]

❖ **VITAMINS AND CHOLESTEROL:**

The median of serum 25(OH)D concentration was 47 (27–92.25) nmol/L in all subjects. The overall percentage of 25(OH)D ≦ 50 nmol/L was 58.5% (males 54.4%, females 63.7%). The serum 25(OH)D levels were inversely associated with TG (β coefficient = -0.24, $p < 0.001$) and LDL-C (β coefficient = -0.34, $p < 0.001$) and positively associated with TC (β coefficient = 0.35, $p < 0.002$) in men. The associations between serum 25(OH)D and LDL-C (β coefficient = -0.25, $p = 0.01$) and TC (β coefficient = 0.39, $p = 0.001$) also existed in women. The serum 25(OH)D concentrations were negatively associated with AIP in men ($r = -0.111$, $p < 0.01$) but not in women. In addition, vitamin D deficient men had higher AIP values than vitamin D sufficient men. Furthermore, the occurrences of dyslipidemias (reduced HDL-C, elevated TG and elevated AIP) correlated with lower 25(OH)D levels in men, whereas the higher TC and LDL-C associated with higher 25(OH)D levels in women. the serum 25(OH)D levels are closely associated with the serum lipids and AIP. Vitamin D deficiency may be associated with the increased risk of dyslipidemias, especially in men. The association between vitamin D status and serum lipids may differ by genders.[18]

❖ **VITAMINS D AND HDL:-**

High density lipoprotein cholesterol (HDL-C) was significantly higher in subjects with sufficient vitamin D compared to those with insufficient or deficient vitamin D (p-value< 0.01). 25-hydroxyvitamin D was positively associated

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with HDL-C (p-value< 0.01) and inversely associated with HbA1c (p-value = 0.02). 25-hydroxyvitamin D was not significantly correlated with other cardiovascular biomarkers including blood pressure, glucose, and other components of lipid profile (p-values> 0.05).[19]

❖ **Anticancer properties of Vitamin D:**

As the beneficial effects of vitamin D in cancer preventionand treatment have been observed in epidemiologicaland preclinical studies, diverse mechanisms havebeen proposed to explain its anticancer effects. Accumulatingdata suggest that vitamin D can regulate theentire process of tumorigenesis, from initiation to metastasis and cell–microenvironment interactions [20]

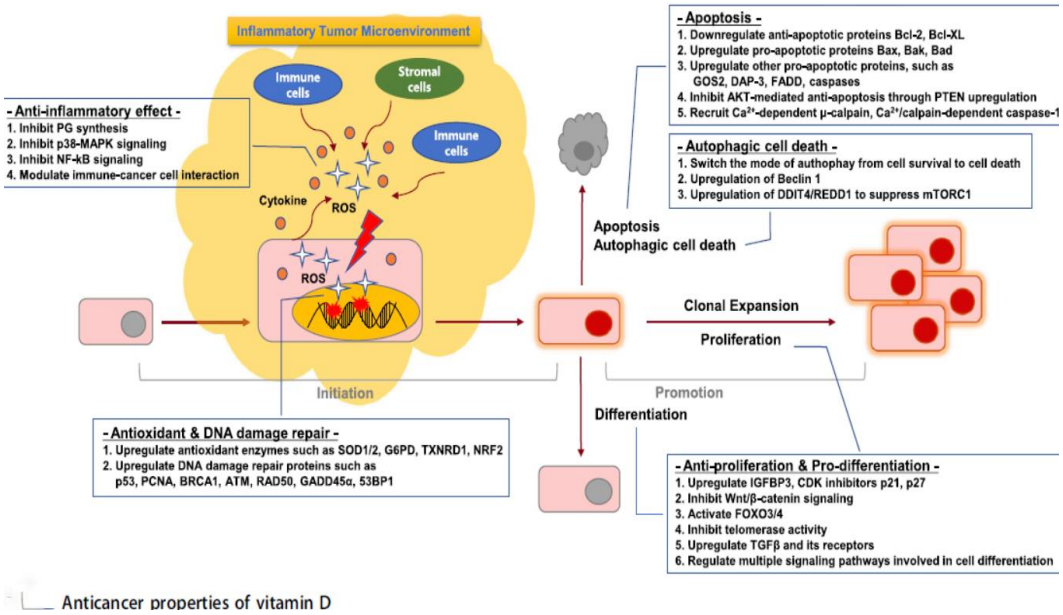

Fig.8 Vitamin D work on tumor cells

Initiation stage: role in anti-inflammation, antioxidant defense and DNA damage repair

Tumor initiation is a process that introduces irreversible genetic mutations in normal cells, consequently inducing transformation. A body of data supports that vitamin D plays a key role in preventing the initiation stage by exerting anti-inflammatory and antioxidant defenses and DNA damage repair processes

Anti-inflammation:-

Chronic inflammation is a low-grade, prolonged inflammatory response resulting in progressive destruction and regeneration of tissues by reactive oxygen species (ROS) and cytokines secreted at the site of inflammation. It is now well-accepted that chronic inflammation is one of the main contributors to the initiation of tumorigenesis. Accumulating data suggest that vitamin D exerts anti-inflammatory effects via at least four mechanisms.

First, calcitriol inhibits the prostaglandin (PG) pathway involved in pro-inflammatory responses through inhibition of the expression of cyclooxygenase-2 (COX-2) and PG receptors, and degradation of PGs. In prostate cancer cells, calcitriol reduces the expression levels of COX-2 and that of PG receptors EP2 and FP, whereas it increases the expression of 15-hydroxyprostaglandin-dehydrogenase (15-PGDH), a NAD^+-dependent enzyme responsible for the degradation of PGE2. In addition, the decrease of COX-2 mRNA expression and PGE2 production has also been reported in calcitriol-treated breast cancer cells. Consistently, the expression of VDR is inversely correlated with that of COX-2 in malignant breast cell lines and ovarian cancer tissues, supporting the role of the calcitriol–VDR axis in suppressing the expression of COX-2 and production of PGs. [27]

Vitamin D-based cancer therapy: future directions:

Although randomized clinical trial data are still lacking, several epidemiological, clinical, preclinical, and in vitro experimental data strongly suggest that the activation of vitamin D signaling could be a promising strategy for prevention, as

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well as treatment of many types of cancer. As such, several therapeutic interventions targeting dysregulated vitamin D metabolism or activity have been investigated and developed for cancer therapy. However, there are some potential limitations of vitamin D-based cancer therapy, which should be taken into consideration to design better therapeutic strategies.

One potential caveat of systemic activation of vitamin D signaling would be the high risk of hypercalcemia, which can result in serious detrimental health effects. To minimize the hypercalcemic effect, many efforts are currently being directed to develop biased agonists of VDR that have little effect on inducing hypercalcemia while retaining anticancer activities comparable to those of calcitriol. To date, nearly 1500 vitamin D analogs have been tested for such effects, but only a few among those compounds have been approved for further evaluation in clinical trials in patients with leukemia, breast, prostate, and colon cancers. Moreover, the metabolites produced from the CYP11A1-driven alternative vitamin D metabolism pathway have been shown to be a biased agonist of VDR with less calcemic effect while retaining anti-proliferative properties in cancer comparable to those of calcitriol. As the alternative vitamin D metabolism pathway via CYP11A1 is just beginning to be understood, its role in cancer and the relative contributions of VDR and ROR are largely unknown. Thus, intensive research on the alternative vitamin D metabolism pathway and successful application of this pathway for cancer therapy is warranted in the future. In addition, increasing local concentrations of calcitriol in cancer cells would be another strategy to avoid the hypercalcemic effect of calcitriol. As a calcitriol degrading enzyme, CYP24A1 is frequently overexpressed in many cancers; the inhibition of CYP24A1 can increase local concentrations of calcitriol in cancer cells. Indeed, recent studies showed that inhibition of CYP24A1 by genetic knockdown or pharmacological inhibition greatly sensitized the anticancer effect of calcitriol. So far, several CYP24A1-specific inhibitors have been developed for clinical purposes and it remains to be seen whether any of these will be used for cancer therapy with suitable clinical effectiveness and safety.[50]

❖ **Vitamin d and heart:**

A reduction in contractility has been observed in vitamin D deficient animals. This may be due to lack of vitamin D or theaccompanying hypocalcemia and hypophosphatemia. However, in vitro 1,25(OH) D stimulates calcium uptake by cardiacmuscle cells. In addition 1,25(OH) D inhibits the expression of atrial naturetic factor, one of the few genes with anegative VDRE in its promoter. Deletion of the VDR specifically in cardiac muslce leads to hypertrophy and fibrosis .Low circulating levels of 25OHD are associated with increased risk of myocardial infarction in men[21]

❖ **Vitamin d and skin:**

Epidermal keratinocytes are the only cells in the body with the entire vitamin D metabolic pathway. As described earlier,production of vitamin D from 7-dehydrocholesterol takes place in the epidermis. However, the epidermis also containsCYP27A1, the mitochondrial enzyme that 25-hydroxylates vitamin D, and CYP27B , the enzyme that produces1,25(OH) D from 25OHD. The CYP27B1 in keratinocytes is differently regulated than CYP27B1 in renal cells. Although PTHstimulates CYP27B1 activity in the keratinocyte, the mechanism appears to be independent of cAMP. Cytokines such astumor necrosis factor-α and interferon-γ stimulate CYP27B1 activity . 1,25(OH) D does not exert a direct effect onCYP27B1 expression in keratinocytes, but regulates 1,25(OH) D levels by inducing CYP24A1 thus initiating the catabolism of1,25(OH) D. CYP27B1 is expressed primarily in the basal cells of the epidermis ; as the cells differentiate the mRNA and protein levels of CYP27B1and its activity decline.[21]

❖ **Vitamin D as a Factor in Improving Insulin Sensitivity:**

The pancreas possesses the VDR and the 1α-OHase and, thus, has the vitamin D machinery for circulating 25(OH)D to be converted to $1,25(OH)_2D$ to work as a paracrine or autocrine hormone Early studies have suggested that vitamin D-deficient rodents are not able to adequately secrete insulin compared with vitamin D-sufficient controls. Several small observational and case-control studies have been published to suggest that vitamin D deficiency is associated with insulin resistance or impaired insulin secretion. Several studies, including 1 published by Scragg et al, demonstrated that lower vitamin D status was associated with increased risk of diabetes and better insulin sensitivity. In a longitudinal study of Finnish men and women, a 40% reduction in risk of developing type 2 diabetes was observed after 17

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years of follow-up in those with 25(OH)D levels >28 ng/mL at baseline. One prospective study evaluated the effect of vitamin D supplementation (400 IU daily) on fasting glucose and found that subjects with impaired fasting glucose at baseline had less of a rise in fasting glucose concentrations during a 3-year period compared with subjects randomized to placebo.Taken together, this early evidence suggests that vitamin D may have an important role in regulating glycemic control, which may also contribute to a beneficial effect on cardiovascular outcomes. [29]

❖ **Vitamin D as a Direct Factor on Cardiac Tissues and the Vasculature:-**

A few in vitro and in vivo studies have evaluated the role of vitamin D acting directly on cardiac tissue, especially in response to injury. Rahman et al demonstrated that matrix metalloproteinases, proteins that contribute to aberrant cardiomyocyte remodeling in response to injury and atherosclerosis, were upregulated in VDR knockout mice. VDR knockout mice have impaired cardiac relaxation and contractility and develop left ventricular hypertrophy. [34-46]

II. CONCLUSION:-

Vitamin D has become one the most talked about supplements in recent years. To control this particular deficiency: The society must adapt a series of e actions. Knowing and applying the right way of treatments .

Vitamin D supplementation correction is advised in all persons whose serum 25(OH)D falls below 50 nmol/I (20 ng/ml), and achieving a target of 75 nmol/I (30 ng/ml) is particularly suited for frail, osteoporotic, and older patients

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