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ARTICLE

MIRACULOUS PHYSIOLOGICAL ACTIVITIES OF VITAMIN D AND ITS ROLE IN HUMAN HEALTH AND DISEASES

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Vitamin D, the sunshine vitamin or calciferol is endowed with the unique property of functioning as a hormone. Chemically, it is a secosterol produced in human skin from 7-dehydrocholesterol in presence of sunlight which contains ultraviolet-B radiations having the wavelength ranging from 290 to 320 nanometer (nm). In addition to exposure of body to sunlight, diet and dietary supplements are also sources of vitamin D to human beings. It is well known that vitamin D has a crucial role in calcium-phosphate homeostasis and in the maintenance of healthy bones and teeth. The discovery of vitamin D receptors (VDR) in almost all the vital organs of human body has opened a new era in vitamin D research. New researches have revealed that besides the known sketal functions, vitamin D is involved in large number of other biological functions.

Introduction

In the realm of vitamins, vitamin D occupies an unique position as it acts as a hormone, and human body gets its supply through diet as well as by its synthesis in human skin from a compound 7- dehydrocholesterol in presence of sunlight. Vitamin D is also known as sunshine vitamin or calciferol. It exists mainly in two forms, vitamin D_2 and vitamin D_3 that are also known as ergocalciferol and cholecalciferol, respectively. These two forms are almost similar in their structures and physiological properties and, therefore, the term vitamin D implies vitamin D_2 and D_3 or both[1,2]. Vitamin D is a fat-soluble prohormone that plays a vital role in the maintenance of bone and muscle health in human beings by promoting absorption and metabolism of calcium and phosphorous[3]. The discovery of vitamin D, and victory over the catastrophic disease rickets are regarded as great achievements in medical science[4]. Thus, exposure to sunlight and use of vitamin D-containing cod liver oil provided effective treatment for the rickets. In this disease, bones of afflicted children become soft like cartilage and consequently, they are unable to sit, crawl and walk. As they grow, these soft bones bend due to the increased weight, and large number of abnormal changes become visible[5]. In adults, vitamins D deficiency causes osteomalacia and osteoporosis which are also serious diseases of bones.

Recent researches on vitamin D indicated that in addition to bone-health, it has a pivotal role in conducting many important metabolic reactions in almost all the organs of human body. Vitamin D receptors (VDR) are present in every tissue and cell of human body[2]. This discovery indicated that vitamin D not only regulates the calcium and bone metabolism, but it has other biological functions also[6,7]. In the words of Dr. Andrew Weil, founder of Arizona Center for Integrative Medicine, " *Increasing the amount of vitamin D in the body can prevent and help treat a remarkable number of ailments, from obesity to arthritis, from high blood pressure to back pain, from*

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diabetes to muscle cramp, from upper respiratory tract infection to infectious diseases and from fibromyalgia to cancers of breast, colon, pancreas, prostate and ovaries. It can safeguard pregnancy, support ideal weight management, reduce abnormal cell growth and stave off infections and chronic diseases. Who would not want these benefits?"[2].

Historical Perspective

The story of vitamin D begins with the discovery of bone deforming disease rickets which was prevalent among children in early 1660s in the west and south of England. It was named as "English disease" also. Soon, this disease assumed the dimension of an epidemic and became evident in other part of the world including northern Europe and North America[8]. The importance of exposure to sun for the treatment and prevention of rickets was discovered by Polish physician, Sniadecki in 1822[9]. In 1890, Theobold A. Palm, a medical missionary, supported the use of curative power of sunlight and promoted systematic use of sunbath to prevent rickets[10]. Subsequently in 1919, Huldschinsky found that exposure to ultraviolet radiations was an 'infallible remedy' for different forms of rickets in children. In 1921, two New York doctors, Hess and Unger, performed an experiment and supported the use of sunlight for the cure of rickets[11,12].

After this discovery, scientists focused their attention on therapeutic potential of some foodstuffs. British doctor Sir Edward Mellanby thought that rickets might be a dietary deficiency disease and suggested the use of cod liver oil for its treatment[13,14]. In 1922, McCollum discovered a factor in cod liver oil which was very effective in the prevention and treatmenst of rickets. This factor was named as vitamin D because it was the fourth vitamin discovered by that time (after the discovery of vitamin A, B and C)[15]. Many forms of vitamin D were later discovered and designated vitamins D_1, D_2, D_3 and D_4. But only vitamin D_2 and vitamin D_3 are of biological significance. Therefore, the term vitamin D (without superscript) is used for vitamin D_2 or D_3 or both.

The isolation and identification of vitamin D_2 was carried out by Askew *et al.* in 1931 by irradiation of ergosterol[16,17]. The high concentration of ergosterol in molds, yeast and certain other vegetable sources indicated that vitamin D_2 is the plant form of of vitamin D. In 1935, 7-dehydrocholesterol was isolated by Adolf Windlauss *et al.* from pig and human skin and subsequently, they prepared it by a synthetic method and converted it to vitamin D_3 by UV irradiation[18,19]. Proper identification of vitamin D_3 and its formation from 7-dehydrocholesterol was confirmed by Esvelt *et al.* in 1978 by mass spectrometry[20]. Both vitamin D_2 and D_3 can be prepared by synthetic method also and their synthetic forms are used for supplementation.

Sources of Vitamin D

Human beings meet their requirement of vitamin D mainly through exposure to sunlight and dietary intake[21,22]. Vitamin D naturally occurs in a limited number of foods such as fatty fishes: salmon, mackerel, sardines, herring and fish oils, mainly cod liver oil. Egg-yolks also contain vitamin D in a considerable amount. Yeast and mushrooms make a large amount of ergosterol, and on exposure to sunlight and UV irradiations they are good dietary source of vitamin D. The amounts of vitamin D naturally present in milk, milk products and meat are very scanty. In many countries of the world, some food items are fortified with vitamin D. In USA and some other countries, it is a common practice to fortify milk, milk products (yoghurt, cheese, etc.), fruit juices, some breads and cereals with vitamin D in order to increase their vitamin D contents.

Sunlight is the primary source of vitamin D for most people in a natural way. However, it requires certain precautions in order to avoid the risk of melanoma, skin cancer and sunburn[22]. The effectiveness of solar radiations to provide vitamin D is adversely affected by certain factors such as climate, clouds, ozone thickness, aerosol, atmospheric pollution, clothing habits including traditional use of '*burqha*' and '*purdah*'. Increased amount of melanin in human skin also retards the formation of vitamin D. Melanin is the pigment responsible for the complexion of human skin. In the skin of people with dark complexion, the concentration of melanin is high and in presence of sunlight, it also absorbs UV-B radiation causing lesser absorption of these radiations by 7- dehydrocholesterol which results in low production of vitamin D.

Production and Metabolism of Vitamin D

Most of the recent studies have reported that vitamin D_2 is as effective as vitamin D_3[2]. Vitamin D_2 is plant-derived and it is produced exogenously by UV-B radiations (Wavelength 290-320 nm) from the ergosterol present in yeast[23]. Vitamin D_3 is produced endogenously in human skin when it is exposed to sunlight. Both forms of vitamin D are biologically inactive and their activation take place only when they enter liver and kidneys[13]. Vitamin D_3 and vitamin D_2, on reaching liver through blood circulation, are metabolized to 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2 respectively (Scheme) which are collectively known as 25-hydroxyvitamin D or calcidiol.

On subsequent movement to kidneys, these two forms are further metabolized to 1,25-dihydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_2, respectively (Scheme) which are collectively known as 1,25-dihydroxyvitamin D or calcitriol. The predominant hydroxy derivative of the vitamin D which circulates in blood, is 25-hydroxyvitamin D, and its quantity in blood is used to determine the levels of vitamin D in human body. 1,25-Dihydroxyvitamin D is the physiologically active derivative of vitamin D which acts as a hormone, regulating and modulating many biologically significant reactions of human life[7,13]. 1,25-Dihydroxyvitamin D is a secosteroid hormone. Its biological potential can be imagined by the fact that directly or indirectly it is involved in targetting more than 25000, genes or about 6% of human genome[2].

Role of vitamin D in the secretion of hormones such as insulin, regulation of immune function, regulation of cellular proliferation of keratinocyte *etc*. has also been reported. These discoveries suggest that vitamin D is not only required for absorption of calcium and phosphorous from food for maintaining the bone health, but it has some more functions. These startling observations started a new era in vitamin D research.

Physiological Activity and Disease Prevention

In the beginning of the present century, it was discovered that vitamin D receptors (VDR) are present in almost all the tissues and cells of human body, and that an enzyme, 25-hydroxyvitamin D-1á-hydroxylase, which is involved in transformation of 25-hydroxyvitamin D into biologically active hormonal form 1,25-dihydroxyvitamin D is present in a multitude of cells in various parts of body, other than kidneys[24]. Several clinical studies revealed that vitamin D can exert preventive effect on a wide range of physiological disorders. Role of vitamin D in resolving the sketal problems was already studied long back since the discovery of rickets and other allied problems. But the crucial role of vitamin D in non-sketal diseases is a consequence of above mentioned revolutionary discoveries.

Sketal Disorders: The well known property of vitamin D is in the treatment of rickets in children and osteomalacia in children and adults. It is well established that absorption of sufficient amount of calcium and phosphorous is necessary for preventation of bone diseases. In the absence of vitamin D, only 10-15% of dietary calcium and about of 60% of phosphorous is absorbed. In presence of vitamin D or its metabolite, 1,25-dihydroxyvitamin D, the efficiency of intestinal calcium and phosphorous absorption is increased to 30 - 40% and 80% respectively[7]. In adults, vitamin D deficiency was found to lead to mineralization defects in the skeleton causing osteomalacia and induced secondary hyperparathyroidism with consequent bone loss and osteoporosis. Osteomalacia is the softening of bone (Greek: *osteo*, meaning bone; *malakia*, meaning softness). In osteoporosis, bones become porous and brittle. The defficiency of vitamin D is associated with low bone mineral content and density. Due to lowering of bone mineral density (BMD), bones become weak and consequently, risk of fractures is increased. It significantly contributes to morbidity and morality in aged persons[22]. Muscle weakness is also attributed to vitamin D deficiency. People with complaints of non-specific muscular weakness, muscle aches and pains have been found to be considerably deficient in their serum vitamin D concentration[22] .Weakness of muscles is known to increase the number of falls which frequently result in fractures, particularly in hip fractures, mostly in those older than 70 years. It is reported that supplementation of vitamin D in reasonable amounts is needed to prevent the incidence of falls.

Non-sketal Disorders: Besides regulating the calcium homeostasis, 1,25-dihydroxyvitamin D has some other roles in human physiology, *e.g.*, inhibiting cellular growth, stimulating the insulin production in pancreas, modulating immune function and inhibiting rennin production. By virtue of these potent properties, vitamin D plays a pivotal role in prevention and treatment of many challenging diseases. Many organs of human body including brain, heart, pancreas, skin and immune system are provided with vitamin D receptors (VDR) indicating that these organs also require vitamin D for their proper functioning and protecting the human beings from diseases resulting from malfunctioning of these vital organs. A glimpse of the vital roles of vitamin D in the prevention of some of the acute and chronic diseases is being given below.

Cancer: The use of sunlight for the prevention of cancer was reported some 70 years ago[25]. Vitamin D is one of the potent hormones for regulating cell growth. Some laboratory experiments indicate that vitamin D helps in preventing uncontrolled cell multiplication (which causes cancer) by reducing cell division, inhibiting the blood supply to tumours (*angiogenesis*), enhancing the death of cancer cells (*apoptosis*) and restricting the expansion of cancer cells (*metastatis*). Vitamin D plays a protecting role against cancer as evident by many research studies[22]. The dreaded disease cancer is one of the leading causes of death in the world. According to a report of World Health Organisation, 19.3 million new cases are anticipated to emerge per year by 2025[26].

Cardiovascular Diseases: These are the diseases that involve heart or blood vessels. The beneficial effect of vitamin D on cardiovascular diseases in due to presence of vitamin D receptors (VDR) in the endothelium and vascular smooth muscle and cardiac muscle cells. Vitamin D possesses anti-atherosclerotic property which is responsible for inhibition of foam cell formation and smooth cell proliferation, the expression of adhesion molecule on endothelial cells and the release of inflammatory mediators[22]. Hypertension is one of the common problems widely prevalent in modern society. Vitamin D provides an effective cure for it also. An interesting study revealed that hypertension patients, on exposure to ultraviolet-B radiations three times a week for three months, showed an elevation in their 25-dihydroxyvitamin D level in blood by approximately 180%, and their systolic and diastolic blood pressure were also found to be normal[7]. According to a report (Times of India, dated July 10, 2018) the death rate due to cardiovascular diseases decreased by 41% in USA, between 1990 and 2016, whereas in India, it increased by about 34% in the same period. Greater awareness about the health benefits of vitamin D in USA, compared to India, may be a probable cause of this fact.

Schizophrenia and Depression: These diseases are linked with brain disorder, and vitamin D is essential for their eradication. Incidences of schizophrenia and depression are associated with vitamin D deficiency. Maintenance of adequate vitamin D levels in utero and during early stage of human life is important for brain development and proper functioning of brain[7].

Autism: It is a serious life-long developmental disorder which impairs the ability to communicate and interact. In India, there are more than one million cases of this disease. Autism typically appears during childhood. This diseases is correlated with vitamin D deficiency and hypovitominosis during the prenatal period or during the early years of childhood. Evidences obtained from epidermiological and clinical examination support this fact. But further confirmation of these studies is necessary[26].

Tuberculosis (TB): Tuberculosis is responsible for two million deaths a year[22]. According to an estimation, 33% of the global population is infected by latent tuberculosis. Mycobacteria cause tuberculosis. Till date, very little work has been done on evaluation of effect of vitamin D on the body's immunity to mycobacteria. In a study, it has been concluded that vitamin D can strengthen the immune system by enhancing the macrophage phagocytosis of *Mycobactericum tuberculosis*[22].

Autoimmune Diseases: Vitamin D is found to be a natural immunomodulator. Its influence on autoimmune processes has been evaluated on many disorders including diabetes, multiple sclerosis (MS), rheumatoid arthritis and Crohan's disease. The presence of VDR in beta cells of pancreas indicates its potential role for the prevention of diabetes[26]. In a study, deffeciency of vitamin D was found to increase insulin resistance as well as insulin production. In another study, it was shown that daily intake of 1200 mg calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes to the extent of 33% as compared with a use of less than 600 mg of calcium and 400 IU of vitamin D per day[27]. Multiple sclerosis (MS) is a demyellinating disease of central nervous system that is a debilitating and can be fatal. There is a vast number of research activities supporting the protecting role of vitamin D in multiple sclerosis and progression. Most of the findings opined that high levels of 25-hydroxyvitamin D at the time of a first demyelinating event indicate a lower MS risk, and decreased risk of MS in offspring whose mother had high 25-hydroxyvitamin D levels[28].

Psoriasis: It is a semiautoimmune disease affecting more than 50 million people worldwide. Psoriasis is a non-malignant disease of skin, in which cells multiply nearly up to ten times faster than normal cells and form scales and itchy, dry patches on skin. Michael F. Holick is the first scientist to discover the antiprolification activity of active vitamin D to restore the psoriatic afflicted cells of skin to their normal growth. Sun-exposure and local application of skin ointment of activated vitamin D are effective remedies for decreasing the painful symptoms of psoriasis[2].

Vitamin D Deficiency and Old Age: Elderly people are more prone to vitamin D deficiency syndrome as their body is unable to synthesize the required amount of vitamin D. In elderly population, obesity, chronic kidney ailments and scanty presence of 7-dehydrocholesterol in skin are the main factors responsible for the inadequate formation of vitamin D. 7-Dehydrocholesterol is the compound present in the skin that produces vitamin D in presence of sunlight. In ageing skin, its concentration is drastically reduced, hence, formation of the vitamin D is also decreased. After the age of 70 years, the formation of vitamin D is reduced almost to a quarter compared of young adults[26].

The deficiency of vitamin D in aged people, is usually manifested as muscular pain, cramps, heaviness in legs, chronic fatigue, defficulty in climbing the stairs and rising from chair or bed. Apart from these infirmities, walking

difficulty, falls and bone fractures are also quite frequent in old age due to muscular and sketal weakness. Vitamin D has also been linked to premature aging, stress and brain-related diseases such as dementia. Alzheimer's disease is the most common type of dementia. Dr. Michael F. Holick has described the importance of vitamin D in mental health and gave an account of recent studies on vitamin D and dementia[2]. It has been found that by maintaining higher levels of 25-hydroxy vitamin D in their blood, the middle aged and older persons can maintain the best brain agility[2].

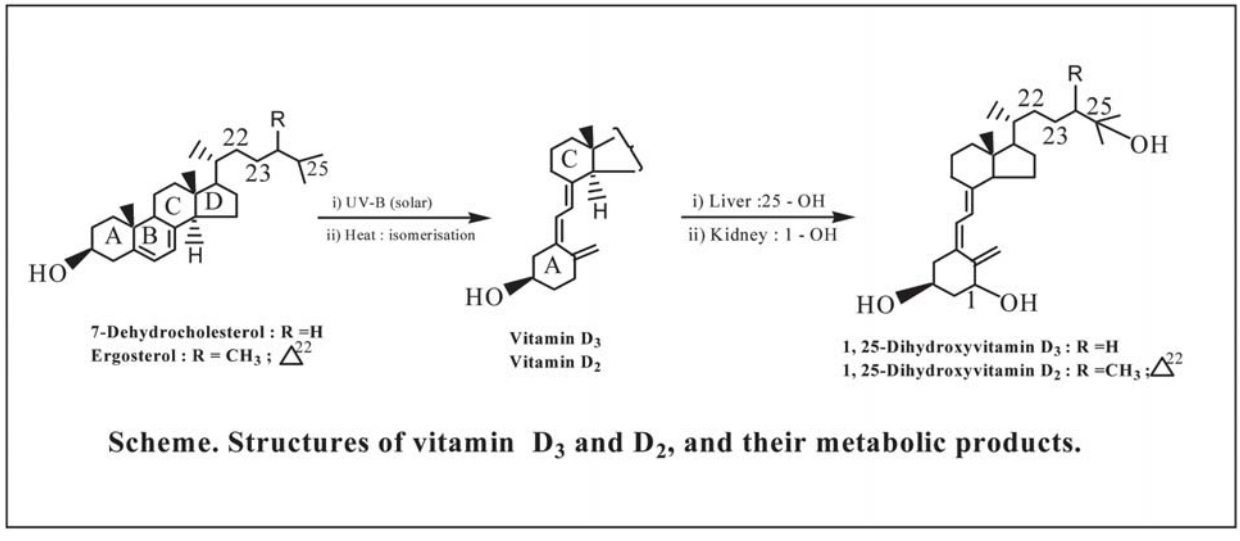
Human Requirement of Vitamin D and its Toxicity

In 2008, the American Academy of pediatrics has suggested to increase the intake of vitamin D from 200 IU/day to 400 IU/day for infants, children and adolescents whereas for adults and elderly persons, recommended dose is 1000 IU/day[29]. But now experts recommended that a minimum of 1,000 IU (preferably 2,000 IU) is essential for both children and adults in order to maintain a healthy status of serum 25-hydroxyvitamin D that is more than 30 ng/mL[2]. Much higher doses of vitamin D are recommended for obese persons, pregnant women and lactating women. Depending upon the severity of vitamin D deficiency and allied complications, much higher doses of vitamin D, ranging from 5,000 to 6,000 IU per day has also been prescribed. While taking vitamin D, it is necessary to include calcium rich foods (milk, orange juice, *etc.*) in diet. Indian Council of Medical Research has recommended 400 IU/day which, in view of recent researches, needs revision. The Endocrine Society of India has recommended vitamin D supplementation as 400 IU/Day for infants, 600-1000 IU/day for children, 1,000 IU/day for adolescents and pregnant women after 12 weeks of gestation and 1,000 – 2,000 IU/day for adults[30].

The occurrence of vitamin D toxicity is very rare[31]. Vitamin D intake below 10,000 IU/day is not usually associated with toxicity, whereas doses equal to or above 50,000 IU/day for several weeks and months are frequently associated with toxic effects[32]. Nausea, vomiting, loss of apetite, constipation, increased thirst, increased frequency of urination, depression and weight loss are the main symptoms of vitamin D toxicity. Vitamin D toxicity manifests itself through hypercalcaemia (high calcium level in blood) which may lead to calcification of kidneys causing kidney failure, calcification of arteries, confusion and bizarre behavior.

Ongoing Research and Future Directions

Vitamin D still remains an interesting research focus and plays a significant role in human health. Research on health benefits of vitamin D continues at a rapid pace as evident by a myriad of research publications. In 2017, the Pubmed Search Engine identifies about 71,000 publications on vitamin D in general, in addition to 14,000 publications on vitamin D and health specifically[33]. In order to depict the recent interest on utility of vitamin D, a few current examples are being cited here. Vitamin D is involved in regulating the female reproductive system, and it has an important role in Polycystic Ovary Syndrome (PCOS), endometriosis, uterine leiomyomas, and *in vitro* fertilization (IVF) [34]. The use of vitamin D is being investigated to find new and effective avenues for the treatment of many infectious diseases including tuberculosis, respiratory tract infection, Human Immunodeficiency Virus infection and sepsis[35]. The association of low 25(OH) D levels with increased risk of microvascular and macrovascular complications in persons with type 2 diabetes mellitus is also under investigation[36]. Recently, it has been reported that vitamin D metabolites naturally pass through the blood-



Scheme. Structures of vitamin D_3 and D_2, and their metabolic products.

brain barrier and they find easy access to neuronal and glial cells. Therefore, vitamin D plays significant role in neurological/neuromuscular disorders in addition to its antiaging property[37].

Modern researches indicate that new facts on physiological activities of vitamin D are likely to emerge in future. Therefore, further genomic investigation and functional studies are required.

Concluding Remarks

The utility of vitamin D for optimal health is quite apparent now. Its significant role in all the stages of human life is fully understood. On the basis of recent researches, most of the scientists are of the opinion that the concentration of 25- hydroxyvitamin D : less than 50 nmol/ L, 50-74 nmol/L, 75-250 nmol/L are indication of vitamin D deficiency, insufficiency and sufficiency, respectively. However, despite such findings, more than one billion children and adults worldwide are facing the problem of vitamin D deficiency. In USA about 200 million people are suffering from vitamin D deficiency syndrome. In India, vitamin D deficiency is prevalent among the general population to the extent of 70-90%. Sun is a major and natural source of vitamin D. Sensible use of sun-exposure daily between 8 to 11 am for at least 20 minutes, and regular use of dietary vitamin D supplements are highly desirable for a healthy life. It should always be remembered that sun is vital to human life like food, clothes, shelter, water and oxygen[2]. In Indian culture, great respect is given to nature and its resources. From the ancient times, sun is worshiped as God. '*Surya Namaskar*' (salutation to sun) and '*Surya Argh*' (offering water to rising sun) are considered very important for worship as well as health. Sun has been highly adored in old scriptures of India. ❐

"नूनं जनाः सूर्येण प्रसूताः।"

(All that exists was born from the sun) **- Brahad devata. I: 61.**

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