

T.R.N.C
NEAR EAST UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES

EFFECTS OF VITAMIN D ON OXIDATIVE STRESS

Mohamed Miftah Salem AHMED

MEDICAL BIOCHEMISTRY PROGRAM

GRADUATION PROJECT

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The Directorate of Graduate School of Health Sciences,

This study has been accepted by the project committee in Medical Biochemistry Program as a Master Project.

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According to the relevant articles of the Near East University Postgraduate Study – Education and Examination Regulations, this project has been approved by the above mentioned members of the project committee and the decision of the Board of Graduate School of Health Sciences.

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ABSTRACT

Ahmed M. Effects of Vitamin D on Oxidative Stress. Near East University, Graduate School of Health Sciences, Graduation Project in Medical Biochemistry Program, Nicosia, 2017.

Vitamins are crucial supplements for human-being, assuming that they are the precursors of coenzymes which are required for the enzymes for the survival of an organism. Currently it has gotten to be obvious that vitamins are of great importance in health and human disease. Vitamin D is a supplement and considered as a key for skeletal health, but currently several studies show that vitamin D plays an important role in preventing numerous serious diseases such as osteoporosis, cardiovascular diseases and some types of cancer. Nowadays it is known that vitamins have a critical relationship with oxidative stress. Previous studies reported that vitamin D has both antiperoxidative and anti-inflammatory action. In this assay we aim to provision a prologue to the idea of oxidative stress as a major participant in tissue harm and the relationship between oxidative stress and vitamin D.

Key words: Vitamin D, oxidative stress, disease

ÖZET

Ahmed M. Vitamin D'nin Oksidatif Stres Üzerine Etkisi. Yakın Doğu Üniversitesi, Sağlık Bilimleri Enstitüsü, Tıbbi Biyokimya Programı, Mezuniyet Projesi, Lefkoşa, 2017.

Vitaminler, enzimlerin işlevlerini gerçekleştirmesi için gereksinim duydukları koenzimlerin öncül molekülleri olduklarından organizmanın yaşamını devam ettirmesinde hayati öneme sahiptir. Vitaminlerin insan sağlığı ve hastalıklarındaki önemi son yıllarda daha belirgin hale gelmiştir. Vitamin D iskelet sistemi sağlığı için kilit rol üstlenmektedir. Ayrıca birçok çalışma vitamin D'nin osteoporoz, kardiyovasküler hastalıklar ve bazı kanser türleri gibi hastalıkların önlenmesinde önemli rol oynadığını da göstermektedir. Günümüzde vitaminler ile oksidatif stres arasındaki ilişki bilinmektedir. Yapılan çalışmalar vitamin D'nin antiperoksidatif ve anti-inflamatuvar etkileri olduğunu göstermektedir. Bu projede doku hasarına neden olan oksidatif stres ile vitamin D arasındaki ilişkinin gösterilmesi amaçlanmıştır.

Anahtar kelimeler: Vitamin D, oksidatif stres, hastalıklar

TABLE OF CONTENTS

	Page No
APPROVAL	iii
ACKNOWLEDGEMENTS	iv
ABSTRACT	v
ÖZET	vi
TABLE OF CONTENTS	vii
LIST OF ABBREVIATIONS	ix
LIST OF FIGURES	xi
1. INTRODUCTION	1
2. GENERAL INFORMATION	3
2.1. Oxidative Stress	3
2.2. Free Radicals	3
2.3. Consequences of Tissue Injury Caused by Free Radicals	5
2.4. Measurement of the Oxidative Stress	5
2.5. Overview of Vitamins	6
2.5.1. Vitamin A	7
2.5.2. Vitamin B's	7
2.5.3. Vitamin C	8
2.5.4. Vitamin D	9
2.5.5. Vitamin E	15
2.5.6. Vitamin K	16
2.6. Relationship Between Vitamin D and Oxidative Stress	16
2.7. Role of Vitamin D in the Protection of Human Endothelial Cells from Oxidative Stress	18
2.8. Vitamin D Treatment Protects Against and Reverses Oxidative Stress Induced Muscle Proteolysis	20
2.9. Complications of Vitamin D Deficiency	20
2.9.1. Vitamin D and Oxidative Stress in Diabetes	21
2.9.2. Vitamin D and Oxidative Stress in Chronic Kidney Disease	22
2.10. Prevalence of Vitamin D Deficiency	23
2.11. Vitamin D Toxicity	25

2.12. Recommendations for Intervention Strategy	26
3. CONCLUSION	27
REFERENCES	28

LIST OF ABBREVIATIONS

$1\alpha,25(\text{OH})_2\text{D}_3$: 1-alpha-25 dihydroxycholecalciferol
AA	: Ascorbic acid
ADHD	: Attention deficit hyperactivity disorder
AGE	: Advanced glycation end product
ARE/EPRE	: Antioxidant / electrophile response element
CAT	: Catalase
CKD	: Chronic kidney disease
CYP-450	: Cytochrome P-450
DBP	: Vitamin D binding protein
DHA	: Dehydroascorbic acid
7-DHC	: 7-Dehydrocholesterol
eNOS	: Endothelial nitric oxide synthase
ERK	: Extracellular signal-regulated kinase
FGF 23	: Fibroblast growth factor 23
GCL	: Glutamate-cysteine ligase
GDM	: Gestational Diabetes Mellitus
GLUTs	: Glucose transporters
GPx	: Glutathione peroxidase
GR	: Glutathione reductase
GSH	: Reduced glutathione
HNO_2	: Nitrous acid
H_2O_2	: Hydrogen peroxide
Keap 1	: Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1
LOOH	: Lipid peroxide
MAPK	: Mitogen-activated protein kinases
MED	: Minimal erythematous dose
N_2H_3	: Dinitrogen trioxide
NF- κ B	: Nuclear factor kappa B
NO	: Nitric oxide
$\text{NO}_2\bullet$: Nitrogen dioxide

Nrf2	: Nuclear factor erythroid 2-related factor 2
O ₂ ⁻	: Superoxide radical
OH [•]	: Hydroxyl radical
25(OH)D	: 25-Hydroxyvitamin D
ONOO ⁻	: Peroxynitrite
PE	: Pre-eclampsia
PTH	: Parathyroid hormone
ROO [•]	: Peroxyl radical
ROS	: Reactive oxygen species
RXR	: Retinoid X receptor
SAM	: S-Adenosylmethionine
SIRT1	: Silent information regulator 1
SOD	: Superoxide dismutase
SVCTs	: Sodium-dependent vitamin C transporters
TNF- α	: Tumor necrosis factor alpha
TRPV6	: Transient receptor potential cation channel subfamily V member 6
α -TTP	: α -Tocopherol Transfer protein
UVB	: Ultraviolet B
VDD	: Vitamin D deficiency
VDR	: Vitamin D receptor
VDDR-1	: Vitamin D–dependent rickets type I
VDDR-2	: Vitamin D–dependent rickets type II
VDREs	: Vitamin D-Responsive Elements

LIST OF FIGURES

Figure 2.1.	Free radical formation	3
Figure 2.2.	Endogenous and exogenous production of reactive oxygen species	4
Figure 2.3.	Synopsis of free radical formation, oxidative stress and pathogenesis of chronic diseases	6
Figure 2.4.	Conversion of 7-dehydrocholesterol to the active form 1,25 dihydroxycholecalciferol (calcitriol)	11
Figure 2.5.	Action mechanism of vitamin D	12
Figure 2.6.	Vitamin D digestion and physiological activity	13
Figure 2.7.	Rickets and Osteomalacia	15

1. INTRODUCTION

The inability of the body to maintain the mechanism to protect and remove the potential oxidative intermediates and to balance the formation of reactive oxygen species (ROS) leads to the oxidative damage. The oxidation and reduction instability in the cell may lead to harmful influences by the formation of free radicals and peroxides which in consequence leads to cellular destruction of proteins, lipids and hereditary material (DNA). Oxidative stress causes base harm and as well as DNA breaks due to ROS formation, e.g. H_2O_2 (hydrogen peroxide), $\text{O}_2^{\cdot-}$ (superoxide radical) and OH^{\cdot} (hydroxyl radical). Moreover, several ROS work as cellular emissaries in oxidation signal. As a result, oxidative stress can bring about problem in ordinary process of cellular signal (Chandra et al., 2015). Oxidative stress may be the result of dietary nutrients imbalance, exposure to chemical or physical factors in surrounding, genetic diseases, injury and vigorous physical activity. Numerous compounds provide a shield against oxidative stress to avoid unfavorable effects of free radicals, vitamin E has a basic and new position in antioxidant resistance (Singh et al., 2005).

In humans, oxidative stress is involved in the development of cancer, atherosclerosis, Asperger syndrome, chronic fatigue syndrome, Parkinson's disease, heart failure, myocardial infarction and attention deficit hyperactivity disorder (ADHD) (Ramalingam and Kim, 2012). In spite of it, ROS are utilized by the immune system as an approach to attack and eliminate pathogens (Vlassara et al., 1994). Oxidative stress may work to prevent aging for short a time by stimulating a procedure called mitohormesis (Gems and Partridge, 2008).

Antioxidant defense systems (either central or local stress limiting systems) are involved in defending the organism at the cell level or at systemic level. The improvement of stress, regardless of its nature (external, physical, aging, cardiovascular and ischemic pathologies, immobilization, diseases of the gastrointestinal tract, burns, hypobaric hypoxia, hyperoxia, radiation, ischemia etc.) prompts a weakening of the vitamin condition. The deficiency in the vitamins C, A, E, B_1 or B_6 has an effect on the antioxidant defense system of the body. Replacement of the missing vitamins in diet restores the action of antioxidant system. Accordingly, the part of vitamins in adjustment

to stressors is apparent. Notwithstanding, vitamins C, E and beta-carotene in high dosages, much higher than the physiological needs of the living being, might not be just antioxidants, as well as pro-oxidants. Maybe this clarifies the absence of beneficial outcomes of antioxidant vitamins used in higher doses for a long period of time (Kodentsova et al., 2013).

Food naturally contains Vitamin D; after absorption, needs exposure of skin to UVB radiation (290–315 nm) followed by a group of biochemical interactions to change 7-dehydrocholesterol to the active type of vitamin D, named calcitriol (1,25-dihydroxycholecalciferol) or vitamin D₃ (Chun-Yen et al., 2016).

2. GENERAL INFORMATION

2.1. Oxidative Stress

The instability in the antioxidant defense system and the formation of the reactive oxygen species in the body which may damage tissues, may be correlated with the Diabetes mellitus in which there is a destruction of the tissue (Halliwell, 1994; Betteridge, 2000). Numerous biochemical processes cause formation of the free radicals for example, stimulated neutrophils and macrophages during inflammation. Likewise, free radicals might be produced in the tissues because of electromagnetic irradiation from the environment. Unavailability of the antioxidant defense may lead to destruction of various tissues (Betteridge, 2000).

2.2. Free Radicals

The chemical that contains unpaired electron is termed as free radical (Figure 2.1). Unpaired electrons raise the chemical reactions of a particle or an atom. A simple example could be nitric oxide (NO), hydroxyl radical (OH[•]), transition iron (Fe) or copper (Cu), peroxyxynitrite (ONOO⁻), superoxide anion (O₂^{-•}), nitrogen dioxide (NO₂[•]), and peroxy (ROO[•]). Also, hydrogen peroxide (H₂O₂), ozone (O₃), nitrous acid (HNO₂), dinitrogen trioxide (N₂O₃) and lipid peroxide (LOOH) are not free radicals and generally named oxidants, but can lead to free radical reactions in living organisms (Genestra, 2007). Biological free radicals are thus highly unstable molecules that have electrons available to react with various organic substrates such as lipids, proteins and DNA.

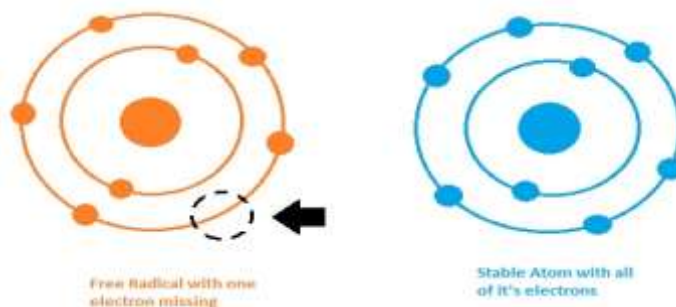


Figure 2.1. Free radical formation (<http://blog.optihealthproducts.com/free-radicals-101/>).

The hydroxyl radical is the most strong oxidant agent known, its half-life is greatly short. Oxygen takes an electron and forms a superoxide which is very reactive. It works as a poorly oxidizing agent, but has a great reducing ability of iron compounds for example cytochrome c. It is prone to be more essential as an origin of peroxides and hydroxyl radicals. While nitric oxide (NO), a physiological radical, is of great benefit as a mediator of vascular tone (Halliwell, 1994). There are two ways for the formation of ROS in cells: enzymatic reactions and non-enzymatic mechanisms. As enzymatic mechanisms prostaglandin synthesis, phagocytosis, respiratory chain and cytochrome P450 system involve in the formation of ROS. As well as they can be generated by non-enzymatic reactions of oxygen with organic molecules also by ionizing radiation and by reduction of molecular oxygen during oxidative phosphorylation (aerobic respiration) to hydroxyl radical and superoxide (Figure 2.2) (Lien et al., 2008).

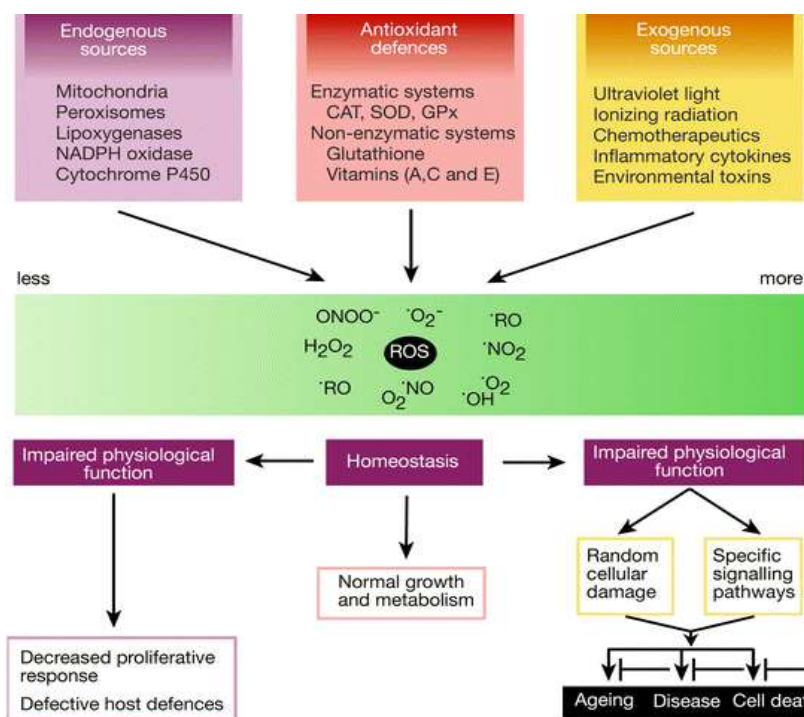


Figure 2.2. Endogenous and exogenous production of reactive oxygen species (Finkel and Holbrook, 2000).

2.3. Consequences of Tissue Injury Caused by Free Radicals

Free radicals are excited particles due to their unpaired electrons. Subsequently, they can be very reactive, in spite of the fact that this change from radical to radical, responding to acknowledge or give electrons to different atoms to accomplish a more stable status. Where a large part of reactants are commonly not free radicals, reaction mostly includes non-radicals. Response to a radical with a non-radical (e.g. nucleic acids, lipids, proteins and starch) generates a free radical chain response with new species of radicals that may further reach other molecules generating more radicals and harm. The main examples are lipid peroxidation and protein cleavage, e.g., addition of carbonyl group or cross linking, this attachment makes the protein easy to be loss its function (Birben et al., 2012), DNA base modifications (e.g., transformation of guanine to 8-hydroxyguanine and different components) and protein/DNA crosslinks (Halliwell and Aruoma, 1991; Spear and Aust, 1995; Hal et al., 1996) (Figure 2.3).

The free radical attacks to the polyunsaturated fats especially due to the fact that two double bonds make the carbon-hydrogen ligation at the adjoining carbon molecule weaker and susceptible to break. The rest carbon-centered radicals undergo molecular rearrangement leading to a conjugated diene. Conjugated dienes can combine with oxygen forming a peroxy radical which can readily digest more hydrogen molecules and start a chain response which proceeds either to the substrate is expended or the response is ended. The subsequent lipid peroxides are sensibly stable compounds, however their decomposition can be stimulated by transition metals and metal compounds, creating peroxy and alkoxy radicals that can invigorate more lipid peroxidation. Interestingly interrupted tissue is further defenseless to lipid peroxidation. Lipid peroxidation can effectively affect cell capacity. Broad peroxidation in cell layers will bring about alterations in ease, expanded penetrability, a lessening in membrane potential and in long term membrane to burst (Witztum, 1993).

2.4. Measurement of the Oxidative Stress

The oxidative stress can be examined by the protein oxidation, DNA oxidation and lipid peroxidation. A reciprocal methodology is the measure of exhaustion of

antioxidants, for example, vitamin C and tocopherol. Lipid peroxidation is assessed with techniques such as thiobarbituric acid-response substance tests, conjugated dienes, hydroperoxides, F2 isoprostanes and nitroxides. Visoli and Galli studied the procedure for oxidative assessment in connection to cardiovascular disease (Visoli and Galli, 1997).

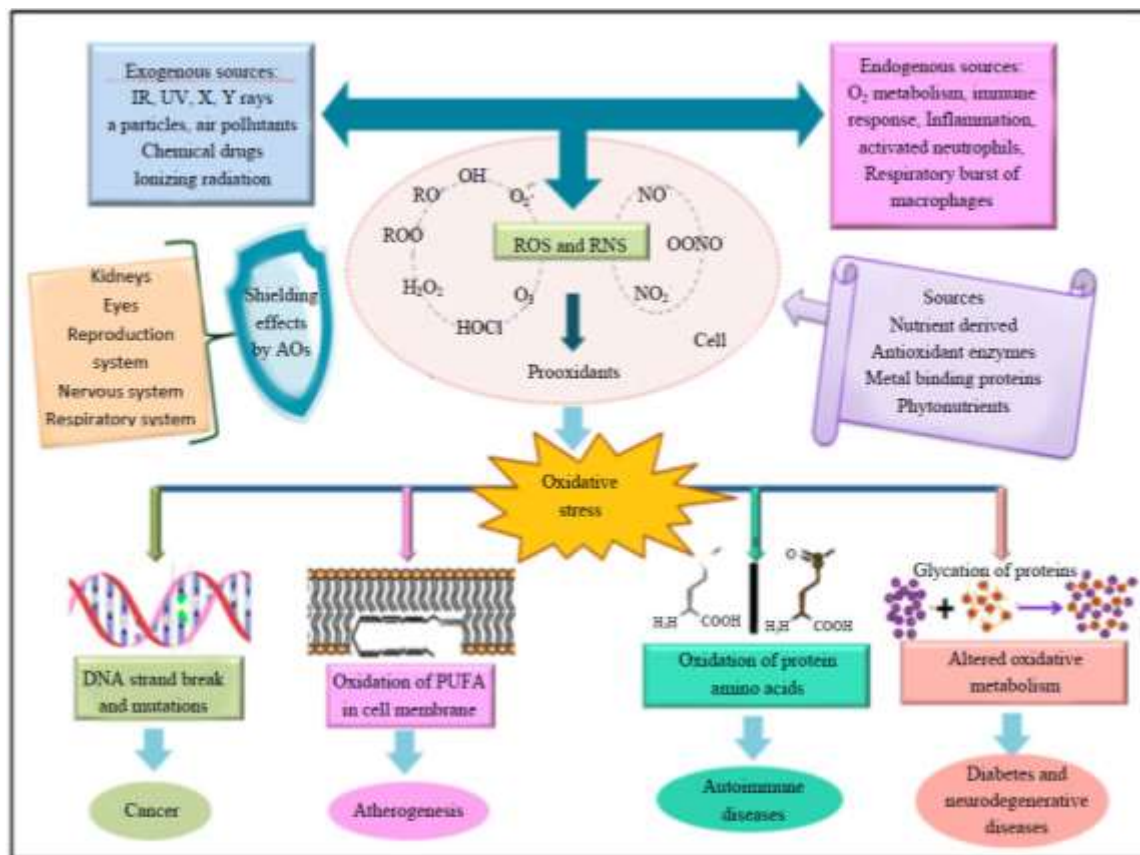


Figure 2.3. Synopsis of free radical formation, oxidative stress and pathogenesis of chronic diseases (Kalam et al., 2015).

2.5. Overview of Vitamins

Vitamins are vital precursors of the coenzymes. There is a correlation between vitamins and the prevention / improvement of certain diseases. In addition, the vitamins have important roles in protecting body against the damaging effects of oxidative stress

(Mamede et al., 2011). Several vitamins act as antioxidants. This study summarizes the relationship between vitamin D and oxidative stress.

2.5.1. Vitamin A

The retinoids are a category that includes natural derivatives and artificial analogues of vitamin A (Smith and Saba, 2005). They participate in numerous physiological functions, including apoptosis, embryogenesis, development, vision, bone arrangement, digestion, hematopoiesis and immunological processes (Sun and Lotan, 2002). Vitamin A and retinoids have a key role in the early tumor therapy. Since the exploration developed by Wolbach and Howe (Wolbach and Howe, 1925) and then by Lasnitzki (Lasnitzki, 1955), a few researches exhibited the importance of retinoids and vitamin A in the oncogenesis of numerous tissues (Trump, 1994). Soon after it was shown *in vitro* and *in vivo* that these compounds affected abnormal cell development in various ways, by blocking the development, apoptosis and dedifferentiation in an assortment of cell lines (Lotan, 1995).

Retinoids and vitamin A have a well-known equilibrium which is adjusted in numerous type of cancers like skin, breast, cervix, oral, leukemia and prostate (Zhang et al., 2000). The diminished transformation of retinol to retinoic acid has been found in breast cancer cell lines, the similar outcomes were obtained in ovary tumor cells (Williams et al., 2009). These outcomes support the hypothesis that a defect in the metabolism of vitamin A contributes to the formation of ovarian tumor.

2.5.2. Vitamin B

Vitamin B complex is composed of many water-soluble vitamins namely: B₁ (thiamine), B₂ (riboflavin), B₃ (niacin), B₅ (pantothenic acid), B₆ (pyridoxine), B₇ (biotin), B₉ (folic acid) and B₁₂ (cobalamin). They commonly exist in oats, rice, liver, dairy, nuts, meat, brewer's yeast, whole-grains, eggs, natural products, fish, verdant green vegetables and numerous different nourishments. The B vitamins keep up and expand the metabolism rate, protect muscle tone, advance development and cell partition, improve the action of the immune and nervous systems (Mamede et al., 2011).

No evidence has been found regarding vitamin B in the prevention of cancer (Mamede et al., 2011). Pyridoxine, folic acid and cobalamin have been extensively studied to clarify their possible roles in the treatment of cancer. Regarding folate, Glynn and Albanes were among those who early reviewed its role in cancer. Although a few researchers propose that reduced vitamin B₆, B₉ and B₁₂ levels cause the development of many cancers, the confirmation emerging from epidemics, animal samples and clinical studies still do not explain the role of these supplements in growth and aggravation of tumor (Glynn and Albanes, 1994).

Cobalamin and folic acid are essential in methylation reactions in the body. Methyl group is transferred from methyltetrahydrofolate to homocysteine to make methionine by methionine synthase. It is a cobalamin-dependent catalyst to provide S-adenosylmethionine (SAM). Low concentration of folic acid and cobalamin will lead to a decrease in the availability of SAM and block DNA methylation (Kim, 2005). Thus, gene expression, formation of DNA and also ordinary controls in the outflow of proto-oncogenes are affected (Mason and Levesque, 1996).

2.5.3. Vitamin C

Vitamin C is a water-soluble, cancer prevention agent and enzyme cofactor present in plants and a few organisms. It is not produced endogenously so must be taken from oral route. It has two chemical forms; the reduced state (ascorbic acid; AA) and the oxidized state (dehydroascorbic acid; DHA). The support of vital convergences of vitamin C to typical cell metabolism includes two groups of vitamin C transporters: glucose transporters (GLUTs) and sodium-dependent vitamin C transporters (SVCTs). The transport of DHA is achieved by the GLUTs, principally by GLUT1, 3 and 4, while the admission of AA is accomplished by SVCT1 and 2. AA is a powerful reducing agent that efficiently prevents potential damage by free radicals. Most cancer cells are not able to transfer AA specifically, that is the reason these cells obtain vitamin C in its oxidized form (Rivas et al., 2008).

Vitamin C functions as an antioxidant. In cancer treatment, it reverses the therapeutic benefit of anti-neoplastic agents which use free radicals to destroy cancer cells (Heaney et al., 2008).

2.5.4. Vitamin D

In the twentieth century, the vitamin D was correlated to the bone health and was recognized as the therapy for rickets. Also there are many target tissues because steroid hormones act like chemical messengers (Norman and Bouillon, 2010). Amassing information demonstrate that vitamin D level is decidedly corresponded with healthful situations, for example, immune disturbance, tumors, cardiovascular infection and diabetes (Holick and Chen, 2008).

The plasma level of the metabolite 25-hydroxyvitamin D (25(OH)D) is specific by the dermal tissue synthesis during sunlight presentation and/or nutrition admission. The metabolite 25-hydroxyvitamin D is the marker of vitamin D level. Vitamin D synthesis is correlated with the presentation of the skin to the sunlight, for example, dress, staying inside and the worry about skin tumor influence the synthesis of Vitamin D (Holick and Chen, 2008).

Vitamin D Metabolism

The UVB irradiation (290–315 nm) causes the conversion of the 7-dehydrocholesterol (DHC), which is present in the dermis and the epidermis, to previtamin D₃. Previtamin D₃ is changed into lumisterol and tachysterol by photoisomerization. Both products are naturally inoperative. As a result of this, cholecalciferol levels are up to about 10–15% of the first DHC content. Once produced, cholecalciferol is specially bound to the vitamin D-binding protein (DBP), permitting its transportation in the blood circulation (Holick and Chen, 2008). The production of vitamin in the skin is affected by different factors, including age, pigmentation, apex point of the sunlight, bad air quality and the surface of skin exposed to the sunlight.

Recent investigations have shown that the methods of protection of the skin from the sun in the United States like wearing long sleeved clothes and staying in the shade

lessened vitamin D levels (Linos et al., 2011). Shockingly sunscreen utilization, even those which have safeguard elements of sunlight, does not essentially influence vitamin D levels. There have been different researches considered the skin pigmentation as a transcendent component for lessening the synthesis of vitamin D (Hall et al., 2010). Notwithstanding it consists in the skin, vitamin D can be acquired from the eating routine as vitamin D₃ (cholecalciferol) or sometimes as vitamin D₂ (ergocalciferol). Though cholecalciferol is obtained from animal sources, human body can make vitamin D₃, so it is the most “natural” form, but body can not synthesis vitamin D₂, ergocalciferol is available in mushrooms irradiated with UVB. Ergocalciferol is considered as abnormal type of vitamin D, and vitamin D represents D₃ or D₂, or both of them (Nair and maseeh, 2012).

After absorption vitamin D is transported in chylomicrons, it binds to DBP until it is discharged in hepatic tissue where it undergoes hydroxylation of the carbon in the 25th position by one of four hepatic cytochrome P-450 compounds. Three of these are microsomal structures, CYP2R1, CYP2J2 and CYP3A4. The fourth protein, CYP27A1 is mitochondrial and is an important structure as it leads commonly to rachitis when it is nonfunctional (Whiting et al., 2008).

The proximal tubule of the kidney is the fundamental location for CYP27B1 (1-alpha-hydroxylase) activity which is regulated by calcium, parathyroid hormone, 1 α ,25 dihydroxycholecalciferol (1 α ,25(OH)₂D₃) and phosphorus (Chanakul et al. 2013). This compound is in charge of the transformation of 25(OH)D to the active form 1 α ,25(OH)₂D₃ (calcitriol) (Figure 2.4). Once made in the kidney, this dynamic metabolite enters circulation, permitting it to act in cells and organs in a hormone-like way. The functions of vitamin D are to increase the absorption of calcium and phosphorus and to stimulate pre-osteoclasts to turn into mature osteoclasts. Different parts may incorporate renin production in the kidney and also incitement of insulin excretion by pancreas (Holick, 2007).

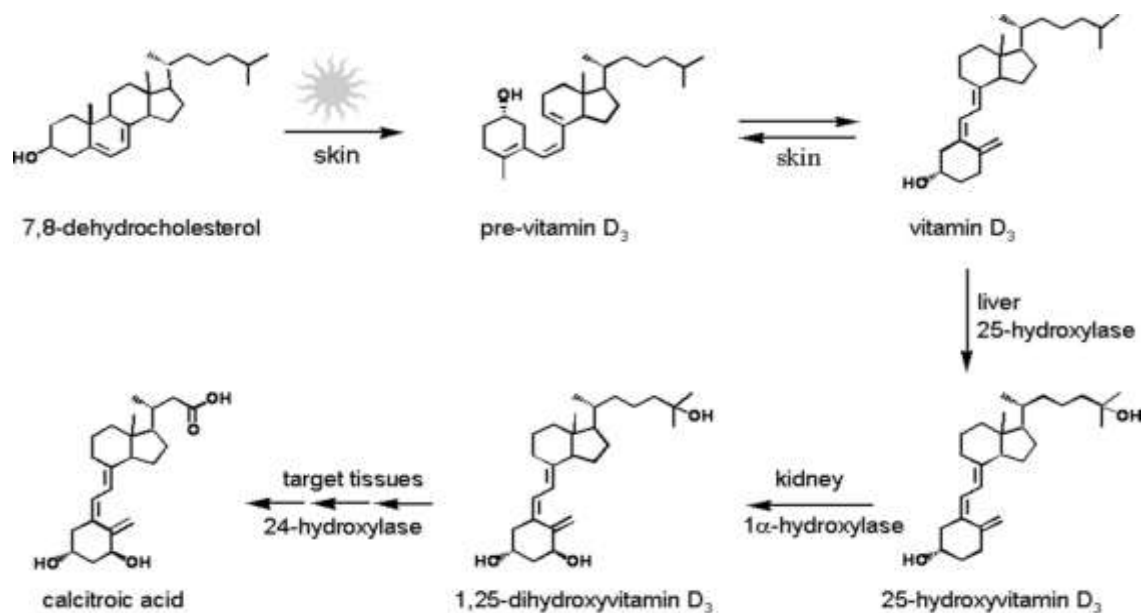


Figure 2.4. Conversion of 7-dehydrocholesterol to the active form 1,25 dihydroxycholecalciferol (calcitriol) (Brown et al., 1999)

Regulation of Vitamin D Metabolism

Exposure to UVB leads to vitamin D production and also expansion in epidermal melanin content. Including both a transcriptional and posttranscriptional regulations, this increment is caused by the raise in the quantity of melanocytes (Hall et al., 1996).

Other factor that influences the skin productivity is the photoisomerization of previtamin D₃ to two inactive forms, tachysterol or lumisterol, which constrain thermal isomerization to vitamin D₃ (Holick et al., 1981). When the level of calcium in blood is low, the parathyroid hormone (PTH) stimulates the increase in 1-alpha-hydroxylase action by increasing CYP27B1 expression in kidney (Henry, 2011).

Mechanism of Action

The 1α,25(OH)₂D₃ metabolite acts through the vitamin D receptor (VDR), which is in the nuclear receptor family. When it is activated via 1α,25(OH)₂D₃, this receptor reacts with the retinoid X receptor (RXR) and after that the 1α,25(OH)₂D₃VDR-RXR complex binds to the vitamin D-response elements (VDREs) directing the transcription

of different genes in the cells (Figure 2.5) (Whitfield et al., 1995). There are more than 2,700 human genome locales participate in VDR binding and $1,25(\text{OH})_2\text{D}_3$ could influence the expression of more than 229 genes (Mizwicki and Norman, 2009; Ramagopalan et al., 2010).

Membrane-bound VDR, through second messenger, could stimulate the fast intestinal ingestion of calcium (transcaltachia), the discharge of insulin by β cells in the pancreas, Ca^{+2} flow in muscle cells and the fast migration of epithelial cells. The membrane mediated fast signalling procedure remains inadequately comprehended and a few models are still under discussion (Ricardo, 2011). An outline of vitamin D digestion system and its physiological activity are introduced in Figure 2.6.

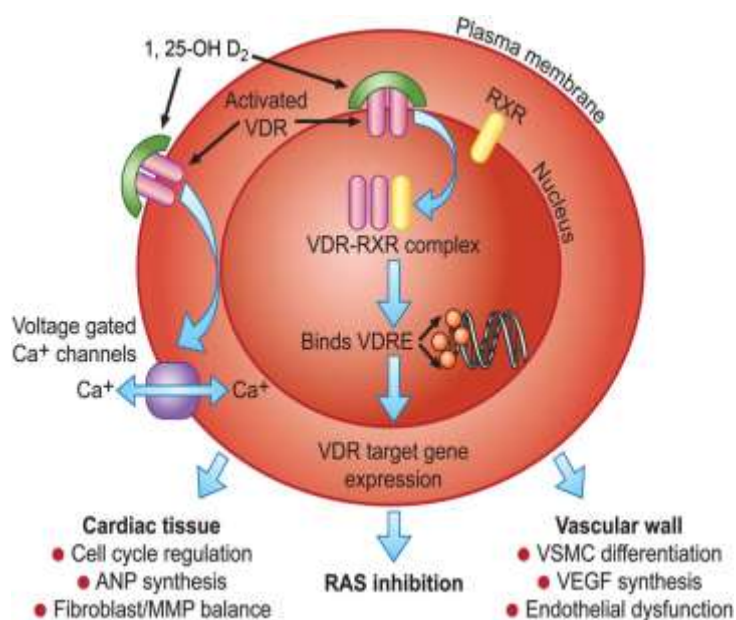


Figure 2.5. Action mechanism of Vitamin D (Al Mheid et al., 2013).

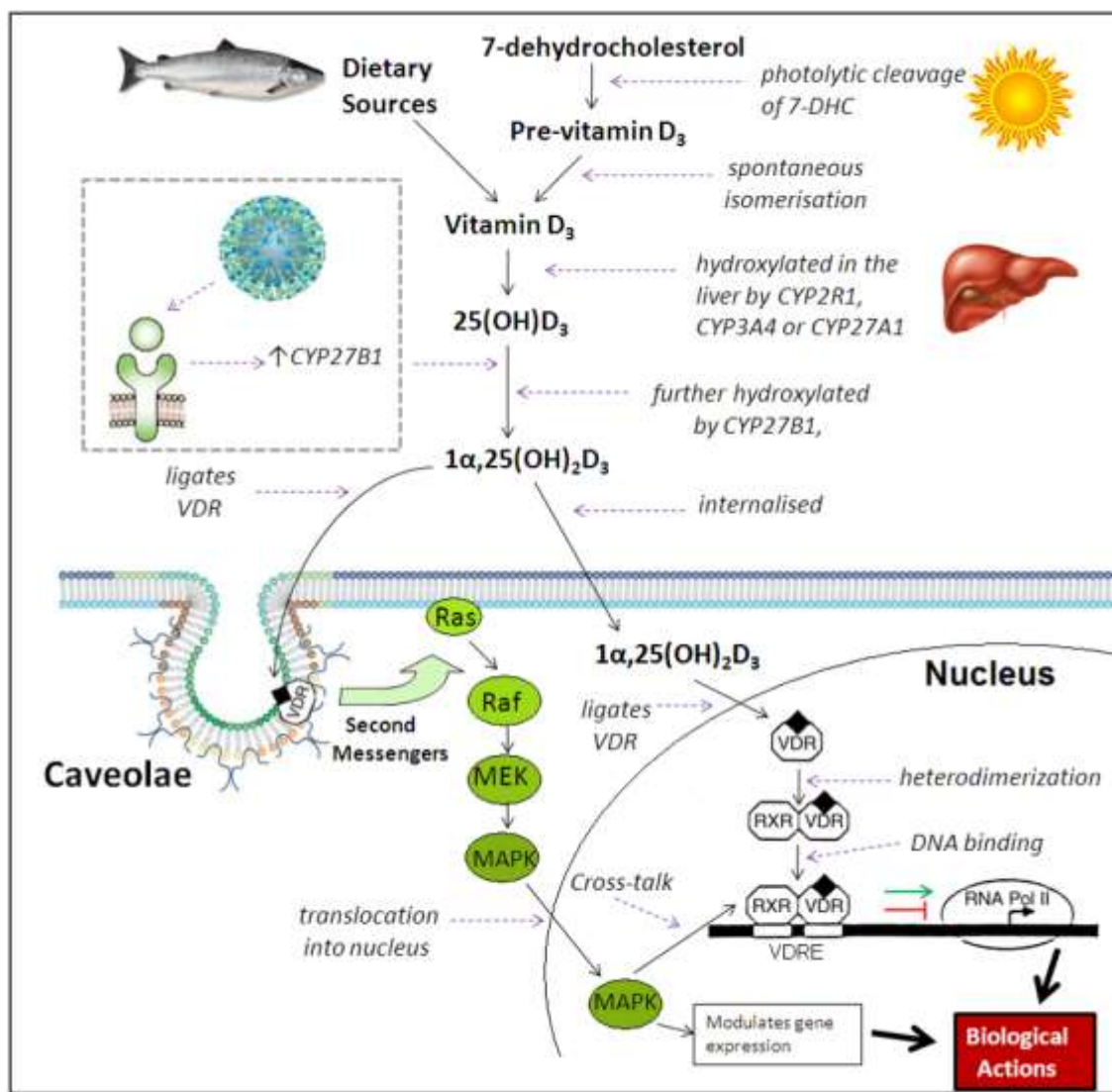


Figure 2.6. Vitamin D digestion and physiological activity (Claire and Adrian, 2015)

Physiopathology

Individuals with extreme hypovitaminosis are susceptible to rickets (particularly in newborn children and youngsters) or osteomalacia (particularly in grown-ups) (Figure 2.7). Shortage of exposure to the sunlight and malnutrition cause vitamin D deficiency. There are also genetic disorders prevent the metabolism of vitamin D (Ebert et al., 2006). Osteomalacia is known as impaired mineralization of osteoid, leading to a formation of non-mineralized bone (Ebert et al., 2006). These bones are weak and they

could bend or break under pressure (Sultan and Vitale, 2003). Vitamin D deficiency paves way to osteopenia which can bring about osteoporosis. Osteoporosis due to an imbalance between rebuilding and resorption, is a loss of mineral density of bones, leading to increased risk for cracks and falls. It occurs in older adults, where the aging diminishes the absorption of calcium and vitamin D. Rickets occur in young children, but aetiology is the same as osteomalacia. If not treated it leads to serious changes in the growth of the skeleton and troubles in respiratory system (Whiting et al., 2008).

Vitamin D-dependent rickets sort I (VDDR-1) is genetic disturbance, caused by a mutation in the 1α -hydroxylase gene (Ebert et al., 2006). Thus, it leads to a decreased 1α -hydroxylase action and lower dynamic metabolite production. Characteristic biochemical anomalies are hypocalcaemia and ordinary plasma $25(\text{OH})\text{D}$ levels whereas the $1\alpha,25(\text{OH})_2\text{D}_3$ plasma level is clearly low (Sultan and Vitale, 2003) Accordingly, the treatment comprises $1\alpha,25(\text{OH})_2\text{D}_3$ supplementation to address the defect.

Vitamin D-dependent rickets sort II (VDDR-2), occasionally termed "vitamin D-dependent rickets", is also a hereditary disturbance characterized by insensitivity of the target cell and organ to $1\alpha,25(\text{OH})_2\text{D}_3$. It is caused by changes in the VDR gene (Sultan and Vitale, 2003). VDDR-2 can differentiate from VDDR-1 by increased plasma levels of $1\alpha,25(\text{OH})_2\text{D}_3$. Medication includes crucial dosages of $1\alpha,25(\text{OH})_2\text{D}_3$ as well as calcium (Sultan and Vitale, 2003).

Impacts on the Skeletal System

$1\alpha,25(\text{OH})_2\text{D}_3$ improves calcium assimilation in the intestine by nuclear VDR that controls the expression of the epithelial calcium channel (TRPV6) and a calcium-restricting protein (calbindin 9K). $1\alpha,25(\text{OH})_2\text{D}_3$ is likewise required in the fast intestinal ingestion of calcium (transcaltachia) and improves the capacity of intestinal phosphate assimilation. Active form of vitamin D can regulate renal phosphate assimilation as well as catalyzes the production of fibroblast growth factor 23 (FGF 23), a protein which acts to elevate renal phosphate secretion. Without a doubt, FGF 23

diminishes articulation of the renal sodium–phosphate cotransporters NaPi-IIa and NaPi-IIc in the proximal tubule (Battault et al., 2013).

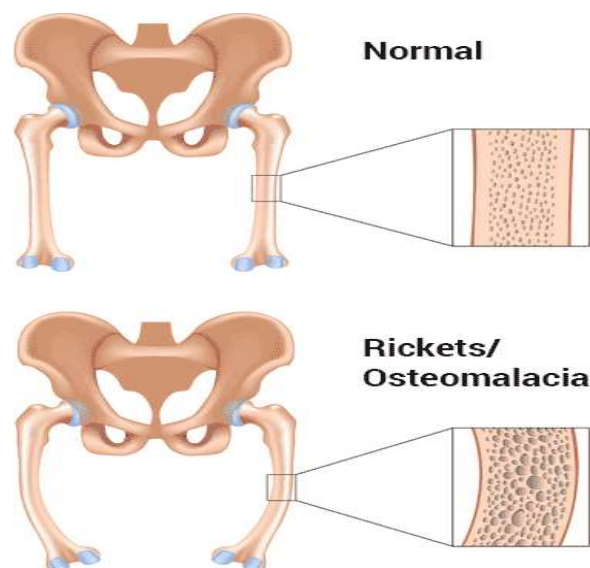


Figure 2.7. Rickets and osteomalacia. Rickets, bone deformities in children; osteomalacia, fractures in adults (<https://ghr.nlm.nih.gov/condition/vitamin-d-dependent-rickets>)

2.5.5. Vitamin E

There are various types of vitamin E: Four tocotrienols (α , β , γ , and δ) and four tocopherols (α , β , γ , and δ). The α -tocopherol is the main form that is present in human serum, tissues of human body and nature. Vitamin E, a lipophilic antioxidant, is absorbed from the upper part of the intestine and reaches circulation by the lymphatics. It is brought together with fats, accumulated into chylomicrons and carried to the hepatic tissue. Vitamin E, a key element in membranes of cell, has particular functions in the regulation of gene expression, signalling, proliferation and cell growth. Also vitamin E is a powerful antioxidant thus it can be useful in the protection and treatment of diseases caused by free radicals. After crossing to the hepatic tissue, only α -tocopherol appears in the plasma because of its hepatic α -tocopherol transport protein (α -TTP). Non- α -tocopherols are ineffective and not recognized by α -TTP. The α -TTP and plasma

phospholipid transport protein have a very much significance in cytosol since they are in charge of the homeostasis of vitamin E in the body (Klein et al., 2000).

2.5.6. Vitamin K

There are three common structures of vitamin K. Vitamin K1 (phylloquinone) is a natural type of the vitamin K and is generally present in leafy vegetables. Vitamin K2 (menaquinone) is likewise a natural and is produced by the intestinal bacteria. Vitamin K3 (menadione) is a manufactured analog. Physiologically, natural vitamin K acts as an assistant of γ -glutamylcarboxylase, thus, stimulates the carboxylation of glutamate to γ -carboxyglutamate in the prothrombin and the vitamin K-dependent coagulation agents x, vii and ix, and in addition others. The research of the anti-tumor activity of vitamin K began in 1947. Vitamin K1 has been found to show anti-cancer property on various organs, including stomach, lungs, liver, colon, leukemia, breast, nasopharynx and oral epidermoid cancer (Wu et al., 1993).

2.6. Relationship Between Vitamin D and Oxidative Stress

Exercise prevents number of diseases like cardiovascular disease, respiratory disease, obesity, hemodynamic disorder and hypertension (Reimers et al., 2012). Studies have shown the inflammation and oxidative stress occur during strenuous exercise until exhaustion (Radak et al., 2013). This leads to a damage to kidney, heart and respiratory system (Ogura and Shimosawa, 2014). Researchers used many antioxidants in the exercise (Aguiló et al., 2005). Vitamin D is included in natural diet; after admission, it needs skin presentation to UVB irradiation (290–315 nm) and many biochemical interactions to convert 7-DHC into an active type of vitamin D, that is named calcitriol (1 α ,25-dihydroxycholecalciferol) (Borel et al., 2015).

Vitamin D₃ is vital in calcium uptake, adjustment of blood-calcium levels and bone-intensity control. Studies have exhibited that vitamin D insufficiency was discovered in exercisers between 2008 and 2010 (Lovell, 2008). If vitamin D improves harm which is caused by exercise, thus taking a suitable amount of vitamin D for

exercise provides different advantages: it eases problems in bone-density and calcium equilibrium created by vitamin D insufficiency.

It was shown that vitamin D has an antioxidant property. It can terminate iron-dependent lipid peroxidation in the membrane of cell (Wiseman, 1993). The combined effect of vitamin D and calcium has been observed in the gestational diabetes mellitus (GDM) (Asemi et al., 2014). Vitamin D and calcium have been hypothesized to act together more efficiently, thus a lack of vitamin D and calcium during pregnancy increases the risk of gestational diabetes (Harinarayan et al., 2013). Harinarayan et al. marked an improvement in pancreatic beta cell work (HOMA-B) after supplementation with 10,000 U/day vitamin D and 1,000 mg/day calcium in vitamin D-insufficient non-diabetic subjects following eight weeks (Harinarayan et al., 2013). Vitamin D and calcium supplementation may influence metabolic profiles and redox stress. It may also have a role in repression of parathyroid hormone (PTH) and activation of antioxidant compounds (Kallay et al., 2002).

The reactive oxygen species produced by the relatively hypoxic placenta are transferred to the maternal circulation and they subsequently cause endothelial dysfunction. Moreover oxidative stress might be an essential mediator in regulating angiogenic pathway in trophoblasts. The pathogenesis of pre-eclampsia includes various natural processes that might be directly or indirectly influenced by vitamin D, including immune defect, implantation of placenta, insulin resistance, unnatural blood vessels, appendicitis and hypertension. Vitamin D levels affect immune function and risk of preeclampsia during conception (Pourghassem et al., 2005). Vitamin D level is disturbed in pregnant women with preeclampsia and negatively linked with oxidative stress biomarkers, thus those mothers with vitamin D inadequacy have a high risk for pre-eclampsia (Pourghassem et al., 2005). Lin et al. reported that vitamin D plays a vital role in reducing redox stress via ending the lipid peroxidation chain reaction (Lin et al., 2005).

2.7. Role of Vitamin D in the Protection of Human Endothelial Cells from Oxidative Stress

Hormonally, dynamic type of vitamin D, $1\alpha,25(\text{OH})_2\text{D}_3$, does not only affect the control of calcium and phosphate homeostasis but on the other hand it can interact with an extensive variety of organs and target tissues including the heart and the vasculature (Martinesi et al., 2006). Vitamin D may reduce cardiovascular mortality and morbidity and regression of cardiac hypertrophy within patient populations who frequently suffer from atherosclerosis (Shoji et al., 2004) and it may improve cardiac structure and function. Vitamin D exerts its physiological effects principally through the binding with the nuclear vitamin D receptor (VDR), regulating the expression of genes responsible for cellular proliferation, apoptosis, differentiation and angiogenesis in local tissues (Thompson et al., 2012). The role of endothelium as a target of vitamin D is demonstrated by the study published by Zehnder et al. (Zehnder et al., 2002), in which the expression of mRNA and protein for 1α -hydroxylase in human endothelium was shown for the first time. Altogether these findings demonstrated the direct effects of vitamin D on endothelial function which plays a critical role in the formation of atherosclerosis. Xiang et al. showed the ability of vitamin D to stimulate endothelial cell proliferation and lead to inhibition of apoptosis by increasing endothelial nitric oxide synthase (eNOS) expression and NO production (Xiang et al., 2011). NO plays a critical role in cardiovascular physiology and its production in the heart by eNOS phosphorylation represents an important regulator of both myocardial perfusion after ischemia and myocardial contractility with its crucial effects on cardiac cell functions e.g. oxygen consumption, myocardial regeneration, apoptosis and hypertrophic remodeling (Mount et al., 2007). On the other hand, ROS, along with NO, show anti-apoptotic effects involving several signaling pathways. For example, the increase in cytosolic-free Ca^{2+} concentration not only activates pro-apoptotic signals (Rizzuto and Pozzan, 2006) but also potently induces autophagy by activating calmodulin-dependent kinase (Høyer et al., 2007). Autophagy can be instigated by starvation, hypoxia or chemical and organic factors. Autophagy has a substantial function in the heart, it is important for the turnover of organelles at low basal levels under natural case. In the

heart, autophagy level change not only in reaction to stress as ischemia/reperfusion, however, also to stress triggered by cardiovascular illnesses like heart failure and cardiac hypertrophy (Nishida et al., 2009). In human cells, vitamin D is able to induce autophagy. The signaling pathways regulated by vitamin D include Bcl-2, beclin 1 and mammalian target of rapamycin (mTOR) (Wu and Sun, 2011). Recycling process is done during autophagy, in which intracellular contents are enveloped in double-layered membrane vesicles that fuse with lysosomes. The interaction among apoptotic and autophagic pathways determines the initiation of apoptosis and beclin 1 and Bcl-2 family are involved. Beclin 1 directly interacts not only with Bcl-2 as well as with other antiapoptotic Bcl-2 family proteins for example Bcl-xl and Bcl-2 are able to inhibit the beclin 1-dependent autophagy (Hamacher-Brady et al., 2006). It shows the intracellular pathways activated by vitamin D in oxidative stress in human endothelial cell. The antioxidant effect of vitamin D in human coronary artery endothelial cells may be through the inhibition of the expression of NADPH oxidase enzyme (Hirata et al., 2013). The protective role of vitamin D is partially attributed to suppression of the accumulation of AGEs in the aortic tissue. This inhibition may be caused by enhanced systemic antioxidant capacity and attenuated the production of oxidative stress in the liver, the crucial organ in the circulation and metabolism of vitamin D (Salum et al., 2013).

Although, lack of sufficient information about the molecular mechanisms of antioxidant vitamin D action, the Ras-mitogen activated protein kinases (MAPKs) have a major work in controlling apoptosis following oxidative stress (Martindale and Holbrook, 2002). MAPKs signaling pathway regulates cellular response to the oxidative stress by controlling the expression of some transcription factors, for example silent mating type information regulation 2 homolog 1 (SIRT1). SIRT1 has been shown to participate in the vascular endothelial homeostasis and to inhibit endothelial cell aging and death which is caused by oxidative stress (Mokhtari et al., 2017). In a study conducted on human endothelial cells, Polidoro et al. found that vitamin D was able to reduce the impairment after H₂O₂ mediated stress by the mitigation of superoxide anion yield and apoptosis. As well, they reported that vitamin D was added to endothelium

before the oxidative stress can induce cell survival (Polidoro et al., 2013). These mechanisms include the suppression of ROS release and the regulation of the interaction between autophagy and apoptosis. This result is achieved by preventing superoxide anion production, protecting the function of mitochondria and cell survival and stimulating extracellular signal regulated kinase 1 (ERK) (Uberti et al., 2013). Therefore, vitamin D may have influences on signaling and survival by improving oxidative stress system of endothelial cells.

2.8. Vitamin D Treatment Protects Against and Reverses Oxidative Stress Induced Muscle Proteolysis

Lack of vitamin D causes an increase in protein oxidation as it can be seen through the rise of protein carbonyls in the muscle (Bhat and Ismail, 2015). Recent reports prove that vitamin D deficiency lead to increased protein deterioration and reduction in protein synthesis (Bhat et al., 2013). Moreover, oxidative stress induced protein oxidation is blocked by therapy with $1\alpha,25(\text{OH})_2\text{D}_3$ in muscle cells. The effectiveness of the glutathione-dependent antioxidant enzymes namely glutathione peroxidase (GPx) and glutathione reductase (GR) is increased, while the activities of catalase (CAT) and superoxide dismutase (SOD) are reduced in the muscle, which is an indicator of an alteration in antioxidant status. All enzyme activities are normal with vitamin D supplementation. SOD stimulates the dismutation of superoxide to oxygen and hydrogen peroxide thus it is the first line of antioxidant defence in body tissues. A recent study showed that SOD is a transcriptional target of vitamin D thus its expression rises with vitamin D therapy. An imbalance between antioxidant system and ROS formation causes atrophy of muscles. Vitamin D acts as an antioxidant and protects proteins and membranes against oxidative harm (Bhat and Ismail, 2015).

2.9. Complications of Vitamin D Deficiency

Vitamin D and the vitamin D receptors (VDR) play an important role in skeletal health by controlling the metabolism and absorption of phosphorus and calcium. Vitamin D is not only responsible for this function, VDR is found in many other tissues

suggesting that vitamin D has other roles. Vitamin D deficiency perceived to be an overall concern. Vitamin D inadequacy is linked with the abnormal metabolism which is called the 'metabolic syndrome' and includes obesity, insulin resistance, dyslipidemia, and cardiovascular disease and/or type II diabetes (Nishida et. al., 2009). Vitamin D deficiency causes low calcium absorption which affects not only the bone density but also most of the metabolic functions. The increase in PTH re-establishes calcium balance by raising the tubular assimilation of calcium in the kidney, increasing bone calcium mobilization and improving $1\alpha,25(\text{OH})_2\text{D}_3$ formation (Alshahrani and Ajohani, 2013).

2.9.1. Vitamin D and Oxidative Stress in Diabetes

Diabetes mellitus is linked with the reduced antioxidant capacity and increased ROS production through increased lipid, protein and DNA oxidation products, glycated biomolecules, such as advanced glycation end products (AGEs) and advanced oxidation protein products (Mokhtari et al., 2017). Oxidative stress has a role in diabetes complications (Giacco and Brownlee, 2010). The outcomes in some experimental studies showed that vitamin D can decrease the ROS formation in diabetes by preventing the expression of NADPH oxidase (Mokhtari et al., 2017). NADPH oxidase is a major source of ROS and its activation is considered as a positive marker for oxidative stress.

Vitamin D reduces the lipid peroxidation and improves the superoxide dismutase (SOD) activity (Hamden et al., 2008; Zhong et al., 2014). The antioxidant enzymes are crucial in defense against free radical attack. They protect membrane and cytosolic components against ROS mediated harm. The most important enzymes are SOD, catalase and glutathione peroxidase (Finkel and Holbrook, 2000).

Also, calcitriol could stimulate the pathway of ROS removal by increasing the intracellular pool of reduced glutathione (GSH), partially by upstream regulation of glutamate-cysteine ligase (GCL) and glutathione reductase (GR) gene expression (Kanikarla and Jain, 2016). GCL is a key enzyme that participates in the synthesis of GSH. A positive relationship between vitamin D and GSH concentration has been reported (Mokhtari et al., 2017). Furthermore, Sardar et al. suggested that this vitamin

was an antioxidant as an outcome of an increase in hepatic GSH concentration after taking cholecalciferol (Sardar et al., 1996). Clinical tests showed that combination of vitamin D and calcium supplementation made a great increase in plasma total antioxidant capacity and GSH concentration compared with calcium and vitamin D separately (Foroozanfard et al., 2015). Several biological activities of the $1\alpha,25(\text{OH})_2\text{D}_3$ are achieved by binding to a nuclear receptor, the vitamin D receptor (VDR) (Reis et al., 2005). Control of oxidative metabolism by vitamin D involves interactions between many nuclear coactivators or corepressors which mediate the regulation of gene transcription at the level of their interaction with receptors of cholecalciferol (VDR). Upon binding its receptor, vitamin D leads to an increase in signaling and efficiently controls the level of free radical formation in liver cells (Bouillon et al., 2008; Zhong et al., 2014; Kanikarla and Jain, 2016).

2.9.2. Vitamin D and Oxidative Stress in Chronic Kidney Disease

Oxidative stress accelerates renal damage by inducing cytotoxicity. ROS causes the oxidation of proteins and DNA and lipid peroxidation which leads to an inflammatory cascade by inflammatory cytokines, containing TNF- α and the activation of NF- κ B. Activated NF- κ B initiates signalling pathways and participates in renal fibrosis (Greiber et al., 2002). The damage of functional renal tissue in chronic renal disease (CKD) leads to a decline in the production of 1α -hydroxylase, causes to diminution of vitamin D levels (Christakos et al., 2012). Patients with CKD have the great diminution in serum 25(OH)D levels, leading to an increased requirement for vitamin D in the CKD patients. Supplementation of calcitriol in CKD subjects reduces the risk of morbidity and mortality (Mokhtari et al., 2017). Active vitamin D could reduce glomerular injury and renal fibrosis through the inhibition of NADPH oxidase expression and enhancement in cytosolic SOD enzyme (Finch et al., 2012). After paricalcitol (VDR activators) treatment in hemodialysis patient, levels of the oxidative stress markers including MDA, nitric oxide and protein carbonyl groups were significantly decreased in serum and the level of antioxidant defenses containing GSH, catalase and SOD activity were increased (Izquierdo et al., 2012). One possible

mechanism was proposed for protecting against oxidative stress in nephropathy by calcitriol is the Nrf2– Keap1 pathway (Nakai et al., 2014). Nuclear factor erythroid 2-related factor 2 (Nrf2) controls the expression of ROS detoxifying and antioxidant agents by the antioxidant response element (ARE/EpRE). In physiological conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1 (Keap1), an actin binding repressor protein. Owing to this mechanism, Keap1 contributes to augmented oxidative stress due to negative regulation of Nrf2 and ARE/EpRE activity (Kobayashi and Yamamoto, 2005). Vitamin D could increase the expression of Nrf2 and also leads to a reduced expression of Keap1 that decreases the development of nephropathy by the inhibition of oxidative stress (Nakai et al., 2014).

2.10. Prevalence of Vitamin D Deficiency

Vitamin D plays several roles in muscle and skeletal health. The state of vitamin D is determined by several factors that affect its synthesis in the skin, such as skin pigmentation, and dietary intake, for example food fortification and taking supplements. The adiposity, demographic and genetic factors and diseases can also play a role (Edwards et al., 2014)

Vitamin D deficiency (VDD) is diagnosed by the measurement of serum 25 hydroxyvitamin D. To date, many specialists concur that 25(OH)D of < 20 ng/mL is thought to be vitamin D deficiency, while a 25(OH)D of < 30 ng/mL is thought to be vitamin D insufficiency (Holick, 2009).

In any case, serious deficiency appears in the Middle East and South Asia, so increased prevalence of rickets in these places is of particular worry. Also deficiency of vitamin D is particularly prevalent in regions with less UV irradiation such as Scandinavia, so the dietary supplements seem to be effective in decreasing the prevalence of deficiency, also the food fortification that increases the serum levels of vitamin D (Edwards et al., 2014).

It has been reported to be prevalent in greater part of the population in spite of the availability of sunlight, as in Vietnam. In adults, prevalence of VDD has increased from

7% in 2009 to 30% in 2012 in females living in Northern areas and to 57% in 19 provinces nationwide in 2013. These data from Vietnam are relatively high compared to those from nearby countries in Southeast Asia which vary from 60–70% (Nimitphong and Holick, 2013) The prevalence is lower in South than Northern areas. In females living in Ho Chi Minh City in 2013 was about 21.5%. It may be due to sunlight being more available in Southern than in Northern areas, also there was a trend toward a higher prevalence of VDD in females than in males. The prevalence of VDD was 30% in females, while it was 16% in males. Moreover, the percentage of vitamin D insufficiency was 46% in females, while it was only 20% in males. It has been demonstrated that the prevalence increased from 19% in 2009 to 36.2% in 2013 in North areas. Similarly, the prevalence of vitamin D inadequacy also rose from 52% in 2009 to 74.2% in 2012. No data exists on VDD in pregnant women from Southern areas. However, this picture raises an alarming problem in Vietnam, because VDD in pregnant women has serious effects on the growth of fetuses and children. The information about VDD status in children is similar to the data for adults, the percentage of VDD in children has been increasing over time. The prevalence of VDD and vitamin D insufficiency rose quickly from 22.8% and 43.1% in 2012 to 61.3% and 86.6% in 2015 among children under 6 months old in urban capital of Hanoi. There was the same trend in youngster's aged 6–11 y old for the prevalence of vitamin D insufficiency to increase from 66.7% in 2012 to calcium and VDD 70.5% in 2014 in Northern regions. The prevalence was also lower in the South which accounted for only 37.5% in the same age children. Considering the differences between urban and rural areas, the percentage of VDD in rural areas (23.6%) was higher than that in urban (22.8%) but the prevalence of vitamin D insufficiency in rural areas (40.7%) was lower than that in urban areas (43.1%). It may be due to differences in vitamin D storage in pregnant women, vitamin D concentration in lactating mothers and especially the custom of exposing children to sunshine between the two areas. Although it is not really big difference, confirming the phenomenon and identifying the reasons behind it are necessary for future nutrition intervention strategies. Nationwide, the prevalence of VDD in children under 5 y was 58% and in children aged 6–11 y old was 48.1%. Compared to other countries, the

prevalence in Vietnamese children is relatively high, since it was 23% in American children aged 1–5 y and 57.8% in Chinese children aged 6–11 y (Tuyen et al., 2016).

2.11. Vitamin D Toxicity

Vitamin D is soluble in fats so excessive intake of vitamin D supplements may increase concerns about toxicity. Hypercalcemia is accountable for the production of most of the markers of vitamin D toxicity which involve the gastrointestinal disturbance such as diarrhea, anorexia, nausea, constipation, vomiting, diarrhea, anorexia, nausea, drowsiness, headache, irregularity in heartbeat and joints pain. Also there are different side effects that show up during the couple of days or weeks such as urination, particularly around evening time, severe thirst, impairment, anxiety and kidney stones (Alshahrani and Aljohani, 2013). There are three theories for vitamin D toxicity: (1) raised plasma $1\alpha,25(\text{OH})_2\text{D}_3$ level leads to an increase in intracellular $1\alpha,25(\text{OH})_2\text{D}_3$ levels. This theory is not generally accepted since many studies have found that vitamin D toxicity is linked with the moderate or slightly higher levels of $1\alpha,25(\text{OH})_2\text{D}_3$. (2) Vitamin D consumption raises plasma 25(OH)D levels to the concentrations which surpass DBP bound capability and when free 25(OH)D enters target cells, it affects gene expression. Lower affinity of $1\alpha,25(\text{OH})_2\text{D}_3$ for the transportation protein DBP and its high affinity for VDR predominate normal physiology. In vitamin D toxicity, other metabolites can enter to the nucleus of the cell. From all the inactive products of metabolism, 25(OH)D has the high affinity for the VDR and consequently at adequately great concentrations could catalyze transcription. (3) Vitamin D intake raises the concentrations of numerous vitamin D metabolites, including vitamin D itself and 25(OH)D and these molecules surpass the DBP bound capability and release free $1\alpha,25(\text{OH})_2\text{D}_3$ that access target cells (Jones, 2008).

The Minimal Erythematous Dose (MED) can be defined as the amount of time needed to cause skin to turn pink. The timeframe varies with geographic site, pigmentation of skin, age and percentage of human body fat. Inordinate exposure to daylight does not give rise to vitamin D intoxication because it lowers any surplus vitamin D (Alshahrani and Aljohani, 2013).

2.12. Recommendations for Intervention Strategy

The exposure to sunlight (generally 5–10 min of exposure of the legs and arms or the arms, face and hands, 2 or 3 times, every seven days) and taking vitamin D supplements are sensible ways to ensuring vitamin D adequacy (Holick, 2004). Children have greater capacity to produce vitamin D than older thus they need less sunlight exposure. Children with dark skins need three times more than recommended quantities of sunlight exposure to keep up the vitamin D levels (Joiner et al., 2000). Diet rich with vitamin D is a proper decision to enhance the intake. Fortification of dairy products is safe and effective way to enhance the consumption. Fortification of grain powders and salt also required (Balasubramanian et al., 2013). In several countries, the requirement for fortification program for vitamin D has been highlighted. At the point when satisfactory exposure to sunlight is not attained due to modernization and the winter season, supplementation and fortification may help in averting vitamin D deficiency (Balasubramanian et al., 2013).

The strategy to prevent vitamin D deficiency and its passive healthful consequences includes food fortification with vitamin D, reasonable sunlight exposure and support the consumption of a vitamin D supplementation when it is required (Wacker and Hollick, 2013). The need for vitamin D can be specified by group of the endogenous (hormonal, genetic) and exogenous (physical activity, nutritional) factors. However, nutrition plays an essential role in bone health and can potentially be controlled. Controlling vitamin D deficiency and along with calcium intake has been paid particular attention as a strategy to maintain “good bone health” (Gennari, 2001). In some areas, there is wide availability of sunlight and calcium-rich foods, but the concentration of vitamin D is low in children and pregnant women as recommended (Hien, et al., 2012). Thus they should follow a strategy to control this problem, such as food fortification, supplementation of vitamin D, sun exposure and follow the nutritional recommendations.

3. CONCLUSION

The vitamins and other micronutrients have a critical importance in the etiology of cancer, Parkinson's disease, Lafora disease, Alzheimer's disease and other numerous diseases. Thus they have attracted attention of researchers in the last years. The comprehensive and precise information to the idea of oxidative stress has been illustrated in this project. There is a vibrant correlation among the vitamin D and oxidative stress. Obviously vitamin D has a defensive role in lessening oxidative stress by terminating the lipid peroxidation chain reaction. There is a space for more research to understand the mechanism of oxidative stress and vitamin D along with other micronutrients.

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