T.R.N.C

NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

THE INTERRELATIONSHIP BETWEEN VITAMIN D AND PRIMARY HEADACHES

Jerry Hussaini GAKU

MEDICAL BIOCHEMISTRY PROGRAM

MASTER OF SCIENCE GRADUATE TERM PAPER

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SUPERVISOR

Assist. Prof. Kerem TERALI, MRes, PhD

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2018

DECLARATION

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last Name:

Signature:

Date:

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ABSTRACT

Introduction: A number of research suggest a relationship between vitamin D and primary headaches, while quite a few studies suggested no relationship between vitamin D levels and migraine. Clinical studies of vitamin D and calcium administration to patients with known condition of migraine and vitamin D deficiency have shown a positive result in improving pain and migraine attack.

Methods: In this research, several journals were collected, information extracted, evaluated and summarized.

Results: The summarized scientific journals suggested that low levels of $25(OH)D_3$ and VDR are associated with migraine patients, vitamin D and calcium supplements administered to migraine patients proved to be effective. Furthermore, the presence of VDR, activating enzymes, and vitamin D in the hypothalamus may suggest that deficiency of vitamin D may be associated with the pathophysiology of primary headaches. VDR polymorphism and reduced magnesium have been associated with migraine and tension type headache respectively. However, some journals suggested no relationship between migraine and vitamin D.

Conclusion: There remains a growing body of both clinical and laboratory evidence pointing to a potential relationship between low levels of 25-hydroxy vitamin D, VDR and primary headache. More focused research involving the above topic is necessary.

Key words: vitamin D; primary headaches; migraine; VDR polymorphism.

ÖZET

Giriş:* Birçok araştırma D vitamini ile primer baş ağrıları arasında bir ilişki olduğunu öne sürerken birkaç çalışma ise D vitamini ile migren arasında hiçbir ilişki olmadığını ileri sürmüştür. Klinik çalışmalar migreni ve D vitamini eksikliği olduğu bilinen hastalara verilen D vitamini ve kalsiyum uygulamalarının ağrı ve migren ataklarının iyileşmesinde olumlu sonuçları olduğunu göstermiştir.

Yöntem: Bu araştırmada çeşitli yayınlar bir araya getirilmiş ve gerekli bilgiler elde edilmiş, değerlendirilmiş ve özetlenmiştir.

Bulgular: Özetlenen bilimsel yayınlar düşük 25(OH)D3 ve VDR düzeylerinin migren hastalığıyla ilişkili olduğunu ve migren hastalarına uygulanan D vitamini ve kalsiyum takviyelerinin etkili olduğunu ileri sürmüştür. Ayrıca VDR, aktive edici enzimler ve D vitamininin hipotalamustaki varlığı D vitamini eksikliğinin primer baş ağrılarının patofizyolojisiyle ilişkili olabileceğini düşündürmüştür. VDR polimorfizmleri ile azalmış magnezyum düzeyleri sırasıyla migren ve gerilim tipi baş ağrısıyla ilişkilendirilmiştir. Buna karşın bazı yayınlar migren ve D vitamini arasında herhangi bir ilişki olmadığını önermektedir.

Sonuç: Düşük 25-hidroksi D vitamini düzeyleri ve VDR ile primer baş ağrıları arasında potansiyel bir ilişki olduğuna işaret eden hem klinik hem de laboratuvar bulgularının sayısı giderek artmaktadır. Yukarıda bahsedilen konuyu içine alan daha odaklı araştırmalara gereksinim olduğu açıktır.

Anahtar kelimeler: D vitamini; Primer baş ağrıları#; Migren; VDR polimorfizmleri

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ABBREVIATIONS

DBP	Vitamin D binding protein
VDR	Vitamin D receptor
CSD	Cortical spreading depression
HPLC	High pressure liquid chromatography
PTH	Parathyroid hormone
TGF	Transforming growth factor
HL	Human promyelocylic leukemia
LIP	Liver enriched inhibitory protein
EGFR	Estimated glomerular filtration protein
15-PGDH	15-prostagladins dehydrogenase
PGE-2	Prostagladin E2
CGRP	Calcitonin gene related peptide
C/EBPβ	Enhancer binding protein beta
ELISA	Enzyme linked immune-sorbent assay
TTH	Tension type headache

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1.0 INTRODUCTION

Vitamin D (cholecalciferol) is a fat-soluble steroid derived from cholesterol, unlike the cholesterol structure, the vitamin structure consists of four steroids ring but one of its bonds is broken. The two kinds of vitamin D that are important both to plants and animals are; ergocalciferol- which is vitamin D_2, and cholecalciferol (vitamin D_3). Ergocalciferol occurs in moulds, yeast, higher-order plants and it is formed through the action of ultraviolet light on ergosterol resulting in bond breaking formation, while cholecalciferol occurs in vertebrates when ultraviolet (UVB) radiation acts on the skin (upper epidermis) containing 7-dehydrocholesterol found on the skin. Supplements containing vitamin D can be made from vitamin D_2 and vitamin D_3, and are non-prescribed, but in the United States, the supplementation available for prescription is made from vitamin D_2 (Holick, 2007).

Vitamin D can be obtained from the sun, when the skin containing 7-dehydrocholesterol is exposed to sunlight. However, the production of the biological, functional metabolite of vitamin D depends on the intensity of ultraviolet light (*i.e*., seasonal variation and latitude plays a vital role in the intensity of ultraviolet light) (Holick, 2006). Vitamin D can be obtained in diet such as sardines, cod liver oil, and salmon; (Chen *et al.*, 2007). Vitamin D is also gotten from; the fortification of milk, cheese, bread, and yoghurt (Holick, 2006). Vitamin D supplements are also available in different amounts ranging from 400 IU to 5000 IU vitamin D_3 (Holick, 2007).

Vitamin D_2 and vitamin D_3 cannot achieve maximum functions because they are biologically inactive. The half-life of vitamin D obtained from the skin (sunlight) is short (1-2 days), the vitamin is rapidly metabolized in the liver and kidney respectively or it is stored in fat cells (Mawer *et al*., 2005). The precursor 7-dehydrocholesterol found on the skin absorbs light and undergoes a rearrangement in its structure to form vitamin D3 (cholecalciferol) (Holick, 2006).

The cholecalciferol in circulation is inert and unable to achieve full hormonal function until it is activated. To achieve full hormonal function, vitamin D_3 must bind to a protein carrier known as vitamin D binding protein (DBP). DBP is responsible for transporting cholecalciferol to the liver. The enzyme 25-hydroxylase in the liver is responsible for adding a functional group (hydroxyl group) cholecalciferol on its carbon-25. A study carried out by (Zisman *et al*., 2005) showed that cytochrome P450 enzymes such as CYP27A1, CYP2D25 and CYP2RI plays a part in the transformation of the metabolite $25(OH)D_3$ from vitamin D_3. The main serum vitamin D metabolite is $25(OH)D_3$, thus, when the metabolite is in circulation, it reflects the influence of the

skin exposed to sunlight or the vitamin D obtained from diet. (Holick, 1995). The concentration of the metabolite in serum is used as a biomarker to indicate the vitamin D status (Holick, 2007). The metabolite the liver produces binds to DBP, to be further metabolized to another vitamin D metabolite in the kidney.

The metabolites produced both in the liver and kidney are regulated within the liver and kidney. Vitamin D and its metabolites helps to regulate the enzyme responsible for the production of $25(OH)D_3$ in the liver. Thus, when the enzyme is regulated, it limits the increase of circulating serum metabolites even upon dietary intake containing vitamin and display of the skin to sunlight (Reichel, 1989). Parathyroid gland regulates the production of the metabolite produced in the kidney (Reichel, 1989).

Active vitamin D (1, $25(OH)_2D_3$) carries out its functions by regulating the absorption of calcium, when the expression of calbindin which is protein acting as an hormone is stimulated (Reichel, 1989). Calbindin is a protein that serves as a transporter, to transport calcium into the blood stream from intestinal lumen and epithelia cells. In the bones, active vitamin D (1, $25(OH)_2D_3$), plays an important function- because it regulates the action of cells which refashion and remodel bones. Reichel, (1989) states that, in the parathyroid gland the production and secretion of parathyroid hormone is decreased by active vitamin D, and it also regulates the growth of parathyroid gland cells.

The action of active vitamin D does not resides only in the control of calcium phosphate homeostasis, but also plays an important role in the regulation of cell-like mechanism which includes cell growth, differentiation of normal and pernicious cells. Additionally, it regulates cardiovascular functions, plays role in immune function and hormones (Colston, *et al.,* 1981).

The influence of sunlight exposure, dietary intake, and supplementation results in the above functions of active form of vitamin D and the proper functioning of the receptor (VDR). These functions could be altered when vitamin D is deficient. All over the world, vitamin D deficiency pose a threat health issue with reported prevalence in normal populations of about 30% to 50% and especially in young women (Hovsepian *et al.*, 2011). Deficiency of vitamin D could either be due to decreased exposure to ultraviolet light which reduces the synthesis of the inert vitamin D (cholecalciferol) from 7-dehydrocholesterol or by staying away from the sun due to health challenges (Deeb *et al.*, 2007).

Both children and adults suffer from insufficiency of vitamin D. In children, deficiency can causes bone deformity, also known as rickets, while in adults, deficiency leads to lack of minerals such as calcium in the skeleton. This results to softening of bones, a condition known as osteomalacia. The lack of minerals as a result of deficiency affects the parathyroid gland, promoting secondary hyper-parathroidism (Cranney *et al*., 2007). Deficiency causes pain in children and adults due to weakness of muscles (Bischoff *et al*., 2003). In cystic fibrosis patients, low levels of the metabolites [25(OH)D_3] leads to a condition in which there is reduction in the minerals, protein content and density of bone which contribute to the persistent pain experienced by vitamin D deficiency patients (Hayes *et al.*, 2011).

Insufficiency of vitamin D has been related with some illness such as headache, abdominal, knee, and back pain, assiduous musculoskeletal pain, tietze's syndrome, and fibromyalgia syndrome (Plotnikoff & Quigley., 2013). Chronic inflammation have been connected to long-standing - vitamin D deficiency. (Munger *et al*., 2006). These dilapidating conditions can negatively affect the quality of life of the patient. This negative effects could include loss of employment and pull out from social livelihood. Huang *et al*., (2013), in their study said that the standard of life can be enhanced in the evaluation of slumber, pain levels, through the administration of vitamin D supplements.

The serum vitamin D_3 metabolite [25(OH) D_3] can be increased through vitamin D supplementation which can correct deficiency of vitamin D (Straube *et al*., 2010). However, there is obscurity at present on the stabilization of serum vitamin D metabolite, the influence on metabolism of vitamin D via dietary intake and reversibility of chronic pain. Thus, considering the short circulating half-life of serum vitamin D, different schedules of vitamin D dosage could be employed through clinical trials and the results could be profound (Hollis & Wagner, 2013). In clinical trials, it is vital to note the entrance of the metabolites of vitamin D into cells. These metabolites are either transported by transporters such as DBP and co-receptors (magalin and cubilin) into cells or by diffusion across the cell membrane (Brannon, 2012).

Vitamin D deficiency has been associated with migraine (primary headaches) (Goadsby, 2009). This is because vitamin D as a neuro-active steroid, modulates neuronal excitability and also modulates brain neuro-transmitters (serotonin and dopamine) involved in the pathogenesis of migraine (Goadsby, 2009).

Primary headaches such as migraine and tension type headache (TTH) are frequent conditions in childhood. (Genizi *et al*., 2013). The TTH is bilateral and around the forehead area and characterized by pressure, or tightness like a band which waxes and wanes with variable duration (Lorde & Rizzoli, 2008).

Migraine is a chronic neurovascular disorder affecting the functions of the autonomic nervous system and a genetic predisposition (Silberstein, 2004). Migraine is a disorder of recurrent attack and according to the World health organization (WHO), it is ranked the 7th most dilapidating disorder. Migraine occurs in all age groups, and its effect, may be dramatic (Seshia, 2012). Preceding to puberty, the disorder is somewhat greater in boys than in girls, but in the course of adolescence, the extensiveness of the disorder tends to increase in girls than boys, more rapidly (Stovner *et al*., 2007). Therefore, women are likely to experience migraine after menarche, probably after their first period, hence, there could be a relationship between migraine and estrogen (Silberstein, 2004). In general, the extensiveness of migraine rise in the course of childhood and prior adulthood until approximately 40 years of age, and then thereafter diminish (Arruda & Guidetti, 2010).

Migraine is a unilateral pulsatile headache, characterized by pain in the head, photophobia (sensitivity to light), phonophobia (sensitivity to sound), vomiting and smell (Olesan, 2008). Levy, (2009) states that, there are internal and external factors that initiate migraine. These factors include disturbance of sleep, stress, meal skipping, fluctuations of hormones and the body senses experiencing over stimulation from the surrounding.

Globally, approximately 16 percent of the population are afflicted from migraine headache. An estimate of one third of those migraines are as a result of the combination of cortical disturbance and neurological symptoms, called migraine aura (Lauritzen, 1994). This disturbances arise from the mechanism of cortical spreading depression (CSD), which is a wave of electrical activity that sleeps slowly across the surface the surface of the cortex before the onset of the headache (Bowyer *et al*., 2001). The susceptibility for its occurrence likely depends on genetic factors that render the cerebral cortex hyper-excitable through abnormal excitatory/inhibitory balance (Vecehia & Pietrobon, 2012).

To find a comprehensive explanation for the underlying pathophysiology of migraine as a disease, attempts have come to form some theories which can somehow justify the heterogeneity of the symptoms. It has been shown that inflammatory substances produced by mast cells, especially in

meninges, can activate the trigeminal nerve which is a central event in the pain of migraine (Levy *et al*., 2006). The vasodilation of blood vessels in hypersensitive migraine patients caused by nitric oxide NO, a vasoactive substance can be a consequence of migraine (Vanmolkot & Hoon, 2010). Evidence has shown that lower levels of vitamin D are related to migraine headache (Prakash & Shah, 2009) but a few studies have proven this relationship. Although, many authors have reported a contradictory relationship of vitamin D status and headache.

1.1 AIM OF THE STUDY

Therefore, the aim of this study is to study, synthesize, organize, evaluate and summarize existing results that examined the association or the disassociation between vitamin D status and migraine.

1.2 SIGNIFICANCE OF THE STUDY

- This study will provide information from different journals regarding the inter-relationship between vitamin D status and headache (migraine).
- The study will serve as reference to other people conducting a similar study.

1.3 OVERVIEW OF THE PROJECT

Chapter 1 is an introduction of the project, including the aim and significance.

Chapter 2 focuses on the theoretical background on vitamin D

Chapter 3 focuses on the literature review on migraine

Chapter 4 organize, evaluate and explains the results from other journals and conclusion.

CHAPTER TWO

Vitamin D is produced endogenously in the skin of humans from the precursor 7-dehydrocholesterol and then converted to vitamin D_3 after exposure to ultraviolet light.

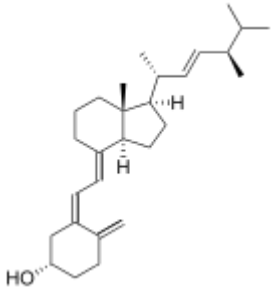
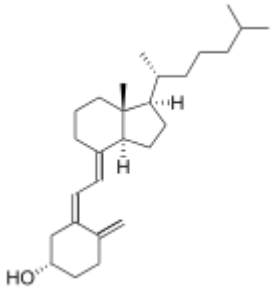
Name	Chemical composition	Structure
Vitamin D_2	Ergocalciferol (made from Ergosterol)	
Vitamin D_3	Cholecalciferol (made from 7 – dehydrocholesterol in the skin)	

Table 1: Chemical composition of vitamin D_2 and D_3

2.0 VITAMIN D SYNTHESIS

The introduction of the skin containing 7-hydrocholesterol to ultraviolet light at a wavelength of (290-315nm) is considered the primary source in the synthesis of vitamin D. The production of active vitamin D is mostly dependent on the intensity of ultraviolet light (Holick, 2004). Upon exposure of the skin to the sun, the 7-dehydrocholestrol found in the upper epidermis of the skin undergoes a structural conformation. It is this modified structure that bounds to a carrier protein called vitamin D binding protein (DBP). DBP transports cholecalciferol to the liver and kidney respectively for further transformation (Holick, 2004).

2.1 SOURCES OF VITAMIN D

Vitamin D can be obtained from various source such as the sun, when the skin is exposed to sunlight. It is worth mentioning that seasonal variation and latitude plays a vital role in the intensity of ultraviolet light (Brot *et al*., 2001). For example, from the month of November to the month of February, in Boston (42.2°N), vitamin D obtained from the sun is void because there is no sunlight, rather vitamin D is obtained from diet or supplement, whereas, vitamin D is produced

all through the year when the skin is exposed to sunlight in San Juan (18°N) (Brot *et al.*, 2001). The production of vitamin D from sunlight can be decreased by the pigment found in the skin called melanin and application of sunscreen (Holick, 2006).

Additionally, vitamin D is also obtained in diet such as sardines, cod liver oil, salmon, and mackerel, (Chen *et al*., 2007). The fortification of milk, cheese, breads, and yoghurts are sources of vitamin D (Holick, 2006). Vitamin D supplements are also available in different amounts ranging from 400IU to 5000IU vitamin D_3 (Holick, 2007).

2.2 METABOLISM OF VITAMIN D

The precursor 7-dehydrocholesterol is transported through a carrier protein to be metabolized in the liver and then in the kidney respectively.

VITAMIN D AND 25(OH) D_3 IN THE LIVER

The vitamin D (7-hydrocholesterol) obtained from the sun is inert (inactive), but when converted to its active metabolite in the liver and kidney, it is able to carry out its biological function. The precursor 7-hydrocholesterol undergoes a restructuring of its bonds upon absorbing light energy to form cholecalciferol. (Holick, 2006).

The cholecalciferol in circulation is inert and unable to achieve full hormonal function until it is activated. The cholecalciferol is transported to the liver to be metabolized upon binding to the carrier molecule DBP. The enzyme 25-hydroxylase in the liver is responsible for adding a functional group (hydroxyl group) to cholecalciferol on its carbon-25, to form a metabolite -25-hydroxyvitamin D [25(OH)D_3]. The main serum vitamin D metabolite is 25(OH) D_3. Thus, when the metabolite is in circulation, it reflects the influence of the skin exposed to sunlight and the vitamin D obtained from diets (Holick, 1995). The concentration of the metabolite in serum is used as a biomarker to indicate the vitamin D status (Holick, 2007). The excess vitamin D not metabolized by the liver and kidney is stored in fats tissue and muscles (Holick, 2006).

Vitamin D and its metabolites play important role in the regulation of the enzyme vitamin D 25-hydroxylase in the liver. Thus, when the enzyme is regulated, it limits the increase of serum circulating metabolites even upon exposure to sunlight and dietary intake (Reichel, 1989). The metabolite 25(OH) D_3 formed in the liver is transported to the kidney through the carrier protein DBP for further transformation.

IN THE KIDNEY

In the kidney, a functional group (hydroxyl group) is added to $25(OH)D_3$ at carbon -1 by the enzyme $25(OH)D_3$ 1-α-hydroxylase, to produce the active form of vitamin D called 1,25-dihydroxyvitamin [$1,25(OH)_2D_3$] or calcitriol. The calcitriol formed can achieve full hormonal functions (Reichel, 1989). In the kidney, the parathyroid gland (PTH) regulates the production of the metabolite [1, $25(OH)_2D_3$] in response to serum calcium and phosphorus concentrations (Reichel, 1989).

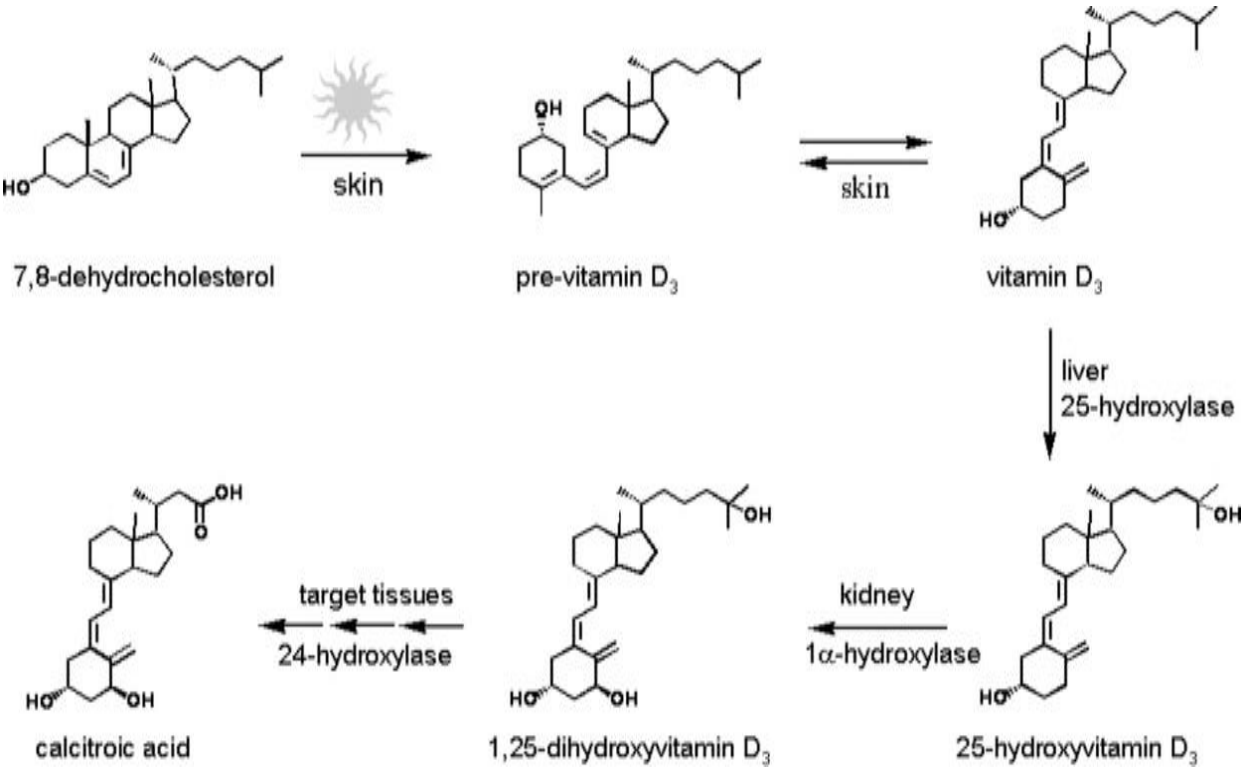


Fig 1: Formation of vitamin D (Holick, 2006)

2.3 WHAT HAPPENS TO THE ACTIVE VITAMIN D

Active D is fairly unstable and can rapidly degrade without protection or the attachment of a protein carrier. This protein carrier primarily consists of a 1, 25 vitamin D molecule, DBP and VDR. The two proteins control the metabolism and mechanism of action of active vitamin D. Vitamin D is primarily transported to its target tissue through the DBP. The affinity of the active

vitamin D to its DBP is one of the many factors that influence its activity and half- life. Free active vitamin D taking up by rapid cells is either metabolized or bound to vitamin D receptor. Upon binding to receptor, it undergoes a conformational changes that allows it to interact with other transcriptional factor within the nucleus (Aranow, 2011). In other to interact with transcriptional factor and affect gene transcription, the active vitamin D complex must react with a retinoid X receptor to form a hetero-dimer that can then bind to selective or promoter site of the target cells DNA (Aranow, 2011). This new complex, then recruits various co-activators and co-repressors which influence gene expression and alters cellular activity (How *et al.*, 1994). These can include protein synthesis and secretion, cellular proliferation or differentiation (How *et al.*, 1994). What determines that the overall cellular response is the cell type and location, the number or availability of vitamin D receptors and the affinity of active vitamin D to these receptors (How *et al.*, 1994).

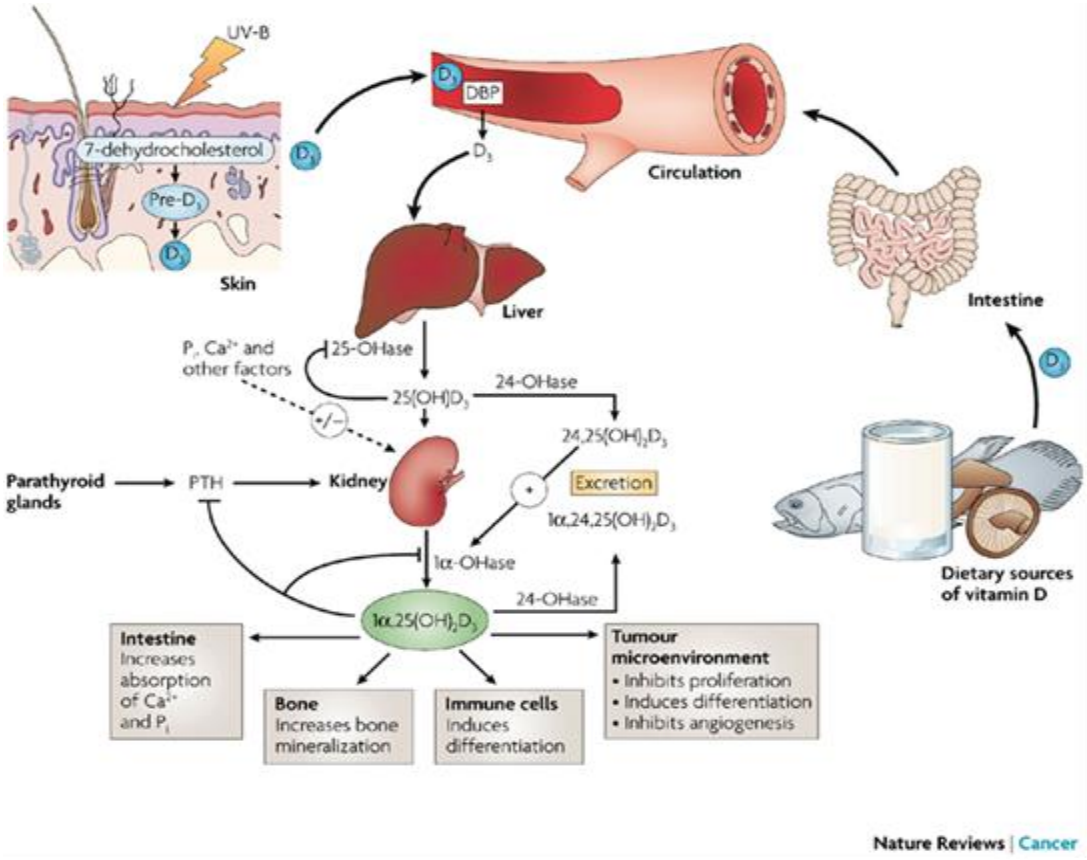


Figure 2: Diagram showing the vitamin D metabolism and some functions **(**Holick, 2008**)**

2.4 PHYSIOLOGICAL EFFECT OF VITAMIN D

2.4.1 REGULATION OF CALCIUM ABSORBTION BY VITAMIN D

The hormonally active vitamin D regulates the absorption activity of minerals such as calcium and phosphate. It also stimulates the expression of a carrier protein called calbindin. Calbindin serves as a transporter of calcium to the blood stream and into cells from the intestine. The process by which active D regulates calcium absorption is through facilitated diffusion. Firstly, the calcium through the calcium channel enters and binds to the calcium binding protein calbindin and finally, the calcium is ejected across the membrane by calbindin D_{9k} (Fig 2) (Christakos *et al*., 2004).

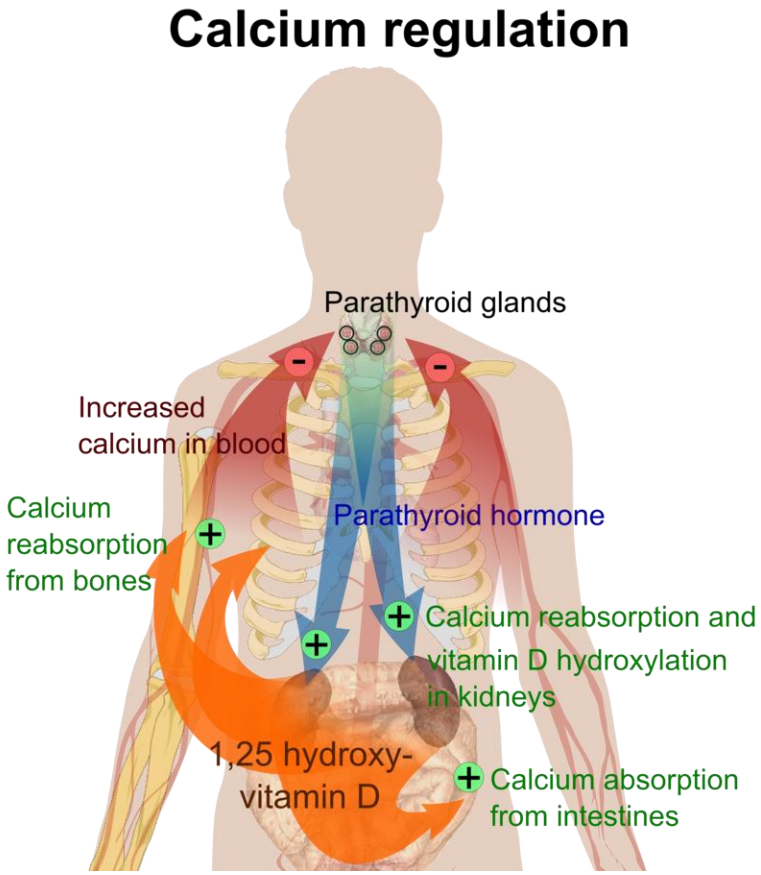


Figure 3: Functions of Vitamin D in Intestinal Calcium absorption
(Holick and Tai, 2008)

2.4.2 BONE

Calcium helps in the strengthening of bones, thus making it one of the most vital constituent or minerals of the bone. Additionally, it also remodel bones and prevent bone deformity, thus the structure of the bone depends on the continuous supply of calcium (Amling *et al*., 1999).

2.4.3 IN PARATHYROID GLAND

The production and secretion of parathyroid gland is regulated by active vitamin D and it also regulates the growth of parathyroid gland cells (How *et al*., 1999). It renders parathyroid gland to be susceptible to the suppressive action of calcium (How *et al.*, 1999).

2.5 ACTIVITY OF VITAMIN D IN THE IMMUNE SYSTEM

VDR and enzymes that metabolize vitamin D are present in many cells, if not all throughout the body. They are found in antigen-presenting cells, T cells, B cells and monocytes. Because of the wide spread of VDR, active vitamin D regulates the innate immune system (natural killer cells) and adaptive immune system (T cells and B cells) (Toubi & Shoenfeld, 2010). Vitamin activates cathelicidins, antimicrobial peptidase present within the lysosomes of macrophages and polymorphonuclear leukocytes (Segaert, 2008). Cathelicidins regulate the transcription of vitamin D receptor as its gene promoter contains the functional response to vitamin D (Gombart *et al*., 2015), it also plays role in the innate immune defence against bacterial infections (Nizet *et al*., 2001). Yim *et al.*, (2007), said that the antimicrobial peptide function in macrophages, karatinocytes, lung epithelial cells, placental trophoblast cells, and myeloid cells lines are regulated by active vitamin D. Active vitamin D inhibits the initiation of many diseases, such as experimental autoimmune encephalomyelitis, thyroiditis, type 1 diabetes mellitus, inflammatory bowel disease, systemic lupus, erthematosus, and lyme arthritis (Adorini *et al*., 2004).

2.6 PLEIOTROPIC EFFECTS OF VITAMIN D

2.6.1 CANCER

Researchers over the years have discovered the influence of the metabolite [1, $25(OH)_2D_3$] in cancer cells. Melanoma cells doubles upon treatment with the active vitamin D (Colston *et al.*, 1981). Shortly, after the treatment of melanoma cells with the active vitamin D, the human promyelocyic leukaemia cells (HL60) was incubated together with the active metabolite and was reported that the HL 60 leukaemia cells separate near the macrophage lineage (Abe, *et al*., 1981). Thereafter, numerous studies demonstrated that active D slows the growth of cancer cells. It does

so by causing the separation of cancer cells or by influencing programmed cell death (Hobaus *et al.*, 2013). Active vitamin D also influence the formation of new blood vessels (angiogenesis), the migration of cancer cells, alteration of cell adhesion, and reduces the invading of cancer cells (Hobaus *et al*., 2013).

The following are the influences of active vitamin D in cancer cells;

(1) The transcription of cyclin-dependent kinase inhibitor is influenced by the active metabolite of vitamin D (1, 25 $(OH)_2D_3$) (Liu *et al*., 1996). This is sufficient to suppress growth of cells of the monocyte-macrophage lineage and promote their differentiation.

(2) The production of cyclin dependent kinase inhibitor is promoted by the active metabolite of vitamin D 1, 25$(OH)_2D_3$ (Li *et al*., 2004).

(3) The proliferation of tumour cells is due to the over expression of the TGF-α/EGFR pathway. Active vitamin D could inhibit the TGF-α/EGFR growth pathway (Cordero *et al.*, 2002).

(4) In human epithelial cell tumors, CCAAT/enhancers binding protein beta (C/EBPβ) is considered to be effective in the inhibition of the carcinogenic cell cycle protein D1 (Lamb *et al*., 2003). In contrast, the C/EBPβ isoform LIP (liver-enriched inhibitory protein) can enhance the activity of the carcinogenic cyclin D1 and induce cell growth. Therefore, the proliferative property of human tumors is inversely correlated to the intracellular C/EBPβ-to-LIP ratio (Zahnow, 2002). The active vitamin D can induce the expression of C/EBPβ and prevent the proliferation of LIP epidermal growth factor receptor, thus reducing the occurrence of (estimated glomerular filtration rate) EGFR-driven related cancers (Baldwin *et al*., 2004).

(5) The active metabolite is vital in the metabolism of cell, it regulates programmed cell death, separation of cells and the maturation of cell (Zittermann, 2013).

2.7 INTERFACES OF PAIN AND VITAMIN D

Insufficiency of vitamin D poses a threat to the well-being of individuals and many diseases such as cardiovascular diseases, pains, headache, assiduous musculoskeletal pain, Tietze's syndrome, and fibromyalgia syndrome have been linked to vitamin insufficiency (Plotnikoff & Quigley, 2013). These dilapidating conditions can negatively affect the quality of life of the patient. These negative effects could include loss of employment and pull out from social livelihood.

2.7.1 PAIN AND VITAMIN D

Vitamin D regulates the activity of the cell that remodels and builds bones and it also stimulates calcium absorption which is needed by the bones. Thus, insufficiency of vitamin D can lead to a decrease in the absorption of calcium and as a result the calcium from the bones will be release just to maintain the concentrations of circulating calcium (Lips, 2001). Vitamin D insufficiency defines the lack of vital minerals to the skeleton. In infants, it causes bone deformities also called rickets (Thacher & Clarke, 2011), while in adults, deficiency facilitates osteoclast genesis with consequent increased bone resorption (Adams & Hewison, 2010), promotes hyper-parathydroidism with consistent bone loss and weakening of bones (Cranney *et al*., 2007).

2.7.2 DEFICENCY OF VITAMIN D AND WEAKNESS OF MUSCLE

Active vitamin D is vital in the regulation of muscles and in the metabolism of bone (Liao et al., 2014). These functions can be impaired when vitamin D is insufficient. Deficiency of this vital mineral leads to rickets in children and osteomalacia in adult (Cranney *et al*., 2007). Deficiency causes pain in children and adults due to weakness of muscles (Bischoff *et al.*, 2003).

2.7.3 Prostaglandins and Vitamin D

The action of Vitamin D on prostaglandin activity is through the inhibition of COX-2 expression and also through 15-prostaglandins dehydrogenase (15-PGDH) expression stimulation (Feldman *et al.*, 2007).There is a degradation of prostaglandins by the 15-PGDH enzyme in which the subtypes of prostaglandin-E2 receptor (PGE-2) and the subtypes of prostaglandin-F2 alpha receptor (Box-2) are inhibited (Feldman *et al.*, 2007). There is a straightforward reaction of prostaglandin on sensory neurons which lowers the threshold firing, increases the number of action that is brought about through a stimulus depolarization, and augmenting SP and CGRP discharge (Richardson and Vasco, 2002). Mediation takes place by prostaglandins in neuropathic pain at the spinal cord through PGE-2 depolarization at very large varying neurons ranges (Moalem and Tracey, 2006).

2.8 VITAMIN D RECEPTOR (VDR) AND 1 α HYDROXYLASE

Both the receptor and the enzyme have a pivotal role to play in the function of vitamin D. The enzyme is found in the kidney and it is responsible for adding a functional group (hydroxyl group) to the metabolite (25(OH) D_3) on its corbon-1 to form the active metabolite (1, 25$(OH)_2D_3$). The gene coding for the receptor was recognized in 1988 (Kalueff & Tuohimaa, 2007). The receptor has been shown to be present in many tissues. The receptor is present in the human central

nervous system and cells like, parathyroid cells, kidney, pancreatic cells, macrophages, hypothalamus (Kalueff & Tuohimaa, 2007). The receptor and the enzyme are present in glial cells and neuronal cells (Eyles *et al*., 2005). In the rat model, DPB has been found in axonal projections in the lateral hypothalamus (Jirikowski *et al.*, 2009). Studies have reported that an estimate of 3% of the entire human genes are regulated by vitamin D through its endocrine effects (Bouillon *et al.*, 2008). Studies have also indicated that the pathophysiology of inflammatory diseases such as pains and headache may be as a result of the presence of vitamin D receptor, the enzymes, and vitamin D binding protein in the hypothalamus (Prakash *et al*., 2010).

2.9 VDR POLYMORHISM

The biological function of vitamin D is exerted by VDR. VDR is said to be expressed in tissues, hypothalamus and the brain. It is a nuclear protein capable of inducing transcriptional factor. The gene coding for the receptor is positioned on 12q chromosome, having polymorphic allele occupied on the gene locus. Polymorphism of the gene coding VDR occurs when the base C is replaced with another base T, a process known as single nucleotide polymorphism. The four alleles occupied on the gene locus are *Fok*I, *Bms*I, *Taq*I, *Apa*I (Kostner *et al*., 2009). In recent years, several research on VDR polymorphism associated/dissociation with other diseases have been reported. Kostner *et al.,* (2009), reported that VDR polymorphisms are associated with several types of cancer and concluded by indicating the polymorphisms associated with several cancers, such as, the allele *Bsm*I and *Fok*I are associated with breast cancer, *Fok*I is associated with prostate cancer and malignant melanoma. Also in a meta-analysis conducted by Yang *et al.*, (2015), no association among the four VDR gene polymorphisms and the risk of end-stage renal disease has been reported. In another study, Mohammadnejad *et al.*, (2012) reported the risk of VDR polymorphism and diabetes mellitus. The report concluded that, the allele *Fok*I polymorphism can raise the risk of diabetes mellitus type II in East Asians. Also, Karray *et al*, showed an association between VDR polymorphism and rheumatoid arthritis and Behcet's disease. Also, a meta-analysis conducted by Huang *et al.,* (2013), reported no association between *Fok*I and *Taq*I VDR polymorphism and multiple sclerosis. In the study of nervous system disease such as Alzheimer's and Parkinson's diseases, Lehmann *et al.,* (2011), reported an association of the allele *Taq*I VDR polymorphism and Alzheimer's disease while Lv *et al.,* (2013), reported no relationship between *Taq*I VDR polymorphism and Parkinson's disease. From all indications, VDR is very vital and

have been shown to be present in cell-like tissues, where it exerts the function of vitamin D and has been linked to several disease conditions.

2.10 VITAMIN D DEFICIENCY

The functions of vitamin D in the body cannot be overemphasized, as it plays vital role in strengthening of bones, helps in the activity of the immune system, headaches, and so many more. However, these functions can be impaired by lack of vitamin D and can lead to severe conditions. Vitamin D deficiency is a global public health issue with reported prevalence in normal populations of about 30% to 50% and especially in young women (Hovsepian *et al*., 2011). Deficiency of vitamin D could either be due to decreased exposure to ultraviolet light which reduces the synthesis of the inert vitamin D (cholecalciferol) from 7-dehydrocholesterol or due to active avoidance of the sun for presumed health reasons (Deeb *et al*., 2007).

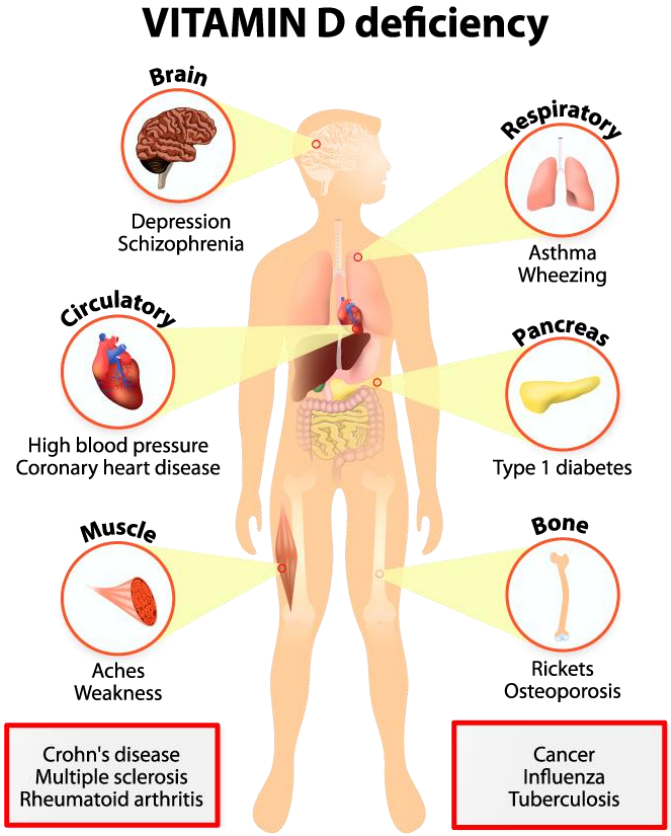


Fig 4: Deficiency of Vitamin D in the body (www.vitamindcouncil.org)

2.11 VITAMIN D ADMINISTRATION

Administration of vitamin D supplements redress issues caused by deficiency of vitamin D and can increases levels serum ($25(OH)D_3$) (Straube *et al*., 2010). Administration of vitamin D

can advance the quality of life, determines slumber, levels of pain and salubrity (Huang *et al.*, 2013).

CHAPTER THREE

3.0 PRIMARY HEADACHES (MIGRAINE)

Primary headaches include TTH, migraine and cluster headaches. Muscle contraction, interaction between blood vessels and nerve abnormalities have been associated to the cause of these headaches.

Migraine is the most disabling disease and it is often classified with migraine with aura or migraine without aura. Migraine occurs in phases, but may not occur in every patients. The prodrome phase of migraine include sensitivity to light, sensitivity to sound, thirst, fatigue and drowsiness, changes in appetite. The aura phases are sensory disturbances that occurs before the migraine attack. The migraine attack phase usually last 4-72 hours if untreated and it is accompanied with symptoms like throbbing pain on one side of the head, visual symptoms, nausea, facial tingling or numbness, severe photophobia and phonophobia (Goadsby, 2009).

	Migraine	Tension	Cluster
Pain description	One sided, throbbing, pain, moderate to severe, lasting about 4-72hours	Pressure, tightness, waxes and wanes	Abrupt onset, deep, continuous, excruciating
Associated symptoms	Sensitivity to light, sound, nausea, vomiting, aura	None	Tearing, sweating, congestion

Table 2: Types of migraine

3.1 THE VARIATIONS OF MIGRAINE

MENSTRUAL MIGRAINES: Migraine is tied to the menstrual cycle of women and possibly during the first trimester of pregnant women.

OPHTHALMOPLEGIC MIGRAINE: younger adults suffer from this form of migraine attack, which can last for hours or months. The pain centres around one eye and symptoms include vomiting, double vision, a droopy eyelid and paralysis of eye muscles.

ABDOMINAL MIGRAINE: this form of migraine occurs in children who have a history of migraine. It is accompanied by abdominal pain, nausea and vomiting.

3.2 CAUSES OF MIGRAINE

Over the years, it was believed that the cause of migraine was as a result of abnormalities of blood vessels in the head. Until recently, doctors believe that central nervous system disorder causes migraine. This disorder creates a chain of neurological and biochemical events which tends to affect the brains vascular system. (Goadsby, 2009).

The following are triggers of migraine which are under investigation.

Peptides: peptides such as substance P, calcitonin gene-related peptide, are proteins that are released by stress. These substances expand blood vessels and produce an inflammatory response that triggers over-excitation of the nerve cells in the trigeminal pathway.

Abnormal Calcium Channels: Migraine can arise from disorders in transportation channels of ions such as calcium (plays important in migraine), magnesium, sodium, and potassium.

Serotonin and Other Neurotransmitter Levels: Serotonin is an important neurotransmitter which aids in sleep, improving well-being and life. Because of its roles, it has been observed that a drop in the levels of serotonin, dopamine, and stress hormones can cause primary headaches.

Low levels of Magnesium: Low levels of magnesium have been reported in people suffering from primary headaches such as (migraine and tension-type). Low levels of magnesium have been associated with misfiring of brain nerves causing migraine attack.

Nitric Oxide: Studies have suggested that nitric oxide could play critical role in triggering migraines, tension-type and cluster headache (Cury, 2011).

Estrogen Fluctuations in Women: It has been observed that fluctuations in hormones can trigger tension-type headaches and migraine headaches in women.

3.3 TRIGGERS OF MIGRAINE

The following events and conditions can bring about nerve excitation and trigger migraine attack, skipping meals, high altitude, lack of sleep, odour, emotional stress, abrupt weather change, bright and flickering lights, caffeine (Levy, 2009).

3.4 MIGRAINE AFFECTING AGE AND GENDER

GENDER

An estimate of 75% of all migraine sufferers are women. It has been observed that migraine attack is common in females. It affects females ranging from age 20–45 (Silberstein, 2004).

Fluctuations in estrogen and progesterone hormones in females may cause migraine attacks in females. Research as shown that there is a slight relationship between menstrual cycle and migraine. And in some women during their first trimester, migraine attack may worsen (Silberstein, 2004).

AGE

Migraine affects almost all ages, ranging from adolescence to adulthood. Migraine attacks also affect children ranging from 5 - 10% of all children, affecting both boys and girls. Research has shown that children with migraine history may likely continue having migraine attacks even in adulthood, but the case is not so with children without migraine history, they either undergo transition to a less severe headache of do not experience migraine attack in adulthood (Prakash *et al.,* 2009).

3.5 MECHANISM OF MIGRAINE

The principal cause of migraine is unknown but there are possible causes as stated by research. Migraine may occur as a result of changes in the trigeminal nerve, which is the major pathway for head pain. Serotonin is an important brain chemical which plays role for sleep, well-being, and factors that affect quality of life. Because of its roles, it has been observed that low levels of serotonin can cause primary headache (Lauritzen, 1994).

Another mechanism of migraine pathophysiology is the cortical spreading depression (CSD). It is a wave of electrical activity that slips slowly across the surface of the cortex. A CSD initiates flashing light or abnormal smells followed by an intense headache. The electrical depolarization results in the release of neurotransmitters and other molecules that causes secondary inflammation, a person now experience nausea, sensitivity to light (Lauritzen, 1994). The chemical reaction of

the CSD affects dura where blood vessels dilate and contract. One type of white blood cells called mast cell tends to release inflammatory chemicals and nerve fibres which send massage to the brain stem. (Lauritzen, 1994).

The triggering of the trigeminal framework results in the torment experienced by migraine patients (Noseda and Burstein, 2013). The generation of pain arises when signs from actuated nociceptor positioned on spacious cranial vessels and the dura meter are relayed to the trigeminal bipolar neurones and further transmitted to the brainstem regions (Ferrari *et al*., 2015).

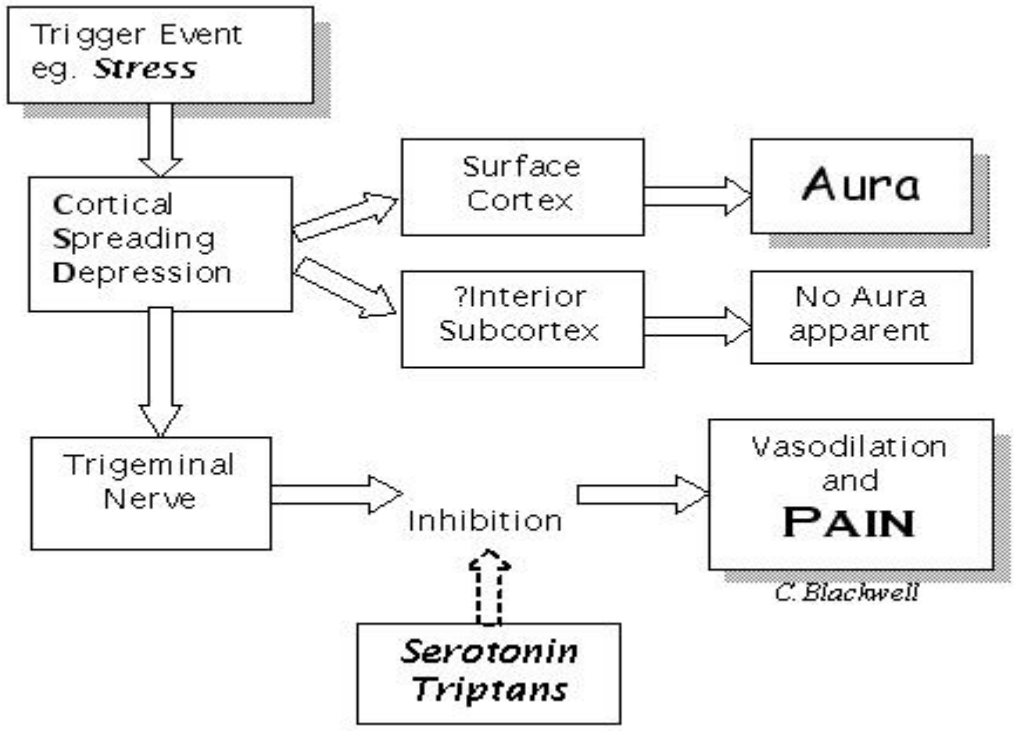


Fig 5: Mechanism of migraine (Noseda, 2013)

Tripans mimics the activity of the neurotransmitter serotonin as a vasoconstrictor. Triptans are used for migraine patients and it's effective in the treatment of pain in migraine (Hildreth, 2008).

3.6 MIGRAINE AND GENETICS

The pathophysiology of migraine has been linked to genetic predisposition and environmental factors (Van der *et al*., 2007). In clinical act, patients who suffered from migraine have ancestral

relatives who suffered from migraine. Several studies published have reported the inheritance of migraine from parents to children (Van der *et al*., 2007).

CHAPTER FOUR

VITAMIN D AND MIGRAINE RELATIONSHIP RESULTS

There are numbers of studies reported on the relationship of headache and vitamin D status. Recently, studies on vitamin D, its functions in the body system cannot be over emphasized. However, vitamin D deficiency is rampant and it's a common problem to the well-being of individuals in different populations. Studies have reported that deficiency of this vital vitamin is associated with disorders such as skin and skeletal, cardiovascular, malignant and autoimmune diseases. Cayir *et al.,* (2014), in a study of fifty three patients ranging from 6–18 years of old. The patients were categorized into groups, on the bases of levels of serum metabolites. The categories are group 1–4, the first group had normal serum vitamin D metabolite level and administered amitriptyline alone, the second group had normal serum vitamin D metabolite level and administered amitriptyline combined with 400 IU/day of vitamin D, the third group had mild deficiency of serum vitamin D metabolite and administered amitriptyline combined with 800 IU/day of vitamin D, while the fourth group were deficient in serum vitamin D metabolite and received amitriptyline combined with 5000 IU/day of vitamin D. All they groups were examined for six months and the number of migraine attack before and after treatment were determined. The results reported a significant reduction of migraine attack upon administration of vitamin D supplementation in comparison with the group that were administered only amitriptyline therapy. Thus, these results indicate the effect or relationship between serum metabolite level serum, and also the reduction of migraine attack upon vitamin D supplementation. In a cross-sectional study conducted by Celikbilet *et al.,* (2010), of fifty two patients diagnosed with migraine ranging from 18–50 years. ELISA kit was used to measure the serum levels of vitamin D. The estimated serum vitamin D is 30-100ng/ml, DBP (20-55ng/ml) and VDR (6.25-400pg/ml). Diagnosis of headache was based on the international classification of headache disorders-II diagnostic criteria. The results were analysed statistically, which suggest that serum metabolite (25(OH) D_3) and VDR levels are low in patients with migraine, and suggested that, this declination of serum levels is associated with migraine. Motaghi *et al.,* (2013), in a case control study, assessed a total number of (*n*) 103 patients with migraine *n* = 100 of patients that are healthy. Patients with migraine filled a pain severity questionnaire called headache impact test (HIT), consisting of six questions namely; how often is the severity of the pain, limitation from daily functioning by headache, how often does headache limit one from social activities, how often headache limits one's vitality,

limitation of cognitive activities and emotional agony. The DNA of all patients was extracted for analysis and genotyping was carried out using genome DNA extraction kit. Statistical analysis such as chi-squared test, and independent t-test were employed. The results indicated that the polymorphic gene of VDR such as *Fok*I and *Taq*I are associated with patients suffering from migraine disorder. A study by Yang *et al.*, (2015), indicated a positive result, showing an association between migraine and deficiency of vitamin D. Controversially, Kjaergaard *et al.*, (2012), in a cross sectional study design, using electro-chemiluminescent immunometric assay method to quantify vitamin D serum in patients (n = 322) with migraine & non-migraine patience (n = 3739). The results indicated a relationship between headache and vitamin D status. In a case study where two patients were examined, one of the patients was a black woman in her fifties, who had a history of migraine with aura. Following all general laboratory examinations such as thyroid functions, anti-nuclear antibody, urea nitrogen, blood count, double standard DNA and electrolytes were normal or within the normal limits. The patient was received 50,000 IU of vitamin D2 weekly combined daily calcium administration of 1000 mg. The results indicated that, administration of vitamin D ease migraine attacks in the patient, showing an association of migraine attack and deficiency of vitamin D. The second patient was a woman in her mid-sixties who suffered from frequent headache, stroke as a result of the migraine attack. The patient received 50,000 IU dose of vitamin D2 weekly combined with daily calcium administration of 2000 mg. Serum level metabolite and active vitamin D metabolite were 52 ng/ml and 59 pg/ml respectively, following supplementation. The migraine attack on the patient was drastically reduced upon therapy. Thus, in this case study, administration of vitamin D_2 combined with calcium reduces migraine attack, indicating relationship between migraine attack and vitamin D. (Thy Jacobs *et al*., 1994). In another case study conducted by Thy Jacobs *et al.,* (1994), showed that administration of calcium and vitamin D supplements D were effective in menstrual related migraine. In a scientific study in a population of Finnish by Jyrki *et al.,* (2007), using coulometric electrode array detector for HPLC to measure serum vitamin D metabolite. The study assessed n = 2601 men (ranging from 42–60 of age). Diagnosis of headache was based on the response of the questions in the study questionnaire. The result was analysed using means and linear regression, which shows an association between the status of serum metabolite (25(OH) D_3) and the risk of frequent headache. Wheeler et al., (2008) in a scientific study indicated that 40.7% of patients with migraine suffered from deficiency of vitamin, thereby reported a relationship between status of vitamin D and migraine. In contrast,

Krusz *et al.*, (2010), indicated no compelling difference from migraine patients and vitamin D levels. In a cross sectional study design by Knutsen *et al.,* (2010), used (HPLC-MS) to quantify vitamin D in patient with headache (n = 63) and the results indicated a clear but frail association in the serum metabolite and headache, but in contrast, Alireza *et al.,* (2014), in a case control study of n = 105 patients diagnosed with migraine and n = 100 control patients. Both patients were classified based on age, sex, place of residence, levels of education, duration of sunlight exposure. Diagnosis of headache was based on the international classification of headaches disorders-II diagnostic criteria. Samples from patient were collected to estimate their vitamin D levels using chemiluminescent immunoassay kit and the results were statistically analysed using SPSS software. The result indicated no association between the disorder migraine and levels of vitamin D and also reported that vitamin D levels are not related with the danger of frequent headache. From the above journals evaluated and summarized, one can deduce that migraine attacks could be as a result of inflammation in the nerves and blood vessels in the brain. Furthermore, the relationship between migraine and vitamin D is somewhat limited and not consistent, with some research indicating a positive relationship (and in combination with other supplements like vitamin D and calcium), while others indicated no relationship.

However, one of the mechanism linking vitamin D and primary headache is low magnesium levels. The absorption and metabolism of magnesium depends on the availability of vitamin D. Thus, deficiency of vitamin D leads to improper metabolism of magnesium. Improper magnesium metabolism is associated with tension type headache. Deficiency of magnesium in the erythrocytes, brain have been found in TTH patients. Patients responded positively upon administration of magnesium supplements (Prakash *et al*., 2009).

Another mechanism linking vitamin D and primary headaches is the presence of VDR, DBP, vitamin D and activating enzymes found in the hypothalamus of the human brain, which is the site for pain sensation in migraine patients. Thus, one can say that, the brain could also synthesis its own active vitamin D (Celikbilet *et al*., 2010). However, deficiency of vitamin D could lead to migraine. This is could be as a result of central sensitization of sensory pathways. That is, the sensitization of the second neurone resulting in the sensitization of the third neuron because of the stimulation of sensory receptors by vitamin D deficiency (Celikbilet *et al*., 2010 & Prakash *et al*., 2009). Reduced levels of serum vitamin D and PTH are found patients with migraine (Prakash *et al*., (2009) & Celikbilet *et al*., (2010)). High levels of PTH could be as a result of secondary hyper-

parathyroidism, which can be treated by administration of optimal levels of vitamin D supplements (Prakash *et al*., 2009). It has been well documented that nitric oxide through vasodilation triggers migraine. Nitric oxide is involved in nociceptive process leading to central sensitization of neuron, macrophages (Edward *et al*., 2015). Vitamin D on the other hand inhibits the synthesis of nitric oxide by inhibiting the enzyme nitric oxide synthase (Edward *et al*., 2015). Thus, deficiency of vitamin D could lead to the release of nitric oxide, thereby resulting in central sensitization. It has also been stated that, PTH regulates endothelial nitric oxide (Rashid *et al*., 2007). Therefore, deficiency of vitamin D can lead to secondary hyper-parathyroidism, leading to increase in PTH. However, the mechanism behind high levels of PTH contributing to migraine attack is not yet established (Alizera *et al*., 2014). Cayir *et al*., (2014), and Thy Jacobs, (1994), also showed that migraine patients had low vitamin D status. Therapeutic supplementation of calcium and vitamin D supplements (Thy Jacobs, 1994) and administration of amitriptyline and vitamin D supplements (Cayir *et al*., 2014) administered to migraine patients proved to be effective in decreasing migraine attacks. This could be as a result of the role of calcium in regulating contraction of smooth muscles and mediate nervous tissue excitability (Thy Jacobs, 1994). Several studies have associated vitamin D deficiency and chronic pain. High levels of nitic oxide, substance P, calcitonin gene related peptide which are triggers of migraine are seen in patients suffering from migraine and chronic pain. However, upon therapeutic administration of vitamin D supplements, there was a drastic decrease of these mediators (Cayir *et al*., 2014). Vitamin D could be useful in decreasing headache occurrences because of its signally pathway through transcriptional regulation. Vitamin D can regulate transcription through the expression of anti-inflammatory cytokine-1L-1025 which is a protective gene, or suppressing pro-inflammatory genes such as 1L-1beta, TNF-alpha, inhibiting pain pathway (Jakir *et al*., 2017). The presence of activating enzymes and VDR in nociceptive sensory neurones could further suggest its role in headache and pain in muscles (Jakir *et al*., 2017). Vitamin D may also regulate the synthesis of inflammatory cytokines (Kjaergaard e*t al*., 2012), which triggers pathological pain. It has anti-inflammatory effects, thereby suppressing pro-inflammatory cytokines such as tumor necrosis factor, regulating interleukin and macrophage activity (Knusten *et al.,* 2010). Because of its regulatory role, vitamin D may inhibit inflammatory pain pathway. Thus, administration of vitamin D supplements may be beneficial in reducing inflammatory pains (Knusten *et al.,* 2010), and may also regulate inflammation in the brain because of the widespread of VDR in the brain.

Apart from vitamin D involved in calcium metabolism, it is also involved in cellular proliferation and differentiation through VDR. The widespread of VDR in tissues contributes to the action of vitamin D in cardiac functions, immune system. On the other hand, VDR plays important role in signalling pathway such as insulin-like growth factor (IGF), estrogen related pathways (Bahar *et al*., 2013). Another mechanism associating vitamin D and migraine is VDR polymorphisms. VDR polymorphisms such as *Taq*I and *Fok*I has been associated with migraine (Motaghi *et al*., 2013). There is a positive association between migraine with VDR-*Fok*I polymorphism, and no association between migraines with VDR *Taq*I polymorphism. Thus, the ff and FF genotype of VDR-*Fok*I polymorphism changes the VDR protein thereby decreasing the transcriptional activity (Motaghi *et al*., 2013). Several studies have indicated the effect of VDR polymorphism in the prognosis of diseases such as migraine, breast, colon, and prostate carcinomas. In a research conducted in Turkish brain cancer patients indicated that ff genotype of VDR-*Fok*I polymorphism may be associated with meningioma and might affect the development of meningioma (Bahar *et al.*, 2013). VDR-*Fok*I have been linked to the development of elevated blood pressure (HBP). Thus changes on VDR as a result of single nucleotide polymorphisms can affect the regulation of transcription, the stability of mRNA, the translational efficiency of proteins and also affects the levels of VDR proteins.

Several studies has linked vitamin D deficiency to type II diabetes, this is possible because of the activity of vitamin D on the secretion of insulin and on beta-cell functions (Qin *et al*., 2008), type I diabetes (Al-Daghri *et al.*, 2014), and rheumatoid arthritis (Mosaad *et al*., 2014). Vitamin D stimulates the formation and resorption of calcium in bones, thus, insufficiency of vitamin D can lead to a decrease in the absorption of calcium and as a result the calcium from the bones will be release just to maintain the concentrations of circulating calcium (Lips, 2001). The presence of VDR in muscle tissues could also account for the relationship between the weakness of muscles and deficiency of vitamin D. Vitamin D deficiency has also been linked with ischemic stroke and cardiovascular diseases (Kilkkinen *et al.*, 2009). In the case of cardiovascular disease, this could be as a result of increase in the secretion of parathyroid hormone due to deficiency of vitamin D. Parathyroid hormone also contribute to the pathological changes in the cardiovascular system (Kilkkinen *et al.*, 2009). The presence of parathyroid hormone receptors in the cardiovascular system (smooth muscle cells, endothelial cells and cardiomyocytes), may suggest that parathyroid hormone plays a role in the pathophysiology of cardiovascular diseases. It has been shown that

patients with high parathyroid hormone are at high risk of cardiovascular diseases and even mortality. However, adequate vitamin D status may also protect against cardiovascular diseases, but the mechanism of action is not understood (Kilkkinen *et al*., 2009).

Table 3: Summary of the effect and relationship between headaches and vitamin status.

AUTHOR	STUDY TYPE	SAMPLE SIZE	DIAGNOSTIC CRITERIA	ASSOCIATION OF VITAMIN D
Kjaergaard *et al.*, (2012)	Cross sectional	Migraine patient (*n*=322), Non migraine (3739)	Electrocemiluminescent immunometric assay	No association
Knutsen *et al.*, (2010)	Cross sectional	Headache Patient (*n*=63)	(HPLC-MS)	Associated
Thy Jacobs (Nov 1994)	Case study	Migraine Patient (*n*=2)	Not reported	Effective
Thy Jacobs (Oct. 1994)	Case study	Menstrual migraine (*n*=2)	Not reported	Effective
Prakash, (2009)	Case study	TTH (N=8)	Not reported	Effective
Alireza *et al.*, (2014)	Case study	Migraine patient (*n*=100), Control Patient (*n*=100)	Not reported	No association

Jyrki *et al.*, (2007)	Scientific study	*n*=2601 men	Study questionnaire, Coulometric electrode detector with HPLC	Associated
Motaghi *et al.*, (2013)	Case study	Migraine patient (*n*=103), Control Patient (*n*=100)	Head impact Test (HIT) and DNA extraction kit	Associated
Celikbilet *et al.*, (2010)	Scientific study	Migraine patient (*n*=52)	ELISA and ICHD-II	Associated
Cayir *et al.*, (2014)	Scientific study	4 groups ranging from 6 to 18 years of age	Administration of Amitriptyline	Effective

CONCLUSION

Reduced vitamin D status pose a threat to the well-being of individual because of its functions and regulations of approximately 3% of the entire human gene cannot be overemphasized. Vitamin D plays vital functions the metabolism of calcium, magnesium, phosphate haemostasis, and in the secretion of parathyroid hormone. Low vitamin D status has been linked to cardiovascular diseases, muscles pain and weakness, ischemic stroke, hypertension, meningioma and migraine. The presence of VDR receptor within the brain (hypothalamus), suggest that secreted VDR may play a role in the pathophysiology of migraine beyond its role in the control of cell growth, differentiation, growth protein synthesis, bone development and mineralization. Thus, one can vividly say that deficiency of this vital vitamin can create a cascade of events in the human body, that is deficiency affects both calcium and magnesium metabolism resulting in osteoporosis and tension type headache respectively, even leading to death in the case of cardiovascular diseases. Administration of magnesium supplements has proven to be effective in reliving patients with tension type headache. Thus, vitamin D deficiency may lead to improper metabolism of magnesium, which is associated with tension type headache because, absorption of magnesium depends of the availability of vitamin D. Activating enzymes, VDR, and DBP found in the brain indicate that the brain itself can make its own vitamin D, however, if the can brain is on able to make its own active vitamin D, resulting to sensitization of the second and third neurone, then there could be a possibility that vitamin D is related to the pathophysiology of migraine. Serum vitamin D is low is patients with migraine and this could further suggest that vitamin D may be related to migraine. This low serum levels leads to high levels of mediators known to be triggers of migraine, such as substances P, nitric oxide, and calcitonin gene related peptide. The widespread of VDR in tissues contributes to the action of vitamin D in cardiac functions, immune system. VDR polymorphisms such as *Taq*I and *Fok*I has been associated with migraine. Thus changes on VDR as a result of single nucleotide polymorphisms can affect the regulation of transcription, the stability of mRNA, the translational efficiency of proteins and also affects the levels of VDR proteins.

However, therapeutic administration of vitamin and calcium supplements proves effective in decreasing migraine attacks. However, more studies are necessary on the subject matter to ascertain whether supplementation of vitamin D or vitamin D itself proves useful in the treatment of migraine. Conclusively, different methods such as ELISA, HPLC, and radioimmunoassay were

employed to estimate the levels of serum vitamin D. These methods used could lead to different levels of serum vitamin D within the same test population. This could be a limitation to really ascertain the relationship between migraine and vitamin D. But notwithstanding, the role vitamin D plays in the entire body is enormous because its effect in cardiac functions, immune system, cardiovascular system, nervous system. Thus deficiency of this vital compound can be dangerous to the body.

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