INTRODUCTION

The prevalence of hypovitaminosis D varies widely by and within regions, prevalence ranges between 30-90%, Despite ample sunshine throughout the year, one-third to one-half of individuals living in the Middle East have serum 25-hydroxyvitamin D level <25mol/l ***(Arabi et al., 2010).***

Vitamin D has been called the neglected neurosteroid. Vitamin D belongs to the super family of nuclear steroid transcription regulators that includes thyroid hormones, vitamin A, androgens and glucocorticoids. As such vitamin D exerts its influence over a vast number of genes. All these agents have well-defined roles to play in shaping brain development and ongoing functions ***(Eyles et al., 2011).***

Neurological disorders with a vitamin D link include multiple sclerosis, Alzheimer's and Parkinson's disease, as well as cerebrovascular disorders ***(Hollo et al., 2013).***

Lower carotenoids and vitamins were independantly associated with cerebral white matter lesions ***(Ohshima et al., 2013).***

Vitamin B6 (VB6)-related seizures, or clinical seizures associated with abnormally low level or abnormal metabolism of VB6, have been classified into VB6 deficient seizures and VB6 dependent seizures. Seizures are immediately suppressed by administrating VB6 in physiologic or pharmacologic doses respectively ***(Ohtahara et al., 2011).***

Ascorbic acid, as an antioxidant and electron donor accumulated in central nervous system, seems to take part in diminishing reactions of oxidative stress in brain and cooperate with other antioxidants like alpha-tocoferol. Vitamin C, easily transported through the blood-brain barrier, is proved to reduce injury in the hippocampus during seizures. Depending on type of seizures, it has mostly inhibitory activity and even decreases mortality. Moreover, vitamin C acts as neuroprotective factor by consolidating cell membrane and decreasing lipid peroxidation ***(Swawick-Glazer et al., 2014).***

Vitamin E is an essential dietary antioxidant with important neuroprotective functions. Vitamin E deficiency manifests primarily in neurological pathologies. Vitamin E deficiency causes an increase in cerebellar oxidative stress evidenced by increased protein nitrosylation, which was prevented by dietary supplementation with the vitamin. Vitamin E deficiency precipitate cellular atrophy and diminished dentretic branching of purkinjy neurons. The anatomic decline induced by vitamin E deficiency was paralleled by behavioral and deficits in motor coordination and cognitive functions ***(Ulatowski et al., 2014).***

Rationale of the study:

We divided the essay into five parts, one for each of the vitamins (A.B.C.D.E.), and through each part we discussed the following:

1- Introduction about the vitamin

We systematically reviewed each vitamin separately, as regards; structure, normal functions, functions in the CNS, sources and requirements, normal Serum level, vitamin deficiency, its clinical manifestations generally and neurological in particular and related effect in specific neurological disease and possible recommended management.

2- Neurological diseases caused by vitamins deficiency

3- Vitamins supplement in the treatment of neurological diseases.

AIM OF THE WORK

The aim of this work is to:

1. Highlight the importance of hypovitaminois (A, B, C, D and E) in different neurological diseases.

2. Highlight the possible management of hypovitaminosis (A, B, C, D and E).

Overview of Vitamins

A Vitamin is an organic compound and a vital nutrient that an organism requires in limited amounts. Vitamins have diverse biochemical functions. Some, such as vitamin D, have hormone-like functions as regulators of mineral metabolism, or regulators of cell and tissue growth and differentiation (such as some forms of vitamin A). Others function as antioxidants (e.g., vitamin E and sometimes vitamin C). The largest number of vitamins, the B complex vitamins, function as precursors for enzyme cofactors, that help enzymes in their

Work as catalysts in metabolism. In this role, vitamins may be tightly bound to enzymes as part of prosthetic groups: For example, biotin is part of enzymes involved in making fatty acids. They may also be less tightly bound to enzyme catalysts as coenzymes, detachable molecules that function to carry chemical groups or electrons between molecules. For example, folic acid may carry methyl, formyl, and methylene groups in the cell. Although these roles in assisting enzyme-substrate reactions are vitamins' best-known function, the other vitamin functions are equally important ***(Bolander, 2006).***

Vitamins are actively involved in many metabolic processes of the nervous system. Their deficit may cause severe and, sometimes, irreversible consequences ***(Kamchatnov et al., 2015).***

Vitamin Deficits are most commonly seen with thiamine, vitamin B12, folate, vitamin D and vitamin E deficiencies. The neurological findings observed with these nutritional deficiencies are variable and include encephalopathy, optic neuropathy, myelopathy, polyradiculoneuropathy, and polyneuropathy ***(Becker et al., 2012).***

Vitamin B12 deficiency is found to cause neurological and psychiatric problems in adults between 40-90 years of age. It rarely affects people younger than this. The neurological manifestations include myelopathy (disease of the spinal cord), neuropathy (disease of the nerves), sensory disturbances, gait abnormalities and weakness while the psychiatric problems range from cognitive and behavioral disturbances to dementia ***(de Jager, 2014).***

The metabolism of folic acid and the metabolism of vitamin B12 are intimately linked such that deficiency of either vitamin leads to an identical megaloblastic anemia. The neurologic manifestations of folate deficiency overlap with those of vitamin B12 deficiency and include cognitive impairment, dementia, depression, and, less commonly, peripheral neuropathy and subacute combined degeneration of the spinal cord. Low folate and raised homocysteine levels are risk factors for dementia, including Alzheimer's disease, and depression. There is interest in the potential role of both vitamins in the prevention of disorders of central nervous system development, mood, and dementia, including Alzheimer's disease, and aging ***(Reynolds, 2014).***

Vitamin D has been associated with many neurological functions and its deficiency with dysfunction. Low serum 25-hydroxyvitamin D concentrations can potentially be reversed. This simple and low-cost correction might contribute to the primo-secondary prevention of various neuropsychiatric disorders ***(Annweiler et al., 2010).***

Vitamin D deficiency is a global public health issue. Prevalence of vitamin D deficiency is about 30 to 50% in normal populations especially in young women ***(Holick et al., 2008).***

So far, scientists have identified nearly 3,000 genes that are influenced by vitamin D status, and a robust and growing body of research clearly shows that vitamin D is critical for optimal health and disease prevention. This includes some of the more difficult-to-treat conditions, including Alzheimer's disease, Parkinson's, and multiple sclerosis (MS) ***(Polívka et al., 2012).***

There is extensive evidence implicating oxidative damage in the development of degenerative diseases and conditions. A number of studies have evaluated the role of Vitamin E, alone or in combination with other antioxidants, in preventing or minimizing oxidative damage associated with development of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, stroke, and ataxia with Vitamin E deficiency and peripheral neuropathy ***(Imounan et al., 2012).***

1. Vitamin A:

Vitamin A is a fat soluble alcohol essential for normal growth, development and reproduction. This vitamin is also essential for vision, as it is the precursor to the molecule (11-cis retinal 3), that forms the pigments in the eye that absorb light. Indeed, the first sign of vitamin A deficiency is night blindness, that is, a failure to see under dim light conditions ***(Rosalie et al., 2014).***

The term retinoid is used for substances which may be defined as (1) vitamin A related compounds (including vitamin A (retinol) and its biological precursor carotenoids, (2) RA (vitamin A metabolite), which activates RARα, β, and γ, and synthetic analogs which bind with RARs with high affinity in an agonistic (similar biological activities to RA) or antagonistic manner, (3) compounds which activate RXRα, β, and γ, which are nuclear receptors different from RARs, (4) compounds which modify the activities of RA by influencing metabolism, biosynthesis or other pathways acting on co-factors, without binding to RARs or RXRs. It should be noted that the activity of vitamin A (retinol) is essentially due to RA generated by metabolism in vivo, except for the participation in vision via rhodopsin ***(Blomhoff and Blomhoff, 2006).***

Retinoids regulate gene transcription in numerous cells and tissues by binding to nuclear retinoid receptor proteins, which act as transcription factors. Much of the research conducted on retinoid signalling in the nervous system has focussed on developmental effects in the embryonic or early postnatal brain. Retinoid signaling pathways have also been implicated in the pathophysiology of Alzheimer's disease, schizophrenia and depression. Overall, the data underscore the likely importance of adequate nutritional Vitamin A status for adult brain function and highlight retinoid signalling pathways as potential novel therapeutic targets for neurological diseases ***(Lane and Bailey, 2005).***

RARs: RARα, β and γ and their ligands (retinoids), such as the endogenous RAR ligand all-*trans*-retinoic acid (RA) are taking into account knowledge about PD, ALS and other neurodegenerative diseases ***(Shudo et al., 2009).***

Many studies on pattern formation have confirmed the importance of retinoids in spinal cord and brain development ***(Maden, 2006).*** These findings prompted detailed analyses of RARs in brain ***(Krezel et al., 1999),*** and extensive studies of RAR signaling pathways in neurological diseases. The results suggest that RA or more generally retinoids are potential therapeutic agents for the treatment of neurodegenerative diseases, promoting tissue regeneration. Studies are advanced in the case of acute phase treatment of severe cognitive impairment (SCI) ***(Goodman et al., 2006).***

Intracellular translocation of RARα (and RXRs) into the nuclei of activated macrophages, surviving neurons and astrocytes near the lesion site has been reported ***(Zhelyaznik and Mey, 2006).***

The localization of retinoid receptors in Schwann cells correlated with inflammatory transduction pathways of interleukin (IL)1β, IL6 and tumor necrosis factor-α (TNF-α) ***(Mey et al., 2007).***

Maden (2006) showed the importance of RARs in SCI, and found that RARβ gene introduction and the coexistence of a RARβ ligand (rather than RARγ) caused neurite growth and improved the recovery of animals after trauma.

The expression profile and functional role of nuclear receptors in retinoid signaling have been profiled in human SCI, anterior lateral sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's disease (PD) ***(Malaspina and Turkheimer, 2007).***

Forms and Structure:

The most common forms of preformed vitamin A in the human diet are retinol and retinyl esters. Retinol has 20 carbons, and the functional group is located on carbon 15. The storage form is retinol esterified to fatty acids predominantly as retinyl palmitate. Retinal is the form involved in vision, whereas retinoic acid is involved in growth and cellular

functions. The enzymatic formation of retinal and retinyl esters from retinol is reversible; however, the oxidation of retinal to retinoic acid is not reversible **(Fig. 1)** ***(Tanumihardjo, 2011).***

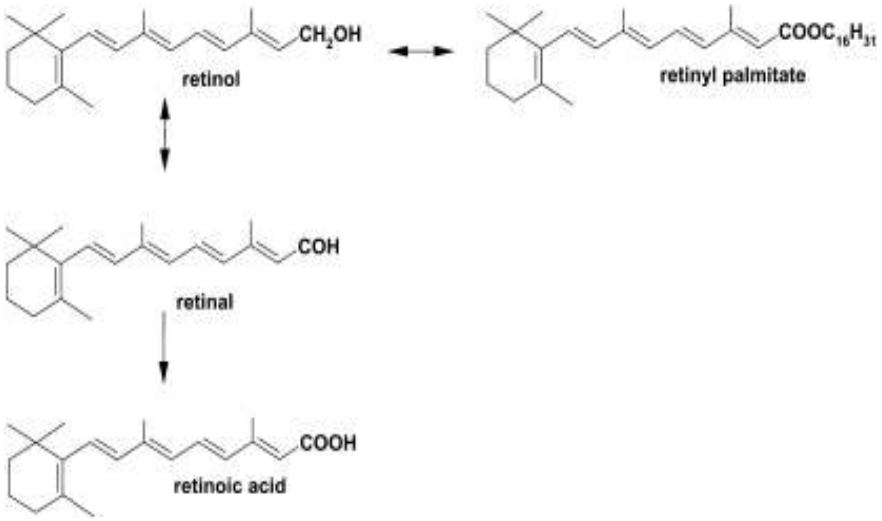

Figure (1): Chemical structures of important functional forms of vitamin A ***(Tanumihardjo, 2011).***

Normal Function of vitamin A:

The biologically active metabolite of vitamin A, retinoic acid (RA), is the ligand of a set of receptors (retinoic acid receptors (RAR) and retinoid × receptors (RXR)) that act as transcriptional regulators restricted to chordates, and it is best known as a signaling molecule during early embryogenesis ***(Campo-Paysaa et al., 2008).***

Vitamin A has many functions in the human body, including growth, vision, epithelial differentiation, immune function, and reproduction ***(Tanumihardjo, 2011).***

A number of genes are regulated directly through the RAR or RXR- response elements by retinoic acid or retinoids binding to RAR of the RAR/RXR heterodimers, or indirectly, possibly through the participation of the directly-regulated genes ***(Balmer and Blomhoff, 2002).***

The biological or pharmacological activities of interest varies, retinoids inhibit angiogenesis ***(Oikawa et al., 1993),*** prevent atherosclerosis and stenosis of vascular vessels ***(Fujiu et al., 2005),*** suppress the differentiation of pre-adipocytes to adipocytes, and promote alveolar regeneration in mammalian lungs ***(Massaro and Massaro, 1997).***

Retinoid signaling is also important throughout adolescence and adulthood, and has been shown to play various roles in the continued formation, differentiation and maintenance of neuronal phenotypes. Owing to its low stability and low abundance in neuronal tissue, retinoic acid has proved challenging to effectively quantify by methods, but recent improvements in direct retinoic acid quantification may prompt its quantification in sub-regions of the brain ***(Kane et al., 2008).***

Retinoid signaling in the brain has often been interfered by the presence of aldehyde dehydrogenase, the terminal enzyme in the retinoic acid synthesis pathway. Three retinaldehyde-specific aldehyde dehydrogenases (RalDH) are present in high levels in the embryo and/or occur in the developing eye ***(Duester, 2009).***

The isoform RalDH2 remains prevalent in post-embryonic and adult brains at lower levels. In embryos, differential expression of RalDHs sets up diffusion gradients of retinoic acid across structures such as the whole body plan, limb bud or eye. These gradients broadly determine patterns of structure formation ***(McCaffery and Drager, 2000).***

Since RalDH2 is expressed by fully differentiated neurons in adults, retinoic acid may be produced in the functional cell bodies of one brain region for axonal transport to other remote regions where it may then direct neuromodulation. In either scenario, poorly understood transport processes and much smaller spatial fields of retinoid signaling are likely the norm in post-embryonic tissues, necessitating the need for a tightly controlled system of retinoid signaling to maintain critical neuronal function ***(Olson and Mello, 2010).***

Vitamin A and/or retinoic acid supplementation provides a model to better understand the therapeutic effects of retinoid signaling. This approach complements vitamin A deficiency (VAD) as it results in excess retinoic acid levels in the brain. This is a significant approach as frequently both deficits of retinoid signaling and overproduction of retinoic acid can have disruptive effects, resulting in a detectable phenotypic response ***(Olson and Mello, 2010).***

Sources and Requirements:

Preformed vitamin A is found almost exclusively in animal products, such as human milk, glandular meats, liver and fish liver oils (especially), egg yolk, and whole milk and dairy products. Preformed vitamin A is also used to fortify processed foods that may include sugar, cereals, condiments, fats, and oils ***(Rodriguez-Amaya, 1997).***

Pro-vitamin A carotenoids are found in green leafy vegetables (e.g., spinach, amaranth, and young leaves from various sources), yellow vegetables (e.g., pumpkins, squash, and carrots), and yellow and orange noncitrus fruits (e.g., mangoes, apricots, and papaya). Red palm oil produced in several countries worldwide is especially rich in pro-vitamin A ***(Booth et al., 1992).***

Estimates for the requirements and recommended safe intakes of vitamin A for adults are estimated from those derived for late infancy, i.e. 4.8 and 9.3 μg RE/kg body weight/day ***(FAO/WHO, 1988).***

Normal serum level:

Specifically, a serum retinol concentration <0.70 lmol/l provides a reliable guide for assessing the extent and severity of deficiency and health risk in a population ***(World Health Organization, 2009).***

It is widely accepted that VAD begins when liver stores of vitamin A fall below 20μg/g (0.07 μmol/g). By convention, serum retinol levels <20 μg/dL (0.70 μmol/L) are considered deficient, although in most well-nourished populations with "adequate" stores, average serum retinol levels generally exceed 30 μg/dL (1.05 μmol/L) ***(Sommer and Davidson, 2002).***

Clinical manifestations of Vitamin A Deficiency disorders (VADD):

VAD is globally one of the most common forms of malnutrition in human populations, with ocular disorders, immunosuppression and impaired growth commonly described, and although considerable political efforts have been undertaken to eliminate VAD over the last half-century it today remains a problem in much of the developing world ***(Arlappa et al., 2008).***

VADD may be subclinical (e.g., impaired iron mobilization, disturbed cellular differentiation, depressed immune response) or clinical (increased infectious morbidity and mortality, growth retardation, anemia, xerophthalmia, Bitot's spots, severe punctate keratitis, corneal scarring and ultimately keratomalacia in severe cases, as vitamin A status declines, systemic consequences of VAD, including increased mortality, begin to occur even before the appearance of appreciable rates of clinical xerophthalmia ***(Sommer and Davidson, 2002).***