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Vitamin d deficiency in relation to psychiatric illness: A Unani conceptual review

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Abstract
Vitamin D is most unique among all vitamins. The term 'vitamin d' is actually a misnomer, as Vitamin D is not a Vitamin but is the only vitamin which is a hormone, synthesized endogenouslyby the kidneys. Vitamin D is a seco-steroid hormone with multiple functions in the nervous system. Physiological brain mechanisms of vitamin D and its receptors include neuroprotection, antiepileptic effects, and Immuno modulation, possible interplay with several brain neurotransmitter systems and hormones, as well as the regulation of behaviours. Vitamin D insufficiency affects almost 50% of the population worldwide. An estimated 1 billion people worldwide, across all ethnicities and age groups, have a vitamin D deficiency (VDD). This hypovitaminosis D can mainly be attributed to lifestyle (for example, reduced outdoor activities) and environmental (for example, air pollution) factors that reduce exposure to sunlight, which is required for ultraviolet-B (UVB)-induced vitamin D production in the skin. Here we review the important role of the vitamin D neuroendocrine system in the brain and outline perspectives for the search and usage of novel neurotropic treatment to treat various vitamin D-related dysfunctions and psychiatric illnesses.

Keywords: Vitamin D, neurosteroid hormone, brain disorders, vitamin D deficiency, hypovitaminosis D

1. Introduction
Vitamin D (calciferol) is a fat-soluble seco-steroid hormone synthesized in skin by photolysis of 7-dehydrocholesterol, or ingested with food. The most important biological function of vitamin D is mineral homeostasis, where together with other endocrine hormones it is involved in Ca metabolism by regulating renal and intestinal Ca transport and bone mineralization. Several additional key functions of vitamin D include the regulation of tissue proliferation, differentiation and apoptosis, as well as cardiovascular (via down regulation of renin-angiotensin system) and immune mechanisms.[1] Vitamin D from the diet, or from skin synthesis, is biologically inactive. A protein enzyme must hydroxylate it to convert it to the active form. This is done in the liver and in the kidneys. As vitamin D can be synthesized in adequate amounts by most mammals exposed to sufficient sunlight, it is not an essential dietary factor, although not technically a vitamin. Instead it could be considered a hormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol, which then produces effects via a nuclear receptor in multiple locations [25].

2. Sun as a source of vitamin D
- UVB rays are main source that activate Vitamin D. Visible light has a wavelength 360nm (violet) -780nm (red).UV-B rays (the deep violet light) with a very narrow band of 290-315nm wavelength don't penetrate deep. They have high energy beta photons which when comes in contact with the skin photolyze the cholesterol into precursor of Vitamin D [9].
- The precursor of Vitamin D is produced in the keratinocytes of two innermost strata of epidermis, the stratum basale and stratum spinosum [26]. This precursor of Vitamin D ie.., Cholecalciferol is metabolized first to 25 hydroxyvitamin D (25OHD) in liver, then to the active hormonal form 1, 25-dihydroxyvitamin D ($1,25(OH)_2D$ or Calcitriol) in the kidneys. Vitamin D has endocrine, paracrine and autocrine actions at its canonical target tissues of the skeleton, gastrointestinal tract and kidney
- UVA rays (>315nm wavelength) penetrate deeper but do not prompt skin to make Vitamin D; cause wrinkles, aging, skin discoloration [9].

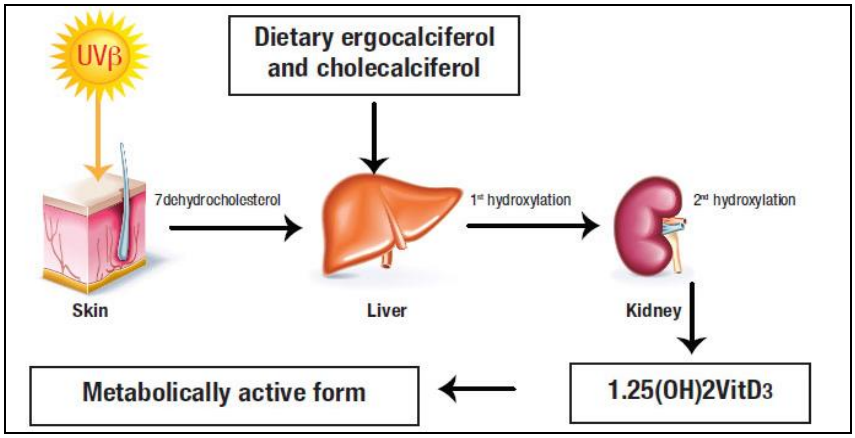

Fig 1: Activation of vit d

Metabolism happens through regular method and in the cells:

- **Regular metabolism**
  Liver(25-D) –> into bloodstream –> kidneys(1,25-D3: active, vital form) –> into bloodstream –> intestinal cells (absorption of Ca, P –> healthy bones)
- **Autocrine cell functions** (metabolism in the tissues and cells, a role discovered based on research in past 20-25 years):
  Liver(25-D) –> most organs of body with Vitamin D receptors(1,25 D3: active, vital form) –> utilized by cells & tissues (essential for preventing cancers & other diseases) [9]. Organs of the Body has 26 Vitamin D responsive tissues that require adequate levels to activate their functions. It affects over 200 genes in the body.

3. Vitamin D –The Healthy Range

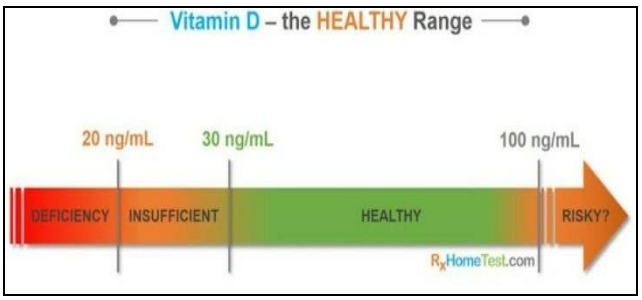

Fig 2: The Healthy range of Vitamin D- Deficient: 10-20 ng/ml, Insufficient: 20-30 ng/ml, Normal: > 30 ng/ml — recommended to maintain 30-40 ng/ml; medical professionals recommend to error on the higher side, Overdose: 40-70 ng/ml, Toxic: > 150 ng/ml [25]

4. Vitamin D Deficiency (Hypovitaminosis D)

Vitamin d regulates a broad spectrum of physiological processes. [7] Its physiological effects are not only limited to bone. Besides its well-known effects on calcium phosphate homeostasis, vitamin D influences the immune response, muscle function, cardiovascular homeostasis and the nervous function. A deficiency or insufficiency of vitamin D with levels of less than 30ng/ml has been associated muscle weakness and high incidence of various chronic diseases such as cardiovascular disease, cancer, multiple sclerosis and many mental disorders such as depression, schizophrenia, alcoholism and cognitive declines. The prevalence of vitamin D deficiency varies, with the groups at greatest risk including housebound, community-dwelling older and/or disabled people, those in residential care, dark-skinned people (particularly those modestly dressed), and other people who regularly avoid sun exposure or work indoors. Most adults are unlikely to obtain more than 5%-10% of their vitamin D requirement from dietary sources. A serum 25-hydroxyvitamin D (25-OHD) level of ≥ 50 nmol/L at the end of winter (10-20 nmol/L higher at the end of summer, to allow for seasonal decrease) is required for optimal musculoskeletal health. There is good evidence that vitamin D plus calcium supplementation effectively reduces fractures and falls in older men and women [9].

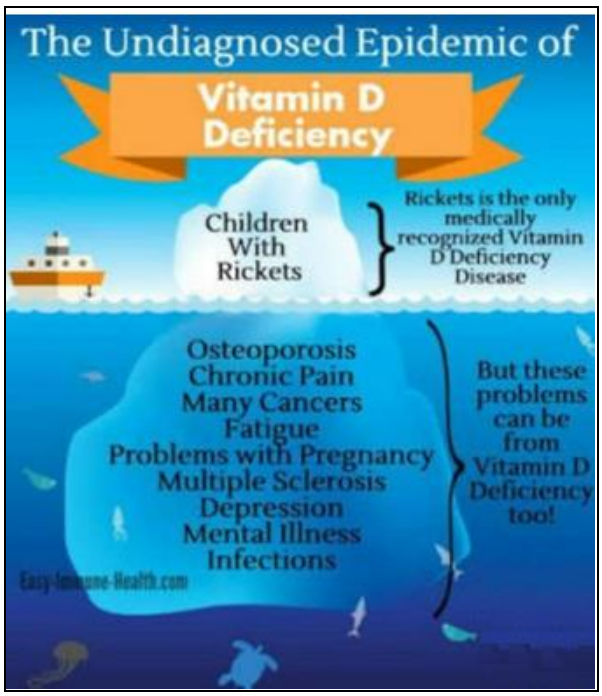

Fig 3: The undiagnosed epidemic of Vitamin D deficiency

5. Psychiatric Relation

Vitamin D plays various roles in normal brain physiology. Converging evidence suggests that vitamin D deficiency affects multiple brain processes, including cognitive functioning, in both healthy people and those afflicted with neuropsychiatric illness. Several studies suggest that symptoms of Seasonal Affective Disorder (SAD) a mood disorder may be due to changing levels of vitamin D3,which may affect serotonin levels in thebrain.1,25(OH)2D indirectly helps in microbial synthesis of B group vitamins which in turn affects neurotransmitter synthesis.

5.1 Depression (*Izmehlaal, Afsurdagi*)

Depression is a common mental health problem that involves a low mood and a loss of interest in activities. There are many researchers who believe that an imbalance in serotonin levels may influence mood in a way that leads to depression.

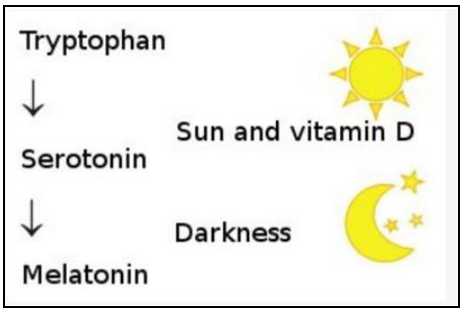

Fig 4: Sun and vitamin D

5.1.1 Serotonin

Serotonin is a neurotransmitter that is vital for a host of brain functions and for regulating dopamine levels. Sufficient amounts of serotonin are needed in the brain in order to have positive thoughts, confidence, and inner rest. A serotonin deficiency increases the risk of negative thoughts, suspicion, depression, irritability, and insomnia [12]. Serotonin is synthesized from an amino acid called tryptophan that is found in a variety of foods. In addition, the process requires vitamin D to support enzymatic processes that convert tryptophan into serotonin. In the night, certain amount of serotonin is used to make melatonin that is highly important for proper sleep. Sunlight and vitamin D are determining factors for enabling the conversion from tryptophan to serotonin, which is then converted into melatonin, a substance that is of vital importance to our mood, 24-hour rhythm, sleep pattern, and general well-being (Fig 4). Vitamin D helps to maintain sleep pattern indirectly and its deficiency may be related to insomnia, which may further create disturbance in mental health.

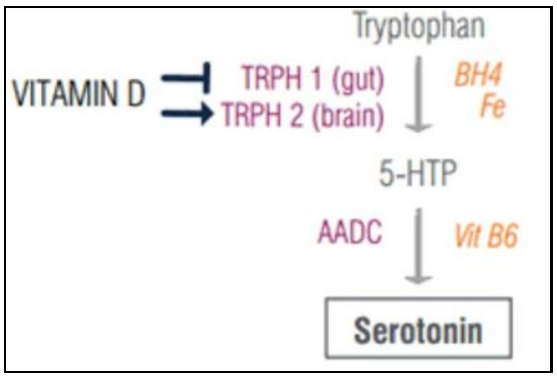

Fig 5: Vitamin D

With respect to serotonin, adequate vitamin D levels are essential for appropriate serotonin biosynthesis. Vitamin D potentiates the expression of neuronal TRPH to stimulate the appropriate production of serotonin in the brain. But remember how there are two types of TRPH and type 1 is present in the gut to regulate the majority of the body's serotonin production? Well, vitamin D inhibits the expression of TRPH 1 to suppress serotonin biosynthesis (Fig 5) [3]. What does this mean for a patient testing their urinary serotonin who is concurrently deficient in vitamin D? Without sufficient vitamin D, this individual may be suffering from low brain serotonin (not enough TRPH 2 stimulation) all the while having high serotonin production in the gut (not enough TRPH 1 suppression). This may explain why a patient who checks depression on the symptom may have a high serotonin result [3, 10].

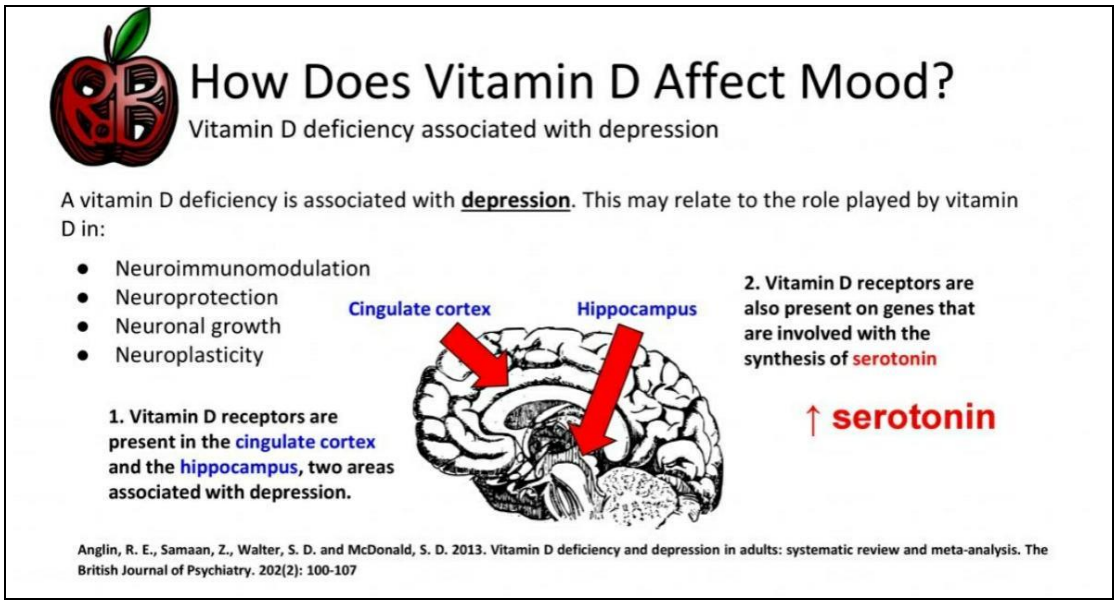

Fig 6: How does vitamin D affect mood?

5.1.2. Vitamin D Receptors

Most body tissues and cells including gut and brain have vitamin D receptors. The glial and neuronal cells in CNS have VDR. In 2005 VDR were identified in multiple areas of human brain like prefrontal cortex, thalamus, hypothalamus, hippocampus, & substantia nigra areas all of which are related to depression. (Fig 6)

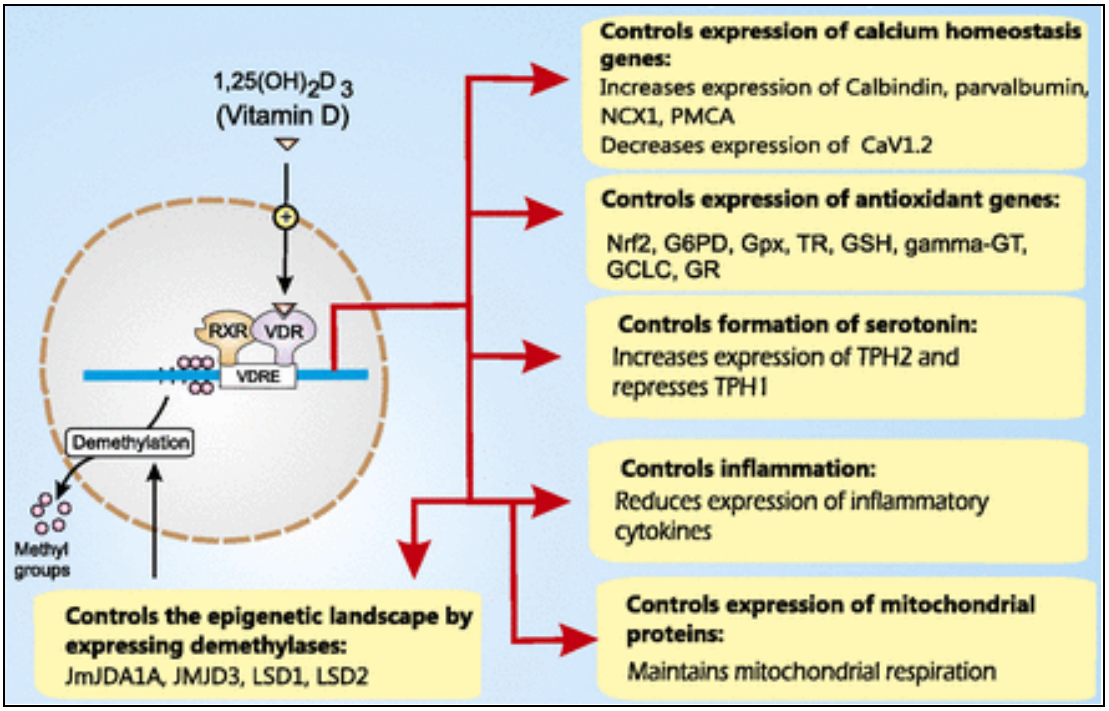

Fig 7: Vitamin D-sensitive processes that prevent depression

5.1.3. Pathophysiology of Depression and Action of Vitamin D *as Muharrik Aasaab*

To understand the pathophysiology of depression and how vitamin D may act to prevent depression, it is necessary to explore what causes the alterations in neural function responsible for the change in mood. An increase in neuronal Ca^{2+} levels is a major factor responsible for driving the onset of depression. Vitamin D acts as *Muharrik e aasaab (nervine stimulant)* by increasing the expression of calbindin, parvalbumin, NCX1, PMCA to maintain Ca^{2+} homeostasis, which suggest that the persistent increase in Ca^{2+} caused by vitamin D deficiency may contribute to the onset of depression. When vitamin D is low, mitochondrial function will be compromised, the *tehreek (stimulation)* to mitrochondria is decreased resulting in an elevation of ROS and a reduction in the formation of ATP, which will have a major impact on Ca^{2+} homeostasis. Another main action of vitamin D is it provides ***tehreek*** to TPH2, the neuronal typtophan for the production of antidepressant neurotransmitter seratonin. Vitamin D deficiency resultantly produces depression.(Fig 7) [8].

5.2 Multiple Sclerosis (*Tasallub-e-Muttaed*)

Multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord (central nervous system). In MS, the immune system attacks the protective sheath (myelin) that covers nerve fibers and causes communication problems between your brain and the rest of your body. Eventually, the disease can cause permanent damage or deterioration of the nerves. Signs and symptoms of multiple sclerosis vary widely and depend on the amount of nerve damage and which nerves are affected. Some people with severe MS may lose the ability to walk independently or at all, while others may experience long periods of remission without any new symptoms [23].

Research over the years has shown that maintaining adequate levels of vitamin D may have a protective effect and lower the risk of developing multiple sclerosis (MS). A number of studies have shown that people who get more sun exposure and vitamin D in their diet have a lower risk of MS. Therefore, vitamin D supplementation is considered an important modifiable environmental risk factor for development of multiple sclerosis.

Some studies suggest that for people who already have MS, vitamin D may offer some benefits. These benefits include lessening the frequency and severity of their symptoms, improving quality of life, and lengthening the time it takes to progress from relapsing-remitting multiple sclerosis to the secondary-progressive phase [22].

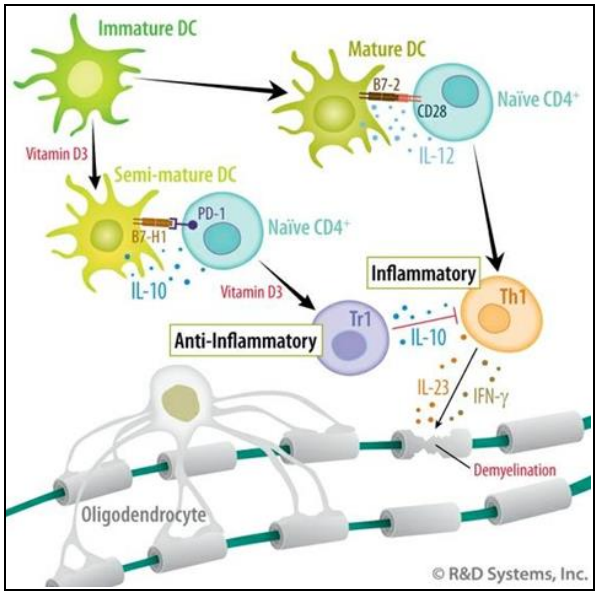

Fig 8: Shows in Central nervous system

5.2.1 Vitamin D Action as *Muhalil E Awraam*

In multiple sclerosis, balance between the anti-inflammatory and inflammatory pathways is compromised. VitD3 helps to regulate this balance by promoting anti inflammation. It promotes the formation of tolerogenic or "semi-mature"

dendritic cells (DCs) rather than mature dendritic cells, thereby helping in differentiation of anti inflammatory T cell, and down- regulating the production of Th1 inflammatory cells which promotes demyelination. (Fig 8) [24]

5.3 Autism Spectrum Disorder And Schizophrenia

Autism spectrum, also known as autism spectrum disorder (ASD), is a range of mental disorders of the neurodevelopmental type. Individuals on the autistic spectrum often experience difficulties with social communication and interaction and may exhibit restricted, repetitive patterns of behavior, interests, or activities. Vitamin D is crucial for several key physiological processes, including brain development, DNA repair, and regulation of many genes. Evidence indicates that prenatal and early postnatal vitamin D Deficiency increases autism risk. Neuroimaging findings in autism included abnormalities in brain chemistry, serotonin synthesis, and brain electrophysiology. These structural and functional abnormalities resemble those found in animals with prenatal exposure to vitamin D deficiency [6].

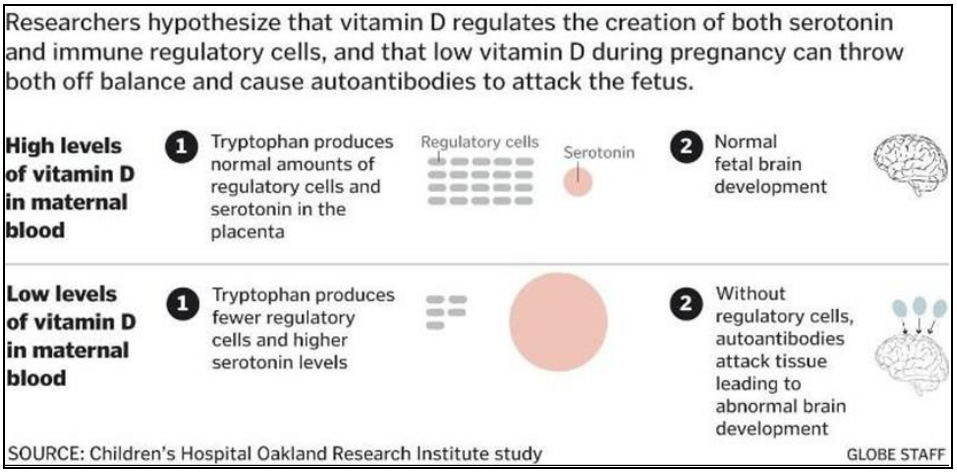

Fig 9: How vitamin D and serotonin protect fetal brains

Vitamin D plays an important role in etiology of Autism Spectrum Disorders (ASDs) by acting as a *Muqawi Dimagh* hormonal element by affecting brain development and function. It plays an essential role in myelination, which is important for connectivity in the brain. Studies have shown that decreased vitamin D levels, decreased maternal vitamin D levels during pregnancy, and decreased exposure to solar UVB might increase the risk of ASD[2].(Fig 9) [16]

Schizophrenia: Newborns with vitamin D deficiency had a 44% increased risk for schizophrenia in later life compared with those with normal vitamin D levels, according to study data reported in Scientific Reports and Universities of Queensland. [18]

5.4 Parkinson's Disease (*Rasha*)

Parkinson's disease (PD) is characterized by a slow and progressive degeneration of dopaminergic neurons in the substantia nigra. Several epidemiologic studies have suggested an inverse relationship between circulating vitamin D levels and the risk of PD. Serum level of vitamin D is significantly lower in patients with PD compared to healthy controls, and serum 25 hydroxy vitamin D (25(OH) D) concentration progressively decreases with the increase in severity of motor symptoms of Parkinson's disease. Vitamin D acts as *Muharrik e aasaab* and enhances the synthesis of dopamine through increasing the level and activity of the enzyme tyrosine hydroxlase (Fig 10) [17]. Futhermore, vitamin D is assumed to have a neuroprotective effect on dopaminergic pathways in the central nervous system[14].

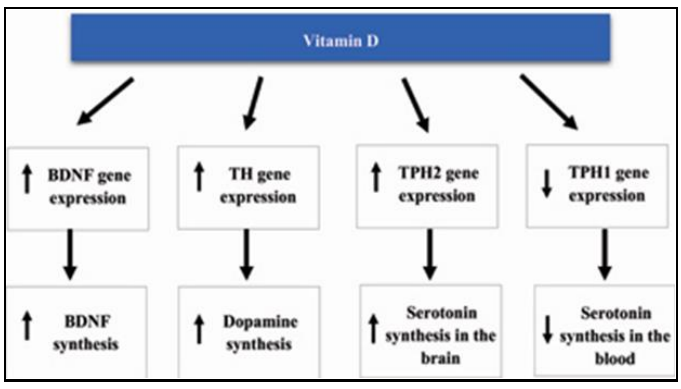

Fig 10: Vitamin D

5.5 Alzhiemers Disease (*Nisyan*)

Alzheimer's disease is a progressive neurologic disorder that causes the brain to shrink (atrophy) and brain cells to die. Alzheimer's disease is the most common cause of dementia — a continuous decline in thinking, behavioral and social skills that affects a person's ability to function

independently. Alzheimer's disease are focused on the role of two proteins which pathologically form beta amyloid plaques and neurofibrillary tangles. Beta-amyloid is a fragment of a larger protein. When these fragments cluster together, they appear to have a toxic effect on neurons and to disrupt cell-to-cell communication. These clusters form larger deposits called amyloid plaques, which also include other cellular debris. Tau proteins play a part in a neuron's internal support and transport system to carry nutrients and other essential materials. In Alzheimer's disease, tau proteins change shape and organize themselves into structures called neurofibrillary tangles. The tangles disrupt the transport system and are toxic to cells. This effect the function and integrity of the neuronal cell and as a result brain gets atrophied.[21] Alzhiemer's disease has a high prevalence of vitamin D deficiency, which is also associated with low mood and impaired cognitive performance in older people.

5.5.1 Vitamin D as Muneqe WA Muqawwi Dimagh

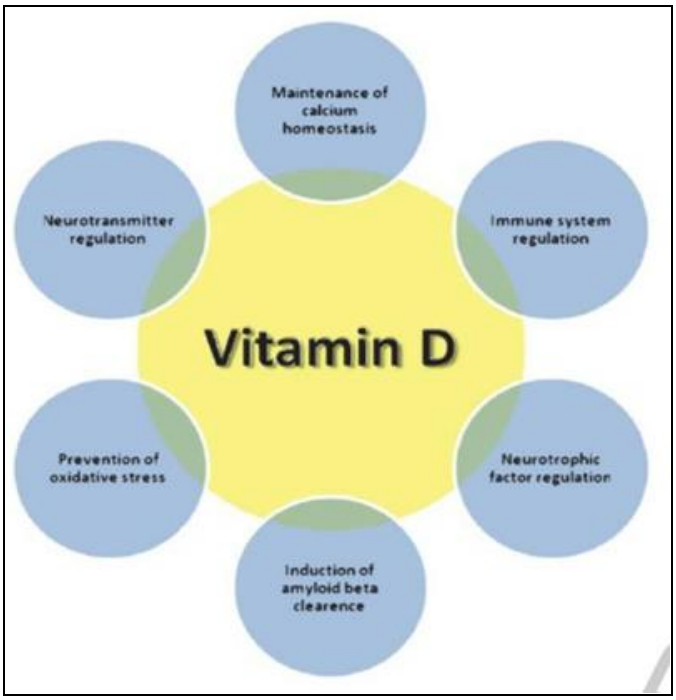

Fig 11: The basic protective effects of vitamin D in Alzheimer's disease. The suggested protective effects of vitamin D in the Alzheimer's disease were summarized as the regulation of neurotrophic factor production, neurotransmitter levels, oxidative stress mechanisms, calcium (Ca2+) homeostasis and immune system functions, and induction of amyloid beta clearance by its detoxification, neuroprotective, and immunomodulation effect [4].

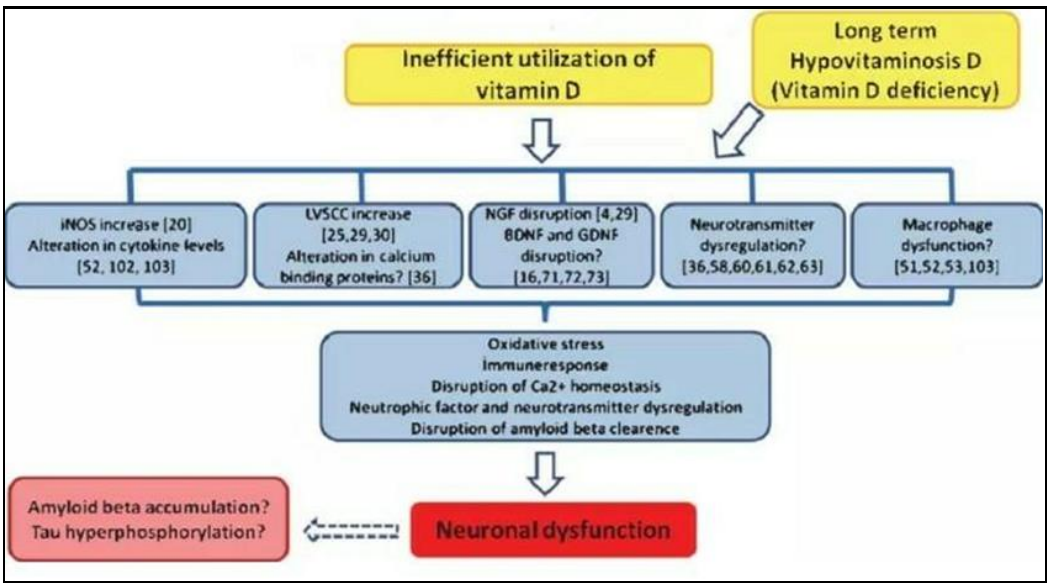

Fig 12: Co-relative pathophysiology of vitamin D Deficiency and Alzhiemer's disease [4]

5.6 Epilepsy (*Saraa*)

Epilepsy is a chronic neurological disorder that causes cognitive and mood impairment, unprovoked recurrent seizures, injuries, and increased risk of death including sudden death in epilepsy. It is often associated with a history of previous lesions in the nervous system. Impaired regulation of the activation and resolution of inflammatory cells and molecules in the injured neuronal tissue is a

critical factor to the development of epilepsy. Pro-inflammatory cytokine IL-Iβ, expressed in activated microglia and astrocytes, enhances the release of glutamate from astrocytes and decreases glutamate re-uptake, thereby increasing glutamate availability in neuronal synapses and promoting neuronal hyper-excitability. It has been suggested that IL-1β induces seizures through the upregulation of NMDA receptors. TNF-α is responsible for upregulate synapses and maintain a certain level of neuronal excitatory input, excess of which leads to neuronal hyper-excitability [13].

5.6.1 Vitamin D3 as *Dafe Tashannuj:* (Fig 13)

Genomic mechanisms behind Vitamin D3's anticonvulsant effect are based on Vitamin D3's ability to regulate the expression of genes, a process that is mediated by a nuclear Vitamin D3 receptor (VDR). VDR is a ligand-specific transcription factor, which is activated by Vitamin D3 and subsequently alters gene expression. Through this mechanism, Vitamin D3 lowers the expression of certain proconvulsant cytokines, such as IL-1β and TNF-α which increases seizure susceptibility and hence are effective in treatment of Epilepsy [11].

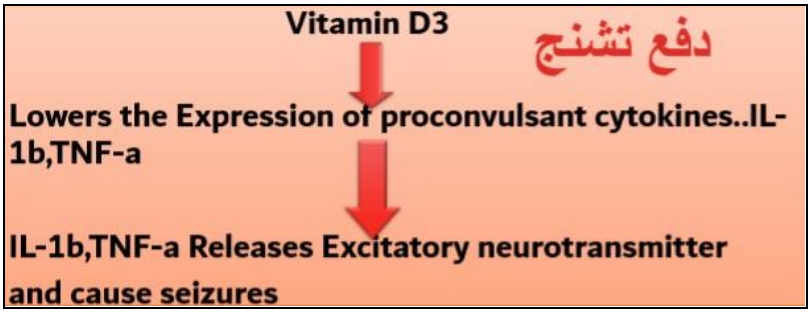

Fig 13: Vitamin D3 As *Dafe Tashannuj*

6. Modern Treatment and Its Side Effects

Modern treatment involves a range of drugs in the form of antidepressants, antianxiety drugs, antiepileptics, antiparkinsonism drugs, antipsychotics among many. But, not always there is a progressive recovery for these chronic nervous disorders, when on the modern medication owing to their side effects. Anti depressant medications like selective serotonin reuptake inhibitors (SSRIs) when taken for long time usually causes anxiety, nausea, agitation, headache, weight gain, drowsiness, constipation among many other.

Antiepileptic drugs (AEDs) are the primary medical treatment for epilepsy. However, even for those whose seizures are well controlled by AEDs, allergies, neurological and systemic toxicity, depression, memory loss, and osteoporosis are common problems. Because of the limitations and potential toxicity of existing AEDs, there is significant clinical interest in finding alternative therapies for epilepsy. People with epilepsy are often Vitamin D3-deficient, along with having decreased bone density and higher rates of osteoporosis.

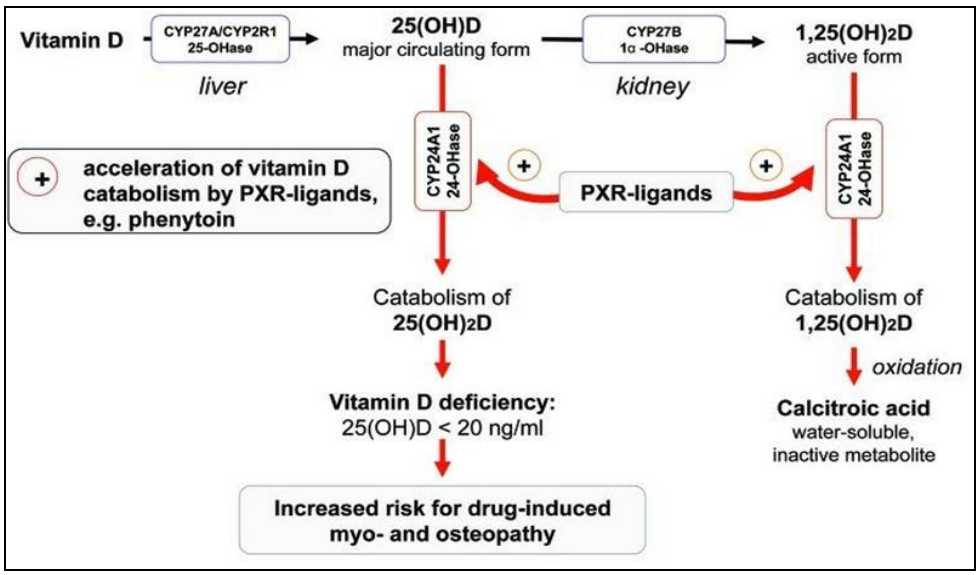

Fig 14: Modern Treatment

Furthermore, certain AEDs, such as carbamazepine and phenytoin, are known to decrease Vitamin D3 levels in people who are taking them due to increased metabolic clearance of Vitamin D3 and conversion to inactive forms. People with epilepsy face a sixfold risk for bone fracture compared to the normal population, likely an interplay between frequent falls, reduced bone density, and low levels of Vitamin D3. Such predisposed weakness is aggravated with catabolism of Vitamin D by PXR ligands resulting in increased risk for drug induced osteopathy and myopathy. (Fig 14) [15].

7. Unani Treatment Modalities

7.1 Ilaj Bil Ghiza (Dietotherapy)

7.1.1 Magnesium rich foods: like Flax seeds (habbul Aas), almonds, cashews, nuts, peas beans. Magnesium assists in

the activation of vitamin D. Vitamin D seem to require magnesium, which acts as a cofactor in the enzymatic reactions in the liver and kidneys.

7.1.2 Omega 3 rich foods like fish, olives, egg, flax seeds, nuts, avocado etc. Serotonin does not function optimally without the omega-3 fatty acids, EPA and DHA. While vitamin D supports serotonin synthesis, we also need omega-3 fatty acids in our diet to make serotonin function optimally in the brain. The omega-3 fatty acids in question are EPA and DHA that we primarily get from oily fish. However, omega-3 in the form of ALA (alpha-linolenic acid) is also contained in linseed oil and certain other vegetable oils, but many people have difficulty with converting ALA into EPA and DHA due to sluggish enzyme processes. DHA contributes in cell communication and also increases the serotonin sensitivity of serotonin receptors in neurons [19].

7.2 Ilaj Bid Dawa (Pharmacotherapy)

Muharrik wa Muqawai dimagh wa aasaab drugs like *zafron, ambar, misk, marwareed, ustukhudoos* are of great benefit in Depression. Drugs like *marwareed* not only act as *muqawi dimagh* but are also potently vitamin D3 efficient. Drugs of *muhalil awram* and immunomodulator effect like *Asgand nagori* exhibit great efficacy in Multiple Sclerosis. Drugs like *kapikachu* or *kaunch* seeds are of great effect in *rasha* (parkinson's disease). They exhibit the tendency to increase dopamine level and possess *muhalil awram* properties along with alleviating stress issues and boosting testosterone levels [20]. Potent anticonvulsants or *Dafe Tashnnuj* drugs like *jund baed satar* (castoreum) or *Ood saleeb* are very among many in epileptic seizures. Along with this dominant humour responsible for *sue mizaj* condition needs to be evacuated by *Tanqia* by *single drugs*, compound drugs or by *Munzij* and *Mushil* procedure.

7.2 Ilaj Bid Tadbeer (Regimenaltherapy)

Actual source of vit D3 being sun Sun bathe –*Hamam shamsia* is the best option for its attainment. During sunbathe, the entire body is exposed to sunrays, and is able to synthesize around 100 micrograms of vitamin D in 30 minutes. Sun exposure to the face and hands only enables us to make around 30 micrograms of vitamin D in the same amount of time. This is a much higher amount than the reference intake (RI). In fact, many researchers claim that our actual need for vitamin D is a lot higher than the RI, and their suggestions lie somewhere in the range of 30-100 micrograms daily. Along with this many regimenal therapies help the body in alleviating neurological symptoms. Saoot (Nasal irrigation) of particular drugs like castoreum and many other is very effective in Epilepsy. Nutool (irrigation) is helpful in Depression, Parkinson's disease, Epilepsy and Alzheimer's disease among many. Likewise Pashoya (Foot bath) and Dalk (Massage) are very much effective in enhancing proper function of brain.

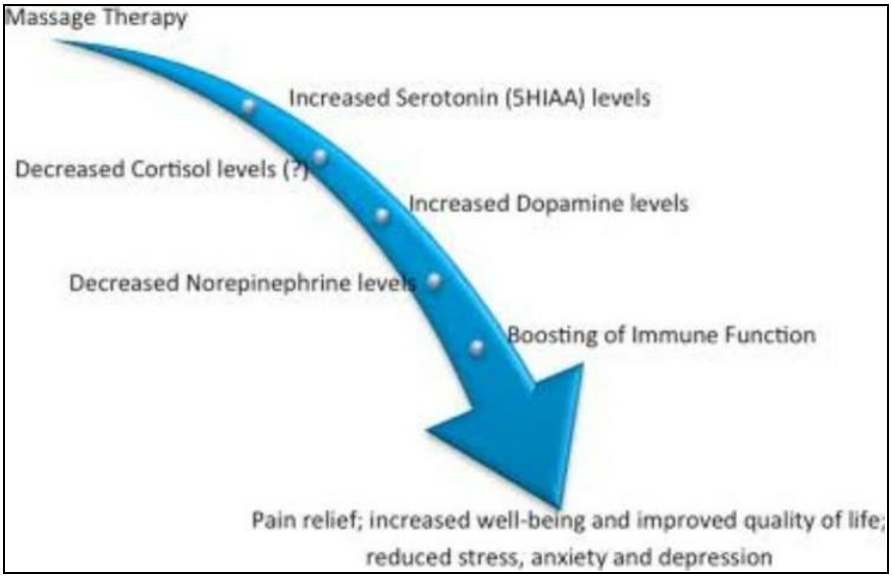

Fig 15: Mechanism of Alleviation neurological symptoms by the means of Dalk (Massage)

8. Conclusion

Vitamin D plays crucial role in the physiological well being of the brain and body. It is a neuroactive steroid which helps in neuroprotection, antiepileptic effects, immunomodulation, possible interplay with several brain neurotransmitter systems and hormones, as well as the regulation of behavior. As with all biochemical systems, none can be viewed in isolation. Hormonal changes are as involved with neurotransmitter systems as they are with the other physiological systems they impact. A better understanding of the interplay between these systems can go a long way to helping practitioners view their patients with psychiatric illnesses by getting to the source of the imbalance rather than treating only the end result.

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