ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1396

Vitamin D Levels as a Neurosteroid Hormone Associated with the Developing of Catecholamines in Healthy Adults: A Clinical Study in a Group of Healthy Adult Women

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Abstract:- Vit D deficiency is a public health problem worldwide. According to epidemiological studies, low Vit D levels have been associated with an increased risk of certain neurodevelopmental disorders, including autism spectrum disorder, but the risk of high concentration of Vit D is not clearly affect in nervous system.. In this research, we studied whether vitamin D concentrations were associated with the activity of the nervous system in healthy people by comparing catecholamines concentrations in blood of 42 healthy women (age = 40-50 years old, body mass index: 22.7 ± 2.1 kg/m2). We had three groups as Vit D levels: (Deficient: vit D: ≤ 20 ng/L), (insufficient vita D 20-29 ng/L), (Sufficient vit D: ≥30≤70 ng/L). In our study:_ Plasma Noradrenaline decreased statistically significant (p<0.005) in high levels of vit D, _ Plasma Adrenaline increased statistically significant (p<0.005) in high levels of vit D,_ Plasma Dopamine increased statistically significant only in high levels of vitamin D. It should be mentioned that high levels of vita D has also been related to mood disorders, movement and a Calcium status. There was a statistical association between several measures of nervous system, hormones activity and vita D levels. This suggests that vita D induces catecholamine synthesis and/or secretion.

Keywords:- *Adrenaline, Dopamine, Catecholamines, MAO, Vitamin D.*

I. INTRODUCTION

A. Vitamin D and its Role:

Vita D is one of the fat-soluble vitamins, it has two different forms: Vit D2 and Vit D3. While vitamin D2 is obtained from the diet, vitamin D3 is produced primarily from 7-dehydrocholesterol (7-DHC) in the skin via ultraviolet (UVB) radiation. It is converted to 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] in the kidney via hydroxylation of 1 α-hydroxylase1.

Several recent studies confirm that 1,25(OH)2D3 (the active form) can affect a wide range of biological functions, including cell proliferation and differentiation, immune responses, the balance of calcium and phosphorus2, and brain development3.

Many epidemiological data have revealed a relationship between vit D deficiency and the occurrence of some neurodevelopmental disorders4,5 ,However, the molecular mechanisms of vita D effects in these diseases is little known 6,7.

Some studies showed that vit D activates the gene that create the enzyme tryptophan hydroxylase 2 (TPH2), which converts the essential amino acid tryptophan, into serotonin in the brain8,9,10. This suggests that adequate levels of vit D may be needed to produce serotonin in the brain where it forms the structure and wiring of the brain, acts as a neurotransmitter, and influences social behavior 11,12,13. They also found evidence that the gene that create the enzyme tryptophan hydroxylase 1 (TPH1) is inhibited by vit D, which subsequently stops the production of serotonin in the intestine and other tissues, where its presence in excess promotes inflammation 14,15.

B. What are Catecholamines:

The production of catecholamines in the body depends on the concentration of tyrosine in the blood. Tyrosine undergoes a hydroxylation process (OH) by the enzyme tyrosine hydroxylase16, forming DOPA, which undergoes a decarboxylation process, producing dopamine16.17.

Dopamine is secreted into the blood, or it undergoes another hydroxylation process, which produces Norepinephrine hormone17, which is also either secreted into the blood, or it undergoes a methylation process (CH3) by the enzyme methyltransferase, so to production of the Epinephrine hormone 17.18.

Catecholamines work to regulate blood pressure by controlling the constriction of blood vessels18,19, improving the contractility of the heart muscles, and controlling constriction20,21.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1396

Catecholamines affect the relaxing of the intestinal tract muscles, the urinary tract, and the bronchioles 22. Catecholamines modify metabolic processes by increasing blood sugar levels, as stimulating the breakdown of glycogen in the liver23, increasing the secretion of the hormone glucagon, reducing the secretion of insulin from the pancreas, and increases the secretion of Glucocorticoids (as Cortisol) from the adrenal gland 23.

Dopamine production essentially occurs in the brain, and the dopaminergic pathways follows have broad implications for cortical neurophysiology24. Dopamine is chemically classified as a catecholamine, undergoes some synthesis in the adrenal medulla, and has an affinity for adrenergic receptors. However, it is not typically considered in the context of clinical adrenal physiology at the same depth level as norepinephrine and epinephrine25. It has a special affinity to receptors found in renal arteries which, when activated, relax and dilate renal blood vessels 26. So, clinically, it has applications to treatment hypotension in patients with shock27.

Norepinephrine can be secreted into the bloodstream or further modified by a methyltransferase to epinephrine (adrenaline) 28,29. Glucocorticoids significantly down regulate methyltransferase activity to increase epinephrine production 30 The degradation of catecholamines into their metabolites occurs either by monoamine oxidase (MAO) located in the outer mitochondrial membrane of the cell and/or by catechol methyltransferase (COMT) located within the cytosol of the cell. MAO and COMT catabolize norepinephrine and epinephrine to vanillylmandelic acid (VMA), and dopamine to homovanillic acid (HVA). VMA and HVA are excreted in urine31.

Some patients suffer from a deficiency in catecholamine functions as a result of a defect in the mechanism of their secretion, absorption, or sensitivity of receptors to them, which results in negative effects in attention and mood 32,33.

High levels of catecholamines in the body lead to increased breathing rate, high blood pressure, and increased blood flow to the body's organs such as the brain, heart, and kidneys 25,34.

➢ *Using of Catecholamines in Treating a Number of Diseases:*

- Epinephrine and Norepinephrine are used to treat cases of acute low blood pressure, and as part of the treatment plan in cases of cardiac arrest, causing local narrowing of the blood vessels to reduce bleeding during surgical operations33. Some medications that work to inhibit the absorption of catecholamines are also used to treat some psychological disorders, such as depression, stress, panic disorder, and others, in addition to treating some chronic cases of muscle pain 31.
- Dopamine: a neurotransmitter that affects movement, feelings, and memory34. The most prominent symptoms of high dopamine in the blood are the following: excessive secretion of saliva, digestive problems, hyperactivity, anxiety, insomnia, depression and schizophrenia35.
- Serotonin regulates a wide range of brain functions and behaviors36. Studies report that serotonin regulates executive function, sensory gating, and social behavior, bipolar disorder, schizophrenia, and reckless behavior all share common deficits in these functions37.
- Mechanisms are proposed by which serotonin synthesis, release, and function in the brain are modulated by vitamin D, omega-3 fatty acids eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)38.

II. RESEARCH AIM

The autonomic dysfunction is associated with an increased risk of cardiovascular mortality 6. In contrast, an in vitro study reported that 1,25-dihydroxy vit D increases the effectiveness of tyrosine hydroxylase, suggesting that vitamin D It may catalyze the rate-limiting step in catecholamine biosynthesis17,18.

With these conflicting results, there is interest in further investigating the relationship between vit D and autonomic nervous system activity.

Increased arterial stiffness and arterial wave reflection, an indirect marker of atherosclerosis, have been proposed as mechanisms linking vit D deficiency and cardiovascular events. These measures, which are major determinants of systolic blood pressure and pulse pressure, and thus cardiovascular risk4,5, were negatively associated with vitamin D concentration6,7,8.

Vit D deficiency has been associated with these structural and functional vascular disorders in some studies6,10,11, but not in others12. Therefore, further investigation into the mechanisms linking serum vit D and atherosclerosis is warranted.

III. RESEARCH MATERIALS AND METHODS

Many women visited the cardiology, neurology, and endocrinology clinics with complaints of high blood pressure (16/10 mm) without any cardiac causes or symptoms of altered thyroid activity. Women were excluded if they had taken calcium , vitamin D supplements or beta-blocker medication in the previous three months, had diabetes, atrial fibrillation or Raynaud's phenomenon, were pregnant.

Our study include 42 women (age = 40-50 years old, body mass index: 22.7 ± 2.1 kg/m2)

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1396

➢ *We Organized the Patient into Three Groups:*

- Group1: 13 women (vitamin D: ≤ 20 ng/L), and no clear symptoms of high blood pressure.
- Group2: 13 women (vitamin D: 20-29 ng/L)
- Group3: 16 women (vitamin D: ≥30≤70 ng/L).

Vitamin D and catecholamines (Adrenaline, Noradrenaline and Dopamine) were assayed in whole blood in the presence of EDTA. Calibrations were performed on an HPLC device, et al., 2015; Petty et al., 2019). were included in the final analysis for most variables.

These studies were conducted within the Endocrinology Research department, Al-Hawash University Hospital. The study was approved by the Research and Ethics Committee of the Ministry of High Education in Syria. All subjects provided written informed consent.

➢ *Statistics:*

Data were analyzed using SPSS 24 with $p<0.05$ considered statistically significant. Results are presented as mean ± standard deviation if normally distributed and median (interquartile range) if the distribution was not normal. Normality was assessed with the Kolmogorov–Smirnov test.

IV. RESULTS AND CONCLUSION

➢ *In our Study:*

- Plasma Noradrenaline (norepinephrine) decreased statistically significant ($p<0.005$) in high levels of vit D Figure 1.
- Plasma Adrenaline (Epinephrine) increased statistically significant ($p<0.005$) in high levels of vit D, Figure2.
- Plasma Dopamine increased statistically significant only in high levels of vit D, Figure3.

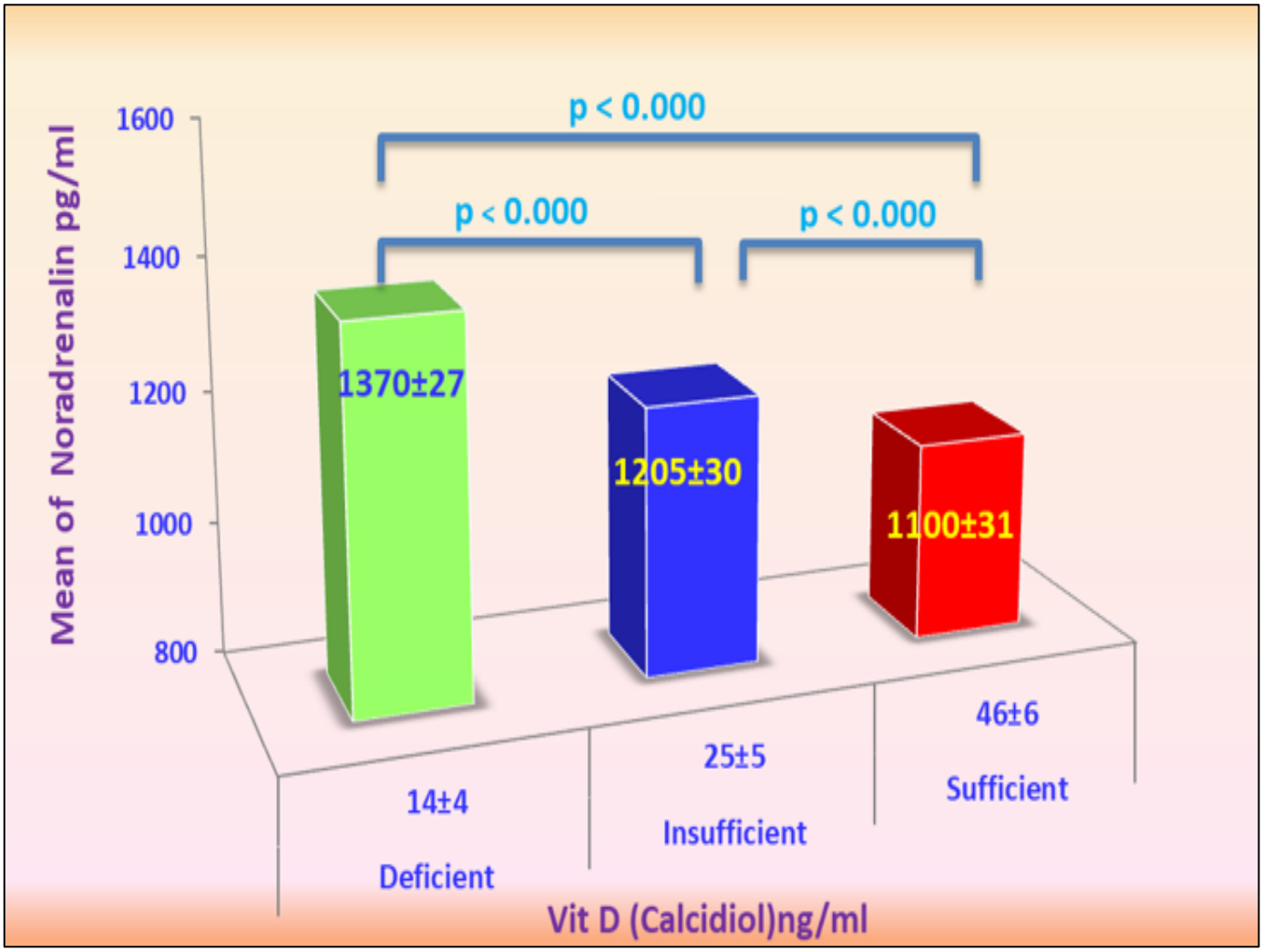

Fig 1: Association of Vitamin D Levels with Noradrenaline Concentrations in Healthy Women.

- Note: Current guidelines for adequate vitamin D levels are concentrations above 30 ng/ml.
- Note: Current guidelines for adequate Noradrenaline: Supine 70-750, Standing: 200-1700 pg/ml.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1396

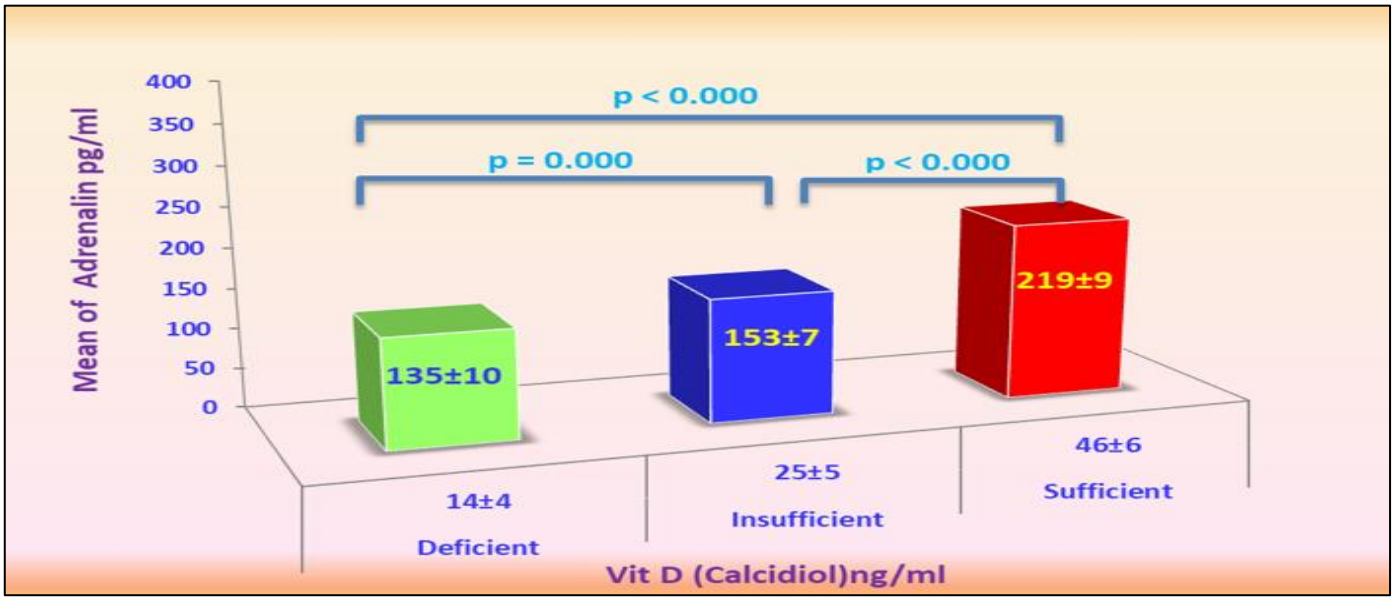

Fig 2: Association of Vitamin D Levels with Adrenaline Concentrations in Healthy Women

- Note: Current guidelines for adequate vitamin D levels are concentrations above 30 ng/ml.
- Note: Current guidelines for adequate Noradrenaline: Supine up to 110, Standing: up to 140 pg/m

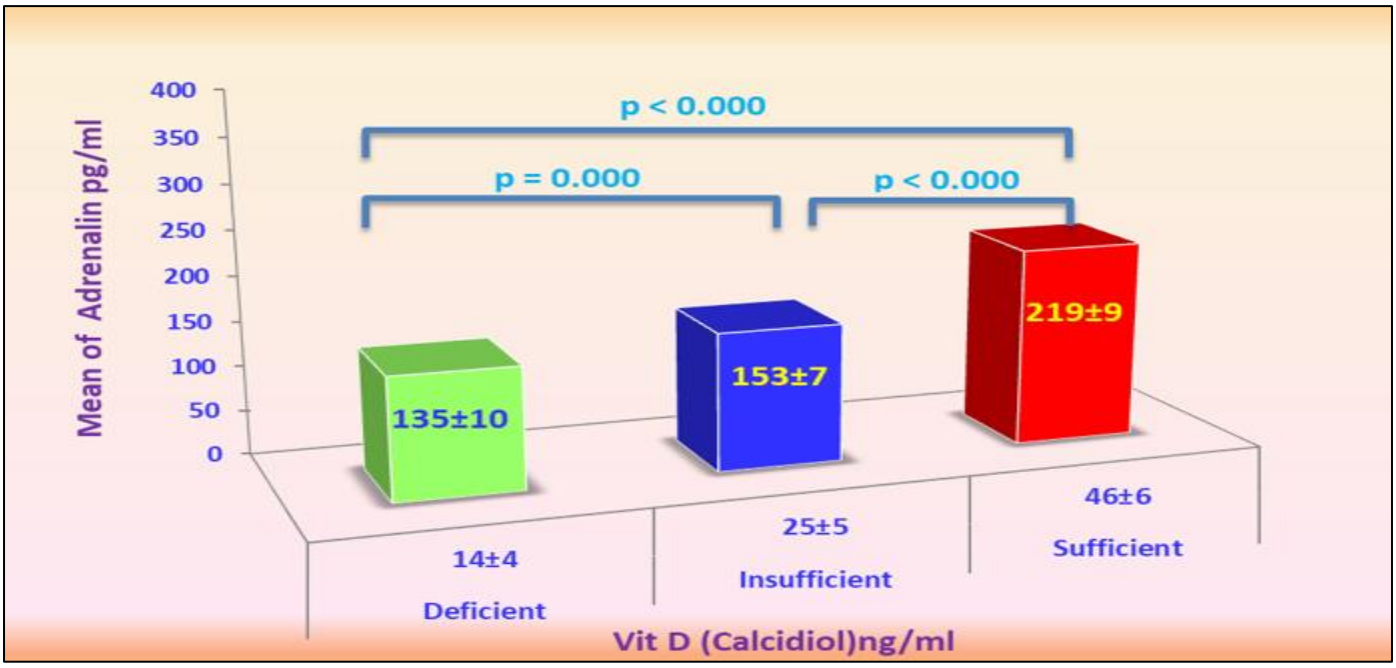

Fig 3: Association of Vitamin D Levels with Dopamine Concentrations in Healthy Women

- Note: Current guidelines for adequate vitamin D levels are concentrations above 30 ng/ml.
- Note: Current guidelines for adequate Dopamine: up to 30 pg/m

There was an independent relationship between several measures of nervous system activity and vit D levels.

➢ *The Proposed Mechanisms of Vit D Explains:*

- Most catecholamines are eliminated by the liver, and the substance resulting from final breakdown is called vanillylmandelic acid, which is excreting it in the urine35,36.
- Aanother suggesting category is that, the transcription of the tryptophan hydroxylase 2 (TPH2) gene in the brain is activated by vitamin D 14,15 so the synthesis of dopamin, adrenaline and nor adrenaline is induces.
- Vitamin D can modulate catecholamine synthesis and/or secretion from the adrenal medulla19, so, we can understand the relationship between serum vitamin D and cardiovascular risk where the high concentrations of catecholamines is the reason.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUN1396

- Vitamin D affects Calcitonin and Thyroxin hormone releasing, so the TSH 37
- Hypercalciuria and Hypercalcemia are caused by the side-effects of vitamin D supplementation, so maybe they result to hypertension symptoms38.

V. CONCLUSION

➢ *For Many Overlapping Reasons:*

High levels of vit D is a cause of or risk for developing depression and hypertension. So vitamin D supplementation must be controlled well.

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