Vitamin D Serum levels and Its Correlation with Major Depressive Disorder and Schizophrenia

Thesis

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By

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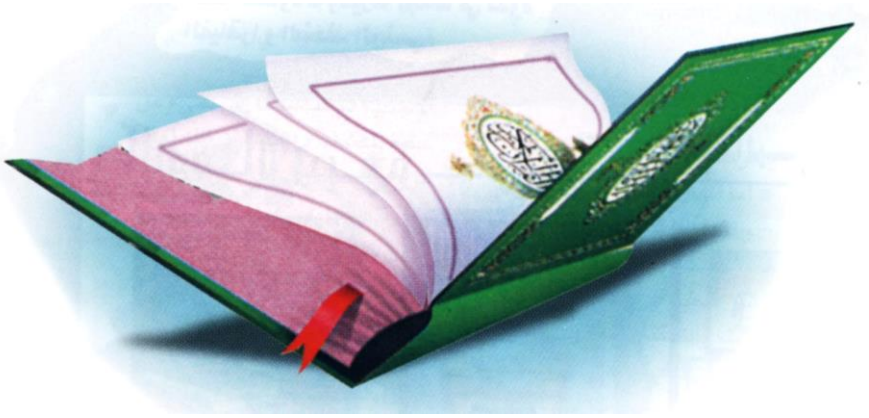
بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ



صدق الله العظيم

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Abdelhamid Mosbah Abdelrahman Abdelhamid

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List of Abbreviations

Abb.	Full term
25 (OH) D	*25 hydroxyvitamin D*
AD	*Alzheimer's disease*
ADHD	*attention deficit hyperactivity disorder*
ASD	*autistic spectrum disorder*
Auc	*area under curve*
Ci	*confidence interval*
CRH	*Corticotropin-releasing hormone*
cyp27b1	*cytochrome 27b1*
Def.	*Deficiency*
DSM	*Diagnostic and Statistical Manual*
DVD	*Develepomental vitamin D*
ELISA OR EIA	*enzyme-linked immunosorbent assay*
fMRI	*Functional Magnetic Resonance Imaging*
GHQ	*General Health questionnaire*
HIV	*Human Immunodeficiency Virus*
HPA	*hypothalamic-pituitary-adrenal axis*
Insuf.	*Insufficieny*
IU	*International Unit*
Mcg	*micrograms*
Mdd	*major depressive disorder*
MoCA	*Montreal Cognitive Assessment*
Ng/ml	*nanogram/milliliter*
OCD	*obsessive compulsive disorder*
Or	*odds ratio*

List of Abbreviations cont...

Abb.	Full term
PET	*Positron emission tomography*
Pth	*parathyroid hormone*
RDA	*Recommended Dietary Allowance*
S.def	*Sever deficiney*
Schiz	*schizophrenia*
SCID	*Structured Clinical Interview for DSM*
Se	*standard error*
SNRI	*Serotonin and Noradrenalin Reuptake Inhibitors*
SSRI	*Selective Serotonin Reuptake inhibitor*
Suf	*Sufficient*
TMB	*tetramethylbenzidine*
VDBP	*Vitamin D binding protein*
VDR	*vitamin D receptor*

INTRODUCTION

Depression is associated with significant disability, mortality and healthcare costs. It is the third leading cause of disability in high-income countries ***(Lopez, 2006).***

Although biological, psychological and environmental theories have been advanced ***(Krishnan and Nestler, 2010)***; the underlying pathophysiology of depression remains unknown and it is probable that several different mechanisms are involved. Yet, the development of major depression is a complex and multifactorial process. There is evidence that dysfunctions in various endocrine axes may be independent risk factors in the development of affective illness ***(Blazer, 2003).***

During the last century, exposure to sunlight has decreased, affecting brain activity. Thus, depression has increased dramatically ***(Zehnder, 2001).***

On the other hand, Schizophrenia is a brain disease that interferes with normal brain functioning. It causes affected people to exhibit odd and often highly irrational *or* disorganized behavior. Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. The early onset of the disease, along with its chronic course, make it a disabling disorder for many patients and their families ***(Lavretsky, 2008).***

Disability often results from both negative symptoms and cognitive symptoms, such as impairments in attention, working memory, or executive function.

Vitamin D is a unique neurosteroid hormone that may have an important role in the development of depression and Schizophrenia. Receptors for vitamin D are present on neurons and glia in many areas of the brain including the cingulate cortex and hippocampus, which have been implicated in the pathophysiology of depression and schizophrenia ***(Eyles,2005)*.**

Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development, ***(Fernandes de Abreu, 2009)*** making it biologically plausible that this vitamin might be associated with depression/schizophrenia and that its supplementation might play an important part in the treatment of depression/ schizophrenia.

The link between vitamin D deficiency and the development of schizophrenia has been researched among patients of all ages around the globe. One meta-analysis reviewed 19 studies published between 1988 and 2013 and found a strong association between vitamin D deficiency and schizophrenia. Of the 2,804 participants from these studies, over 65% of the participants with schizophrenia were vitamin D deficient. Vitamin D deficient participants were 2.16 times

more likely to have schizophrenia than vitamin D sufficient participants ***(Valipour, 2014).***

Low serum vitamin and elevated PTH levels have been linked with various psychiatric disorders including depression ***(Hoogendijk et al., 2008)*** and schizophrenia ***(McGrath et al., 2004).***

However, ***(Schneider et al., 2000)*** found that although vitamin D levels were significantly lower in people with schizophrenia or major depression than in normal controls; there were no differences in vitamin D levels among patients with psychiatric disorders, suggesting that vitamin D is not specifically involved in the pathogenesis of depression.

Some studies have demonstrated a strong relationship between vitamin D and depression ***(May, 2010)***; as a study supports that vitamin D deficiency is associated with increased odds of depression ***(Vidgren et al., 2018)***, while another have shown no relationship ***(Chan, 2011).***

Aim of the Work

To estimate the level of vitamin D in patients with Schizophrenia and MDD compared to controls and to study the association between vitamin D level and the clinical characteristics of patients suffer from MDD and Schizophrenia.

Chapter I

VITAMIN D WITH PSYCHIATRIC DISORDERS

Vitamin D deficiency is being associated with a number of psychiatric conditions. In particular for disorders with a developmental basis, such as autistic spectrum disorder and schizophrenia the neurobiological plausibility of this association is strengthened by the preclinical data indicating vitamin D deficiency in early life affects neuronal differentiation, axonal connectivity, dopamine ontogeny and brain structure and function ***(Elyes et al., 2013).***

For instance in early life, vitamin D plays a vital role in neuronal development. Some studies conducted recently show the effect of vitamin D on early life brain development. In May 2018, a study conducted that deficiency of vitamin D in maternal and offspring shows some disabilities in early life including learning, memory problems, and grooming behaviors. There was also some evidence of increased lateral ventricle volume and altered neural expression of genes involved in dopamine and glucocorticoid-related pathways suggesting autism and schizophrenic-like disorders ***(Yates et al., 2018).***

1. Mechanism:

One of the most prominent functions of vitamin D is its potent differentiation actions in a variety of tissues ***(Mehta et***

al., 2002). Vitamin D differentiates brain cells, regulates axonal growth, regulates calcium signalling directly in the brain, modulates the production brain-derived reactive oxygen species, and stimulates the production of neurotrophic factors. Many of these outcomes could be relevant to the variety of neuropsychiatric conditions now being linked with deficits of this vitamin.

Moreover, the immunohistochemical presence of vitamin D receptor (VDR) has been described in the developing rodent brain. Studies in foetal rat dorsal root ganglion cells first suggested the VDR was present in a developing brain ***(Johnson et al., 1996).***

Likewise, the temporal nature of VDR expression in development was immunohistochemically mapped in both rat ***(Veenstra et al., 1998)*** and mouse brain ***(Erben et al., 2002).*** The VDR is first detected on embryonic day (E) 12 in rats and E11.5 in mouse. As found in the adult human brain there is a broad distribution across a variety of regions in rodent. In support of a role for vitamin D in brain cellular differentiation the VDR appeared to be preferentially localized in differentiating fields ***(Veenstra et al., 1998).***

Accordingly, there may be a number of possible molecular mechanisms for its diverse actions in the developing brain and adult brain. The number of functions proposed for vitamin D in the brain is impressive ***(McCann et al., 2008).***