Vitamin D Level and its Relation to Clinical Features of Major Depressive Disorder

Thesis

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Psychiatry

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ABSTRACT

Background: Vitamin D possibly helps in the regulation of neurotransmission, neuroprotection, and nerve growth factor synthesis. Therefore, a vitamin D deficiency might lead to inactivated receptors and a disruption to the pathway that may result in depression.

Aim: To assess the relationship between serum level of vitamin D and clinical features of major depressive disorder including its severity, symptomatology, and cognitive dysfunction (memory and attention).

Methodology: Serum levels of 25-hydroxy vitamin D were measured with electo-chemiluminescence binding assay technique in 75 patients with major depressive disorder. The patients were recruited from Psychiatry and Addiction Hospital Kasr Al Ainy from the outpatient clinic. Patients were subjected to SCID, Hamilton depression scale, Mini-mental status examination, Wechsler memory subtests (story A and paired associate learning test), Benton visual retention test and Trail B test.

Results: 94.6% of patients had vitamin D deficiency (< 20 ng/ml); there was no significant correlation between levels of vitamin D and severity of depression according to HAM-D. Regarding depression symptoms there was a statistically significant difference (p= 0.032) between levels of vitamin D, being more deficient in the presence of genital symptoms (decreased libido and menstrual disturbances) and decreased concentration. There was also no statistically significant correlation between level of vitamin D and different psychometric tests (MMSE, Trail B, story A, PALT and BVRT) although they were globally impaired.

Conclusion: Major depressive disorder is strongly associated with vitamin D deficiency but no statistical significant correlation could be established between serum levels of vitamin D and severity of depression.

Key words: Vitamin D, Major depressive disorder, depression severity.

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LIST OF ABBREVIATIONS

1,25(OH)2D	:	1,25 dihydroxy vitamin D
24,25(OH)2D	:	24,25 dihydroxy vitamin D
25(OH)D	:	25 hydroxy vitamin D
5-HT	:	5-hydroxytryptamine
6OHDA	:	6-hydroxydopamine
AD	:	Alzheimer 's disease
AMH	:	Anti-mullerian hormone
ASD	:	Autism spectrum disorder
BDI	:	Beck depression inventory
BDNF	:	Brain derived neurotrophic factor
BMI	:	Body mass index
BVRT	:	Benton Visual Retention test
CAM kinase II	:	Calcium/calmodulin-dependent protein kinase II
CNS	:	Central nervous system
CRH	:	Corticotropin releasing hormone
CSF	:	Cerebrospinal fluid
CYP24A1	:	Cytochrome 24A1
CYP27B1	:	Cytochrome 27B1
DA	:	Dopamine agonist
DBP	:	Vitamin D3-binding protein
Dex	:	dexamethasone
DNA	:	Deoxyribonucleic acid
DRI	:	Dietary reference intakes
DSM-IV	:	Diagnostic statistical manual of psychiatry-IV
DSST	:	Digit symbol substitution test
EC	:	Expected correct score
EE	:	Expected error score
EF	:	Executive functions

G	:	Gram
GABA	:	Gamma-Aminobutyric acid
GAP 43	:	Growth-associated protein-43
GDNF	:	Glial cell line derived neurotrophic factor
GR	:	Glucocorticoid receptor
HADS	:	Hospital anxiety and depression scale
IU	:	International unit
Kg	:	Kilogram
LTP	:	Long-term potentiation
MAP2	:	Microtubule-associated protein
Mcg	:	Microgram
MDD	:	Major depressive disorder
MMSE	:	Mini-Mental State Examination
MR	:	Mineralocorticoid
mRNA	:	Messenger ribonucleic acid
NBM	:	Nucleus Basalis of Meynert
ng/ml	:	Nano gram per milliliter
NGF	:	Nerve Growth Factor
NIMH	:	National institute of mental health
Nm	:	Nanometer
NMDA	:	N-methyl D-aspartate
nmol	:	Nanomole
NT	:	Neurotrophin
OC	:	Obtained correct score
OE	:	Obtained error score
PALT	:	Paired Associate Learning test
PMDD	:	Premenstrual dysphoric disorder
PMS	:	Premenstrual syndrome
POMS	:	Profile of mood states
PTH	:	Parathyroid hormone

RNA	:	Ribonucleic acid
ROCF	:	Rey-Osterrieth Complex Figure
S	:	Seconds
SAD	:	Seasonal affective disorder
SBT	:	Short Blessed Test
SD	:	Standard deviation
SPF	:	Sun protection factor
SPSS	:	Statistical package for social science
TH	:	Tyrosine hydroxylase
TMT	:	Trail Making test
TSH	:	Thyroid stimulating hormone
UK	:	United Kingdom
US	:	United States
UV	:	Ultraviolet
UVB	:	Ultraviolet B
VDR	:	Vitamin D receptor
WHO	:	World health organisation
WMS-R	:	Wechsler Memory Scale-Revised

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INTRODUCTION

Depression is the leading cause of disability worldwide, affecting about 121 million people **(World Health Organization [WHO], 2008).** Currently, the WHO has determined that depression is ranked fourth on the global burden of disease list. The rates of depression continue to increase and the WHO predicts that it will be the second most common global burden of disease by the year 2020 **(Kessler, 2008).**

Vitamin D deficiency has been identified as a global problem with an estimated one billion people worldwide suffering from vitamin D deficiency or insufficiency. Studies in United States, Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, have indicated that 30 to 50% of children and adults have 25-hydroxyvitamin D levels under 20 ng per milliliter **(Holick, 2007).**

Few persons are screened for vitamin D deficiency; the proportion of individuals with unrecognized vitamin D deficiency is potentially large. The primary source of vitamin D is derived from cutaneous synthesis after ultraviolet exposure so that nutritious diets may not preclude vitamin D deficiency **(Thomas et al., 1998).**

Various population groups have been identified as high risk for vitamin D insufficiency or deficiency. Those with limited sun exposure, due to being homebound, and/or clothing that cover most of the body are at risk for vitamin D deficiency **(Office of Dietary Supplements [ODS], 2009).**

Findings from the National Health and Nutrition Examination Survey (NHANES-III, 1988–1994), which included more than 15,000 adults, indicated significantly lower levels of vitamin D for female than male participants. In addition, vitamin D levels were highest in whites, followed by Hispanics and then African Americans **(Zadshir et al., 2005**). For individuals who have darker skin, decreased vitamin D is more common; due to higher melanin levels, dark-skinned individuals experience reduced subcutaneous vitamin D synthesis compared to those with lighter pigmentation, making them another high risk group for vitamin D deficiency **(Harris, 2006).**

Although 1,25-dihydroxyvitamin D (1,25[OH]2D3) is the biologically active form of vitamin D, its circulating half-life is only 4 to 6 hours. Therefore, 25-hydroxyvitamin D (25[OH]D) is the principal vitamin D metabolite measured to determine vitamin D status. Vitamin D levels commonly are expressed as ng/mL or nmol/L. The Institute of Medicine has defined vitamin D deficiency as a serum 25(OH) D level of <30 nmol/L (<12 ng/mL). However, many experts define vitamin D insufficiency as a 25(OH)D level of 21 to 29 ng/ml, and deficiency as <20 ng/mL. The upper limit is more difficult to define, but symptoms of vitamin D intoxication appear with blood levels >150 to 200 ng/ml **(Holick, 2009).**

Vitamin D's role in psychiatric illnesses is suggested by region-specific expression of vitamin D receptors (VDR) in the cingulate cortex, thalamus, cerebellum, amygdala, and hippocampus**.** Most of these regions also express 1α-hydroxylase enzymes capable of metabolizing 25(OH)D to 1,25(OH)2D3, which suggests that vitamin D may have an autocrine or paracrine function in brain **(Eyles et al., 2005).**

Vitamin D regulates expression of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of dopamine, norepinephrine, and epinephrine **(Garcion et al., 2002).** Vitamin D also promotes survival of monoaminergic neurons through up regulation of glial cell line-derived neurotrophic factor, which supports survival of midbrain dopaminergic neurons and confers resistance to neurotoxins that deplete dopaminergic neurons **(Smith et al., 2006)**.

Vitamin D possibly helps in the regulation of neurotransmission, neuroprotection, and nerve growth factor synthesis **(Annweiler et al., 2010).** Therefore, a vitamin D deficiency might lead to inactivated receptors and a disruption to the pathway that may result in or contribute to depression.

Vitamin D also promotes neuronal survival by inhibiting oxidative pathways in the brain through inhibition of inducible nitric oxide synthase (reducing free radical formation) **(Garcion et al., 1997),** and up regulation of γ-glutamyltranspeptidase (increasing antioxidant production) **(Smith et al., 2006).**

A beneficial effect of vitamin D for cognition potentially could be mediated through a number of mechanisms including increasing acetylcholine concentration in the brain (which plays an important role in attention and arousal state), as suggested by the finding that treatment with 1,25-Dihydroxyvitamin D3, increase choline acetyltransferase activity in specific rat brain nuclei (**Sonnenberg et al., 1986).**

Additionally, vitamin D can protect neurons from excess calcium entry that are deleterious for memory formation through regulation of

cellular calcium homeostasis by down-regulating the expression of L-type voltage-sensitive calcium channel transcripts **(Leclerc et al., 2006).** Vitamin D is also known to affect the Ca binding protein; calbindin-D28k and calmodulin. Calbindin-D28k is involved in synaptic plasticity and memory formation **(Dumas et al., 2004).** Ca2+/calmodulin complex can regulate CAM kinase II, which is believed to play a central role in a variety of brain functions including learning and memory. It has been suggested that CAM kinase II is the molecular basis of long-term synaptic memory **(Poulsen et al., 2007).**

Vitamin D may also affect neuronal plasticity processes such as axogenesis. It has been reported that vitamin D has a trophic role in differentiation and maturation of neurons **(Taniura et al., 2006).**

It is of particular importance to report that metabolic pathways for 1,25(OH)2D3 were discovered within brain structures critical for mental processing and formation of new memories **(Cherniack et al., 2009).**

The questionable relationship between vitamin D and depression deserves to be objectively studied because establishing a role for vitamin D deficiency in depression, may help in improving the depressive symptoms through vitamin D supplementation.

AIM OF THE WORK

This study aimed to assess the relationship between serum level of vitamin D and clinical features of major depressive disorder including its severity, symptomatology, and cognitive dysfunction (memory and attention).