In: Environment, Mood Disorders and Suicide
Editors: T.T. Postolache and J. Merrick, pp. 59-74

ISBN: 978-1-61668-505-8
2011 Nova Science Publishers, Inc.

Chapter 5

VITAMIN D AND SUICIDE RISK FACTORS

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Abstract

Low vitamin D levels are negatively associated with certain prosuicidal factors such as exacerbation of depression, anxiety, psychosis, and certain medical conditions. Therefore, we hypothesize that they may also be associated with completed suicides. In particular, lower vitamin D levels at the end of winter, secondary to the lower vitamin D production in the skin, (as a result to reduced skin surface exposure as well as reduced duration of exposure, an after effect of uncomfortably low heat index and lower solar radiation). In preparation to test this hypothesis in future research, we now briefly review the existent literature on vitamin D, its deficiency and its reported association with certain risk factors for suicide.

Introduction

Suicide is the 10th leading cause of death worldwide and the second leading cause of death in adolescents and adults ages 15-35 years (1-3). Suicide attempts are 2 to 3 times more likely than fatal completions (4). Approximately 90% of individuals who die by suicide are diagnosable with a psychiatric illness. About 9.5% of the United States population suffers from a mood disorder including 6.7% suffering from major depressive disorder, 18.1% diagnosed with an anxiety disorder and 1.1% with a psychotic disorder expressed by

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schizophrenia (1-3,5). The risk of suicidal behavior markedly increases if an individual manifests co-morbidity. For instance, in a study performed on adolescents and young adults with suicide attempts, 79% of suicidal individuals had co-morbid psychiatric disorders, and individuals with 3 or more diagnoses of these disorders were significantly more likely to attempt suicide as compared to healthy controls (4, 6).

Vitamin D deficiency results from insufficient amounts of the circulating vitamin D, which is essential for proper bone and mineral metabolism, growth, neurodevelopment and immune maturation. A significant amount of vitamin D is synthesized in the skin under the influence of ultraviolet light from the sun.

Many individuals reside in areas of the world with limited sunlight exposure, such as cold climate and higher latitudes. Other implications include clothing choices that tend to cover the skin while outside, or not eating enough foods rich in vitamin D, such as fatty fish or dairy products. These, if not adequately corrected with vitamin supplements, could lead to vitamin D deficiency.

The objective of this chapter is to evaluate evidence suggesting an association between vitamin D serum levels and suicide risk factors, such as 1) Psychiatric Disorders, including anxiety, mood and psychotic disorders, 2) family history of suicide, including genetic and early developmental factors and 3) chronic medical illnesses. We will also discuss Vitamin D physiology and the possibility of its use as a preventive measure for suicidal behaviors.

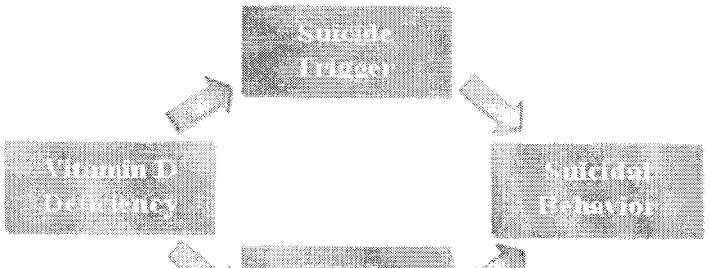

Figure 1. Vitamin D deficiency, and suicide predispositions and triggers such as negative life events, if combined, can lead to suicide.

What Is Vitamin D?

Vitamin D is a group of fat-soluble prohormones, the two forms of which are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). The difference between these two forms lies in their side chain. Vitamin D_3 is either formed in the skin after exposure to ultraviolet light (natural sunlight or artificial) or it is obtained orally from dietary sources. Natural, enriched and supplemental sources of vitamin D are shown in Table 1.

7-dehydrocholesterol (pre-vitamin D_3) is the derivative of cholesterol and is formed in skin under the influence of ultraviolet (UV) light. Vitamin D_2 is obtained by irradiation of plant materials or foods. The highest concentrations of 7-dehydrocholesterol are present in epidermal layers of the skin. This pre-vitamin D_3 is then spontaneously isomerized to vitamin D_3 in the skin.

NATURAL, EN
Nutritional Sources
NATURAL
Salmon
Fresh (3.5 oz)
Farmed (3.5 oz)
Canned Tuna (3.6
Shiitake Mushroon
Fresh (3.5 oz)
Sun-Dried (3.5 oz)
Yolk of an egg
ENRICHED
Milk (8 oz)
Orange Juice (8 oz
Cereals (1 serving
SUPPLEMENTS
Infant formula (8 o
Ergocalciferol
Dristol liquid supp
Over-Counter Mul
UV-B Radiation (5

This Vitamin D_3 converted into active transported to the live undergo the same acti by 1 alpha-hydroxyla $1,25[OH]_2D_2$ and 1,25 forms differ in their m of $1,25[OH]_2D_3$, most s

The metabolic act containing enzymes. Fi D_3 (calcidiol) by the $1,25[OH]_2D_3$ by the ac located in the inner mi renal 1alpha-hydroxyla calcium. This renal enz

Excretion

Both synthesis and D involves 24-hydroxy 450 enzyme and is inv also catalyses 1,25[OH

Table 1. Sources of vitamin D

NATURAL, ENRICHED AND SUPPLEMENTAL SOURCES OF VITAMIN D	
Nutritional Sources	Vitamin D Content
NATURAL	
Salmon	
Fresh (3.5 oz)	600-1000 IU
Farmed (3.5 oz)	100-250 IU
Canned Tuna (3.6 oz)	250 IU
Shiitake Mushrooms	
Fresh (3.5 oz)	100 IU
Sun-Dried (3.5 oz)	1,600 IU
Yolk of an egg	20 IU
ENRICHED	
Milk (8 oz)	100 IU
Orange Juice (8 oz)	100 IU
Cereals (1 serving portion)	100 IU
SUPPLEMENTS	
Infant formula (8 oz)	100 IU
Ergocalciferol	50,000 IU/Capsule
Dristol liquid supplement	8000 IU/Ml
Over-Counter Multivitamin	400 IU
UV-B Radiation (5-10 min in sunlight)	3,000 IU

This Vitamin D_3 formed in the skin, where it can meet one of two fates. It can be converted into active vitamin D_3 ($1,25[OH]_2D_3$) (calcitriol) within the skin or it can be transported to the liver after binding with proteins in the blood. Both vitamin D_2 and D_3 undergo the same activation process involving first, 25-hydroxylation in the liver, followed by 1 alpha-hydroxylation in the kidney to make the biologically active compounds $1,25[OH]_2D_2$ and $1,25[OH]_2D_3$, respectively. There is little evidence that these two active forms differ in their mode of action, and since most is known about the synthesis and action of $1,25[OH]_2D_3$, most studies focus on D_3.

The metabolic activation of vitamin D_3 is carried out by specific cytochrome P-450 containing enzymes. First, vitamin D_3 passes through the liver and is metabolized to $25[OH]D_3$ (calcidiol) by the action of 25-hydroxylase. Then $25[OH]D_3$ is metabolized to $1,25[OH]_2D_3$ by the action of 1alpha-hydroxylase in the kidney. Both of these enzymes are located in the inner mitochondria in the kidney cells. The synthesis of $1,25[OH]_2D_3$ by the renal 1alpha-hydroxylase appears to be tightly regulated by levels of plasma $1,25[OH]_2D_3$ and calcium. This renal enzyme is induced by the parathyroid hormone (PTH).

Excretion

Both synthesis and degradation of vitamin D are tightly regulated. Catabolism of vitamin D involves 24-hydroxylase which is a third, vitamin D related mitochondrial cytochrome P-450 enzyme and is involved in the catabolism of $25[OH]D_3$ to $24,25\ [OH]_2D_3$. This enzyme also catalyses $1,25[OH]_2D_3$ to $1,24,25[OH]_3D_3$. Both $24,25[OH]_2D_3$ and $1,24,25[OH]_3D_3$ are

ultimately excreted after metabolism. 24-Hydroxylase is strongly induced in target cells by $1,25[OH]_2D_3$ and it prefers 1, 25 $[OH]_2D_3$ to $25[OH]D_3$ as a substrate. This hydroxylation by 24-hydroxylase is now known to occur in all vitamin D target tissues including enterocytes, osteoblasts, keratinocytes and parathyroid cells.

UVB Induced Synthesis of Active Vitamin D ($1,25[OH]_2D_3$) in Skin and Its Significance

Epidermal synthesis of calcitriol under influence of UVB regulates important cellular functions in keratinocytes and immunocompetent cells. The antiproliferative and prodifferentiating effects of calcitriol and other vitamin D analogues are highly effective in the treatment of psoriasis vulgaris.

The known antipsoriatic effects of sunlight could in part be mediated via UV-B induced synthesis of calcitriol. Vitamin D synthesis is also of high importance for the prevention of a broad variety of diseases, including various malignancies.

Also, the discovery of 1 alpha-hydroxylase in the central nervous system (CNS) suggests that the CNS can synthesize the active form of vitamin D (7). Thus, serum 25-hydroxycholecalciferol levels may also influence paracrine production of 1, 25 dihydroxycholecalciferol directly in the CNS (8-10).

Mechanisms of Action of Vitamin D

Vitamin D metabolites are bound in the circulation to vitamin D binding proteins. The active metabolite enters the target cells and binds to vitamin D receptors (VDRs), which are nuclear receptors.

This complex, forms a heterodimer with a retinoid receptor and binds to the vitamin D responsive element on a responsive gene leading to gene expression, either up regulation or down-regulation of gene products such as calcium binding protein or osteocalcin, a process that might take anywhere from hours to days. On the other hand, 1, $25[OH]_2D_3$ may also work through a plasma membrane receptor and a second messenger such as Mitogen-Activated Protein (MAP) Kinase or Cyclic Adenosine Monophosphate (cAMP) and may influence calcium channels (11). The rapid response through a second messenger includes the effects on the pancreas beta cells, on vascular smooth muscle, on the intestines and on monocytes.

Functions of Vitamin D

A key function of $1,25[OH]_2D_3$ is to increase calcium absorption from the intestine. For calcium absorption, longitudinal bone growth, osteoblast and osteoclast activity, both $1,25[OH]_2D_3$ and VDR are essential (12). Genes up-regulated by 1, 25 $[OH]_2D_3$ include osteocalcin, osteopontin, calbindin, 24-hydroxylase and others (13). Metabolites of the active form of vitamin D, down regulate inflammatory markers such as IL-1 and IL-12 and have an antiproliferative effect. They also decrease Parathyroid Hormone (PTH) and Parathyroid Hormone-related Protein (PTHrP) through a negative vitamin D responsive element (13). In summary, the active metabolite $1,25[OH]_2D_3$ stimulates calcium absorption, decreases PTH secretion, stimulates osteoclastic bone resorption, stimulates the osteoblasts, decreases the production of collagen type I, influences muscular function, stimulates cell differentiation and

the immune system and
between serum 25[OH]D

Measuring Vitam

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Table 2. C

CLASSIFICAT
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Possible Toxicity

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ultraviolet light much le

Consequences of

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hand, deficiency causes
PTH causes high bone
fractures especially hip

Vitamin D deficien
metabolite $1,25[OH]_2D$
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